ACR/ARHP 2010 Annual Scientific Meeting Overall Needs Assessment/Practice Gaps

The American College of Rheumatology and the Association of Rheumatology Health Professionals are committed to providing comprehensive education to improve the knowledge and performance of physicians, health professionals and scientists. Through evidence-based educational programs, the organization strives to enhance practice performance and improve the quality of care in those with or at risk for arthritis, rheumatic and musculoskeletal diseases. The 2010 ACR/ARHP Annual Scientific Meeting program has been developed independent of commercial influence. The following groups were involved in the planning process: the ACR Committee on Education; the ACR Annual Meeting Planning Committee; the ARHP Education Committee and the ARHP Annual Meeting Program Planning Committee.

The program is the result of a planning process that identified educational needs to change or enhance the knowledge, competence or performance of rheumatology professionals. The program’s content was derived from both needs assessment and practice gap analysis based on professional activities, practice setting, ABIM recertification requirements and physician attributes.

Program Highlights

- Educational tracks to help attendees identify content targeted to them. Tracks include: business of rheumatology, clinical, clinical and research, clinical practice, educators, fellow-in-training, pediatrics, pediatrics and clinical, and research
- Latest science and best-practices presented through peer-reviewed and selected clinical and scientific abstracts, and invited speakers providing clinical, evidence-based and quality focused content
- Diverse formats of education delivery, including: didactic lectures, debates, and interactive sessions, such as poster tours, Meet the Professors and Workshop sessions
- A larger forum for discussion of practical management issues such as the Curbside Consults – Ask the Professors session and Medical Aspects lectures
- Extensive learning opportunities in the basic science of rheumatology, an area of the program developed by a subcommittee of U.S. and internationally prominent basic scientists. Offerings include: the Basic Science Symposia, State-of-the-Art Lectures, a series of Immunology Updates for the Clinicians, and a Basic Science pre-meeting course
- Clinical management sessions, including the Thieves’ Market and basic management of difficult issues
- A specific pediatric rheumatology track plus content integrated throughout the program designed to provide a high-level educational program to pediatric rheumatologists; and relevant updates to adult rheumatologists
- Formal presentations of new practice guidelines provided to alert the membership and explain, in an open forum, the data supporting the guidelines and propose approaches for implementation
- Over 40 workshops designed to provide hands-on skills training

About ACR/ARHP Education

ACR/ARHP Program Objectives

The American College of Rheumatology and the Association of Rheumatology Health Professionals, a division of the ACR, are organizations of physicians, health professionals and scientists serving members through programs, including education and research. Through these programs, the ACR and the ARHP foster excellence in the care of people with rheumatic and musculoskeletal diseases.

The 2010 ACR/ARHP Annual Scientific Meeting programs have been independently planned by the ACR Committee on Education, the ACR Annual Meeting Planning Committee, the ARHP Annual Meeting Program Committee, and the ARHP Clinical Focus Course Task Force.

This program is sponsored by the American College of Rheumatology for educational purposes only. The material presented is not intended to represent the only or the best methods appropriate for the medical conditions being discussed, but rather are intended to present the opinions of the authors/presenters, which may be helpful to other healthcare professionals. Attendees participating in this medical education program do so with the full knowledge that they waive any claim they may have against the ACR for reliance on any information presented during these educational activities. The ACR does not guarantee, warrant or endorse any commercial products or services.

Program Objectives

At the conclusion of the 2010 ACR/ARHP Annual Scientific Meeting, participants should be able to:

- identify recent developments in the diagnosis and management of patients with rheumatic diseases
- outline new technologies for the treatment of rheumatologic problems
- describe potential challenges in the delivery of care to patients with rheumatic diseases and to specify possible solutions
- utilize new research data to improve the quality of care of patients with rheumatic diseases

CME Credit and Certificates of Participation

Accreditation Statement: The American College of Rheumatology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.
**Statement of Designation:** This activity has been approved for 48.5 AMA PRA Category 1 Credit™.

**International Physicians:** International physicians, who register as part of a group and require AMA PRA Category 1 Credit(s)™, must provide the following information to your tour leader: full name, mailing address, telephone and fax numbers, and e-mail address. The information will be used to verify your meeting attendance.

**Health Professional participants** may claim hours to receive a Certificate of Participation for an activity designated for AMA PRA Category 1 Credit(s)™ credit.

For non-CME sessions, attendees may also request a certificate of participation.

**Meeting Evaluations, CME Credit/Certificates of Participation**

Computers are available on-site for you to complete your CME/Certificate of Participation application and meeting evaluation form online during the meeting. In addition, you can complete the evaluation and print your certificate after you return home. *Paper CME application forms will not be available.*

If you are an international physician and require a Certificate of Attendance, this is enclosed in your meeting bag. If your country recognizes AMA PRA Category 1 Credit(s)™ in accordance with AMA PRA requirements, please complete a meeting evaluation and CME application.

Your evaluation of the meeting is very important. The ACR/ARHP annual meeting planning committees use feedback from attendees to assist in the development of future educational activities; therefore, we encourage you to complete your evaluation and CME/Certificate application online.

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Acquired Resistance to Activated Protein C Is a Feature of Both Systemic Lupus Erythematosus (SLE) and Antiphospholipid Syndrome (APS) and Is More Marked in Patients with SLE and APS. Denis Wahl1, Stephanie Zaully2, Agnès Brunette2, Marie Prestat-Tilly2, Véronique Regnault1, Jean Devignes1 and Thomas Lecompte1. 1Biological Haematology Department, Nancy University Hospital, Vandoeuvre les Nancy, France, 2INSERM U961, Nancy University, Vandoeuvre les Nancy, France, 3Vascular Medicine Unit, Vandoeuvre les Nancy, France, 4Vascular Medicine Unit, Nancy University Hospital, Vandoeuvre les Nancy, France

Vascular manifestations of antiphospholipid syndrome (APS) include both venous (VTE) and arterial (ATE) thromboembolic events. However VTE are more frequent than ATE. Among the underlying mechanisms of VTE in APS, it has been suggested that acquired activated protein C (APC) resistance may be a candidate mechanism. However this is difficult to demonstrate with tests based on aPTT because of the effects of lupus anticoagulants on this parameter. In order to investigate APC resistance in APS we have conducted a study with a thrombin generation test (calibrated automated thrombography). APC resistance was determined with measurement of endogenous thrombin potential (ETP) at baseline and after addition of APC. The APC sensitivity ratio (sr) was defined as ETP with APC/baseline ETP.

We included 92 patients (37 with primary antiphospholipid syndrome, 15 with SLE without antiphospholipid antibodies PAPS, 11 with both APS and SLE and 29 with antiphospholipid antibodies (APA) but without APS) and 39 controls. APCsr was higher in all patient groups compared to controls indicating resistance to activated protein C: APCsr was 0.45 ± 0.20, p=0.005 in PAPS, 0.55 ± 0.16, p<0.001 in SLE, 0.65 ± 0.16, p<0.001 in patients with both PAPS and SLE and 0.53 ± 0.22, p<0.001 in patients with APS without APA whereas controls 0.30 ± 0.11. Of note APCsr was also higher in patients with both SLE and APS than in patients with PAPS (p=0.009). Moreover APCsr in patients with venous thrombosis was higher than in controls: 0.47 ± 0.22 vs 0.30 ± 0.11, p<0.001.

Overall these results suggest that acquired APC resistance is a potential risk factor for thrombosis in SLE and PAPS and is more marked when both conditions are present. Furthermore APC resistance seems to be more specifically associated with venous thromboembolism.

Disclosure: D. Wahl: None; S. Zaully: None; A. Brunette: None; M. Prestat-Tilly: None; V. Regnault: None; J. Devignes: None; T. Lecompte: None.

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AGTRL1 and PRKCH Are Genetic Risk Factors for Antiphospholipid Syndrome. Hisako Nakagawa1, Tetsuya Horita2, Toshio Odani2, Yuichiro Fujieda2, Masaru Kato2, Kotaro Otomo2, Yasuko Nakagawa2, Shinshuke Yasuda2, Tatsuya Atumi2 and Takao Koike2. 1Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan, 2Department of Medicine II, Hokkaido University Graduate School of Medicine.

Background: Single nucleotide polymorphisms (SNPs) of Angiotensin receptor-like (AGTRL1) and Protein kinase C eta (PRKCH) were reported to be associated with cerebral infarction in recent genomewide association study in Japanese population. AGTRL1, also named APJ, is a member of the G protein-coupled receptor gene family and has important roles for the modulation of angiogenesis and also act as a human immunodeficiency virus coreceptor. PRKCH regulates various important cellular functions including proliferation, differentiation and apoptosis is mainly expressed in vascular endothelial cells and foamy macrophages in human atherosclerotic lesions. In this study, we investigated the possible association of the functional SNP in an Sp1-binding site of AGTRL1 gene (rs9943582, G/A) and the nonsynonymous SNP (rs2230500, G/A, Val372Ile) in PRKCH gene with antiphospholipid syndrome (APS) in Japanese population.

Patients and Methods: Genomic DNA samples were obtained from 111 patients with APS (45 primary APS and 66 secondly APS), 296 patients with systemic lupus erythematosus (SLE) in the absence of APS and 428 healthy controls. Among APS group, seventy nine patients (71%) had arterial or thrombosis, 58 (52%) arterial thrombosis, 37 (33%) venous thrombosis and 52 (47%) cerebral infarction, respectively. AGTRL1 SNP (rs9943582) was genotyped using TaqMan SNP genotyping assay and PRKCH SNP (rs2230500) was genotyped using direct sequencing. Chi-square tests and Odds ratio were used for statistical analysis after evaluation for Hardy-Weinberg equilibrium. In addition, the stratification analysis by thrombotic events was performed.

Results: Both AGTRL1 rs9943582 G allele and PRKCH rs2230500 A allele frequencies were significantly increased in patients with APS (OR=1.43, 95%CI:1.03–2.31 and OR=1.89, 95%CI: 1.17–3.05, respectively). No association was found between these 2 SNPs and SLE in the absence of APS. In the stratification analysis by clinical manifestations of APS, both AGTRL1 and PRKCH alleles were associated with arterial or venous thrombotic events in patients with APS (OR=1.69, 95%CI:1.15–2.49 and OR=1.58, 95%CI: 1.04–2.38, respectively).

Conclusion: The functional SNP in an Sp1-binding site of AGTRL1 gene (rs9943582, G/A) and the nonsynonymous SNP (rs223050, G/A, Val372Ile) in PRKCH are associated in APS and thrombotic events in patients with APS. Our results suggest that these 2 SNPs are additional genetic risk factors for APS, especially thrombotic events in Japanese population.

Disclosure: H. Nakagawa: None; T. Horita: None; T. Odani: None; Y. Fujieda: None; M. Kato: None; K. Otomo: None; Y. Nakagawa: None; S. Yasuda: None; T. Atumi: None; T. Koike: None.

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Anti-b2 Glycoprotein I Antibodies from Leprosy Patients Do Not Show Thrombogenic Effects in an In Vivo Animal Model. Ricardo Forastiero1, Marta Martinuzzo2, Mariano Vega-Ostertag2, Gabriela de Larranaga2 and Silvia S. Pierangeli1. 1Univ of TX Medical Branch, Galveston, TX, 2Universidad de Favaloro, Buenos Aires, Argentina

Background: The APS-associated aPL are autoantibodies directed against b2GPI and prothrombin. Patients with leprosy present high frequency of IgM aPL that bind b2GPI, but they do not develop thrombosis. Anti-b2GPI from APS mainly bind to domain I of b2GPI while in leprosy are directed against domain V. There is convincing evidence that aPL/anti-b2GPI from APS are pathogenic in vivo and in vitro.

Objective: to investigate the thrombogenic and pro-inflammatory effects of aPL from leprosy and to compare with aPL from APS.

Methods: Sera from 6 patients with APS and 6 with leprosy were used as the source of IgM. All APS and 5 leprosy patients had strong LA activity, and high titers of IgM aCL/anti-b2GPI. The remaining leprosy patient was aPL negative (control). We tested CD11c mice, in groups of 5, at 0 hours and 48 hours later with IgM aPL/anti-b2GPI isolated from patients with leprosy (IgM-leprosy) or APS (IgM-APS) or with IgM from 2 healthy controls (IgM-NHS) or 1 leprosy aPL negative control. Seventy-two hours after the first injection, the adhesion of leukocytes (#WBC) to endothelial cells (EC) in cremaster muscle (as an indication of EC activation in vivo), as well as the size of an induced thrombus in the femoral vein of the mice were examined.

Results: IgM-APS significantly increased the thrombus size (in mum2) when compared to IgM-NHS or IgM-leprosy treated mice (p<0.001). There was no difference in mice injected with IgM-leprosy, IgM-NHS or IgM-leprosy control. IgM-APS increased the #WBC adhering to EC, when compared to IgM-NHS or IgM-leprosy (p<0.001).

Conclusions: Our data shown that aPL/anti-b2GPI from leprosy patients have not thrombogenic and pro-inflammatory effects in vivo when compared with aPL derived from APS.

Disclosure: R. Forastiero: None; M. Martinuzzo: None; M. Vega-Ostertag: None; G. de Larranaga: None; S. S. Pierangeli: None.
Antiphospholipid Antibodies in Children with Systemic Lupus Erythematosus – 18 Years of Clinical Experience from North India. Surjit Singh1, Jasmina Ahluwalia1, Shano Naseem2, Deepthi Sun2 and Amit Rawat3.
1Department of Hematology, Post Graduate Institute of Medical Education and Research, Chandigarh, India, 2Division of Pediatric Allergy and Immunology, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India, 3Division of Pediatric Hematology, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Background: Pediatric systemic lupus erythematosus (p-SLE) is usually more severe than its adult counterpart and frequently involves vital organs (e.g. kidneys). Anti-phospholipid antibodies (APLA) have been reported in 38–87% patients with p-SLE in and reports suggest that presence of APLA can modify disease expression. Higher incidence of neuropsychiatric, renal and hematological manifestations has been reported in APLA positive p-SLE, but influence of APLA on disease course remains unclear. While APLA have been extensively studied in adults with SLE, there is paucity of data on APLA in p-SLE.

Materials and Methods: We report a single centre study on 64 patients with p-SLE seen during the period June 1992 - May 2010 in whom APLA testing was performed. Diagnosis of SLE was based on ACR criteria. Mean age at diagnosis was 10.3 years (range 3–17) with a female:male ratio of 3:1. Of these 24 (37.5%) had renal, 17 (26.6%) hematological (7-hemolytic anemia, 6-thrombocytopenia and 4-leucopenia), 14 (21.9%) neurological, 8 (12.5%) pulmonary, 29 (45.3%) musculo-skeletal and 42 (65.6%) had mucocutaneous involvement. APLA tested included: i) lupus anticoagulant [by kaolin clotting time, diluted Russell viper venom time (LA Screen and LA Confirm, Dade Behring) and STACLOT-LA kit] ii) anticardiolipin antibodies (ACLA) – IgG, IgM and iii) anti-beta2-glycoprotein I (β2 GPI) antibodies – IgG, IgM (Ogentec GmBH by ELISA). Our laboratory is registered in World Health Organization’s United Kingdom National External Quality Assurance Scheme for these tests.

Summary of Results: Patients were tested for APLA on 155 occasions - minimum being once and maximum being 10 during a mean follow-up period of 59.3 months (range 1–211 months). Thirty eight (59.4%) patients were positive for one or other APLA at some point of time of their disease. Overall LA was positive in 39.1%, IgG ACA in 23.4% and IgM ACA in 18.6%. At diagnosis, 37.8% children were positive for LA, 16.3% for IgG ACA and 20.9% for IgM ACA. During follow-up LA was positive in 26.2% patients, IgG ACA in 31%, IgM ACA in 19% patients. Anti-β2GPI (IgG and IgM) could be tested in 10 patients only and was found to be positive for anti-β2GPI IgG in 1 patient.

Thrombosis was seen in 5 patients - of these, 4 (80%) were positive for APLA. Of the 24 patients with nephritis, class II nephritis was seen in 4—of these none was positive for any of the APLA; class III nephritis was seen in 1—patient tested positive for APLA; class IV nephritis was seen in 15—of these 9 (60%) were positive for 1 of the APLA; class V nephritis was seen in 3—of these 2 (66.6%) were positive for APLA. Of the 17 patients with hematological involvement, 11 (64.7%) had positive APLA; of 14 with neurological involvement, 12 (85.7%) had positive APLA. Six (9.4%) children had a fatal course—5 (83.3%) of these had positive APLA.

Conclusion: 59.4% p-SLE patients had APLA positivity during the disease course. The commonest APLA was LA (39.1%), followed by IgG ACA (23.4%) and IgM ACA (18.6%). APLA positivity is more common in p-SLE patients with advanced nephritis, neurological involvement, thrombosis and a fatal course. Presence or persistence of these antibodies, however, may not always predict thrombosis in children with p-SLE.

Disclosure: S. Singh: None; J. Ahluwalia: None; S. Naseem: None; D. Sur: None; A. Rawat: None.

5 Antiphospholipid Score (aPL-S): A Comprehensive Predictive Marker of Developing Thrombosis in Autoimmune Diseases. Kotaro Otono1, Tatsuya Atsumi2, Yuichiro Fujieda3, Masaru Kato3, Olga Amengual3, Tetsuya Machin3, Thomas Ortel1, Silvia S. Pierangeli4, Robert A. S. Roubey5, Michael D. Lockshin2 and on Behalf of APS Clinical Research Task Force. 1Duke University Health System, Durham, NC, 2Hospital for Special Surgery, New York, New York, NY, 3Univ Estado Do Rio de Janeiro, Rio de Janeiro, Brazil, 4Univ of TX Medical Branch, Galveston, TX, 5University College London Hospitals, London, UK, 6University Medical Centre, Utrecht, Netherlands, 7University of North Carolina, Chapel Hill, NC

Background: The 13th International Congress on Antiphospholipid Antibodies (aPL) was held in Galveston, TX in April 2010. The APS CRTF was one of six task forces developed by the meeting organization committee with the purpose of: a) evaluating the limitations of APS clinical research and developing guidelines for researchers to help improve the quality of APS research; and b) prioritizing the ideas for a well-designed multicenter clinical trial and discussing the pragmatics of getting such a trial done (organization, ideal protocols, practical protocols, and financing).

Objective: The purpose of this abstract is to summarize the discussions and progress of APS CRTF.

Methods: The original eight members of CRTF were chosen among experienced APS researchers. The task force working algorithm was: a) a questionnaire that was sent to the members before the congress; b) a summary report that was prepared based on the responses to facilitate discussions during the pre-meeting workshop; c) a pre-meeting workshop; d) two plenary sessions based on the conclusions of the task force discussions where input from all the meeting attendees was received; and e) a final report that was circulated among all the task force chairs for final remarks.

Results: The task force identified five major issues that impede APS clinical research and the ability to develop evidence-based recommendations for the management of APL positive patients: 1) aPL detection has been based on partially or non-standardized tests, and clinical (and basic) APS research studies have included patients with heterogeneous aPL profiles with different clinical event risks; 2) clinical (and basic) APS research studies have included a heterogeneous group of patients with different aPL-related manifestations of its efficacy for the diagnosis of antiphospholipid syndrome (APS) as well as its predictive value for the development of thrombotic events in patients with autoimmune diseases (Presentation Number 1216 in ACR 2009). In the present study, we further analyzed the associated-risk of thrombosis for each aPL assay in autoimmune diseases. Further, we investigated the relationship between the aPL-S and each single aPL test.

Patients and Methods: This study comprised 411 patients with autoimmune diseases who visited the rheumatology department at the University of Texas Medical Branch, Galveston, TX from June 2002 to June 2007. The diagnosis of SLE was based on ACR classification criteria. PA was tested in 10 patients only and was found to be positive for aPL-S more than 30 and 50 were higher than any other value of each single aPL test (see figure.). The negative predictive values of aPL-S more than 30 and 50 were higher than any other value of each single aPL test (see figure.). The positive predictive values of aPL-S, LAC and IgG aPSPT were within the similar levels (90.7–92.9%).

Conclusion: The aPL-S may be a useful comprehensive quantitative marker for predicting thrombosis in autoimmune diseases.

Disclosure: K. Otono: None; T. Atsumi: None; Y. Fujieda: None; M. Kato: None; O. Amengual: None; T. Horita: None; S. Yasuda: None; T. Koike: None.
Future studies including larger patient materials and controls may shed further light on the etiology of APS and may thereby contribute to better risk assessment and management for APS patients.

Disclosure: A. Vikerfors: None; A. Antovic: None; E. Svenungsson: None; K. Bremme: None; M. Holmström: None.

8

Global Analyses of Antiphospholipid Antibodies That Impair Anti-thrombin Inactivation of Procoagulant Factors. Meifang Wu1, Jennifer M. Grossman2, John FitzGerald2, Bevra H. Hahn3 and Pojen P. Chen1. 1UCLA SchI of Medicine, Los Angeles, CA, 2UCLA School of Medicine, University of California Los Angeles, Sherman Oaks, CA, 3University of California Los Angeles School of Medicine, Los Angeles, CA

Background: Previously, we reported that 6 of the 8 patient-derived IgG monoclonal anti-phospholipid antibodies (aPL) bound to thrombin, and that one such reactive aPL (CL24) significantly impaired inactivation of thrombin by antithrombin (AT). Subsequently, we found that all 6 thrombin-reactive aPL also bound to FXa; and that all 6 thrombin-reactive aPL plus two later generated IgG monoclonal aPL (i.e., B2 and P1) also interacted with FIXa. Importantly, some of these reactive aPL (such as CL24) could reduce AT inactivation of FXa and FIXa. The purpose of this study was to study the overall effects of such aPL on hindering AT from inactivating its target procoagulant factors.

Methods: First, we developed an activated-partial-thromboplastin-time (APTT)-based assay to study the overall effects of aPL on impairing AT function and shortening plasma clotting times. Second, to avoid the problem that some aPL possess lupus-anticoagulant activity (that prolongs clotting times) and could obscure shortened clotting time (from aPL-impaired AT function), we evaluated each test aPL (or purified IgG, or plasma sample) individually by determining its clotting times in plasma in the presence or absence of heparin (with optimal AT function, or little AT function, respectively), and then dividing the former clotting time by the latter clotting time, and expressing the result as a "clotting ratio". Third, as a first step to translate the above findings of AT-interfering IgG aPL into a feasible clinical assay, we adapted the above assays to study two chosen patient plasma samples. Plasma P76 contained IgG aPL that reacted with FXa and FIXa; and P80 contained IgG aPL that interacted with thrombin, FXa and FIXa.

Results: First, monoclonal antibodies B2 and CL24 at the final concentration of 27 µg/ml (representing about 0.3% of total plasma IgG) significantly shortened clotting times from 85 seconds to about 60 seconds (p < 0.001), most likely reflecting that B2 and CL24 impaired AT inactivation of one or more procoagulant factors in plasma. Second, using the "clotting ratio" analyses, B2 and CL24 at the physiological concentration reduced clotting ratios from 250% for normal human IgG to 144 % (p < 0.01) and 171% (p < 0.05), respectively. Moreover, purified IgG from 2 patients with antiphospholipid syndrome (APS) also reduced clotting ratio to 153% and 145%, as compared with a clotting ratio of 175% for normal human IgG. Third, when heparin was added, the clotting times of normal plasma, P76 and P80 were increased respectively to 96 seconds, 99 seconds and 166 seconds. These led to a clotting ratio of 178% for the normal plasma, while those of plasma P76 and the P80 were respectively 13% and 13% (p < 0.001). These data suggested that both patient plasma samples had the AT-interfering Ab. The above reduced clotting ratios apparently reflected that certain aPL reacted with the target procoagulant factors of AT and paradoxically impair AT inactivation of the involved procoagulant factors in plasma.

Conclusion: These results show the AT-interfering IgG aPL are present in some APS patients and could contribute to thrombosis in such patients.

Disclosure: M. Wu: None; J. M. Grossman: None; J. FitzGerald: None; B. H. Hahn: None; P. P. Chen: None.

9

Influenza Vaccination Can Induce New Onset Anticardiolipins but Not B2-Glycoprotein-I Antibodies among Patients with Systemic Lupus Erythematosus. Evan Glenn Vista1, Sherry R. Crowe2, Amy B. Dedeka3, Jourdan R. Anderson4, Linda F. Thompson5, Gillian Air6 and Judith A. James1. 1Oklahoma Med Research Foundation, Oklahoma City, OK, 2Oklahoma Medical Research Foundation, 3Oklahoma Medical Research Foundation, Oklahoma City, OK, 4University of Oklahoma Health Science Center, Oklahoma City, OK.
**Background:** Antiphospholipid syndrome is characterized by pathogenic autoantibodies against antiphospholipids (aCLs), lupus anticoagulant, and independent β2-glycoprotein I (β2GPI). The factors causing production of these antiphospholipid antibodies (aPLs) remain unidentified but have been documented in a large number of infectious diseases. Controversy exists as to whether vaccination triggers the same autoimmune reactions as infections in systemic lupus erythematosus (SLE) patients. Among the aPLs, β2GPI has been described as the actual target antigen for autoimmune aPLs, but conflicting reports still exist.

**Methods:** A total of 102 patients fulfilling the ACR criteria for SLE and 104 age, race and gender matched healthy controls enrolled in our lupus flu cohort from 2005 to 2009 and received regular seasonal influenza vaccinations. Sera were tested by ELISA for aCL IgG at the time of vaccination and 2, 6 and 12 weeks after vaccination. The international standardized ratios for aCL reactivity were calculated for each and manufacture cut-offs were used to define low, moderate, and high levels of aCL. Logistic regression was used to account randomly for those enrolled in multiple years to select the unique 206 individuals. Vaccine responses were ranked either as high or low according to an overall anti-influenza antibody response index (which includes hemagglutination inhibition, relative avidity and maximum native antibody responses), Those who have new onset reactivity to aCL IgG were further tested for β2GPI IgG antibodies. Paired t-testing for all patients with aCL reactivity was used to determine changes after vaccination at 2, 6, and 12 weeks compared to baseline.

**Results:** More SLE patients compared to healthy controls developed new low aCL reactivity (14/102 cases and 4/104 controls; OR 4.1, p 0.02) and new moderate aCL reactivity (13/102 cases and 3/104 controls; OR 5.1, p 0.01) after influenza vaccination. From specific time points after vaccination, new low aCL reactivity were significant for SLE patients after 6 weeks (11/102 cases and 1/104 control) and 12 weeks (10/102 cases and 2/104 control) (OR 12.8, p 0.02 and 0.5, p 0.03 respectively) and for new moderate aCL reactivity only after 6 weeks (10/102 cases and 1/104 controls; OR 11.5, p 0.02). High aCL reactivity was only seen among 2 patients with low and moderate aCL reactivity pre-vaccination. Overall, vaccine response was significantly higher among patients with new onset aCL reactivity compared to controls (p 0.02). No new β2GPI antibodies were detected post-vaccination among patients with new aCL reactivity. The normalized optical density measurements for patients with recorded aCL reactivity at any time points were significantly higher after 2 weeks (0.43±0.24, p 0.0013), 6 weeks (0.49±0.37, p 0.004), and 12 weeks (0.47±0.43, p 0.03) after vaccination compared to the baseline (0.30±0.15).

**Conclusions:** This study shows transient increases in aCLs, but not anti-β2GPI responses, after influenza vaccination supporting the possibility that these changes in autoantibody levels may not be clinically important for increased thrombosis risk post-vaccination.

**Disclosure:** None; S. R. Crowe; None; A. B. Dedek; None; J. R. Anderson; None; L. F. Thompson; None; G. Air; None; J. A. James; None.

10 Platelet Activation and Paradoxical Inhibition of ADP Induced Aggregation by Antiphospholipid Antibodies. Kenji Oku1, Tatsuya Atsumi2, Olga Amengual3, Masahiro Ieko1, Shin Furukawa1, Hirohiyo Kitakawa1, Yuji Hori1, Kazuyoshi Nihei1, Yuuichiro Fujieda1, Kotaro Otomo1, Masaru Kato1, Tetsuya Horita1, Shinsuke Yasuda1 and Takao Koike1. 1Health Sciences University of Hokkaido, 2Hokkaido University Graduate School of Medicine, 3Internal Medicine II, Sapporo, Japan, 1Hokkaido University Graduate School of Medicine Internal Medicine II, 2Hokkaido University Graduate School of Medicine Internal Medicine II, 3Hokkaido University Graduate School of Medicine Internal Medicine II, Kushiro Red Cross Hospital, Japan, 2Hokkaido University Graduate School of Medicine Internal Medicine II, Kushiro Red Cross Hospital, Japan. 1Kushiro Red Cross Hospital.

**Purpose:** Autoantibodies against beta2-glycoprotein I (β2GPI) and those against prothrombin are two major populations of antibodies found in patients with antiphospholipid syndrome (APS). The platelet activation and aggregation are crucial procedures in the development of arterial thrombosis. There are some reports suggesting a link between platelet activation and anti-β2GPI antibodies, but only little data are available regarding antiprothrombin antibodies and platelets. We previously showed that presence of IgG phosphatidylserine-dependent antiprothrombin antibodies (aPS/PT) was a strong risk of having arterial thrombosis in our cohort of 500 patients with autoimmune diseases, and that monoclonal aPS/PT affected ADP induced platelet aggregation in vitro (abstract 1594, ACR 2009).

In this study, we investigated further the in vitro behaviour of platelet exposed by aPS/PT and anti-β2GPI antibodies. Additionally, we quantitatively-analyzed CD62P, a surface marker of activated platelets and thrombomodulin B2(TXB2), a member of eicosanoid family molecules produced by activated platelets.

**Methods:** A monoclonal aPS/PT, 231D, that shared the properties with autoimmune aPS/PT, a human monoclonal anti-β2GPI antibody, EY2C9, and purified IgG from APS patients’ sera were used for the following experiments. Normal platelets were treated with monoclonal antibodies or purified IgG. Conventional ADP or collagen induced platelet aggregation assay by turbidimetric method were performed with platelet rich plasma (PRP) spiked with monoclonal antibodies or purified IgG. To explore, in this system, the involvement of P2Y12, one of the ADP receptors on platelet controlling the secondary aggregation, we evaluated the activation of vasodilator stimulated phosphoprotein (VASP), using a standard assay. VASP represents P2Y12 inhibition as the intra-molecular signal protein. Positive ratio of CD62P was detected by two-colored flow-cytometry. TXB2 was quantitatively-analyzed by Enzyme-Linked ImmunoSorbent Assay (ELISA.).

**Results:** ADP induced secondary platelet aggregation was significantly inhibited in 231D, EY2C9, and purified IgG affected PRP, whereas collagen induced platelet aggregation was not affected by any of the antibodies. VASP activities were significantly increased in 231D and EY2C9 treated platelets (p<0.01).

**Conclusion:** Both positive rates of CD62P and TXB2 levels were significantly raised on platelets treated with 231D or EY2C9 in the presence of their antigen. The effects of monoclonal aPS/PT on platelets were similar to those of monoclonal anti-β2GPI antibodies and IgG fractions of APS patients’ sera. Antiphospholipid antibodies activated platelets shown by CD62P expression and TXB2 production. Paradoxical inhibition of ADP induced platelet aggregation by antiphospholipid antibodies might be correlated with P2Y12 signal suppression. Those observations suggest that the platelet involvement with aPS/PT and anti-β2GPI are paradoxical and complex, leading to the heterogeneous clinical features of patients with APS.

**Disclosure:** K. Oku: None; T. Atsumi: None; O. Amengual: None; M. Ieko: None; S. Furukawa: None; H. Kitakawa: None; Y. Hori: None; K. Nihei: None; Y. Fujieda: None; K. Otomo: None; M. Kato: None; T. Horita: None; S. Yasuda: None; T. Koike: None.

11 Prevalence and Prognostic Significance of Thrombotic Microangiopathy in Rheumatologic Patients: Clinical and Immunological Associations. Spyros Aslanidis, Athina Pyrpasopoulou, Stella Douma, Areti Triantafyllou, Michail Doumas and Chrysanthos Zamboulis. 2nd Propedeutic Dept of Internal Medicine, Hippokration Hospital, Thessaloniki, Greece

**Background/Aim:** The aim of this study was to assess the prevalence of microangiopathy in rheumatologic patients featuring signs of vasculopathy. As the occurrence of small-vessel occlusions (thrombotic microangiopathy) in the nail fold of patients with antiphospholipid syndrome is well documented, a major target point of this study was to evaluate capillaroscopy in the diagnosis of APS. Capillaroscopic findings and matching autoantibody profiling were subsequently correlated with the incidence of arterial and venous thrombotic events.

**Materials/Methods:** 738 patients from a Rheumatology Outpatients cohort were consecutively screened with capillaroscopy. Criteria for selection included Raynaud’s phenomenon, livedo reticularis, diagnosis of SLE, positive antiphospholipid profile and/or previous thrombotic events, and atypical musculoskeletal symptomatology. Scleroderma patients were excluded. Patients with microhemorrhages were tested for ACL and anti-b2GPI Abs and data was analyzed with the SPSS 16.0 software.

**Results:** 149 of the screened patients (85.2% /14.8%, 49.28±14.31 yrs) exhibited capillary microhemorrhages. Running diagnosis in these patients was MCTD (24.2%), SLE (18.8%), RA (16.1%), APS (12.8%), Sjogren’s syndrome (4.7%), B51 (3.4%), and vasculitis (2%). Antiphospholipid profile was tested in the affected individuals, and revealed an additional 14.7% of secondary laboratory APS in 28.6% of the SLE and 22.2% of the MCTD patients. The presence of ACL and anti-b2GPI Abs was found to both independently significantly correlate with thrombotic events (p<0.001). Subanalysis of the type of anti-b2GPI Abs indicated that the correlation with thrombotic events was significant for G-type (p<0.001) and M-type (p=0.012), but not A-type Abs (p=0.292, NS). No significant prediction for arterial or venous thromboses was observed in patients with ACL Abs; patients with anti-b2GPI Abs exhibited a trend for arterial thromboses, p=0.174, NS.

**Conclusions:** Capillaroscopy is a useful microangiopathy screening tool in rheumatologic patients featuring signs of clinical vasculopathy, and can aid...
diagonstically to screen for, or verify, APS in patients with a history of thrombotic events. Associations of autoantibody profiling of patients with capillaroscopic microangiopathy with clinically manifested thromboses resulted in similar findings with studies involving patients with clinical APS. The observation that, although IgA-b2GP1 Abs were detected in patients with microangiopathy, they lacked any significant association with thrombotic complications, suggests, that additional factors may be needed for the development of clinical thrombotic events.

Disclosure: S. Aslanidis: None; A. Pyrassopoulos: None; S. Douma: None; A. Triantafyllou: None; M. Doumas: None; C. Zamboulis: None.

12
Prevalence of Antibodies to Prothrombin (PT) and Prothrombin/Phosphatidylserine (PS) in a Cohort of Lupus Anticoagulant (LAC) Positive Samples. R. Aguilar-Valenzuela1, J. Dlott2, U. Khan2, M. Belter2, E. Doan3, N. Gould4, A. Schleh5 and S. Pierangeli6. 1Quest Diagnostics, Chantilly, VA, 2Univ of TX Med Branch, Galveston, TX

Background: ELISA tests have been developed to detect anti-PT and anti-PT/PS antibodies in serum but the clinical diagnostic value and their relationship with the LAC remains elusive.

Objective: to evaluate anti-PT/PS and anti-PT antibodies in a cohort of 150 confirmed LAC and the corresponding controls.

Methods: 150 LAC positive and 150 LAC negative plasma samples were tested by ELISA for anti-PS/PT (IgG and IgM) and LAC PS/PT screening assay (kindly provided by INOVA Diagnostics) and anti-PT (IgG and IgM) in-house assay. LAC positivity was confirmed by either dRVVT Confirm (American Diagnostica) or by the STA-CLOT LA (Diagnostica Stago) tests (3% of samples were positive for dRVVT only and 94% were positive for STA-CLOT only, 3% were positive for both).

Results: aPS/PT IgG aPS/PT IgM aPS/PT Screen aPT IgG aPT IgM # of positive (95% CI) P-value

<table>
<thead>
<tr>
<th>Assay</th>
<th>Number (%) positive</th>
<th>Odds Ratio CI 95% P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG beta2 GPI</td>
<td>18 (5.5%)</td>
<td>3.6 (1.3, 8.7) 0.0083</td>
</tr>
<tr>
<td>IgG beta2 GPI Domain 1</td>
<td>11 (6.7%)</td>
<td>1.3 (0.5, 3.2) 0.5845</td>
</tr>
<tr>
<td>Anticardiolipin</td>
<td>22 (13.8%)</td>
<td>1.5 (0.8, 3.0) 2.475</td>
</tr>
<tr>
<td>PSPT</td>
<td>26 (16.3%)</td>
<td>2.1 (1.1, 4.2) 0.0315</td>
</tr>
<tr>
<td>IgM beta2 GPI</td>
<td>18 (13.8%)</td>
<td>1.5 (0.6, 2.6) 0.0577</td>
</tr>
<tr>
<td>Anticardiolipin</td>
<td>26 (16.3%)</td>
<td>1.9 (1.1, 3.3) 0.0187</td>
</tr>
<tr>
<td>IgA beta2 GPI</td>
<td>48 (30.0%)</td>
<td>2.5 (1.5, 4.4) 0.0007</td>
</tr>
<tr>
<td>Anticardiolipin</td>
<td>10 (6.3%)</td>
<td>5.5 (1.2, 25.4) 0.0156</td>
</tr>
</tbody>
</table>

Conclusions: It appears that the combination of two severe conditions, thrombotic and thrombocytopenic, has a more negative influence on reported PCS, compared to having SLE or APS alone. This influence was not seen for the MCS score.

Disclosure: A. K. Balitsky: None; V. Peeva: None; J. Su: None; E. Yoo: None; C. Landolt-Marticorena: None; D. D. Gladman: None; M. B. Urowitz: None; P. R. Fortin: GlaxoSmithKline, 5.

14
Utility of Anti-Phosphatidylserine/Prothrombin and IgA Antiphospholipid Assays in Antiphospholipid Syndrome. Ehtisham Akhter1, Walter L. Binder2, Zakera Shums2 and Michelle A. Petri1. 1Timmion, MD, 2Inova Diagnostics Inc, San Diego, CA, 3Johns Hopkins University, Baltimore, MD

Purpose: Currently three antiphospholipid assays are in wide use clinically (lupus anticoagulant, anticardiolipin (aCL), and anti-beta2 glycoprotein 1 (anti-beta2 GPI)). The lupus anticoagulant is the most specific assay, conferring the highest risk of thrombosis and pregnancy loss, but it cannot be validly performed in an anticoagulated patient. We investigated antiphosphatidylserin/prothrombin (anti-PS/PT), which detects most lupus anticoagulants, in terms of its association with thrombosis. We also investigated the utility of IgA assays for APS in SLE.

Methods: Stored samples from SLE patients with and without past thrombosis were assayed for anti-beta2 GPI (IgG/IgM/IgA), Domain 1 (IgG) and Domain 4/5 (IgA), aCL (IgG/IgM/IgA) and anti-PS/PT (IgG, IgM and IgG/M).

Results: For any thrombosis, the highest association was with aCL IgA, followed anti-beta2 GPI IgG and anti-beta2 GPI IgA. Anti-PS/PT IgG, IgM and IgG/M were similar (Table 1).

Table 1: Any Thrombosis

<table>
<thead>
<tr>
<th>Assay</th>
<th>Thrombosis (n = 160)</th>
<th>No thrombosis (n = 166)</th>
<th>Odds Ratio 95% CI P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG beta2 GPI</td>
<td>18 (5.5%)</td>
<td>6 (3.3%)</td>
<td>3.4 (1.3, 8.7) 0.0083</td>
</tr>
<tr>
<td>IgG beta2 GPI Domain 1</td>
<td>11 (6.7%)</td>
<td>5 (3.4%)</td>
<td>1.3 (0.5, 3.2) 0.5845</td>
</tr>
<tr>
<td>Anticardiolipin</td>
<td>22 (13.8%)</td>
<td>16 (9.6%)</td>
<td>1.5 (0.8, 3.0) 2.475</td>
</tr>
<tr>
<td>PSPT</td>
<td>26 (16.3%)</td>
<td>28 (16.6%)</td>
<td>2.1 (1.1, 4.2) 0.0315</td>
</tr>
<tr>
<td>IgM beta2 GPI</td>
<td>18 (13.8%)</td>
<td>15 (9.0%)</td>
<td>1.3 (0.6, 2.6) 0.0577</td>
</tr>
<tr>
<td>Anticardiolipin</td>
<td>42 (26.3%)</td>
<td>26 (15.7%)</td>
<td>1.9 (1.1, 3.3) 0.0187</td>
</tr>
<tr>
<td>IgA beta2 GPI</td>
<td>48 (30.0%)</td>
<td>24 (14.5%)</td>
<td>2.5 (1.5, 4.4) 0.0007</td>
</tr>
<tr>
<td>Anticardiolipin</td>
<td>10 (6.3%)</td>
<td>12 (7.2%)</td>
<td>0.5 (1.2, 25.4) 0.0156</td>
</tr>
<tr>
<td>IgA beta2 GPI D4/5</td>
<td>35 (21.9%)</td>
<td>28 (16.6%)</td>
<td>1.4 (0.8, 2.4) 0.2523</td>
</tr>
<tr>
<td>IgG/M PSPT</td>
<td>38 (23.8%)</td>
<td>24 (14.5%)</td>
<td>1.8 (1.0, 3.2) 0.0326</td>
</tr>
</tbody>
</table>
For venous thrombosis, the highest association was again with aCL IgA, followed by anti-beta2 GPI IgG, and then anti-PS/PT IgG and IgG/M (Table 2).

**Table 2: Venous Thrombosis**

<table>
<thead>
<tr>
<th>Assay</th>
<th>IgG beta2 GPI</th>
<th>IgG beta2 GPI Domain 1</th>
<th>Anticardiolipin</th>
<th>IgM beta2 GPI</th>
<th>Anticardiolipin</th>
<th>PSPT</th>
<th>IgA beta2 GPI</th>
<th>IgG/M PSPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) positive</td>
<td>15 (14.7%)</td>
<td>9 (4.0%)</td>
<td>17 (16.7%)</td>
<td>21 (20.0%)</td>
<td>13 (12.8%)</td>
<td>27 (26.5%)</td>
<td>31 (30.4%)</td>
<td>29 (28.4%)</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>9.4 (1.7, 9.8)</td>
<td>1.9 (1.0, 3.8)</td>
<td>1.9 (1.0, 3.8)</td>
<td>1.4 (1.0, 5.5)</td>
<td>1.5 (0.7, 3.1)</td>
<td>1.6 (0.9, 2.8)</td>
<td>1.9 (1.1, 3.3)</td>
<td>2.3 (1.3, 4.1)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.006</td>
<td>0.571</td>
<td>0.020</td>
<td>0.289</td>
<td>0.014</td>
<td>0.924</td>
<td>0.017</td>
<td>0.035</td>
</tr>
</tbody>
</table>

For Stroke, the only assay with a significant association was antibody-2 GPI Domain 4/5 (32.7% vs. 17%, OR 2.4, p = 0.0001). Conclusion: The importance of IgA isotypes (beta2GPI, aCL) in secondary antiphospholipid syndrome has not been previously recognized. We also found that IgA antibody-2 glycophosphoprotein domain 4/5 was associated with stroke. Domain 1 IgG is not by antithrombotic activity. Anti-PS/PT, either IgG/M or IgG, is promising alternative to coagulation assays to detect lupus anticoagulant.


**ACR Poster Session A**

**Cytokines, Mediators, Gene Regulation I**

Monday, November 8, 2010, 9:00 AM–6:00 PM

15

**BAFF Expression Correlates with Idiopathic Inflammatory Myopathy Disease Activity Measures, Interferon Signature and Autoantibodies.** Kelly T. McNallan¹, Hatice Bilgic², Cynthia S. Crowson³, Steven R. Ytterberg², Shreyasee Amin², Peterson J. Erik³, Emily C. Baechler³, and Ann M. Reed³. ¹Mayo Clinic, Rochester, MN; ²Mayo Clinic; ³University of Minnesota

**Background:** We have previously reported increased mRNA levels of BAFF, in blood cells of patients with idiopathic inflammatory myopathies (IIM). Elevated BAFF and BAFF receptor levels influence increased survival of autoreactive B cells. Therefore we investigated the relation of disease activity, autoantibody profiles and interferon pathway in IIM to B cell survival cytokines (BAFF, APRIL, BCMA, TACI) and their receptor expression (BAFF receptor (BAFFR), transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) and B cell maturation antigen (BCMA)).

**Methods:** RNA was extracted from whole blood in 108 IIM subjects (74 adult and juvenile dermatomyositis, 25 polymyositis and 9 inclusion body myositis). Gene expression of BAFF, BAFF, APRIL, BCMA, TACI, BAFFR and three type 1 interferon (IFN)-regulated genes were measured by quantitative real-time RT-PCR. The whole-blood IFN gene expression signature was defined by average expression levels of 3 IFN-regulated genes (G1P2, IFIT1 and IRF7). Autoantibodies including Jo-1, Scl-70, Ribosome P, Chromatin, Sm, RNP, SSA, SSb were measured on the Luminex platform.

**Results:** Disease activity was assessed using visual analog scale (VAS) ratings defined by the International Myositis Assessment and Clinical Research (IMACS) group. Associations of gene expression with IFN gene score, disease activity measures and autoantibodies were assessed by Spearman correlation analysis.

**Results:** We find a positive correlation of BAFF and BAFF expression with disease activity measures, including the global VAS score, muscle VAS score and extraskeletal muscle VAS score. Elevated BAFF and BAFF expression also correlate with increased IFN gene scores. Furthermore, we find IIM subjects with autoantibodies to SSA, SSb or any RNA-binding protein (SSA, SSb, RNP and Sm) have increased expression of BAFF and BAFF. APRIL, BAFFR, TACI and BCMA expression did not correlate with disease activity measures, autoantibodies or IFN score.

**Disclosure:** K. T. McNallan: None; H. Bilgic: None; C. S. Crowson: None; S. R. Ytterberg: None; S. Amin: None; P. J. Erik: None; E. C. Baechler: Genentech and Biogen IDEC Inc; 2; A. M. Reed: None.

16

**Blockade of TLR2 Prevents Spontaneous and Induced Cytokine Release from Rheumatoid Arthritis Ex Vivo Syfnal Explant Cultures.** Saned Nic An Ualtaigh¹, Tjuur Saber¹, Jerome Dellacasagrande¹, Brian Keogh², William McCormack³, Mary Reilly³, Luke O. Neill³, Peter McGuirk³, Ursula Fearon³, and Douglas J. Veale³. ¹Dublin Academic Medical Centre, Dublin, Ireland; ²Opsona Therapeutics Ltd, Dublin, Ireland

**Objective:** Toll-like receptors are involved in activation of the immune system by triggering release of inflammatory cytokines that can contribute and/or perpetuate inflammation, and have been implicated in autoimmune diseases such as Rheumatoid Arthritis (RA). The aim of this study is to examine the effect of blocking Toll-like receptor 2 (TLR2) in RA synovial cells.

**Methods:** RA synovial tissue (ST) biopsies, obtained under direct visualization at arthroscopy, were established as synovial explant cultures ex vivo or snap frozen for immunohistology. Mononuclear cell cultures were isolated from peripheral blood (PB) and synovial fluid (SF) of RA patients. Cultures were incubated with the TLR1/2 ligand, Pam3CSK4 (20mg, 1 and 10μg/ml), an anti-TLR2 antibody (OPN 301, 1μg/ml) or an IgG (1μg/ml) matched control. The comparative effect of OPN301 and Humira on spontaneous release of proinflammatory cytokines from RA synovial explants was determined using quantitative cytokine MSD multiplex assays or ELISA. OPN301 penetration into RA synovial tissue explants cultures was assessed by immunohistology.

**Results:** Pam3CSK4 significantly upregulated IL-6 and IL-8 in RA PBMCs, RA SFMCs and RA synovial explant cultures (p<0.005). OPN301 significantly decreased Pam3CSK4-induced cytokine production of TNF-α, IL-1, IL-6, IFN-γ and IL-8 compared to IgG control in RA PBMCs and SFMCs cultures (all p<0.005). OPN301 penetration of RA synovial tissue cultures was demonstrated, with expression localized to the lining layer and perivascular regions. OPN301 significantly decreased spontaneous cytokine production of TNF-α, IL-1, IFN-γ and IL-8 from RA ST explant cultures (all p<0.05). Importantly, the inhibitory effect of OPN on spontaneous cytokine secretion was comparable to inhibition by anti-TNF mAb Humira.

**Conclusion:** Our findings further support targeting TLR2 as a potential therapeutic agent for the treatment of RA.

**Disclosure:** S. Nic An Ualtaigh: None; T. Saber: Centocor Ortho Biotech Inc.; 2; J. Dellacasagrande: None; B. Keogh: Opsona Therapeutics Ltd; 3; W. McCormack: Opsona Therapeutics Ltd; 3; M. Reilly: Opsona Therapeutics Ltd; 3; L. O. Neill: Opsona Therapeutics Ltd; 9; P. McGuirk: Opsona Therapeutics Ltd; 3; U. Fearon: None; D. J. Veale: Abbott Laboratories, 2, 5, 8, Centocor Ortho Biotech Inc., 5, 8, GlaxoSmithKline, 2, 5, 8, Mundipharma, 2, 8, Opsona Therapeutics Ltd, 2, 8, Pfizer Inc, 5, 8, Schering-Plough, 5, 8, Wyeth Pharmaceuticals, 2, 5, 8.

17

**CCL15/Leukotactin-1: A Novel Mediator of Rheumatoid Arthritis Fibroblast-Like Synoviocyte Migration Via CCR3 and MAP Kinases.** Eric K. Owens¹, Karolina Klosowska², Michael V. Volin³, Brian Zanotti³ and James M. Woods³. ¹Midwestern University, Downsers Grove, IL; ²Midwestern University
**Background:** Rheumatoid arthritis (RA) fibroblast-like synoviocytes (FLS) play a key role in mediating inflammation and joint destruction. CCL15 has previously been shown to be expressed in RA synovial tissue and synovial fluids. CCL15 has been characterized to interact with its receptors, CCR1 and CCR3, where the former serves as a weak agonist and the latter serves more potent functions. We hypothesized that CCL15 induces RA FLS migration and proliferation, acting through CCR1 and/or CCR3, and signaling through mitogen-activated protein (MAP) kinases.

**Methods:** FLS were derived from hip or knee synovial membrane at the time of joint replacement due to RA with IRB approval, and were subsequently analyzed using Alexa Fluor 488 Phalloidin staining of F-actin, proliferation assays, chemotaxis assays, and flow cytometry. In addition, we used MAP kinase inhibitors in combination with chemotaxis assays to determine whether MAP kinase signaling was required for CCL15-induced RA FLS migration.

**Results:** Evaluation of F-actin staining subsequent to CCL15 stimulation demonstrates significant reorganization of the cytoskeletal structure. When stimulated with 1 or 10 nM CCL15, maximal cytoskeletal rearrangement occurs after 2 to 3 hrs, consistent with the slow migration associated with fibroblasts. Chemotaxis assays demonstrate that CCL15 is a novel chemottractant for RA FLS, effectively inducing migration of all 4 RA patients that we tested (p<0.05). Concentrations of 1 to 50 nM CCL15 induced migration that was significantly higher than background, however, similar concentrations of CCL15 had no effect on RA FLS proliferation. Flow cytometry demonstrates that a significant number of RA FLS express CCR3 but not CCR1. On average, 73% of RA FLS express CCR3. Consistent with CCR3 being a G protein coupled receptor, pertussis toxin (PTX) completely abolishes CCL15-induced migration. Finally, pre-incubation of FLS with a MEK 1/2 inhibitor (U0126), the kinase which activates ERK 1/2, significantly decreased chemotaxis induced by CCL15 in RA FLS derived from 2 of 3 patients. Similarly, pre-incubation of cells with a JNK inhibitor (SP600125) likewise decreased CCL15-induced migration in FLS from 2 of 3 patients.

**Conclusions:** Our results suggest the novel finding that CCL15 regulates the migration and cytoskeletal structure of RA FLS. Migration is likely induced by a G protein (Gi/Go) coupled receptor, since this event is inhibited by PTX. To our knowledge, these are the first results to suggest that RA FLS express CCR3. Finally, migration of RA FLS from some patients can be significantly decreased by inhibiting the ERK and JNK pathways.

Disclosure: E. K. Owens: None; K. Klosowska: None; M. V. Volin: None; B. Zanotti: None; J. M. Woods: None.

**18**

**Chronic Exposure to IL-6 Amplifies Macrophage Response to Toll-Like Receptor (TLR) Ligands.** Raffaele Strippoli1, Francesco Carvello2, Loredana De Pasquale2, Luisa Bracci-Laudiero2 and Fabrizio de Benedetti2.

1IRCCS Ospedale Pediatrico Bambino Gesu, Rome, Italy, 2IRCCS Ospedale Pediatrico Bambino Gesu, Rome, Italy

**Background:** High levels of IL-6 are a characteristic feature of chronic inflammatory arthritis. Little is known on the effect of IL-6 on innate immune responses in particular regarding TLR activation mediated by both endogenous and exogenous TLR ligands, the latter being important in the relation between infections and exacerbations. In this study, we analyzed whether endogenous and exogenous TLR ligands, the latter being important in the relation between infections and exacerbations. In this study, we analyzed whether endogenous and exogenous TLR ligands, the latter being important in the relation between infections and exacerbations.

**Methods:** Splenocytes and peritoneal macrophages were isolated from IL-6 transgenic mice with IL-6 plus sIL-6R and then stimulated with LPS. Cells were then analyzed as above.

**Results:** Treatment of splenocytes from IL-6 transgenic mice with different TLR ligands led to increased production of inflammatory cytokines, such as IL-1 beta, TNF alpha, IL-6, with respect to cells from WT mice. This was accompanied by increased phosphorylation of STAT3, ERK and by increased NF-kappaB nuclear translocation. Human macrophages treated with IL-6 plus sIL-6R and then stimulated with LPS showed also increased expression of cytokines, such as IL-1 beta, and chemokines such as IL-8 and a similar increased activation of stimulatory pathways. IL-6 transgenic mice treated with LPS showed increased lethality and higher levels of IL-1 beta, TNF alpha and IL-6 than WT mice.

**Conclusions:** Our results show that prolonged exposure to IL-6 alters the response of macrophages to TLR ligands suggesting that signals from IL-6 and from TLR cooperate in the amplification of the inflammatory response. Our data also show the presence of a positive amplification loop between IL-1 beta and IL-6. These results suggest that IL-6 may contribute, on the one hand, to the amplification of chronic inflammation and, on the other, to abnormal responses to infectious agents that may trigger clinical relapses or an acute manifestation such as macrophage activation syndrome in the course of systemic JIA.

Disclosure: R. Strippoli: None; F. Carvello: None; L. De Pasquale: None; L. Bracci-Laudiero: None; F. de Benedetti: Hoffmann-La Roche, Inc., 5.

**19**

**CX3CR1 Deficient Mice Have Decreased Th17 and Antigen-Specific Humoral Responses in the Collagen Induced Arthritis (CIA) Model.** Teresa K. Tarrant2, Peng Liu3, Kishi Rampersad3, Denise Esserman3, Lisa Rothlein, Marcus W. McGinnis3, David J. Fitzhugh3, Dhaval Kumar D. Patel1 and Alan M. Fong3.

1Novartis Pharma AG, Basel, Switzerland, 2UNC School of Medicine, Chapel Hill, NC, 3UNC School of Medicine

**Objective:** CX3CR1 is a chemokine receptor that uniquely binds to its ligand fractalkine (FKN or CX3CL1) and has been shown to be important in inflammatory arthritis responses, largely due to effects on cellular migration. In this study, we tested the hypothesis that genetic deficiency of CX3CR1 would be protective in the chronic inflammatory arthritis model, collagen induced arthritis (CIA). Because CX3CR1 is expressed on T cells and antigen-presenting cells, we additionally examined adaptive immune functions in this model.

**Methods:** Autoantibody formation, clinical, histologic, T cell proliferative, and cytokine responses were evaluated in DBA/1J mice deficient in (−/−) or wildtype (+/+) for CX3CR1 after immunization with heterologous type II collagen.

**Results:** CX3CR1−/− mice had an approximately 30% reduction in arthritis by two independent measures of paw swelling (p<0.01) and clinical disease index(p<0.0001).
Proinflammatory MMP-13 and cytokines IL-6, IL-1β, and TNF-α were reduced in CX3CR1−/− mice, but were not statistically significant.

**Conclusions:** Deficiency of CX3CR1 is protective in inflammatory arthritis and may have effects that extend beyond migration that involve adaptive immune responses.

**Disclosure:** T. K. Tarrant: None; P. Liu: None; R. Rampersad: None; D. Esserman: None; L. Rothlein: None; M. W. McGinnis: None; D. FitzHugh: None; D. D. Patel: Novartis Pharmaceuticals Corporation, 3; A. M. Fong: None.

**20**

**Cytokine Expression in Synovial Tissue of Psoriatic Arthritis and Its Relation to Lymphoid Neogenesis, Erosive Disease and Disease Activity: A Longitudinal Study.** Raquel Celis1, Julio Ramírez1, Raimon Sanmartí1, José L. Pablos2 and Juan D. Cañete1, 1Servicio Reumatología, Hospital Clinic of Barcelona, 2Department of Clinical Immunology and IDIBAPS, Barcelona, Spain

**Objective:** To analyse the expression of a wide range of cytokines in synovial tissue (ST) of patients with psoriatic arthritis (PsA) and its relation with synovial lymphoid neogenesis (LN), erosive disease and EULAR response to therapy.

**Methods:** ST samples were obtained by needle arthroscopy from the inflamed knee joint of 30 patients fulfilling the CASPAR criteria for PsA. Five samples from each patient were paraffin-embedded and sections were immunostained with CD3 (T cell), CD20 (B-cell) and MECA-79 (high endothelial venules).

Total RNA was extracted from ST samples from 30 patients and from 2 controls without synovial inflammation following the recommendations of the Rneasy FFPE Kit (Qiagen). mRNA was measured by TaqMan Gene Expression Assay (Applied Biosystem). Relative changes in gene expression were assessed by comparative analysis of quantitative PCR by the delta-delta Ct method using GAPDH as a endogenous control gene. The following genes were analysed: CCR7, Lymphotoxin (LT)-beta, IL-7, IL-10, IL-1-beta, IL-6, TNF-alpha, IL-17A, IL-21, IL-22 and IL-23. Data were collected at inclusion and at the end of follow-up.

**Results:** Clinical and demographic data of patients are in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Clinical and demographic data of PsA patients (n=30) at time of arthroscopy*</th>
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<tbody>
<tr>
<td>Age (years) at time of arthroscopy</td>
</tr>
<tr>
<td>Disease duration before arthroscopy (months)</td>
</tr>
<tr>
<td>Time of follow-up after arthroscopy (months)</td>
</tr>
<tr>
<td>Tender Joint Count</td>
</tr>
<tr>
<td>Swollen Joint Count</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
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<tr>
<td>ESR (mm/1st hour)</td>
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<td>ACPA (UI/mL) (n, positive &gt;25)</td>
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<td>Rheumatoid Factor (UI/ml)</td>
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<td>Joint Pattern Polyarthritis, n (%)</td>
</tr>
<tr>
<td>Oligoarthritis, n (%)</td>
</tr>
<tr>
<td>Type of Psoriasis</td>
</tr>
<tr>
<td>Type I (&lt;40 years), n (%)</td>
</tr>
<tr>
<td>Type II (&gt;40 years), n (%)</td>
</tr>
</tbody>
</table>

| * Data are expressed as median and IQR. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ACPA: anti-citrullinated peptide/protein antibodies; DAS: disease activity score. |

**LN.** Twelve out of 30 patients (40%) had LN. These patients had significantly higher expression of CCR7 and LT-beta than patients without LN (p<0.005 and p<0.04, respectively). LN positive patients had a trend to higher IL-23 (p=0.051) and TNF-alpha (p=0.075) expression than patients LN negative. There was no association between LN and clinical or biological variables.

**Erosive disease.** Fifteen out of 30 (50%) of patients had erosive disease at end of follow-up. Disease duration, DAS28, PCR and SJC at inclusion were all correlated with erosive disease (p<0.05).

**Disease activity.** There was a positive correlation between IL-6 expression and SJC, CRP and DAS28 at inclusion (p=0.02, p=0.001 and p=0.034, respectively) and between IL-1b expression and CRP levels at inclusion (p=0.015). We found also a strong negative correlation between IL-10 expression at inclusion and ESR levels (p=0.008). **Conclusion:** PsA patients with LN have a different profile of cytokine expression in ST compared with patients without LN, with significantly higher expression of CCR7, LT-beta, which are implicated in the follicular organization, and higher expression of IL-23, a relevant cytokine in joint inflammation and damage. Also IL-6 and IL-1 are positively and IL-10 negatively correlated with markers of inflammation and/or disease activity.

**Disclosure:** R. Celis: None; J. Ramírez: None; R. Sammarti: None; J. L. Pablos: None; J. D. Cañete: None.

**21**

**DNA Hypomethylation Upregulates CXCL12 in Rheumatoid Arthritis Synovial Fibroblasts.** Emmanuel Karouzakis1, Yvonne Rengel1, Astrid Jungel1, Christoph Kolling2, Renate E. Gay3, Beat A. Michel1, Paul P. Tak2, Steffen Gay3, Michel Neidhart1 and Caroline Ospelt3, 1Center of Experimental Rheumatology and Zurich Center of Integrative Human Physiology (ZIHP), University Hospital Zurich, 2Department of Clinical Immunology and Rheumatology, University of Amsterdam, 3Schulthess Clinic, Zürich

**Objective:** Previously we described global genomic hypomethylation in rheumatoid arthritis synovial fibroblasts (RASF). Now, we searched for specific genes that are induced by DNA hypomethylation in RA. Since CXCL12 was reported to be upregulated in RA, we investigated its expression in RA SF as well as the DNA methylation status of its promoter and determined the contribution of this chemokine to the expression of matrix metalloproteinases (MMPs).

**Methods:** DNA was isolated from SF and methylation was analysed by bisulphite sequencing. CXCL12 protein was quantified by ELISA before and after stimulation with CXCL12. DNA from SF was treated with 5-azaC. Twelve out of 30 patients (40%) had LN. These patients had significantly higher expression of CCR7 and LT-beta than patients without LN (p<0.005 and p<0.04, respectively). LN positive patients had a trend to higher IL-23 (p=0.051) and TNF-alpha (p=0.075) expression than patients LN negative. There was no association between LN and clinical or biological variables.

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**Disease activity.** There was a positive correlation between IL-6 expression and SJC, CRP and DAS28 at inclusion (p=0.02, p=0.001 and p=0.034, respectively) and between IL-1b expression and CRP levels at inclusion (p=0.015). We found also a strong negative correlation between IL-10 expression at inclusion and ESR levels (p=0.008). **Conclusion:** PsA patients with LN have a different profile of cytokine expression in ST compared with patients without LN, with significantly higher expression of CCR7, LT-beta, which are implicated in the follicular organization, and higher expression of IL-23, a relevant cytokine in joint inflammation and damage. Also IL-6 and IL-1 are positively and IL-10 negatively correlated with markers of inflammation and/or disease activity.

**Disclosure:** R. Celis: None; J. Ramírez: None; R. Sammarti: None; J. L. Pablos: None; J. D. Cañete: None.
induces the expression of MMPs in SF. Thereby we describe an endogenously activated pathway in RASF which promotes joint destruction.

Disclosure: E. Karouzakis: None; Y. Rengel: None; A. Jüngel: None; C. Kolling: None; R. E. Gay: None; B. A. Michel: None; P. P. Tak: None; S. Gay: None; M. Neidhart: None; C. Ospe: None.

22

Downregulation of the Chemokine Receptor CX3CR1 in Active RA Associated with a Pro-Osteoclastogenic Phenotype. Graine Murphy1, John Ryan1, Harney Sneed1, Fergus Shanahan1, Michael Molloy2 and Noel Caplice3. 1Cork University Hospital, Cork, Ireland, 2University College Cork, Cork, Ireland

Monocytes are the primary source of inflammatory cytokines in RA. They can be further defined by their surface expression of CD14 and CD16. CD16+ cells are more inflammatory in nature and possess discordantly high surface CX3CR1, the receptor for the chemokine fractalkine (FKN). The interaction of FKN with CX3CR1 contributes to the chemotaxis and transmigration of the CD16+ monocytes and subsequent cytokine release. The FKN-CX3CR1 interaction has been implicated in the pathological T cell response in RA, however little is known about this relationship in monocytes, despite CX3CR1’s ubiquitous expression.

Objective: To characterize the expression of CX3CR1 on monocyte sub-populations in early and established RA. To assess the functional consequences of FKN interactions with CX3CR1 in relation to osteoclastogenesis and cytokine release.

Methods: We recruited 83 subjects with early (21), established active (46) or inactive RA (16) and 13 healthy controls as a comparator group. Monocyte subsets (CD14+CD16- and CD14+CD16+) were defined by flow cytometry and CX3CR1 surface expression was determined by its Relative Fluorescent Intensity (RFI). Soluble FKN (sFKN) was quantified in peripheral blood (PB) and synovial fluid (SF) by ELISA. The effect of membrane-bound FKN (mFKN) on osteoclast differentiation of monocyte subsets was assessed in vitro. Serum from subjects with the combination of elevated CD16+ monocytes and increased sFKN were analysed using a multiplex cytokine array and compared with controls.

Results: The CD16+ monocyte subset was expanded in the active RA groups [early, mean (+/-SEM) 24.22% (3.9) and active RA, 21.99% (2.61)] in comparison with inactive disease 12.9% (2.2), p=0.04, and healthy controls 11.1% (0.89), p=0.03. Furthermore, individuals with elevated CD16+ monocytes and increased sFKN had significantly more circulating IL1a, IL-1b, IL-10 and TNFα than controls.

CX3CR1 surface expression was down-regulated on CD16+ monocytes in established RA but not in early arthritis, p=0.004. Downregulation of CX3CR1 on the osteoclast progenitor CD16- sub-population was restricted to active RA, p<0.005. Similarly in active RA there was a significant increase in serum and SF sFKN, p=0.02. CX3CR1 down-regulation was replicated in vitro by co-incubation with sFKN. mFKN significantly enhanced the osteoclastogenesis of the CD16-monocyte subset (p=0.0001) potentially mediated by a decrease in CX3CR1 surface expression.

Conclusion: These findings support the presence of a unique monocyte phenotype in established RA. The downregulation of CX3CR1 on osteoclast precursors is mediated by the interaction with FKN. In addition the pro-osteoclastogenic effect of mFKN strongly supports that this chemokine partnership is critical to the erosive process in RA.

Disclosure: G. Murphy: IRCSET; 2. J. Ryan: None; H. Sneed: None; F. Shanahan: None; M. Molloy: None; N. Caplice: None.

23

Downstream Targets of IL-17 in Rheumatoid Arthritis. Sarah R. Pickens1, Richard M. Pope1, Michael V. Volin2 and Shiva Shahrara3. 1Northwestern University, 2Northwestern Univ Feinberg, Chicago, IL, 3Northwestern University Med School, Chicago, IL

IL-17 plays an important role in the pathogenesis of rheumatoid arthritis (RA) since anti-IL-17 therapy ameliorates the clinical symptoms of RA. However, the downstream targets of IL-17 are undefined in RA.

Purpose: Studies were performed to identify the downstream targets of IL-17 in human microvascular endothelial cells (HMVECs), macrophages and RA synovial tissue (ST) fibroblasts, and subsequently the expression of the identified factors were confirmed in RA ST explants.

Methods: HMVECs, peripheral blood in vitro differentiated macrophages and RA ST fibroblasts were treated with IL-17 for 0–8h. Real-time RT-PCR was used to identify IL-17-induced downstream molecules in these cell types. Next, expression of IL-17-induced factors was verified by real-time RT-PCR in RA ST explants that were activated with IL-17.

Results: Genes differentially regulated by IL-17 in HMVECs were neutrophil chemokines such as CXCL1, CXCL2, CXCL3, CXCL12 and monocyte chemokines including CCL2, CCL19 and CXCL16 and adhesion molecule VCAM1. Similarly, IL-17 was able to modulate neutrophil (CXCL1, CXCL3 and CXCL5) and monocyte (CXCL16, CCL20 and CCL2) chemokines in peripheral blood in vitro differentiated macrophages. In RA ST fibroblasts, in addition to neutrophil (CXCL1, CXCL2, CXCL3 and CXCL5) and monocyte (CCL2, CCL7 and CCL20) chemokines, IL-17 greatly upregulated expression of proangiogenic factors such as VEGF and FGF. Further, to determine which of these factors may play an important role in the pathogenesis of RA, IL-17-activated RA ST explants were screened for the identified molecules. Factors that were induced by IL-17 in two or more cell types were highly upregulated in RA ST explants compared to those expressed in only one cell type. Among the factors that were greatly induced by IL-17 in RA ST explants were CXCL1 (150 fold increase), CXCL3 (10 fold increase), CXCL5 (360 fold increase), CCL2 (20 fold increase), CCL7 (14 fold increase) and CCL20 (30 fold increase). Since neutrophil and monocyte chemokines are strongly induced by IL-17 in the RA synovium, cell trafficking may be an important mechanism by which IL-17 contributes to inflammation.

Conclusion: These results suggest that IL-17 may play an important role in acute and chronic inflammation seen in patients with RA in part through promoting neutrophil and monocyte migration. Therefore, the decrease in clinical symptoms seen with anti-IL-17 treatment of RA may be in part due to this decrease in leukocyte migration.

Disclosure: S. R. Pickens: None; R. M. Pope: None; M. V. Volin: None; S. Shahrara: None.

24

Elevated BLyS Levels Are Associated with an Increase in Autoantibody Specificities and ANA Titer in Systemic Lupus Erythematosus. Lauren L. Ritterhouse1, Amanda R. Moyer2, Virginia C. Roberts3, Amy B. Dedek3, Sherry R. Crowe2, Gillian M. Air4, Linda F. Thompson1, Joel M. Guthridge1 and Judith A. James1. 1Oklahoma Med Research Foundation, Oklahoma City, OK, 2Oklahoma Medical Research Foundation, Oklahoma City, OK, 3Oklahoma Medical Research Foundation, 4University of Oklahoma Health Sciences Center

B Lymphocyte Stimulator (BLyS) is a cytokine that belongs to the TNF ligand family, and has been shown to play an important role in the proliferation and differentiation of B cells. Elevated serum levels of BLyS have been demonstrated in autoimmune disease patients, including those with SLE. BLyS is hypothesized to contribute to SLE pathogenesis by affecting survival signals and apoptosis of autoantibody-producing B cells. In this study we sought to investigate the relationship between serum BLyS levels and humoral immunity, as well as the effect of serum BLyS on an antigen-specific humoral immune response.

This study enrolled 61 female SLE patients who met ACR criteria. BLyS levels were measured by a quantitative sandwich enzyme immunosassay. Lupus-associated autoantibodies (Ro, La, Sm, rNRP, ribosomal P, dsDNA, ANAs and phospholipid antibodies) and influenza vaccination humoral immune response parameters including Bmax (relative amounts of anti-influenza antibodies against native antigen), Ka (relative affinity), and hemagglutination inhibition (relative protective antibody response) were measured. SLE patients were given a cumulative index score based on these three vaccination response parameters and classified as being either a “high responder” (greater than the median cumulative index score) or a “low responder” (less than the median cumulative index score). African Americans (AA, n=24) had significantly (p=0.021, unpaired t-test) higher serum BLyS levels than did European Americans (EA, n=35) (1649 ± 224 pg/mL in AA versus 1045 ± 144 pg/mL in EA). No differences were seen in BLyS levels between high responders to influenza vaccination (n=31) and low responders (n=30) (p=0.72, unpaired t-test). SLE patients with greater than or equal to 2 autoantibody specificities had higher BLyS levels than those patients with less than 2 specificities (p=0.035, unpaired t-test with Welch’s correction). Additionally, BLyS levels were increased in patients with an ANA titer of greater than 1:120 (p=0.0012, unpaired t-test with Welch’s correction). ACR classification criteria and disease activity measures were assessed in relation to serum BLyS levels. Increased serum...
BLyS correlated with an increase in disease damage as measured by SLICC (r2 = 0.12, p = 0.006), and an increase in disease activity as measured by PGA (r2 = 0.10, p = 0.013), and SLAM (r2 = 0.07, p = 0.046). Patients with the criteria discord rash, proteinuria, and lymphopenia had higher serum BLyS levels than did those patients without these criteria (p = 0.029, p = 0.011, and p = 0.008, respectively, unpaired t-test).

Increased serum BLyS levels were observed in African Americans, but were not associated with the ability to make a humoral response to influenza vaccination. Elevated BLyS levels were also associated with an increased number of autoantibody specificities, as well as an increase in ANA titer. Additionally, increased disease activity measures correlated with increased serum BLyS levels. This evidence strongly supports the role for BLyS in humoral autoimmunity and SLE disease pathogenesis.

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Elevated Levels of CXCL9 or CXCL10 in Sera of Patients with Early RA Predict Greater Difficulty in Achieving Remission during the First Year of Treatment. Gregory R. Emkey1, Klemen Strle1, Christopher R. Antonlini2, Deborah S. Collier2, Margaret Seton3, Arezou Khosroshahi4, Mark Fisher5, Nancy D. Kim6, John H. Stone7, Andrew D. Luster7, and Allen C. Steere8. Massachusetts General Hospital, Sudbury, MA, 1Massachusetts General Hospital, Haddon Heights, NJ, 2Massachusetts General Hospital, Denver, CO, 3Massachusetts General Hospital, Charlestown, MA, 4Massachusetts General Hospital, Boston, MA, 5Massachusetts General Hospital.

Purpose: The inflammatory immune response in patients with early rheumatoid arthritis (RA) is not well characterized. Depending on the series, dominant Th1-, Th2-, or Th17-type immune responses have been reported. We hypothesized that cytokine and chemokine levels, which act as indicators of these types of responses, may serve as biomarkers to help stratify subgroups of RA patients and predict their disease course. Here we report a preliminary analysis of a prospective study evaluating immune responses in early RA patients.

Methods: Patients who met EULAR criteria for RA, had symptoms for <12 months, and had not yet received DMARD therapy, were entered into the study and followed at 3, 6, and 12 months. They were treated with DMARDs, primarily methotrexate; and with a TNF inhibitor if the response was incomplete. At each visit, clinical parameters were determined (HAQ and DAS28 [CRP]), and serum samples and synovial fluid, if available, were collected. The levels of 20 cytokines and chemokines were determined in all samples at the same time using bead-based Multiplex assays. Elevated levels of each factor were defined as >2SD above the mean value of 40 control subjects.

Results: To date, 35 patients have been enrolled in the study; 30 patients have completed 3 months follow-up, and 12 have completed 12 months follow up. Of the 20 cytokines and chemokines measured, elevated levels of CXCL9 or CXCL10 (IFN-inducible chemokartactants for Th1 effector cells) or IL-23 (a marker for Th17 responses) were most common. In the initial visit, prior to DMARD therapy, 17 patients (49%) had elevated levels of CXCL9 or CXCL10, 17 (49%) had elevated IL-23 levels, and 26 (74%) had one or both of these responses. At study entry, patients who had elevated levels of CXCL9 or 10 had similar DAS28 scores (median, 5.2) as patients who did not have elevated levels of these chemokines (4.8). However, at the 3 month follow-up, patients with elevated levels of CXCL9 or 10 had a median DAS28 score of 3.1 compared with 2.2 in patients without elevated levels (P = 0.03), and by 12 months, the 2 groups had diverged more (3.1 versus 1.25, P = 0.004). Similar differences between the 2 groups were observed with HAQ scores. All 5 patients in whom it was possible to obtain joint fluid had elevated levels of both CXCL9 and 10 in serum and at least 10-fold higher levels of both chemokines in joint fluid. Elevated serum levels of IL-23 alone, without CXCL9 or 10, were not a risk factor for more severe disease.

Conclusions: Patients with early RA who had elevated serum levels of CXCL9 or CXCL10 prior to DMARD therapy had greater difficulty in achieving remission during the first year of treatment. This predictive information was not apparent from standard biomarkers of disease activity. Measurement of these chemokines at disease onset may help in the management of patients with early RA.

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Elevated Serum CX3CL1 Levels in Adult-Onset Still’s Disease: Potential Involvement in Hemophagocytic Syndrome. Tsuyoshi Kasama1, Kumiko Ohtsuka2, Michihito Sato3, Ryo Takahashi3, Kuninobu Wakabayashi2 and Takeo Isozaki4. 1Showa University School of Med, Shinagawa-ku-Tokyo, Japan, 2Showa University School of Med.

Objective: Adult-onset Still’s disease (AOSD) is a rare systemic inflammatory disease of unknown etiology characterized by chronic and fluent fever with accompanying rash, polyarthritis and involvement of multiple organs, especially lymphoid tissues. To investigate the prevalence of AOSD and its clinical characteristics, serum chemokines levels and the associated systemic manifestations, especially hemophagocytic syndrome (HPS), were assessed in patients complicated with AOSD.

Methods: Seventeen patients diagnosed with AOSD and 20 healthy controls were enrolled after obtaining informed consent, and clinical and laboratory findings were analyzed. Serial serum samples were collected from patients with active and inactive AOSD and from the controls, after which levels of the chemokines including CXCL8, CXCL10, CCL2 and CX3CL1, and soluble IL-2 receptor (sIL-2R) were determined by ELISA. Multivariate analysis was used to evaluate the correlation between serum chemokine levels and disease activity and the clinical features of AOSD.

Results: Serum CXCL8, CXCL10, CCL2 and CX3CL1 levels were significantly higher in patients with active untreated AOSD than in healthy controls. The elevated CX3CL1 levels seen in AOSD patients correlated positively with either CRP, sIL-2R or ferritin levels. While, there were no significant correlations between serum levels of the other chemokines and either CRP or ferritin. Among the 17 AOSD patients, 4 were complicated with HPS, and serum levels of both CX3CL1, sIL-2R and ferritin were significantly higher in AOSD patients with HPS than in those without HPS. Notably, serum CXCL1 levels were significantly diminished following successful treatment and clinical improvement.

Conclusion: The serum CXCL1 level may be a useful clinical marker of disease activity in AOSD. We suggest that especially high levels of CXCL1 as well as either ferritin or sIL-2R reflect the presence of HPS, and that the association between chemokine profiles and distinct clinical manifestations reflects the heterogeneity of the pathogenesis of AOSD.

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Gallic Acid Diminishes Cellular Proliferation and Pro-Inflammatory Gene Expressions in Fibroblast Like Synoviocytes from Patients with Rheumatoid Arthritis. Soo-Jin Chung1, Tae-Yeon Kim2, Yong-Jin Kwon2, Yong-Doon Park4, Soo-Kon Lee5 and Min-Chan Park2. 1Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, 2Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea, 3Division of Rheumatology, Yonsei University College of Medicine, Seoul, Korea, Republic of Korea.

Purpose: Gallic acid is naturally occurring substance which is found in gallnuts, grapes, tea leaves, and oak bark. Gallic acid has been known as an antioxidant and to exhibit anti-tumor activity through regulation of tumor cell differentiation and induction of apoptosis by suppression of NF-kB. NF-kB regulates the expression of several genes involved in inflammation, thus these anti-inflammatory properties of gallic acid can be used for treatment of immune-mediated diseases. A previous study showed that gallic acid treatment inhibited the production of inflammatory mediators in oral epithelial cells, indicating a certain role of gallic acid in immune response. This study was performed to investigate the efficacy of gallic acid in regulating cellular proliferation and pro-inflammatory gene expressions in fibroblast like synoviocyte (FLS) from patients with rheumatoid arthritis (RA).

Method: Synovial tissues were obtained from patients with RA during total knee replacement surgery. RA FLS were subsequently isolated and cultured. RA FLS were treated with various concentrations of gallic acid (1 μM, 10 μM, and 100 μM) with or without TNF-α (10 ng/mL) stimulation. The mRNA expression of pro-inflammatory cytokines (IL-1β, IL-6), chemokines (CCL-2, CCL-7), cyclo-oxygenase2 (COX-2), and matrix metalloproteinase-9 (MMP-9) were determined using quantitative real-time PCR. The proliferation of RA FLS in response to gallic acid treatment was measured by the MTT assay.

Disclosures: None.
Results: Gallic acid treatment induced dose-dependent reduction in constitutinal mRNA expression of IL-6 in RA FLS. Constituional mRNA expressions of CCL-2, CCL-7, IL-1β, COX-2, and MMP-9 were increased by treatment with lowest dose (1 μM) of gallic acid, but these expressions were decreased as the doses of gallic acid were escalated. After stimulating with TNF-α, gallic acid treatment inhibited the mRNA expression of all pro-inflammatory genes tested in dose- and time-dependent manner in RA FLS. Gallic acid treatment also suppressed the cellular proliferation of RA FLS (10% by 1 μM, 18% by 10 μM, 39% by 100 μM, at 72 hr).

Conclusion: In this study, we found that gallic acid treatment suppressed cellular proliferation and mRNA expressions of pro-inflammatory mediators in RA FLS. These findings suggest that gallic acid may play a role in regulation inflammation and synovial hyperplasia in RA patient and can be considered as a potential candidate for RA treatment.

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28 WITHDRAWN

29 Interleukin 34 Is Expressed in the Synovial Tissue from OA and RA Patients. Celine Cozic1, Benoit Le Goff2, Anne Riet1, Marie-Francoise Heymann1, Celine Charrier1, Regis Brion1, Sophie Touchais3, Marguerite Chemel4, Dominique Heymann1 and Jean-Marie Berthelot2. 1INSERM UMR S 957, 2INSERM UMR S 957 and Rheumatology Unit, CHU 100/H9262 Patient.

Background: Interleukin 34 (IL-34) is a recently discovered cytokine involved in monocyte differentiation and survival. This cytokine can bind to M-CSF receptor and induce colony-forming-unit macrophages (CFU-M) formation from human bone marrow cells. Interestingly, IL-34 also promotes osteoclastogenesis and can be substituted for M-CSF in RANKL induced osteoclastogenesis. It is expressed in spleen, skin, brain, and other tissues. The aim of this study was to assess the expression of IL-34 in the synovial tissue of rheumatoid arthritis (RA) and osteoarthritis (OA) patients by immunohistochemistry.

Methods: Synovial biopsy specimens were obtained surgically at the time of an arthroplasty in 17 RA patients, 4 patients with other inflammatory arthritis and 3 patients with OA. The mean duration of the RA was 11+/−5 years, with 15 patients treated with Methotrexate and 3 with anti-TNF α therapy. All the samples were embedded in paraffin and immunohistochemistry for IL-34 expression was performed using an automated staining system. The histopathological severity of synovitis was graded using the synovitis score described by Krenn et al, which quantitatively evaluates on a scale from 0 to 3 the hyperplasia of the synovial lining layer, activation of synovial stroma, and inflammatory infiltrates, giving a total score ranging from 0 to 9. Clinical and biological characteristics of the patients were also recorded. Statistical analysis was performed using a Mann-Whitney non parametric test. P<0.05 was considered as statistically significant.

Results: Overall, 27 biopsies were available for the histological analysis. The mean synovitis score was 4.7+/−1.9 (range 2–8). The mean score of synovial hyperplasia, stroma activation and inflammatory infiltrates was 1.42+/−1.2, 1.58+/−0.9 and 1.7+/−0.5 respectively. According to the grading system, of all the biopsies, 9 had slight synovitis, 8 had moderate synovitis, and 8 had strong synovitis. IL-34 was detected in 24 of the 27 biopsies with 3 samples from RA patients being negative. In the synovial tissue, IL-34 was expressed by the synovial fibroblasts (SFs), endothelial cells and the smooth muscular cells. A significant correlation was found between IL-34 expression by the SFs and the proliferation and infiltration of the synovial lining layer: the mean score of synovial hyperplasia was 2.15+/−0.8 and 0.54+/−0.3 in the biopsies with and without IL-34 positive SFs respectively (p=0.0013). We found also an association between IL-34 expression and the histological severity of the synovitis with a mean score of 5.5+/−1.9 and 3.7+/−1.5 in the IL-34 SFs positive and negative biopsies respectively (p=0.026). No significant association was found between IL-34 expression and any of the clinical or biological parameters.

Conclusion: IL-34 is expressed in the synovial tissue from RA and OA patients. Interestingly, we found a significant correlation between IL-34 expression by the synovial fibroblasts and the histological severity score of the synovitis. Considering the importance of IL-34 in monocyte maturation and osteoclastogenesis, the role of this cytokine in the pathogenesis of OA and RA should be further explored.

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30 Oncostatin M, Acting through Oncostatin M Receptor, Is a Potent Regulator of IL-6 and RANKL Expression in Mouse Synovial Fibroblasts. Benoit Le Goff3, Narella M. McGregor4, T. John Martin2, Evagne Romas1, Natalie A. Sims1 and Nicole C. Walsh1. 1St Vincent’s Institute, Fitzroy, VIC, Australia, 2St Vincent’s Institute, Fitzroy, Australia, 3St Vincent’s Institute and INSERM, UMR-S 957, Fitzroy, VIC, Australia

Background: In rheumatoid arthritis, synovial fibroblasts (SFs) mediate many effects of inflammatory cytokines that contribute to focal bone loss within the arthritic joint. The IL-6 family cytokine oncostatin M (OSM) is produced at high levels by macrophages and T cells in RA synovial fluid and synovial tissues, and is known to induce osteoclast formation via its action on osteoblasts. OSM acts by binding to the signal transducer gp130 and recruiting its ligand specific receptor α-chain, OSM Receptor (OSMR) or the leukemia inhibitory factor receptor (LIFR). It is not known which receptor complex mediates OSM effects on gene expression in SFs. In this study we sought to identify the effects of murine (m) OSM signalling via OSMF on SF expression of molecules modulators of inflammation and osteoclast function, in comparison with the prototypical inflammatory cytokine, TNF.

Methods: Immunohistochemical staining (IHC) for OSMR was performed in tissues from mice induced with mono-articular antigen induced arthritis (AIA). Synovial fibroblasts (SFs) were isolated from hind paws of mice deficient in OSMR (OSMR KO) and strain-matched wildtype control mice (WT). Isolated SFs were passaged at least 4 times prior to stimulation with mOSM (2 ng/mL and 50 ng/mL) or TNF (7.5 ng/mL, maximal, non-apoptotic dose). Cells were harvested at 1, 6 and 24 hours following stimulation, and RNA was isolated for subsequent quantitative RT-PCR analyses.

Results: OSMR protein expression detected by IHC staining was observed in SFs within normal knee joints and its expression was increased with the induction and progression of AIA, indicating a possible role in mediating AIA. OSMR mRNA expression was observed in WT SFs but not in OSMR KO SFs. mOSM treatment increased OSMR mRNA levels in WT SFs at 6 and 24 hrs. In contrast, gp130 and LIFR mRNA levels were similar in OSMR KO and WT SFs and were not modified by mOSM treatment. TNF did not modify OSMR, gp130 or LIFR mRNA expression but did increase LIF mRNA expression at 1, 6 and 24 hrs in both OSMR KO and WT SFs. mOSM treatment increased IL-6 mRNA expression 50–100 fold in WT SFs at 1, 6 and 24 hrs. This effect was absent in OSMR KO SFs. In contrast, TNF transiently induced IL-6 expression by both WT and OSMR KO SFs at 1 and 6 hrs (10–15 fold), with no effect at 24hrs. In WT SFs, mOSM significantly increased expression of the osteoclast differentiation factor RANKL at 1, 6 and 24hrs, with only a maximum of 2 fold increase in expression of the RANKL inhibitor, OPG. This effect was not observed in SFs derived from OSMR KO mice. In contrast, TNF treatment resulted in increased RANKL mRNA expression at 1 and 6 hrs with expression returning to baseline by 24 hrs in both OSMR KO and WT SFs.

Conclusion: Our results demonstrate that OSM acts on SFs, through the OSMR, to stimulate sustained IL-6 and RANKL expression in SFs. Induction of OSMR mRNA expression in SFs by OSM suggests that this may contribute to the sustained effect on RANKL and IL-6 expression. Increased expression of OSMR protein in SFs in arthritic tissues and OSM’s dependence on OSMR for its effects on IL-6 and RANKL expression identifies OSMR as a potential therapeutic target in the treatment of RA, which could reduce both inflammation and bone erosion.

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Little is known about mitogen-activated protein kinase (MAPK) contribution to disease in rheumatoid arthritis (RA), although inhibitors targeting one of these enzymes, p38, have already entered the clinic. Here we investigated synovial MAPK activation status in disease-modifying antirheumatic drug (DMARD) naïve early arthritis patients.

**Methods:** 50 DMARD naïve early arthritis patients (disease duration < 1 year) were prospectively followed and diagnosed at baseline and after 2 years according to criteria for undifferentiated arthritis (UA), rheumatoid arthritis (RA), or spondyloarthritis (SpA). Synovial biopsies from actively inflamed joints were obtained at baseline by needle arthroscopy and examined by immunohistochemistry for expression and phosphorylation of p38, ERK 1/2 and JNK MAPKs, using computer-assisted image analysis. Results were compared between patients with different diagnoses and disease outcomes.

**Results:** Activation of ERK was enhanced inclusion in patients meeting RA criteria after two years (n = 27) compared to SpA (n = 7) (P < 0.05) and UA (n = 16) (P < 0.005). JNK activation was significantly higher in RA than in SpA (P < 0.005) and UA (P < 0.01). p38 activation was similar between diagnostic groups. Logistic regression analysis demonstrated that synovial JNK activation, but not p38 or ERK activation, predicts fulfillment of RA classification criteria after two years (P = 0.59, P = 0.02). Comparing patients diagnosed with UA at baseline who fulfilled RA classification criteria after two years (n = 8) with those who remained UA (n = 16), activation of JNK (P < 0.005), but not p38 or ERK was significantly enhanced. Activation of ERK (P < 0.01) and JNK (P < 0.01) at baseline was also enhanced in RA patients with progressive joint destruction as assessed by comparison of X-rays at baseline and after two years. Comparing all early arthritis patients, activation of p38 (P < 0.05), ERK (P < 0.005) and JNK (P < 0.001) was elevated in patients with erosive disease.

**Conclusions:** In patients with early arthritis, elevated ERK and JNK activity distinguish RA from other forms of arthritis, and JNK activation is already elevated in patients with RA even before classification criteria of RA are met. Activation of MAPKs is also associated with development of erosive disease, and JNK activation predicts the development of erosive disease in early arthritis patients. Together, our data suggest that strategies targeting ERK and JNK, rather than p38, may be beneficial in treating RA and preventing joint destruction early in the disease process.

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**Serum Concentrations of Cytokines in the IL-23/IL-17A Pathway May Be Modulated by Polymorphisms in IL-23R.** Lisa K. Stamp, Jody Hazlett, Tony Merriman, John Highton and Paul Hessian. 1University of Otago, Christchurch, New Zealand, 2University of Otago.

**Purpose:** The IL-17/IL23 pathway has been recognised as an important pro-inflammatory system in RA. IL-23 is required for maintenance of Th17 cells whereas IL-12 inhibits IL-17A production from Th17 cells. Polymorphisms of the IL-23 receptor (IL-23R) and IL-21 have been associated with RA. The aims of this study were to determine the effect of polymorphisms in interleukin (IL)-23R, IL-12 and IL-21 on serum cytokine concentrations in patients with RA and to assess the relationship between serum cytokines in the IL-17/IL23 pathway and these genes.

**Methods:** Serum and DNA were collected from 81 patients with RA. Concentrations of IL-1β, IL-12, IL-17A, IL-21, IL-22, IL-23, and TNF-α were measured using a bead-based multiplex assay. Genotyping of individual SNPs was determined by Taqman assays and PCR-RFLP. Data were analyzed using Prism software. For statistical analysis the genotypes were grouped as positive or negative for the minor allele.

**Results:** The mean age was 57.7 years (22–80), 74% female, 70% RF +ve and 58% CCP +ve. In 18 patients none of the cytokines were detectable.

There was no significant difference in serum concentrations of any of the cytokines examined in patients with the major vs minor alleles of IL-23R rs11209026, IL-12B rs3213337, IL-12p40 rs17860508 and IL-21 rs6822844.

In the subgroup of 48 patients who had detectable IL-17A, patients homozygous for the IL-23R rs11209026 major allele had significantly higher

**Disclosure:** None.
IL-17A concentrations as compared to patients with the IL-23 minor allele (394.51 ± 529.72 pg/ml vs. 176.11 ± 277.32 pg/ml; p = 0.017). Similar differences were not observed in IL-21 or IL-22 concentrations. There was a strong positive correlation between serum IL-17A concentrations and IL-23 in patients with the IL-23R major allele (p = 0.0003), which was not present with the IL-23R minor allele. Similarly, while there was a significant positive correlation between serum IL-12 and IL-23 in patients with the IL-23R major allele (p = 0.036), this was not evident in patients with the IL-23R minor allele (p = 0.24).

Conclusions: These data suggest that the IL-23R rs11209026 polymorphism may have an impact on IL-23R function. However, this SNP as not been associated with RA. In patients with the variant higher concentrations of IL-23 may be needed to produce similar IL-17A concentrations as seen in patient with the major allele IL-23R, indicating reduced IL-23R function in those patients with the minor allele.

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Synovitis in Rheumatoid Arthritis: Paradoxical Inverse Relationship between Kinase Phosphorylation Status and CXCL13, a Biomarker of Inflammation. Sanna Rosengren and David L. Boyle. UCSD School of Medicine, La Jolla, CA

Purpose: Serum levels of the B-cell attracting chemokine, CXCL13 has been proposed as a marker of synovitis in rheumatoid arthritis (RA). In previous studies, we observed a strong correlation between serum CXCL13 protein and synovial CXCL13 mRNA. Hence, we sought to examine the relationship of synovial CXCL13 expression to putative markers of synovitis: 1) expression of inflammatory markers, and 2) the synovial phosphorylation state of several inflammation-associated signaling kinases.

Methods: RA synovial tissues were obtained during arthroplasty. Message RNA expression levels were determined by qPCR and were normalized to GAPDH yielding relative expression units (REU). Synovial kinase phosphorylation status was determined by Western blot. Phospho-Stat3 and MMP3 protein levels were measured by ELISA on synovial extracts. All statistical analysis was performed on log-transformed data.

Results: A screen of 58 individual RA synovial tissues revealed that CXCL13 REU ranged over 2600 fold, and when log-transformed, exhibited a bimodal distribution with two distinct maxima. From these, twelve each were selected from the upper and lower tertiles of the CXCL13 expression to yield High and Low CXCL13 sets. When compared to the Low CXCL13 tissues, significantly higher expression of TNF and MMP3, as well as the B- and T-cell markers CD19 and CD3E, respectively, were observed in High CXCL13 expression synovia (p < 0.0028 for all). In parallel, MMP3 protein levels also differed significantly between the two sets. Interestingly, no difference in expression of IL6 or MCP1 was observed between High and Low CXCL13 synovia. Surprisingly, p38, Erk, Stat3, and Akt were significantly less phosphorylated in High CXCL13 synovia. For example, when normalized to the Low CXCL13 within-gel mean, the phospho/total p38 ratios were 0.55 ± 0.086 and 1.00 ± 0.077, respectively, for High and Low CXCL13 tissues (p < 0.001). For Stat3, the corresponding numbers were 0.46 ± 0.077 and 1.70 ± 0.11, respectively (p = 0.001). No difference was observed in total p38/GAPDH or total Stat3/GAPDH protein ratios between the two synovial sets. The phospho-Stat3 results were confirmed using phospho-ELISA. Interestingly, expression of the anti-inflammatory factors SOCS1, SOCS3, and IL10 was significantly higher in High CXCL13 synovia. For example, the geometric mean (95% confidence interval) for SOCS1 REU was 0.0774 (0.048–0.11) and 0.015 (0.010–0.025) for High and Low CXCL13 tissues, respectively (p < 0.001). For SOCS3, the geometric mean (95% confidence interval) was 0.05 (0.04–0.06) for High and Low CXCL13 tissues, respectively (p < 0.001).

Conclusions: Rheumatoid synovial tissues with elevated CXCL13 express higher levels of inflammatory mediators and contain more infiltrating cells. Unexpectedly, the same tissues display reduced phosphorylation of several kinases crucial to pro-inflammatory signaling, such as p38, Erk, Stat3, and Akt, when compared to synovia with low CXCL13 levels. These data might be explained by signaling kinetics or the fact that High CXCL13 tissues also contain lower levels of anti-inflammatory factors, such as SOCS and IL10. These findings might be relevant to the therapeutic application of kinase inhibitors in RA synovitis, suggesting that stratification of patients might lead to improved clinical response.

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The microRNA 18a Enhances IL-6 Signaling through Inhibition of PIAS3. Matthias Brock, Michelle Trenkmann, Renate E. Gay, Beat A. Michel, Steffen Gay, Rudolf Speich and Lars C. Huber. Center for Experimental Rheumatology and Zurich Center for Integrative Human Physiology (ZIHP), University Zurich, Zurich, Switzerland. 2Rheum Clinic, Univ Hospital, Zurich, Switzerland, 3University Hospital Zurich, Zurich, Switzerland, 4University Hospital Zurich, Zurich, Switzerland, 5University Hospital Zurich, Zurich, Switzerland, 6Working Group for Pulmonary Hypertension, Department for Internal Medicine, University Hospital Zurich, Zurich, Switzerland

Introduction: Interleukin-6 (IL-6), a key proinflammatory cytokine in the pathogenesis of certain diseases, mediates the hepatic production of cytokines and acute phase proteins such as fibrinogen gamma chain (FGG) and haptoglobin (Hp). We have shown that signal transducer and activator of transcription 3 (STAT3), which is the major intracellular mediator of IL-6 signaling, regulates the expression of the microRNA (miRNA) cluster miR-17-92. Here we addressed whether miRNAs derived from this cluster might modulate IL-6 signaling and acute phase response in human hepatoma (HePG2) cells.

Methods: Overexpression of miRNA precursor molecules (pre-miR-17-5p, -18a, -19a, -20a and -92a) in HePG2 cells (n = 6) was achieved by nucleofection (AMAXA). Following an incubation period of 72h, cells were stimulated with IL-6 for 4h. Gene expression of FGG, Hp, suppressor of cytokine signaling 3 (SOCS3), and protein inhibitor of activated STAT 3 (PIAS3) were measured by SYBR Green real-time PCR. HePG2 cells (n = 5) were further transfected with reporter gene constructs of FGG or Hp promoters. 4h after stimulation with IL-6, cells were lysed and promoter activities were measured using the Dual-Luciferase Reporter Assay System (Promega).

Novel miRNA targets were identified by a computational algorithm (TargeScan) and validated by constructing a luciferase-based reporter gene system which contained the 3‘UTR of the predicted target gene. Luciferase expression was assessed after co-transfection of HEK293 cells (n = 7) with precursors of miR-18a and the respective reporter gene constructs.

Results: Stimulation of HePG2 cells with IL-6 for 4h resulted in overexpression of miRNA levels of SOCS3 (48.11 ± 15.3), FGG (2.86 ± 0.93) and Hp (4.43 ± 1.0) as compared to unstimulated control cells. Additional transfection with miR-18a further increased these expression levels (SOCS3: 81.49 ± 20.84, p < 0.05; FGG: 3.89 ± 1.35, p = 0.08; and Hp: 6.31 ± 0.75, p < 0.05). These data could be confirmed by performing reporter gene assays revealing 15.96 ± 4.62 fold change in the promoter activity of FGG for mock transfected cells upon stimulation with IL-6 and 26.67 ± 4.15 fold change in pre-miR-18a transfected cells (p < 0.05). For Hp, similar results were achieved showing 15.48 ± 4.51 in mock and 26.4 ± 4.47 fold change in pre-miR-18a transfected cells (p < 0.05). Next, we identified PIAS3 as a novel target of miR-18a. Transfection of miR-18a resulted in reduced mRNA expression levels of PIAS3 (0.86 ± 0.09, p < 0.05). Similarly, the activity of Luciferase containing the 3‘UTR of PIAS3 was reduced in pre-miR-18a transfected cells (0.127 ± 0.038) when compared to mock transfected cells (0.21 ± 0.044, p < 0.05). Conversely, this effect could be abrogated by mutation of the miR-18a seed match (0.247 ± 0.049 for mock and 0.265 ± 0.063 fold change for pre-miR-18a transfected cells).

Conclusion: We show here that miR-18a enhances IL-6 signaling in HepG2 cells thereby increasing the production of acute phase proteins. We further identified PIAS3, an endogenous inhibitor of STAT3, as a direct target of miR-18a. Our data emphasize an important link between miR-18a and STAT3 activity in the regulation of inflammation and acute phase response.

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TL1A Expressed on the Rheumatoid Fibroblast-Like Synoviocytes Mediates Signalling Induced by DeR3. Masayasu Takahashi. Dept. of Orthopaedic Surgery, Kobe Univ. Graduate School of Medicine, Kobe, Japan

Background: TNF-like ligand 1A (TL1A) vascular endothelial growth inhibitor (VEGI)-251, is a member of the TNF superfamily (TNFSF-15) and exerts its effects by binding to its specific receptor, death receptor 3 (DR3). TL1A activates multiple signalling pathways including NFkB, p38MAPK, S13
ERK, and FADD for mitosis, inflammation, and apoptosis. Recently, it is reported that TL1A is expressed in rheumatoid fibroblast-like synoviocytes (RA-FLS) and synovial fluids of rheumatoid factor (RF) seropositive patients. TL1A aggravate collagen-induced arthritis in mice. Meanwhile, decoy receptor 3 (DcR3) TNFRSF6b, a soluble receptor binding to TL1A, LIGHT, and Fasl, does not only inhibit the signals by competitively binding to these ligands, but also directly induces the differentiation of macrophage to osteoclasts as a ligand. In this study, we tested the interaction of DcR3 and TL1A in RA-FLS for cell proliferation and activation of MAPKs.

Methods: The relative expression levels of DcR3-specific ligands (TL1A, LIGHT, and Fasl) in RA-FLS were quantified by real-time PCR. RA-FLS were starved for 24h in OPTI-MEM media and incubated with various concentrations of recombinant DcR3-Fc protein, TNFRs, IL-1β, anti-TL1A Ab, and control Ig for 24h, and the proliferation rate was analysed by WST assay. RA-FLS pretreated with anti-TL1A Ab or control Ig for 24h was stimulated with DcR3-Fc for 30sec, 2 and 5min, and the phosphorylation of p38MAPK and ERK was detected by Western blotting.

Results: Real-time PCR showed that mRNA of TL1A s expressed in RA-FLS 140 times of FasL and 14 times of LIGHT. DcR3-Fc significantly inhibited the proliferation of RA-FLS induced by 0 ng/ml TNFα (7.8% with 100ng/ml and 25.4% with 1000ng/ml) or 0.05ng/ml IL-1β (33.6% with 100ng/ml and 40.7% with 1000ng/ml) in a dose dependent manner. DcR3-Fc did not inhibit the proliferation of RA-FLS induced by TNFα or IL-1β when the cells were pre-treated with anti-TL1A Ab. p38 MAPK and ERK signalling was activated 3.2 times and 5.2 times of control at 2min by 100ng/ml of DcR3-Fc, and the activation was suppressed by the pre-treatment with anti-TL1A Ab.

Conclusion: DcR3 activates p38MAPK and ERK in RA-FLS and inhibits the proliferation of RA-FLS induced by the inflammatory cytokines. TL1A expressed on RA-FLS is essential for the effect. Hence, DcR3 may directly bind to TL1A on RA-FLS and activate p38MAPK and ERK resulting negative regulation of cell proliferation induced by the inflammatory cytokines. DcR3 overexpressed in RA-FLS stimulated by TNFα protects the cells from Fas-induced apoptosis. Further, TL1A binds to DR3 and act mainly pro-inflammatory, but also induce apoptosis. Both DcR3 and TL1A have reciprocal functions in RA-FLS and DcR3/DR3-TL1A axis may play a critical role for the regulation of RA-FLS proliferation.

Disclosure: M. Takahashi: None.

37 Visfatin/NAMPT-Mediated NGF Stimulation in Articular Chondrocytes: A Potential Link between Pain and Obesity-Induced Osteoarthritis.
Sabrina Priam1, Emilie Pecchi2, Marjolaine Gosset3, Xavier Houard2, and Francis Berenbaum1.
1Faculty of Medicine P&M Curie, Paris, France, 2UPMC, Paris, France, Metropolitan, 3UPMC.

Background and Aim: Obesity is the main risk factor for knee OA. The two main features of the pathophysiology of obesity-induced OA are based on a pro-inflammatory (systemic, synovial, and metabolic) and anabolic (inflammatory adipokines). Nervous growth factor (NGF) is present within OA synovial fluid and may be involved in pain associated with OA. We previously showed that visfatin/NAMPT, an adipokine, has pro-degradative effects (Gossert et al. Arthritis Rheum. 2008). However, its role in OA pain has not been evaluated yet.

Methods: Primary cultures of newborn mouse articular chondrocytes or cartilage explants were stimulated by increasing amounts of visfatin/NAMPT, IL-1 beta, prostaglandin E2 (PGE2), and release (3.7 fold). When stimulated by IL-1 beta, a dose-dependent increase in NGF mRNA expression (5.7 fold increase with 10 ng/ml IL-1) and NGF release (19 fold increase with 10 ng/ml) in chondrocyte conditioned media was observed. Neither siRNA visfatin/NAMPT nor APO866, an inhibitor of NAMPT enzymatic activity, prevented the production of NGF by IL-1 beta. Interestingly, PGE2, which is produced by chondrocytes in response to IL-1 beta and visfatin/NAMPT, did not stimulate NGF production. Consistently, indomethacin, a cyclooxygenase inhibitor, did not counteract IL-1-induced NGF production.

Conclusion: These results suggest that obesity-induced OA pain may involve NGF mediated by the overexpression of visfatin/NAMPT and NGF. These effects seem to be independent of the well-known pro-inflammatory mediators involved in OA pain, IL-1β and PGE2. Thus, along with reduction of weight, visfatin/NAMPT could be an interesting target for pain in OA.

Disclosure: S. Priam: None; E. Pecchi: None; M. Gosset: None; X. Houard: None; F. Berenbaum: None.

38 Vitamin D Suppresses Th17 Cytokines Via Down Regulation of RORgammat and NFATC2 and by Differential Regulation of GATA3.
Anne-Marie Mus1, Jan Peter van Hamburan2, Patrick Asmawidjaja3, Johannes M. W. Hazes4, Hans van Leeuwen5, Louis Boon1, Edgar Colvin6 and Erik Lubberts1.
1Bioceros, 2Erasmus MC, University Medical Center, 3UPMC, Paris, France, 4Academic Medical Center Amsterdam, 5Radboud University, Nijmegen, and 6VUmc.

Introduction: Recently, we showed that vitamin D modulated Th17 polarization and IL-22 expression by memory T cells from patients with early rheumatoid arthritis and stimulates IL-4 production by PBMC from early RA patients. Furthermore, it has been shown that vitamin D inhibited collagen-induced arthritis and diminished the severity of existing CIA, although the mechanism is unknown.

Objective: To identify the molecular mechanism of vitamin D on suppression of Th17 cytokines and Th17 differentiation in an ex vivo model using CD4+ T cells from the prone autoimmune DBA-1 mice with and without collagen-induced arthritis or naive CD4+ T cells from DBA-1 mice.

Methods: Spleenic CD4+ T cells of non-immunized DBA-1 and type II collagen immunized DBA-1 mice were isolated using the MACS system. In addition, naive spleen CD4+CD62L+ T cells were FACS sorted from DBA-1 mice. These cells were stimulated in vitro under either Th0, Th1 (IL-12/anti-IL-4) or Th17 (IL-23, TGF-β, IL-6, anti-IL-4 and anti-IFN-γ) conditions with or without the presence vitamin D. Intracellular flowcytometric staining for the detection of cytokine and transcription factor expression were performed. In addition, cytokine expression in supernatant was detected by specific ELISA. Moreover, mRNA expression of factors involved in Th differentiation and function was analyzed by Q-PCR.

Results: Higher percentages of IL-17+IFN-g- (Th17) cells were obtained after Th17 polarization cultures of splenic CD4+ T cells of CIA-immunized mice, compared to non-immunized mice DBA-1. In cultures of both non-immunized mice and CIA-immunized DBA-1 mice, Vitamin D significantly inhibited Th17 polarization, as indicated by reduced IL-17A and IL-17F cytokine expression. Moreover, reduced RORgt expression and enhanced GATA3 expression was noted. Interestingly, vitamin D showed an increase in IL-4 and IL-10 positive cells under Th17 polarizing conditions both of non-immunized and CIA-immunized DBA-1 mice. However, using FACS sorted naive CD4+ T cells, vitamin D enhanced IL-4 and GATA3 under Th0 conditions, but not under Th17 polarizing conditions. Interestingly, in this latter condition, RORgt and NFATC2 were markedly suppressed. No effect of vitamin D on Tbet and RUNX1 expression was noted.

Conclusion: These data show that vitamin D is a strong inhibitor of Th17 polarization and Th17 cytokine expression of splenic CD4+ T cells from non-immunized and CIA-immunized DBA-1 mice. Furthermore, Th17 differentiation from naive T cells was affected by Vitamin D. These data implicate a regulatory mechanism on Th17 cells by Vitamin D, through the reduction of RORgt expression. This regulatory function of Vitamin D in memory Th17 cells, may in part be dependent on the induction of GATA3 expression leading to a induced Th2 cytokine expression profile.

Disclosure: A.-M. Mus: None; J. P. van Hamburan: None; P. Asmawidjaja: None; J. M. W. Hazes: None; H. van Leeuwen: None; L. Boon: None; E. Colvin: None; E. Lubberts: None.

39 XCL1/Lymphotactin Induces Rheumatoid Arthritis Fibroblast-Like Synoviocytes Migration through MAP Kinases.
Karolina Klosowska and James M. Woods.

Purpose: Chemokines are small secreted molecules that function in leukocyte recruiting and trafficking during an immune response. They play a key role in rheumatoid arthritis (RA), a chronic disorder that results in joint destruction. Fibroblast-like synoviocytes (FLS) are key contributors to the pathogenesis of RA, and they accumulate in the synovial lining, where they are positioned to aid in driving perpetual inflammation. XCL1 (Lymphotactin) is a chemokine known to be prominently present in the synovial tissue and
fluid of RA patients. In this study, we investigated the effect of XCL1 on FLS migration, proliferation, F-actin localization, and the role of MAP kinases in RA FLS stimulation.

**Results:** RA FLS were obtained with IRB approval from knee or hip synovial membrane at the time of joint replacement and were employed in chemotaxis assays, proliferation assays, and Alexa Fluor 488 Phalloidin staining of F-actin. Further, MAP kinase inhibitors were utilized in conjunction with chemotaxis assays to evaluate whether MAP kinases played a role in signaling that contributed to RA FLS migration.

**Conclusions:** We have identified a novel role for XCL1 in regulating RA FLS migration, which is consistent with changes in cytoskeletal structure. XCL1 induces RA FLS migration in a dose dependent manner, whereas application of PTX, a MEK1/2-, or a JNK-specific inhibitor significantly reduces cell migration. This suggests involvement of ERK and JNK pathways in XCL1-induced RA FLS migration, presumably through its receptor, XCR1. A better understanding of XCL1 and FLS is warranted, since FLS are known to be directly responsible for cartilage destruction and driving inflammation and autoimmunity in RA, where XCL1 is present.

**Disclosure:** K. Klooswka: None; J. M. Woods: None.

**ACR Poster Session A**

**Education**

Monday, November 8, 2010, 9:00 AM–6:00 PM

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**An Audit on Patients’ Knowledge of Methotrexate.** Evin Sowden, Wajeed Hassan, Ann Gooden, Bridget Jepson, Tamsheela Kausar, Ifraz Shafait, John Brockbank, Robert Ley and Lee-Suan Teh. Royal Blackburn Hospital, Blackburn, United Kingdom

**Background:** Methotrexate is a first line disease modifying agent and anchor drug for biologics therapy used in rheumatoid arthritis and other inflammatory rheumatic disorders. Adverse effects may occur in patients and are a common cause of drug discontinuation. Analysis of serious and fatal toxicity incidents led the National Patient Safety Agency (NPSA) to issue an alert identifying patient education and drug monitoring as an important part of a harm reduction strategy. In view of this, we audited patients prescribed methotrexate to assess adherence to patient education and patient knowledge in the rheumatology clinic setting of a district general hospital in the north of England.

**Methods:** All patients prescribed methotrexate for inflammatory rheumatic disease were eligible to take part. A proforma to record clinical and demographic characteristics, provision of patient education and monitoring, knowledge of drug administration, potential side effects and drug interactions was completed by case record review and patient self-administration. Questionnaire answers were discussed and an information leaflet on methotrexate was given to the patient at the end of their audit participation.

**Results:** 51 patients were audited. The mean age was 58.6 ±13.1 years and median duration of disease 3.7 (IQR 1.7–7.6) years. Counselling by specialist nurses prior to starting methotrexate was documented in 94.1%, written information was provided in 94%, methotrexate dose and frequency were known to the patient in 84% and 100%, folic acid was co-prescribed in 90% and awareness of pregnancy and breastfeeding risks was 87.5% in females of reproductive age (<45 years). There was limited awareness of methotrexate’s mode of action (60%), true side effects (21.6–62.7%), false side effects (5.9–37.3%), risks related to alcohol (68.4% in drinkers), risks related to male conception (47.1%), true drug interactions (7.8–11.8%) and false drug interactions (11.8–19.6%). The mean patient global knowledge score was 6.3 ±1.2 on a scale of 0–10 points. Univariate and multivariate analyses identified male gender, non-speakers of English as a first language and a trend toward longer duration of therapy as significant predictors of lower levels of patient knowledge.

**Conclusion:** Our audit shows that despite systematic patient education interventions as part of routine care, knowledge of important aspects of methotrexate therapy is limited. A number of recommendations are suggested: 1. Use of clearer safety-driven booklets such as that produced by the National Patient Safety Agency (NPSA); 2. Provision of information in languages other than English and in audio or audiovisual formats; 3. Regular knowledge assessments using validated tools; and 4. Targeted education to ensure consistent levels of knowledge to prevent unnecessary methotrexate-related harm.

**Disclosure:** E. Sowden: None; W. Hassan: None; A. Gooden: None; B. Jepson: None; T. Kausar: None; I. Shafait: None; J. Brockbank: None; R. Ley: None; L-S. Teh: None.
Administrative claims data can be employed successfully to measure the impact of a CME program on changes in clinical practice. A program focused on PCP education concerning RA resulted in increased referrals to rheumatologists to provide optimal pt care. This emphasizes the continuing importance of PCP education to improve outcomes for RA pts.

Disclosure: C. Bingham: Chatham Institute CME, 5; K. Costenbader: Chatham Institute CME, 5; S. Bender: Curatio CME, 3; D. Duch: Curatio CME Institute, 3; M. Weinblatt: Chatham Institute CME, 5.

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Information Sources for Rheumatoid Arthritis: More Than Just the Rheumatologist. Katie Gameau1, Maara Iversen2, Saira Jan3, Hsun Tsao4, Daniel Hal Solomon5 and Kavita Parmar5. 1Brigham and Women’s Hospital, 2Brigham and Womens Hospital, Boston, MA, 3Horizon Blue Cross Blue Shield, 4Northeastern University, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA

Background: Studies show that patients who make high quality medical decisions are more likely to have better health outcomes. One defining characteristic of what constitutes a high quality decision is a well-informed patient. However, there has been little research studying patient behaviors regarding how they seek information about treatments for RA.

Methods: We surveyed beneficiaries of Horizon Blue Cross Blue Shield of New Jersey from 2009–2010, who were over age 18 and had 2 or more visits coded with RA (ICD 9 714.x). 101 (13%) of 799 invited subjects agreed to and completed interviews. Subjects answered a questionnaire consisting of items regarding sources of RA treatment information (provider and non-provider) and their usefulness, sociodemographic items, as well as 10 validated scales shown in table 1. Provider sources of information included primary care physician, rheumatologist, nurse practitioner or physician’s assistant, and occupational or physical therapist. Non-provider sources included the Arthritis Foundation, books or magazines, friends or family, advertisements, health insurance, and the World Wide Web. Outcomes of interest include the average number of sources described (range 0 – 10) and the rating of usefulness for each source (1 = not useful and 4 = extremely useful).

Results: Most subjects (95%) reported at least 2 years of disease and had a mean age of 59 years. 76% of respondents were female, 71% had completed at least some college, and 43% reported earning over $100,000 in the past year. Methotrexate was the most widely used medication reported (85%). The average number of sources utilized was 5.0 (SD 2.1). Participants rated the information they utilized with an average score of 2.5 (SD 0.8). We found no strong patient correlates of these outcomes when comparing with the aforementioned domains, however positive correlations were noted between number of sources and social supports as well as usefulness of sources and trust in physician (see Table). 87% of the 98% of the total sample that used a Rheumatologist for information gave that source a 4 out of 4. The internet was the most frequently used non-provider source, with 63% of subjects reporting use, and an average usefulness rating of 3.0 (SD 1.03).

Conclusion: Participants, on average, use 5 sources of information regarding treatment decisions for RA. Participants rated these sources as useful, with Rheumatologists rated extremely useful. Strategies to enhance care and appropriate use of DMARDs should take this information into consideration.

Table 1. Correlations between patient characteristics and information sources for RA treatment decision making

<table>
<thead>
<tr>
<th></th>
<th># of sources</th>
<th>Usefulness of sources</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient (r)</td>
<td>p-value</td>
</tr>
<tr>
<td>Trust in Physician</td>
<td>0.12</td>
<td>0.23</td>
</tr>
<tr>
<td>Self-Efficacy</td>
<td>0.43</td>
<td>0.67</td>
</tr>
<tr>
<td>Beliefs In Medicines</td>
<td>0.22</td>
<td>0.03</td>
</tr>
<tr>
<td>Social Support</td>
<td>0.20</td>
<td>0.04</td>
</tr>
<tr>
<td>Brief Illness</td>
<td>0.12</td>
<td>0.24</td>
</tr>
<tr>
<td>Perception*</td>
<td>0.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Higher scores indicate a higher perception of illness, all other high scores denote more of the measured attribute.

Disclosure: K. Garneau: None; M. Iversen: Arthritis Foundation, 2, 5, 6, Editorial Board APTA, 2, 5, 6, NIH, 2, REF Board Member, 2, 5, 6, University of Denmark, 2, 5, 6; S. Jan: None; H. Tsao: None; D. H. Solomon: Abbott Immunology Pharmaceuticals, 2, Amgen Inc., 2, Bristol-Myers Squibb, 9; K. Parmar: None.

43 Knee and Shoulder Cadaver Teaching Improves Internal Medicine Residents’ Self-Reported Anatomy, Exam and Injection Skills. Jessica Berman1, Michael H. Pillinger2, Bradley Jensen3, Jennifer Hammann4 and Stephen A. Paget5. 1Hospital for Special Surgery, New York, NY, 2Hospital for Special Surgery, New York, NY, 3NYU-Manhattan VA Med Hospital, New York, NY

Purpose: Medicine residents need to gain confidence and ability in basic musculoskeletal skills such as the joint exam, anatomy knowledge and joint injections. However, opportunities to develop these skills are frequently limited. Possible impediments include inadequate hands-on experience and the ineffectiveness of lectures and simulation models. To address these limitations, we have developed a series of innovative modules that focus on instruction in knee and shoulder anatomy, examination and injection teaching in the cadaver lab.

Methods: Rheumatology knee and shoulder teaching modules were designed for 3–4 second-year medicine residents each month, with over forty completing the program in the past year. Residents were surveyed (9-point Likert scale) before and after the rotation for their self-assessed ability to perform joint examination and aspiration. Modules were taught by an experienced rheumatologist and consisted of twice-monthly participation in interactive lectures with demonstrations of the relevant anatomy and injection classes employing cadaveric models. Examination skills relevant to the area discussed were also emphasized. Ample opportunity was given to practice injections using different approaches on the cadaver knee and shoulder joints.

Results: Before and after completing the above curriculum, second-year residents surveyed rated their abilities (1=poor to 9=very good) in specific musculoskeletal tasks as follows:

<table>
<thead>
<tr>
<th>Task</th>
<th>Pre-lab (N=43)*</th>
<th>Post-lab (N=24)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection knee</td>
<td>2.42</td>
<td>6.12</td>
</tr>
<tr>
<td>Injection shoulder</td>
<td>1.56</td>
<td>5.54</td>
</tr>
<tr>
<td>Examination knee</td>
<td>4.23</td>
<td>6.76</td>
</tr>
<tr>
<td>Examination shoulder</td>
<td>3.93</td>
<td>6.40</td>
</tr>
<tr>
<td>Anatomy knee</td>
<td>4.09</td>
<td>6.44</td>
</tr>
<tr>
<td>Anatomy shoulder</td>
<td>4.05</td>
<td>6.28</td>
</tr>
</tbody>
</table>

*p<0.001 for all comparisons

The average number of joints injected by each resident prior to the rotation was 0.88. By the end of the rotation this had risen only to 2.08.

Conclusion: Even in the setting of only limited opportunity to perform actual joint procedures, a rheumatology curriculum that includes an integrated, intense, hands-on exposure to musculoskeletal anatomy and injection teaching in the cadaver lab can improve residents’ perceptions of their abilities and confidence in the anatomy, examination and injection of the knee and shoulder. This teaching approach may be a valuable alternative for programs wishing to improve musculoskeletal procedure skills, particularly in settings where actual experience may be limited.

Disclosure: J. Berman: None; M. H. Pillinger: None; B. Jensen: None; J. Hammann: None; S. A. Paget: None.

44 Medical Student Education in the Electronic Age: A Web-Based Virtual Teaching Tool. Ernesto J. Rodriguez1, Abie Alia1, Aasim Rehman2, Vanessa Osting1, Tanisha Battle1, Lara Westphal1, Ashley G. Sterrett1, Helen Bateman1, John D. Carter1 and Joanne Valeriano-Marcet1. 1University of Florida, Jacksonville, FL

Objective: Musculoskeletal (MSK) complaints have a high prevalence in primary care practice, yet many physicians continue to identify themselves as deficient in MSK medicine. Recognizing joint pattern involvement in rheumatic diseases is integral to establishing a differential diagnosis. Therefore there is an impetus to improve the quality and consistency of MSK teaching.

Table 2. Comparison of pre- and post-training scores on joint examination and injection knowledge.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pre-training</th>
<th>Post-training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee examination</td>
<td>2.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Shoulder examination</td>
<td>2.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Knee injection</td>
<td>2.0</td>
<td>6.7</td>
</tr>
<tr>
<td>Shoulder injection</td>
<td>2.0</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Disclosure: E. J. Rodriguez: None; A. Alia: None; A. Rehman: None; V. Osting: None; T. Battle: None; L. Westphal: None; A. G. Sterrett: None; H. Bateman: None; J. D. Carter: None; J. Valeriano-Marcet: None.
Methods: “Arthur” is a web-based virtual education program that teaches joint pattern recognition of MSK disorders. Thirty cases highlight different joint pattern presentations (ie. Symmetric polyarthritis illustrated in above case). “Arthur” was developed by the University of South Florida Rheumatology and Education Departments. All fourth year medical students had access to “Arthur” and the accompanying survey. This survey contained open-ended questions designed to gather feedback on the students’ experience, as well as the program’s utility and possible areas of improvement.

Results: A total of 64 out of 107 (59.8%) fourth year medical students completed “Arthur” and the follow up survey. In response to the question regarding the strengths of “Arthur”: 35% of the respondents identified the program to be a useful tool for learning joint pattern recognition, 42.4% stated it was helpful in learning differential diagnoses of rheumatic diseases, and 20.3% reported “Arthur” to be useful as a visual aid. In response to the question regarding areas for improvement: 48.4% identified the need for addition of explanations for each differential diagnosis, 10.9% reported the need for additional history, and 9.3% felt that “Arthur” did not need any improvement.

Conclusions: The “Arthur” virtual interactive teaching program was found to be most helpful in determining differential diagnoses, joint pattern recognition, and as a visual aid for learning. Based on this data, the most recent version of “Arthur” includes detailed explanations of the differential diagnoses for each case.

Disclosure: E. J. Rodriguez: None; A. Alias: None; A. Rehman: None; V. Osting: None; T. Battle: None; L. Westphal: None; A. G. Sterrett: None; H. Bateman: None; J. D. Carter: None; J. Valeriano-Marcet: None.

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Rheumatology Fellowship Curricular Rotation in Musculoskeletal Ultrasound. Dimitrios A. Pappas1, Marzouq A. Qubti1, Clifton O. Bingham III1 and Allan C. Gelber1. 1Baltimore, MD, 2Johns Hopkins University, Baltimore, MD

Background: Within the American rheumatology community, musculoskeletal ultrasound (MSK-US) has over the last decade gained substantial support as a valuable diagnostic tool to evaluate swollen joints, bursae and tendons. Notwithstanding ongoing efforts to integrate MSK-US training into fellowship training, there remains a paucity of information detailing the experience of individual rheumatology programs at furnishing MSK-US training in their respective curricula.

Methods: We describe our new curricular rotation with MSK-US at a single academic medical center in the United States. In the 2009–2010 academic year, a new clinic was implemented wherein patients referred in consultation for acute sites of musculoskeletal swelling could be scheduled and evaluated within 72 hours of referral receipt. The attending rheumatologist was previously trained in musculoskeletal ultrasound. At this clinic, faculty-mentored, ultrasound-focused rheumatologic evaluations were conducted one afternoon each week over the course of 11 consecutive months.

Results: Between July, 2009 and May, 2010, there were 100 consecutive patients evaluated in tandem by a rheumatology fellow and faculty preceptor at this acute musculoskeletal clinic. These ultrasound-focused evaluations were conducted across a broad spectrum of patients with arthritis and rheumatic disorders, including osteoarthritis (n=20), rheumatoid arthritis (n=14), trochanteric bursitis (n=10), unspecified arthritis (n=9), gout (n=9), spondylarthropathy (n=8), shoulder tendinitis/bursitis (n=7), pseudogout (n=5), tendinopathies (n=5), and other miscellaneous diagnoses (n=13). Ultrasound guidance was used to evaluate a knee (n=27), shoulder/rotator cuff (n=13), wrist (n=11), hip (n=10), elbow (n=5), ankle (n=5), interphalangeal joint (n=10), and other miscellaneous sites (n=19). Among these patients, a subset of 75 underwent an ultrasound-guided procedure, consisting of 52 patients who underwent ultrasound-guided joint, bursal or tendinous injections; 15 additional patients who underwent aspiration & injection, and 8 who underwent an aspiration procedure alone.

Conclusions: In the context of this new fellowship curricular offering, a single rheumatology trainee, working in unison with a single faculty preceptor, was able to achieve considerable exposure across a broad range of rheumatic disorders. Substantial proficiency was attained at use of ultrasonography, to identify and localize sites of joint, tendinous and bursal swelling, and to guide aspiration and/or injection procedures. Moreover, completion of 100 ultrasound-guided evaluations is a recognized target for an intermediate level of knowledge and skills for performing MSK-US [J Clin Rheum 2010;16:113].

Disclosure: D. A. Pappas: None; M. A. Qubti: None; C. O. Bingham III: None; A. C. Gelber: None.

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Team-Based Learning in Rheumatology Resident Education: Two-Year Results on Receptiveness and Attitudes of Residents towards Collaborative Learning and Teamwork. Karina Marianne D. Tornabba, Beatrice A. Bouten1, Ron Ben-Ari1 and Francisco P. Quisimoro2. 1Arkansas Children’s Hospital-University of Arkansas for Medical Sciences, 2University of Southern California-Los Angeles County Medical Center, Pasadena, CA, 3University of Southern California-Los Angeles County Medical Center, Los Angeles, CA, 4University of Southern California-Los Angeles County Medical Center
Objective: Team-based learning (TBL) is a structured small group learning approach that is well-recognized in medical education. It encourages accountability, teamwork, and has been demonstrated to improve board scores and patient care. Since 2008, TBL has been utilized for Internal Medicine core curriculum learning sessions (CCLSs) in Rheumatology. Two of the aims of this study are to determine the level of satisfaction or receptiveness by residents of the strategy in improving their overall learning experience, and to determine their attitudes towards teamwork in learning and professional success.

Methods: Seven TBL modules had been developed on various topics including Rheumatoid arthritis, Osteoarthritis. Over 2 years, 13 modified-TBL sessions have been conducted. Learning materials provided a week before are reviewed briefly at start of class. Residents undergo individual readiness assessment test (IRAT), followed by group-RAT (GRAT) and case application done in teams of 3–4 members. Class discussion is supervised by the instructor. To assess receptiveness, a 5-point Likert scale evaluation survey with two open-ended questions was anonymously filled out by residents at end of each session. To evaluate perception of collaborative learning, Value of Teams Survey (VOTS) was filled out yearly at the end of the CCLS series. In-training and board exam scores were tracked to determine effectiveness of TBL (results in separate abstract). Descriptive statistics and t-tests were used.

Results: Of 240 residents over a two year period (60 per year, including graduated residents and new PGY1s), 220 have gone through TBL-CCLSs. Over two years a sustained majority (80–100%) agreed strongly agreed that TBL was conducive for CCLSs due to organization of activities, accountability, learning and teamwork and instructor interactions. Most commonly cited themes: 1) as to what was they liked best was that it was a fun and interactive format, it allowed them to learn from co-residents, it allowed them to review materials they already knew and to also advance their knowledge by using critical thinking; 2) as to what they liked least was the time constraint. For VOTS, a sustained majority (85–100%) agreed that utilizing teamwork is an effective way of learning, and is a necessary and valuable skill to learn, and is needed for better decision-making. At least 80% felt teamwork is necessary for professional success in their careers.

Conclusion: There is sustained acceptance and satisfaction by medical residents of TBL as a teaching strategy for CCLSs from year 1 to year 2 of implementation. Collaborative learning through teamwork is a recognized effective way of learning and a valuable skill to acquire.

Disclosure: K. M. D. Torralba: None; B. A. Boa teteng: None; R. Ben-Ari: None; F. F. Quisimoria: None.

48 Utilization of Ambulatory Medical Clinic for Rheumatology Education.
James M. Ross Lehigh Valley Health Network, Macungie, PA

Purpose: Development and assessment of a model of rheumatology education using medical residents own clinic patients with direct supervision of rheumatic cases by an academic rheumatologist.

Methods: An education model was developed utilizing an academic rheumatologist for direct supervision and education concerning rheumatic cases seen during internal medicine resident’s clinic. The rheumatologist attended each resident’s clinic monthly and saw scheduled patients specifically for rheumatology and non-scheduled rheumatic cases. The diagnoses, residents involved and any procedure performed were recorded. Assessment of this educational experience included testing of general rheumatology knowledge with multiple-choice questions, an annual assessment of overall resident impression and assessment of utility of the experience using a 5 point scale. This assessment was performed at baseline and yearly.

Results: Patient visits: There were 90 sessions attended by the rheumatologist over 24 months. 253 patients including 193 scheduled patients with rheumatology issues were seen. Due to initiation of EMR there was a transient decline in patients seen in the past year. 35% of the cases were followed over time giving residents experience of continuity of care of rheumatic disorders. Cases encompassed all aspects of rheumatology with the most common diagnoses being rheumatoid arthritis, osteoarthritis and soft tissue rheumatism with need for injections. Waiting time for patient seen with this program was 0–40 days. Sixty different residents were supervised in this model including 40 without previous rheumatology rotation experience.

Educational assessment: At baseline the majorities of the first and second year groups of residents were not comfortable with rheumatic patients and scored poorly on basic rheumatology questions. As a group the third year residents were less than moderately comfortable in seeing rheumatology patients. On repeat assessment each of the resident groups demonstrated improvement in basic knowledge including those residents without a previous rheumatology rotation experience. They also reported an improvement in their level of comfort in dealing with rheumatic patients and performing arthritis aspirations. The overall resident impression was that this model provided a useful clinical and educational experience.

Conclusions: This medical clinic educational model provides several additional benefits in addition to or combined with a standard rheumatology rotation. Benefits include residents having more responsibility for the care of these cases plus an increase in comfort level. This model provides an increased and earlier exposure to rheumatology that may interest residents into considering this field, in addition to improved medical clinic patient access to care and quality of care.

A Novel Baseline Biomarker of Acute-Phase Serum Amyloid A (A-SAA) and Serum Interleukin–2 Receptor alpha (sIL-2Rα) Predicted Long-Term (18 to 35 Yrs) Mortality of Incident Rheumatoid Arthritis (RA) and Matched Non-RA Cohort Controls (CN). Alfonse T. Masi1, Jean C. Aldag2 and Jean D. Sipe3. 1Center for Scientific Review, NIH, Bethesda, MD; 2University of Illinois College of Medicine at Peoria, Peoria, IL.

Purpose: Research on biomarkers of mortality has high priority, especially for cardiovascular causes. Serum markers have predicted such mortality but not over decades-long intervals. This prospective study aimed to identify baseline, long-term biomarker predictors of mortality outcomes of incident RA and matched non-RA cohort CN.

Design: 1044 patients who had enrolled into a community-based cohort (n = 21061) who later had onset of ACR-positive RA, positive to 3A (mean 12) years (1977 – 1994). Each RA case was matched by age, gender, and race (all Caucasian) at baseline with 4 cohort non-RA CN. Baseline stored (-70°C) sera were assayed (ELISA) blindly for biomarkers. High sensitivity CRP (hsCRP) and A-SAA were assayed (Hemagen kits) at Boston University (sensitivity 0.1 μg/ml for hsCRP and 1 μg/ml for A-SAA). Three cytokine receptors, IL-1β, IL-6, and TNF-α, and the IL-1α receptor were assayed (R & D Systems, high sensitivity kits) at Specialty Laboratories, Santa Monica, CA. Two baseline (1974) biomarkers correlated with mortality of all subjects from 1992–2009, i.e., A-SAA, p = 0.001 and sIL-2Rα (CD25), p = 0.036 (but not CRP, p = 0.125). Sex- and age-specific upper quartile values of A-SAA and sIL-2Rα were determined and a gradient score of their combined results was formulated: 1 = all negative tests (single only or both assayed); 2 = one test negative and other positive (or neither test assayed); and 3 = all positive tests (single only or both assayed). All cause, primary cardiovascular (ICD-9, 390–459 & ICD-10, 00–99), and all other combined mortality was monitored from 1992 thru 2009, excluding 12 pre-1992 deaths. Percentages of deaths by the biomarker gradient were determined. Hazard ratios (HR) of the biomarker gradient for mortality were estimated by Cox regression models.

Results: Deaths from all causes occurred in 27 (50%) of 54 RA vs 63 (31%) of 204 non-RA, 1974–2009, 95% CI 1.22 – 4.12, p = 0.010. For all causes, HRs of the biomarker gradient were significant for deaths in RA (p = 0.026), non-RA (p = 0.002), and total (p < 0.001) subjects. For circulatory mortality, HRs of the biomarker gradient were significant for deaths in total (p < 0.001) and non-RA (p = 0.001) subjects, and nearly in RA (p = 0.072). For non-circulatory deaths, the biomarker only weakly predicted deaths in total subjects, p = 0.049 (Table):

### Causes of Deaths and the Biomarker Gradient

<table>
<thead>
<tr>
<th>Causes of Deaths</th>
<th>Rheumatoid Arthritis (N=54)</th>
<th>Non-Rheumatoid Arthritis (N=204)</th>
<th>Total Cohort Subjects (N=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Causes of Deaths</td>
<td>8 (34.8%) of 23</td>
<td>22 (22.2%) of 99</td>
<td>30 (24.6%) of 122</td>
</tr>
<tr>
<td>No Assays or Neg &amp; Pos</td>
<td>15 (56.5%) of 23</td>
<td>31 (31.6%) of 86</td>
<td>44 (40.4%) of 109</td>
</tr>
<tr>
<td>Positive Only</td>
<td>6 (75.0%) of 8</td>
<td>10 (52.6%) of 19</td>
<td>16 (49.3%) of 27</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>27 (50.0%) of 54</td>
<td>63 (30.9%) of 204</td>
<td>90 (34.9%) of 258</td>
</tr>
<tr>
<td>Cox Regression Model: Biomarker Gradient for Mortality (p Values)</td>
<td>1.80 (1.07–3.03) (p = 0.0026)</td>
<td>1.78 (1.24–2.55) (p = 0.002)</td>
<td>1.83 (1.36–2.46) (p &lt; 0.001)</td>
</tr>
</tbody>
</table>

### Circulatory Deaths

<table>
<thead>
<tr>
<th>Causes of Deaths</th>
<th>Rheumatoid Arthritis (N=54)</th>
<th>Non-Rheumatoid Arthritis (N=204)</th>
<th>Total Cohort Subjects (N=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Assays or Neg &amp; Pos</td>
<td>4 (17.4%) of 23</td>
<td>14 (16.3%) of 86</td>
<td>18 (16.5%) of 109</td>
</tr>
<tr>
<td>Positive Only</td>
<td>6 (75.0%) of 8</td>
<td>10 (52.6%) of 19</td>
<td>16 (49.3%) of 27</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>27 (50.0%) of 54</td>
<td>63 (30.9%) of 204</td>
<td>90 (34.9%) of 258</td>
</tr>
<tr>
<td>Cox Regression Model: Biomarker Gradient for Mortality (p Values)</td>
<td>1.80 (1.07–3.03) (p = 0.0026)</td>
<td>1.78 (1.24–2.55) (p = 0.002)</td>
<td>1.83 (1.36–2.46) (p &lt; 0.001)</td>
</tr>
</tbody>
</table>

### Non-Circulatory Deaths

<table>
<thead>
<tr>
<th>Causes of Deaths</th>
<th>Rheumatoid Arthritis (N=54)</th>
<th>Non-Rheumatoid Arthritis (N=204)</th>
<th>Total Cohort Subjects (N=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Assays or Neg &amp; Pos</td>
<td>7 (30.4%) of 23</td>
<td>16 (16.2%) of 99</td>
<td>23 (19.5%) of 122</td>
</tr>
<tr>
<td>Positive Only</td>
<td>9 (39.1%) of 23</td>
<td>17 (19.8%) of 86</td>
<td>26 (23.0%) of 109</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>29 (47.0%) of 54</td>
<td>67 (32.8%) of 204</td>
<td>96 (37.1%) of 258</td>
</tr>
<tr>
<td>Cox Regression Model: Biomarker Gradient for Mortality (p Values)</td>
<td>1.59 (0.87–2.92) (p = 0.134)</td>
<td>1.33 (0.82–2.17) (p = 0.253)</td>
<td>1.47 (1.00–2.16) (p = 0.049)</td>
</tr>
</tbody>
</table>

Conclusions: Baseline (1974) upper quartile values of serum A-SAA and sIL-2Rα predicted long-term (18 to 35 yrs) mortality (p < 0.001), mainly attributable to circulatory (p < 0.001), than other (p = 0.049), causes of death. This novel biomarker deserves further testing as a long-term predictor of cardiovascular mortality.

Disclosure: A. T. Masi; None; J. C. Aldag; None; J. D. Sipe; None.

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### A Prediction Score To Differentiate Rheumatoid Arthritis from Undifferentiated Arthritis in an Early Arthritis Cohort

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1CONAART, Buenos Aires, Argentina, 2CONAART, Argentina

Objective: to identify predictor factors for progression into rheumatoid arthritis (RA) in patients with undifferentiated arthritis (UA).

Methods: A prediction score was developed in a way to identify predictor factors for progression into RA in patients with undifferentiated arthritis (UA). The population consisted of 515 patients, 83.2% of whom were women, median age 47 years, median disease duration 6 months. Results: 619 patients were included (UA=312, RA=307), 515 (83.2%) were women, median age 47 years, median disease duration 6 months. Patients with RA had significantly higher disease activity (DAS28), and worse functional capacity and quality of life compared to UA patients. In the logistic regression analysis, the independent predictive variables for development of RA and their corresponding ORs were: 1 point (one only or both assayed); 2 points (-> 4), 4 points (one test and continue variables using student T test and continue variables using student T test and continue variables using student T test and continue variables using student T test).

Conclusions: The present score had an excellent ability to discriminate between RA and UA using simple variables obtained from daily practice.

Disclosure: C. Waimann; None; F. DalPra; None; J. Hogrefe; None; J. Marcos; None; S. Retamozo; None; F. Caéro; None; L. Castilla; None; M. Benegas; None; O. Rillo; None; H. Berman; None; A. Berman; None; R. Garcia Salinas; None; A. Catalán Pellet; None; F. Cecotto; None; S. Pina; None; J. C. Marcos; None; J. Maldonado Cocco; None; L. Cattoggio; None; E. Soriano; None; G. Citera; None.

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### Association of Patient Cost-Cutting Behaviors with Clinical Outcomes, Health Status, and Lost Work Productivity in Individuals with Rheumatoid Arthritis

Susan C. Bolge1, Ahmad B. Naim2, Chureen Carter2, L. Cattogio3, F. Ceccato4, A. Berman5, G. Citera5, L. Casalla2, J. C. Aldag2, J. C. Marcos3, S. Paira2, M. Maldonado Cocco3, R. Garcı´a Salinas2, A. Carlos TarHealth

Background: In an effort to reduce rising healthcare costs, there has been a trend in managed care toward greater patient cost sharing. However, in this time of economic recession, high costs may necessitate cost-cutting decisions by patients, especially those with multiple, costly, chronic conditions. This study seeks to quantify cost-cutting behaviors in patients with rheumatoid

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arthritis (RA) and assess the association of these behaviors with patient-reported clinical outcomes, health status, and work productivity loss.

**Methods:** In August 2009, individuals aged ≥18 and reporting an RA diagnosis completed a cross-sectional, self-administered, Internet-based questionnaire. Cost-cutting behaviors were assessed for the prior six months. Differences in outcomes were compared between patients with identified cost-cutting behaviors and those without. Patient-reported clinical outcomes included the Health Assessment Questionnaire (HAQ) and severity of morning stiffness, fatigue, and pain, measured as ≥1-none experienced to ≥10-severe. Health status was assessed using the SF-36, and work productivity loss was assessed using the Work Productivity and Activity Impairment questionnaire. Patient demographics and comorbidities were adjusted using linear regression for clinical outcomes and health status and negative binomial regression for lost work productivity.

**Results:** Of 1580 patients, 41.6% (n=658) reported at least one cost-cutting behavior. The most frequently reported behaviors were delaying RA related physician visits (59.0%), taking RA prescription medication less often (25.7%), and reducing number of RA prescriptions filled (22.9%). After adjustment, cost-cutting behavior was associated with greater functional disability (HAQ: regression coefficient b=0.19, P<0.001); severity of morning stiffness (b=0.76, P<0.001), fatigue (b=0.80, P<0.001), and pain (b=0.84, P<0.001); and poorer health status (SF-36 physical component summary: b=−1.75, P<0.001 and mental component summary: b=−3.33, P<0.001). Among the employed, patient cost-cutting behaviors were associated with 1.39 times (P<0.001) the amount of overall work impairment compared to those without.

**Conclusion:** A substantial proportion of RA patients engage in cost-cutting behaviors which are associated with worsening patient-reported clinical outcomes, poorer health status, and decreased work productivity; however, due to the cross-sectional nature of the study, the direction of these associations cannot be determined. Further research is needed to investigate the potential impact of patient cost sharing on clinical effectiveness and disease progression markers.

**Disclosure:** S. C. Bolge: Centocor Ortho Biotech Services, LLC, 3; A. B. Naim: Centocor Ortho Biotech Services, LLC, 3; C. Carter: Centocor Ortho Biotech Services, LLC, 3; M. DiBonaVentura: Centocor Ortho Biotech Services, LLC, 5; M. Ingham: Centocor Ortho Biotech Services, LLC, 3.

## 52 Baseline Factors Related to Response to Conventional DMARD Treatments

Kimberly L. Sterling1, Gebra Cuyun Carter2, Susan Messing3, George Reed4, Rui Chen5, Kimberly Kaukeinen5, Xin Tu6, David R. Nelson7, Khaled Sarsour8, Ronald A. Cantrell9, Carlos I. Alatorre10 and Jeffrey Greenberg11.

**Background:** Heterogeneity of treatment response exists in rheumatoid arthritis (RA), while there is a lack of understanding of genetic and non-genetic factors that predict treatment response. Identifying baseline factors associated with patient response to RA treatment will assist tailoring therapies for patients. This study aimed to determine non-genetic baseline factors associated with treatment response at one year among RA patients initiating conventional disease-modifying antirheumatic drugs (DMARD) therapy with no previous biologic use.

**Methods:** The study included RA patients previously naïve to biologic therapy who initiated a conventional DMARD and had at least one year of follow-up in the Consortium of Rheumatology Researchers of North America (CORRONA) registry. Treatment response was assessed using the Clinical Disease Activity Index (CDAI) at one year (+3 months), evaluated in both a continuous (change from baseline to endpoint) and categorical (endpoint score ≤19.6 and improvement from baseline > 4.3) manner. The registry allowed for exploration of a broad set of baseline factors including socio-demographics, clinical factors, patient reported measures (i.e. behaviors, comorbidities, function), and prior healthcare use. Multivariate stepwise regression using backward elimination was conducted to determine variables significantly associated (P<0.05) with improvement.

**Summary of the Results:** A total of 1,350 patients met the entry criteria, and 893 (66%) of those had complete data and were included in the multivariate analyses. Of those with complete data, the mean age was 59.7 years, 662 (74%) were female, 750 (84%) were white, and the mean initial CDAI score was 14.5. The following baseline factors were associated with greater CDAI improvement (continuous) (R2=0.39): higher initial CDAI score (β=−0.598, P=0.0001), lower BMI (β=−0.86, P=0.05), lower modified Health Assessment Questionnaire (mHAQ) score (β=−3.738, P=0.0001), no history of infection (β=−1.336, P=0.03), no use of analgesics (β=1.303, P=0.04), and not being disabled (β=−3.839, P=0.0002). For the categorical CDAI improvement outcome, the odds of improvement in disease activity is greater for those at baseline with a higher initial CDAI score (odds ratio [OR]=1.101, P<0.0001), younger in age (OR=0.986, P=0.03), light to no alcohol (OR=0.50, P=0.01), and are not disabled (yes vs no, OR=0.413, P=0.002) (R2=0.22).

**Conclusions:** This study identified that higher baseline disease activity and not being disabled were consistently associated with treatment response (continuous and categorical CDAI). Additional exploration is needed to understand the predictive role of variables such as BMI, physical function, history of infections, and analgesic use, which were inconsistently associated with response; and differences in sets of risk factors between medication classes (e.g. conventional vs biologic DMARDs). With a broad set of predictors, clinicians will be able to tailor treatment based on baseline characteristics to improve patient outcomes.

**Disclosure:** K. L. Sterling: Eli Lilly and Company, 1, 3; G. Cuyun Carter: Eli Lilly and Company, 1, 3; S. Messing: None; G. Reed: Corrona, 5; R. Chen: None; K. Kaukeinen: Corrona, 5; X. Tu: None; D. R. Nelson: Eli Lilly and Company, 1, 3; K. Sarsour: Eli Lilly and Company, 1, 3; R. A. Cantrell: Eli Lilly and Company, 1, 3; C. I. Alatorre: Eli Lilly and Company, 1, 3; J. Greenberg: Corrona, 9.

## 53 Cerebrovascular and Venous Thromboembolic Events Predict Mortality in Rheumatoid Arthritis


**Purpose:** While survival in patients with rheumatoid arthritis (RA) appears to have improved in recent years, RA patients still experience excess mortality compared to patients without RA. The purpose of our study was to examine the potential of cerebrovascular events, venous thromboembolic events, and peripheral arterial events as predictors of mortality in RA patients.

**Methods:** A population-based inception cohort of RA patients who fulfilled 1987 ACR criteria for RA between 1/1/1980 and 12/31/2007 was assembled and followed until death, migration, or the present. The occurrence of cerebrovascular events (hemorrhagic stroke, nonhemorrhagic stroke, transient ischemic attack or amaurosis fugax), venous thromboembolic events (deep venous thrombosis or pulmonary embolism), and peripheral arterial events (abdominal aortic aneurysm, renal artery stenosis, peripheral vascular disease, or arterial thromboembolism), was ascertained by review of the medical record. Cox proportional hazard models were used to examine these noncardiac vascular disease events as predictors of mortality after adjusting for risk factors.

**Results:** The study population included 814 RA patients (mean age [SD] 55.9 [15.7] years; 68% women). The average length of followup was 9.6 [6.9] years. In this cohort, 204 have died. After adjusting for age, sex, calendar year of RA incidence, smoking status, rheumatoid factor positivity, history of alcoholism, obesity, cardiovascular disease (including hospitalized or silent myocardial infarction, heart failure, revascularization, angina, or physician diagnosis of coronary artery disease), renal disease, liver disease, cancer, metastases, dementia, severe extra-articular manifestations (i.e. pleuritis, pericarditis, Felty’s syndrome, RA vasculitis, scoliosis, neuropathy or glomerulonephritis), and steroid use, we found cerebrovascular events (hazard ratio [HR]: 1.60, 95% confidence interval [CI]: 1.06, 2.43; p=0.026) and venous thromboembolic events (HR: 2.52; 95% CI: 1.61, 3.95; p<0.001) were independent predictors of mortality. Additional adjustment for RA therapies (methotrexate, hydroxychloroquine, other disease modifying antirheumatic drugs, and biologics) did not change these results.

**Conclusion:** Our findings suggest that cerebrovascular events and venous thromboembolic events are associated with increased mortality in RA patients. Further study is needed to understand the contribution of these events to the excess mortality in RA patients.

**Disclosure:** A. K. Bacani: None; S. E. Gabriel: None; C. S. Crowson: None; E. L. Matteson: None.
Changes in Corticosteroid Use after DMARD Initiation in Patients with Rheumatoid Arthritis. Vivian K. Kawai1, Carlos Grijalva2, Patrick Arbogast2, Jeffrey R. Curtis2, Daniel Hal Solomon4, Elisabeth Delzell3, Rita Ouellet-Hellstrom2, Ed Mitchell2, C. Michael Stein5 and Marie R. Griffin6. 1Brigham and Women’s Hospital, Boston, MA, 2University of Alabama, 3University of Alabama–Birmingham, Birmingham, AL, 4University of Tennessee Health Science Center, Memphis, TN, 5University of Minnesota, Minneapolis, MN, 6University of Washington, Seattle, WA

Background: Disease modifying anti-rheumatic drugs (DMARDs) and biologics are both used to treat rheumatoid arthritis (RA). DMARDs and biologics have dose-related side effects, and therefore, clinicians strive to minimize their use. Biologic and non-biologic DMARD use reduces RA disease activity and thus would be expected to result in decreased use of corticosteroids. There is, however, little information about the effect of DMARD therapy on corticosteroid use. Thus, we examined the hypothesis that initiation of DMARD therapies decrease corticosteroid use.

Methods: We assembled 4 retrospective cohorts of patients with RA from 1998 to 2005 enrolled in Tennessee’s Medicaid program (TennCare), Kaiser Permanente Northern California (KPNC), Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE), and multi-state Medicaid programs (MAX) and identified 5 mutually exclusive patient groups initiating DMARD regimens: new methotrexate (MTX) without (new MTX) or with (MTX) use of other non-biologic DMARDs in the previous year; new hydroxychloroquine and/or sulfasalazine with use of MTX in the previous year (HCQ/SSZ); new leflunomide with use of MTX in the previous year (LEF); and new TNF-α antagonists. We used McNemar’s test to assess within-person differences in any use of oral corticosteroids (≥1 prescription) during the 6 months before versus 6–12 months after starting one of the study DMARD regimens.

Results: We identified 32476 initiators of study DMARD regimens who had a full year of baseline and one follow-up year of data available: 13% from TennCare, 18% from KPNC, 7% from PACE and 62% from MAX. In all groups, the percentage of users of corticosteroids increased in the 0–6 months before new DMARD initiation compared to the previous 6 months, likely representing worsening of the disease that led to the new DMARD regimen. In most groups, the percentage of users of corticosteroid then decreased significantly by 6 to 12 months after DMARD initiation (Figure 1). Across the 4 datasets, the absolute decrease in % of RA patients using corticosteroids ranged from 8.0% to 10.9% in new MTX users and 9.3% to 12.1% in MTX users (all changes less than 2/3 prescription) during the 6 months before versus 6–12 months after starting one of the study DMARD regimens.

Conclusions: The percentage of patients with RA receiving corticosteroids increased in the 6 months prior to the initiation of a new DMARD regimen and then decreased 6–12 months after initiation. Decreased corticosteroid use may be due to DMARD effectiveness or other reasons for disease improvement.
Conclusion: This group of RA pts treated with RTX in a real life setting gained a mean of 0.22 units in EQ-5D during the first 6 months. Improvement in EQ-5D was associated with clinical response. The data also demonstrated that changes in EQ-5D and SF-6D can differ considerably, and thus the choice of instrument may substantially influence the cost-utility results.

Disclosure: E. Lie: Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 8, Roche, 5; K. Chatzidionysiou: Roche, 5; E. Nasonov: Roche, 5; G. Lukina: Roche, 5; C. Gebay: Roche, 5; K. Pavelka: Roche, 5; D. Nordström: Roche, 5; M. Tomsiè: Roche, 5; M. L. Hetland: Roche, 5; U. Tarp: Roche, 5; P. L. C. M. van Riel: Roche, 5; J. J. Gomez-Reino: Roche, 5; R. Van Vollenhoven: Roche, 5; T. K. Kviens: Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Merck Pharmaceuticals, 5, Pfizer Inc, 5, Roche, 5, UCB, Inc., 5, Wyeth Pharmaceuticals, 5.

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Clinical trials for a direct comparison of efficiency data between TNFα-inhibitors and tocilizumab are not available yet. Meta analysis could demonstrate no differences at least for various TNFα-inhibitors.

Objectives: The aim of this study was to compare the efficacy of TNFα-inhibitors and tocilizumab on the Disease Activity Score (DAS28) in patients with an inadequate response to DMARDs.

Methods: Retrospective, pseudonymous data from RA patients who received their first biologic, were documented. Two cohorts were formed: patients who received a first biologic TNFα-inhibitor (TNF cohort) or tocilizumab (TCZ cohort). Each center documented pseudonymous data of at least 3, maximum of 5 patients per cohort. From each of these groups each center selected the two best patients with justification. DAS28 data at baseline and either 4, 8, 12 or 16 weeks were documented.

Results: Data of 298 patients from 47 centres have been documented. The patients in both cohorts have similar clinical characteristics and can be considered to be representative of RA patients in accordance with the German Registry RABBIT.

After 12 weeks the DAS28 in the TCZ cohort had fallen by 52%, which corresponds to a reduction of 2.6 points. In the cohort of TNF, DAS28 decreased by 38% and an absolute value of 1.8 points. For each of the observation dates was a greater reduction in DAS28 of TCZ cohort compared with the TNF cohort found (see figure).

Summary: In RA patients after failure or inadequate response to a DMARD therapy was a greater improvement in DAS28 with a tocilizumab therapy in comparison with a TNFα-inhibitor therapy during the observation period of 16 weeks.

Disclosure: J. Kaufmann: Roche, 5; E. Feist: Roche, 2, 5, 6; H. Schmidt: Roche, 5; A.-E. Roske: Roche, 3; A. Kiellhorn: Roche, 3.

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Demyelinating Events in Seniors with Rheumatoid Arthritis (RA): A Population-Based Study. Jessica Widdifield, Sasha R. Bernatsky, J. Michael Paterson, Nadia Guarra, Janet E. Pope, J. Carter Thorne, Alfred A. Cividino and Claire Bombardier. 1,3Institute for Clinical Evaluative Science, 2McGill University, Hamilton, ON, Canada, 4Southlake Regional Health Care, Newmarket, ON, Canada, 5St Joseph Health Care London, London, ON, Canada, 6University of Toronto, Toronto, ON, Canada, 7University of Toronto.

Background: Up until recently, multiple sclerosis and other demyelinating syndromes were reported only rarely in rheumatoid arthritis (RA). However, since the introduction of RA therapies targeting tumour necrosis factor (TNF), numerous case reports have arisen in the literature. Currently there are very few cohort-based assessments of the incidence of demyelinating events in RA, or the possible influence of drug exposures. The Ontario Biologics Research Initiative (OBRi) is an innovative undertaking to promote real-world rheumatic drug surveillance. Some of the OBRi analyses make use of Ontario’s administrative healthcare databases. Since universal drug coverage occurs comprehensively for Ontario residents aged ≥65 years, we were able to assess the risk for developing demyelinating events in seniors with RA, and explore for potential drug effects in this sample.

Methods: An RA cohort was assembled from Ontario billing and hospitalization data, 1992–2009. Analyses were limited to subjects aged ≥65 with a diagnosis of RA, who filled at least 1 prescription for an anti-TNF agent, disease-modifying agent (DMARD) or biologic. We excluded any individuals with a diagnosis of a demyelinating event, prior to their entry into the RA cohort. Then, over 1998–2009, we identified all new cases of demyelinating events occurring within this cohort. Our case definition of a demyelinating event was based on one or more hospitalization diagnoses, or at least 2 billing claims diagnoses (at least 8 weeks apart, but within 2 years). Identified cases were matched (on age, sex, and date of cohort entry) to up to 5 controls from the same RA cohort. We calculated the incidence rate of demyelinating events in the cohort of seniors with RA, and described medication use in relationship to these events.

Results: In 85,458 seniors with RA (over 614,915.5 person-years), 51 demyelinating events occurred. This provides an event rate of 8.3 events/100,000 person-years, which is comparable to recent figures for demyelinating events for seniors in the Canadian general population. Biologic exposures were rare in our cohort, and none of the cases of demyelinating events in our RA cohort had been exposed to an anti-TNF agent at the time of the event, or within the 12 months preceding the event. In both cases and controls, the most common medication exposures were NSAIDs/COXIBs, glucocorticosteroids, hydroxychloroquine, and methotrexate.

Conclusions: We provide novel data on the incidence of demyelinating events in a cohort of seniors with RA. The incidence rate of 8.3 new demyelinating events/100,000 patient-years is comparable to recent rates for Canadian seniors. None of these events appeared to have been triggered by anti-TNF drug exposures. Estimating the risk for demyelinating events due to these agents was problematic in our sample, given relatively low drug exposure rates.

Disclosure: J. Widdifield: None; S. R. Bernatsky: None; J. M. Paterson: None; N. Guarra: None; J. E. Pope: None; J. C. Thorne: None; A. A. Cividino: None; C. Bombardier: None.

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Descriptive Epidemiology of Adult Rheumatoid Arthritis in an Insurance Claims Database. Martin M. Crane, Maneesh Juneja, Fayaz A, Aziz, Regina H. Kurrasch, Myron E. Chu, Emilia Quattrocchi, Stephanie Manson and David J. Chang. 1,2GlaxoSmithKline R&D, Research Triangle, NC, 3GlaxoSmithKline R&D, King of Prussia, PA, 4GlaxoSmithKline R&D, United Biosource.

Background: Our goal was to estimate the incidence and prevalence of rheumatoid arthritis (RA) in a US administrative medical claims database. Databases such as this one contain the majority of encounters for any disease that can be defined using an ICD9 code in an insured US population (‘real-world’ practice); however, the major disadvantages are lack of any clinical information, left-censoring (incom-
complete medical history) and right-censoring (truncated follow-up) of data, and under-representation of the elderly due to Medicare coverage at age 65 years.

Methods: The study population was defined as all patients ≥ 18 years having medical information for the entire 4.75-year period of 1-Jan-2004 to 30 Sept-2008 (N=4.65 million) in a health claims database (IMS LifeLink: Health Plan Claims Database, PharMetrics, Inc, Watertown, WA.) Prevalent RA was defined as having at least one occurrence of a code (ICD9 7140–7142) prior to 2006, and one occurrence during 2006, with the two occurrences at least 30 days apart. Incident RA was defined as no RA codes prior to 2006, and two codes at least 30 days apart during the interval 1-Jan-2006 to 31-March 2007. Polyarthritis or undifferentiated arthritis (7149) was not part of the algorithm; however, an “aggressive” incident subset was defined based on having ≥ 8 RA physician visits in the 12 months post diagnosis and no prior 7149 code.

Summary: Prevalence was 0.65% overall (0.92% in females and 0.36% in males) and incidence was 0.07% (0.10% female; 0.04% male). Median age at the occurrence of the first RA code was 57.0 in the incident and 55.0 years in the prevalent patients and, prior to 2006, 47.8% of the latter had received at least one prescription for methotrexate. Other connective tissue diagnoses (based on two occurrences 30 days apart) were present in 7.9% and 9.7% of the incident and prevalent patients respectively. In the 12 months after the first RA visit, 64.0% of incident and 55.1% of prevalent patients were prescribed a non-biologic DMARD and 20.4% and 22.1% were prescribed an anti-TNF. The “aggressive” subset was approximately 11% of all incident patients.

Conclusions: Prevalence rate (0.65%) was lower than in other cohorts (Mayo Clinic – 0.72%; UK Norfolk– ~0.80%) that used ACR diagnostic criteria and fully captured RA in the aged. Incidence (0.07%) was greater than reported in either prior cohort (0.04% and ~0.25% respectively for Mayo Clinic, US and Norfolk, UK). Claims databases probably underestimate the true prevalence of RA but may better reflect the proportion of patients actively seeking care; incidence is likely to be overestimated due to left-censoring.

Disclosure: M. M. Crane: None; M. Juneja: None; F. A. Aziz: None; R. H. Kurrench: None; M. E. Chur: None; I. Quacochi: None; S. Manson: None; D. J. Chang: None.

Different Factors Are Important for RA Patients and Rheumatologists Regarding DMARD Escalation. Laura van Hulst1, Wieetske Kievit2, Piet van Riel1 and Liana Fraenkel3. 1Radboud University Nijmegen Medical Centre, Department of Rheumatology, Nijmegen, The Netherlands, 2Radboud University Nijmegen Medical Centre, Department of Rheumatology, 3Yale University School of Medicine, Department of Medicine, VA Connecticut Healthcare System, Section of Rheumatology.

Background: Studies showed that treatment is not always escalated in RA patients with active disease which might be explained by differences in how rheumatologists and patients prioritize the factors relevant to the decision to escalate DMARDs. We determined which factors are most important to patients and rheumatologists in deciding whether or not to escalate DMARDs and if the importance that patients and rheumatologists assign to these factors differs.

Methods: We administered a Maximum Difference Scaling survey to 106 Dutch rheumatologists and 93 RA patients. The survey was composed out of 58 factors related to DMARD escalation. Respondents were presented with 24 choice tasks. For each choice, composed out of 5 items, respondents were asked to indicate the factor that was most important to them in their decision whether or not to escalate DMARDs. The design of the survey was determined by the Sawtooth Software. Data were analyzed using Hierarchical Bayes modelling resulting into individual item importance scores (IS) ranging from 0 to 100. Independent sample t-tests were performed to compare the importance scores of the top 5 reasons amongst rheumatologists and patients.

Results: Patients’ mean age was 60.2 (sd: 12.6) years, mean disease duration was 12.3 (sd: 12.6) years, and 66% were female. Rheumatologists’ mean age was 47.2 (sd: 9.3) years, 51% were male. The 5 most important reasons to escalate DMARDs for rheumatologists were: number of swollen joints (mean IS: 5.2; sd: 0.4), DAS28 (mean IS: 5.2; sd: 0.5), their global assessment of RA disease activity (mean IS: 5.2; sd: 0.6), worsening of patient’s erosions (mean IS: 5.2; sd: 0.6) and RA disease activity now compared to 3 months ago (mean IS: 5.1; sd: 0.6). For patients, the top 5 was: current level of physical functioning (mean IS: 4.2; sd: 1.2), trust in their rheumatologist (mean IS: 4.0; sd: 1.2), number of painful joints (mean IS: 3.5; sd: 1.2), satisfaction with current DMARDs (mean IS: 3.4; sd: 1.4) and overall general health (mean IS: 3.3; sd: 1.5). Figure 1 shows that these 5 items are approximately twice as important for rheumatologists compared to patients (all statistically significant; p<0.001).

A comparison of the 5 most important factors for patients vs rheumatologists showed that patient’s trust in the rheumatologist (4.0 vs 0.4), number of painful joints (3.5 vs 3.0) and satisfaction with current DMARDs (3.4 vs 2.3) were statistically more important for patients than for rheumatologists, respectively (p<0.001). Physical functioning (4.2 vs 4.4) and current general health (3.3 vs 3.1) were equally important.

Conclusions: Different factors are important for patients and rheumatologists regarding DMARD escalation. Improved communication between physicians and patients regarding the factors influencing decision making might increase the number of RA patients receiving treatment concordant with published guidelines.

Disclosure: L. van Hulst: None; W. Kievit: None; P. van Riel: None; L. Fraenkel: None.

DMARD Use for Rheumatoid Arthritis as Reported in the National Ambulatory Medical Care Survey, 1996–2007. Daniel Hal Solomon1, John Ayajian1, M. Alan Brookhart2, Sebastian Schneeweiss2, Tamara Shayaevich2, Edward H. Yelin3 and Jeffrey N. Katz3. 1Brigham and Women’s Hosp, Boston, MA, 2Brigham and Women’s Hospital, 3University of California, San Francisco, CA, 4University of North Carolina.

Background: There is broad agreement on the value of disease modifying anti-rheumatic drug (DMARD) treatment for rheumatoid arthritis (RA). In fact, a DMARD prescription for patients with RA has become a quality measure for various US-based health insurance programs. There are few population-based estimates of the rates of DMARD use for RA. We studied correlates of DMARD use in a large nationally representative US sample.

Methods: The study database consisted of visits in the US National Ambulatory Medical Care Survey (NAMCS), 1996–2007. Visits for RA were defined based on diagnosis codes reported by the providers.
Providers list all medications, up to 8, used by the patient. Medication lists were checked for DMARDs, synthetic or biologic. Unadjusted and adjusted risk ratios were calculated to assess associations between patient and provider characteristics and receipt of any DMARD, as well as a biologic DMARD. All models accounted for the sampling design of NAMCS, using Rlogist in SUDAAN.

**Results:** From the 317,416 visits recorded in NAMCS over the study period, we identified 859 (0.3%) visits associated with an RA diagnosis. 404 (47%) of these visits had a DMARD noted in the medication list—273 (72%) visits to rheumatologists and 131 of 482 (27%) to non-rheumatologists. Nine percent of RA visits had a biologic DMARD noted. There was no significant trend towards improved DMARD use rates over the 12 year study period. In adjusted models, black race was associated with reduced DMARD use and use of more medications was associated with increased DMARD use (see Table). Visits to non-rheumatologists were associated with a 60% reduction in DMARD use and a 50% reduction for biologic DMARDs.

Table: Risk Ratios for DMARD use in the National Ambulatory Medical Care Survey, 1996–2007

<table>
<thead>
<tr>
<th>Age</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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<tbody>
<tr>
<td>65+</td>
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<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<td>1.0</td>
</tr>
<tr>
<td>45–64y</td>
<td>1.3 (1.1–1.5)</td>
<td>1.1 (0.9–1.4)</td>
<td>1.4 (1.3–1.7)</td>
<td>1.2 (1.0–1.4)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>0–4y</td>
<td>1.3 (1.0–1.6)</td>
<td>1.1 (1.0–1.3)</td>
<td>1.5 (1.1–1.8)</td>
<td>1.3 (1.0–1.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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</tr>
<tr>
<td>Female</td>
<td>0.9 (0.8–1.1)</td>
<td>0.9 (0.8–1.1)</td>
<td>0.9 (0.8–1.2)</td>
<td>1.0 (0.8–1.2)</td>
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<tr>
<td>Race/ethnicity</td>
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<tr>
<td>White, non-Hispanic</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Hispanic</td>
<td>1.1 (0.9–1.4)</td>
<td>1.1 (0.9–1.4)</td>
<td>1.1 (0.9–1.4)</td>
<td>1.0 (0.8–1.4)</td>
<td>1.1 (0.9–1.3)</td>
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<tr>
<td>Black</td>
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<td>0.6 (0.4–1.0)</td>
<td>0.7 (0.5–1.0)</td>
<td>0.7 (0.4–1.2)</td>
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<td>0.7 (0.5–1.1)</td>
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<tr>
<td>Other race, non-Hispanic</td>
<td>0.9 (0.5–1.5)</td>
<td>0.8 (0.5–1.4)</td>
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<tr>
<td># of non-DMARD drugs</td>
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<td></td>
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</tr>
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<td>1-2</td>
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<td>1.8 (1.4–2.4)</td>
<td>1.8 (1.2–2.5)</td>
<td>1.7 (1.3–2.3)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rheumatologist</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>No</td>
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<td>0.5 (0.4–0.6)</td>
<td>0.4 (0.3–0.5)</td>
<td>0.5 (0.4–0.6)</td>
<td>0.4 (0.3–0.5)</td>
<td>0.5 (0.4–0.6)</td>
<td>0.4 (0.3–0.5)</td>
<td>0.5 (0.4–0.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Any DMARD includes methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, cyclosporine, gold preparations, D-penicillamine, azathioprine, cromolyn, salicylamide, indomethacin, rituximab, abatacept, anakinra. Model 1 only includes race/ethnicity and calendar year of NAMCS visit. Model 2 also includes age, gender, and number of drugs. Model 3 includes all of Model 2 variables and rheumatologist.

**Conclusions:** While there is likely misclassification of some visits, the use rate for DMARDs for RA was sub-optimal as reported in NAMCS over the 12-year study period. A visit to a rheumatologist was associated with increased DMARD use or steroids for RA and bilateral joint swelling. Compared to 30,951 women without reported RA, cases were more likely to report childhood food insecurity (13% vs. 8%), younger maternal age (under age 21; 13% vs. 7%), and lower household income and education (chi-squared p-values <0.01). After adjusting for age, significant associations were seen for food insecurity (OR = 1.8; 95% CI 1.2, 2.7), low household education (OR = 1.7; 95% CI 1.0, 2.9; less than high school versus college degree) and young maternal age (OR = 1.8; 95% CI 1.2, 2.9; ages < 21 vs. ≥32 years at birth). Non-significantly elevated ORs were also seen for low household income and younger paternal age. In mutually-adjusted models, significant associations persisted for food insecurity (OR = 1.7) and young maternal age (OR = 1.8), and were not confounded by race/ethnicity.

**Conclusions:** These results suggest lower socioeconomic status in childhood may be related to DMARD-treated RA in women. Few studies have addressed early life factors in RA, but research across a broad spectrum of other diseases supports an important role of early life influences on the immune system in both humans and experimental models. The etiologic pathway linking childhood socioeconomic factors and RA may include maternal and childhood characteristics and environmental exposures, as well as adult socioeconomic status and exposures. Disease severity, reporting, and survival may impact case identification, so these preliminary findings need to be confirmed in incident cases.

**Disclosure:** C. G. Parks: None; A. A. D’Aloisio: None; L. A. DeRoo: None; H. Kirstin: None; D. P. Sandler: None.

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**Effect of Disease-Modifying Anti-Rheumatic Drug (DMARD) Exposure on Head and Neck Cancer in a National Cohort of Veterans with Rheumatoid Arthritis.** Christopher R. Phillips1, Angelique L. Zeringue1, Jay R. McDonald1, Seth A. Eisen2, Liron Caplan3 and Prabha Ranganathan3.

1Division of Infectious Disease, St. Louis Veterans Affairs Medical Center, 2Division of Rheumatology, Washington University School of Medicine, Paducah, KY, 3St. Louis Veterans Affairs Medical Center, 4Univ of CO–Denver Med Sc, Aurora, CO, 5Washington University School of Medicine, St. Louis, MO

**Purpose:** A role for virus-induced malignant transformation has been postulated for primary squamous cell carcinoma of the head and neck (HNC). Previous studies have examined the effect of disease-modifying ant-rheumatic drug (DMARD) exposure on the risk of overall malignancy in patients with rheumatoid arthritis (RA). The effect of tumor necrosis factor (TNF) antagonists on the natural history of HNC in RA, which may be detrimental, given the possible viral etiology of these cancers, has not been explored. Our aim was to determine the effect of exposure to TNF antagonists on HNC in terms of incidence, recurrence, and death from HNC in a national cohort of veterans with RA.

**Methods:** We examined a retrospective cohort of 49,539 patients with an International Classification of Disease, Version 9, (ICD-9) diagnosis of RA and at least one DMARD prescription from the Department of Veterans’ Affairs (VA) national administrative data.
bases enrolled between October 1, 1998 and September 30, 2008. Pharmacy data was obtained from national VA databases. Subjects with an ICD-9 code for HNC after entry into the cohort underwent medical record review to confirm the diagnosis of HNC and RA. Details on HNC diagnosis, recurrence, treatment, HNC-related death, and comorbidities were abstracted.

**Results:** Of 807 patients with an ICD-9 diagnosis of RA and HNC, 255 patients had both RA and HNC after validation by medical record review. Demographic and clinical characteristics of these patients are presented in Table 1. Of these, 65 patients received a TNF antagonist, and 190 received only non-biologic DMARDs. Of the 65 patients exposed to TNF antagonists, 43 were exposed prior to diagnosis of HNC, 20 had continued exposure after diagnosis, and 20 received TNF antagonists only after HNC diagnosis. Of the 255 patients, 201 had HNC remission, 42 had a recurrence or developed a second HNC (at a different site), and 60 had HNC-related death. Of the 40 patients exposed to a TNF antagonist post-HNC diagnosis for whom information was available, 7 developed a recurrence, and 5 had a HNC-related death. The incidence of HNC recurrence and HNC-related death was 27.3 and 18.8 per 1000 patient-years in patients exposed to TNF antagonists after HNC diagnosis compared to 29.3 and 30.3 per 1000 patient-years in patients exposed only to non-biologic DMARDs.

**Conclusion:** Exposure to TNF antagonists does not appear to increase the risk of HNC recurrence or HNC-related death in patients with RA compared to exposure to non-biologic DMARDs. The use of TNF antagonists may be safe in patients with RA and head and neck cancer with careful monitoring.

<table>
<thead>
<tr>
<th>Exposed only to non-biologic DMARDs</th>
<th>Exposed to TNF Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>190</td>
</tr>
<tr>
<td>Age (std dev)</td>
<td>62.9 (9.1)</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>188 (99.0%)</td>
</tr>
<tr>
<td>White race (%)</td>
<td>57 (87.7%)</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>180 (94.7%)</td>
</tr>
<tr>
<td>Alcohol Abuse (%)</td>
<td>132 (69.5%)</td>
</tr>
<tr>
<td>Other Cancers (%)</td>
<td>13 (6.8%)</td>
</tr>
</tbody>
</table>

**Disclosure:** C. R. Phillips: None; A. L. Zeringue: None; J. R. McDonald: None; S. A. Eisen: None; L. Caplan: None; P. Ranganathan: None.

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Elaboration and Validation of a Questionnaire To Assess the Impact of Rheumatoid Arthritis (RA) on Sexuality, with Patient Involvement: QUALISEX. Laure Gossec, Catherine Solano, Simon Paternotte, Catherine Beauvais, Christelle Sordet, Philippe Gaudin and Aleth Perdriger.

**Background:** RA may have consequences on sexual life either through physical or psychological aspects. These consequences are not evaluated, because current questionnaires do not assess the impact of RA on sexuality. A new questionnaire is needed with a particular attention to face validity and phrasing to avoid missing data in this sensitive field of research.

**Objective:** To develop a questionnaire assessing the impact of RA on sexuality (QUALISEX) then to assess the psychometric properties of this questionnaire.

**Methods:** Four-step process. (1) A steering group of 6 patients (5 women, 1 man) with RA, 2 rheumatologists and 1 sexologist elaborated during a one-day focus-group type meeting, an exhaustive list of issues relating to impact of RA on sexuality. Relative weights by importance were obtained for each item. (2) A preliminary questionnaire was developed with input from these patients, with particular attention for phrasing so as to avoid missing data. (3) The questionnaire was assessed by 5 external reviewers (2 physicians, 1 sexologist, 2 allied health professionals), then pre-tested in fact-to-face meetings with 10 patients. (4) The questionnaire was tested for psychometric properties in a longitudinal multi center study (missing data, correlations with other disease aspects, reliability).

**Results:** The list of aspects related to impact on sexuality included 32 aspects, categorised into general aspects (5), psychological issues/self-esteem (9), couple/relationship issues (7), partner/spouse issues (4) and physical issues (7). The list was brought down to 10 items according to the relative weights of the items. A 10-question questionnaire was constructed, with assessment by numeric rating scales (NRS) from 0 (no impact of RA) to 10 (full impact of RA). Preliminary validation was obtained on 53 patients (44 women, mean age 50.7 years; mean disease duration 15.5 years, mean DAS: 3.5). The Qualisex mean score was 3.3±2.5, missing data was acceptable (7 patients, 13%, had more than one missing question). Qualisex results were correlated with RAID (R = 0.65), DAS28 (R = 0.55), fatigue (R = 0.55), pain (0.54) and mHAQ (R = 0.50), (p < 0.001); but not with demographics, depression or coping. Qualisex was reliable in 40 patients: the intra-class correlation coefficient was 0.83 (95% CI: 0.70–0.91).

**Conclusion:** A simple (10 NRS) and valid tool investigating impact of RA on sexuality has been developed with the involvement of patients. This tool could be useful to assess the efficacy of oriented interventions or of biologics.

**Disclosure:** L. Gossec: None; C. Solano; None; S. Paternotte: None; C. Beauvais: None; C. Sordet: None; P. Gaudin: None; A. Perdriger: None.

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**Background:** Past studies have displayed geographical variation in RA incidence, suggesting the influence of environmental factors on RA etiology. We aimed to investigate geographical distribution of risk of developing RA within Stockholm County, Sweden.

**Methods:** We studied spatial variation in incident RA among 1095 incident cases and 1251 controls participating in a Swedish case-control study. The Swedish RA study is a population-based case-control study that has collected information from almost all newly diagnosed RA cases in Stockholm County. Analyses were limited to those subjects living in Stockholm County prior to RA diagnosis for cases and prior to matched date for controls and having geocoded addresses. We used Generalized Additive Models (GAM) to create a risk surface, calculate odds ratios and adjust for potential confounding by smoking and socioeconomic status defined through occupation held at the time of diagnosis. We performed a stratified analysis based on presence/absence of antibodies to citrullinated peptides (ACPA).

**Results:** We found significant spatial variation regarding risk of developing RA in adjusted models (p < 0.05, Figure 1.). The spatial variation decreased for some areas but remained significant after adjusting for potential confounding from smoking and socioeconomic status. The stratified analysis for ACPA positive RA cases (n = 700) showed similar results as for the non-stratified analysis. We did not manage to estimate valid odds ratios for the RA subgroup without ACPA because of few cases (n = 395) in that subgroup.
as retaining baseline employment or gaining employment during the trial. Multivariate logistic regression models were used to evaluate association between FES at the end of the study for pts in each country vs. the other countries as a group. Adjustments were made for age, sex, Health Assessment Questionnaire Disability Index (HAQ DI), total Sharp score (TSS), treatment, and time on treatment. Baseline work-related outcomes were compared by country, including self-reported employed/homemaker status, missed work, % unfit for work at home, hours of missed work, and work productivity measured on a visual analog scale.

Results: Four countries enrolled >25 working pts at baseline: Germany, Australia, the United States (US), and Canada. Approximately half of the pts were employed at baseline in Germany and Canada vs. about two-thirds in Australia and the US. Pts in Germany tended to miss work more often and for more days than pts in other countries. Germany had fewer homemakers vs. other countries. Impacts of RA on performance at work and at home were similar across countries. Multivariate regressions comparing the odds ratios (ORs) for FES by country relative to all other countries showed that residing in the US (OR=2.3, p<0.0001) had an independent effect on FES. Age, male sex, HAQ DI, and TSS were predictors for FES. ADA + MTX vs. MTX alone was a predictor of FES in every country studied, whereas ADA monotherapy was not.

Independent Effect of Country of Residence on Favorable Employment Status

<table>
<thead>
<tr>
<th>Country</th>
<th>Employed Workers</th>
<th>Homemakers</th>
<th>Favorable Employment Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Missed % at Baseline</td>
<td>Unfit % for Work</td>
<td>% at Baseline</td>
</tr>
<tr>
<td>Australia</td>
<td>28</td>
<td>70</td>
<td>46</td>
</tr>
<tr>
<td>Canada</td>
<td>37</td>
<td>49</td>
<td>38</td>
</tr>
<tr>
<td>Germany</td>
<td>42</td>
<td>52</td>
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</tr>
<tr>
<td>United States</td>
<td>130</td>
<td>68</td>
<td>33</td>
</tr>
</tbody>
</table>

Conclusions: Employment status and % missing work, which are driven by health and social policies, differed more than performance at work or at home. Residents of the US were more likely to achieve favorable employment status, perhaps because of greater access to employment, a tendency for employees to miss less work, and greater financial pressure to return to remunerative employment. These results are important in consideration of transferability of data between countries. Patients who received ADA + MTX (vs. MTX) were more likely to achieve favorable employment status in all countries, regardless of health care and social system differences.

Disclosure: R. van Vollenhoven: Abbott Laboratories, 2, 5, Bristol-Myers Squibb, 2, 5, Centocor, Inc., 2, 5, Merck/Schering, 2, 5, Roche, 2, 5; M. Cifaldi: Abbott Laboratories, 1, 3; A. Boonen: Abbott Laboratories, 2, 8, Pfizer Inc, 2, Pfizer/Wyeth, 8; S. Roy: Abbott Laboratories, 1, 3; N. Chen: Abbott Laboratories, 3; V. Strand: Abbott Laboratories, 5, 9, Alder, 5, 9, AstraZeneca, 5, Biogen Idec, 5, 9, Bristol-Myers Squibb, 9, Caniffi Pharma, 5, 9, Chio, 5, 9, Centocor, Inc., 5, 9, Chelsea, 5, 9, Crescendo, 5, 9, Cypress Biosciences, Inc.

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HLA Class II Associations Differ in Indian (Asian) Patients Suffering from RA: Regional Population (Urban and Rural) Surveys Using COPCORD Bhigwan Model. Anuradha Venugopalan1, Arvind Chopra2 and Renu Bharadwaj2. 1BJ Medical College, Pune, India, 2Center for Rheumatic Diseases, Pune, India, 3Center for Rheumatic Diseases

The prevalence of RA and its association with HLA Class II alleles has varied considerably in different ethnic groups and populations. The data from Indian (Asian) studies, largely hospital based, is limited and supports association with HLA DRB1*04. We reported a striking prevalence (0.55%) of RA (ACR) in Bhigwan rural community but association with HLA DRB1*04 alleles was negligible (Chopra. Arthritis Rheum 2000: 7(Suppl)S71). Later, we completed 8150 population survey (house-house) in neighboring urban Pune using a similar COPCORD (Community oriented program for control of Rheumatic Diseases) Bhigwan model and found an unusually low prevalence (0.3%) of RA (Chopra. J Rheumatol 2009: 36:614).

Seropositive RF (nephlometry, cut off 40 IU/ml) and anti-CCP (second generation ELISA, cut off 5 RU/ml) were 45% and 59% in Bhigwan: corresponding 57% and 89% in Pune. There were several other differences found in the results from the surveys. We decided to determine HLA associations of RA in Pune and Bhigwan population based cohorts which included post survey incident cases. After ethic committee approval, consent-
ing patients were bled. 101 rural and 54 urban subjects, ethnically matched and unrelated, were selected as healthy controls. HLA Class II typing for DRB1 (34), DQ (A1=10, B1=21) and DP (A1=5, B1=21) region alleles was performed by Polymerase Chain Reaction using sequence specific primers: number of alleles tested shown in parenthesis.

**Results:** Table 1 shows significant OR of alleles and shared epitope (SE) genotype; 95% confidence interval (CI) is shown in parenthesis. DRB1*04 and *01 were conspicuous by their absence/low frequency. Though not significant, HLA-DQA1*0101 and HLA-DQB1*0601 was more frequent in seropositive (RF) RA patients. None of the alleles tested showed significant association with anti-CCP antibody or articular deformities. None of the haplotype chosen showed significant association with RA or its selected features.

**Conclusions:** This COPCORD study demonstrated HLA Class II including SE associations of RA in an ethnically distinct Indian (Asian) community. To an extent, our small RA sample size is offset by the community study design and population sampling frame. Our results differ from several Cau-
casian and other ethnic studies and support the complex gene-environment interactions in the etiology of RA.

**Disclosure:** A. Venugopalan: None; A. Chopra: None; R. Bharadwaj: None.

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**Hospitalizations Following Heart Failure Diagnosis in Rheumatoid Arthritis Patients.** Cynthia S. Crowson, John M. Davis III, Veronique L. Roger, Eric L. Matteson, Terry M. Therneau and Sherine E. Gabriel. Mayo Clinic, Rochester, MN

**Purpose:** Patients with rheumatoid arthritis (RA) suffer from an excess burden of cardiovascular disease, especially heart failure (HF). In addition, RA patients have a higher mortality rate following HF diagnosis compared to patients without RA. Hospitalizations in patients with HF are a major public health problem. The purpose of our study was to compare the rate of hospitalizations and length of stay after HF diagnosis in patients with and without RA.

**Methods:** A population-based inception cohort of RA subjects who fulfilled 1987 ACR criteria for RA and subsequently developed HF (Framing-
ham diagnostic criteria) between 1-1-1987 and 7-1-2008 was assembled and compared to an age, sex and calendar year matched (3:1) sample of HF patients without RA from the same population. Patients in both groups were followed until death, migration, or 1-1-2010 and all hospital admission and discharge dates were obtained. Person-year methods were used to estimate hospitalization rates. Andersen-Gill models, a modification of Cox models accounting for multiple hospitalizations per patient, were used to compare hospital admission rates between the groups.

**Results:** The study included 548 HF patients (137 with RA and 411 non-RA). Both groups had mean age of 77 (s.d. 10) years with 64% women. The RA patients were followed up for a mean of 3.9 years (528 person-years) after which the majority (83%) were deceased; similarly for the non-RA patients the mean follow-up was 4.8 years (1991 person-years) and 72% died. During this time RA patients experienced a higher rate of hospitalization (1.09 hospitalizations per year compared to 0.88 year for non-RA; p<0.001). Thus, RA patients experienced 20% more hospitalizations (hazard ratio: 1.2; 95% confidence interval: 1.01, 1.5; p=0.038) compared to non-RA patients. In addition the length of stay per hospitalization was on average 0.66 days longer for the RA patients compared to the non-RA patients (p=0.025). Significant independent predictors of hospitalization among patients with RA and HF include male gender, duration of RA, ischemic heart disease, diabetes, comorbidities (cerebrovascular disease, ulcers, renal disease, and cancer). In addition, steroid users were more likely to be hospitalized, even after adjusting for all other significant predictors (hazard ratio: 1.4; 95% CI: 1.03, 1.8; p=0.03).

**Conclusion:** Patients with RA and HF have a higher rate of hospitalization than HF patients without RA and they experience longer hospital stays. A complex constellation of comorbidities and other factors, including steroid use, are associated with the risk of hospitalization for RA patients with HF. More research is needed to improve the outcomes for RA patients with HF.

**Disclosure:** C. S. Crowson: None; J. M. Davis III: None; V. L. Roger: None; E. L. Matteson: None; T. M. Therneau: None; S. E. Gabriel: None.

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**WITHDRAWN**

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**Importance of Changes in People/Patient Reported Outcomes in Rheumatoid Arthritis Patients Treated with Anti-TNF Therapies.** The Example of the RAID (Rheumatoid Arthritis Impact Disease) Score after Etanercept Therapy. Maxime Dougdas2, Mahaut Ripert3, Pascal Hilli-
quen1, Patrice Fardelle1, Olivier Brocq1 and Isabelle Logeat3. 1CH sud Francilien, Corbeil-Essonnes, France, 2Hopital Cochin and University of Paris, Paris, France, 3Hopital Princesse Grace de Monaco, Monaco, 4Pfizer France, la Défense, France, 5University Hospital Amiens, Amiens, France

**Purpose:** OMERACT has emphasized the role of People/Patient Reported Outcomes (PROs) in the evaluation of rheumatic disorders. Under the umbrella of EULAR, a preliminary new score, a patient-derived composite response index, has been elaborated to assess the impact of rheumatoid arthritis (RA), the Rheumatoid Arthritis Impact Disease (RAID) score. The objective was to evaluate the importance of changes in the RAID score in RA patients treated with etanercept.

**Methods:** Study design: Open-label, 12-week duration. Study treatment: etanercept 50 mg once a week. Patients: adult (≥ 18 years old) with active rheumatoid arthritis (DAS ≥ 3.2 and 4 clinical synovitis or CRP > 10 mg/l or ESR > 28 mm/h). Outcome measures: Apart from the RAID score composite index including the 7 following domains: pain, functional disability, fatigue, sleep disturbances, coping and overall assessment of physical and psychological well being, and the DAS, at week 12, the patients were asked whether their condition was acceptable using the PASS (Patient Acceptable Symptom State) question. Statistical analysis: Standardized Response Mean (mean change/SD of change) and its 95% confidence interval (Bootstrap method) were calculated to evaluate the magnitude of changes (a SRM over 0.60 is meaningful). Moreover, the changes in RAID were compared in the groups of patients who achieved or not a PASS at week 12.

**Results:** Of the 87 screened patients, 81 (female: 72%, age: 54±13 years, old disease duration: 8.4±7.1 years) were enrolled. At baseline, patients had active disease (DAS: 5.5±0.8, CRP: 18.9±33.5 mg/l, painful joints: 10.5±5.6 and swollen joints: 8.5±4.1). During the 12 weeks of the study, 9 patients discontinued the treatment. At week 12, 49% the patients had a DAS below or equal to 3.2 (LDA), and 67% considered their condition as acceptable (PASS).

After etanercept therapy, both the RAID score and its different components improved significantly (table). Moreover, the changes in RAID were of much higher magnitude in the group of patients who achieved (versus those who did not) a PASS condition at week 12 (P<0.001).

**Disclosure:** None.

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[Table: Outcome measures and improvement from baseline]
Conclusion: This study 1) confirms the symptomatic efficacy of etanercept in rheumatoid arthritis; 2) demonstrates the clinically relevant sensitivity of change of both the different domains and the composite index (e.g. RAID score) of the PROs’ perceived as important for the patients.

This study was sponsored by Wyeth Pharmaceuticals France (Wyeth has been acquired by Pfizer in October 2009)

Disclosure: M. Dougados: None; M. Ripert: None; P. Hilliquin: None; P. Fardellone: None; O. Broucq: None; I. Logeart: None.

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Inadequate Treatment of Rheumatoid Arthritis (RA), K. Andrew Crichton1, Elliot D. Rosenstein2, Jared S. Young3, Yukiko Kimura3 and Victor S. Sloan4. 1Celgene Corporation, Summit, NJ, 2Hackensack Univ Medical Ctr, Hackensack, NJ, 3Prudential Financial, Newark, NJ, 4Saint Barnabas Medical Center, Livingston, Far Hills, NJ, 5Thomson Reuters, Ann Arbor, MI

Objective: Assess the adequacy of pharmacologic treatment of patients with RA.

Background: Treatment guidelines recommend DMARDs for all RA patients unless contraindicated. We recently assessed DMARD utilization in a large database and determined that RA patients were receiving suboptimal treatment.

Methods: The initial study used a database of Medical and Pharmacy claims for Prudential’s employee and dependent population (PD) (~87,000 lives). Additional data were obtained from Thomson Reuters MarketScan Commercial Database (TRD), which assesses ~18 million lives. Not only is TRD substantially larger than PD, but it has a geographic breakdown reflecting a broader experience outside the northeastern US. There were 849 (PD) and 99,687 (TRD) RA pts defined as: • ≥18 yrs old as of 2007 • Treated for RA in 2007-8, with claims having these ICD9 codes: 714.0, 714.1, 714.2, 714.3, 714.31, 714.32, 714.33, 714.4, 714.81 • Continuously enrolled in a medical and pharmacy plan in 2007-8

DMARDs included small-molecule and biologic, identified by National Drug Code (Pharmacy Claims) and by Health Care Common Procedure Coding System (Medical Claims).

Subgroups were defined as: • Non-compliant (NC): 0 days DMARD supply and 0 office procedures for DMARD administration (infusion) in 1 yr. • Partially compliant (PC): 1 – 269 days DMARD supply or 1 – 11 office DMARD administration in 1 yr. • Fully compliant (FC): ≥ 270 days DMARD supply or ≥ 12 office DMARD administration in 1 yr.

Subgroups were analyzed by demographic factors (age group, geography, job grade and whether subject was seen by a rheumatologist).

Results: <40% of patients received adequate DMARD therapy, as defined by being FC, and >40% were not on any DMARD (NC). There was no clear relation between adequacy of treatment and age (PD & TRD). Slight geographic differences were observed, with better results in the South and Midwest (TRD). Based on earning level, cost did not appear to be a factor in adequacy of treatment. (PD)

57% were seen by a rheumatologist and were more likely to receive adequate treatment, but 25% were not on a DMARD. (PD) The most commonly prescribed traditional, self-administered biologic and IV biologic (adjusted to reflect standard dosing intervals) DMARDs were methotrexate, etanercept, and infliximab respectively. (PD)

Limitations: This is a retrospective, observational study based on administrative data. The diagnosis of RA was not independently adjudicated, but the prevalence is consistent with that observed in the US population (~1%). The consistency of the findings in the 2 databases support our initial findings.

Conclusions: Despite the proven benefits of DMARD therapy and recommended guidelines, most RA patients receive inadequate treatment. Adequacy of treatment does not appear to be influenced by age, income, or geography. As in other studies, RA patients in this population are more likely to receive adequate treatment from a rheumatologist, yet even specialist care remains deficient. Our findings warrant further investigation to determine those factors which impede effective treatment of RA patients.

Disclosure: K. A. Crighton: None; E. D. Rosenstein: None; J. S. Young: None; Y. Kimura: None; V. S. Sloan: None.

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Increased Risk of Total Mortality with Anti-Cyclic Citrullinated Peptide (Anti-CCP) Positivity among Postmenopausal Women Reporting RA. Rachel H. Mackey2, Lewis H. Kuller2, Michael Holers2, Kevin Deane3, Brian Walitt4, Bill Robinson4, Yuefang Chang5, Charles Eaton5, Julia Grillo6, Monica Bertoia7 and Larry W. Moreland8. 1Brown University, 2Georgetown University, 3Stanford University, 4University of Colorado, 5University of Pittsburgh

Background: The objective of this report is to evaluate the relationship between rheumatoid arthritis (RA) and total mortality among postmenopausal women from the Women’s Health Initiative (WHI). Among the 161,808 postmenopausal women aged 50–79 years who enrolled in the Women’s Health Initiative (WHI) at baseline and who have been followed up for ~ ten years, we evaluated total mortality risk for women who reported rheumatoid arthritis (RA) at baseline or followup (n = 16,461 (10.2%) compared with women with no reported RA (n=125,372). A study in 2 WHI centers documented that ~15% of self-reported RA was probable clinical RA, and that self-reported use of disease-modifying anti-rheumatic drugs (DMARDS) improved the positive predictive value of the self-report RA to 62%. To further improved classification we measured anti-cyclic citrullinated peptide (anti-CCP), a sensitive and specific marker of RA.

Methods: We sampled n=9,988 (66%) of the white, black, or Hispanic WHI participants who reported RA at baseline or followup and who had adequate stored serum specimens, and measured anti-CCP via 2nd generation ELISA. Cox proportional hazards regression was used to model the relationships of self-reported RA, DMARD use and anti-CCP positivity to total mortality using followup data through April 2009.

Results: At baseline, mean(SD) age was 64.7 years, 24.5% were African-American and 10% were Hispanic. The overall prevalence of anti-CCP positivity was 8.13% (n=812), but was much higher (~51%) among women reporting both RA at baseline and DMARD use (Table.)

Table: Anti-CCP positivity and age-adjusted mortality rates by self-reported RA and DMARD use

<table>
<thead>
<tr>
<th>Reported RA</th>
<th>DMARD*</th>
<th>Anti-CCP</th>
<th>N</th>
<th>Total Mortality rate/1000 Person Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>At BL (or BL &amp; followup)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>–</td>
<td>4650</td>
<td>95.8%</td>
<td>14.16 (12.50, 16.06)</td>
</tr>
<tr>
<td>n=4855</td>
<td>+</td>
<td>205</td>
<td>4.2%</td>
<td>22.38 (15.12, 33.34)</td>
</tr>
<tr>
<td>Yes</td>
<td>–</td>
<td>395</td>
<td>49.3%</td>
<td>18.35 (10.84, 32.34)</td>
</tr>
<tr>
<td>n=802</td>
<td>+</td>
<td>407</td>
<td>50.7%</td>
<td>25.74 (17.01, 39.23)</td>
</tr>
<tr>
<td>At followup only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>–</td>
<td>3852</td>
<td>96.5%</td>
<td>10.45 (8.91, 12.26)</td>
</tr>
<tr>
<td>n=3992</td>
<td>+</td>
<td>140</td>
<td>3.5%</td>
<td>18.70 (10.65, 33.49)</td>
</tr>
<tr>
<td>Yes</td>
<td>–</td>
<td>279</td>
<td>82.3%</td>
<td>23.14 (13.40, 41.50)</td>
</tr>
<tr>
<td>n=339</td>
<td>+</td>
<td>60</td>
<td>17.7%</td>
<td>32.95 (8.02, 128.14)</td>
</tr>
<tr>
<td>Never</td>
<td>n/a</td>
<td>n/a</td>
<td>128,758</td>
<td>8.39 (8.15, 8.64)</td>
</tr>
</tbody>
</table>

Age-adjusted all-cause mortality rates were strikingly higher among anti-CCP positive women, regardless of reported DMARD use. Compared with women in WHI who never reported RA, total mortality was also substantially elevated among women who reported RA but did not report DMARD use and who were negative for anti-CCP (Table). Among those who reported RA at baseline (excluding women with CVD or cancer at baseline), the hazard ratio (HR)(95% CI) for total mortality was 1.74 (1.33, 2.27) for anti-CCP positivity and 1.90 (1.42, 2.53) for reported DMARD use, in Cox models adjusted for age, white blood cell count (WBC), ethnicity, smoking, waist circumference, hypertension, diabetes, education and hormone therapy. Age, smoking, diabetes and WBC were also significant predictors.

Conclusions: Among postmenopausal women in WHI, anti-CCP positivity was associated with a substantial excess in total mortality compared with women who reported RA but were anti-CCP negative (regardless of self-reported DMARD use), or with women who did not report RA. Evaluation of additional risk markers is in progress to understand the reasons for this anti-CCP -associated excess mortality in older women.

Disclosure: R. H. Mackey: None; L. H. Kuller: None; M. Holers: None; K. Deane: None; B. Walitt: None; B. Robinson: None; Y. Chang: None; C. Eaton: None; L. Walitt: None; M. Bertoia: None; L. W. Moreland: None.
Independent Impact of Statin Discontinuation on Mortality in Patients with Rheumatoid Arthritis: A Population-Based Study. Mary A. De Vera, Hyon K. Choi, Michal Abramowicz, Jacek Kopeć and Diane V. Lacaille. Arthritis Research Centre of Canada, Vancouver, BC, Canada. 2McGill University, Montreal, QC, Canada. 3Univ of British Columbia, Vancouver, BC, Canada.

**Purpose:** Discontinuation of statin therapy is common and associated with increased risk of mortality in the general population, but no corresponding data are available among individuals with rheumatoid arthritis (RA). Since cardiovascular diseases (CVD) are the primary cause of excess mortality in RA, RA-specific data are highly relevant to clinical care of RA. Our objective was to evaluate the impact of statin discontinuation on risk of mortality in individuals with RA.

**Methods:** We conducted a population-based cohort study of RA patients with incident statin use followed from May 1996 to March 2006 with administrative health data. Exposure was statin discontinuation for ≥3 months at any time during follow-up, measured both as a categorical (y/n) and continuous (time since discontinuation) variable. Primary outcome was death due to all CVD and secondary outcome was death due to all causes. We used Cox’s proportional hazards analyses, modeling statin discontinuation as a time-dependent dichotomous variable updated every month and in separate analyses, as a continuous time-dependent variable that increased with every month since discontinuation. Factors known to influence statin discontinuation, CVD, or mortality were considered as covariates, including age, gender, comorbidities (e.g., coronary heart disease, cerebrovascular disease, diabetes, malignancy, infections, chronic obstructive pulmonary disease, gastrointestinal diseases, renal failure, angina, use of diabetes, hypertension, and congestive heart failure medications), and use of medications known to influence cardiac risk (hormone replacement therapy, anticoagulants), all measured at baseline. As well, markers of RA severity (RA medication use [DMARDs, glucocorticosteroids, NSAIDs, methotrexate] and rate of RA-related medical visits) were included as time-dependent covariates. Established risk factors for mortality in RA (e.g., AMI, malignancy) were forced into multivariable models and for putative risk factors, a forward selection procedure with p < 0.20 criterion for entry, was used.

**Results:** The cohort of RA patients with incident statin use included 4,102 individuals with 16,144 person-years of follow-up (60% females; mean age 66 years). We documented 467 deaths overall with 198 due to CVD. Statin discontinuation was associated with a 60% increased risk of CVD mortality (adjusted hazard ratio [HR] = 1.60 [95%CI: 1.15–2.23]). When we modeled statin discontinuation as a continuous time-dependent variable, we found that with each additional month of discontinuation, the risk of CVD mortality was increased by 0.4% (adjusted HR = 1.004 [95%CI: 1.001–1.016]). We found similar increased risks associated with statin discontinuation in analyses of all cause mortality outcomes (adjusted HR [statin discontinuation as a dichotomous variable]: 1.79 [95%CI: 1.46–2.19]; adjusted HR [statin discontinuation as continuous variable]: 1.010; 95%CI: 1.002–1.015]).

**Conclusion:** These population-based data indicate that RA patients who discontinue statins have a higher risk of death from cardiovascular diseases and from all causes. Findings emphasize the importance of compliance with statin therapy in RA.

Disclosure: D. Aletaha None; H. K. Choi: None; M. Abramowicz: None; J. Kopeć None; D. V. Lacaille None.

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**Large Discrepancy between Expected and Observed Ratios of Biologic Treated Rheumatoid Arthritis Patients Also Compliant on DMARDs.** Denis Choquette’, Mark Arundine’ and Olivier Thomas’. Mississauga, ON, Canada. Institut de Rhumatologie de Montréal, Montreal, QC, Canada.

**Objective:** It is common for most Canadian Rheumatologists to prescribe a biologic in combination with one or more DMARDs to 80–90% of their RA patients. Despite this practise, databases linked to drug plans indicate that RA patients receiving biologics do not fulfill DMARD scripts, and especially methotrexate at the same level as is prescribed by physicians. This study, examines this discrepancy more closely and suggests potential causal etiologies.

**Methods:** Biologic and DMARD concomitant therapy based on actual patient purchases was examined by tracking 6,744 anonymous patient records from public and private drug plans in Quebec and Ontario through a licensed 3rd party. A treatment algorithm criterion was applied to isolate RA patients. All patients who purchased a biologic for the treatment of RA over a 1 month period were monitored to determine if they filled prescriptions for DMARDs within a period of 90 days before and 90 days after they purchased their biologic. The month of September 2009 was randomly selected and deemed as a typical representative month. Each patient was linked in the public or private system with a unique identifier so that their acquisition of all drugs through their drug plan could be monitored over time to determine the relative prevalence of DMARDs and biologic monotherapy vs. combination therapy with a DMARD based on drug purchases.

**Results:** Among patients on their first biologic for more than 6 months, 45% did not purchase a DMARD. Likewise, 41% of patients who were on biologic therapy for more than 24 months did not purchase a DMARD. For patients on their 2nd biologic, rates of patients who did not purchase a DMARD ranged from 36% to 38% over the same time period. Furthermore, the proportion of patients on their first biologic who did not purchase methotrexate ranged from 58% for those on biologic therapy for more than 6 months to 54% for those on therapy for more than 24 months.

**Conclusion:** Despite what is prescribed by physicians, the data suggests that many RA biologic patients do not comply with taking DMARDs as
directed. This is especially evident for those patients prescribed methotrexate. These findings also suggest that approximately half of RA biologic patient's studied in this cohort failed to adhere to expected treatment regimes. This rate is inconsistent with the majority of physician's intended treatment regimens. Reasons for this discrepancy include efficacy and safety elements. Closer examination of actual combination therapy, compliance rates and therapy discontinuation at the patient level warrants further investigation.

**Disclosure:** D. Choquette: Hoffmann-La Roche, Inc., 2, 8, 9; M. Arundine: Hoffmann-La Roche, Inc., 3; O. Thomas: Hoffmann-La Roche, Inc., 3.

**Leflunomide and the Risk of Hepatotoxicity: A Review of Post-Marketing Data**

**Authors:** Jane L. Gilbert1, Kate Gelperin1, Joanne Lee2, Poonam Mishra2, Lauren Cho2, Allen Brinker2, David Graham2, Robert Boucher2, Mark Avigan2 and John Senior2. 1FDA, Washington, DC, 2FDA

**Background:** This abstract summarizes a review undertaken by FDA to evaluate the risk of hepatotoxicity in patients receiving leflunomide (LEF). LEF is an oral, disease-modifying, antirheumatic drug (DMARD), approved in the US for the treatment of rheumatoid arthritis (RA) in 1998. ACR guidelines (2008) recommend “leflunomide monotherapy for RA patients with all disease durations and for all degrees of disease activity.” Combination therapy with methotrexate (MTX) is “recommended for patients with intermediate or longer disease duration. . . as long as disease activity is high.” The potential for LEF hepatotoxicity was noted at the time of product approval and a bolded warning describing severe liver injury with LEF as well as a recommendation to monitor serum transaminase levels every 6–8 weeks was added to the U.S. label in 2003.

**Methods:** Using pre-specified criteria, a comprehensive search of FDA’s Adverse Event Reporting System (AERS) database was undertaken to identify post-marketing cases (US and foreign) of serious liver injury and acute liver failure (ALF) from 8/25/2002 through 5/1/2009. Additional cases reported to the Drug-Induced Liver Injury Network (DILIN), a multicentre network established to assess liver injury due to medications, were also retrieved. A multidisciplinary group of experts from the FDA, including hepatologists, adjudicated these cases based on DILIN criteria. Cases involving death and ALF were further analyzed for common features.

**Results:** A total of 111 reports were identified (106 from AERS and 5 from DILIN). Many of these reports (62) were either duplicates, had insufficient information or were clearly unrelated to LEF. The remaining 49 reports (including 27 describing ALF) met criteria for the DILIN definition of severe liver injury, formed the case series, and were adjudicated. Based upon DILIN causality criteria, adjudicators classified all 27 cases of ALF (including 12 deaths and 5 liver transplants) as at least possibly associated with leflunomide. Case series analysis revealed that LEF hepatotoxicity may be rapid in onset and progress to ALF. This contrasts with MTX hepatotoxicity which usually involves chronic fibrosis or cirrhosis. Among the cases resulting in death or transplant, 88% (15 of 17) of patients were using concomitant hepatotoxic medications such as MTX, TNF inhibitors or statins.

**Conclusion:** Leflunomide is approved in the US (for RA) and Europe (RA and psoriatic arthritis). It is recommended by the ACR for mono- or combination therapy. Our review shows a LEF risk for hepatotoxicity which may present with rapid onset. The review further points to specific risk factors: concomitant hepatotoxic medication and pre-existing liver disease. Appropriate patient selection and careful monitoring may mitigate this risk.

**Disclosure:** J. L. Gilbert: None; K. Gelperin: None; J. Lee: None; P. Mishra: None; L. Choi: None; A. Brinker: None; D. Graham: None; R. Boucher: None; M. Avigan: None; J. Senior: None.

**Meta-Analysis and Biologics—Comparing Apples to Apples: An Example Using Radiographic Outcomes in Rheumatoid Arthritis**

**Authors:** Mike Ingham1 and Chureen Carter2. 1Centocor Ortho Biotech Services, LLC, Horsham, PA, 2Centocor Ortho Biotech Services, LLC

**Background:** Many meta-analyses exist for biologics in rheumatoid arthritis (RA). Most have focused on signs and symptoms. Few have attempted to look at radiographic outcomes of disease progression.

**Methods:** This study used meta-analytic techniques to compare adalimumab (ADA), certolizumab (CER), etanercept (ETA) and infliximab (IFX). Randomized controlled trials (RCTs) of biologics in active RA, added to methotrexate, reporting 1 year radiographic outcomes, Erosion scores (ES), Joint Space Narrowing scores (JSN) and modifications of Total Sharp scores (mTSS) were included. Sources for trials were drawn from recent Cochrane and Agency for Health Care Research and Quality publications. Moderator variables related to outcome were created from trial baseline patient population results, with dichotomization of continuous variables to allow for simplified stratification of trials. Data were split into higher or lower dose intensity, based on trial arms. Primary outcomes included differences in mean change scores from baseline of mTSS between active and control groups (MD). Due to varying versions of mTSS used in trials, standardized mean differences (SMD) were also analyzed (standardized by change scores' standard deviation). Negative results favor the biologic.

**Results:** Four trials met inclusion criteria (one for each product). For higher dose intensity, mTSS MD [95% confidence limits] were ADA: –2.60 [–3.82 to –1.38]; CER: –2.60 [–2.74 to –2.46]; ETA: –3.34 [–3.46 to –3.22]; IFX: –6.80 [–9.26 to –4.34]; SMD were: –0.44, –3.10, –5.24, –0.92 respectively. Simultaneous inclusion of all four trials however was complicated by observed differences in baseline moderator variables, confirmed by an I² heterogeneity score of 99.5 out of 100. Stratifying the ADA/IFX separately from the ETA/CER trials optimized reduction in the I² statistic vs. all four trials together. Within these strata, for SMD comparisons, IFX demonstrated twice the effect size of ADA, while ETA was 1.7 times that of CER.

**Conclusion:** Meta-analytic comparisons that do not consider more in depth RCT inclusion criteria risk ignoring important baseline population differences that might mask clinically meaningful results or lead to inaccurate conclusions. In the absence of access to patient level data, this type of stratification may prove useful for reducing heterogeneity. Confirmation using other outcomes and larger numbers of trials, while keeping treatment constant, is warranted.

**Disclosure:** M. Ingham: Centocor Ortho Biotech Services, LLC, 3; C. Carter: Centocor Ortho Biotech Services, LLC, 3.
lations and blood testing to investigate the relationships of genetic and environmental factors to RA-related autoimmunity. From this cohort, we selected 113 FDRs who had been positive for any of 5 RA-associated autoantibodies (Ab): rheumatoid factor (RF), RF isotypes— IgM, IgG, or IgA, or anti-cyclic citrullinated peptide (anti-CCP) on at least one of their visits. Additionally, we selected 100 FDRs (frequency-matched on age, sex, and ethnicity) who had never been autoantibody positive. The study population had a mean age of 50 years, was 75% female, and 83% non-Hispanic white. A panel of 27 cytokines/chemokines was measured using a bead-based assay in serum obtained from 397 visits of these FDRs. HeteroBlock™ was used to minimize effects of RF in these samples. For analyses, cytokine/chemokine levels were log transformed, and the relationship between cytokine/chemokine levels (as continuous variables) and autoantibody positivity (dichotomous, either RF alone or combination of RF isotypes with or without anti-CCP positivity) was calculated using a non-linear mixed model [SAS PROC NLMIXED]. Results are reported as odds ratios (OR), which were calculated to indicate change in risk of RA-related autoimmunity for every 1 standard deviation increase in cytokine/chemokine levels.

Results: Of 397 visits, 73 were positive for RF, and 50 were positive for the high-risk autoantibody profile. Eleven cytokines/chemokines were significantly associated with either RF or the high-risk autoantibody profile or both in RA-free FDRs, as summarized in Table 1. For example, for each standard deviation increase in IL-6 levels, there is an ~3-fold increased risk of RF and a 67% increased risk of the high-risk autoantibody profile. Cytokines/chemokines that were not associated with autoantibody positivity in this dataset include: PDGF, IL-1β, -1ra, -7, -8, -13, -15, -17, FGF-basic, G-CSF, MCP-1-1MCAF, MIP-1α, -1β, RANTES, TNF-α, and VEGF.

Table 1. Summary of Significant Odds Ratios (OR) for Positivity for Either Rheumatoid Factor or the High-Risk Autoantibody Profile (Bold ORs indicate p<0.05)

<table>
<thead>
<tr>
<th>Cytokine/Chemokine</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>1.20 (0.67, 2.16)</td>
<td>1.62 (1.06, 2.49)</td>
</tr>
<tr>
<td>IL-4</td>
<td>2.44 (1.09, 5.44)</td>
<td>1.37 (0.86, 2.18)</td>
</tr>
<tr>
<td>IL-5</td>
<td>2.92 (1.19, 7.18)</td>
<td>1.39 (0.89, 2.17)</td>
</tr>
<tr>
<td>IL-6</td>
<td>2.89 (1.34, 6.22)</td>
<td>1.67 (1.08, 2.58)</td>
</tr>
<tr>
<td>IL-9</td>
<td>2.51 (1.17, 5.41)</td>
<td>2.56 (1.47, 4.44)</td>
</tr>
<tr>
<td>IL-10</td>
<td>2.46 (1.10, 5.52)</td>
<td>1.64 (1.05, 2.58)</td>
</tr>
<tr>
<td>IL-12</td>
<td>2.68 (1.21, 5.93)</td>
<td>1.71 (1.08, 2.71)</td>
</tr>
<tr>
<td>Eotaxin</td>
<td>3.35 (1.31, 8.54)</td>
<td>1.28 (0.78, 2.13)</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>3.36 (1.48, 7.65)</td>
<td>1.68 (1.03, 2.74)</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>3.12 (1.30, 7.50)</td>
<td>1.39 (0.88, 2.18)</td>
</tr>
<tr>
<td>IP-10</td>
<td>2.07 (1.01, 4.24)</td>
<td>1.42 (0.87, 2.32)</td>
</tr>
</tbody>
</table>

* This autoantibody profile has been shown in prior work using pre-clinical RA samples to be >96% specific for future RA

Conclusion: Increases in multiple cytokines are associated with RA-related autoantibody positivity in FDRs, suggesting that autoantibodies are associated with evidence for circulating inflammation in subjects without clinically apparent RA. Further longitudinal study is needed to determine the significance of these findings in relation to the natural history of RA-related autoimmunity and RA.

Disclosure: J. M. Hughes-Austin: None; K. D. Deane: None; L. Derber: None; J. R. Kolfenbach: None; M. Weisman: None; J. Buchner: None; J. R. O'Dell: None; T. R. Mikuls: None; P. K. Gregersen: None; R. M. Keating: None; V. Holers: None; L. Derber: None; J. Norris: None.


Purpose: Patients with rheumatoid arthritis (RA) suffer from an excess burden of cardiovascular disease, but little is known about the incidence of noncardiac vascular disease in RA patients. The purpose of our study was to examine whether the incidence of venous thromboembolic events and other noncardiac vascular disease events has changed in recent years among RA patients and to compare the incidence to that in a non-RA cohort.

Methods: A population-based inception cohort of RA patients who fulfilled 1987 ACR criteria for RA between 1/1/1980 and 12/31/2007 and a cohort of non-RA subjects from the same underlying population were assembled and followed until death, migration, or the present. The occurrence of venous thromboembolic events (deep venous thrombosis or pulmonary embolism), cerebrovascular events (hemorrhagic stroke, nonhemorrhagic stroke, transient ischemic attack or amaurosis fugax), and peripheral arterial events (abdominal aortic aneurysm, renal artery stenosis, peripheral vascular disease, or arterial thromboembolism), was ascertained by review of the medical record. Cox proportional hazard models were used to compare development of noncardiac vascular disease in RA subjects diagnosed in 1980–1994 to those diagnosed in 1995–2007 and to compare RA patients diagnosed in 1995–2007 to the non-RA comparison cohort.

Results: The study included 814 RA patients (mean age [SD] 55.9 [15.7] years; 68% women). The average length of follow-up was 9.6 years [SD 6.9] and 66% were rheumatoid factor positive. Among RA patients, the incidence of venous thromboembolic events was more than 3-fold higher in the 1995–2007 time period compared to the 1980–1994 time period (cumulative incidence [±SE] 7.6 ± 1.9 vs 2.4 ± 0.9, respectively; p=0.004). The incidence of cerebrovascular events was similar in the 1995–2007 time period compared to the 1980–1994 time period (cumulative incidence [±SE] 4.4 ± 1.3 vs 3.3 ± 1.0, respectively; p=0.52), as was the incidence of peripheral arterial events (cumulative incidence [±SE] 3.5 ± 1.1 vs 3.7 ± 1.1, respectively; p=0.81).

Patients diagnosed with RA in 1995–2007 were compared to non-RA subjects of similar age and sex (mean age [SD] 55.6 [15.5] years; 69% women). RA patients had a higher incidence of venous thromboembolic events compared to non-RA subjects (cumulative incidence [±SE] 7.6 ± 1.9 vs 3.1 ± 1.2, respectively; p=0.003). The incidence of cerebrovascular events was similar between RA patients and non-RA subjects (cumulative incidence [±SE] 4.4 ± 1.3 vs 4.6 ± 1.6, respectively; p=0.38), as was the incidence of peripheral arterial events (cumulative incidence [±SE] 3.5 ± 1.1 vs 4.1 ± 1.6, respectively; p=0.54).

Conclusion: The incidence of venous thromboembolic events appears to have increased over time among RA patients and is increased in RA patients compared to non-RA subjects. The incidence of cerebrovascular events and peripheral disease events was similar over time among RA patients and was similar in RA patients compared to non-RA subjects. Further investigation is needed to explore the reasons for the increased incidence of venous thromboembolic events among RA patients.

Disclosure: A. K. Bacani: None; S. E. Gabriel: None; C. S. Crowson: None; E. L. Matteson: None.

79 Perception of RA Disease Activity by Patients and Physicians: Reasons for and Estimators of Discrepancies. Paul Stuebic, Josef S. Smolen and Daniel Aletaha. Medical University of Vienna, Austria

Background: In clinical practice, the perception of disease activity in rheumatoid arthritis (RA) often differs between physicians and patients. These discrepancies may impact the patient-physician relationship. It is not completely clear in what proportion of patients the perception is different, and why. We aimed to investigate this discordant perception in more detail.

Methods: We identified RA patients from an observational, prospective RA outpatient database, and obtained visual analogue scores (VAS) for global disease activity perception by the patients (PGA) and evaluators (EGA). Patients were divided into tertiles by PGA and by EGA, and the groups were then cross-tabulated. We explored the other RA core set variables in patient groups, formed according to concordant (tertile of PGA equivalent to tertile of EGA) or discordant tertiles (differing tertiles: PGA > EGA or EGA > PGA). For statistical comparisons, Mann-Whitney-U-Test was performed.

Results: Of the 302 RA patients (81% women, 61% rheumatoid factor positive, mean disease duration: 10.1 years). 49.3% fell into concordant tertiles (PGA and EGA) or discordant tertiles (PGA > EGA or EGA > PGA). For statistical comparisons, Mann-Whitney-U-Test was performed.

Given the impact of swelling for EGA and pain for PGA, we calculated the SJC/TJC ratio as an estimate for this discrepancy, finding good correlation with the additional variable “EGA minus PGA” (r=0.399, p=0.0001, Spearman-rho) and association with the respective tertiles (Figure). A SJC/TJC ratio of 0.6–0.7 appears associated with a balanced perception by patients and evaluators, irrespective of disease activity (Figure).
Permanent Working Disability Caused by Rheumatoid Arthritis Is Declining, Partly Due to Use of TNF-Inhibitors—Results from a Nationwide Finnish Register in 2000–2007.

Background: Rheumatoid arthritis (RA) often leads to premature retirement. Globally, the treatment of RA has intensified, but whether this active strategy helps preserving the patients’ working ability, is unclear.

Methods: From a nationwide register maintained by The Finnish Social Insurance Institution (SII) we collected information on sex, age, and date of medicine reimbursement decisions indicating the date of diagnosis (index date), of all new, not-retired, RA patients during the time period from 1 Jan 2000 to 31 Dec 2007. Patient cohorts were analyzed in 2-year time periods (2000-01, 2002-03, 2004-05, 2006-07) and work disability pensions due to RA up to 31 Dec 2008 were identified. Initial disease modifying antirheumatic drugs (DMARDs) during the first 3 months after the index day, as well as the initiation of etanercept or adalimumab at any time point were elucidated.

Results: A total of 7,909 (73% female, 61% RF-positive) patients were identified. During the first 2 years after the index day, the incidence of RA related work disability pensions were 8.8%, 9.3%, 7.2%, and 4.7% in the year cohorts 2000-01, 2002-03, 2004-05, and 2006-07, respectively (age, sex, and RF adjusted p<0.001 for linearity) (Figure). In a Cox multivariate analysis for the 8-year follow up, the year cohort (HR 0.67, 95% CI 0.64 to 0.72), higher age (HR 1.06, 95% CI 1.05 to 1.07), male gender (HR 1.53, 95% CI 1.33 to 1.75), and the presence of RF (HR 1.17, 95% CI 1.01 to 1.34) were related to premature retirements.

Throughout the follow-up, the use of single-DMARD treatment during the first 3 months decreased from 57 to 35%, and that of combination-DMARDs increased from 36 to 61%. The use of methotrexate, either alone or in combinations, increased from 31 to 67%. However, presumably due to the confounding effect of indication, in seronegative patients, the ones with more active initial treatments (methotrexate, combination-DMARDs) had a higher risk of disability pensions than the ones with less active treatments during the present millennium, parallel to increasingly active treatment strategies, the frequency of disability pensions in early RA has declined. Even though we failed to confirm any protective effect of aggressive initial DMARD treatment, the commencement of adalimumab or etanercept seemed to help preserve the patients’ working capacity.

Conclusions: During the present millennium, parallel to increasingly active treatment strategies, the frequency of disability pensions in early RA has declined. Even though we failed to confirm any protective effect of aggressive initial DMARD treatment, the commencement of adalimumab or etanercept seemed to help preserve the patients’ working capacity.

Disclosure: P. Studenic: None; J. S. Smolen: None; D. Aletaha: None.

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Prescription Patterns in Pregnant Women with Rheumatoid Arthritis, Bindie Kurita1, Sonia Hernandez-Diaz2, Jun Liu3, Gregory Daniel4 and Daniel Hal Solomon5.1 Brigham and Women’s Hospital, Boston, MA, 2Brigham and Women’s Hospital, 3Harvard School of Public Health, Brookline, MA, 4Harvard School of Public Health, 5HealthCore Inc., Wilmington, DE.

Background: Little is known about how pregnant women with RA are treated in routine clinical practice. Our aim was to characterize the frequency and type of therapy prescribed during pregnancy to women with RA.

Methods: We conducted a cohort study using data from a U.S. commercial insurance plan from 2002–2008. We included women aged 18–45 years with RA (≥ 2 ICD-9 diagnoses) who had pregnancies ending in delivery (1° delivery, 2 ICD-9 diagnoses) who had pregnancies ending in delivery (1° analysis) or abortion, identified by diagnostic/procedural codes. The estimated date of conception (EDC) was calculated as date of delivery - 270 days. We examined the use of therapeutic drug classes, including NSAID/coxibs, glucocorticoids (GCs), non-biologic DMARD and biologic DMARD during pregnancy trimesters and two 90-day periods prior to pregnancy. Drugs were categorized by the U.S. FDA pregnancy risk system. We defined exposure as the first filling of a drug from each class during each of the 90-day periods. We analyzed the distribution of drugs used for RA in the peri-partum period. Differences in the distribution between periods, and between women with deliveries compared to abortions, were determined by chi-square tests. Annual exposure, by year of EDC, for deliveries, to each therapeutic class was also calculated. Drug use was evaluated in the 180 days prior to abortion date due to risk of misclassification.

Conclusions: During the present millennium, parallel to increasingly active treatment strategies, the frequency of disability pensions in early RA has declined. Even though we failed to confirm any protective effect of aggressive initial DMARD treatment, the commencement of adalimumab or etanercept seemed to help preserve the patients’ working capacity.


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S32
Results: 393 pregnancies were identified among 34,169 women. The mean age for women with deliveries was 32.8 ± 4.8 years and for abortions was 33.7 ± 5.3 years. More than 1/3 of women used ≥ 1 DMARD in the pre-conception period (Table). During pregnancy, 64 women were dispensed ≥ 1 DMARD and the proportion of use significantly declined from the first to third trimester (p = 0.03). More women were prescribed GCs during pregnancy than before pregnancy. In contrast, use of NSAID/corticoids, any DMARD, combined use of DMARD or exposure to category D/X medications was significantly lower compared to pre-pregnancy use (p < 0.015). Use of biologics occurred in ~ 13% of women during pregnancy. GCs were the most prescribed therapy in each of the study years, and the pattern of exposure to other classes remained relatively constant over time. Women who experienced abortions were more frequently exposed to each therapeutic class in the 180 days before abortion, compared to deliveries, except for GCs or biologics (p < 0.05). Dispensing of category D/X medications was also higher in women with abortions compared to deliveries, and primarily involved methotrexate (p < 0.01).

Summary:

- Maternal:
  - Methotrexate
  - Nimesulide (CDK)
  - Combination of prednisolone and biologics
- Any DMARD used
- Duration of treatment

Conclusions: Our results suggest that continued efforts directed at counseling women on the risk of DMARD use during pregnancy are warranted. 55.5% of pregnant women used DMARD during pregnancy. The proportion of use significantly declined from the first to third trimester (p = 0.03). More women were prescribed GCs during pregnancy than before pregnancy. In contrast, use of NSAID/corticoids, any DMARD, combined use of DMARD or exposure to category D/X medications was significantly lower compared to pre-pregnancy use (p < 0.015). Use of biologics occurred in ~ 13% of women during pregnancy. GCs were the most prescribed therapy in each of the study years, and the pattern of exposure to other classes remained relatively constant over time. Women who experienced abortions were more frequently exposed to each therapeutic class in the 180 days before abortion, compared to deliveries, except for GCs or biologics (p < 0.05). Dispensing of category D/X medications was also higher in women with abortions compared to deliveries, and primarily involved methotrexate (p < 0.01).

Table: Treatment patterns and changes in disease activity and health status during pregnancy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Initiation</th>
<th>Maintenance</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Yes</td>
<td>Yes</td>
<td>Randomized</td>
<td>12 months</td>
</tr>
<tr>
<td>Nimesulide (CDK)</td>
<td>Yes</td>
<td>No</td>
<td>Open-label</td>
<td>6 months</td>
</tr>
<tr>
<td>Combination of prednisolone and biologics</td>
<td>Yes</td>
<td>Yes</td>
<td>Open-label</td>
<td>12 months</td>
</tr>
<tr>
<td>Any DMARD used</td>
<td>Yes</td>
<td>Yes</td>
<td>Open-label</td>
<td>12 months</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>3 months</td>
<td>6 months</td>
<td>Placebo-controlled</td>
<td>12 months</td>
</tr>
</tbody>
</table>

Disclosure: B. Kuriya: None; S. Hernandez-Diaz: Novartis Pharmaceuticals Corporation, 2; Pfizer Inc, 2; J. Liu: None; G. Daniel: None; D. H. Solomon: Abbott Laboratories, 2; Pfizer Inc, 2, Bristol-Myers Squibb, 2.

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Respiratory Cause Mortality Was Greater in 54 Incident Rheumatoid Arthritis (RA) Patients Than 204 Community-Based, Non-RA Matched Cohort Controls (CN). Alfonse T. Masi and Jean C. Aldag. University of Illinois College of Medicine at Peoria, Peoria, IL.

Purpose: Mortality from interstitial lung disease (ILD) is known to be increased in RA (Bongartz T et al. A&R 2010; 62: 1583-91). This study aimed to analyze non-malignant respiratory cause mortality in incident RA cases from a prospective, community-based cohort, and as compared to matched non-RA CN.

Design: The 54 cases studied had onset of ACR-positive RA, 3 to 20 (mean 12) years, after entry into the cohort (n = 21,061 adults) in 1974. RA cases were matched by age, gender, and race (all Caucasian) at baseline with 204 non-RA CN. All study subjects (n = 258) had baseline (1974) data on: demographic variables; cigarette smoking, and immunological testing on stored (−70°C) sera. A novel baseline biomarker predicted cohort mortality (data separately submitted), consisting of upper quartile values of acute-phase reactant fractions in stored (−70°C) sera. A novel baseline biomarker predicted cohort mortality (data separately submitted), consisting of upper quartile values of acute-phase reactant fractions in stored (−70°C) sera.

Results: Deaths from non-malignant respiratory causes (ICD-9: 460–519 & ICD-10: J00-J99) were analyzed, over the period 1992–2009. Hazard ratio (HR) for respiratory cause mortality was estimated using Cox regression models, adjusting for covariates.

Results: Deaths from non-malignant respiratory causes occurred in 8 (15%) of 54 RA vs 10 (5%) of 204 non-RA, OR = 3.37 (95% CI 1.30 – 8.79), p = 0.017. None of the 8 RA had deceased from chronic airway disease (ICD-9: 496 or ICD-10: J44.9) or pulmonary edema (ICD-9: 518.4 or ICD-10: J11), unlike 5 of the 10 respiratory deaths in non-RA CN (p = 0.036). Respiratory deaths occurred in 4 (25%) of 18 male RA, and 4 (11%) of 36 female RA. Three of the 4 males who had respiratory deaths were treated in 1995 with oral methotrexate (MTX) doses of ≥20 mg weekly and with prednisone (Pred) doses of 10+ mg daily during the remaining 14 male RA (p = 0.019). Only 2 of 4 female RA respiratory deaths had received low-dose MTX (5 mg wk) and prednisone (5 mg/d) therapy, similar to the other 32 female RA. Respiratory cause mortality was greater in RA than non-RA (RA = 2.88, 95% CI 1.06-7.82), after adjusting for cohort entry age (p = 0.027), baseline heavy cigarette (30+ daily) smoking (p = 0.018), limited therapy responses (p = 0.033), and the biomarker (p = 0.056). Mean (± 1 SE) features of the 8 RA deceased from respiratory causes vs the other 46 RA are shown (Table):
Rheumatoid Arthritis (RA) Is the Only One of 8 Diseases for Which a Patient History and Physical Examination (Versus Laboratory Tests and Ancillary Studies) Were Rated as Most Important for Clinical Decisions by >50% in a Physician Survey. Lauren McCollum1, Sangmo Park2, Tsuuliki Sokka3, Hasan Yazici1 and Theodore Pincus1. 1Cerrapaha Medical Faculty, Istanbul, Turkey, 2Jyvaskyla Central Hospital, Jyvaskyla, Finland, 3New York University Hospital for Joint Disease, Hastings-on-Hudson, NY, 4NYU Hospital for Joint Diseases

**Purpose:** To survey physicians concerning the relative importance of 5 sources of information in the clinical encounter—vital signs, patient history, physical examination, laboratory tests, and ancillary studies—in diagnosis and management of 8 chronic diseases: congestive heart failure (CHF), diabetes mellitus, hypercholesterolemia (HC), hypertension (HTN), lymphoma, pulmonary fibrosis (PF), rheumatoid arthritis (RA), and ulcerative colitis (UC).

**Methods:** An Internet survey using Survey Monkey™ was sent to about 6,636 rheumatologists and 6,964 non-rheumatologists, with the following query: “Please indicate the relative importance of 5 sources of information in diagnosis of CHF, diabetes, HC, lymphoma, HTN, PF, RA, and UC.” A second query with identical language addressed management decisions in the 8 diseases. Response options were 0–20%, 21–40%, 41–60%, 61–80%, and 81–100%. The proportions of physicians who estimated each element as most important (or tied for most important) in diagnosis or management of each disease was computed.

**Results:** The survey was completed by 588 physicians (5% response rate), including 329 rheumatologists and 254 non-rheumatologists (5 unknown specialty), and 313 U.S. and 187 non-U.S. physicians (88 unknown country). Substantial differences were seen in the physicians’ estimates of the most important element in diagnosis and management of the 8 diseases (Table 1): vital signs for HTN (82–83%), physical examination for RA (70–72%), laboratory tests and ancillary studies for RA (54–63%), and management of PF (40–44%) and UC (55–57%). RA was the only disease for which history and physical examination were rated as most important by >50%, including rheumatologists and non-rheumatologists.

**Conclusion:** A patient history and physical examination are estimated by physicians to provide a larger proportion of the information for clinical decisions in diagnosis and management of RA than for 7 other chronic diseases. The patient history and physical examination may be regarded as “clinician-intensive,” compared to vital signs, laboratory tests, and ancillary studies. This greater physician effort might be recognized in policies for scheduling, reimbursement, and allocation of physician resources by planners, regulators, and payers.

**Disclosure:** A. T. Masi: None; J. C. Aldag: None.

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**Similar Performance of New and Old Criteria for Rheumatoid Arthritis in an Early Arthritis Cohort in Amsterdam.** Karin Britsenermer, Jennie Ursum and Dirkjan van Schaardenburg. Jan van Bremen Institute Amsterdam

**Background:** The 1987 RA classification criteria of the American College of Rheumatology (ACR) were developed using patients with established RA. At least partly for this reason, the usefulness of these criteria in newly diagnosed RA, where early intervention is needed, is questioned. Recently an ACR/EULAR taskforce presented a revised set of criteria for RA. The aim of the present study was to validate the diagnostic capacity of the ACR/EULAR RA classification criteria for the diagnosis of early RA compared to the 1987 ACR criteria in an independent EAC, and to evaluate the capacity of the new criteria to identify erosive disease.

**Methods:** Data were used of those patients from the EAC at the Jan van Bremen Institute in Amsterdam who were included from 2000 onwards. The inclusion criteria of this EAC were age >18 years, symptom duration <= 2 years, at least 2 swollen joints, no prior DMARD treatment. Exclusion criteria are osteoarthritis, crystal arthropathy, connective tissue diseases and infectious arthritis. Thus the study population consists of patients with oligo- or polyarthritis, who would formerly be classified as having RA or undifferentiated arthritis.

The gold standard for the diagnosis of RA was methotrexate (MTX) treatment at 6 and/or 12 months. The classification criteria were applied as proposed by the ACR/EULAR task force. 3-year radiographic progression was assessed with the Sharp/Van der Heijde Score (SHS) in patients with available scores at the time of data collection.

**Results:** 383 patients were included (mean age 52 [SD13] years, 69% female, median symptom duration 4 months, median swollen and tender joint count 5 [IQR 2–9] and 4 [IQR 2–8], respectively, mean DAS28 4.63 ± 1.34, 48% of patients had RF and RA according to the gold standard. Sensitivity and specificity of the new criteria for RA were 77% and 69%, respectively, the positive and negative predictive values were 91% and 44%, respectively. The corresponding values of the 1987 ACR criteria for RA were 75%, 64%, 89% and 40%, respectively. The Area Under the Curve of the Receiver Operating Characteristics curve shows good discrimination between patients who did and did not use MTX at 6 or 12 months (0.79, p<0.0001).

Radiographic scores were available of 156 patients, of whom 121 fulfilled the new criteria at baseline. The median SHS progression was 0 (IQR 0–0) and 0 (IQR 0–4) in patients with and without RA according to the new classification, respectively (P 0.008). 71% of “non-RA” patients according to the new criteria used MTX in the first year. A similar difference in radiographic progression was observed between the groups of patients with and without RA according to the 1987 ACR criteria (data not shown).

**Conclusion:** The performance of the new ACR/EULAR RA classification criteria in this EAC was similar compared to the ACR 1987 RA criteria. Patients with RA according to the ACR/EULAR criteria had significantly higher median radiographic progression rates versus those without RA, which supports the aim of the new criteria to identify patients who are at high risk of joint damage. However, the low radiographic progression in the group of “non-RA” patients may be more a consequence of a high rate of MTX use than of a good prognosis per se.

**Disclosure:** K. Britsenermer: None; J. Ursum: None; D. van Schaardenburg: None.
The Impact of Health Beliefs on Therapeutic Adherence in Patients with Rheumatoid Arthritis (RA). Tara J. Rizvi1, John Gomez2, Sofia de Achaval1, Michael A. Kallen2, Vanessa L. Cox3, Marsham N. Richardson2, Bernard Ng1, John D. Reveille3 and Maria E. Suarez-Almazor4. 1Baylor College of Medicine, Houston, TX; 2The University of Texas M. D. Anderson Cancer Center, Houston, TX; 3Univ Texas Health Sci Ctr, Houston, TX; 4University of Texas, MD Anderson Cancer Center, Houston, TX

Objective: To determine whether the health beliefs of persons with RA influence their adherence to planned treatment.

Methods: We ascertained a cohort of patients with RA followed at publicly funded hospitals in Houston, TX. Eighteen specific components of the health belief model (HBM), including perceived severity and susceptibility, perception of self efficacy, benefits and risks of treatment, and barriers to treatment were measured using a self-report questionnaire. Treatment adherence was assessed with a previously validated questionnaire used in patients with rheumatic disease: de Klerk’s Compliance Questionnaire Rheumatology (CQR). Pearson correlations between HBM components at baseline and CQR at baseline and 24 months were calculated. Stepwise linear regression modeling to predict adherence was then conducted, using HBM components that were statistically significantly (p<.05) correlated with adherence; select demographic and clinical patient characteristics such as age, gender, education level, and disease duration, were included in the modeling.

Results: 201 patients with RA were included: 75% were female; mean age was 51 years; 172 patients completed the 24 month follow-up. Ten of 18 HBM components ascertainment were significantly related to treatment adherence at baseline and/or 24 months (Table 1). HBM components with a negative impact on treatment adherence were: belief in natural remedies, barriers in access to care, barriers due to beliefs about medication side effects, and beliefs about therapeutic lack of efficacy of RA therapies. Positive correlations with treatment adherence were observed with the following HBM components: belief in treatment benefits, belief in traditional medical treatment benefits, and positive attitudes towards risks of treatment. In the multi-variable regression analysis, belief in benefits of traditional treatment, willingness to take more risk, and longer disease duration were independent predictors of increased baseline treatment adherence, while higher levels of forgetting, financial barriers, and side effects were independent predictors of decreased adherence.

Table 1. Pearson Correlations of HBM Components with de Klerk Adherence (CQR)

<table>
<thead>
<tr>
<th>HBM Component</th>
<th>CQR Baseline</th>
<th>CQR 24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived Severity/Susceptibility</td>
<td>.20*</td>
<td>.14</td>
</tr>
<tr>
<td>Perceived Threat</td>
<td>.11</td>
<td>.21*</td>
</tr>
<tr>
<td>Self Efficacy-Pain</td>
<td>-.15*</td>
<td>-.09</td>
</tr>
<tr>
<td>Self Efficacy-Function</td>
<td>.01</td>
<td>.04</td>
</tr>
<tr>
<td>Self Efficacy-Symptoms</td>
<td>-.03</td>
<td>.03</td>
</tr>
<tr>
<td>Self Efficacy-Optimism</td>
<td>.20*</td>
<td>.17*</td>
</tr>
<tr>
<td>Health Beliefs &amp; Attitudes</td>
<td>.01</td>
<td>.18*</td>
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<tr>
<td>Risk Items</td>
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<td>.24*</td>
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<tr>
<td>Benefits Traditional Remedies</td>
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<td>Barriers Scheduling</td>
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<td>Barriers Financial</td>
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<tr>
<td>Barriers Forget</td>
<td>-.46*</td>
<td>-.37*</td>
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<tr>
<td>Barriers Side Effects</td>
<td>-.33*</td>
<td>-.41*</td>
</tr>
<tr>
<td>Barriers Inefficacy</td>
<td>-.30*</td>
<td>-.30*</td>
</tr>
</tbody>
</table>

*p < .05.

Conclusion: A number of patient perceptions and beliefs impact therapeutic adherence in patients with RA. Based on our findings, strategies to improve adherence may include interventions to positively modify patients’ beliefs regarding treatment benefits and side effects, and to limit modifiable barriers leading to non-adherence.

Disclosure: T. J. Rizvi: None; J. Gomez: None; S. de Achaval: None; M. A. Kallen: None; V. L. Cox: None; M. N. Richardson: None; B. Ng: None; J. D. Reveille: None; M. E. Suarez-Almazor: None.

TNF and Natural Atheroprotective Antibodies Against Phosphorylcholine: Implications for Biologics in RA. Sofia Ajeganova, Roland Fiskesund, Ingrid Hafström and Johan Frostegård. Karolinska Institutet, Sweden

Background: We have recently determined that natural antibodies against phosphorylcholine (anti-PC) are protection factors for cardiovascular disease (CVD), where low levels of anti-PC independent of other risk factors increase the risk of CVD. Further, anti-PC is anti-inflammatory, inhibiting proinflammatory effects of inflammatory phospholipids. Levels of IgM anti-PC are low in individuals living a traditional life-style in New Guinea (where CVD and rheumatic diseases are very uncommon) as compared to a western population. We have hypothesized that an immune deficient state – low levels of anti-PC—predispose to chronic inflammatory diseases. TNF is of major importance not only in rheumatic disease but also in CVD, atherosclerosis and metabolic syndrome. We here determine the role of TNF and TNF-inhibition on anti-PC levels and anti-PC production. We compared effects by TNF-inhibitors with rituximab.

Methods: In vitro anti-PC production by B-cells isolated from peripheral blood was determined by ELISA after 6 days of cell culture. Two hundred fifteen RA patients, aged 57.9±12.4 years with a mean disease duration of 8.5 (5-15) years were investigated with a one year follow up. Of these patients, 60 were treated with etanercept, 60 with infliximab and 42 with adalimumab as the first biologic, furthermore, 53 patients were treated with rituximab. The patients were followed and blood sampled at 0, 3, 6 and 12 months.

Results: TNF at 1 ng/ml was shown to drastically (more than tenfold) decrease anti-PC production in vitro (p<0.0001) without inducing apoptosis. Anti-TNF treatment induced a 26% increase in anti-PC after 12 months of treatment (28%, 27.8% and 22% on etanercept, infliximab and adalimumab respectively), p<0.001, while rituximab decreased anti-PC levels by 14%, p=0.023. Non-responders had lower anti-PC levels at baseline than responders in both anti-TNF, p=0.007, and Rituximab-treated subjects, p=0.041.

Conclusion: TNF was demonstrated to inhibit anti-PC production, a finding which suggest a novel mechanism by which anti-PC IgM could be decreased. Anti-TNF treatment may decrease risk of CVD by raising anti-PC levels. The adverse effect of rituximab on anti-PC levels may influence CVD-risk negatively. If treatment with anti-PC could have a role in some patients with RA including non-responders to biologics deserves further investigations.

Disclosure: S. Ajeganova: None; R. Fiskesund: None; I. Hafström: None; J. Frostegård: Athera Biotechnologies, I, 5, 6, 9.

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TNF Therapy Reduces the Odds of Worsening Disability Trajectories in Rheumatoid Arthritis over at Least 2 Years—Data from the NDB-Portugal Cohort. Sofia Pedro1, Elizabeth Benito-Garcia1, Joana Vasconcelos1, Irina Chaves1, Rita Marques1, Andreia Rodrigues1, Kaleb Michael2 and Fred Wolfe3. 1Bioptech Clinical and Translational Research Center, Oeiras, Portugal; 2National Databank for Rheumatic Diseases, Kansas, 3University of Nebraska Medical Center, NE

Background: The trajectories of the health assessment questionnaire (HAQ) disability scores among rheumatoid arthritis (RA) patients are known to have different courses. Wolfe et al. (2000) characterized them as being non linear, chaotic and non-time deterministic. It is suggested that HAQ be measured between clinic visits to monitor disability and the effect of therapy. Many studies have defined the predictors of HAQ, but few have evaluated the predictors of HAQ trends among RA patients.

Objective: To investigate the predictors of worsening disability trends compared to improving, no change or other patterns of disability trajectories among RA patients over at least 2 years.
Methods: 646 RA patients from the ongoing biannual NDB-Portugal cohort (started in 2003) with at least four consecutive HAQ scores per patient during their follow-up were used in this analysis. Questionnaires included socio-demographics, disease characteristics, function, etc.

The proportion defined by the number of 6-month positive increments in HAQ scores (worsening function) divided by the total number of differences was computed per patient and used to define patients' trajectories. The outcome was then defined as the presence of a trend of worsening disability (when the proportion was > 0.5). Univariate (UV) and multivariate (MV) generalized estimating equations (GEE) were used to study the predictors of a worsening disability trend. Age, educational level, disease duration, paid form of work, retirement, number of total major comorbidities, SF-36 mental component (MCS) (0–100, 0 is worse), RADAI (0–10, 10 is worse), the VAS scales of sleep, fatigue and pain (VAS 0–10, 10 is worse), the use of current TNF (with or without concomitant DMARDs) vs. traditional DMARD therapy and corticosteroids, were used as possible predictors.

Results: 168 patients of 646 (26%) had worsening disability trends. The UV analyses showed that all of the following factors were statistically relevant: age, educational level, number of major comorbidities, sleep disturbances and fatigue, RADAI and the use of TNF therapy. The final MV model included pain (OR: 1.003 (95%CI: (1.000; 1.005))), age (OR: 1.02 (1.01; 1.02)) and the use of TNF (OR: 0.94 (0.91; 0.97)).

Conclusions: In our study, we showed that older age and more pain predicted worsening HAQ disability trends. The use of TNF therapy (with or without concomitant DMARDs) when compared with traditional DMARD was the only factor that decreased the odds of having a worsening HAQ trajectory.

Disclosure: S. Pedro: None; E. Benito-Garcia: None; J. Vasconcelos: None; I. Chaves: None; R. Marques: None; A. Rodrigues: None; K. Michaud: None; F. Wolfe: None.

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TNF-alpha Blocking Therapy Lowers Cardiovascular Risk in Rheumatoid Arthritis. Ingrid M. Visman1, Alper M. van Sijl1, Mike J. L. Peters3, Carlo J. J. van Dongen1, Ben A. C. Dijkmans3 and Michael T. Nurmohamed2. 1Jan van Breemen Institute, 2Jan van Breemen Institute and VU Medical Centre, Amsterdam, The Netherlands, 3Jan van Breemen Institute and VU Medical Centre, 4VU Medical Centre, Amsterdam, The Netherlands, 5VU Medical Centre

Background: Patients with rheumatoid arthritis (RA) have an increased risk of developing cardiovascular (CV) disease and the underlying chronic inflammatory process appears to play a pivotal role. As tumor necrosis factor (TNF)-alpha blocking agents have powerful anti-inflammatory effects it is conceivable that these agents will lower CV risk in RA. The objective of this study was to compare the CV disease incidence rate in RA patients receiving TNF-alpha blocking therapy with RA patients not receiving these drugs.

Methods: Two prospective cohort studies of individuals with RA (the CARRE study and the Biologicals-cohort of the Jan van Breemen institute in Amsterdam, the Netherlands) were followed for several years. The CARRE study is a prospective cohort of individuals with RA, most of whom did not use biologic agents at inclusion. Patients who did use biologics were excluded from further analysis. The Biologicals-cohort is a prospective cohort of adult RA patients starting therapy with TNF-alpha blocking agents. Data was collected regarding traditional cardiovascular risk factors, RA related factors, cardiovascular morbidity and mortality. Cardiovascular events were defined as objectified myocardial infarction, cerebrovascular accident, transient ischaemic attack, peripheral arterial reconstruction, or coronary stent- or by-pass procedure. Cox proportional hazard model was used to evaluate the difference in cardiovascular incidence between RA patients and models were adjusted for age, sex and previous cardiovascular disease.

Results: 377 and 322 individuals, with and without TNF-alpha blocking therapy, respectively, were followed for a mean duration of 2.1 and 2.7 years, resulting in 793 and 888 patient years, respectively. Cardiovascular incidence was 10.1/1000 patient years and 24.8/1000 patient years, respectively. Cox proportional hazard model showed a statistically significantly decreased cardiovascular incidence in individuals using TNF-alpha blocking therapy, hazard ratio (95%-confidence interval): 0.42 (0.18–0.97). After adjustment for age, gender and previous CVD there was still a 30% lower cardiovascular risk in RA patients treated with TNF-blockers, but this was not longer statistically significant (hazard ratio (95%-confidence interval): 0.71 (0.29–1.72.).

Figure 1. Cox-regression analysis of cardiovascular event free probability for patients with and without TNF-blocking therapy, corrected for age, gender and previous CVD.
Validation of the Work Performance Visual Analog Scale: Measuring Work and Household Productivity of Patients with Early, Aggressive Rheumatoid Arthritis. Dennis Revicki1, Sanjoy Roy1, Miriam Kimel2, Chris Thompson2 and Mary Cifaldi1. 1Abbott Laboratories, Abbott Park, IL, 2United Biosource Corporation, Bethesda, MD

Background and Purpose: Visual analog scales (VASs) have been used in clinical and observational studies to assess the impact of rheumatoid arthritis (RA) on work performance for employed patients and homemakers. To date, however, the psychometric properties of these scales have not been described. To assess the appropriateness for use in clinical trials, we evaluated the psychometric properties of a work performance VAS in both employed workers and homemakers with RA.

Methods: Data from PREMIER and DE032 (health economic companion study of PREMIER), clinical trials of adalimumab (ADA) with or without methotrexate (MTX) in patients with early RA, were analyzed. The VAS measured the impact of RA on work performance on a scale of 0 to 100, in which 0 = not affected at all and 100 = completely affected. Data were pooled across treatment groups (ADA alone, MTX alone, and ADA + MTX) and analyzed separately for employed patients and homemakers. Psychometric assessments of the VAS included test-retest reliability, convergent validity, known-groups validity, and responsiveness based on minimum clinically important difference (MCID) criteria.

Results: This analysis included 664 patients from PREMIER who participated in the health economic companion study. Test-retest reliability for performance in employment-related and household work was evaluated for patients with no change in clinical status based on Health Assessment Questionnaire (HAQ) and Patient Global Assessment of Disease Activity (PaGA) scores from Weeks 4 to 8 and Weeks 8 to 12 (intraclass correlation coefficients of 0.78–0.85). Convergent validity for employed work performance was demonstrated through moderate to large correlations (0.40–0.72, absolute values; all p < 0.0001) with the HAQ, 28-joint Disease Activity Score (DAS28), Functional Assessment of Chronic Illness Therapy-Fatigue scale, PaGA, Health Utilities Index Mark 3, Short Form 36 Health Survey, and tender joint counts. Similar findings were observed for household work performance (correlation coefficients ranged from 0.47 to 0.84, absolute values; all p < 0.0001). Mean VAS scores for both employment-related and household work performance varied significantly across different levels of physical function and disease severity based on HAQ and DAS28 scores; patients with better clinical status had better work performance scores, demonstrating good known-groups validity. From anchor-based methods using American College of Rheumatology response criteria, MCID estimates for VAS scores ranged from 8.6 to 13.2 points for employment-related work performance, and the MCID estimate for household work performance was 13.1 points for all. Based on DAS28 remission status, MCID estimates for VAS scores ranged from 10.7 to 17.0 points for employment-related work performance and from 19.8 to 23.4 points for household work performance.

Conclusions: Results suggest that the work performance VAS scores for employment-related and household work possess acceptable reliability and validity, making them appropriate for use in clinical research to evaluate the impact of RA and treatment on work performance.
Dependent Variable | Predictor | Mean ± SD | Odds Ratio* | 95% CI
--- | --- | --- | --- | ---
≥3,722 steps/day | Employed vs. unemployed | 2.28 | 1.29–4.02
| # of co-morbidities | 1.0 | 0.62 | 0.45–0.84
| BMI, kg/m² | 31.4 ± 7.2 | 0.63 | 0.47–0.85
| Total FIQ | 67.0 ± 12.7 | 0.65 | 0.47–0.89
| PHQ-8 depression severity | 12.5 ± 4.9 | 0.71 | 0.54–0.94
| Age, years | 45.8 ± 11.3 | 0.71 | 0.54–0.94
| FM duration, years | 9.0 ± 7.0 | 0.74 | 0.56–0.98
| # of medications | 5.0 ± 1.6 | 0.78 | 0.59–1.03
| BPI pain intensity Moderate PA ≥77 minutes/week | 6.0 ± 2.1 | 0.80 | 0.61–1.06

* Change in odds of being above median, relative to below, associated with a 1-SD increment in the predictor variable except for total FIQ where a 14% change is considered clinically meaningful.

In the multivariate analysis, being relatively active (≥3,722 steps/day) was associated with lower BMI (OR: 0.62, 0.45–0.86), fewer co-morbidities (OR: 0.71, 0.51–0.99), shorter disease duration (OR: 0.72, 0.52–1.0) and lower Total FIQ (OR: 0.61, 0.43–0.88). Alternatively, time spend in PA of moderate or greater intensity (≥77 min/wk) was limited by greater BMI (OR: 0.64, 0.48–0.86) and increased depressive symptomatology (OR: 0.74, 0.56–0.99), and increased depressive symptomatology (OR: 0.74, 0.56–0.99) and increased depressive symptomatology (OR: 0.74, 0.56–0.99).

**Conclusions/Implications:** Active lifestyles were rare in this sample of FM patients. Employed patients were more active than unemployed ones. While several associations with clinical variables may be bidirectional, sedentary patients tended to be more obese and have greater duration and severity of FM and more numerous co-morbidities. Clinicians may take these associations as evidence supporting the encouragement of PA early in the disease process. However, attainment of appreciable levels of moderate intensity of PA may be difficult without attention to weight loss and mood, when indicated.

**Disclosure:** D. Ang: None; A. Kaleth: None; S. Bigatti: None; S. Mazzucca: None; C. Saha: None; R. Bandy: None.

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**Development of Responder Definitions for Fibromyalgia Clinical Trials.** Lesley M. Arnold1, Philip J. Mease2, David A. Williams7, Susan A. Martin3, Fujun Wang2, Biro Elmir3, Chinglin Lai4 and Rong Zabolocki1. 1Cypress Bioscience, Inc.; 2Eli Lilly and Company; 3Jazz Pharmaceuticals, 4Pfizer, Inc.; 5RTI Health Solutions; 6Seattle Rheumatology Associate, Seattle, WA; 7Univ of MI Ilhth System–Lobby M, Ann Arbor, MI; 8University of Cincinnati College of Medicine, Cincinnati, OH

**Background:** Previous analyses of fibromyalgia (FM) clinical trial databases found patient perceptions of global improvement relied not only on improvements in pain but also on improvements in accompanying symptoms such as fatigue, sleep problems, physical functioning, and mood. These symptom and functional domains may form the components of a responder definition for FM clinical trials. The objective of this study was to develop and test responder definitions for FM clinical trials using key symptom and functional domains.

**Methods:** Informed by existing responder definitions for other rheumatologic disorders, 8 candidate responder definitions were developed by expert consensus. These 8 definitions were evaluated in the context of randomized placebo-controlled clinical trials of 4 medications for FM between baseline and 3 months. For each of the proposed definitions, treatment effects of the medication compared with placebo were analyzed using the Cochran-Mantel-Haenszel test. A meta-analysis of the pooled results for the 4 medications established risk ratios so as to determine the definitions that best favored medication over placebo.

**Results:** Two definitions performed best in the analyses and shared common features. Both definitions included ≥30% reduction in pain and both included ≥10% improvement in physical function. They differed in that one (FM 30 short version) included ≥30% improvement in sleep or fatigue, and the other (FM 30 long version) required ≥30% improvement in 2 of the following symptoms: sleep, fatigue, depression, anxiety, or cognition. In the analysis of both versions, the response rate was about 20% or greater for each medication and was significantly greater than placebo. The risk ratio (95% CI) in the pooled analysis of the FM 30 short version was 1.69 (1.04, 2.72), P=0.03; the risk ratio (95% CI) for the FM 30 long version was 1.60 (1.31, 1.96), P=<0.00001.

**Conclusion:** Among the 8 responder definitions tested, 2 were identified as most sensitive in identifying response to treatment. The identification of responder definitions for FM clinical trials that include assessments of key symptom and function domains will hopefully improve the sensitivity of clinical trials to identify meaningful improvements, leading ultimately to improved management of FM.


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**Does Obesity in Patients with Fibromyalgia Modify Response to Tai Chi Therapy: Analysis of a Randomized Controlled Trial.** Chenchen Wang1, Christopher H. Schmid2, Yoojin Lee2 and Timothy McAlindon1. 1Tufts Medical Center, Boston, MA; 2Tufts Medical Center

**Purpose:** Fibromyalgia (FM) is a chronic pain disorder of complex etiology. Recent evidence about the association between obesity and FM suggests that this might obfuscate therapy. We evaluated the association of obesity and changes in FM severity, sleep quality and health related quality of life in a randomized controlled trial of FM patients.

**Methods:** We studied a sample of 66 eligible individuals (age 21 or older, and fulfilled the American College of Rheumatology 1990 diagnostic criteria for FM) who participated in a single-blind, randomized controlled trial. Using computer-generated numbers, we randomly assigned participants to Tai Chi mind-body exercise (Classical Yang style, n=33) or attention control (stretching and wellness education n=33) in three cycles of 22 patients each. The 60-minute group sessions occurred twice-weekly for 12 weeks. We defined obesity as body mass index (BMI) ≥30.00 kg/m². Study endpoints included changes from baseline to 12 weeks in FM Impact Questionnaire (FIQ) score (range, 0 to 100; higher scores indicate more severe symptoms), Pittsburgh Sleep Quality Index (range, 0–21, higher scores indicate worse sleep quality), and Physical Component Summary and Mental Component Summary of the Short Form-36 (SF-36) to assess quality of life (range 0–100; lower scores indicate worse health status). We estimated the relationship between obesity and the treatment effect by the interaction of treatment and obesity in linear regression using each of the three study endpoints.

**Results:** The 66 participants had mean age 50y (SD 11.1), mean disease duration 11 y (SD 7.1), mean BMI 33 kg/m² (SD 8.2), and were mainly female (86%) and white (56%). Thirty-six patients were obese (BMI≥30) and 29 patients were not obese (<30.00) and 1 had missing BMI. The proportion of obese BMI remained stable in both Tai Chi and control groups. Obese patients assigned to Tai Chi group exhibited significantly greater improvement in FIQ total score (between-group difference ~17.5, 95% CI, [−34.1 to −1.0]; P=0.04)
than the non-obese group. The SF-36 Physical Component Summary and Mental Component Summary tests also favored obese group but did not reach statistical significance. Both groups improved their sleep quality (Pittsburgh Sleep Quality Index) equally.

Table. Changes in FM severity, sleep quality and health status by BMI group at Week 12*

<table>
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<th>BMI level</th>
<th>Groups</th>
<th>Baseline (SD)</th>
<th>12 week Mean change (95% CI)</th>
<th><em>p</em> value</th>
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<tr>
<td>BMI ≥ 30</td>
<td>Tai Chi</td>
<td>38.7 (7.9)</td>
<td>0.0 (0.1, 0.3)</td>
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<td>Control</td>
<td>38.2 (6.4)</td>
<td>0.1 (0.0, 0.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>BMI &lt; 30</td>
<td>Tai Chi</td>
<td>24.7 (5.5)</td>
<td>-0.4 (-0.7, 0.0)</td>
<td>0.04</td>
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<tr>
<td></td>
<td>Control</td>
<td>25.9 (6.2)</td>
<td>-0.6 (-0.9, -0.3)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*FQ (0-100) * Table

| BMI ≥ 30  | Tai Chi         | 66.8 (14.4)   | -12.9 (-14.6, -11.3)        | <0.0001  |
|           | Control         | 67.5 (10.3)   | -14.9 (-16.4, -13.4)        | <0.0001  |
| BMI < 30  | Tai Chi         | 71.5 (10.3)   | -14.9 (-16.4, -13.4)        | <0.0001  |
|           | Control         | 72.7 (9.5)    | -15.4 (-16.9, -13.9)        | <0.0001  |

**Table 1.** Nucleotide distribution.

<table>
<thead>
<tr>
<th>Rs-6754031</th>
<th>Patients</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>Percentile 25</td>
<td>Median</td>
<td>Percentile 75</td>
</tr>
<tr>
<td>GG</td>
<td>69.74</td>
<td>80.38</td>
<td>88.74</td>
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<tr>
<td>GT</td>
<td>58.55</td>
<td>63.29</td>
<td>77.53</td>
</tr>
<tr>
<td>TT</td>
<td>64.23</td>
<td>71.25</td>
<td>77</td>
</tr>
</tbody>
</table>

**Table 2.** Total FIQ score in patients with Rs-6754031

Conclusions: In this ethnic group, a disabling form of FM was associated with a particular SCN9A gene variant. These preliminary results raise the possibility that patients with severe FM may have a sodium channelopathy.

Financial support: American Fibromyalgia Syndrome Association.

Disclosure: G. Vargas-Alarcon: None; E. Alvarez-Leon: None; J.-M. Fragoso: None; A. Vargas: None; A. Martinez: None; M. Vallejo: None; M. Martinez-Lavin: None.

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**Dorsal Root Ganglia/Sympathetic Ganglia Sodium Channels Gene Polymorphisms in Fibromyalgia.**

Ilberio Vargas-Alarcon, Edith Alvarez-Leon, Jose-Manuel Fragoso, Angelica Vargas, Alina Martinez, Maite Vallejo and Manuel Martinez-Lavin. National Institute of Cardiology, Mexico

**Background:** A consistent line of investigation suggests that autonomic dysfunction may explain the multi-system features of fibromyalgia (FM), and that FM is a sympathetically maintained neuropathic pain syndrome. Dorsal root ganglia (DRG) are potential sympathetic-nociceptive short-circuit sites. Sodium channels located in DRG (particularly Nav1.7) act as molecular gatekeepers for pain detection. Nav1.7 is encoded in gene SCN9A of chromosome 2q24.3 and is predominantly expressed in the DRG pain-sensing neurons and sympathetic ganglia neurons. Several SCN9A sodium channelopathies have been recently recognized as the cause of rare painful-dysautonomic syndromes such as paroxysmal extreme pain disorder and primary erythermalgia (Ann N Y Acad Sci. 2010;1184:196, Med Hypotheses. 2009;72:64). SCN9A polymorphisms (particularly rs6746030) have been linked to altered pain perception (Proc Natl Acad Sci USA 2010;107:5148).

**Objective:** To identify associations between fibromyalgia and several Nav1.7 polymorphisms encoded in gene SCN9A.

**Methods:** We studied 73 Mexican women with FM according to the 1990 ACR criteria and 48 Mexican women who considered themselves healthy. All participants filled out the Fibromyalgia Impact Questionnaire (FIQ). Genomic DNA from whole blood containing EDTA was extracted by standard techniques. The following SCN9A single-nucleotide polymorphisms (SNPs) were studied: rs4371369, rs4387806, rs4453709, rs4579545, rs6746030, rs6754031, rs7607967, rs12620053, rs12994338, and rs13017637. SNPs were analyzed by 5-exonuclease TaqMan assays on a 7900HT fast real-time PCR system.

**Results:** Are summarized in table 1. Rs6754031 nucleotide distribution was significantly different in both groups (p = 0.036) mostly due to an absence of GG genotype in controls. Interestingly, patients with this rs6754031 GG genotype had higher total FIQ scores, than patients with the other two rs6754031 genotypes (p = 0.039). Table 2.

**Table 3.** Nucleotide distribution.

<table>
<thead>
<tr>
<th>Rs-6754031</th>
<th>Patients</th>
<th>Controls</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Genotype</td>
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**Conclusions:** In this ethnic group, a disabling form of FM was associated to a particular SCN9A gene variant. These preliminary results raise the possibility that patients with severe FM may have a sodium channelopathy.

Financial support: American Fibromyalgia Syndrome Association.

Disclosure: G. Vargas-Alarcon: None; E. Alvarez-Leon: None; J.-M. Fragoso: None; A. Vargas: None; A. Martinez: None; M. Vallejo: None; M. Martinez-Lavin: None.

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**Durability of Response in a 38-Week Open-Label Study of Sodium Oxybate in Patients with Fibromyalgia.**

Michael Spath1, I. Jon Russell2, Sergio Perrot3, Sarah Alvarez-Horine3, Diane R. Guinta1, Y. Grace Wang2 and Robert M. Bennett3, 1Jazz Pharmaceuticals Inc., Palo Alto, CA, 2Jazz Pharmaceuticals Inc., 3Jazz Pharmaceuticals, Inc., 4Oregon Health and Science Univ, Portland, OR, 5Rheumatological Schwerpunktrapris, 6Service de Medecine Interne et Centre de la Douleur, Hôtel-Dieu, 7University of Texas Health Science Center, San Antonio, TX

**Background:** Two pivotal phase 3 clinical trials demonstrated the efficacy and tolerability of sodium oxybate (SXB) for the treatment of fibromyalgia (FM). Fibromyalgia is a chronic disorder characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, and functional impairment. The current report describes the durability of response of SXB in a FM population.

**Methods:** Patients with FM who completed a 14-week, placebo-controlled, phase 3 study of SXB were eligible to enroll in this international, open-label extension within 7 days after completing the previous study. Eligible subjects received open-label treatment for up to an additional 38 weeks. SXB was initiated at 4.5 g/night (administered in equally divided doses 2.5 to 4 hours apart), and increases were permitted in increments of 1.5 g/night, at intervals of at least 1 week, up to 9 g/night. Dose reductions were permitted in increments of 1.5 g/night to a minimum of 4.5 g/night; subjects unable to tolerate this dose were discontinued. Efficacy was evaluated based on reductions in pain and fatigue, recorded daily on a 100 mm Visual Analogue Scale (VAS), and improvement in function assessed using the Fibromyalgia Impact Questionnaire (FIQ) at each study visit. Study endpoint was defined as the last available data, whether obtained at study completion or early discontinuation.
Results: Of 560 subjects who were treated (mean age, 46.9 years; 91.1% female), 366 subjects (65.4%) received study drug for at least 24 weeks and 269 subjects (48.0%) received study drug at least 38 weeks. Mean dose was 6.28 g/night at last dose for all subjects. Improvements seen on multiple measures in the previous trials were maintained. At study endpoint, the mean change from prior study baseline in pain VAS for all treated patients was 6.28 g/night at last dose for all subjects. Improvements seen on multiple measures included sleep, physical function, and pain. Of 560 subjects who were treated (mean age, 46.9 years; 91.1% female), 366 subjects (65.4%) received study drug for at least 24 weeks and 269 subjects (48.0%) received study drug at least 38 weeks. Mean dose was 6.28 g/night at last dose for all subjects. Improvements seen on multiple measures included sleep, physical function, and pain.

Conclusions: This open-label study demonstrated the long-term durability of effect of SXB for the treatment of FM over a dose range of 4.5 to 9 g/night for 38 weeks. Treatment effects were substantial across multiple fibromyalgia symptoms, including pain, fatigue, and impairments in daily living and physical functioning. SXB was generally well-tolerated over the 38 weeks of treatment.


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Effects of Milnacipran Added to Pregabalin on Cognition and Mental Clarity in Fibromyalgia Patients. Robert S. Katz1, Robert H. Palmer2, Yong Wang3 and R. Michael Gendreau.1 1Cypress Bioscience, Inc., San Diego, CA, 2Forest Research Institute, Jersey City, NJ, 3Forest Research Institute, 4Rush University Medical Center, Chicago, IL.

Purpose: Fibromyalgia (FM) is characterized by chronic widespread pain accompanied by a host of symptoms that include perceived cognitive dysfunction, which is also known as fibrofog. Cognitive impairments associated with fibrofog include problems with attention, mental confusion, and short-term memory loss. A recent clinical trial evaluating the efficacy of milnacipran when added to pregabalin utilized the Mental Clutter Scale, a new 16-item measure of fibrofog, to assess improvements in cognitive impairment in FM patients.

Methods: The Mental Clutter Scale is composed of 2 subscales that measure cognition and mental clarity; each subscale consists of 8 items. This randomized, open-label, controlled study evaluated the efficacy and tolerability of milnacipran 50 mg BID when added to pregabalin 150 mg BID or 225 mg BID in FM patients who had an incomplete response to pregabalin during a 4- to 12-week open-label run-in phase. Pregabalin incomplete responders (defined as patients with weekly recall VAS pain score ≤40 and ≤90 [0 to 100 scale], Patient Global Impression of Severity score ≥4 [moderately ill to extremely ill], and Patient Global Impression of Change [PGIC] score ≥3 [minimally improved to very much worse]) were randomized to either pregabalin alone (n=180) or milnacipran added to pregabalin (n=184) for 11 weeks. Least squares mean changes from baseline in Mental Clutter Scale subscale and item scores were analyzed at endpoint using a LOCF approach.

Results: Patients treated with milnacipran added to pregabalin demonstrated significant improvements compared to pregabalin alone in the Mental Clutter Scale full scale score (P<.001) as well as the Cognition and Mental Clarity subscale scores (P=.001). All item scores of the Cognition subscale were significantly improved in the milnacipran added to pregabalin group compared with pregabalin alone except for memory assessment (P=.052). Scores for concentration (P=.043), staying focused (P=0.008), multitasking (P=.009), expressing self (P=.004), thinking clearly (P<.001), perceptual clarity (P=.002), and mental speed (P=.001) were all significantly improved in the milnacipran added to pregabalin group compared with pregabalin alone. In addition, significant improvements were demonstrated on all items of the Mental Clarity subscale: spaciousness (P<.001), haziness (P<.001), confusion (P<.001), cluttered thinking (P=.005), foginess (P=.009), rushing thoughts (P=.002), fuzzy headness (P=.007), and information overload (P=.002).

Conclusions: When added to pregabalin, milnacipran resulted in significant improvements in the cognitive impairments perceived by FM patients, as measured by a new self-report tool intended to measure cognition and mental clarity.


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Fatigue in Fibromyalgia Patients: A Qualitative Study Exploring a Conceptual Framework. Philip J. Mease1, Lisa D’Ambrosio3, Asha Haereudran2, Maureen Mohyde2, Robin Pokrzywinski3, Kristin Seymour3 and Steven Blum1.1Forest Research Institute, 2Outcome Sciences, 3Outcome Sciences and MIT AgeLab, 4Seattle Rheumatology Associate, Seattle, WA, 5Seattle Rheumatology Associates, 6United BioSource Corporation.

Purpose: In addition to pain, fatigue is a common and important symptom of fibromyalgia (FM) and has been included in the OMERACT (Outcome Measures in Rheumatology Clinical Trials) core domain set and the 2010 ACR Preliminary Diagnostic Criteria for FM.2 The FDA Guidance on Patient-Reported Outcome (PRO) Measures recommends input from patients in development or modification of PRO instruments. This study was conducted to further explore FM patients’ experience of fatigue and to provide insight into how it can be measured in a way that captures concepts that are most relevant to patients with FM.

Methods: Two focus group discussions among clinically diagnosed FM patients were conducted (n=18). All patients were female and were recruited from a single clinical practice site. The focus groups were conducted using a semi-structured interview guide. Initial discussions began with open-ended questions about challenges of living with FM, effects of FM on daily life, interactions with others and experience with fatigue. Patients were then further probed about their experience with fatigue due to FM. Audio recordings were transcribed and analyzed using a researcher developed coding book and atlas.ti software.

Results: The data support existing frameworks for FM but offers additional insights in the experience of fatigue among patients with FM. The data suggest that fatigue in FM varies within a week and even within a single day. FM patients perceive the severity of their fatigue in terms of its implications for daily function, impacts on sleep, cognition, motivation and emotions. When discussing the impact of fatigue on functioning, patients described activities they are no longer able to participate in, such as personal care, housework, work productivity, cooking, making or keeping plans, and losing spontaneity. Although sleep disturbances were reported by patients, many perceived being fatigued and tired as separate concepts. Fatigue was not necessarily improved by sleep. Fatigue and cognitive dysfunction were closely intertwined, such as being in a ‘fibro fog’, not being able to concentrate, forgetting things, difficulty making decisions, and feeling like there is a mental curtain or veil. Lack of motivation as a result of fatigue was exemplified by having to push to start or complete activities, lacking initiative, and feeling depleted. The emotional impact of fatigue stemmed from feeling frustrated with not being able to do things they wanted and not being able to remember things. Patients also expressed feeling embarrassment or guilt for not being able to do things, especially with family and friends. Patients perceived physical experience of fatigue as if being weighed down, such as wearing heavy clothing made of cement.

Conclusion: This qualitative work has provided additional insights for a framework for evaluating fatigue in FM. It is important to evaluate more than the frequency and severity of being tired. The variability of patients’ experience of fatigue in FM suggests the need for more frequent assessment as well as a broader set of concepts to be evaluated when measuring fatigue in FM.


Fibromyalgia Criteria and Severity Scales for Clinical and Epidemiological Studies: A Modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. Frederick Wolfe², Daniel J. Clauw¹, Mary Ann Fitzcharles¹, Don L. Goldenberg³, Robert S. Katz², Philip J. Mease², Anthony S. Russell¹, I. Jon Russell¹, and John B. Winfield¹.¹Montreal West, QC, Canada, ²National Data Bank for Rheumatic Diseases, Wichita, KS, ³Newton-Wellesley Hosp, Newton, MA, 4Rheumatology Associates, Chicago, IL, 5Seattle Rheumatology Associates, Seattle, WA, 6Technical University Munich, Munich, Germany, 7UM/Chronic Pain & Fatigue Res, Ann Arbor, MI, 8University of Alberta, Edmonton, AB, Canada, 9University of North Carolina, Chapel Hill, NC, 10University of Texas HSC, San Antonio, TX.

**Purpose:** To develop a FM survey questionnaire for epidemiologic and clinical studies using a modification of the 2010 ACR Preliminary Diagnostic Criteria for Fibromyalgia (ACR2010). We also created a new FM symptom scale to further characterize fibromyalgia [FM] severity.

**Methods:** The ACR2010 consists of two scales, the Widespread Pain Index (WPI) and the Symptom Severity (SS) scale. We modified these ACR2010 criteria by eliminating the physician’s estimate of the extent of somatic symptoms and substituting the sum of 3 specific self-reported symptoms. The 3 specific symptoms score was sum of the number of the following symptoms occurring during the previous 6 months: headaches, abdominal pain, and depression. We made this change because the physician’s estimate of the extent of somatic symptoms was an evaluative measure that could not be performed in a survey. The 3 new symptoms were not incorporated into the WPI. We also created a 0–31 FM Symptom scale (FS), also known as the Fibromyalgianess scale, by summing the WPI and the modified SS scale. We administered the questionnaire to 729 patients previously diagnosed with fibromyalgia, 845 with osteoarthritis or with other non-inflammatory rheumatic conditions (OA), 439 with lupus, and 5,210 with RA.

**Results:** The modified ACR2010 criteria were satisfied by 60% with a prior diagnosis of fibromyalgia, 21.1% with RA, 16.8% with OA, and 36.7% with SLE. The criteria properly identified diagnostic groups according to FM severity variables. An FS score ≥13 best separated criteria (+) and criteria (-) patients, classifying 93.0% correctly, with a sensitivity of 96.6% and a specificity of 91.8% in the study population, as shown in Figure 1.

![Graph showing Fibromyalgia symptom scale](Image)

Characteristics of patients according to entry and criteria status demonstrated appropriate classification.

<table>
<thead>
<tr>
<th>Variable</th>
<th>FM (+) Criteria +</th>
<th>FM (+) Criteria -</th>
<th>FM (-) Criteria +</th>
<th>FM (-) Criteria -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Widespread pain index</td>
<td>Mean or %</td>
<td>Mean or %</td>
<td>Mean or %</td>
<td>Mean or %</td>
</tr>
<tr>
<td>0.0–19</td>
<td>12.9</td>
<td>5.6</td>
<td>11.7</td>
<td>3.6</td>
</tr>
<tr>
<td>4-item Modified SS score</td>
<td>8.0</td>
<td>4.0</td>
<td>7.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Fibromyalgia symptom scale</td>
<td>20.9</td>
<td>9.6</td>
<td>19.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Fatigue (0–10)</td>
<td>7.2</td>
<td>4.2</td>
<td>7.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Sleep disturbance (0–10)</td>
<td>6.5</td>
<td>3.8</td>
<td>6.1</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Conclusions: A slight modification to the ACR2010 will allow their use in epidemiologic and clinical studies without the requirement for an examiner. The modified criteria can also be used to determine widespread pain according to the 1990 ACR classification criteria. The modified criteria are simple to use and administer, but they are not to be used for self-diagnosis. The FS may have wide utility beyond the bounds of FM, including substitution for widespread pain in epidemiological studies and measurement of FM severity.

**Disclosure:** F. Wolfe: None; D. J. Clauw: None; M. A. Fitzcharles: None; D. L. Goldenberg: None; W. Häuser: None; R. S. Katz: None; P. J. Mease: None; A. S. Russell: None; I. J. Russell: None; J. B. Winfield: None.

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Fibromyalgia Is Associated with a Disruption of Emotional Modulation of Pain, but Not Emotional Modulation of Spinal Nociception. Jennifer L. DelVentura¹, Ellen L. Terry², Emily J. Bartley², Ashley Vincent³, Ewa Olech⁴ and Jamie L. Rhudy⁵. ¹The University of Tulsa, Tulsa, OK, ²The University of Tulsa, ³University of Oklahoma, Health Sciences Center.

**Background:** Fibromyalgia syndrome (FM) is a disorder of unknown etiology that is characterized by chronic, widespread musculoskeletal pain and hyperalgesia. Recent functional imaging research has shown that FM patients exhibit differing patterns of brain activation during anticipation of and experience of experimental pain, as compared with rheumatoid arthritis (RA) patients and healthy controls (HC). Therefore, FM-related hyperalgesia may be due to an amplification of the nociceptive signal via cognitive-emotional mechanisms at the supraspinal level. Indeed, individuals with FM tend to report increased negative affect and reduced positive affect; a finding consistent with their higher rates of anxiety and depressive disorders. Given that emotion modulates pain and nociception, such that negative emotions augment pain and positive emotions inhibit it, and that FM patients exhibit hyperalgesia and greater negative affect, the present study examined whether FM patients would show disrupted emotional modulation of pain and nociception relative to RA and HC.

**Methods:** Patients with physician-verified diagnoses of FM or RA, and HCs with no chronic pain were recruited (N=33; FM=11, RA=8, HC=14). Participants were shown pictures that varied in emotional content (mutilation, neutral, erotica). To elicit pain and the nociceptive flexion reflex (NFR, a physiological correlate of spinal nociception), suprathreshold electrocutaneous stimuli were delivered to the left ankle over the sural nerve pseudorandomly, during and in between pictures.

**Results:** Pain and NFR during different picture contents were analyzed using a linear mixed model analysis. Results suggested that all groups exhibited emotional modulation of the NFR—unpleasant pictures augmented NFR and pleasant pictures inhibited NFR. Conversely, emotional modulation of pain ratings was exhibited in the RA and HC groups, but not in the FM group. Average pain ratings were not significantly different between groups (p=28).

**Conclusions:** Thus, only FM patients exhibited abnormal emotional modulation of pain, while cerebrospinal modulation of the NFR was similar across groups. These data support prior research indicating disrupted supraspinal processing of the pain signal in FM. This study was funded by NIAMS (grant number: 5R03AR054571).

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Fibromyalgia (FM) is associated with abnormalities of dopaminergic neurotransmission. Because iron is an important cofactor for dopamine
metabolism, we investigated whether FM symptom severity might correlate with iron stores as indicated by serum ferritin level (FE). Positional cervical cord compression (PC3) has also been recently identified as a common abnormality among FM patients (J Pain 2008;9:613-22). We therefore investigated whether FM patients with (FM/PC3+) or without (FM/PC3-) this cervical abnormality might differ with regard to symptom severity or their potential relationship to FE.

Methods: A convenience sample of 150 patients referred to a community-based FM specialty clinic was analyzed. All subjects met ACR 1990 diagnostic criteria for FM. Among these, 50% (n = 75) were randomly selected from a pool of patients with: (1) a clinical history of cervical trauma and/or exacerbation of symptoms on cervical extension; and (2) PC3 on dynamic magnetic resonance imaging (dMRI). The other 50% (n = 75) were randomly selected from among patients who either (1) denied a history of cervical trauma and had no exacerbation of symptoms on cervical extension, or (2) had undergone cervical dMRI and had no evidence of cord compromise. FE was drawn on all patients at intake and processed at the same clinical reference laboratory. All patients completed a comprehensive series of medical questionnaires, including a scaled review of systems and Adult ADH Self-Report Scale (ARSS). Categorical indices of symptom severity were derived by summation of scaled symptoms from the intake review of systems (0–5 scale: 0 = none; 1 = minimal; 2 = mild; 3 = moderate; 4 = severe; 5 = extreme). Student’s t-test for non-paired samples was used to compare FE and symptom severity between groups. Pearson’s correlation was used to evaluate potential correlations between FE and symptom severity within each group.

Results: There were no significant differences between groups concerning FM/PC3 vs. FM/PC3+, mean ± SD: 49.4 ± 33.8 ng/ml vs. 56.4 ± 35.9 ng/ml (p = .22) or the severity of any clinical index. However, among FM/PC3−, significant negative correlations were found between FE and the severity of several measures, including ARSS scores (r = −.377, p = .001), dyscognition (r = −.488, p < .001), dys-coordination (r = −.392, p = .001), affective disturbance (r = −.384, p = .001), and clinical pain (r = −.231, p = .047). Conversely, among FM/PC3+, no significant correlations were found between FE and the severity of any symptoms.

Discussion: Among FM patients without comorbid PC3, negative correlations exist between FE and the severity of symptoms ostensibly linked to dopaminergic neurotransmission, including dyscognition, dys-coordination, affective disturbance, and clinical pain. These remarkable differences among FM patients suggest distinct pathophysiological subtypes within the greater ‘FM construct’. Further research is needed to determine whether FM might be associated with abnormal iron metabolism and to evaluate for potential correlations between FE and objective measures of dopaminergic neurotransmission.

Disclosure: P. B. Wood: None; T. Schmidt-Wilcke: None; A. J. Holman: None.

103 Flt3-L Is a Novel Biomarker Increased in Cerebrospinal Fluid of Patients with Primary Fibromyalgia and Sjogren Syndrome. Jan L. Bjersing, Mats Dehlin, Henrik Zetterberg, Anette Larsson, Malin Erlandsson, Kaisa Mannerkorpi and Maria Bokarewa. Dept Rheumatology, Gothenburg University, Sweden

Primary fibromyalgia syndrome (FM) is a non-inflammatory condition, characterised by chronic generalized pain with allodynia. Primary Sjogren syndrome (pSS) is an autoimmune inflammation of exocrine glands. Fms-like tyrosine kinase 3 (Flt3-L) is a growth factor expressed in brain microglia and regulating differentiation and recruitment of monocytes into dendritic and glial cells. Both FM and pSS are commonly associated with fatigue and non-restorative sleep, and occasionally with depression and cognitive dys-function. The aim of the study was to compare inflammatory and axonal biomarkers in cerebrospinal fluid (CSF) of pSS and FM patients.

Paired samples of CSF and serum from female patients with pSS (age 48±12 years, disease duration 10±8 years) and FM (age 49±8 years, symptom duration 12±5 years) were evaluated for the levels of Flt3-L and related to inflammatory (IL-6, IL-8) and axonal (NFL, Tau, phosphorylated Tau, GFAP) biomarkers.

Flt3-L in CSF was significantly higher in FM patients compared to pSS patients (table 1). The proportion of phosphorylated Tau (pTau) to total Tau (tTau) was significantly higher in FM compared to SS. However, total levels of tTau and pTau were not different between the groups. Flt3-L in CSF correlated with levels of tTau and pTau, in both pSS (r = 0.68, r = 0.65) and FM (r = 0.38, r = 0.45). In FM, Flt3-L was also associated with neurofilament light chain (NFL, r = 0.41) and astrocyte marker glial fibrillary acidic protein (GFAP, r = 0.58). Flt3-L in CSF correlated with Flt3-L in serum of patients with pSS (r = 0.53) but not in FM. IL-6 in CSF was significantly higher in pSS patients compared to FM (table 1). No correlation was found between Flt3-L and IL-6. Serum levels of IL-6, IL-8 or Flt3-L were not significantly different between pSS and FM patients.

Table 1. Levels of biomarkers in cerebrospinal fluid in primary fibromyalgia (FM) and primary Sjogren syndrome (pSS)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>pSS</th>
<th>FM</th>
<th>pSS/FM</th>
<th>pSS/FM</th>
<th>pSS/FM</th>
<th>pSS/FM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flt3-L pg/ml</td>
<td>1.3 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>IL-6 pg/ml</td>
<td>4.2 ± 2.1</td>
<td>4.2 ± 2.1</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>IL-8 pg/ml</td>
<td>4.2 ± 2.1</td>
<td>4.2 ± 2.1</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>tTau ng/ml</td>
<td>24.5 ± 7.3</td>
<td>24.5 ± 7.3</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>pTau ng/ml</td>
<td>24.5 ± 7.3</td>
<td>24.5 ± 7.3</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>NFL ng/ml</td>
<td>4.2 ± 2.1</td>
<td>4.2 ± 2.1</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>GFAP ng/ml</td>
<td>1.3 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Flt3-L is a novel biomarker in CSF, distinguishing patients with FM and pSS. Levels of Flt3-L are positively related with axonal products, suggesting potential clinical impact of Flt3-L in fatigue and pain of patients with FM and pSS.

Disclosure: J. L. Bjersing: None; M. Dehlin: None; H. Zetterberg: None; A. Larsson: None; M. Erlandsson: None; K. Mannerkorpi: None; M. Bokarewa: None.


Background: Clinical observation and preliminary studies suggest that gynecological surgeries impact symptom severity in fibromyalgia. However, the literature is deficient in published studies assessing this relationship. Our objective was to compare differences in Fibromyalgia Impact Questionnaire (FIQ) scores in women with fibromyalgia who had a hysterectomy and/or oophorectomy and those who did not.

Methods: We conducted a retrospective chart review of 889 women with fibromyalgia, seen in the Fibromyalgia Treatment Program at a tertiary medical center between 2001 and 2004. Patients completed the FIQ at the time of their initial evaluation and data on age, race, duration of fibromyalgia symptoms, hysterectomy status, oophorectomy status and use of hormone therapy was abstracted from the clinical record. Linear regression analysis was used to compare FIQ scores between women who had a hysterectomy and those who did not.

Results: Of the women included in our review, 43.4% had a hysterectomy. Twenty-nine percent had a bilateral oophorectomy and 4.3% had a unilateral oophorectomy. After adjusting for age, duration of fibromyalgia symptoms and use of hormone therapy, total FIQ scores of women who had a hysterectomy were significantly higher than those who did not (p = .0013). Similarly, FIQ subscales of physical impairment (p = .0405), pain (p = .0001), stiffness (p = .0397) and depression (p = .0079) were also higher in women who had a hysterectomy than in those who did not. Though not statistically significant, trends were also observed in subscales of fatigue (p = .0979) and anxiety (p = .0517). These associations were independent of oophorectomy status and the timing of the hysterectomy.

Conclusions: Our results indicate that presence of hysterectomy influences symptom severity in women with fibromyalgia. The prevalence of hysterectomy is also higher than the rate of approximately 33% by age 60 reported in general population. To our knowledge, this is the first retrospective review assessing this relationship. Since, our retrospective review was limited by incomplete information on duration of hormone therapy use in relationship to timing of hysterectomy, we are unable to speculate on the influence of surgical menopause on FIQ scores. A prospective study with longitudinal follow-up will better characterize this influence.

Disclosure: M. O. Whipple: None; A. Vincent: None; T. H. Oh: None; C. A. Luedtke: None; T. L. Hoskin: None.

105 Improvement in Multiple Dimensions of Fatigue in Fibromyalgia Patients Treated with Duloxetine. Lesley M. Arnold, Fujun Wang, Jonna Ahl, Paula Gaynor and Madeleine Wohrle. Lilly USA LLC, Indianapolis, IN, ‘Women’s Health Research Program, Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH
Background: In addition to widespread pain, fatigue is one of the most common and disabling symptoms of fibromyalgia. Fatigue was assessed as a secondary objective in this 2-phase 24-week trial of duloxetine in patients with ACR-defined fibromyalgia.

Methods: Outpatients 18–65 years of age, with Brief Pain Inventory average pain ≥4 were randomized to duloxetine 60–120 mg/d (N = 263) or placebo (N = 267) for the 12-week acute phase. At Week 12, all patients in the placebo group were switched to double-blind treatment with duloxetine for the 12-week extension phase. Fatigue was assessed at baseline and every 4 weeks by the Multidimensional Fatigue Inventory (MFI), which is comprised of the following subscales: General Fatigue (GF), Physical Fatigue (PF), Mental Fatigue (MF), Reduced Activity (RA), and Reduced Motivation (RM). The frequency of treatment-emergent adverse events (TEAE) that might be associated with fatigue, such as fatigue, insomnia and somnolence, was also assessed. Changes from baseline in MFI subscale scores during the acute phase, and from Week 12 during the extension phase were analyzed by mixed-effects model repeated measures analysis. For the acute phase, the model included baseline value, acute phase treatment, investigator, visit, treatment-by-visit, and baseline-by-visit interactions; for the extension phase, the model included: investigator, visit, Week 12 baseline score and baseline-by-visit interaction (the model was fitted separately for patients randomized to duloxetine and patients randomized to placebo then switched to duloxetine in the extension phase).

Results: At the end of the acute phase, patients who received duloxetine versus placebo had significantly reduced scores on each MFI subscale (all p < .05) indicating improvement (Arnold et al.). In the extension phase, mean MFI subscale scores indicated that improvement was maintained for patients who received duloxetine for up to 24 weeks (n = 176). For placebo-treated patients who were switched to duloxetine (n = 187), significant within-group improvement in MFI subscale scores was observed at Weeks 16, 20 and 24 for PF, Weeks 20 and 24 for GF, Week 20 for MF, and Weeks 20 and 24 for RA. Individual subscale scores after switching to duloxetine were similar to those for patients who received duloxetine for 24 weeks. This suggests that patients treated with duloxetine for 6 months maintained improvement in all dimensions of fatigue assessed by the MFI, and that placebo patients switched to duloxetine quickly reached the level of improvement in fatigue observed in the active treatment group. In the acute phase, TEAE rates of fatigue, somnolence and insomnia were 9.5%, 5.7% and 9.1% for duloxetine; 7.1%, 3.4%, and 7.1% for placebo. In the extension phase, overall rates for these TEAEs were: fatigue 4.1%; somnolence, 2.5%; and insomnia, 3.6%.

Conclusion: Treatment with duloxetine significantly improved multiple dimensions of fatigue in patients with fibromyalgia, and improvement was maintained with duloxetine treatment up to 24 weeks.


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Novel Treatment of Tendinopathies with a Sulfated Disaccharide of Hyaluronic Acid—Promising In Vitro Results. Anna Torrent1, Ramon Ruhı́2, Carlos Alaez3, Constanze Buhrmann2 and Mehdi Shakibaei3. 1BIOIBERICA S.A., Palafrugell, Barcelona, Spain; 2Ludwig-Maximilians-University, Munich, Germany; 3Ludwig-Maximilians-University Munich, Munich, Germany

Purpose: As tenons regenerate slowly and inefficiently after trauma, tendinopathies pose a serious musculoskeletal problem. Recent studies in Munich, Germany demonstrated that BIS014 exerts a potent stimulatory effect on human tenocyte proliferation and was able to suppress catabolic, apoptotic and inflammatory effects induced by IL-1β. Suppression of IL-1β-induced up-regulation of activated caspase-3, Cox-2 and MMP-1, -9 and -13 by western blotting further confirmed these results.

Conclusion: These results demonstrate that the synthetic disaccharide of hyaluronic acid BIS014 may have therapeutic utility for the healing, regeneration and repair of tendons.


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Outcome for a Prospective Cohort of Fibromyalgia Patients Receiving Tailored Treatments in a Multidisciplinary Pain Center. Mary-Ann Fitzcharles, Pantelis Panopalis, Ann Gamsa, Mark Ware and Yoram Shir. McGill University

Background: The ideal management of fibromyalgia (FM) is still under debate. There is increasing appreciation of the importance of the various core component symptoms in FM patients, contributing to the complexity of management. Expert opinion suggests that multimodal treatment including non-pharmacologic and pharmacologic interventions are desirable. In view of the complexity of combining various treatment strategies, observational studies in real life clinical settings should provide helpful information regarding outcome. We have examined the outcome in FM patients being followed in a multidisciplinary setting with treatments tailored to individual patient needs.

Methods: Patients newly referred to a multidisciplinary pain clinic with a primary diagnosis of FM were entered into a prospective cohort study. All patients were evaluated by a physician and a psychologist, a treatment plan was developed and patients had access to nursing or physiotherapy consultation when deemed necessary. Treatments were individually based taking into consideration previous treatments and severity of core symptoms. Demographic, disease and psychosocial variables included the following: Fibromyalgia Impact Questionnaire (FIQ), visual analogue scale (VAS) for patient global status and pain scores, McGill Pain Questionnaire (MPQ), Arthritis Impact Measurement Scale, anxiety and depression (AIMS), pain catastrophizing scale (PCS), and pain disability index (PDI). All patients were advised to participate in a regular physical activity program of their choice, and were asked to identify outcome and functional goals. At follow-up, patients were queried about overall change in symptoms, and were categorized into one of two groups: improved or same/worse. Univariate comparisons were made between the two groups using Student’s t-tests for continuous variables and chi-squared tests for categorical variables. Logistic regression was used to model the association between selected variables.

Results: Of the 184 patients entered in the cohort, 114 had at least one follow-up assessment at least one year after entry and were included in the analysis. The average age of the study sample was 49.0 (SD 10.0) and 92.1% were female. Improvement was reported in 80 patients (70%) whereas 34 patients (30%) reported symptoms as same or worse. Improvement was associated with improvement in measurements of the following disease parameters: FIQ (p = 0.001), global VAS score (0.02), pain VAS score (p = 0.004), PDI (p < 0.001), AIMS (depression) (p < 0.001) and PCS (p = 0.002). MPQ scores and AIMS (anxiety) were not associated with improved global outcome. A logistic regression model including all significant univariate associations found that only reduced AIMS (depression) was associated with improved global outcome (OR 1.4, 95% CI 1.1–2.0).

Conclusion: More than two thirds of FM patients, receiving tailored multidisciplinary treatment, had a favourable outcome. This was observed even in the setting of longstanding symptoms, and for patients seen in a tertiary care centre, likely representative of those with disease at the severe end of the spectrum. Targeting depression may improve outcome for FM patients.

Disclosure: M.-A. Fitzcharles: None; P. Panopalis: None; A. Gamsa: None; M. Ware: None; Y. Shir: None.
Predictors of Clinical Outcome in Fibromyalgia: Single Center Experience of a Brief Interdisciplinary Fibromyalgia Treatment Program. 

Terry H. Oh, Tanya L. Hoskin, Connie L. Ludetke, Toby N. Weingarten, Ann Vincent and Jeffrey M. Thompson. Mayo Clinic, Rochester, MN, Mayo Clinic, Kingston, ON, Canada

Purpose: To determine which patient characteristics are associated with a positive response to a brief interdisciplinary fibromyalgia treatment program.

Methods: Prospectively designed follow-up questionnaire study among patients who underwent the Fibromyalgia treatment program at a tertiary medical center. Patients with confirmed fibromyalgia, underwent a one and half day interdisciplinary fibromyalgia treatment program, and completed the Fibromyalgia Impact Questionnaire (FIQ) at baseline and again 6-12 months after treatment were studied (n=536). Minimally clinically important difference (MCID) in fibromyalgia derived from FIQ changes was reported to be 14%. Therefore, we defined responders as participants who reported an improvement of ≥14% in the FIQ total score from baseline to 6-12 months after treatment, and non responders as participants who either worsened or improved < 14 % in the FIQ total score 6-12 months after treatment.

Predictor variables included demographic variables, baseline FIQ depression score, psychosocial variables, numeric rating scale (NRS) pain scores and number of fibromyalgia tender points. Univariate associations with responder status were assessed using two-sample t-tests and chi-square tests. Multivariate analysis used logistic regression; these results are reported with odds ratios (OR) and 95% confidence intervals (CI). Response status (responder or non responder) were assessed using two-sample t-tests and chi-square tests.

Results: Mean (SD) age of participants was 50.3 (13.0) years; 515 (96%) women and 23 (4%) men. Two hundred forty-eight patients (46%) were responders. In univariate analysis, responders were younger (p=0.008), achieved a higher level of education (p=0.02), had fewer tender points (p=0.048) and higher FIQ depression subscores (p=0.02) when compared to non responders. Positive abuse history did not reach statistical significance but showed a trend (p=0.05).

In multivariate analysis, these factors remained statistically significant. In addition, positive abuse history became significant (p=0.03). Younger age (OR:1.03, 95% CI: 1.01 to 1.05 per 1 year decrease), having a college or graduate degree (OR: 1.59, 95% CI: 1.07 to 2.36) and higher baseline FIQ depression score (OR:1.11, 95% CI: 1.05 to 1.20 per 1 unit increase) were associated with increased odds of being a responder, while increasing number of tender points (OR:0.91, 95% CI: 0.83 to 1.0 per 1 point increase), and abuse history (OR:0.62, 95% CI: 0.40 to 0.96) were associated with decreasing odds of being a responder. Gender, duration of symptoms, marital, employment, or smoking status, geographical location and 3 NRS scores were not statistically different between the responders and non responders.

Conclusions: Younger age, college or graduate degree, higher baseline FIQ depression score, lower tender point count and absent history of abuse were all associated with increased odds of treatment response.

Disclosure: T. H. Oh: None; T. L. Hoskin: None; C. L. Ludetke: None; T. N. Weingarten: None; A. Vincent: None; J. M. Thompson: None.


Sassan Ghazan-Shahi, Tanveer E. T. Towheed and Wilma Hopman. Queen’s University, Kingston, ON, Canada

Background: Fibromyalgia is a controversial widespread chronic pain disorder that includes a wide constellation of somatic and emotional symptoms. This study surveyed the opinion of Ontario Rheumatologists with respect to their beliefs about the nature and management of fibromyalgia. A key objective was to ascertain if Rheumatologists should continue to be the main care providers for these patients.

Methods: A survey questionnaire comprising 13 questions was sent electronically to all 150 Ontario Rheumatologists. The questionnaire was designed to obtain demographic data as well as opinions regarding different aspects of fibromyalgia. Data were analyzed descriptively and comparisons were made using chi-square tests.

Results: A total of 80 respondents (58% male) completed our survey for a completion rate of 53%. The majority had completed their training in Canada (85%) and had been practising for more than 15 years (50%). 55% worked in University hospitals and 45% worked in the Community. Key findings were: (1) 71% believe that Rheumatologists should not retain ownership of fibromyalgia, (2) 55% believe that fibromyalgia is primarily a psychosomatic illness as opposed to a physical illness, (3) 60% are accepting new referrals for fibromyalgia, (4) 60% are managing patients with fibromyalgia, (5) 89% believe that the family physician should be the main care provider for these patients, (6) 31% usually consider psychiatric referral for these patients, (7) 79% recommend behavioural treatment methods, (8) 58% consider severe fibromyalgia to be a potentially disabling condition that warrants financial compensation through disability, (9) Rheumatologists who consider fibromyalgia to be a physical illness were also significantly more likely to believe that Rheumatologists should retain ownership of this disease (p=0.023). They were also more likely to accept new referrals for this disease (p=0.044), and also more likely to continue managing these patients in their practice (p=0.011).

Conclusions: The majority of Ontario Rheumatologists do not wish to retain ownership of fibromyalgia. However, most of them continue to accept new referrals and continue to manage these patients, even though they believe that the family physicians should be the main care provider for patients with fibromyalgia. Rheumatologists may be providing care to these patients primarily because this care is not available to them from their primary care physicians.

Disclosure: S. Ghazan-Shahi: None; T. E. Towheed: None; W. Hopman: None.

The Course of Fibromyalgia—A Long-Term Longitudinal Cohort Study.

Brian Walitt, Winfried Häuser, Afton Hassett, Robert S. Katz and Frederick Wolfe. National Databank for Rheumatic Diseases, Rush University, Technische Universität München, University of Michigan Medical School, Washington Hospital Center, Washington, DC

Purpose: Fibromyalgia (FM) is a chronic condition in which treatment is of limited effectiveness. However, the ACR 2010 criteria study reported that 25% of FM patients improved sufficiently so that they did not meet classification criteria at follow-up. Other studies have also reported various degrees of improvement. Much of the uncertainty about the course of FM can be attributed to selection bias and non-standardized measures of improvement. In this report, we followed 1,555 criteria positive FM patients for a mean of 4.0 years (range 1.0 to 11.5 years) to determine the symptomatic course.

Methods: Patients were participants in a longitudinal study of FM outcomes. They were assessed semi-annually in 11,006 observations (6,251 pt-years). Assessments included the Wide spread Pain Index, fatigue, sleep disturbance, functional status and a general measure of FM severity (the Fibromyalgianess Scale). Criteria status was assessed with a study modification of the ACR 2010 diagnostic criteria. We used generalized estimating equations (GEE) to assess the rate of change of study variables over time and Cox regression to assess incidence of loss and regain of FM diagnostic status.

Results: Patients switched between criteria positive and negative states. 716 patients became criteria negative during the study (44.0%), for an incident rate of 16.9 (15.7, 18.2) per 100 pt-years; and 378 patients (24.3%) who satisfied FM criteria at entry no longer satisfied criteria at the study close, an incident rate 6.0 (5.5, 6.6) per 100 pt-years. All FM related variables followed the transition between positive and negative states. The strongest predictor was the 0–31 fibromyalgianess scale, which decreased by −0.36 (0.32, 0.40) units annually. Other study variables also decreased during the study. Figure 1 shows fibromyalgianess in patients remaining criteria positive (23.8 ± 4.5) and those who became criteria negative (12.9 ± 4.2).
Figure 2 demonstrates minimum and maximum pain, symptom count, fatigue, and mood scores during follow-up.

**Conclusions:** FM patients often switch between criteria positive and negative states and have a wide variation in symptoms. These data indicate limitations in the usefulness of the discrete diagnosis of FM. Symptom severity, as opposed to diagnosis, appears to be more clinically reliable and relevant. The fluctuating nature of FM diagnosis has important implications for clinical care and treatment indications.

Disclosure: B. Walitt: None; W. Häuser: None; A. Hassett: None; R. S. Katz: None; F. Wolfe: None.

The Development of Fibromyalgia: Examination of Rates and Predictors in Patients with Osteoarthritis (OA).

Frederick Wolfe 1 and Winfried Häuser 2. 1National Data Bank for Rheumatic Diseases, Wichita, KS, 2Technische Universität München, Munich, Germany

**Purpose:** Using modified ACR 2010 fibromyalgia (FM) criteria, we have reported that in 9,739 rheumatoid arthritis (RA) patients without FM, a series of demographic, RA, FM, and psychological variables predict FM development. However, it is possible that RA damaged joints or systemic illness may interfere with FM measurements and predictors, and prediction and predictive strength might be different in RA compared with regional rheumatic disorders such as osteoarthritis (OA). To examine this possibility, to compare FM in RA and OA, and to confirm our prediction models, we analyzed predictors of FM in OA.

**Methods:** After excluding patients with FM and those with high levels of FM symptoms (fibromyalgianess score ≥10), we studied the FM development in 1,888 OA patients during 6,892 patient-years of follow-up over a mean follow-up time of 4.3 (SD 3.5) years (range, 5 to 11). We defined FM using a modification of the ACR 2010 FM diagnostic criteria. We used Cox regression to predict future FM, and examined the discriminatory power and accuracy of predictions using Harrell’s C concordance coefficient.

**Results:** At the last observation, 6.0% of OA compared with 7.4% of RA patients satisfied FM criteria, although 18.8% of OA and 19.8% with RA did so at some point during follow-up, for an OA FM incidence rate of 5.0 (95% CI 4.2, 5.3) and an RA rate of 5.3 (5.1, 5.6) per 100 pt-years. The rate in women was 5.5 (4.9, 6.2) and was 3.5, (4.7, 5.5) in men. Among those satisfying criteria, half of follow-up time after diagnosis was FM criteria (+), and was associated with markedly abnormal OA and FM variable scores. C-statistics, adjusted for age and sex, are shown in Figure 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>H.R (95% CI)</th>
<th>z</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Widespread pain (0–19)</td>
<td>1.28 (1.21, 1.36)</td>
<td>8.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAQ (0–10)</td>
<td>2.06 (1.67, 2.54)</td>
<td>6.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptom count (0–34)</td>
<td>1.10 (1.07, 1.13)</td>
<td>6.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatigue (0–10)</td>
<td>1.21 (1.17, 1.35)</td>
<td>6.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mood (0–10)</td>
<td>1.11 (1.02, 1.21)</td>
<td>2.50</td>
<td>0.013</td>
</tr>
<tr>
<td>Opioid use</td>
<td>1.29 (0.99, 1.67)</td>
<td>1.87</td>
<td>0.062</td>
</tr>
<tr>
<td>Comorbidity None</td>
<td>1</td>
<td>1.34 (0.97, 1.84)</td>
<td>1.8</td>
</tr>
<tr>
<td>1</td>
<td>1.72 (1.25, 2.37)</td>
<td>3.35</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>1.70 (1.15, 2.49)</td>
<td>2.69</td>
<td>0.007</td>
</tr>
<tr>
<td>3–9</td>
<td>1.35 (0.86, 2.12)</td>
<td>1.29</td>
<td>0.196</td>
</tr>
</tbody>
</table>

Clinically important HRs were noted for cognition, depression, comorbidity and high levels of OA and FM continuous variables.

**Conclusions:** FM is predicted similarly in patients with OA and RA. Multiple factors contribute to FM development, including sociodemographic disadvantage, comorbidity, psychological distress, drug and service utilization, FM symptoms (particularly somatic symptom reporting), and functional status; but there is little evidence of the effect of underlying causes.

Disclosure: F. Wolfe: None; W. Häuser: None.
The Development of Fibromyalgia: Examination of Rates and Predictors in Patients with Rheumatoid Arthritis (RA). Frederick Wolfe1, Winfried Häuser2, Afton L. Hassett2, Robert S. Katz2 and Brian T. Walitt3. 1National Data Bank for Rheumatic Diseases, Wichita, KS; 2Rush University Medical Center, Chicago, IL; 3Technische Universität München; 4University of Michigan Medical School; 5Washington Hospital Center, Washington, DC.

Purpose: There are no prospective studies of the development of criteria-based fibromyalgia (FM) that consider multiple risk factors. The purpose of the study was to determine rates and predictors of future development of FM in patients with rheumatoid arthritis (RA). We studied FM in RA because of its intrinsic interest and because RA patients provided a substrate of patients that were unselected, particularly with respect to FM characteristics. In addition an extensive set of demographic and severity covariates were available.

Methods: After excluding patients with FM and those with high levels of FM symptoms (fibromyalgianess score >10), we studied the development of FM in 9,739 RA patients during 42,591 patient-years of follow-up. We defined FM using a modification of the ACR 2010 FM diagnostic criteria. We used Cox regression to predict future FM, and examined the discriminatory power and accuracy of predictions using Harrell’s C concordance coefficient.

Results: At the last observation, 7.4% of patients satisfied criteria, although 19.8% satisfied criteria at some point during follow-up, for an incidence rate of 5.3 (95% CI 5.1, 5.6) per 100 patient-years, and at rates that were similar in men (7.8%) and women (8.1%). Among those satisfying criteria, during 11,363 years of follow-up from the time of first fibromyalgia diagnosis, approximately half of follow-up time was fibromyalgia criteria, during 11,363 years of follow-up from the time of first fibromyalgia diagnosis, approximately half of follow-up time was fibromyalgia+ and was associated with markedly abnormal RA variable and FM variable scores. C-statistics for individual variables, adjusted for age and sex, are shown in the Figure.

Conclusion: FM can be predicted with clinically available variables. Multiple correlated factors contribute to the development of fibromyalgia. These factors include socio-demographic disadvantage, comorbidity, psychological distress, drug and service utilization, fibromyalgia symptoms (particularly somatic symptom reporting), and functional status; but there is little evidence of the effect of underlying causes. After diagnosis, patients move in both directions across the diagnostic criteria cut point.

Disclosure: F. Wolfe: None; W. Häuser: None; A. L. Hassett: None; R. S. Katz: None; B. T. Walitt: None.

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The Effect of Duloxetine on Cognition in Patients with Fibromyalgia. Philip J. Mease1, Lesley Arnold2, Fujun Wang3, Jonna Ahl4, Richard Mols5, Paula Gaynor6 and Madelaine Wohltreich7. 1Eli Lilly and Company, 2Lilly USA, LLC, 3Seattle Rheumatology Associate, Seattle, WA; 4Women’s Health Research Program, Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH.

Background: Cognitive difficulties are common complaints among patients with fibromyalgia and include perceived deficits in attention, concentration and memory. Cognitive testing was conducted in a subset of patients participating in a randomized, double-blind, placebo-controlled trial of duloxetine in fibromyalgia.

Methods: At selected sites, patients eligible for the main study were asked if they would like to participate in the cognitive testing and provided separate informed consent for this testing. Patients were ≥18 years of age, met ACR criteria for fibromyalgia, and ≥4 score on the Brief Pain Inventory (BPI) 24-h average pain severity item. Patients who consented to cognitive testing were randomized to duloxetine (n=80) or placebo (n=76) for 24 weeks of double-blind treatment. The primary endpoint was at Week 12, after which placebo patients were switched to double-blind treatment with duloxetine.

Results: The results presented here are for the first 12 weeks. Verbal learning and memory was tested using the 15 word Verbal Learning and Recall Test (VLRT); speed of processing, visual attention and executive function were tested using the Symbol Digit Substitution Test (SDST), the Two Digit Cancellation Test (2DCT), and the Trailmaking Test (Trails A and B). Change from baseline to endpoint (last-observation-carried-forward) was analyzed by an analysis of covariance model, which included baseline, treatment, investigator and treatment-by-investigator interaction.

Conclusion: Impairment in cognitive function in patients with fibromyalgia was not evident on VLRT, SDST, 2DCT or Trails A or B. Overall, treatment with duloxetine did not have a positive or negative effect on cognition when measured with these tests.


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The Effectiveness of Botulinum Toxin Type-A and Prilocaine Injections in Myofascial Pain Syndrome. Mehmet Zeki Kiralp, Baki Ozdemir, Engin Cakar, Oguz Durmus, Levent Tekin and Umit Dincer. Gülhane Military Medical Academy, Haydarpasa Training Hospital, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey.

Objective: The objective of this study was to compare the effectiveness of botulinum toxin-A (Btx-A) and prilocaine injections in the treatment of myofascial pain syndrome (MAS).

Methods: Forty-six eligible patients who had diagnosed as MAS were recruited and were randomized into two treatment groups namely Btx group...
The Patient Specific Functional Scale Outperforms the Fibromyalgia Impact Questionnaire Physical Function Scale. Chad S. Boonershine1, Kim A. Edwards2, Jennifer Y. Hong2 and Kenneth A. Wallston2. 1Vanderbilt University, Nashville, TN, 2Vanderbilt University

Background: Fibromyalgia (FM) is a disease defined by chronic widespread pain and tenderness that causes functional impairment in many patients. The FM impact questionnaire physical function scale (FIQFPS) has been the standard used by rheumatologists to measure functional impairment in FM patients. However, its clinical utility is limited due to its length (11 questions), complex scoring, and assessment of rarely performed activities. The patient specific functional scale (PSFS) is a brief (3 question) functional impairment measure that assesses difficulty with patient-selected activities on an easily scored 0 to 10 numeric rating scale (NRS) commonly used by physical therapists. We hypothesized that the PSFS is a more clinically useful functional measure than the FIQFPS due to its brevity, ease of scoring and patient-specific nature. However, performance of the PSFS has never been compared to the FIQFPS. We compared baseline psychometric properties of the PSFS and the FIQFPS and the ability of both scales to measure global change in patients treated with physical therapy (PT).

Methods: Patients (N=340) sent for PT treatment were assessed at baseline and after treatment for 1 month. Baseline and follow-up evaluations included demographics, a pain NRS, regional pain scale (RPS), fatigue and sleep scale (FSS), disease-neutral FIQFPS, PSFS, and patient global impression of change (PGIC). Baseline pain NRS scores ≥4 identified pain patients. FM survey criteria (RPS ≥8 and FSS ≥6) at baseline identified FM patients. Spearman rank correlations were used to compare questionnaire scores. Statistical methods were performed using PASW Statistics 17.

Results: At baseline, the PSFS had lower floor effects for all patients (n=340) compared to the FIQFPS (0.9% vs 17.3%, respectively). In patients with pain (n=249), the PSFS also had lower floor effects compared to the FIQFPS (1.2% vs 8.8%, respectively). In FM patients (N=82), the PSFS had no floor effects whereas the FIQFPS had 7.3%. Ceiling effects were negligible for both scales in all patient groups (<1%). PSFS scores were normally distributed for all patient groups, while FIQFPS scores were not normally distributed for any group. At follow-up, PGIC scores significantly correlated with change in PSFS scores for all patients (p=0.52, p<0.001), pain patients (p=0.52, p<0.001) and FM patients (p=0.91, p<0.001).

Figure 1. Patient global impression of change score correlates with change in patient specific functional scale score in fibromyalgia patients.

PGIC scores did not correlate significantly with change in FIQFPS scores for any patient group [all patients (p=0.13, p=0.314), pain patients (p=0.09, p=0.584), or FM patients (p=0.272, p=0.347)].

Conclusions: The PSFS has superior psychometric properties compared to the FIQFPS and significantly correlates with PGIC scores in patients treated with PT. Our results indicate the PSFS may be a better questionnaire to evaluate functional impairment and response to therapy than the FIQFPS in many patient groups including FM patients.

Disclosure: C. S. Boonershine: Eli Lilly and Company, 8, Forest Pharmaceuticals, Inc, 8, NIH, 2, Pfizer Inc, 2, 8; K. A. Edwards: None; J. Y. Hong: None; K. A. Wallston: None.

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Purpose: Despite its shortcomings, the Fibromyalgia Impact Questionnaire (FIQ) is widely used to assess clinical symptoms and measure therapeutic changes in patients with fibromyalgia (FM). Recently, the updated version (FIQR) was released. In this study, we validated the Korean version of the FIQR and evaluated whether the revised version is superior to the original one in reflecting the physical function and quality of life of these patients.

Methods: After translating the FIQR into Korean, the FIQR was administered to 50 FM patients to assess its comprehensibility. Next, 340 patients were trained about the stretching exercises and instructed to do at home regularly. Clinical assessment parameters were visual analog scale (VAS) for pain during function, pain score (PS) during digital pressure, short form-36 (SF-36) for quality of life and Beck depression inventory (BDI) for general well-being. The assessments were performed at baseline and at 2nd and 6th weeks after the injections.

Results: There were no statistical differences between the groups at baseline. The study was finished with 38 patients (19 patients in each group). Both of the groups’ VAS, PS, BDI scores at 2nd and 6th weeks and all of the subscale scores of SF-36 at 6th week improved according to baseline. In inter-group comparison it was seen that the VAS score at 2nd and 6th weeks and PS at 6th week improved statistically better in Btx-A group than prilocaine group (p<0.05). In addition, all of the subscale scores of SF-36 except physical functioning were statistically better in Btx-A group (p<0.05) at 2nd and 6th weeks.

Table 1. The intra- and inter-group comparisons of the treatment effects of Btx-A and prilocaine

<table>
<thead>
<tr>
<th></th>
<th>Baseline mean ± SD</th>
<th>2nd week mean ± SD</th>
<th>6th week mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>8.95 ± 1.13</td>
<td>4.26 ± 1.41</td>
<td>3.74 ± 1.66</td>
</tr>
<tr>
<td>PS</td>
<td>8.37 ± 1.38</td>
<td>3.21 ± 1.03</td>
<td>2 ± 0.88</td>
</tr>
<tr>
<td>%</td>
<td>0.16</td>
<td>0.012</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*: p score of intra-group changes according to baseline
**: p score of inter-group changes
%: the percentage of change according to baseline

Conclusions: Both Btx-A and prilocaine injections combined with appropriate exercise program were beneficial treatment choices in MAS management. It was also seen that Btx-A injections have better effects especially in regard to pain and health quality in short to medium term. It was noticeable that there was no difference between the groups at 2nd week in regard to PS, but Btx-A group’s PS scores were statistically better at 6th week control. This might be interpreted as the progressive cumulative effect of Btx-A.

These outcomes were the preliminary results of an ongoing follow-up study. Further studies are needed for the clarification of the long term effects of Btx-A injections in MAS management.

Disclosure: M. Z. Kiralp: None; B. Ozdemir: None; E. Cakar: None; O. Durmus: None; L. Tekin: None; U. Dincer: None.

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Purpose: Despite its shortcomings, the Fibromyalgia Impact Questionnaire (FIQ) is widely used to assess clinical symptoms and measure therapeutic changes in patients with fibromyalgia (FM). Recently, the updated version (FIQR) was released. In this study, we validated the Korean version of the FIQR and evaluated whether the revised version is superior to the original one in reflecting the physical function and quality of life of these patients.

Methods: After translating the FIQR into Korean, the FIQR was administered to 50 FM patients to assess its comprehensibility. Next, 340 patients were trained about the stretching exercises and instructed to do at home regularly. Clinical assessment parameters were visual analog scale (VAS) for pain during function, pain score (PS) during digital pressure, short form-36 (SF-36) for quality of life and Beck depression inventory (BDI) for general well-being. The assessments were performed at baseline and at 2nd and 6th weeks after the injections.
FM were invited to complete a questionnaire that included the original FIQ, FIQR, Multidimensional Health Assessment Questionnaire (MDHAQ), Rheumatology Attitudes Index (RAI), and Medical Outcome Study Short-Form 36 (SF-36) and were examined for tender points using thumb palpation.

**Results:** The test-retest reliability was assessed in 53 patients after 1 week, and the correlation coefficients were between 0.604 and 0.825 (Cronbach’s alpha = 0.961). The total score on the FIQR was closely correlated with that on the original FIQ (r = 0.869, p < 0.001), and each of the three FIQR domains was also significantly correlated with the three related FIQ domains (all p < 0.001). The FIQR was significantly correlated with tender point counts and scores, pain visual analogue scale (VAS), fatigue VAS, RAI, MDHAQ, and the physical and mental component summary scores of the SF-36 (all p < 0.001). The FIQR was more strongly associated with the MDHAQ and SF-36 than with the original FIQ.

**Table.** Comparison of FIQR and FIQ with symptoms, physical function, and quality of life.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment Mean (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Off Rx</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>40.6 (39.7, 41.5)</td>
<td>0.441</td>
</tr>
<tr>
<td>Fatigue</td>
<td>68.6 (67.7, 70.0)</td>
<td>0.203</td>
</tr>
<tr>
<td>Global</td>
<td>30.7 (30.1, 31.3)</td>
<td>0.216</td>
</tr>
<tr>
<td>MCS</td>
<td>31.0 (30.4, 31.6)</td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>40.8 (40.0, 41.7)</td>
<td></td>
</tr>
</tbody>
</table>

As shown in the table, most variables were not significantly different by treatment class. The 0–10 pain scale was minimally improved by 0.22 units and the 0–31 fibromyalgia severity scale by 0.63 units. We also analyzed the effect of each drug separately. In none of the separate analyses was a significant treatment effect detected.

**Conclusion:** Our study showed that the updated FIQR is a reliable, valid instrument for assessing FM patients and performs better at predicting physical function and health status than does the original FIQ.

**Disclosure:** S.-R. See: None; S.-J. Lee: None; T.-J. Kim: None; Y.-W. Park: None; S.-S. Lee: None.

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**Treat**

**Purpose:** Usual treatment for fibromyalgia (FM) is generally considered to be unsatisfactory. Recently, the US Food and Drug Administration approved several drugs specifically for treatment of FM based on controlled clinical trials that showed modest improvement compared to placebo. These treatments include pregabalin, duloxetine, and milnacipran. The treatments are now widely advertised and available in the US. However, whether such treatments are superior to prior conventional FM therapy, as used in the community, is not known. In this study we compare the new therapies to usual therapy to determine the degree to which they improve patients with FM.

**Methods:** We compared clinical status in patients who received at least one of the 3 therapies when they were receiving the treatments compared with when they were not receiving any of the treatments. Patients were assessed longitudinally at 6 month intervals. We assessed 611 patients during 4,415 observations, 1,895 of which (42.9%) were on treatment and 2,520 (57.1%) when they were not receiving any of the treatments. Patients were assessed to assess treatment effect we used generalized estimating equations (GEE), controlling for age, sex and baseline fibromyalgia severity. The study outcome variables included visual analog scales for pain, fatigue and global, HAQ, SF-36 PCS, MCS and mood, and fibromyalgia severity—using a severity measure from the American College of Rheumatology 2010 fibromyalgia criteria.

**Results:** The mean age (SD) of treated patients was 56.5 (10.7), and 97% were women. Table 1 shows the adjusted means by treatment category.

**Table.** Comparison of FIQR and FIQ with symptoms, physical function, and quality of life.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment Mean (95% CI)</th>
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<tbody>
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<tr>
<td>PCS</td>
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</tr>
</tbody>
</table>

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**A Novel Tool for Fully Automatic Quantification of MRI Synovitis in Rheumatoid Arthritis Is More Sensitive to Change Than the Current Standard Semi-Quantitative Assessment.** Michael A. Bowes1, Jane E. Freeston2, Edward J. Vitali1, Graham Vincent2, Gwenaëll Guillard3, Paul Bird2, Paul Emery2, and Philip G. Conaghan3. 1Imorphics Ltd, Manchester, United Kingdom, 2Imorphics Ltd, 3rrrpe@leeds.ac.uk.

**Background:** Current MRI evaluation in rheumatoid arthritis (RA) employs a semi-quantitative tool (OMERACT RAMRIS). Fully automated quantification of change in MRI pathology remains a highly desirable outcome for clinical trials and practice. 3D statistical appearance models have been used in osteoarthritis to detect very small physical changes in bone, cartilage and soft tissue.

**Objectives:** To determine the responsiveness of a novel 3D automated measurement of MRI synovitis in the MCP and wrist joints of RA subjects in an open label study and to compare this with the RAMRIS synovitis assessment.

**Methods:** 3T VIBE MR images pre- and post-contrast of 47 established RA patients who had recently commenced the same biological therapy were evaluated. Subjects were imaged at baseline and regular intervals after 6 months. 3D models or ‘masks’ of the joints assessed by RAMRIS were created from a separate dataset of RA images. Masks were created for the MCP joints, the radio-carpal joint, the radio-ulnar joint, and a mask for the carpal bones. These masks were fitted to each pre-contrast image and then subtraction images were created using a shuffle transform method. Synovitis volume (in mm³) was calculated automatically from the enhancing voxels within each mask. RAMRIS scoring was performed by a single experienced reader, blinded to time point.

**Results:** Mean age of patients was 54.7 years, 88% women, 88.9% RF positive, mean number of previous DMARDs 2.88, 22/55 patients had received previous anti-TNF [10 1TNF, 9 2TNFs, 3 3TNFs] therapy. The numbers of patients with scans available at each time point were: 46 (6 months), 35, 15, 21, and 14 (14 months). At the group level, significant...
changes in automated synovitis volume were demonstrated at all time points except 10 months (where the size of the cohort was 15 individuals). RAMRIS scoring showed a similar pattern of change but with no significant change at any time point (Figure 1).

Figure 1. Change in synovitis volume (ml) and RAMRIS scores from baseline, with 95% confidence limits. Cohort size at each time point is shown on left hand graph. RAMRIS synovitis change scores did not achieve statistical significance at any time point. * = p<0.05, ** = p<0.005.

Conclusions: Fully automated quantitative synovitis measurement is now feasible and practical, and in this observational study proved to be more responsive than semi-quantitative scores. This method could also be applied to clinical practice as well as clinical trials, as synovial volume is measured at the individual joint level.

Disclosure: M. A. Bowes, Imorphics Ltd, 1; J. E. Freeston, None; E. J. Vital, None; G. Vincent, Imorphics Ltd, 1; G. Guillaud, None; P. Bird, None; P. Emery, Abbott Immunology Pharmaceuticals, 2, 8, Bristol-Myers Squibb, 8, Centocor, Inc., 8, Merck Pharmaceuticals, 8, Novartis Pharmaceuticals Corporation, 8, Pfizer Inc, 2, 8, Roche, 8, UCB, Inc, 8; P. G. Conaghan, AstaZeneca, 8, Bioiberica, 8, Bristol-Myers Squibb, 8, Centocor, Inc., 8, Merck Pharmaceuticals, 8, Novartis Pharmaceuticals Corporation, 8, Pfizer Inc, 2, 8, Roche, 8.

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Application of High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT) To Quantify Bony Damage in Rheumatoid Arthritis. Cheryl C. M. Barnabe1, Liam Martin1, Steven K. Boyd2 and Susan G. Barr1.

1University of Calgary, Calgary, AB, Canada, 2University of Calgary

Background: High-resolution peripheral quantitative computed tomography (HR-pQCT) (isotropic voxel size of 82 µm) provides three-dimensional information on bone microarchitecture. We investigated the ability of HR-pQCT to provide quantitative assessments of features of RA bony damage, and diagnostic performance.

Methods: Fifteen patients with established RA and damage of the MCP orPIP joints and 15 age- and sex-matched control patients were recruited and scanned by HR-pQCT (XtremeCT, Scanco Medical, Switzerland). A semi-automated segmentation method identified bone mineral based on changes in the gray-scale, with manual correction of any errors made by the program. These images were used to create a three-dimensional reconstruction of the joint. The minimum joint space width was calculated by counting the number of voxels between articular surfaces (Image Processing Language). The number and location of erosions were assessed visually from the two-dimensional images. Quantitative measures of bone density were obtained for the 2nd, 3rd and 4th MCP joints. Diagnostic test performance for HR-pQCT compared to the clinical diagnosis of RA was calculated. Reproducibility was assessed by re-contouring a subset of the images.

Results: Joint space narrowing was detected in RA patients compared to controls (Table 1). In RA, the majority of erosions occurred at the proximal bone surface (mean 23.6 (SD 17.6)). Some controls were found to have erosions, mainly in the IP and PIP joints. Quantitative assessment of bone density parameters did not reveal significant differences between RA patients and controls (Table 2). The best test performance for the clinical diagnosis of RA was determination of an erosion in MCP2 (sensitivity 76.9%, specificity 93.3%, ROC area 0.851, positive likelihood ratio 11.5 (95%CI 1.7–78.4)). Reproducibility was good for bone density parameters (all root square mean coefficients of variance were under 1%), but less so for joint space measurements (17%), perhaps related to difficulties in contouring angulated joints.

Table 1. Relative (and standard deviation) joint space of controls compared to RA patients (positive value indicates the control has a wider joint space).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MCP 2</th>
<th>MCP 3</th>
<th>MCP 4</th>
<th>MCP 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average cortical thickness (mm)</td>
<td>.007 (.047)</td>
<td>.004 (.037)</td>
<td>.015 (.046)</td>
<td></td>
</tr>
<tr>
<td>Average trabecular number per mm (mm^-1)</td>
<td>.04 (.20)</td>
<td>.01 (.21)</td>
<td>.36 (.16)</td>
<td></td>
</tr>
<tr>
<td>Average trabecular thickness (mm)</td>
<td>.004 (.03)</td>
<td>.002 (.03)</td>
<td>.10 (.02)</td>
<td></td>
</tr>
<tr>
<td>Average trabecular spacing (mm)</td>
<td>.003 (.07)</td>
<td>.014 (.06)</td>
<td>.006 (.06)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: We have developed methods to provide quantitative measurements of bony damage in established RA using HR-pQCT. Differences in joint space width are most pronounced at the MCP joints. Erosions at MCP2 are highly specific for RA, but erosions were detected in controls unrelated to clinical disease. A larger sample size may reveal detectable differences in bone density parameters between subjects with active inflammatory arthritis and those without. In this preliminary study, HR-pQCT demonstrated good performance characteristics for RA diagnosis.

Disclosure: C. C. M. Barnabe: None; L. Martin: None; S. K. Boyd: None; S. G. Barr: None.

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Baseline CRP Predicts Early Improvement in Synovitis, Osteitis, and Erosion on MRI in RA Patients Treated with Tocilizumab: Results from the ACT-RAY MRI Substudy. Orrin M. Troum3, Charles G. Peterfy5, Jeffrey L. Kaine1, Carol Chung2, Andrew Anisfeld2, Ewa Olech2 and Philip G. Conaghan5. 1Genentech, a Member of the Roche Group, South San Francisco, CA, 2Oklahoma University Health Sciences Center, Oklahoma City, OK, 3Sarasota Arthritis Research Center, Sarasota, FL, 4Spire Sciences and Synarc, San Francisco, Kentfield, CA, 5University of Leeds, Leeds, United Kingdom, 6University of Southern California, Santa Monica, CA, 7Santa Monica, CA

Purpose: IL-6R inhibition with tocilizumab (TCZ) inhibits progression of radiographic joint damage in patients (pts) with RA within 6 months. However, clinical and biochemical markers of disease activity, including CRP, and bone and cartilage turnover markers show improvement 2–4 weeks after TCZ initiation. Synovitis (SYN), particularly osteitis (OST), on magnetic resonance imaging (MRI) and elevated CRP levels have been shown to be strong predictors of radiographic progression of joint damage in patients with RA. This analysis examined early effects of TCZ on SYN, OST, and erosion (ERO) in pts with erosive RA who were inadequate responders to methotrexate (MTX-IR).

Methods: As part of a randomized, double-blind, phase 3b study (ACT-RAY) in MTX-IR pts, 63 RA pts on stable MTX were randomly assigned to continue stable MTX or to receive placebo, both in combination with TCZ 8 mg/kg IV every 4 weeks. In this substudy, 0.2T extremity MRI of one hand (metacarpophalangeal joints [MCP] 1–5) and wrist was acquired at baseline and at weeks 2 and 12. MR images were quality controlled and scored by two radiologists using a RAMRIS method blinded to visit order. In this interim analysis, blinded data from both TCZ arms were pooled and analyzed. CRP values were measured at baseline and every 4 weeks.

Results: By week 2, SYN scores improved in 44% of pts and improved ≥ smallest detectable change (SDC) in 7% of pts. By week 12, SYN and OST scores improved ≥ SDC in 32% and 28% of patients, respectively. Median ERO score did not change at either time point, but 10 pts showed ERO score change ≥ SDC (7 progressed [12%], 3 progressed [5%]) at week 12. Baseline CRP levels were variable, with a mean of 1.2 mg/dL (range 0.1–10.3); 93% of patients achieved normal CRP levels by week 12. Exploratory analysis stratifying MRI RAMRIS sub scores by baseline CRP levels revealed that mean baseline SYN, OST, and ERO scores were numerically higher in patients with baseline CRP ≥ 1.0 than in those with CRP ≤ 0.3, or 0.3–1.0. Pts with high baseline CRP (≥ 1.0) were 1.7–7.2, and 3.2-fold more likely to achieve improvements ≥ SDC in SYN, OST, and ERO, respectively, at week 12 than were pts with normal baseline CRP levels (< 0.3) (Table).

Conclusions: TCZ reduced synovitis in only 2 weeks and pre-erosive OST within 12 weeks of treatment initiation. Pts with baseline CRP levels ≥ 1.0 mg/dL were more likely than pts with baseline CRP levels < 1 mg/dL to achieve improvements in MRI measures of inflammation and erosive activity, indicating that CRP may have the potential to predict which pts will
experience the greatest MRI improvements after treatment with TCZ. Analysis of the upcoming 52-week visit from this study will offer an opportunity to confirm this observation. MRI evidence of early improvement with TCZ is in line with prior demonstration of inhibition of X-ray joint damage at 1 year and the observation that baseline CRP predicts radiographic progression.

**Results:** The relation between actual BD and BD in mmAl was most importantly influenced by regular clinical post-processing settings. Specifically switching off the post-processing module during acquisition improved the linear relation from $R^2 = 0.82$ to $R^2 = 0.93$. When a third order polynomial representation of the step wedge was used, the relation improved to $R^2 = 0.95$ with clinical post-processing and to $R^2 = 0.98$ when post-processing was off. Variation in the other radiographic settings (kVp, mAs, position, and filter) moderately influenced the linearity: $R^2 = 0.71 - 0.87$.

**Conclusion:** Bone density evaluation on digital radiographs is hampered by the default post-processing as used in clinical practice. By use of an aluminium reference step wedge and by using a third order polynomial function in KIDA, BD on digital radiographs can be reliably expressed in mmAl equivalents.

**Reference:**

**Sponsor:** Dutch Arthritis Association (CHECK).

**Acknowledgement:** We acknowledge the radiology department for their cooperation and Paco Welsing for statistical support.

**Disclosure:** None.

**122 Bone Marrow Lesion (BML) Size in Osteoarthritic Knees Correlates with Extent of Cartilage Damage and Predicts Longitudinal Cartilage Loss.** Jeffrey B. Driban, Grace H. Lo, Ji Yeon Lee, Robert J. Ward, Eric Miller and Timothy E. McAlindon. Tufts Medical Center, Houston, TX, Tufts Medical Center, Brookline, MA, Tufts Medical Center, Boston, MA, Tufts Medical Center Box 406, Boston, MA, Tufts University.

**Purpose:** Although BMLs appear to be associated with cartilage damage in knee osteoarthritis (OA), the nature of the relationship is unclear. Prior studies have used semi-quantitative BML scales which limit analyses of longitudinal relationships and measurements of BML change. Therefore, our aim was to evaluate the cross-sectional and longitudinal relationships between BML size and the extent of cartilage damage using quantitative 3-dimensional measurements (BML size; cartilage volume, thickness and area of denudation).

**Methods:** The sample comprised 44 knees (baseline Kellgren Lawrence score ≥ 2) from participants in a clinical trial who had sagittal and coronal intermediate-weighted fat-suppressed T1W FS images located within 1.0 cm of hyaline cartilage and present on ≥ 2 sagittal or coronal images and classified them within 2 regions: index femur or tibia. Two rheumatologists defined the index compartment as the compartment (medial or lateral) with greater pathology based on radiograph and MRI findings. We measured the maximal anterior-posterior, medial-lateral, and vertical dimensions of each BML. Their product represented the volume of each BML (intra-tester ICC = .96). When multiple BMLs were present in a region their volumes were summed to calculate regional volume. Cartilage measurements were determined by manual segmentation of registered DESS images using Analyze® (intra-tester ICC > .99).

**Results:** Participants were 65 ± 9 years of age (m ± sd), 52% female, and body mass index of 29.8 ± 5.8 kg/m2. Among femurs, 91% had full thickness cartilage loss at baseline (baseline = 11.0 ± 10.4% of subchondral bone; 2 incident knees; change = 1.5 ± 1.8% of subchondral bone) and 91% had baseline BMLs (baseline = 15.3 ± 16.0 cm3; 1 incident knee; change = 1.6 ± 12.4 cm3). Among tibias, 66% had full thickness cartilage loss at baseline (baseline = 16.3 ± 16.8% of subchondral bone; 3 incident knees; change = 2.1 ± 4.2% of subchondral bone) and 85% had BMLs (baseline = 30.7 ± 31.5 cm3; 2 incident knees; change 3.9 ± 14.8 cm3).

Table 1 demonstrates intra-region correlations among BML and cartilage. Baseline BML volume had direct associations to area of full thickness cartilage loss (baseline and change). There was also a direct association between tibia BML volume change and tibia cartilage volume change ($r = .32, p = .047, n = 39$). There were no other correlations between BML volume change and cartilage parameters (baseline or change).
Table 1. Spearman Coefficients among Baseline BML and Cartilage Parameters

<table>
<thead>
<tr>
<th></th>
<th>Femur BML Volume: Baseline (n = 40)</th>
<th>Tibia BML Volume: Baseline (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage Volume: Baseline</td>
<td>−.06</td>
<td>−.31*</td>
</tr>
<tr>
<td>Cartilage Thickness: Baseline</td>
<td>.02</td>
<td>−.37*</td>
</tr>
<tr>
<td>Area of Full Thickness Cartilage Loss: Baseline</td>
<td>.33*</td>
<td>.63**</td>
</tr>
<tr>
<td>Cartilage Volume: Change</td>
<td>.03</td>
<td>.16</td>
</tr>
<tr>
<td>Cartilage Thickness: Change</td>
<td>−.11</td>
<td>−.13</td>
</tr>
<tr>
<td>Area of Full Thickness Cartilage Loss: Change</td>
<td>.48**</td>
<td>.43**</td>
</tr>
</tbody>
</table>

* significant findings (p ≤ 0.05)
** significant finding after Bonferroni corrections (18 multiple comparisons; p < .003)

Conclusion: In knees with cartilage denudation, BML size indicates the level of risk for further full thickness cartilage loss.

Disclosure: J. B. Driban: None; G. H. Lo: None; J. Y. Lee: None; R. J. Ward: None; E. Miller: None; T. E. McAlindon: None.

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Decreased Incidence of Synovitis, Osteitis, and Erosion in Early RA Patients Treated with Adalimumab Plus Methotrexate Compared to Those with Methotrexate Alone: High-Field MRI Analysis from OPTIMA. Charles Peterfy1, Boulos Harouei2, Patrick Durez2, Kaushik Patra3 and Hartmut Kupper4, Abbott GmbH & Co. KG, Ludwigshafen, Germany, 2Abbott Laboratories, Abbott Park, IL, 3Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, 4Spiré Sciences, San Francisco, CA, 5University of Montreal Hospital Centre, Hospital Notre Dame, Montreal, QC, Canada

Background: Combination therapy with adalimumab (ADA) and methotrexate (MTX) has been shown to reduce X-ray progression of joint damage in rheumatoid arthritis (RA). Magnetic resonance imaging (MRI) is more sensitive than X-ray for bone erosion and also visualizes pre-erosive synovitis and osteitis.

Objective: To determine the proportion of early RA patients showing progression or improvement in synovitis, bone erosion, and osteitis on high-field MRI after 26 weeks of therapy with ADA+MTX or MTX monotherapy in a substudy of OPTIMA (Optimal Protocol for Treatment Initiation With Methotrexate and Adalimumab Combination Therapy in Patients With Early Rheumatoid Arthritis).

Methods: OPTIMA is an ongoing 78-wk study with 26- and 52-wk periods including MTX-naïve patients with RA <1 year, DAS28≥3.2, ≥6 SJC, ≥8 TJC, ESR ≥28 mm/hr or CRP ≥1.5 mg/dL, and ≥1 of the following: >1 joint erosion, RF+, or anti-CCP+. Patients were randomized to ADA (40 mg every other wk)+MTX (titrated to 20 mg/wk by wk 8) or placebo (PBO)+MTX. Fifty-nine patients had 1.5-Tesla MRI of metacarpophalangeal and wrist joints before and after i.v. gadodiamide. Of these, 23 patients had baseline MRI after the first dose of study drug; 19 (83%) within 40 days of study drug administration. MRI scores were defined as positive or negative change from baseline using the OMERACT-RAMRIS scoring system. Progression or improvement of MRI scores were defined as positive or negative change from baseline ≤ smallest detectable change (SDC)1, respectively.

Results: Mean (SD) baseline MRI scores for PBO+MTX (N=32) and ADA+MTX (N=27) were comparable for synovitis: 6.8 (4.33) and 6.2 (4.18), P=0.63; for erosions: 4.1 (5.85) and 6.1 (7.43), P=0.26; and for osteitis: 3.3 (4.74) and 5.4 (7.93), P=0.25. Subjects in the PBO+MTX and ADA+MTX groups, respectively, had mean changes in synovitis of −2.0 and −3.6 (P=0.003), in erosion of 1.4 and −0.8 (P=0.004), and in osteitis of 0.0 and −4.0 (P=0.006), indicating that joint inflammation and damage were significantly alleviated by ADA+MTX. Clinical responses to treatment (ACR20/50/70 and DAS28) were correspondingly greater in the ADA+MTX group. The SDC values for synovitis, erosion, and osteitis were 1.8, 1.2, and 3.8, respectively. Subjects receiving ADA+MTX were more likely to exhibit improvements in synovitis, erosion, and osteitis ≥SDC; only one subject in the ADA+MTX group showed progression of bone erosion ≥SDC, compared with 12 subjects in the PBO+MTX group (Table). A similar pattern was seen among the 36 patients who received MRI prior to the first dose of study drug (data not shown).

Table. Proportion of subjects demonstrating progression or improvement ≥SDC in 26 weeks

<table>
<thead>
<tr>
<th>α (%)</th>
<th>SDC</th>
<th>PBO+MTX (N = 32)</th>
<th>ADA+MTX (N = 27)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression Synovitis</td>
<td>2 (6%)</td>
<td>0</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Erosion</td>
<td>12 (38%)</td>
<td>1 (4%)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Osteitis</td>
<td>4 (13%)</td>
<td>0</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Improvement Synovitis</td>
<td>14 (44%)</td>
<td>20 (74%)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Erosion</td>
<td>3 (9%)</td>
<td>6 (22%)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Osteitis</td>
<td>3 (9%)</td>
<td>8 (30%)</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

* for comparison between treatment groups, based on Fisher’s exact test

Conclusion: Treatment of early RA with ADA+MTX for 26 weeks yielded better MRI profiles than did treatment with MTX alone; the improvements in joint inflammation and damage corresponded with enhanced clinical outcomes.

References:
2 Disclosure: C. Peterfy: Abbott Laboratories, 5, Agen Inc., 5, Biogen Idec, 5, Bristol-Myers Squibb, 5, Celgene, 5, Centocor, Inc., 5, Crescendo, 3, 5, Genentech and Biogen IDEC Inc, 5, Lilly USA, LLC, 5, Novartis Pharmaceuticals Corporation, 5, Pfizer; B. Harouei: None; P. Durez: None; K. Patra: Abbott Laboratories, 1, 3; H. Kupper: Abbott Laboratories, 1, 3.

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Detection of Radiographic Progression in Early Knee Osteoarthritis (CHECK): Sensitivity to Change of Knee Images Digital Analysis Compared to Altman Grading. M. B. Kind5, S. M. A. Biema-Zeinstra5, A. C. A. Marinussen5, M. A. Viergever2, J. W. J. Bijlsma5, P. M. J. Welsing6 and F. P. J. G. Lafeber5. 1General Practice, Erasmus University Rotterdam, the Netherlands, 2Image Sciences Institute, University Medical Center Utrecht, The Netherlands, 3Rheumatology & Clinical Immunology, Image Sciences Institute, University Medical Center Utrecht, The Netherlands, 4Rheumatology & Clinical Immunology, Julius Center for Health Sciences & Primary Care, University Medical Center Utrecht, The Netherlands, 5Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

Background: In the detection of radiographic progression in osteoarthritis, semi-quantitative measurement commonly results in low sensitivity to change. Quantitative measurement of separate radiographic OA features using Knee Images Digital Analysis (KIDA)5 theoretically enables more precise measurement and greater sensitivity to change. In the longitudinal Cohort Hip & Cohort Knee (CHECK) radiographic progression is evaluated early in OA. The objective of this study was to determine whether the sensitivity to change of separate radiographic features of OA can be improved by using digital analysis (KIDA).

Methods: Knee radiographs (PA semiflexed) were evaluated for the OA parameters: joint space narrowing (JSN; lateral and medial), osteophytes (lateral and medial femur, lateral and medial tibia), and bone density (BD; lateral femur and medial tibia) by quantitative measurement with KIDA and by semi-quantitative grading according to the Altman atlas5. For KIDA measurement sensitivity to change was determined by calculation of the smallest detectable difference (SDD), which accounts for the variability of the radiographic procedure and digital analysis. SDD was determined in a subset of unchanged knees from baseline to 2 year follow-up based on an Altman grade of 0 for all parameters at both time points (313, 303, and 213 pairs of knee radiographs for JSN, osteophyte area, and BD parameters respectively). Each of all 1002 participants in CHECK available baseline and follow-up knee radiographs were evaluated. The percentage of knees changing on the radiographic parameters was determined for KIDA, defined as a change larger than the SDD, and for the Altman atlas defined as a change of at least one grade. Further, for each parameter knees with a change on KIDA measurement and the Altman atlas. According to both KIDA and Altman, OA progression was found in 4.1–11.0% (JSN), 3.3–10.6% (osteophyte), and 0.9–1.3% (BD) of knees. According to both KIDA and Altman, in two years of follow-up only in a limited number of knees radiographic progression occurred; e.g. 3% for JSN medial, and 2% for osteophytes at medial tibia. In 82% and 84% of knees no change occurred. In 15% of cases disagreement existed between knees changing according to KIDA measurement and the Altman atlas.

Conclusion: Sensitivity to change for the detection of radiographic progression in early OA is not improved by using KIDA. Quality of acquisition of radiographs seems to be at least as important as quality of analysis.
Discriminative Power of Different Combinations of Bones and Joints for Assessing Change in Rheumatoid Arthritis with MRI: Results Based on Pooled Data from Four Multisite Clinical Trials. Charles G. Peterfy, Peter Countryman, Julie DiCarlo, Annaria Gabriele, Tim M. Shaw, Andrew Anisfeld, Wayne H. Tsuji, Ewa Olech and Norman B. Gaylis. 1Amgen, Seattle, WA, 2Arthritis & Rheumatic Disease, Aventura, FL, 3F Hoffmann-LaRoche Ltd, Welwyn Garden City Herts, United Kingdom, 4F Hoffmann-La-Roche Ltd, Italy, 5Genentech, A Member of the Roche Group, 6Oklahoma Medical Research Foundation, Oklahoma City, OK, 7Spire Sciences, LLC, San Francisco, CA, 8Spire Sciences, LLC, Kentfield, CA

Background: We previously showed that different combinations of bones and joints in the hand and wrist varied in their ability to discriminate significant change in synovitis, osteitis and erosion with MRI in patients with RA in a multicenter clinical trial. In this study, we corroborated these findings using pooled data from 4 multisite clinical trials.

Methods: A total of 522 RA patients from 4 clinical trials were included in the analysis. Three of these studies (459 patients) included 1.5T MRI, and 2 studies (118 patients) included 0.2T MRI. All scans used a hand frame to ensure reproducible positioning, and were read by the same 2 radiologists. Metacarpophalangeal joints (MCP) 1–5 and all bones and joints in the wrist were scored using the RAMRIS scale for erosion and osteitis in all 4 trials and synovitis in all but one of the 1.5T trials. Six combinations (RAMRIS, 23 bones and 7 joints in original RAMRIS; RAMRIS +, V-Sharp, MCP1 +5 – 6 wrist bones in van der Heijde-Sharp X-ray score; G-Sharp, MCP1 – 5 + 5 wrist bones in Genant-Sharp X-ray score [V-Sharp – lunate]; MCPs, MCP1 +5 – Wrist, 15 bones and 3 joints in RAMRIS) were compared for percentages of patients changing (increase or decrease) ≥ smallest detectable change (SDC) at week 12 or 24.

Results: Frequency of involvement at baseline varied by location (Fig.1), but showed a similar pattern in all 4 studies and between patients with early (<2y) RA and those with established (>10y) RA (data not shown). Inter-reader agreement, expressed as intraclass correlation coefficient (ICC), also varied among locations (median = 0.64, 0.88 and 0.81, for erosion, osteitis and synovitis, respectively.) Percent of patients changing ≥ SDC at 12 or 24 weeks varied among the different combinations (Fig. 2). Adding MCP1 to RAMRIS (RAMRIS +) increased discrimination for erosion and synovitis. G-Sharp showed the highest discrimination for osteitis and synovitis, and was equivalent to RAMRIS for erosion. Excluding all wrist locations (leaving only MCPs) actually increased discrimination for erosion over that with RAMRIS, but decreased discrimination for synovitis and osteitis.

Figure 1. Frequency of involvement of different bones and joints of MCPs and wrist with erosion, osteitis and synovitis (RAD, radius; ULN, ulna; SCP, scaphoid; TRQ, trapezial; PIS, pisiform; TPM, trapezoid; TPD, trapezoid; CAP, capitate; HAM, hamate; PMC, proximal metacarpal; DMC, distal metacarpal; PP, proximal phalanx; DRU, distal radioulnar joint; RC, radiocarpal joint; ICMC, intercarpal and carponmeta-

Figure 2. Proportion of patients showing change (increase or decrease) from baseline in erosion, osteitis or synovitis scores ≥ ± SDC for different combinations.

Conclusions: Filtering out noisy and infrequently involved bones and joints may improve discriminative power of RAMRIS. Determining the combination that optimally balances functional relevance with reading reliability requires further investigation.

References:

Disclosures: M. B. Kinds: None; S. M. A. Bierma-Zeinstra: None; A. C. A. Marijnissen: None; M. A. Viergever: None; J. W. J. Bijlsma: None; P. M. J. Welsing: None; F. P. J. G. Lafeber: None.

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Objective(s): To evaluate whether high field Magnetic Resonance Imaging (MRI) can demonstrate mural edema and inflammation within the superficial temporal artery and other intra- and extracranial arteries and how it compares to temporal artery biopsy results in patients who meet American College of Rheumatology (ACR) criteria for giant cell arteritis (GCA).

Method(s): 49 patients meeting ACR criteria for GCA, and 6 patients otherwise suspicious of GCA were examined by 3T MRI using a head coil. The MRI protocol matured over the course of the study but, in general, high-resolution fluid-sensitive and Gadolinium enhanced images of the clinically-affected STA were obtained, in addition to larger field of view sequences to visualize the other scalp arteries. The images were graded according to protocols reported in recently published studies. All patients except 1 underwent temporal artery biopsy. Images and biopsy were obtained as soon as possible after initiating corticosteroid therapy.

Result(s): Overall 23/35 patients had positive scalp artery MRI findings and 8/55 patients had positive biopsy findings. Of these positive biopsies, MRI was reported as positive in 7 with evidence of STA inflammation present in 6 and the seventh patient demonstrating only cavernous carotid artery inflammation. One false negative occurred but an inadvertent protocol deviation had occurred with suboptimal image resolution obtained for that patient. The average biopsy length was 2.79 cm. The average number of days from corticosteroid to MRI was 3.9 days and the average number of days to biopsy was 8.98 days.

Other important MRI findings in patients who had negative artery inflammation included 1 case ipsilateral pachymeningitis, 1 cortical infarct, 1 bone lesion questionable for metastatic disease, 1 ipsilateral pansinusitis and 1 case of multiple meningiomas requiring neurosurgical referral.

Conclusion: In patients meeting ACR criteria for GCA, MRI demonstrates evidence of STA inflammation in 43% of patients. This appears superior to our biopsy positive rate of 13%. These results support previous studies and suggest that MRI could replace or complement biopsy as an effective and non-invasive way to diagnose GCA. The MRI protocol and image resolution are crucial components in MRI evaluation of scalp artery
inflammation. MRI is clearly useful in diagnosing other pathologies that may clinically mimic giant cell arthritis.

Disclosure: M. I. Clements-Baker: None; S. Patel: None; R. Rebello: None; G. Ionnadis: None; N. Khalidi: None.

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High-Field MRI and Powerdoppler Sonography—Supplementary Imaging Techniques in Assessing Disease Activity in Patients with Psoriasis Arthritis (PsA) and Rheumatoid Arthritis (RA) in Sustained Clinical Remission. Maria Hoehle Rheumatologic Practice, Hamburg, Germany

Background: Patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) responding to anti-TNF therapy show a rapid decrease in inflammatory parameters as well as sustained improvement of clinical signs and symptoms. However inflammatory activity, e.g. synovitis, tenosynovitis, edema still can persist at the joints in patients with clinical remission. These rheumatic processes can be monitored using modern imaging techniques such as high-field MRI and powerdoppler sonography (PD-US).

Objectives: To evaluate whether MRI and US are helpful to stratify patients in clinical and imaging remission for discontinuation of anti-TNF treatment, 41 patients were followed-up for six years.

Methods: 41 patients (30 women) with RA (35) and PsA (6) starting treatment with adalimumab in 2004 were followed-up for six years. Every six months patients were monitored by standard routine diagnostics as well as by high-field MRI and PD-US. Thereby, the clinically dominant joint was evaluated using RAMRIS and semiquantitative PD-US-score (0-3). Clinical remission was defined as DAS28<2.6. Imaging remission was defined as no detectable synovitis at the clinically dominant joint using MRI and PD-US (RAMRIS synovitis = 0, PD-US synovitis score = 0) (Ref 1,2).

Results: In sixteen patients (16) with early RA (disease duration < 2 years, mean DAS28 = 3.9, mean RAMRIS synovitis = 2.8, mean PD-US synovitis score 2.9) responding to anti-TNF therapy with adalimumab in combination with methotrexat by showing sustained clinical remission (mean DAS28 = 1.5) and imaging remission of at least 12 months adalimumab was discontinued. Clinical and imaging remission persisted in the follow-up period.

In twenty-five patients (25) with established inflammatory rheumatic disease (RA (19), PsA (6), disease duration > 2 years, mean DAS28 = 3.8, mean RAMRIS synovitis = 2.9, mean PD-US synovitis score 2.7) responding to anti-TNF therapy with adalimumab in combination with methotrexat by showing sustained clinical remission (mean DAS28 = 1.4) subclinical synovitis persisted (mean RAMRIS synovitis = 2.1, mean PD-US synovitis score 2.1), Combination therapy was continued in the follow-up period.

In both groups flares of disease activity, erosive progression at hands, severe infections e.g. tuberculosis infections, reactivation of tuberculosis infections or malignoma were not observed since 2004.

Conclusion: According to current evidence patients with RA and PsA should be monitored clinically (DAS28) as well as by modern imaging modalities in a tight and continuous fashion. Early use of adalimumab in the course of the rheumatic disease may allow discontinuation of anti-TNF treatment in true responders as both clinical and imaging remission persisted for five years in the early treatment group. MRI and PD-US seem helpful to stratify patients for discontinuation of biologics.

References:

Disclosure: M. Hoehle: None.

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Inflammatory Osteophyte Formation Is Different from Degenerative Osteophyte Formation. Stephanie Finzel, Christian Ernet, Christian Stach, Klaus Engikel, Matthias Englbrecht and Georg Schett. University of Erlangen-Nuremberg

Objectives: To investigate the differences in the pattern of periarticular osteophyte formation in patients with psoriatic arthritis and hand osteoarthritis by a high-resolution micro-computed tomography scanner (μCT) designed to visualize bone architecture. Both psoriatic arthritis (PsA) and osteoarthritis (OA) lead to joint destruction via deforming osteophytic proliferation but may differ substantially in their periarticular bone changes.

Methods: 24 patients with PsA and 24 patients age- and sex-matched with OA received a micro- computed tomography scan of the dominantly affected hand to compare structural bone changes in the metacarpophalangeal joints. Number, size and distribution of osteophytes were recorded.

Results: Number and size of osteophytes in PsA were comparable to OA. However osteophytes in OA were exclusively found at the palmar and dorsal sites of the MCP-joints. Moreover, in OA patients the metacarpal heads were by far more affected than the phalangeal bases. Osteophyte formation in PsA did also involve skeletal sites which are normally spared in OA patients, such as the radial and ulnar sites, usually leading to affection of the entire circumference of the periarticular bone surface (“bony corona”). Also significant affection of the phalangeal bases was observed in PsA in contrast to OA.

Conclusions: High-resolution μCT imaging shows profound differences in periarticular bone changes between PsA and HFE. The differential pattern of osteophyte formation between PsA and OA patient suggest different mechanisms to be involved in bone spur formation in consequence of inflammatory and degenerative arthritis of the finger joints. In particular the wide spread corona- shaped osteophyte formation in PsA suggests a profound involvement of the insertion sides of the tendons which is also supported by a far more severe affection of the phalangeal bases. Theses data suggest that it is possible to differentiate between inflammatory and degenerative osteophyte formation by advanced imaging technology.

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Background: Hepatic magnetic resonance elastography (MRE) allows for noninvasive assessment of liver fibrosis. The purpose of this study was to evaluate the usefulness of MRE in detecting and quantifying liver fibrosis in patients with rheumatoid arthritis (RA) who have received methotrexate (MTX).

Methods: Patients receiving MTX for > 5 years or with an abnormal serum AST value in the two years preceding the study onset were evaluated with MRE. Logistic regression and linear regression models with and without adjustment were used to assess the association between mean liver stiffness value as determined by MRE and variables of interest. Prior analyses have shown that a diagnostic cut-off value of 2.9 kilopascals (kPa) can predict all stages of liver fibrosis when compared to normal liver with a sensitivity and specificity of 98% and 99%, respectively. Study participants with an abnormal liver stiffness were subsequently offered evaluation in the hepatology clinic and the decision for a liver biopsy was made based on clinical judgment.

Results: Sixty-five RA patients were enrolled. Mean liver stiffness value by MRE was abnormal in 7 patients, suggestive of hepatic injury. As a result of findings from the MRE, biopsies were performed in 5 patients and all correlated with elevated liver stiffness values (Table). The biopsies revealed chronic inflammation in all subjects; 4 individuals had evidence of fibrosis. There was a significant association between elevated mean liver stiffness and abnormal AST values ever and in the preceding 2 years prior to the scan (p=0.035 and p=0.031, respectively). Elevated mean liver stiffness values were associated with body mass index (BMI) (OR= 1.18 per 1 kg/m²; 95% CI: 1.03, 1.36; p=0.017), and this remained significant following adjustment for MTX dose, MTX treatment duration, diabetes mellitus, hyperlipidemia, and impaired fasting blood glucose. Neither the total MTX dose nor the duration of MTX treatment was associated with mean liver stiffness value (p=0.51 and p=0.20, respectively). Eleven patients reported using alcohol more than once a month. Alcohol use was not associated with abnormal mean liver stiffness values (p=0.96).

Conclusions: MRE provides a reliable, non-invasive assessment of liver fibrosis in patients with RA receiving MTX. Patients with RA receiving MTX who have an elevated BMI may be at increased risk for chronic hepatic injury, regardless of MTX cumulative dose or duration of treatment.
Table. Abnormal Hepatic Magnetic Resonance Elastography (MRE) Scans in Patients receiving Methotrexate for Treatment of Rheumatoid Arthritis.

<table>
<thead>
<tr>
<th>Patient (years)</th>
<th>Sex</th>
<th>BMI (kg/m²)</th>
<th>Total MTX dose (mg)</th>
<th>Frequency abnormal AST 2 years prior to MRE</th>
<th>Mean liver stiffness value (kPa)</th>
<th>Liver biopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>31.1</td>
<td>14235</td>
<td>4/9</td>
<td>3.36</td>
<td>Mildly active (grade 1 of 3) steatohepatitis with focal pericellular fibrosis and mild portal fibrosis (stage 1 of 4)</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>37.9</td>
<td>2950</td>
<td>1/13</td>
<td>3.46</td>
<td>Mild reactive hepatitis with mild portal fibrosis (stage 1 of 4)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>42.1</td>
<td>11880</td>
<td>0/15</td>
<td>3.23</td>
<td>Mildly active steatohepatitis without fibrosis.</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>44.9</td>
<td>6875</td>
<td>5/7</td>
<td>2.92</td>
<td>Moderately active steatohepatitis, grade 2 (of 3) with portal, periportal, and pericellular fibrosis, stage 2 (of 4).</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>27.4</td>
<td>6340</td>
<td>1/8</td>
<td>3.26</td>
<td>Not pursued; repeat MRE showed results within a normal range.</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>37.3</td>
<td>3680</td>
<td>0/10</td>
<td>3.13</td>
<td>Mild fatty change with mild portal fibrosis.</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>31.8</td>
<td>9295</td>
<td>7/17</td>
<td>3.15</td>
<td>Discontinued MTX; no biopsy performed.</td>
</tr>
</tbody>
</table>

Abbreviations: AST-aspartate aminotransferase; BMI-body mass index; MTX-methotrexate; kPa-kilopascal

Disclosure: D. D. Hoganson: None; J. Chen: None; R. L. Ehman: None; J. A. Talwalkar: None; C. J. Michet: None; M. Yin: None; E. L. Matteson: None.

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Magnetic Resonance Imaging (MRI) of the Spine May Be Useful in Patients with Non-Radiographic Axial Spondyloarthritis (NRASpA) without Active Sacroiliitis on MRI. Guillaume Driez1, Manuel Couchot2, Philippe Cotty3, Denis Mulleman2, and Philippe M. Goupille1. 1University Hospital, Tours, Tours, France, 2University Hospital, Tours, Tours, France, 3University Hospital, Tours, Tours, France

Background: MRI of the sacroiliac joints (SIJ) is useful for the diagnosis of axial spondyloarthritis (SpA) in patients who don’t fulfil the modified New York criteria (1). However, about 25 to 30 % of patients with NRASpA have no active sacroiliitis on MRI, according to ASAS/OMERACT criteria (2). MRI of the spine may show lesions such as Romanus and fatty Romanus which, when multiple or severe, may be highly suggestive of the diagnosis of axial SpA.

Objective: To assess, in a NRASpA cohort without active sacroiliitis on MRI, the prevalence of spine lesions on MRI highly suggestive of SpA.

Methods: Retrospective analysis of the MRI of SIJ and of the thoracic and lumbar spine, performed between 2005 and 2009, in patients with NRASpA. Blind analysis was performed by two independent radiologists (SIJ and spine were independently assessed). Active sacroiliitis on MRI was defined according to ASAS/OMERACT criteria, and a positive spinal MRI was defined according to the presence of highly suggestive lesions (Romanus, fatty Romanus, Andersson spondylitis, inflammatory posterior lesions) and the experience of the two radiologists (study performed before the definition of a positive spinal MRI by the ASAS group).

Results: MRI of 93 NRASpA patients were analysed. Mean age was 39.4 years, mean disease duration was 4.5 years; 39% of the patients were HLA B27 positive, all patients fulfilled ASAS criteria or Amor criteria of SpA and had a diagnosis of NRASpA by their rheumatologist. Thirty-eight of 93 patients (40.8%) had active sacroiliitis on MRI, 25/93 (26.8%) had sacroiliitis and spine lesion highly suggestive of SpA, 10/93 (10.7%) had a normal MRI of SIJ and spine, 10/93 (10.7%) had some inflammatory lesions of SIJ and/or spine not sufficient for the diagnosis of SpA.

Conclusion: Knee malalignment is associated with increased risk of incident and enlarging Subchondral Bone Marrow Lesions in the More Loaded Compartments: The MOST Study. Daichi Hayashi1, Martin Englund2, Frank Roemer3, Jingbo Niu4, Leena Sharma4, Neil Segal5, Cora Lewis6, David T. Felson7, Michael C. Nevis8, and Ali Gurm8. 1Boston University, Boston, MA, 2Boston University School of Medicine, Boston, MA, 3Boston University School of Medicine, Boston, MA, 4Boston University School of Medicine, 5Lund University, Sweden, 6Northwestern University, Chicago, IL, 7UCSF, San Francisco, CA, 8University of Alabama at Birmingham, 9University of Iowa

Objective: To assess, in a NRASpA cohort without active sacroiliitis on MRI, the prevalence of spine lesions on MRI highly suggestive of SpA.

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Conclusion: Knee malalignment is associated with increased risk of incident and enlarging BMLs in the more loaded compartments of the tibiofemoral (TF) joint.

Purpose: Malalignment of the lower limb influences the load distribution across the articular surfaces of the knee joint. We hypothesized that subchondral bone marrow lesions (BML) result from increased mechanical loading. The aim of this study was to assess if malalignment is associated with incident and enlarging BML in the more loaded compartments of the tibiofemoral (TF) joint.

Methods: The Multicenter Osteoarthritis Study (MOST) is an NIH-funded longitudinal observational study of individuals who have or are at high risk for knee OA. Full limb radiographs of both legs were taken at baseline and hip-knee-ankle mechanical axis was measured (varus <179°, neutral 179–181° and valgus >181°). MRI was performed on a 1.0T extremity system. MR images were assessed semiquantitatively in known order using the WORMS system. BML was scored on a 0–3 scale at baseline and at 30 months in 5 TF regions of the medial and lateral compartment, respectively. Outcome was defined as any increase in BML score, including within-grade increase not fulfilling the criteria of a full-grade change. Relative risk of an incident and enlarging BML in the more loaded compartment of the TF joint.

Results: 1,782 knees from 1,338 subjects were included (62% women, mean age 62.2±7.9 years, mean BMI 29.9±4.8 kg/m²). Compared to neutral alignment, baseline varus alignment was associated with increased BML scores in the medial compartment (adjOR [95%CI] 1.8 [1.5–2.3]) and valgus alignment with BML score increases in the lateral compartment (2.2 [1.7–3.4]). Increase in BML score was more likely in the more loaded compartments (2.2 [1.8–2.6]) in malaligned knees compared to neutral knees. After stratification, this association remained in knees with ipsilateral meniscal and cartilage pathology (i.e. no meniscal or cartilage pathology; meniscal discal or articular cartilage pathology; meniscal discal or articular cartilage pathology present; cartilage loss present; both meniscal and cartilage pathology present) and also by compartments with or without pre-existing BML (i.e. ‘incident’ if no BML at baseline or ‘enlarging’ if pre-existing BML).

References:
3 – Herrmann KG et al. EULAR 2010 abstractOP0149

Disclosure: G. Direz: None; M. Couchot: None; P. Cotty: None; D. Mulleman: None; F. M. Goupille: None.
MRI and X-Ray Measured Changes in Joint Space Narrowing Are Closely Associated in Early RA Patients: A Pilot Study

Background: Magnetic Resonance Imaging (MRI) is commonly used to assess erosions, synovitis, tenosynovitis and bone marrow edema in rheumatoid arthritis (RA) patients. During the development of the OMERACT RA MRI score (RAMRIS) joint space narrowing (JSN) was tested, but left out due to insufficient image resolution. However, MRI image quality has now improved, and a MRI JSN score with encouraging inter-reader reliability was presented at the 2010 OMERACT meeting.

Objectives: To investigate the intra- and inter-reader reliability of the OMERACT JSN score in a longitudinal setting, and to assess the association with X-ray changes.

Methods: 10 patients were selected from a cohort of early RA patients (disease duration less than one year at baseline) with 5-year follow-up. The patients were examined by X-ray of both hands and MRI of the dominant wrist (GE Signa 1.5 T MRI scanner). The 10 patients were chosen according to 5-year change of van der Heijde Sharp JSN score (hands only), with two patients selected from the two lowest quartiles, and three patients from each of the two highest quartiles. The MRI images were assessed on coronal T1-weighted sequences by two readers (PB and SL), both familiar with the RAMRIS score and with experience from previous JSN exercises. 18 joint sites in the wrist were scored 0 (no JSN) - 4 (anklylosis/total loss of joint space). The images were assessed twice on consecutive days, with anonymization and randomization between the readings. Intra-class correlation coefficients were calculated for intra-reader (single measures), inter-reader (average measures) reliability and association to X-ray (average measures).

Results: The median (25th percentile, 75th percentile) age was 54 (47, 67) years, disease duration 98 (48, 139) days, 8 were female and 4 were anti-ccp positive. 5-year change in van der Heijde Sharp JSN score ranged from 0 to 5, with a median of 4. Table 1 shows the intra-reader ICCs, inter-reader ICCs and comparison of MRI scorings and X-ray for each reader.

The figure shows an example patient with x-ray and MRI images.

Table 1. Intra-reader ICCs, inter-reader ICCs and comparison of MRI and X-ray JSN score.

<table>
<thead>
<tr>
<th>Reader 1</th>
<th>Reader 2</th>
<th>Reader 1</th>
<th>Reader 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.60</td>
<td>0.75</td>
<td>0.67</td>
</tr>
<tr>
<td>5 year</td>
<td>0.87</td>
<td>0.91</td>
<td>0.95</td>
</tr>
<tr>
<td>Change</td>
<td>0.90</td>
<td>0.97</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Figure. Patient example with development of JSN at several wrist joints: MRI images from baseline (A) and 5-year follow-up (B) left, X-ray images from baseline (C) and 5-year follow-up (D).

Few of the patients had much change in JSN assessed by MRI, with a median change (range)[25th percentile, 75th percentile] for scorer 1 of 0 (0–30) [0, 1.25] and for scorer 2 1.5 (0 – 28) [0.75, 3.5].

Conclusion: This small study shows promising results for the assessment of JSN on MRI, with strong association between change in JSN on MRI and X-ray. However, these results need to be confirmed in other cohorts, especially including patients with more JSN.

Disclosure: S. Lillegren: None; P. Bøyesen: None; M. Østergaard: None; S. Sesseng: None; T. K. Kvien: None; E. A. Haavardsholm: None.

MRI Bone Edema Is an Independent Predictor of Development of Rheumatoid Arthritis in Patients with Early Undifferentiated Arthritis

Objectives: To study magnetic resonance imaging (MRI) as a tool for early diagnosis of rheumatoid arthritis (RA) in patients with early undifferentiated arthritis (UA).

Methods: 116 patients without a specific rheumatological diagnosis, but 227 tender and/or swollen metacarpophalangeal, proximal interphalangeal, wrist or metatarsophalangeal (MTP) joints for >6 weeks but <24 months, underwent clinical, biochemical, conventional radiography and MRI examinations (qualitatively assessed for various pathologies and according to the OMERACT RAMRIS scoring method (CMC1 and MTP1 joints excluded)) and were followed for >12 months for final RA/non-RA diagnosis.

Based on univariate analyses, clinical, biochemical and imaging parameters were selected as explanatory variables in multiple logistic regression analysis with development of RA as dependent variable.

Results: 27 patients (23.3%) developed RA. The gender distribution and median age in the RA/non-RA groups were 81.5/76.4% women and 50 yrs (range 21–80)/47 yrs (19–82), respectively, and the symptom duration 4 mth (2–18)/7 mth (1.5–24). The final prediction model, consisting of presence of hand arthritis, positive rheumatoid factor (RF), morning stiffness >1 hour and OMERACT sum score of bone edema in MTP and wrist joints, correctly identified 82% of patients, who eventually developed RA or not RA (sensitivity/specificity: 81%/82%) (table, model 1). An alternative model (table, model 2), in which OMERACT sum score of bone edema in MTP and wrist joints was replaced by OMERACT sum score of bone edema in MTP, wrist and PIP joints, confirmed bone edema as independent predictor.

Table. Baseline predictors of development of rheumatoid arthritis (logistic regression analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Model 1 OR (CI)</th>
<th>p-value</th>
<th>Coefficient</th>
<th>Model 2 OR (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis of the hand</td>
<td>2.367</td>
<td>10.7 (2.9–39.7)</td>
<td>&lt;0.001</td>
<td>2.309</td>
<td>10.1 (2.7–37.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rheumatoid factor positive</td>
<td>0.881</td>
<td>6.6 (2.0–22.0)</td>
<td>0.001</td>
<td>1.889</td>
<td>6.6 (2.0–21.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt;1 hour of morning stiffness</td>
<td>1.997</td>
<td>7.4 (2.3–24.1)</td>
<td>0.001</td>
<td>1.944</td>
<td>7.0 (2.3–22.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>OMERACT bone edema sum score in wrist + MTP joint areas (per unit)</td>
<td>0.365</td>
<td>1.4 (1.0–2.0)</td>
<td>0.035</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>OMERACT bone edema sum score in wrist + MTP + PIP joint areas (per unit)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.348</td>
<td>1.4 (1.0–2.0)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Abbreviations: MTP=met at metacarpophalangeal, PIP=proximal interphalangeal, OR=Odds Ratio, CI=Confidence interval for OR

Conclusion: MRI bone edema in MTP and wrist joints is an independent predictor of future RA in patients with early UA. A prediction model,
MRI Inflammation in the Sacroiliac Joints Is Associated with CTX-II and Changes in Systemic Inflammation during TNFα Inhibitor Therapy.

Susanne Juul Pedersen2, Inge Jul Sørensen3, Robert Lambert3, Kay-Geert Hermann17, Patrick Garnero18, Julia S. Johansen1, Ole Rintek Madsen9, M. Ostergaard: None; K. Hørslev-Petersen: None; L. Bak: None; B. Eijbjerg: None; M. S. Hansen: Roche, 6, UCB, Inc., 6; J. S. Johansen: None; H. M. Lindegaard: Abbott Laboratories, 5, Roche, 5; H. Vinterberg: None; J. M. Møller: None; M. Østergaard: None.

Objectives: To investigate the relation between inflammation in the sacroiliac joints (SIJ) on magnetic resonance imaging (MRI) and biomarkers of inflammation (C-reactive protein (CRP), interleukin-6 (IL-6), YKL-40), angiogenesis (vascular endothelial growth factor (VEGF)), cartilage turnover (CTX-II, matrix metalloproteinase 3 (MMP3), total aggregan, cartilage oligomeric matrix protein (COMP)) and bone turnover (CTX-I, total osteocalcin) in patients with axial spondyloarthritis (SpA) treated with TNFα inhibitors.

Methods: Forty-three patients (34 men, 9 women; median age 40 yrs (range 21–62); disease duration 14 yrs (1–45)) initiated treatment with TNFα inhibitors (infliximab (n = 31), etanercept (n = 9) and adalimumab (n = 3)) and were followed for 46 weeks. MR Images were evaluated according to the Berlin SIJ inflammation scoring method at baseline, week 22 and 46. Biomarker levels of the patients were compared to these scores and biomarker levels of healthy subjects.

Results: The patients had a pretreatment MRI SIJ score of median 5 (range 0–23) and SIJ inflammation was seen in 33 (77%) patients. The SIJ scores correlated with CTX-II (rho = 0.57, p < 0.0001) and COMP (inversely, −0.36, p = 0.02), whereas no correlations were seen with the other 8 biomarkers. Compared to patients without pretreatment SIJ inflammation, patients with SIJ inflammation (MRI score ≥ 1) had higher baseline urine CTX-II levels (median 490 ng/mmol (IQR: 396–766) vs. 245 (128–345), p = 0.003), and higher time-integrated mean concentrations of CTX-II from baseline to week 22 (461 ng/mmol (313–665) vs. 311 (185–404), p = 0.04) and to week 46 (418 ng/mmol (286–610) vs. 214 (175–306) p < 0.0009) and lower YKL-40 from baseline to week 46 (41 μg/l (25–62) vs. 69 (46–106), p = 0.03). After 22 weeks of anti-TNFα therapy 17 (52%) patients with SIJ inflammation on baseline MRI decreased in score, whereas 16 (48%) patients were unchanged or increased in score. A decrease in SIJ scores after 22 weeks was associated with larger percentage decreases in CRP (−84% (−94–−67) vs. −45% (−65–−18), p = 0.008) and IL-6 (−76% (−88–−73) vs. −43% (−84–15), p = 0.03) but not with any other biomarker as compared to unchanged/increased SIJ score. CRP and IL-6 frequently normalized after 22 weeks (i.e. CRP ≤8 mg/l and IL-6 ≤3.3 ng/l) in a decrease in SIJ score as compared to patients with unchanged/increased SIJ score (Table 1).

| Table 1. Changes in biomarkers of inflammation (CRP and IL-6) versus change in Berlin MRI inflammation score |
|---|---|---|---|---|---|---|
| Changes from baseline to week 0–22 | Decreased | Unchanged/Persistent | N = 17 | N = 16 | p-value |
| CRP decreased to ≤8 mg/l | 12 (71) | 5 (29) | 0.36, p < 0.03 |
| CRP remained >8 mg/l | 1 (0) | 7 (100) | 0.01† |
| CRP remained ≤8 mg/l | 4 (50) | 4 (50) | NS§ |
| IL-6 decreased to ≤3.3 ng/l | 15 (79) | 4 (21) | 0.57, p < 0.005† |
| IL-6 remained >3.3 ng/l | 1 (14) | 6 (86) | 0.005§ |

Number (%). Chi² test and Fisher’s Exact test. ∆Normalization vs. persistently increased biomarker levels. §Normalization vs. normal levels at baseline

Conclusion: Inflammation in SIJ on baseline MRI was associated with higher urine levels of the cartilage degradation biomarker CTX-II. Decrease in MRI inflammation during treatment with TNFα inhibitors was associated with decrease in systemic inflammation.

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Quantitative Characterization of Bone Marrow Edema in Patients with Rheumatoid Arthritis.

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Objective: When assessed qualitatively or semi-quantitatively, bone marrow edema (BME) pattern, the hyperintense region within trabecular bone/bone marrow on T2-weighted fat-suppressed magnetic resonance imaging (MRI), predicts radiographic erosion progression in rheumatoid arthritis (RA). The goal of this study was to develop quantitative measures of BME, including volume, signal intensity and perfusion parameters, in the wrist using 3 Tesla (3T) MRI.

Methods and Materials: 10 patients (56.8 ± 12.9 years, 7 females) who fulfilled ACR classification criteria for RA and 3 healthy controls (36.2 ± 17.2 years, 2 females) were recruited. All patients were on disease-modifying anti-rheumatic drugs with (n = 2) or without (n = 5) biological agents. All MRI data were acquired with a 3T GE Sigma scanner using an 8-channel wrist coil. Coronal T2-weighted fast spin echo (FSE) images (TR/TE = 3500/50ms, in plane resolution = 0.2 mm, slice thickness = 2 mm) were acquired using iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) sequences. Coronal 3D dynamic contrast enhanced images were acquired during Gd-DTPA injection (TR/TE = 6.42/1.1ms, in plane resolution = 0.4 mm, slice thickness = 3 mm, temporal resolution 12 s, 32 time points). A semi-automatic algorithm was developed to segment BME in T2-weighted IDEAL FSE images. Volume, and signal intensity change of BME compared to normal bone marrow (NBM), defined as (SIBM – SINBM)/SINBM, were calculated automatically. Perfusion parameters were calculated on the signal-time curve obtained from DCE-MRI, including slope (S) = (Smax–Sbaseline)/(Sbaseline* Tmax) and maximum enhancement (E) = (Smax–Sbaseline)/Sbaseline. Two subjects were scanned twice and coefficients of variation (CV) of BME quantification were calculated for evaluating reproducibility. Spearman correlation coefficients between imaging measures and clinical evaluation (DAS28, ESR, and C-reactive protein, CRP) were calculated. Perfusion measures within BME were compared to outside BME using a paired t-test.

Results: The mean DAS28, ESR and CRP was 3.2± 1.43, 18 ± 17 mm/h, and 2.9 ± 2.3 mg/l, respectively. Nine patients had BME. The mean volume and signal intensity change of BME was 0.89 ± 1.05 cm³ and 6.09 ± 1.51%, respectively. Quantification of BME volume showed good reproducibility (mean CV 6.9%). The maximum enhancement and slope were significantly higher in BME compared to normal bone marrow (NBM), defined as (SIBM – SINBM)/SINBM, were calculated automatically. Perfusion parameters were calculated on the signal-time curve obtained from DCE-MRI, including slope (S) = (Smax–Sbaseline)/(Sbaseline* Tmax) and maximum enhancement (E) = (Smax–Sbaseline)/Sbaseline. Two subjects were scanned twice and coefficients of variation (CV) of BME quantification were calculated for evaluating reproducibility. Spearman correlation coefficients between imaging measures and clinical evaluation (DAS28, ESR, and C-reactive protein, CRP) were calculated. Perfusion measures within BME were compared to outside BME using a paired t-test.

Conclusions and Discussion: BME quantification using IDEAL sequences was highly reproducible. In this preliminary study, there were discrepancies between BME burden and clinical measures of disease activity, with BME present in the majority of patients in remission by DAS28. Quantifying BME may provide a useful parameter to assess the adequacy of therapeutic response on the
Quantitative In Vivo HR-pQCT Imaging of 3D Radiocarpal and Metacarpophalangeal Joint Space Distances in Rheumatoid Arthritis. Andrew J. Burghardt, Christina Kurhanewicz, John B. Imboden, Thomas M. Link and Xiaojuan Li. 1Department of Medicine, University of California, San Francisco and Division of Rheumatology, San Francisco General Hospital, 2Musculoskeletal Quantitative Imaging Research Group, Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, 3Musculoskeletal Quantitative Imaging Research Group, Department of Radiology and Biomedical Imaging, University of California, San Francisco

Purpose: In this technique development study, high-resolution peripheral quantitative computed tomography (HR-pQCT) was applied to non-invasively image the radioulnar (RU), radiocarpal (RC) and metacarpophalangeal (MCP) joints of patients with established rheumatoid arthritis (RA). Automated image processing methods were developed to quantify 3D MCP joint space morphology.

Methods: HR-pQCT imaging (82μm isotropic resolution) of the dominant hand was performed in patients with diagnosed rheumatoid arthritis (RA, N=7, age:54±14) and young healthy controls (CTRL, N=2, age:36±17). An automated segmentation technique was developed to individually segment the articulating joint space in the RU, two RC, and the 2nd to 4th MCP joints. The 3D distance transformation approach was applied to spatially map joint space distance and was normalized by the mean joint space distance (JSD) and standard deviation (JSD SD) – a measure of joint space heterogeneity. The in vivo precision for each measure was characterized using root mean square coefficient of variation (RMSCV%) from repeat acquisitions performed on two RA patients.

Results: The in vivo reproducibility was high for JSD (RMSCV: 1.3%) and moderate for JSD SD (RMSCV: 9.4%) despite one repeat measure with substantial motion artifacts. Qualitatively, the HR-pQCT images and JSD maps showed global joint space narrowing as well as focal defects in RA patients compared to CTRL (Fig 1).

In a modest number of subjects there was a general trend for decreased JSD at the MCP and comparable or greater JSD at the radial joints in RA subjects compared to CTRL. Joint space heterogeneity (JSD SD) all tended to be greater in RA patients compared to CTRL (Fig 2).

Conclusions: This study has established the feasibility of in vivo quantification of 3D joint space morphology in RA using HR-pQCT. This technology has the potential to provide a highly resolved, longitudinal assessment of joint morphology, which could provide new insights into clinical research studies of early disease progression and the efficacy of therapeutic interventions.

Disclosure: A. J. Burghardt: None; C. Kurhanewicz: None; J. B. Imboden: None; S. Majumdar: None; T. M. Link: None; X. Li: None.
**Objective:** Multicenter evaluation of low-field MRI as a tool for monitoring treatment response in patients with rheumatoid arthritis (RA) on the REMISSION PLUS pilot project.

**Methods:** RA patients initiating treatment with a DMARD or biologic at 9 sites throughout Germany underwent low-field MRI (C-scan, Esaote, 0.2 T) of the clinically dominant hand at time points T0 (baseline), T1 (3 months) and T2 (6 to 12 months). The images were evaluated semiquantitatively using the RAMRIS scoring system and correlated with clinical and lab chemistry markers.

**Results:** 206 RA patients (T0), 58 = m, 148 = f, age (years): (mean = 55.87, min.19, max. 84), time since diagnosis: (median = 20.32 months, min. 0.2 months, max. 45 years), DAS28 (mean = 4.83, 2.1 – 8), rheumatoid factor positive n = 118, CCP antibody positive n = 118, treatment naive: n = 64, switching treatments: n = 187; MRI follow-up at 3 months (T1) and at 6 to 12 months (T2); T0 and T2: n = 96; T0, T1 and T2: n = 55; RAMRIS (T0-T1-T2): 41.58-29.62-21.91; MCP: 13.31-8.76-6.38; wrist: 28.19-20.74-15.50; synovitis score (MCP): 5.11-3.06-1.60; wrist: 13.68-11.49-10.06; SRF (standardized response mean (> 0.5 moderate potential to detect changes)) T0-T2 synovitis: 0.999 (MCP); 0.709 (wrist), edema: 0.702 (MCP); 0.792 (wrist); p-correlations T0-DAS28 for synovitis: 0.010 (MCP); 0.037 (wrist); for edema: 0.140 (MCP); 0.050 (wrist).

**Conclusions:** Low-field MRI is a sensitive imaging method and RAMRIS a practicable scoring system for morphological and semiquantitative evaluation of therapeutic response to real-life rheumatologic care in significant correlation to clinical and lab data. The added benefit of low-field MRI is that it provides in-depth information on the severity of synovitis, edema (significant reduction on treatment) and erosion during follow-up, hence enabling early identification of responders/non-responders and providing a basis for individual prediction of prognosis and optimal disease management.

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**Repair of Bone Erosions in Patients Treated with TNF Antagonists in the Real World.** Kaoru Takase1, Kouji Kobayashi1, Kayo Terauchi1, Yoshiyuki Watanabe1, Reikou Watanabe1, Maasa Hama1, Rhusuke Yoshimi, Hiroshi Kobayashi2, Atsuhisa Ueda3, Mitsuhiro Takeno3, Haruko Ideguchi3, Shigeru Ohno1 and Yoshiaki Ishigatsubo3. 1Center for Rheumatic Diseases, Yokohama City University Medical Center, 2Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, 3Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine

**Objectives:** A number of clinical studies have shown that TNF antagonists suppress not only clinical symptoms but also the progression of joint destructions in patients with RA. Moreover, the therapeutic effects are accompanied by repair of bone erosions in some patients, though the prevalence is uncertain in the real world. We have previously reported that repair of bone erosions was found in 10.7% of RA patients treated with nonbiologic DMARDs. This study investigated the frequency of repair in RA patients receiving TNF antagonists and characterized clinical features in the patients.

**Methods:** Seventy RA patients (63 female, 7 male; age range, 28–76 years) who fulfilled the 1987 ACR classification criteria and received TNF antagonists for longer than one year were enrolled in this study. Radiographs of hands and feet were evaluated before the initiation of the TNF antagonists including infliximab, etanercept, and adalimumab, and thereafter annually including infliximab, etanercept + MTX + PSL 1, etanercept + MTX 1, etanercept + PSL 1, etanercept alone 1, and infliximab + MTX + PSL 1. Three of them were concurrently treated with MTX. There were no differences in Stage, Class, and DAS28 before the initiation of TNF antagonists. The repaired group showed more favorable clinical responses to TNF antagonist therapy compared with the non-repair group. Most patients had a good response according to EULAR criteria. DAS28 was statistically more reduced in the repaired group than that in non-repaired group during the first one year of TNF antagonist therapy (P < 0.05).

**Discussions:** The present study showed that repair of bone erosion is associated with good response to treatment with TNF antagonists. Well-controlled disease activity is a precondition for structural recovery, irrespective of therapeutic agents.

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**Responsiveness to Change and Reliability of Radiographic Joint Space Width in Osteoarthritis of the Knee: A Systematic Review.** William M. Reichmann2, Jean Francis Maillefer1, David J. Hunter2, Jeffrey N. Katz2, Philip G. Conaghan1 and Elena Losina1. 1Brigham & Womens Hosp, Boston, MA, 2Brigham and Womens Hospital, Boston, MA, 3Chapel Allerton Hospital, Leeds, United Kingdom, 4Dijon University Hospital, Dijon, France, 5University of Sydney, Boston, MA

**Introduction:** The quest for disease modifying OA drugs is anchored on the availability of responsive and reliable methods of measuring structural progres-
Synovitis and Osteitis Is Very Frequent in Rheumatoid Arthritis (RA) Patients in Clinical Remission: Results from a MRI Study of 300 RA Patients in Clinical Remission or Low Disease Activity State. Frederique Gandjbakhch1, Philipp G. Conaghan1, Bo Ebbjerg1, Esben Haavardsholm1, Violaine Foltz2, Andrew Brown2, Uffe Møller Døhler3, Marissa Lassere2, Jane Freesteroe4, Børge Bøyesen5, Paul Bird6, Bruno Fautrel7, Merete Lund Hørslev-Petersen2, Siri Lillegraven2, Barbara Slatkowsky-Christensen2, Espen Haavardsholm3, Solve Sesseng4, Tore K. Kvien1, Desiree M. Van Der Heijde3 and Pernille Bøyesen2. 1Diakonhjemmet Hospital, Oslo, Norway, 2Diakonhjemmet Hospital, University of Oslo, Oslo, Norway, 3Leiden University Medical Center, Meerssen, The Netherlands, 4Division of Epidemiology, Karolinska Institutet, Stockholm, Sweden, 5WHO Collaborating Centre for Rheumatic Diseases, University of Copenhagen, Copenhagen, Denmark, 6Hospital Pité-Salpêtrière, Université Paris VI - UPMC, Paris, France, 7Hôpital Pité-Salpêtrière, Université Paris VI - UPMC, Paris, France, 8St. George Hospital, University of NSW, Sydney, Australia, 9St. George Hospital, University of NSW, Sydney, Australia, 10Chapel Allerton Hospital, Leeds, United Kingdom, 11Copenhagen University Hospitals at Hvidovre and Glostrup, Denmark, 12Diakonhjemmet Hospital, University of Oslo, Oslo, Norway, 13Division of Medicine, University of NSW, Sydney Australia, 14Hôpital Pité-Salpêtrière, Université Paris VI - UPMC, Paris, France, 15Hvidovre University Hospital, Hvidovre, Denmark, 16King Christian X’s Hospital for Rheumatic Diseases, University of Southern Denmark, 17St. George Hospital, University of NSW, Sydney, Australia, 18Uni of Auckland Sch of Med, Auckland, New Zealand, 19University Hospitals at Hvidovre and Glostrup, Denmark, 20University of Leeds, Leeds, UK

The occurrence of synovitis and bone edema was not significantly different between patients in DAS28-clinical remission (synovitis/osteitis 96%/35%) and patients in LDA but not remission (synovitis/osteitis 91%/36%)(p=0.15/0.87). A trend towards lower frequencies of synovitis and osteitis in patients fulfilling more stringent remission criteria (SDAI and CDAI) was observed (data not shown).

Conclusion: Subclinical inflammation was revealed by MRI in the majority of RA patients in clinical remission or LDA state. This may explain structural progression in such patients. It should be considered whether future remission criteria should include modern imaging.

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The Intra- and Inter-Reader Reliability of the Oslo Hand Osteoarthritis (HOA) Magnetic Resonance Imaging (MRI) Score. Ida Kristin Haugen1, Siri Lillegaard2, Barbara Slatkowsky-Christensen2, Espen Haavardsholm2, Solve Sesseng2, Tore K. Kvien1, Desiree M. Van Der Heijde3 and Pernille Bøyesen2. 1Diakonhjemmet Hospital, Oslo, Norway, 2Diakonhjemmet Hospital, Paris, France, 3Diakonhjemmet Hospital, Oslo, Norway, 4Leiden University Medical Center, Leiden, The Netherlands

Background: HOA is increasingly recognized to involve the whole joint, incl. articular cartilage, subchondral bone, synovium, capsule and ligaments. MRI has a unique advantage to depict all joint components, and may be useful in evaluation of emerging treatments.
**Objectives:** To examine if pathological HOA features can be reliably assessed by testing the intra- and inter-reader reliability of the proposed Oslo HOA MRI score [1].

**Methods:** The exercise was performed using MRI scans from 10 patients (9 women) with mean (SD) age of 69.5 (6.1) years from the Oslo HOA cohort [2]. The patients were selected from quintiles of radiographic severity. The dominant hand was anchored in a cylindrical coil (diameter 100 mm), and the distal (DIP) and proximal interphalangeal (PIP) joints of the 2nd-5th fingers were examined using a high-field extremity MRI unit (1.0 T). Coronal, sagittal and axial T1w fat-suppressed pre-and post-gadolinium images were reproduced from a 3D dual echo Dixon technique (TR 20 ms, TE 5 ms, 1 mm slice thickness), in addition to coronal and axial Short T1 Inversion Recovery (STIR) images (TR 2850/3150 ms, TE 16.3/21 ms, 2/3 mm slice thickness). A training session and two exercises were arranged prior to this study. The images were read by three assessors (IKH, S60, P. Bøyesen). The images were read twice with one week interval, and were anonymised and rearranged prior to the last scoring session. Mean scores for all features across the three readers were calculated. The intra- and inter-reader reliability of the individual subscales was assessed by intra-class correlation coefficients (ICCs) (two way mixed effect model, single and average measure).

**Results:** Table shows mean (man, max) scores and ICCs for intra- and inter-reader reliability. The range of each feature is reported in brackets. Inter-reader reliability was good to excellent for synovitis, tenosynovitis, erosions, OP, JSN, malalignment, BML and CL presence. The median intra-reader reliability was good to excelent for most features except synovitis, tenosynovitis and cysts.

### Table

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mean Score (min, max)</th>
<th>Inter-reader AvmICC</th>
<th>Intra-reader SmICCC median (min, max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovitis [0–24]</td>
<td>11.6 (3.6–15.0)</td>
<td>0.48</td>
<td>0.99 (0.09–0.70)</td>
</tr>
<tr>
<td>Flexor tenosynovitis [0–24]</td>
<td>5.9 (1.7–10.3)</td>
<td>0.64</td>
<td>0.61 (0.49–0.65)</td>
</tr>
<tr>
<td>Erosions [0–48]</td>
<td>13.1 (2.3–29.0)</td>
<td>0.94</td>
<td>0.92 (0.91–0.96)</td>
</tr>
<tr>
<td>Cysts [0–16]</td>
<td>0.4 (0.0–2.0)</td>
<td>0.59</td>
<td>0.21 (0.00–0.57)</td>
</tr>
<tr>
<td>Osteophytes [0–48]</td>
<td>22.7 (7.3–34.0)</td>
<td>0.91</td>
<td>0.88 (0.86–0.89)</td>
</tr>
<tr>
<td>Joint space narrowing [0–24]</td>
<td>10.8 (7.1–15.3)</td>
<td>0.99</td>
<td>0.97 (0.93–0.99)</td>
</tr>
<tr>
<td>Malalignment frontal [0–8]</td>
<td>0.9 (0.2–3.2)</td>
<td>0.95</td>
<td>0.79 (0.77–1.00)</td>
</tr>
<tr>
<td>Malalignment sagittal [0–8]</td>
<td>0.0 (0.0–0.3)</td>
<td>0.00</td>
<td>*</td>
</tr>
<tr>
<td>BMLs [0–48]</td>
<td>4.2 (0.3–9.7)</td>
<td>0.83</td>
<td>0.89 (0.65–0.89)</td>
</tr>
<tr>
<td>CL presence [0–16]</td>
<td>10.0 (3.0–14.3)</td>
<td>0.79</td>
<td>0.81 (0.61–0.81)</td>
</tr>
<tr>
<td>BML at CL insertion sites [0–32]</td>
<td>2.4 (0.5–5.0)</td>
<td>0.42</td>
<td>0.42 (0.07–0.82)</td>
</tr>
</tbody>
</table>

**AvmICC =** Average measure ICC, **SmICCC =** single measure ICC, **BMLs** = bone marrow lesions, **CL** = collateral ligaments, * = no variance.

**Conclusion:** The proposed Oslo HOA MRI score could reliably assess key features of HOA. Further validation of the system to clinical and radiological findings should be performed.

**References:**
1. Haugen IK. Abstract EULAR 2010
2. Slatkowsky-Christensen B. Akr 2007

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**ACR Poster Session A**

**Metabolic and Crystal Arthropathies—Therapeutics and Outcomes I**

Monday, November 8, 2010, 9:00 AM–6:00 PM

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**Validity and Responsiveness to Change of Radiograph-Based Joint Space Narrowing Metric Measurement: A Systematic Review.** Delphine Chi, Miow Lin1, William M. Reichmann2, Laura Gossec3, Elena Losina1, Philip G. Conaghan1, William M. Reichmann2, Laure Gossec4, Elena Losina1, Philip G. Conaghan1, Delphine Chu Miow Lin1, None; W. M. Reichmann: None; L. Gossec: None; E. Losina: None; P. G. Conaghan: None; J.-F. Maillefer: None.

**Introduction:** The quest for disease modifying Osteoarthritis (OA) drugs is anchored on the availability of responsive and reliable methods of measuring structural progression. The goal of this systematic review was to report the responsiveness to change and reliability of conventional hip radiographic joint space width (JSW). We performed a systematic analysis of the literature on the concurrent validity, predictive validity and responsiveness of radiographic metric measurement of coxofemoral joint space in hip OA.

**Method:** We searched studies reporting any data on 1-hip OA patients in whom a metric measurement of the coxofemoral JSW on X-rays was performed and 2- on correlations with clinical symptoms and/or with further symptomatic state, joint space loss or joint replacement, and/or JSW change over time. We searched the PubMed and Embase databases using the following search terms ((Osteoarthritis[MeSH] and (hip)) AND (x-ray or radiography OR diagnostic imaging OR radiology OR disease progression) AND (joint space OR JSW OR disease progression)). Pooled SRA were evaluated using data obtained in articles in which the SRA were available or could be calculated from the mean change and standard deviation of change. For randomized clinical trials (RCTs), only the placebo arms were entered. Pooled SRA were obtained for minimum JSW metric measurement. Additional analyses restricted to cohorts and RCTs, to intention to treat (ITT) and completer analyses, to measurement of joint space performed with manual and computer-based methods, were performed.

**Results:** Twenty four studies were identified. Five suggested an association between JSW and symptoms in the general population. Two evaluated the correlations between the coxofemoral JSW and symptoms in hip OA patients, with heterogeneous results. Two suggested that joint symptoms are moderately correlated to further joint space loss. Five demonstrated that minimal JSW is predictive of further hip joint replacement. Responsiveness (11 studies, see table) was good, but tended to be lower in randomized clinical trials than in cohort studies, using an intention to treat rather than a completer analysis, and using computer-based rather than manual measurement.

**Conclusion:** There is some evidence of a weak association with symptoms and evidence of at least moderate responsiveness of metric measurement of JSW and symptoms in hip OA.

**Disclosure:** D. Chu Miow Lin: None; W. M. Reichmann: None; L. Gossec: None; E. Losina: None; P. G. Conaghan: None; J.-F. Maillefer: None.
chronic use. Pegloticase is a pegylated recombinant uricase designed to have an extended half life and reduced that has been previously studied as a single intramuscular dose in a phase 1 study in gout patients. It has not yet been studied as an intravenous agent.

Methods: This was an open label, single dose escalation phase 1 study in healthy volunteers and gout patients. Subjects of age 40-75 with screening plasma uric acid ≥ 6 mg/dL for men and ≥5 mg/dL for women were eligible to participate. The study enrolled five cohorts (4 subjects per cohort) at doses of 0.05, 0.1, 0.2, 0.3, and 0.4 mg/kg, respectively. Pegloticase was administered via intravenous infusion over one hour without premedication, and subjects were followed for 24 days. The primary endpoint was safety and tolerability and the secondary endpoints were pharmacodynamics (plasma uric acid), and pharmacokinetics (serum uricase activity). Adverse events were graded according to the Common Toxicity Criteria for Rheumatology, version 2.0.

Results: Pegloticase was well tolerated in this study. No serious or grade 3 adverse events were observed, and no infusion or allergic reactions were observed in any subjects. The only observed grade 2 toxicities were gout flares. Plasma uric acid level decreased upon infusion of pegloticase, with the rate of uric acid decrease exhibiting dose-dependence. At 0.05 mg/kg, uric acid levels decreased from a baseline of 8.3 mg/dL to almost undetectable levels within 24 hours of the infusion, whereas at the highest dose (0.4 mg/dL), plasma uric acid decreased from a mean of 7.8 mg/dL to undetectable levels within 3 hours. All subjects responded to pegloticase, and the duration of uric acid suppression below 2 mg/dL ranged from 7 to 24 days, in a dose-dependent manner. In the highest dose cohort, all four subjects maintained plasma uric acid at or near the limit of detection for the entire 24 day follow-up period.

Conclusions: A single intravenous infusion of pegloticase was safe and well-tolerated in these 20 subjects, and was capable of profoundly suppressing uric acid levels for up to 24 days. Further study of intravenous pegloticase as a chronic therapy in gout patients is warranted.

Disclosure: T. Fiorino: EnzymeRx, 1, 3; A. J. Kivitz: None; P. Pardo: None; R. Flores: EnzymeRx, 1, 3; Z. Zhang: EnzymeRx, 1, 3; J. S. Bomalaski: EnzymeRx, 6.

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Canakinumab (ACZ885) Relieves Pain and Controls Inflammation Rapidly in Patients with Difficult-To-Treat Gouty Arthritis: Comparison with Triamcinolone Acetonide. A. So1, M. De Meulemeester2, A. Pikhak3, A. E. Yücel4, U. Arulmani5, D. Richard1, V. Murphy1, P. Sallstig6 and N. Schlesinger7. 1Baskent University, Ankara, Turkey, 2Moscow State University of Medicine and Dentistry, Moscow, Russian Federation, 3Novartis Pharma AG, Basel, Switzerland, 4Private Practice, Gozée, Belgium, 5UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, 6University of Lausanne, Lausanne, Switzerland

Purpose: Monosodium urate (MSU) crystals stimulate the production of interleukin (IL)-1β, a potent inflammatory cytokine. Targeted IL-1β blockade with canakinumab, a fully human monoclonal anti-IL-1β antibody, is a novel treatment for gouty arthritis. Its effects on pain and inflammation in acute gouty arthritis flares were compared with triamcinolone acetonide (TA). TA has been shown to be effective in the treatment of acute gouty arthritis flares8.

Methods: This was an 8-week, dose-ranging, multicenter, blinded, active-controlled trial. Patients ≥18 to ≤80 years with an acute gouty arthritis flare, refractory to or contraindicated to NSAIDs and/or colchicine were randomized to 1 subcutaneous dose of canakinumab (10, 25, 50, 90, or 150 mg; n=143) or 1 intramuscular dose of TA (40 mg; n=57). Primary outcome was pain intensity at 72 hours post dose on VAS scale (0-100 mm). Secondary outcomes included C-reactive protein (CRP), serum amyloid A (SAA), and physician’s assessment of tenderness, swelling and erythema of target joint at 72 hours, 7 days, 4- and 8-weeks post dose.

Results: 191/200 patients completed the study. Canakinumab showed a statistically significant dose response at 72 hours. The 150 mg dose group reached superior pain relief compared to TA group starting from 24 hours as previously reported9. At 72 hours post dose, 78% of canakinumab 150 mg treated patients achieved ≥75% and 96% achieved ≥50% reduction in pain from baseline. In contrast, 45% and 61% of patients treated with TA achieved ≥75% and ≥50% pain reduction, respectively. Median CRP/SAA levels were normalized by Day 7 for all canakinumab doses above 10 mg and remained below the Upper Limit of Normal ([ULN]: CRP 3.0 mg/L; SAA 6.7 mg/L) for rest of the study. In TA group, median CRP levels remained above the ULN throughout the study while median SAA levels decreased below ULN only 28 days after first dose. At 72 hours post dose, canakinumab 150 mg group was 3.2 (95% CI, 1.27-7.89) times more likely to have less joint tenderness and 2.7 (95% CI, 1.09-6.5) times more likely to have less joint swelling than TA group (p<0.05). At 72 hours post dose, erythema disappeared in 74.1% of patients receiving canakinumab 150 mg and 69.6% of patients receiving TA. At 7 days post dose, erythema was absent in 96.3% of canakinumab 150 mg treated patients vs. 83.9% of patients receiving TA. The overall incidence of AEs was similar for canakinumab (41%) and triamcinolone acetonide (42%). Serious AEs (canakinumab treatment groups n=4; TA n=1) were not considered treatment related by investigators. No discontinuations due to AEs were observed.

Conclusions: Canakinumab 150 mg provided superior pain relief compared to TA for acute flares in difficult-to-treat gouty arthritis patients. Canakinumab provided rapid normalization of markers of inflammation accompanied by reduction of clinical signs and symptoms of inflammation.

Reference:

Disclosure: A. So: Abbott Laboratories, 5; Bristol-Myers Squibb, 5; Essex, 5; MSD, 5; Novartis Pharma AG, 5; Pfizer Inc, 5; Roche, 5; UBC, 5; Wyeth Pharmaceuticals, 5; M. De Meulemeester: None; A. Pikhak: Novartis Pharma AG, 2; A. E. Yücel: None; U. Arulmani: Novartis Pharma AG, 1, 3; D. Richard: Novartis Pharma AG, 1, 3; V. Murphy: Novartis Pharma AG, 1, 3; P. Sallstig: Novartis Pharma AG, 1, 3; N. Schlesinger: EnzymeRx, 8, 9; Novartis Pharmaceuticals Corporation, 2, 5, 9; Savient Pharmaceuticals, 9; Takeda, 8, 9; URL Pharma, 9.

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Change in Uric Acid Level Is Associated with Change in Patient Reported Outcomes in the Context of a Clinical Trial for Chronic Gout. Will Taylor1, Steve Hamburger2, Lisa K. Stump3, Zebulun D. Horowitz3 and Nicola Dalbeth4. 1Department of Medicine, University of Otago Christchurch, New Zealand, 2Savient Pharmaceuticals, Inc., E. Brunswick NJ, 3Savient Pharmaceuticals, Inc., E. Brunswick NJ, Baskingridge, NJ, 4Univ Auckland, Auckland, New Zealand, 5University of Otago Christchurch, Christchurch, New Zealand

Background: Serum uric acid (SUA) is an important endpoint for clinical trials of gout therapy. It is strongly endorsed by rheumatologists as the most important indicator of response in the context of a clinical trial for chronic gout. It fulfils most of the OMERACT biomarker criteria as a biomarker for patient reported outcomes (PRO), except that change in SUA has never been shown to be independently associated with change in PRO.

Methods: Data from 2 replicate Phase 3 randomised controlled trials of pegloticase were analysed for the association between change in uric acid levels from baseline to final follow-up (6 months) and change in PRO scores (pain, patient global, HAQ-DI, SF-36 MCS and SF-36 PCS). In this study, plasma uric acid levels were measured (PUA). For each PRO, a linear regression model was developed that incorporated final value of PUA, age and sex and a separate model that incorporated the change in PUA, age and sex. Change and final value of PUA were not incorporated together in the same model because of collinearity (correlation = 0.815).

Results: Change in PUA and also final value of PUA was significantly associated with changes in all PRO except the mental health summary score of SF-36. The magnitude of the beta coefficients for change and final value in PUA were similar. The magnitude of the association is weak.

Table 1. Regression models for each PRO by change in PUA and final PUA (all models adjusted for age and sex)

<table>
<thead>
<tr>
<th>PRO</th>
<th>p-value</th>
<th>Beta coefficient</th>
<th>Overall model r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in PUA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 month PUA</td>
<td>0.012</td>
<td>0.201</td>
<td>0.055</td>
</tr>
<tr>
<td>6 month PUA</td>
<td>0.002</td>
<td>-0.26</td>
<td>0.074</td>
</tr>
<tr>
<td>As a predictor of Apatient global</td>
<td>&lt;0.001</td>
<td>-0.299</td>
<td>0.096</td>
</tr>
<tr>
<td>Change in PUA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 month PUA</td>
<td>&lt;0.001</td>
<td>0.357</td>
<td>0.129</td>
</tr>
<tr>
<td>As a predictor of Apatient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in PUA</td>
<td>0.041</td>
<td>0.164</td>
<td>0.027</td>
</tr>
<tr>
<td>6 month PUA</td>
<td>0.004</td>
<td>-0.233</td>
<td>0.051</td>
</tr>
<tr>
<td>As a predictor of ASF36-PCS</td>
<td>0.002</td>
<td>0.247</td>
<td>0.078</td>
</tr>
<tr>
<td>Change in PUA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 month PUA</td>
<td>0.003</td>
<td>-0.236</td>
<td>0.070</td>
</tr>
<tr>
<td>As a predictor of ASF36-MCS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in PUA</td>
<td>0.921</td>
<td>0.008</td>
<td>0.055</td>
</tr>
<tr>
<td>6 month PUA</td>
<td>0.702</td>
<td>0.031</td>
<td>0.056</td>
</tr>
</tbody>
</table>
Conclusion: Although weak, the association of changes in PUA with changes in PRO help confirm that uric acid is a valid biomarker for outcomes of direct relevance for people with chronic gout.

Disclosure: W. Taylor: None; S. Hamburger: Savient Pharmaceuticals, 3; L. K. Stamp: None; Z. D. Horowitz: None; N. Dalbeth: None.

Background: Typical patients with gout have multiple comorbidities such as metabolic and cardiovascular (CV) disorders, hypertension, and kidney disease; concern for these conditions can make gout treatment conditions complex. This post hoc analysis was conducted to examine the relationship of age and comorbidities (renal, hepatic, CV function, and body mass index [BMI]) on the adverse event (AE) profile of patients with acute gout who were treated with colchicine.

Methods: A phase 3 multicenter, randomized placebo-controlled trial (AGREE) compared safety and tolerability of 2 different colchicine regimens, low dose (2 × 0.6 mg initially, then 0.6 mg 1 hr later to 1.8 mg/day total) and high dose (2 × 0.6 mg initially, then 0.6 mg/hr to 4.8 mg/day total) versus placebo in patients with gout (N = 185). Data were pooled for the low-dose and high-dose groups. For the present analyses, logistic regression was undertaken using presence or absence of AEs as the dependent variable and the following as independent variables: creatinine clearance (≥60 mL/min); alanine aminotransferase and aspartate aminotransferase ([ALT, AST] above upper limit of normal [ULN]); albumin (≥3.5 g/L); alkaline phosphatase (≥ULN); gout duration (years); BMI (>30); age (years); and presence or absence of CV history (eg, myocardial infarction, CV or cerebrovascular illness). Odds ratios (OR) were reported and compared. A Pearson chi-square P value <0.05 was used as the measure of statistical significance.

Results: At baseline, patients had a mean age of 51.5 (standard deviation [SD] = 11.1) years, with a diagnosed gout duration of 10.5 (SD = 8.9) years, a BMI of 33.0 (SD = 5.7), and serum uric acid level of 8.8 (SD = 1.8) mg/dL, and had experienced ≥2 acute gout flares in the 12 months before enrollment. Across the study, 83 patients (45%) experienced an AE; most of these were mild to moderate gastrointestinal AEs (~73%). Incidence of AEs in patients treated with colchicine was not significantly affected by any of the independent variables analyzed in this study (Table). Additional sensitivity analyses using cutoffs of 3 × ULN for AST (n = 0), ALT (n = 0), and alkaline phosphatase (n = 1), and 3.0 g/L for albumin (n = 0), were not performed because numbers of patients meeting these criteria were negligible.

Table

<table>
<thead>
<tr>
<th>Independent variables analyzed</th>
<th>Patients, n (%)</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (continuous)</td>
<td>185 (100.0)</td>
<td>1.00</td>
<td>0.97, 1.03</td>
<td>0.999</td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>125 (67.6)</td>
<td>1.22</td>
<td>0.93, 2.37</td>
<td>0.348</td>
</tr>
<tr>
<td>Gout duration &gt;8 years</td>
<td>91 (49.2)</td>
<td>1.24</td>
<td>0.68, 2.25</td>
<td>0.476</td>
</tr>
<tr>
<td>Cardiovascular history (yes/no)</td>
<td>107 (57.8)</td>
<td>1.13</td>
<td>0.60, 2.10</td>
<td>0.707</td>
</tr>
<tr>
<td>Creatinine clearance ≤60 mL/min</td>
<td>161 (87.0)</td>
<td>0.87</td>
<td>0.34, 2.22</td>
<td>0.778</td>
</tr>
<tr>
<td>AST &gt; ULN</td>
<td>12 (6.5)</td>
<td>1.19</td>
<td>0.31, 4.61</td>
<td>0.805</td>
</tr>
<tr>
<td>ALT &gt; ULN</td>
<td>31 (16.8)</td>
<td>0.57</td>
<td>0.23, 1.44</td>
<td>0.236</td>
</tr>
<tr>
<td>Albumin ≤3.5 g/L</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alkaline phosphatase &gt; ULN</td>
<td>2 (1.1)</td>
<td>1.04</td>
<td>0.06, 19.01</td>
<td>0.976</td>
</tr>
</tbody>
</table>

Conclusions: In these regression analyses of 185 patients with gout in a randomized phase 3 study, there was no effect of chronologic age, gout duration, renal function (indicated by creatinine clearance), liver function (as assessed by AST, ALT, albumin, and alkaline phosphatase), presence of CV history, or obesity with the incidence of AEs following colchicine treatment (inclusive of all doses). Although additional studies would be needed to corroborate these results, these data offer reassurance regarding the safety of colchicine in patients with several comorbid conditions.


148 Colchicine Use Is Associated with Decreased Diagnosis of Myocardial Infarction (MI) and Trend toward Reduction of All-Cause Mortality and C-Reactive Protein (CRP) Levels: Insights from the NY VA Gout Cohort.


Background: The potential relationship between gout and cardiovascular disease (CVD) is a topic of great interest. Studies have demonstrated the presence of systemic inflammation in gout, with increased levels of C-reactive protein (CRP), as well as increased risk of cardiovascular disease (CVD). However, the role of colchicine, a colchicine response marker, in reducing cardiovascular disease or mortality is not well established. This study aimed to evaluate the association of colchicine use with the diagnosis of acute MI, CVD mortality, all-cause mortality, and CRP levels among patients with gout.

Statement of Purpose: The purpose of this study was to investigate the association of colchicine use with the diagnosis of MI, CVD mortality, all-cause mortality, and CRP levels among patients with gout.

Methods: This was a retrospective cohort study conducted in the electronic medical record systems (EMRs) of the New York Harbor Healthcare System (N=40,107). All patients with an ICD-9 gout code at the Manhattan, Brooklyn, and St Albans Veterans Affairs Hospitals in New York City between August 2007 and August 2008 were included. Demographics, cardiovascular co-morbidities, and endpoints were collected by chart review, including review of each patient’s EMR problem list and note review as appropriate. Primary (MI) and secondary (all-cause mortality, CRP level) outcomes were analyzed based on presence/absence of colchicine use. Use of colchicine was defined as 5% (no colchicine) vs 3.9% (colchicine) (n.s.). CRP levels were 3.53 (no colchicine) vs 2.49 (colchicine) mg/dL (n.s.). Use of allopurinol was not associated with reduced MI in either group.

Conclusion: In this retrospective study, patients ever vs never treated with colchicine had similar rates of atherosclerosis and fixed cardiovascular disease. Nonetheless, patients treated with colchicine demonstrated decreased diagnosis of MI, and trends toward lower CRP levels and all-cause mortality. These data suggest a possible protective effect of colchicine on the incidence of acute coronary syndromes.

metabolism of 1-methylxanthine to 1-methyluric acid is mediated by xanthine oxidase (XO). Febuxostat is not expected to have any inhibitory effect on the 
CYP isozymes involved in metabolism of theophylline. However, since 
febuostat is a nonpurine selective inhibitor of XO, it could affect the 
XO-mediated metabolism of theophylline and potentially alter the clearance of 
theophylline. Since theophylline is a low therapeutic index drug and 
coadministration with high doses of the XO inhibitor allopurinol results in 
decreased clearance of theophylline, this study was performed to evaluate 
the effect of febuostat and its metabolites at steady-state on the pharmacokinetics 
of theophylline.

**Methods:** This was a Phase 1, double-blind, randomized, 2-period 
crossover study. Twenty-four subjects (12 male and 12 female) were 
enrolled in the study and were randomly assigned in a 1:1 ratio to receive febuostat 
or matching placebo for 7 days. On Day 5 of each period, 400 mg of 
theophylline was administered followed by collection of plasma and urine 
pharmacokinetic samples until 72 hours postdose.

**Results:** Theophylline was absorbed with median T\textsubscript{max} value of 6 hrs and 
eliminated with a mean T\textsubscript{1/2} of 9.69 hrs following oral administration of 
theophylline 400 mg with placebo or febuostat. Mean theophylline C\textsubscript{max} values 
were 4.14 and 4.39 µg/mL when subjects were coadministered placebo and febuostat, respectively. Mean theophylline AUC\textsubscript{Clast} values 
were 115 and 122 µg/hr/mL when subjects were coadministered placebo and 
febuostat, respectively. Likewise, mean AUC\textsubscript{Clast} and T\textsubscript{1/2} CL/F, and V\textsubscript{z}/F values were also comparable between regimens. The mean amount of 
theophylline excreted in the urine over a 72-hour interval was comparable 
between the 2 regimens. The mean amounts of 1,3-dimethyluric acid and 
3-methylxanthine was also similar between the 2 treatment arms. In contrast, 
the amount of 1-methyluric acid decreased and 1-methylxanthine increased in 
subjects following administration of theophylline with febuostat compared to 
placebo. These changes in the amounts of metabolites excreted in urine have 
little or no clinical significance, as neither of these metabolites has pharmacological 
activity.

The point estimate for the ratio of theophylline C\textsubscript{max} central values 
following administration of theophylline with febuostat or placebo, and 
responding 90% confidence intervals (CIs) were 1.03 and (0.917, 1.149), 
respectively. The point estimate for the ratio of theophylline AUC\textsubscript{Cmax} central values 
following administration of theophylline with febuostat or placebo, and 
responding 90% CIs were 1.04 and (0.927, 1.156), respectively. Both 
90% CIs fell within the no-effect range of 0.8 and 1.25.

**Conclusions:** Coadministration of febuostat with theophylline has no 
effect on the pharmacokinetics of theophylline. No dose adjustment for 
theophylline is required when coadministered with febuostat.

**Disclosure:** M. Tsai: Takeda Global Research and Development Center, Inc., 3; J. Wu: 
Takeda Global Research and Development Center, Inc., 3; L. Gunawardhana: Takeda 
Global Research and Development Center, Inc., 3; H. Naik: Takeda Global Research 
and Development Center, Inc., 3

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**Efficacy and Tolerability of Celecoxib in the Treatment of Moderate to Extreme Pain Associated with Acute Gouty Arthritis: A Randomized Controlled Trial.** H. Ralph Schumacher¹, Manuel Berger², Julie Li-Yu³, Fernando Perez-Ruiz³, Ruben Burgos Vargas³ and Chumming (Mark) Li⁴.

**Background:** Although nonsteroidal anti-inflammatory drugs (NSAIDs) 
such as indomethacin are widely used for the treatment of acute gouty arthritis, 
adverse events (AEs) have limited their use to date. This study was 
performed to evaluate the efficacy and tolerability of various doses of the 
cylooxygenase (COX)-2 selective NSAID celecoxib in the treatment of 
moderate to extreme pain and inflammation associated with acute gouty arthritis.

**Methods:** Multinational, randomized, double-blind, double-dummy, 
active-controlled trial in patients (aged ≥ 18 y) with acute gouty arthritis 
(onset of pain ≤48 h prior to enrollment). Patients were required to have 
moderate to extreme pain in the index joint over the previous 24 h (5-point 
Patient’s Assessment of Pain Intensity) and to be candidates for daily therapy 
with NSAIDs and/or analgesics. Patients with polyarticular (> 4 joints 
affected)/chronic gout, or other form of arthritis (except mild to moderate 
osteoarthrosis not affecting the index joint) were excluded. The study consisted 
of an 8-day treatment period followed by 1-week follow-up. Patients were 
randomized 1:1:1:1 to receive: 1) celecoxib 50mg bid, 2) celecoxib 400mg 
followed by 200mg on Day 1 and then 200mg bid for 7 days, 3) celecoxib 
800mg followed by 400mg on Day 1 and then 400mg bid for 7 days and 4) 
indomethacin 50mg tid. The primary objective was to evaluate the analgesic 
efficacy of a high-dose celecoxib regimen (800/400mg) compared with a 
low-dose regimen (50mg bid) in the treatment of moderate to extreme pain at 
Day 2. Secondary objectives included the evaluation of the analgesic and 
anti-inflammatory effects of different celecoxib doses compared with indomethacin 
50mg tid; safety and tolerability were also assessed.

**Results:** Of 443 patients screened, 402 patients were randomized and 400 
received treatment. Baseline demographics were comparable between 
treatments. For the primary endpoint, patients receiving high-dose celecoxib 
(800/400 mg) experienced a significantly greater reduction in patients' 
assessment of pain intensity on Day 2 compared with low-dose celecoxib (50 
mg bid; least squares [LS] mean difference = 0.46, P = 0.0014). All high-dose 
celecoxib 800/400mg, the change in pain scores from baseline to Day 2 was 
comparable to indomethacin 50mg tid (LS mean difference 0.11, P = 0.4331). 
Compared to indomethacin 50mg tid, celecoxib 400/200mg and 50mg bid 
produced small reductions in pain (LS mean difference 0.33 [P < 0.05] and 
0.57 [P < 0.001], respectively). Secondary efficacy and safety findings are 
presented below.
Physician’s Assessment of Tenderness of the Index Joint (measure of inflammation on Day 5 change from Baseline)

vs Celecoxib 50mg bid
LS mean Difference (SE)
95% CI
P value

vs Indomethacin 50 mg tid
LS mean Difference (SE)
95% CI
P value

Safety, number (%) of

Number of AEs
59
43
51
80

AEs
33 (32.7)
27 (27.3)
28 (28.6)
44 (43.1)

Headache
5 (5.0)
4 (4.0)
3 (3.1)
4 (3.9)

Diarrrhea
3 (3.0)
2 (2.0)
2 (2.0)
5 (4.9)

Dizziness
2 (2.0)
1 (1.0)
2 (2.0)
6 (5.9)

Upper Abdominal Pain
1 (1.0)
0
1 (1.0)
5 (4.9)

Severe AEs
5 (5.0)
3 (3.0)
2 (2.0)
1 (1.0)

Discontinuations due to AEs
5 (5.0)
3 (3.0)
1 (1.0)
9 (8.8)

Deaths
0
0
0
0

SE=standard error; CI=confidence interval

Conclusions: High-dose celecoxib (800/400 mg) is significantly more effective than low-dose celecoxib (50 mg bid) in the treatment of moderate-to-severe pain and inflammation associated with acute gouty arthritis. Furthermore, this regimen is comparable in efficacy to indomethacin 50 mg tid and appears to offer an improved tolerability profile.

Disclosure: H. R. Schumacher: Pfizer Inc, 5; M. Berger: Pfizer Inc, 1, 3; J. Li-Yu: Pfizer Inc, 8; F. Perez-Ruiz: Ardea Biosciences, 5, 8; Menarini, 5, 8; Novartis Pharmaceuticals Corporation, 8; Pfizer Inc, 5; R. Burgos Vargas: Abbott Laboratories, 5, 8; Bristol-Myers Squibb, 5, 8; Merck Pharmaceuticals, 5, 8; Pfizer Inc, 5, 8, Roche, 5, 8; C. M. Li: Pfizer Inc, 1, 3.

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Evaluation of Rilonacept for Prevention of Gout Flares during Initiation of Urate-Lowering Therapy: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial. Robert Terkeltaub, H. Ralph Schumacher, Kenneth G. Saag, James Clower, William Jennings, Robert R. Evans, Jian Wang, Shirletta King-Davis and Steven P. Weinstein. 1Radiant Research, San Antonio, TX, 2Regeneron Pharmaceuticals, Inc., Tarrytown, NY, 3Regeneron Pharmaceuticals, Inc., 4University of Alabama-Birmingham, Birmingham, AL, 5VA Medical Center and UPenn, Philadelphia, PA, 6VA Medical Ctr, San Diego, CA, 7Westside Center for Clinical Research, Jacksonville, FL

Background: The present study evaluated the efficacy and safety of rilonacept (IL-1 Trap) for the prevention of gout flares (GFs) during initiation of urate-lowering therapy (ULT) with allopurinol. While attaining target serum levels is critical to the long-term management of gout, ULT can elicit or prolong acute attacks during the initial months of therapy. This paradoxical finding may be attributable to remodeling of crystal deposits during dissolution.

Methods: This North American multicenter trial included adults with gout (ARA criteria), urate levels ≥7.5 mg/dL, and self-reported history of ≥2 GFs in the previous year. Eligible patients were initiated on allopurinol 300 mg daily (or lower dose in those with renal dysfunction, with subsequent titration to achieve urate <6 mg/dL) and randomized to receive treatment with weekly subcutaneous (SC) injections of placebo (Pbo; n=80), rilonacept 80 mg (R80; n=80), or rilonacept 160 mg (R160; n=81) (loading dose on Day 1). GFs were reported by the patient via interactive voice response diary and treated, as appropriate, with NSAIDs or oral glucocorticoids while continuing study treatments. Efficacy endpoints included the number of GFs, % of patients with 1 or more flares, and number of flare days. Safety and tolerability were also assessed.

Results: Baseline characteristics were similar among treatment groups; 92.9% were male, the mean ± SD age was 52.3 ± 12.6 years, and the number of flares reported in the prior year was 4.6 ± 3.3. Fewer patients on Pbo completed the 16-wk treatment period (72.5%) compared with those receiving active treatment (80.0% R80; 86.4% R160). Observed serum urate levels decreased similarly in all 3 groups. Through wk 16, the mean number of GFs per patient (primary endpoint) was significantly lower in both R groups relative to Pbo: 1.06 (84 flares) for Pbo; 0.29 (23 flares) for R80, and 0.21 (17 flares) for R160 (95% CI, 0.22 to 0.46; p<0.0001 vs Pbo). One or more flares were reported by 46.8% Pbo, 18.8% R80, and 16.3% of R160 patients (p<0.0001). The number of flare days per patient was significantly lower with rilonacept: 5.52, 2.36, and 0.98 for Pbo, R80, and R160, respectively (p<0.0001 vs Pbo). From day 1 to wk 16, the proportion of patients who experienced multiple flares was 31.6% Pbo (95% CI, 21.6 to 43.1) vs 5.0% R80 (95% CI, 1.4 to 12.3) vs 3.7% R160 (95% CI, 0.8 to 10.6; p<0.0001 for both comparisons), resulting in an 84% and 88% reduction in the respective R groups. The overall incidence of adverse events (AE) was similar between Pbo (60.8%) and rilonacept (63.4%). Injection site reactions were the most frequent AE with rilonacept (14.3% vs 1.3%). Other common AEs, reported by ≥5% of patients, were respiratory infections, musculoskeletal system disorders, and headache, and rates were generally similar among the treatment groups. Three patients in each group experienced serious AEs; no rilonacept-related SAEs, deaths, or serious infectious AEs were reported.

Conclusions: This phase 3 trial confirmed that IL-1 blockade with rilonacept markedly reduced the occurrence of gout flares during initiation of urate lowering therapy. Rilonacept demonstrated an acceptable safety and tolerability profile.


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Evaluation of Rilonacept in Patients with Gouty Arthritis Experiencing an Acute Gout Attack. Robert Terkeltaub, H. Ralph Schumacher, Craig Curtis, Neil Patterson, Robert R. Evans, Jian Wang, Shirletta King-Davis and Steven P. Weinstein. 1 Compass Research, Orlando, FL, 2Private Practice, Oviedo, FL, 3Regeneron Pharmaceuticals, Inc., Tarrytown, NY, 4Regeneron Pharmaceuticals, Inc., 5VA Medical Center, Philadelphia, PA, 6VA Medical Ctr, San Diego, CA

Background: The role of IL-1β as a central mediator of acute gouty inflammation has been confirmed by animal models and gout prevention studies in patients initiating urate lowering therapy. Although IL-1 appears to trigger gout flares (GFs), available data on IL-1 inhibition in the treatment of GFs is limited to case reports and a single dose-ranging study.

Objective: To report initial findings from SURGE (Study of Rilonacept in Gout Exacerbations), a large phase 3, randomized, double-blind, double-dummy, active-controlled study of the IL-1β and IL-1α blocker rilonacept for the treatment of acute GFs, conducted at approximately 80 sites in North America.

Methods: Eligible patients with gout aged ≥18 to ≤70 y presenting within 48 hrs of onset of a GF with at least moderately severe pain, evidence of swelling and tenderness in the gouty index joint (most painful joint), and who had not initiated treatment for GF symptoms were randomized to 1 of 3 regimens: SC placebo (Pbo) at baseline (BL), plus oral indomethacin (IN) for at least 3 days (d) [50 mg tid x 3 d, then 25 mg tid x 9 d (IN group); SC rilonacept 320 mg at BL, plus IN for at least 3 d (R+IN group); or SC rilonacept 320 mg at BL, plus oral Pbo for at least 3 d (R group). Patient assessment of pain intensity in the gouty index joint was recorded using a 5-point Likert scale (0 = none; 4 = extreme) at BL (pre-dose) and 4, 8, 12, 24,
Results: 225 patients with an acute GF were randomized to treatment (IN n=76; R+IN n=74; R n=75). Baseline characteristics were similar among groups. IN resulted in a statistically significant (p<0.0001) within-group reported reduction from BL in pain intensity similar to that reported in previous studies of IN. Although a numerically greater reduction in pain intensity was observed with R+IN compared with IN alone (mean ± SD change R+IN −1.55 ± 0.92 vs IN −1.40 ± 0.96), the difference was not statistically significant (95% CI, −0.44 to 0.15; p=0.33). Therefore, comparison of the IN with the R group (mean change ± SD R −0.69 ± 0.97 from baseline) was not performed, per the analysis plan.

Treatment with rilonacept was generally well-tolerated, with 3 patients reporting serious adverse events in the R+IN group, none considered drug-related. Adverse events reported at an incidence of at least 5% in any group were headache and dizziness.

Conclusions: Under conditions in which the reduction of acute gout flare pain in the indomethacin alone group was similar to published reports, inhibition of IL-1 with rilonacept did not provide additional pain relief within 72 hours of flare onset. In comparison with prior studies, the results suggest that blockade of IL-1 for treatment of an early, established acute gout flare is less effective clinically than for acute gout flare prophylaxis.


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Febuxostat Versus Allopurinol in the Treatment of Gout in Subjects ≥65 Years of Age: A Subgroup Analysis of the CONFIRMS Trial. Eswar Krishnan1, Patricia A. MacDonald2, Barbara Hunt2 and Robert Jackson3. 1Stanford University, Stanford, CA, 2Takeda Global Research & Development Center, Inc, 3; R. Jackson: Takeda Global Research & Development Center, Inc, 3.

Purpose: Efficacy and safety of urate-lowering therapy (ULT) in an older gout population has been infrequently reported. Febuxostat is a novel, non-purine, selective inhibitor of xanthine oxidase for the treatment of hyperuricemia in patients with chronic gout. This is a subset analysis of 374 elderly subjects (≥65 years of age) from a total of 2269 subjects treated with febuxostat (FEB) or allopurinol (ALLO) for 6 months from the CONFIRMS study.1

Methods: Subjects with gout and serum urate levels (sUA) ≥8.0 mg/dL were randomized to FEB 40 mg, FEB 80 mg, or ALLO (200/300 mg based on renal function) once daily. Gout flare prophylaxis (colchicine or naproxen) was provided for the entire study duration. The outcomes of interest were percent of elderly subjects with sUA <6.0 mg/dL by renal functional status and safety in this at-risk population.

Results: The 374 subjects were predominately male (86%), Caucasian (85%), and obese (51% with body mass index [BMI] ≥30 kg/m²), with a mean age of 71 years. Baseline characteristics and comorbidities were similar across groups; 82% had hypertension, 25% diabetes, 24% coronary artery disease, 21% cardiac arrhythmia, and 11% previous myocardial infarction. The three treatment groups were similar in age, gender, race, and duration of gout. The mean duration of gout was 15 years with a baseline sUA 9.4 mg/dL with history of tophi (19%) and kidney stones (20%); 98% of subjects had some degree of renal impairment. Urate-lowering therapy use, at some time across groups, was provided for the entire study duration. The outcomes of interest were presented in the table. The most frequently reported AEs irrespective of treatment were diarrhea (10%) and upper respiratory infection (8%). The majority were transient and resolved while on treatment. Serious AEs were reported by 8% in the FEB 40 mg, 6% in the FEB 80 mg, and 11% in the ALLO group. The most common serious AEs were cardiac disorders, 1%, 2%, and 3%, and lower respiratory tract infections, 1%, 0%, and 2%, in the FEB 40 mg, FEB 80 mg, and ALLO treatment groups, respectively. There were no hypersensitivity reactions. Overall response rates were similar to those seen in the combined CONFIRMS population.

Percent of Subjects Achieving sUA <6 mg/dL

<table>
<thead>
<tr>
<th></th>
<th>FEB 40 mg n/N (%)</th>
<th>FEB 80 mg n/N (%)</th>
<th>ALLO 200/300 mg n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (CLcr ≥90 mL/min)</td>
<td>2/3 (67)</td>
<td>1/2 (50)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Mild (CLcr ≥60 to 89 mL/min)</td>
<td>33/45 (73)</td>
<td>39/44 (89)*</td>
<td>31/50 (62)</td>
</tr>
<tr>
<td>Moderate (CLcr &gt;30 to 59 mL/min)</td>
<td>36/67 (54)</td>
<td>65/82 (79)**</td>
<td>30/80 (38)</td>
</tr>
</tbody>
</table>

*p <0.05, FEB 80 mg vs ALLO; **p <0.05, FEB 80 vs FEB 40 mg.

Conclusions: Treatment with FEB reduced sUA to <6.0 mg/dL in this elderly population with significant cardiovascular comorbidities and was well tolerated. Response in the elderly moderately renally impaired population was statistically significantly better with either dose of FEB vs ALLO.


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Healthcare Utilization and Productivity at Home and Work Place in Tophaceous vs. Non-Tophaceous Gout. Puja Khanna1, Jay Persselin1, Ron Hays2, Daniel Furst3, Harold Paulus4, Paul Maranian5 and Dinesh Khanna5. 1Greater Los Angeles VA, 2UCLA, 3UCLA and Greater Los Angeles VA

Objective: Gout is a painful inflammatory arthritis that causes debilitating acute attacks and is associated with increased resource utilization. Retrospective claims data has shown economic impact of gout on both direct and indirect medical costs including office visits, emergency room visits, medications, and time lost from work. However, there is lack of prospective data in a well-defined gout cohort. In addition, no study has reported the impact of gout on productivity. We assessed the impact of gout on health care utilization and productivity at home and work place.

Methods: Patients with tophaceous and non-tophaceous gout were recruited at VA and University medical centers. Productivity was assessed using Work Productivity Survey (Osterhaus, J. Arthritis Research & Therapy 2009). Patients indicated whether or not they were employed outside of the home, how many days in last month they missed work (employment or household work) due to gout, how many days/month productivity was decreased 50% due to gout, and how much gout interfered with work/ household chores (0–10 scale), days/month they missed family and social activities, and days/month they required outside help. Health care utilization was assessed using UCSD Health Care Utilization Questionnaire (HCU). HCU asked about resource utilization during past 3 months on office/hospital visits, surgeries, medical supplies, prescription and OTC medications due to their ongoing medical conditions (not just gout).

Results: Of 71 patients, 45 (63%) patients had non-tophaceous gout. There were no statistical differences in demographics between tophaceous and non-tophaceous gout. On average, patients were 68.2 years old, 96% were male, 70% were Caucasian. Patient with tophaceous gout had similar disease duration, serum uric acid and Charlson comorbidity index; patients with tophi had worse HAQ-DI score (1.1 vs. 0.7; p=0.06). Only 20% of patients were employed. Patients missed an average of 3.7 days of work at home or work place per month, had work or home productivity reduced by more than 50% in 3 days per month, had 3 days with reduced family and social activities, and had 1.4 days where they required outside help to do work at home. Tophaceous gout was associated with greater loss of productivity at home and work place compared to non-tophaceous gout (Table). Resource utilization was not significantly different between the 2 groups.
Table: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total Population (N=71)</th>
<th>Non-Tophaceous (N=45)</th>
<th>Tophaceous (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean (SD))</td>
<td>68.2 (10.0)</td>
<td>67.5 (10.1)</td>
<td>68.7 (9.9)</td>
</tr>
<tr>
<td>Charlson Comorbidity index, mean (SD)</td>
<td>3.0 (2.6)</td>
<td>3.0 (2.7)</td>
<td>3.1 (2.4)</td>
</tr>
<tr>
<td>Severity of Gout scale, 0–10, mean (SD)</td>
<td>3.0 (2.9)</td>
<td>2.1 (2.3)</td>
<td>4.7 (3.2)</td>
</tr>
<tr>
<td>Productivity</td>
<td>14 (19.7)</td>
<td>8 (17.8)</td>
<td>8 (23.1)</td>
</tr>
<tr>
<td>Days missed due to gout, mean (SD)</td>
<td>3.7 (8.1)</td>
<td>3.2 (7.5)</td>
<td>4.5 (9.1)</td>
</tr>
<tr>
<td>Days with reduced productivity due to gout, mean (SD)</td>
<td>3.2 (7.5)</td>
<td>2.4 (6.1)</td>
<td>4.2 (8.8)</td>
</tr>
<tr>
<td>Gout interfered (0–10), mean (SD)</td>
<td>3.3 (3.6)</td>
<td>2.8 (3.4)</td>
<td>4.4 (3.7)*</td>
</tr>
<tr>
<td>Days with reduced family and social activities, mean (SD)</td>
<td>3.9 (6.8)</td>
<td>1.6 (3.3)</td>
<td>5.6 (10.4)</td>
</tr>
<tr>
<td>Days requiring outside help due to gout, mean (SD)</td>
<td>1.4 (5.3)</td>
<td>0.4 (1.7)</td>
<td>3.1 (8.4)</td>
</tr>
</tbody>
</table>

* p<0.05 for comparison between tophaceous and non-tophaceous gout

Conclusions: Tophaceous gout negatively impacts work place and home productivity. The lack of significant differences in utilization in patients with and without non-tophaceous gout is likely due to similar comorbidity profiles.

Disclosure: P. Khanna: ACR REF, 2; J. Persslein: None; R. Hays: None; D. Furst: None; H. Paulus: None; P. Maranian: Savient Pharmaceuticals, 5; D. Khanna: Savient Pharmaceuticals, 2, 5.

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Patient Knowledge and Beliefs Concerning Gout and Its Treatment
Leslie R. Harrold1, Kathleen M. Mazor2, Daniel Peterson3, Cassandra Firneno1 and Robert A. Yood1. 1Fallon Clinic, Worcester, MA, 2Meyers Primary Care Institute/UMass Medical School, 3Meyers Primary Care Institute, 4UMass Medical Schi, Worcester, MA

Objectives: We sought to examine patients’ knowledge and beliefs concerning gout and its treatment to order to identify ways to improve gout care.

Methods: We identified all members (≥18 years of age) of a group-model health maintenance organization (HMO) with documentation of at least one health care encounter associated with a gout diagnosis during the period 2008–2009 (n=1346). From this population a random sample of 500 subjects were sent a questionnaire assessing knowledge with regard to gout, beliefs about prescription medications used to treat gout, satisfaction with care providers, we identified several knowledge deficits that may worsen disease management including lack of knowledge regarding dietary triggers and lack of awareness of the risk of gout flare with initiation of ULDs.

Results: Two hundred and forty patients returned surveys and research authorization forms. The majority of patients were male (80%), white (94%), and aged 65 and older (66%). Only 14% of patients were cared for by a rheumatologist. The vast majority of patients were aware that gout was related to uric acid and flares were the result of crystals inducing inflammation. Many participants were unaware of foods that may lead to a gout flare. Specifically, more patients reported vegetables (58%), chicken (55%) and legumes (39%) as triggers as compared to seafood (23%), beef (22%) and pork (7%). Only 43% reported beer could increase the chances of a gout flare. Awareness of dietary triggers was not greater among those with more encounters for gout or chronic gout (identified by use of urate-lowering drugs [ULDs]). For the management of acute flares, nonsteroidal anti-inflammatory drugs were considered easy to take (86%) and effective in decreasing pain (78%) with only 22% having side effects to the agents. Among colchicine users, colchicine was considered easy to take (91%) and effective (76%) but 37% reported side effects to the medication. There were 101 patients prescribed a ULD of whom 21% reported forgetting to take their medication in the past month. Only a minority of ULD users (12%) were aware of the risk of tophi when initiating treatment with this medication class. The majority of patients reported high levels of trust in their physician and good patient-provider communication.

Conclusion: In this gout patient population cared for mostly by primary care providers, we identified several knowledge deficits that may worsening disease management including lack of knowledge regarding dietary triggers and lack of awareness of the risk of gout flare with initiation of ULDS. In addition, providers should explore with their patients reasons for missed doses of ULDS in order to improve adherence.


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Progressive Reduction in Tophus Burden with Pegloticase Therapy in Patients with Chronic Gout Refractory to Conventional Therapy, Herbert Baraf1, Sergio R. Gutierrez-Ureña2, Janitza Vazquez-Mellado3, Claudia Rehrig4, Faith Ottery5, John S. Sundy6 and Robert A. Yood1. 1Arthritis & Rheumatism Association, Wheaton, MA, 2Duke University Medical Center, Durham, NC, 3Fallon Clinic, Worcester, MA, 4Hospital Civil de Guadalajara, Guadalajara, Mexico, 5Hospital General de México, México City, 6Savient Pharmaceuticals, Inc

Purpose: To evaluate the effect of up to 30 months of i.v. pegloticase therapy on tophi in patients (pts) with treatment refractory chronic gout.

Methods: Pts completing one of two 6-month, randomized, double-blind, placebo-controlled Phase 3 trials (RCT) of pegloticase were eligible for continued therapy in an open label extension study (OLE). Treatment in RCT was pegloticase (PGL) 8 mg (q2wk or q4wk) or placebo (PBO) and in OLE was PGL (q2wk or q4wk). OLE pts could switch dose arms after 6 months. Primary response endpoint in RCT was plasma uric acid (PUA) <6.0 mg/dL 80% of the time in months 3 and 6. Secondary outcomes included treatment effects for tophus, flares, other rheumatologic variables and pt reported outcomes. Tophus response was assessed using CAPER (Computer-Assisted Photographic Evaluation in Rheumatology) methodology (Abstract 1111, ACR 2009) with blinded central readers of standardized digital photos taken of hands, feet (accounting for maximum of 5 target tophi for serial assessment) and up to 2 other tophi sites at RCT baseline and throughout RCT and OLE. While PGL effect on tophi was analyzed in a number of ways using CAPER, this analysis addresses individual target tophus response.

Results: At RCT baseline, 154 of 212 (73%) dosed pts had ≥1 tophus; 107 had ≥1 tophus entering OLE. 151/157 (96%) of RCT completers enrolled in the OLE (82 q2wks, 67 q4wks, 2 observation). 50 of 60 RCT PUA-responders maintained serum UA <6 mg/dL during OLE. Tophus response was related to UA-responder status, with tophus progression during OLE in 13 RCT nonresponders and 0 RCT responders. Individual target tophus complete response data for pts on pegloticase in both RCT+OLE are summarized below. In addition, 12 of 28 pts with ≥1 tophus on PBO in RCT had their first target tophus CR in the OLE (data not shown).

Complete Responses (CR) for Target Tophi in Patients on Pegloticase in Both RCT and OLE

<table>
<thead>
<tr>
<th></th>
<th>Total number of patients with baseline target tophi, N</th>
<th>Total # target tophi</th>
<th>Total number of patients having ≥1 tophus CR, n (n/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>79</td>
<td>308</td>
<td>53/79 (67%)</td>
</tr>
<tr>
<td>• Pts having 1st CR for target tophi during RCT, n (n/%)</td>
<td>29/79 (37%)</td>
<td>24/79 (30%)</td>
<td></td>
</tr>
<tr>
<td>• Pts having 1st target tophus CR during OLE, n (n/%)</td>
<td>85/308 (28%)</td>
<td>42/308 (14%)</td>
<td></td>
</tr>
<tr>
<td>• Number of tophi undergoing CR in RCT</td>
<td>53/308 (17%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusion: Pegloticase has a remarkable effect on tophus resolution in pts with chronic gout refractory to conventional therapy. Approximately 28% of baseline target tophi assessed by digital photography completely resolved during the first 6 months of pegloticase therapy. Resolution continued during pegloticase therapy for up to 30 months with a total of 58% of baseline target tophi eliminated.

Disclosure: H. Baraf: Investigator, 9, Savient Pharmaceuticals, 5, 9, Takeda Pharmaceuticals North America, 8; S. R. Gutierrez-Urena: Savient Pharmaceuticals, 9; J. Vazquez-Mellado: Savient Pharmaceuticals, 9; C. Rehrig: Savient Pharmaceuticals, 3; F. Ottery: Savient Pharmaceuticals, 3; J. S. Sundy: Alnara, Anadys, Array BioPharma, Phamoss, 5, 9, Ardea Biosciences, 5, 9, CME through Duke University, 5, 9, Genentech and Biogen IDEC Inc, 9, Managing Partner, 5, 9, Regeneron Pharmaceuticals, Inc., 9, Roche, 5, Savient Pharmaceuticals; R. A. Voor: Savient Pharmaceuticals, 9, Takeda Pharmaceuticals North America, 2.

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Safety and Efficacy ofFebuxostat (FEB) Treatment in Subjects with Gout and Severe Allopurinol (ALLO) Adverse Reactions. Saima Chohan and Michael A. Becker. University of Chicago, Chicago, IL

Background: ALLO, a purine base analog inhibitor of xanthine oxidase (XO) activity, remains the standard for pharmacologic urate-lowering (UL) management of gout. ALLO is efficacious and safe in most patients, but intolerance is estimated to occur in up to 10% of treated patients. Severe or life-threatening ALLO adverse reactions (ALLO-ARs) occur in <0.4% of treated patients, and include severe cutaneous ALLO reactions (SCAR), vasculitis, and/or a multisystem ALLO hypersensitivity syndrome (AHSS). During clinical development of FEB, a recently approved Xanthine Oxidase Inhibitor (XOI), ALLO-ARs have not been observed. FEB is a nonpurine analog of XOI with a lower incidence of cutaneous AEs (cAEs) compared with ALLO. The incidence of ALLO-ARs (SCAR, vasculitis, and/or a multisystem ALLO hypersensitivity syndrome) was assessed in this long-term study.

Methods: In this retrospective study, safety and UL efficacy of FEB was assessed in 133 gout patients treated with FEB 40 to 80 mg/day (median 40 mg/day) for 36 months. Efficacy was evaluated by changes in serum urate (sUA) levels, the number of gout attacks per 6-month period, and the change in tophus number. Safety was evaluated by the incidence of FEB-related AEs and laboratory abnormalities.

Results: The mean (±SD) duration of FEB treatment was 36 (±12) months. The mean (±SD) baseline sUA level was 7.3 ± 2.7 mg/dL. The mean (±SD) decrease in sUA from baseline to the last observation was 3.0 ± 2.1 mg/dL. FEB was well tolerated in 12 patients. FEB-related AEs (≥10%) were headache (21%), nausea (15%), and diarrhea (10%). The incidence of laboratory abnormalities (≥10%) was hematologic abnormalities (10%) and renal function abnormalities (10%). FEB was well tolerated in the majority of patients, with a mean treatment exposure of 10 months (range 1–24 months).

Conclusion: Despite the high incidence of ALLO-ARs, FEB treatment was well tolerated. The incidence of laboratory abnormalities and FEB-related AEs was similar to that reported for ALLO. FEB treatment was associated with significant decreases in sUA levels, reducing the number of gout attacks, and reducing tophus number.

Disclosure: H. Baraf: Investigator, 9, Savient Pharmaceuticals, 5, 9, Takeda Pharmaceuticals North America, 8; S. R. Gutierrez-Urena: Savient Pharmaceuticals, 9; J. Vazquez-Mellado: Savient Pharmaceuticals, 9; C. Rehrig: Savient Pharmaceuticals, 3; F. Ottery: Savient Pharmaceuticals, 3; J. S. Sundy: Alnara, Anadys, Array BioPharma, Phamoss, 5, 9, Ardea Biosciences, 5, 9, CME through Duke University, 5, 9, Genentech and Biogen IDEC Inc, 9, Managing Partner, 5, 9, Regeneron Pharmaceuticals, Inc., 9, Roche, 5, Savient Pharmaceuticals; R. A. Voor: Savient Pharmaceuticals, 9, Takeda Pharmaceuticals North America, 2.

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Serum Urate Levels Have an Impact on Renal Function in Patients with Gout Withdrawing Urate-Lowering Therapy (ULT). Fernando Perez-Ruiz1, Ana M. Herrero-Beites2 and Miguel A. Gonzalez-Gay3. 1Hospital de Cruces, Jolapena, Spain, 2Hospital de Göríz, 3Hospital Universitario Marques de Valdecilla

Objective: to evaluate whether serum urate levels have an impact on renal function in patients with gout.

Methods: patients who gave consent to withdraw ULT after 5-yr treatment (for non-tophaceous) or 5-yr after disappearance of tophi were included in an ongoing observational study of recurrence of flares (Perez-Ruiz F. Arthritis Rheum 2006, Arthritis Rheum 2009-abstract). Renal function was estimated with clearance of creatinine at baseline and treatment, and with MDRD formula after withdrawing ULT. Outcome measure for renal dysfunction was considered as MDRD renal function estimation < 60 ml/min at last observation of follow-up. Patients with recurrence of gout were started on ULT, and stopped for follow-up in this cohort. Kaplan-Meier survival analysis (log rank test) was used to identify variables associated with outcome, including age, time from onset of gout, tophi, serum urate at baseline, withdrawal (average) and follow-up (average), time on ULT, clearance of creatinine at baseline and withdrawal, urate-lowering drugs, hypertension, diabetes, hyperlipidemia, vascular episodes, proteinuria (> 500 mg/day). Multivariate Cox proportional hazard regression analysis was used to study those variables associated with the outcome as survival variable.

Results: from a 202 patient cohort, 179 had all variables to estimate renal function with MDRD equation at last observation, and were included in analysis. Mean age at ULT withdrawal was 61±11 (35–89), time on treatment was 65±6 months (60–116), time on follow-up 34±23 months (1–124). Serum urate was 8.9±1.31, 4.9±0.83, and 8.5±1.45 at baseline, withdrawal and follow-up. Tophi were present at baseline in 25%, 49% received allopurinol, and 51% benz bromarone. Hypertension (33%), diabetes (14.9%), diuretics (13.7%), hyperlipidemia (49.7%), and vascular events (17.1%) were common in this hospital-based cohort. Renal dysfunction was present in 24 (13.4%), 33 (18.4%), and 39 (21.8%) patients at baseline, withdrawal and follow-up respectively, 8 patients showing proteinuria. Multivariate Cox regression analysis showed three variables to be independently and significantly associated with renal dysfunction: lower clearance of creatinine at withdrawal, presence of proteinuria, and increasing serum urate levels during follow-up, but only for the two upper quartiles of the distribution (median 8.45 mg/dl).

Conclusion: renal function and proteinuria, but also the highest quartiles of serum urate levels, are independently associated with poor renal outcome after ULT withdrawal.

Disclosure: F. Perez-Ruiz: None; A. M. Herrero-Beites: None; M. A. Gonzalez-Gay: None.

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The Combination of Tranilast with Allopurinol Results in Enhanced Urate Lowering. John S. Sundy4, Michael M. Kitt5, Sue G. Griffith1, Randall R. Stoltz2 and Ronald Goldblum3. 1ClinPharma Resources, San Diego, CA, 2Covance, Evansville, IN, 3CPC Inc, Carlsbad, CA, 4Duke University Medical Center, Durham, NC, 5Nuon Therapeutics, Inc., San Mateo, CA

Background: Reduction of serum urate (sUA) can be achieved with uricosuric drugs, which enhance excretion of uric acid, or with inhibitors of xanthine-oxidase, which interrupt the enzymatic cascade converting xanthine to urate. Combination therapy utilizing both mechanisms may be useful in producing lower sUA levels and higher responder rates than a single mechanism in patients with hyperuricemia and gout.

Study Design: A double-blind, 5-treatment period, crossover Phase 2 study evaluated co-administration of tranilast and allopurinol in patients with hyperuricemia. Subjects were randomized 1:1:1 in an initial 3-treatment crossover phase to 300 mg tranilast (T300), 300 mg allopurinol (A300), or a combination of A300 + T300 (C300). At the end of the third period, patients were randomized 1:1 in a 2-treatment crossover phase of allopurinol 400 mg (A400)
or a combination of A300 + T300 (C300). Each period within a phase was 14 days in duration with 7 days treatment orally once daily (Days 1–7), followed by a 7-day washout interval. sUA levels were obtained each day of dosing and 24 hours after last dose. Plasma concentrations of tranilast, allopurinol, and oxypurinol (allopurinol’s active metabolite) were evaluated over the 24-hour interval after last dose of each 7-day period. The primary objective was to compare % change from baseline sUA of the combination with tranilast or allopurinol alone.

**Results:** Twenty male patients were enrolled with mean age 43 years, BMI 29.7 kg/m², and baseline sUA 8.1 mg/dL. Combination treatment resulted in greater percentage decrease in sUA than tranilast or allopurinol alone (see table). With C400, 61% of patients achieved sUA levels ≤4.0 mg/dL, which was significantly greater than the 11% achieved with C300 or A400 alone (p=0.0027).

<table>
<thead>
<tr>
<th></th>
<th>T300 N=19</th>
<th>A300 N=19</th>
<th>(T300+C300) N=18</th>
<th>A300 N=19</th>
<th>C300 N=18 + A300 N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean % sUA Change from Baseline</td>
<td>-14%</td>
<td>-35%</td>
<td>-43%b</td>
<td>-38%</td>
<td>-49%c</td>
</tr>
<tr>
<td>Responders &lt;6 mg/mL sUA</td>
<td>28%</td>
<td>94%</td>
<td>100%</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td>Responders &lt;4 mg/mL sUA</td>
<td>0%</td>
<td>6%</td>
<td>11%</td>
<td>11%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Coadministration of allopurinol with tranilast did not affect plasma tranilast Cmax or AUC. Although tranilast had no effect on plasma allopurinol pharmacokinetics, tranilast decreased plasma oxyipurinol Cmax and AUC by ~25–30%, which was an expected interaction, as uricosurics such as tranilast inhibit the reabsorption of both uric acid and oxyipurinol in the renal tubules. All treatment regimens were well-tolerated.

**Conclusion:** In patients with hyperuricemia, combining tranilast 300 mg with allopurinol 400 mg is more effective in reducing sUA to normal levels than allopurinol alone.

**Disclosure:** A. Krishnamurthy: None; D. M. Lazaro: None; D. R. Blumenthal: None; D. A. Gerber: None; P. L. Flom: None.

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**The Impact of Deficits in Gout Care on Hospitalizations.** Prachaya Nitiachaiakitavan1, Katherine Upchurch2 and Leslie Harrold3. 1University of Massachusetts Medical School, Worcester, 2University of Massachusetts Medical School

**Objective:** To identify hospital admissions and complicated hospital stays due to gout and examine the contribution deficits in gout care had on hospitalizations.

**Methods:** We performed a retrospective chart review of all hospitalized patients between January 1, 2008 and December 31, 2009 in whom a rheumatologist consultation was requested and a diagnosis of gout was made by the treating rheumatologist. We included only the first inpatient consultation on each patient. Deficits in gout care were identified based on published gout treatment recommendations and quality of care indications. Descriptive statistics were performed.

**Results:** A total of 700 rheumatologist inpatient consultations were performed during the study period of whom 120 patients were diagnosed with gout and met inclusion criteria. At the time of hospitalization, 33 (28%) had no prior diagnosis of gout, although tophi were present in 7 (21%). In the 87 patients with a prior diagnosis of gout, 32 (27%) were crystal proven while in 35 (46%) the diagnosis was made clinically. The majority of patients were Caucasian (82%) and male (78%). The mean age was 69 years. Comorbidities such as hypertension (71%) and renal disease (54%) were common, as well as outpatient use of diuretics (56%) and low dose aspirin (40%). Deficits in pre-hospital gout care were found in 29%. Specifically, urate lowering drugs were not used in the setting of tophi, radiographic erosive changes presumed to be secondary to gout or recurrent gouty attacks. Therefore, acute gout episodes in these settings were considered preventable. Patients with non-crystal proven gout were found to have the most pre-hospitalization deficits of care (21 out of 35). Thirty two patients had a prior evaluation by a rheumatologist (27%). Previous outpatient rheumatology management of gout improved the quality indicators of gout care (P value < 0.02 in patients with a history of gout).

Nine patients (8%) among the study group were rehospitalized due to gout or complications related to gout during the two year study period. Five out of nine (56%) were not treated with urate lowering agents when indicated during their initial hospitalizations.

**Table 1. Identification of potential gout triggers stratified by gout diagnosis prior admission.**

<table>
<thead>
<tr>
<th></th>
<th>Prehospitalization Diagnosis of Gout</th>
<th>No previous history of gout</th>
<th>Total N=120</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crystal proven gout N=32</td>
<td>Non-crystal proven gout N=55</td>
<td></td>
</tr>
<tr>
<td>Lack of ULD use when indicated</td>
<td>7</td>
<td>21</td>
<td>35 (29%)</td>
</tr>
<tr>
<td>Nonadherence to ULD treatment</td>
<td>0</td>
<td>2</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>5</td>
<td>11</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>Aggressive diuretic use</td>
<td>1</td>
<td>8</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Fluid shifts from surgery</td>
<td>2</td>
<td>2</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

**Conclusion:** This study demonstrates that both outpatient and inpatient deficits in gout quality of care occur commonly and were associated with both complicated hospitalizations and inpatient admission. Addressing gout quality of care in order to reduce the frequency and intensity of acute flares has the potential to reduce the frequency of hospitalizations, and hospital length of stay.

**Disclosure:** P. Nitiachaiakitavan: None; K. Upchurch: None; L. Harrold: None.
The Safety and Efficacy of Anakinra in the Treatment of Acute Gout in Hospitalized Patients. Michael Cho1, Pradipta Ghosh2, Gurpreet Hans3, Julia J. Rhiannon4, Gregory C. Gardner1 and Peter A. Simkin1. 1University of Washington, Seattle, WA, 2University of Washington, Seattle, WA, 3University of Washington, Lake Forest Park, WA, 4University of Washington, Kirkland, WA

Background: The management of acute gout in the hospital setting can be a difficult clinical problem due to co-morbidities that may limit the use of traditional anti-inflammatory medications. The anti-IL1 receptor antagonist, anakinra, has been successful in the treatment of acute/chronic gout in two published series and 4 case reports totaling 24 patients. The purpose of this study was to review our use of anakinra in acute gout in the hospital setting for efficacy of single and multiple courses of anakinra and to investigate any potential safety concerns.

Methods: We reviewed our consult records over the past three years to identify patients with acute gout treated with anakinra while hospital inpatients. Data extracted from the charts included age, gender, BMI, co-morbidities, uric acid level, results of arthrocentesis, number of anakinra courses, joint(s) and soft-tissue sites involved, anakinra dosing, time to initial improvement, time to complete resolution of signs and symptoms of inflammation, and any possible side effects in particular infection or leukopenia.

Results: We identified 15 patients with acute gout who had received 22 courses of anakinra. The group consisted of 13 males and 2 females, mean age of 53 years (range 32–72 yrs). The major co-morbidities, often in combination, were CKD in 10 patients, DM in 5, CHF in 5, post-solid organ transplant in 2, acute leukemia in 2, and systemic infection in 1. Seven patients had tophaceous disease. The mean BMI was 34.9 (range 22.8–57.8).

Reasons for choosing anakinra were failure of prophylactic low dose colchicine and therapeutic steroids (oral, IV or IA) to reduce pain and inflammation in 14 courses of anakinra and co-morbid disease limitations in 8. Dosing of anakinra was generally 100 mg subcutaneously daily for 3 days. In 18 of the 22 courses, joint involvement was pauci-polyarticular. Ten patients received 1 course of anakinra and 5 patients had 2–4 courses during different hospital stays. In 19/22 anakinra courses, patients reported pain improvement (often dramatic) in 1 day or less. In 3/22 courses pain improvement was noted by day 2. In 9/22 courses patients had complete resolution in 5 or less days, 11/22 in 6–10 days, and in 1/22 it took >10 days for the gouty attack to completely resolve. There was no decrement in response to multiple courses separated by time. There were no cases of anakinra-associated leukopenia but one patient developed a post-operative wound infection 5 days after starting an anakinra course.

Conclusion: Anakinra is an effective therapy for acute gout in hospitalized patients with multiple co-morbidities. It was successful in 14 courses where the patients had no apparent response to steroids. It also appears to be effective in multiple courses in the same patient. Dosing strategies, length of therapy, and positioning of anakinra therapy in this setting are areas that will continue to be investigated. The post-operative wound infection is of concern but of uncertain significance. Use of anakinra in the post-operative period should be considered with caution.

Disclosure: M. Cho: None; P. Ghosh: None; G. Hans: None; J. J. Rhiannon: None; G. C. Gardner: None; P. A. Simkin: None.

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Urate-Lowering (UL) Efficacy and Safety of Febuxostat (FEB) and Allopurinol (ALLO) in Women with Gout, an Older Subset of Gout Subjects with Increased Comorbidity. Saima Chohani1, Michael A. Becker2, Patricia A. MacDonald3, Solomon Chefo2 and Robert Jackson2. 1Takeda Global R&D Inc, Lake Forest, IL, 2Takeda Global Research & Development Center, Inc, Deerfield, IL, 3University of Chicago, Chicago, IL

Background: Although the incidence and prevalence of gout is increasing in the older population of both genders, literature on women with gout confirms later mean onset of the disease in women than men (averaging a decade or more after menopause) and suggests that the frequent comorbidities (renal impairment, cardiovascular disease, metabolic syndrome components, diuretic use) accompanying hyperuricemia/gout in men may be even more common in women. Given this background, we evaluated the UL efficacy and safety of therapy with FEB or ALLO in the subset of women enrolled in a series of randomized controlled clinical trials (RCTs) comparing these xanthine oxidase inhibitors.

Methods: 4101 subjects (3875 men/226 women) participated in the 12-month FACT or the 6-month APEX or CONFRMS trials. This post-hoc subset analysis focuses on female subjects with gout and serum urate levels (sUA) ≥8.0 mg/dL who were randomized (study specific) to daily PBO (n=11 subjects), FEB (n=139), or ALLO (n=76). Baseline renal functional status was assessed by estimated creatinine clearance (eCler) calculated using the Cockcroft-Gault formula. UL efficacy results are reported according to study drug and dose administered and stratified by baseline renal function.

Disclosure: A. Mandal: None; D. Emerling: Nuon Therapeutics, 3; T. Serafini: Nuon Therapeutics, 3; D. B. Mount: None.
Results: The 5.5% women subjects in these RCTs had a mean age of 62 y (vs 52 y men), and 74% had BMI ≥30 kg/m² (62% men). Comorbid history (women vs men), was significant for hypertension (81% vs 48%), diabetes (26% vs 10%), hyperlipidemia (46% vs 37%) and renal impairment (64% eCrCl <60 mL/min vs 13%). Gout history: 19% of women and 21% of men had tophi; 86% and 85%, respectively, had experienced a gout flare in the prior year, and mean disease duration was 8 y women and 12 y men. Mean sUAt baseline was 9.7 mg/dL for both men and women. Proportions of women subjects with final visit sUAt <6.0 mg/dL were presented by renal functional status in the Table.

Table. Proportions of Women Subjects With Final Visit sUAt <6.0 mg/dL

<table>
<thead>
<tr>
<th>Baseline Renal Function (eCrCl)</th>
<th>PBO</th>
<th>FEB 40 mg</th>
<th>FEB 80 mg</th>
<th>FEB 120 mg</th>
<th>FEB 240 mg</th>
<th>ALLO 100/200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (≥ 90 mL/min)</td>
<td>0/1 (0)</td>
<td>1/2 (50)</td>
<td>7/7 (100)</td>
<td>1/1 (100)</td>
<td>NA</td>
<td>1/2 (50)</td>
</tr>
<tr>
<td>Mid (≥ 60 &lt; 90 mL/min)</td>
<td>0/5 (0)</td>
<td>8/10 (80)</td>
<td>21/25 (84)</td>
<td>4/5 (80)</td>
<td>3/3 (100)</td>
<td>9/18 (50)</td>
</tr>
<tr>
<td>Moderate or severe (17–59 mL/min)</td>
<td>0/5 (0)</td>
<td>10/23 (44)</td>
<td>35/42 (83)</td>
<td>12/15 (80)</td>
<td>4/4 (100)</td>
<td>24/54 (44)</td>
</tr>
</tbody>
</table>

*2 subjects with CrCl <80 mL/min received ALLO 100 mg and 32 received ALLO 200 mg NA=not applicable

The most frequently reported AEs among women were: URI (16%), diarrhea (11%), and musculoskeletal/connective tissue (11%). The major-ized to PGL 8 mg q2wk (n 43) pegloticase or placebo (PBO) in the Phase 3 RCTs. Pts were random-


### Purpose: To assess the therapy response of pegloticase for a spectrum of non-flare, non-tophus, gout-related rheumatologic variables in patients (pts) with treatment refractory chronic gout (TRCG) in 2 replicate Phase 3, randomized, double-blind, placebo-controlled trials (RCTs).

### Methods: TRCG was defined as: ≥3 flares in the previous 18 months, or ≥1 tophus, or gouty arthropathy; serum urate >8.0 mg/dL; and prior failure of maximum medically appropriate dose of allopurinol or contraindication to allopurinol. 212 pts were treated with IV pegloticase or placebo (PBO) in the Phase 3 RCTs. Pts were randomized to PGL 8 mg q2wk (n=85), 8 mg q4wk (n=84), or PBO (n=43) and were infused every 2 weeks for 6 months in a blinded fashion.

Primary response endpoint was plasma uric acid (PUA) <6.0 mg/dL 80% of the time in months 3 and 6. Data were pooled for secondary endpoints: reduction of tophus size, gout flare incidence, swollen joints (SJ), tender joints (TJ), pt-reported outcomes by SF-36 and Health Assessment Questionnaire (HAQ). Change from baseline for each secondary rheumatologic variable was compared by regimen and PUA responder status.

Results: Baseline characteristics: 82% male; mean age 55 yrs; high degree of comorbidity: hypertension (71%), chronic kidney disease (43%), cardiovascular disease (31%), and diabetes (22%). As previously reported at ACR 2008, both pegloticase groups were significantly superior to PBO for the primary efficacy endpoint in both studies. Tender joint or swollen joint counts (Table 1) and HAQ-Patient Global Assessment (Table 2), assessed for change from baseline to last visit (last observation carried forward) or week 25, were significant for pooled PGL vs PBO (≤0.001). Changes within each pegloticase group were consistently better in PUA responders® vs non-responders (NR).

### Table 1. Tender Joint and Swollen Joint Counts

<table>
<thead>
<tr>
<th>Swollen Joint Count</th>
<th>Pegloticase q2wk</th>
<th>Pegloticase q4wk</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>NR</td>
<td>Total</td>
<td>R</td>
</tr>
<tr>
<td>Baseline, n</td>
<td>36</td>
<td>49</td>
<td>84</td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>10.3 (1.7)</td>
<td>10.6 (1.7)</td>
<td>8.9 (1.1)</td>
</tr>
<tr>
<td>Week 23, n</td>
<td>36</td>
<td>28</td>
<td>64</td>
</tr>
<tr>
<td>Week 23, mean (SD)</td>
<td>8.6 (1.0)</td>
<td>3.4 (1.0)</td>
<td>8.0 (1.3)</td>
</tr>
<tr>
<td>Final visit, n</td>
<td>35</td>
<td>43</td>
<td>78</td>
</tr>
<tr>
<td>Final visit, mean (SD)</td>
<td>8.6 (1.0)</td>
<td>3.0 (1.0)</td>
<td>8.5 (1.0)</td>
</tr>
<tr>
<td>p-value [1]</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. HAQ Patient Global Assessment

<table>
<thead>
<tr>
<th>R</th>
<th>HR</th>
<th>Total</th>
<th>R</th>
<th>HR</th>
<th>Total</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, n</td>
<td>35</td>
<td>49</td>
<td>84</td>
<td>24</td>
<td>43</td>
<td>Placebo</td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>42.7 (28.1)</td>
<td>42.2 (24.0)</td>
<td>42.4 (24.8)</td>
<td>49.8 (25.2)</td>
<td>49.8 (25.6)</td>
<td>49.8 (24.9)</td>
</tr>
<tr>
<td>Week 25, n</td>
<td>32</td>
<td>20</td>
<td>52</td>
<td>25</td>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td>Week 25, mean (SD)</td>
<td>23.3 (20.7)</td>
<td>23.1 (24.6)</td>
<td>27.3 (25.8)</td>
<td>26.2 (19.6)</td>
<td>41.4 (26.3)</td>
<td>34.9 (24.5)</td>
</tr>
<tr>
<td>A from BL</td>
<td>20.0 (27.0)</td>
<td>13.2 (21.1)**</td>
<td>17.5 (24.9)</td>
<td>23.4 (24.8)</td>
<td>6.2 (25.7)**</td>
<td>13.6 (25.5)</td>
</tr>
<tr>
<td>p-value [1]</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final visit, n</td>
<td>33</td>
<td>36*</td>
<td>69</td>
<td>25</td>
<td>47</td>
<td>72</td>
</tr>
<tr>
<td>Final visit, mean (SD)</td>
<td>22.8 (20.7)</td>
<td>37.5 (27.2)</td>
<td>30.4 (25.2)</td>
<td>26.2 (19.6)</td>
<td>42.9 (25.3)</td>
<td>37.1 (24.7)</td>
</tr>
<tr>
<td>A from BL</td>
<td>19.94 (26.5)</td>
<td>4.2 (27.6)**</td>
<td>11.9 (28.0)</td>
<td>23.4 (24.8)</td>
<td>6.9 (26.6)**</td>
<td>12.6 (27.0)</td>
</tr>
<tr>
<td>p-value [1]</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P-value significant or comparison of corresponding pegloticase group vs. placebo.
**P-value significant or comparison of within group P vs. NR.

### Conclusions: Successful pegloticase therapy in patients with chronic gout refractory to conventional urate-lowering therapy (defined as UA < 6 mg/dL 80% of the time in months 3 and 6 during replicate Phase 3 trials), is associated with improvement in tender joint and swollen joint counts and Patient Global Assessment.

A Specific Chemokine Expression Pattern Is Associated with Synovial Inflammation and Symptoms in Patients with Traumatic Knee Injury Undergoing Arthroscopic Meniscectomy. Carla R. Scanzello1, Brian McKeon2, Bryan H. Swain3, Edward DiCarlo3, Eva Umoh4, Veero Kanda5, Anjali Nair5, David M. Lee6, John C. Richardson7, Jeffrey N. Katz7, Mary K. Crow8 and Steven R. Goldring1. 1Brigham & Womens Hosp, Boston, MA, 2Brigham and Womens Hospital, Boston, MA, 3Hospital for Special Surgery, New York, NY, 4Hospital for Special Surgery, New York NY, 5Hospital for Special Surgery, New York NY, 6New England Baptist Hospital, Boston MA, 7Rush University Medical Center, Chicago, IL, 8Rush University Medical Center, Chicago IL.

Objective: In established OA, the presence of synovitis is associated with pain and progression, but a relationship between synovitis, symptoms and meniscal pathology in isolated meniscal disease has not been previously investigated. The present studies were undertaken to characterize synovial pathology in patients with traumatic knee injuries associated with meniscal tears, and to determine the relationship between synovial inflammation, meniscal and cartilage pathology, and symptoms. Furthermore, the synovial gene expression patterns were analyzed to gain insight into the gene products and molecular pathways that may contribute to development of meniscal pathology and synovial inflammation in these patients.

Methods: Patients without clinical or radiographic evidence of OA undergoing arthroscopic meniscectomy for traumatic knee injuries were recruited. Pain and function were assessed preoperatively utilizing the Lysholm score (a patient-administered questionnaire measuring knee-specific symptoms and dysfunction); meniscal and cartilage abnormalities were documented at the time of surgery. Inflammation was scored histologically on synovial biopsies and associations between inflammation and Lysholm scores determined. Microarray analysis of synovial tissue was performed and expression patterns in patients with or without inflammation compared. The microarray results were confirmed by real-time PCR.

Results: Synovial inflammation was present in 42% of the patients and was associated with worse pre-operative Lysholm scores, independent of age, gender, or pre-existing cartilage pathology. Microarray analysis and real-time PCR revealed a chemokine signature in synovial biopsies with increased inflammation scores. Increasing synovial transcript levels of the chemokine receptor pair CCL19/CCR7, identified by microarray and quantitated by real-time PCR, were significantly associated with worse Lysholm scores (Spearman r = −0.86 and −0.79 respectively, p = 0.002).

Conclusion: In patients with traumatic meniscal injury without clinical or radiographic evidence of OA undergoing arthroscopic meniscectomy, synovial inflammation was a frequent finding and was associated with increased pain and dysfunction. Synovium with inflammatory infiltrates exhibited a chemokine signature, and expression levels of CCL19 and its receptor CCR7 were strongly associated with symptoms measured by the Lysholm score. Chemokines play a role in the development of synovial inflammation in patients with meniscal pathology and represent potential therapeutic targets to reduce inflammatory symptoms and potentially modulate the long-term risk for the development of OA.

Disclosure: C. R. Scanzello: Amgen Inc., 9; B. McKeon: None; B. H. Swain: None; E. DiCarlo: None; Eva Umoh: None; V. Kanda: None; A. Nair: None; D. M. Lee: None; J. C. Richardson: Carmell Therapeutics, 1, 5, DePuy-Mirel, 1, 5, Enshea Therapeutics, 1, 5, Lifent, 1, 5, Serica, 1, 5, Stryker, 1, 5; J. N. Katz: None; M. K. Crow: None; S. R. Goldring: Boehringer Ingeheim, 2, Bone Therapeutics, 5, Merck Serono, 5, Novartis Pharmaceuticals Corporation, 5, Roche, 5.

A Systematic Review and Meta-Analysis of the Impact of Total Shoulder Arthroplasty on Health-Related Quality of Life. Michael J. Carter1, Ted R. Mikuls1, Smita Nayak2, Edward V. Fehringer1 and Kaleb D. Michaud1. 1Univ. of Nebraska Med Ctr, Omaha, NE, 2University of Pittsburgh, Pittsburgh, PA.

Background: Total shoulder arthroplasty (TSA) is becoming more common as an arthritis treatment. However, the effect of TSA on health related quality of life (HRQoL) has not been established. The goal of this systematic review and meta-analysis was to characterize the change in HRQoL as a result of TSA. A quantitative value would establish the potential benefit from the procedure, and also help to evaluate future modifications to the TSA procedure.

Methods: We identified published studies that showed preoperative and postoperative HRQoL outcomes for patients receiving TSA. Articles were included if: 1) patients received primary TSA with an uncontrolled pre- and postoperative measure, with synthetic humeral and glenoid components, and 2) preoperative and postoperative HRQoL measures with at least 6 months of follow-up were reported. Reports were examined to identify all HRQoL measures reported, and meta-analysis was used to calculate standardized mean differences (SMD, reflective of the effect size) and 95% confidence intervals (CI) for each scale.

Results: There were 20 studies (1576 total shoulders) examining TSA outcomes meeting criteria for inclusion in the meta-analysis. Nearly all shoulders had treatment indications of primary osteoarthritis (n = 1499) and rheumatoid arthritis (n = 60). The most commonly examined HRQoL outcome measures included the Short Form-36 (SF-36), the visual analog scale for pain (VAS), and three shoulder specific measures: Constant score, American Shoulder and Elbow Surgeons score (ASES), and Simple Shoulder Test (SST). Effects of TSA on study outcomes are summarized in the Table, with the average follow-up at 45.2 months:

<table>
<thead>
<tr>
<th>HRQoL Outcome (number of studies reporting)</th>
<th>Standardized Mean Difference (95% CI)</th>
<th>Mean Difference in Outcome Measure (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 physical component score (n = 4)</td>
<td>0.69 (0.52 to 0.86)</td>
<td>7.02 (1.78)</td>
</tr>
<tr>
<td>SF-36 mental component score (n = 4)</td>
<td>−0.04 (−0.20 to 0.13)</td>
<td>−0.10 (0.56)</td>
</tr>
<tr>
<td>Constant score (n = 11)</td>
<td>2.67 (2.55 to 2.79)</td>
<td>38.1 (19.9)</td>
</tr>
<tr>
<td>ASES (n = 5)</td>
<td>2.61 (2.43 to 2.80)</td>
<td>53.6 (25.3)</td>
</tr>
<tr>
<td>SST (n = 3)</td>
<td>2.20 (1.96 to 2.44)</td>
<td>6.51 (2.60)</td>
</tr>
<tr>
<td>Pain VAS (n = 5)</td>
<td>−2.63 (−2.86 to −2.40)</td>
<td>−5.79 (2.58)</td>
</tr>
</tbody>
</table>

Conclusions: Total shoulder arthroplasty is efficacious, offering significant improvement in both function and pain. Shoulder-specific measures demonstrate far greater changes postoperatively than does the global SF-36 instrument. However, the change in SF-36 physical component score is statistically significant, and an SMD of 0.69 is a moderate to large effect size. Because most patients receive TSA on an elective basis, establishing the effect of TSA on HRQoL measures via systematic review and meta-analysis has important implications for both patients and payers.

Disclosure: M. J. Carter: None; T. R. Mikuls: None; S. Nayak: None; E. V. Fehringer: Tournaire, 7; K. D. Michaud: None.

Cane Use in Hip Osteoarthritis. Karen L. Perrell-Gerson1, Constance Heiney4, Nancy D. Harada4, Jennifer M. Yentes2, Sulabha Masih3 and Meika A. Fang3. 1Georgia Gwinnett College, Lawrenceville, GA, 2University of Nebraska at Omaha, 3VA Greater Los Angeles Healthcare System, Los Angeles, CA, 4VA Greater Los Angeles Healthcare System, Los Angeles, CA.

Purpose: Symptomatic hip osteoarthritis (OA) affects ~5% of the population over the age of 60 years, is often highly disabling and progressive, and accounts for most total hip replacements in Western countries. Although canes are often prescribed as part of the therapy for hip OA, little information is available regarding the impact of canes on pain, function, and gait characteristics. The aim of this pilot study was to evaluate the effects of walking aids on hip OA by testing the hypothesis that the use of a single-point cane would alter gait characteristics, decrease pain and improve function in hip OA patients.

Methods: Fourteen male participants with symptomatic hip OA (mean Kellgren-Lawrence grade 2.6) were given a single point cane to use contra-lateral to the painful limb for four weeks. All participants underwent gait assessment with and without a cane at baseline and after four weeks of cane use via a three-dimensional motion capture system (Motion Analysis Corp., Santa Rosa, CA) and an in-shoe dynamic pressure distribution system (Novel Electronics, St. Paul, MN). OA-related pain, stiffness, and function were assessed with the Western Ontario and McMaster Universities Osteoarthritis Index. Participants also completed a questionnaire regarding frequency of cane use, falls, and their opinions regarding cane use.

Results: Fourteen male participants (mean age 67.5 ± 5.8 years) completed the study. At the baseline visit, mean cadence was 99 steps/min when subjects ambulated without a walking aid and the cadence decreased to 85 steps/min when they walked with a cane contralateral to the painful limb.
Among those patients who fully recovered from their sciatica, the number of SHC was reduced to the level of the general population. Among those with persisting or worsening sciatica, the number of complaints increased to a level almost double that of the general population.

Disclosure: L. Grøvle: None; A. J. Haugen: None; C. Ihlebaek: None; A. Keller: None; B. Natvig: None; J. I. Brox: None; M. Grotle: None.

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Early Progressive Rehabilitation Following Total Knee Arthroplasty Improves Outcomes. Michael J. Bade1, Tami Stuessel2 and Jennifer E. Stevens-Lapsley1. 1University of Colorado Denver, Aurora, CO, 2University of Colorado Denver

Background: Although total knee arthroplasty (TKA) reliably reduces pain, research indicates that current rehabilitation methods do not adequately rehabilitate patients to the level of their healthy peers. The purpose of this study was to assess the initial efficacy of a progressive rehabilitation program (PROG) compared to a standard rehabilitation program (historical controls).

Patients: Eight patients (PROG group) undergoing a unilateral, primary TKA for end-stage osteoarthritis participated (65.3 ± 11.5 years; 5 women, 3 men). Patients were compared to a historical cohort of 37 patients (64.9 ± 8.6 years; 19 women, 18 men). Patients from both groups were excluded if they had uncontrolled hypertension, uncontrolled diabetes, body mass index >35 kg/m2, contralateral knee pain, other significant lower extremity orthopaedic problems, or neurological impairments.

Rehabilitation: The historical cohort completed a previously published standard rehabilitation program. The PROG group completed a rehabilitation program that differed in several key ways: a longer duration of treatment (12 weeks vs. 10 weeks); a higher frequency of treatment (28 vs. 18 sessions); the use of single-leg, machine-based resistive exercise; and an emphasis on higher level functional exercises (e.g. lunges, step-downs).

Results: There were no differences in baseline demographics between groups (age, BMI or sex). Compared to historical controls at one month after surgery, the PROG group walked 78.3 m farther on the 6MW, were 3.5s faster on the TUG, 10.1s faster on the SPT, demonstrated 57.4% greater quadriceps strength, and 17.4% better quadriceps activation. At 3 months, the PROG group walked 47.2 m farther on the 6MW, were 1.4s faster on the TUG, 1.9s faster on the SCT, demonstrated 33.9% greater quadriceps strength, and 7.8% better quadriceps activation than controls. At 6 months after surgery, the PROG group walked 67.0 m farther on the 6MW, were 1.1s faster on the TUG, 1.2s faster on the SCT, demonstrated 35.5% greater quadriceps strength, and 9.3% better quadriceps activation than controls.

Although there were baseline differences on AROM, at 6 months the PROG group demonstrated better knee extension (-1.9° vs. 1.2°) and better flexion (120° vs. 113°).

Conclusions: A progressive program of rehabilitation which includes higher frequency, longer duration, and higher level of exercise leads to improved outcomes compared to a standard rehabilitation program. This higher intensity rehabilitation did not impair ROM and did not result in any increased incidence of injury.

Funding: 2009 ACR REF/Abbott Health Professional Graduate Student Research Preceptorship, NIH K23AG029978

Disclosure: M. J. Bade: None; T. Stuessel: None; J. E. Stevens-Lapsley: None.
their facet joints on radiographs. Severity of back pain was assessed at baseline and after one month. Patients were asked about any improvement in back pain, activities of daily living (ADLs) and walking ability they expected as a result of the procedure. These responses were measured using 10mm VAS and correlated with the actual outcomes one month after injection. The Roland-Morris disability (RDQ) [2] and the Oswestry [3] questionnaires were also administered at baseline and one month after the intervention.

**Results:** 40 patients underwent facet joint injection (11 males, 29 females). There was significant improvement in pain and disability according to the RDQ. The mean score at baseline was 13.1 (CI 12.33–17.76) while after one month it was 10.4 (CI 9.63–15.5), p=0.008. No significant improvement was found using the Oswestry questionnaire (p=0.9). There was a strong correlation between high expectations of improvement at baseline and actual improvement at one month in ADLs (r=0.7; p=0.001), improvement in back pain (r=0.37; p=0.026), but not for walking ability (r=0.25; p=0.132). Gender, BMI, age and severity of back pain did not influence outcomes.

The lack of correlation between severity of back pain at baseline and the actual improvement in back pain at one month suggests that the degree of improvement depended more on the individual’s expectation of benefit rather than the actual back pain severity.

More than 70% felt the procedure helped and 60% of them were willing to undergo the procedure again. Prior to the procedure over 60% expected complications although none occurred, confirming that the procedure is safe.

**Conclusions:** Evaluating treatment outcome for low back pain has always generated considerable interest. This study shows that facet joint injections reduce disability as measured by the RDQ with a clinically significant change of nearly three points in the scale. This study further suggests that the two disability measures studied should not be used uncritically as their complexity varies and the domains that they cover are different.

Additionally, the patient’s expectation of improvement from the facet joint injection was a better predictor of improved outcome than the initial severity of back pain reinforcing the concept of a multifactorial aetiology for the pain. Patients with very low expectations of benefit from this procedure tended to have poorer outcomes and little improvement in quality of life. This is relevant when selecting patients for facet joint injection. Facet joint injections are a safe and useful adjunct in the treatment of low back pain.

**References:**

**Disclosure:** C. Mericca: None; S. Chetcuti Zammit: None; J. Lauri: None; A. A. Borg: None.

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**173**

**Fat Mass Is a Predictor of Disabling Foot Pain: A Cross-Sectional Study.** Stephanie Tanamas4, Anita Wluka1, Patricia Berry4, Hylton Menz2, Boyd Fat Mass Is a Predictor of Disabling Foot Pain: A Cross-Sectional Study.

**Background:** To examine the relationship between body composition and disabling foot pain as assessed by the Manchester Foot Pain and Disability Index (MFPDI). Disabling foot pain was determined from the MFPDI and defined as current pain that limited the patient’s ability to carry out daily activities.

**Methods:** 137 subjects aged 25–62 years were recruited as part of a study examining the relationship between obesity and musculoskeletal health. Disabling foot pain was determined from the MFPDI and defined as current foot pain and pain in the last month, and recording 7 or 8 disability item on the MFPDI (an MFPDI score of ≥ 1). Body composition was measured using dual x-ray absorptiometry.

**Results:** The BMI in this population was normally distributed around a mean of 32.2 kg/m². The prevalence of foot pain was 54.7%. In multivariate analysis, body fat mass, but not muscle mass, was associated with foot pain. This suggests that obesity may affect foot pain not only through increased loading but also act via a systemic mechanism through increased adiposity.

Further work is needed to clarify the mechanisms for this effect and the importance of reducing body fat rather than simple weight loss in the reduction of foot pain.

**Disclosure:** S. Tanamas: None; A. Wluka: None; P. Berry: None; H. Menz: None; B. Strauss: None; M. Davies-Tuck: None; J. Proietto: None; J. Dixon: Abbott Immunology Pharmaceuticals, 9, Allergan Inc, 5, 8, Bariatric Advantage, 5, 8, Eli Lilly and Company, 8, Merck Pharmaceuticals, 8, Scientific Intake, 5, 8, Sharp and Dohme, 5, 8, G. Jones: None; F. Cicuttini: None.

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**174**

**Is There an Association between Living Situation and Pain Severity at the Time Patients Choose Total Hip Replacement?** Yvonne C. Lee1, Hong T. Do2 and Lisa A. Mandl3,4,5. Brigham and Women’s Hospital, Boston, MA, 5Hospital for Special Surgery, New York, NY, 1Hospital for Special Surgery

**Background:** Living situation is an important measure of social support and could influence when patients choose to undergo total hip replacement (THR). We examined whether living situation is associated with pain severity, the main reason patients decide to undergo THR, and whether living situation is a potential effect modifier of the relationship between sociodemographic variables and pain.

**Methods:** This single center study evaluated a cohort of 3079 patients over 40 years of age who decided to undergo primary unilateral THR between May 2007 and September 2009. Participants with a systemic inflammatory disease were excluded. Living situation was categorized as: 1) those who lived alone (N=770) and 2) those who lived with others. Education was dichotomized as < college or some college or more. Self-reported pain after scheduling THR surgery was assessed using the WOMAC pain score. Univariate associations between clinical variables and pain were assessed using two sample t-tests. Variables associated with pain with P-value < 0.01 were considered for inclusion in the multivariable model, in which pain at time of THR was the dependent variable. The final multivariable model was obtained using a backward selection process. Stratified analyses were performed to assess the role of living situation as an effect modifier.

**Results:** Mean age was 62.5 ± 11.0 years. Fifty percent were female. Ninety-four percent were Caucasian. In univariate analyses, living situation was significantly associated with pain at the time of THR (P-value = 0.01). In multivariable analyses adjusted for age and sex, living situation was not significantly associated with pain severity at the time of THR. Race, education level, Elixhauser comorbidity index, fatigue and vitality were significantly associated with pain severity. In analyses stratified by living situation, age, sex, fatigue and vitality remained significantly associated with pain severity in both models. Non-Caucasian race was more strongly and significantly associated with greater pain at the time of THR (B = 5.3, P-value = 0.03) among patients living alone (N = 659) than among patients living with others (N = 2383) (B = 2.1, P-value = 0.18). Less education was more strongly and significantly associated with more severe pain (B = 4.6, P-value < 0.0001) among patients living with others than among patients living alone (B = 2.9, P-value = 0.16).

**Conclusions:** Although living situation is not independently associated with pain severity at the time of THR, it appears to act as an effect modifier. This raises the possibility that living situation could influence how much pain patients are willing to tolerate before choosing THR. While statistical significance is dependent on sample size, these differential relationships should be explored further.

**Disclosure:** Y. C. Lee: Merck Pharmaceuticals, 1, Novartis Pharmaceuticals Corporation, 1; H. T. Do: None; L. A. Mandl: None.

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**175**

**OMERACT Responder Analysis: Analysis of Patients Treated with Duloxetine for Chronic Low Back Pain.** Vladimir Skljarevski1, Matthew J. Buir2, Melissa J. Ossanna3, Eli Frakes2, Shuyu Zhang1 and Karla Alaka1,3. Eli Lilly and Company, 3Roudebush VA Medical Center

**Background:** There are no standardized outcome measures to assess treatment effect in chronic low back pain (CLBP) clinical trials. The OMERACT (Outcome Measures in Rheumatology) group proposed a preliminary approach to assessing treatment responders in CLBP trials (Simon et al, 2007). This current analysis utilizes the OMERACT approach to measure response in trials of duloxetine for the treatment of CLBP.

**Methods:** We analyzed three randomized, double-blind, placebo-controlled clinical trials of duloxetine in the treatment of adult patients with CLBP. Additionally, the patient’s expectation of improvement from the facet joint injection was a better predictor of improved outcome than the initial severity of back pain reinforcing the concept of a multifactorial aetiology for the pain. Patients with very low expectations of benefit from this procedure tended to have poorer outcomes and little improvement in quality of life. This is relevant when selecting patients for facet joint injection. Facet joint injections are a safe and useful adjunct in the treatment of low back pain.

**References:**

**Disclosure:** C. Mericca: None; S. Chetcuti Zammit: None; J. Lauri: None; A. A. Borg: None.
CLBP. Duloxetine treatment dose was 60 mg daily, 120 mg daily or flexible doses of 60–120 mg daily over 12 or 13 weeks. OMERACT treatment response was a composite outcome defined as a ≥30% reduction in Brief Pain Inventory average pain, a Patient Global Impression score PGI-I ≤2 (“much improved”) at endpoint and Roland Morris Disability Questionnaire (RMDQ) total score reduction from baseline ≥2.

Results: In Study 1, 35.4% of patients taking duloxetine 60–120 mg (N = 90) met the defined response criteria versus 18.1% of patients assigned to placebo (N = 105; p = 0.007). In Study 2, response criteria was met by 36.1% of patients taking 60 mg duloxetine (N = 83) and 34.1% of patients taking 120 mg duloxetine (N = 82), versus 27.2% of patients taking placebo (N = 92; p = 0.254 and p = 0.328, respectively). In Study 3, 37.9% of patients taking duloxetine 60 mg (N = 177) responded versus 26.8% of those taking placebo (N = 179; p = 0.031).

Conclusions: Our analysis demonstrates that duloxetine was more efficacious than placebo in 2 out of 3 separate trials of patients with chronic low back pain, as assessed by the OMERACT composite outcome, including pain severity, patient perception of improvement and functional limitations. These findings suggest that duloxetine may be helpful in the clinical armamentarium for the treatment of chronic low back pain.


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The Clinical Benefit of Joint Distraction in Treatment of Advanced Ankle OA May Be Partly Explained by Subchondral Bone Changes

Background: In osteoarthritis (OA), it has long been understood that cartilage degeneration is accompanied by sclerosis of subchondral bone. The subsequent stiffening of the bone decreases its capacity to absorb mechanical impact energy, which might play a role in the development and/or progression of cartilage degeneration. Joint distraction as a treatment for advanced ankle OA has been shown to provide pain relief and improve clinical function, with some evidence accruing that cartilage repair is involved. However, the underlying mechanism(s) remain unclear. This study evaluated whether long-term changes in subchondral bone density are associated with extended joint distraction.

Methods: Twenty-six patients with advanced post-traumatic ankle OA were treated with joint distraction for three months using an Ilizarov frame. Follow-up was two years, and clinical outcome was assessed using the ankle OA scale (AOS).

Results: Dual-contrast CT scans were obtained at baseline (before treatment), and at one- and two-year follow-ups after treatment, to analyse joint space width and bone density. The tibia and talus bones were manually segmented at each time point, and the bone segmentations from the two follow-up CT scans were registered to the baseline scans for each patient. The resulting spatial transformations were then used to bring all CT datasets for a given patient into a common spatial reference frame, using purpose-written MATLAB code. Changes in bone density (Hounsfield Units (HU), relative to baseline) were calculated at a number of discrete locations beneath the tibial and talar weight-bearing regions. The measurement grid covered a subchondral patch of nominally 650 mm2, with 4000 point measurements per surface (~0.17mm2/point). Bone density calculations were performed at 1 mm intervals beneath the bone surface, along the surface normals and extending subchondrally up to 8 mm (total of roughly 30,000 sampled point locations for each bone).

Results: Joint distraction resulted in a statistically significant long-term decrease in pain (mean value decreased from 60 to 35, on a scale of 100; p < 0.01) and function (mean decreased from 67 to 36; p < 0.01) at two years post-treatment. These clinical changes were accompanied by changes in bone density. The initial subchondral bone density was 569±14 HU for the tibia, and 490±19 HU for the talus. The average decrease in density was 133±17 HU (p < 0.01) for the tibia and 95±17 HU (p < 0.01) for the talus, one year after treatment. These density changes persisted two years after treatment (124±16 HU; p < 0.01, and 88±18 HU; p < 0.01, for tibia and talus, respectively), and they were not significantly different from the bone density one year after treatment (p = 0.11).

Conclusions: Treatment of advanced post-traumatic ankle OA with three months of joint distraction produced decreases in subchondral bone density that persisted for at least two years of follow-up. This could lead to a more physiologically normal distribution of mechanical stresses by the less dense bone, encouraging cartilage repair activity. As such, these prolonged bone changes may in part explain the clinical benefits of joint distraction.

Disclosures: F. Intema: None; T. P. Thomas: None; D. D. Anderson: None; J. Elkins: None; S. C. Mastbergen: None; F. J. G. Lafeber: None; T. D. Brown: None; A. Amendola: None; C. L. Saltzman: None.

177

The Safety and Patient Acceptability of Suprascapular Nerve Block

Background: Suprascapular nerve block is an effective therapy for shoulder pain from arthritis. To date however, the safety of the procedure has not been fully validated. This is because the numbers of patients in the trials to establish the efficacy of the treatment are far smaller than those required to establish its safety. Since 2003 the rheumatologists at the Repatriation General Hospital Fliinders Medical Centre and the Queen Elizabeth Hospital have been regularly performing this procedure for the relief of shoulder pain. The safety and patient satisfaction of their experience with this procedure has now been assessed.

Aim: To audit the safety and patient satisfaction of patients receiving at least one suprascapular nerve block performed by rheumatologists in South Australia between 2003 and 2009.

Methods: All nerve blocks performed between 2003–2009 were included in the study. The interventions were sourced through an electronic search of the medical records. In all, 1005 individual procedures were reviewed. Case note reviews of all the procedures were performed and each patient contacted. Case notes were audited for patient demographics, and recorded complications. Patients were surveyed for complications and also satisfaction using the Patient Satisfaction Questionnaire in Musculoskeletal Care. Supplementary questions were added to ensure specifically about satisfaction for the nerve block procedure.

Results: 1005 nerve block were performed on 293 patients (mean age 78, 75% with one or more co morbidities). 6 minor complications (presyncope, transient arm weakness and facial flushing) were reported or recorded. There were no major complications, giving a maximum significant complication rate of 0.3%. The overall response rate to the satisfaction survey was 55%, 87% of respondents were satisfied with the results of the nerve block.

Conclusions: Suprascapular nerve block is a safe procedure which is well tolerated by patients, even those with multiple co morbidities. Patients rate the procedure highly in terms of the ease of procedure and the pain relief that it confers.

Disclosures: E. M. Shanahan: None; K. R. Shanahan: None; C. Hill: None; M. Smith: None; M. J. Ahern: None.

178

Using the Patient Generated Index (PGI) To Measure Personalized Quality of Life (QoL) in Patients Undergoing Total Knee Arthroplasty (TKA)

Background: Personalized respondent-generated measures such as the Patient-Generated Index (PGI) can be used as an adjunct to other measures to assess individual quality of life, to improve patients’ outcomes through interventions aimed at improving patients’ values for health, and to identify changes in individual responses. The objective of this study was to assess how patients redefine their components of quality of life after a total knee arthroplasty (TKA) during the first six months of recovery.

Methods: We interviewed 122 patients with knee osteoarthritis (OA) at baseline, 12 and 24 weeks post TKA. PGI, a semi-quantitative instrument that...
allows patients to select the areas of their lives that are most affected by their disease, and to rate them using ranking and ordinal scores. The PGI is made up of three stages; each stage is linked to the other stages in sequence: i) the first stage focuses on those areas of life affected by the patients’ health; ii) the second stage rates how badly patients are limited by their condition; and iii) the third stage reduce ambiguity in the weighting of life areas by rating the relative importance of potential improvements in the area.

Results: 66% of the patients were female; mean age was 65 (8.9) yrs. 63% were married, 70% were White and 25% African American. At baseline, patients were able to select the areas of their lives that were most affected by their knee OA. Patients presented with different combinations problem areas. To reduce the amount of possible combinations, we used the same areas reported at baseline for the 12 and 24 weeks assessments. Five major areas were identified as the most salient: (i) family—this included relationships with family; (ii) physical function—e.g. walking, kneeling, activities of daily living; (iii) health—sleep, fatigue, personal care; (iv) professional life—work and school; and (v) spirituality—church, religious activities. There was a statistically significant difference between observed PGI total scores pre and post TKA: 2.5±1.2 at baseline, 4.2±1.4 at 12 weeks (p<0.001), and 4.3±1.4 at 24-weeks (p=0.001). Mean score for each area are shown in table 1. Substantial variation was observed in the areas that patients described as affected. Additionally, we observed that the perception of the area that is most affected by the knee OA changed over the time in each patient.

**Table 1.** Weighted mean PGI scores specific to each domain – 6 months.

<table>
<thead>
<tr>
<th>Area</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>24 weeks (fresh)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>29%</td>
<td>2.8</td>
<td>31%</td>
<td>4.5</td>
</tr>
<tr>
<td>Physical function</td>
<td>36%</td>
<td>2.5</td>
<td>36%</td>
<td>4.2</td>
</tr>
<tr>
<td>Gen health</td>
<td>12%</td>
<td>2.5</td>
<td>8%</td>
<td>4.2</td>
</tr>
<tr>
<td>Professional life</td>
<td>11%</td>
<td>2.2</td>
<td>7%</td>
<td>4.4</td>
</tr>
<tr>
<td>Spirituality</td>
<td>7%</td>
<td>2.5</td>
<td>7%</td>
<td>4.7</td>
</tr>
<tr>
<td>Other areas</td>
<td>5%</td>
<td>2.4</td>
<td>11%</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Conclusion: Physical function and interference with family life were the most frequently identified areas by patients as detrimental to their QoL. The PGI was responsive to changes in patient’s chosen domains for QoL.

Disclosure: M. A. Lopez-Olivo: None; M. A. Kallen: None; C. H. Pak: None; S. J. Siff: None; G. C. Landon: None; D. Edelstein: None; K. C. Robinson: None; M. E. Suarez-Almazor: AHRQ, 2, NIH, 2.

ACR Poster Session A
Osteoarthritis - Clinical Aspects: Biomechanics, Function, and Imaging I

Monday, November 8, 2010, 9:00 AM–6:00 PM

179 Adiponectin but Not Leptin and Resistin, Is Associated with the Progression of Hand Osteoarthritis. Erlangaa Yusuf1, Andreeaa Ioan-Facisnay1, Jessica Bijsterbosch2, Jommeke Kwekkeloom2, P. Eline Slagboom2, Tom W. J. Huizinga1 and Margreet Kloppenburg2. 1LUMC, Leiden, The Netherlands, 2LUMC, The Netherlands

Purpose: The link between obesity and osteoarthritis (OA) may be explained by the increased joint stress accompanying obesity. However, it does not explain why being obese is also associated with OA in non-weight-bearing joints, such as the hands. It is suggested that systemic products of fat with systemic metabolic activity (adipokines) may influence the onset and/or progression of osteoarthritis. We investigated here the association between three most common adipokines: leptin, adiponectin and resistin and the progression of hand OA.

Methods: We selected patients with radiographic hand OA from a cohort consisted of Caucasian sibs with symptomatic OA at multiple sites. We defined hand OA as Kellgren and Lawrence score ≥ 2 in at least two from 20 hand joints (four proximal interphalangeal joints (PIP’s), four distal interphalangeal joints (DIP’s), one interphalangeal (IP-1) and one carpometacarpal (CMC-1) on each hand). Using the Osteoarthritis Research Society International atlas, the baseline and 6-years follow-up radiograph were assessed for the joint space narrowing (JSN, grade 0 to 3: 0 normal, 3: severe narrowing) of 20 joints (four DIP’s, four PIP’s, one IP-1 and one CMC-1) per patient. JSN reflects articular cartilage damage. The radiographs were assessed by two readers in consensus and the intra-class correlation coefficient for intra-reader reproducibility based on 25 randomly selected pairs of radiographs was high (0.87). Progression was defined as a change in JSN above the smallest detectable change (SDC) of 2, reflecting change above measurement error. Baseline serum adiponectin concentration was measured by Bio-Plex Pro Assay (Bio-Rad, USA). With logistic regression analysis odds ratios of hand OA progression were computed and transformed to risk ratio (RRs). Adjustments for confounders as age, sex, body mass index (BMI) and family effect were made. We categorized all adipokines in tertiles.

Results: Complete follow-up data were available from 164 patients out of 248 included patients, (66%, mean age [SD]: 60 [7] years, 81% female, mean BMI [SD]: 27.5 [5] kg/m²). Fifty-five patients showed hand OA progression. BMI was positively correlated with leptin (Pearson’s correlation coefficient, r=0.3) and resistin (r=0.2) and negatively correlated with adiponectin (r=-0.2). Leptin, adiponectin and resistin did not significantly correlate to each other. BMI was not associated with radiographic hand OA progression (β-regression coefficient -0.04 (95% confidence interval -0.08 to 0.05). The association between adipokines and progression of hand OA is shown in the Table.

<table>
<thead>
<tr>
<th>Adipokine</th>
<th>Risk Ratio (95% Confidence Interval) after adjustment for age, sex, BMI and family effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin (ng/mL)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>&lt;4.4</td>
<td>1.4 (0.8 to 2.3)</td>
</tr>
<tr>
<td>4.41 to 8.2</td>
<td>0.7 (0.3 to 1.6)</td>
</tr>
<tr>
<td>&gt;8.2</td>
<td>1.1 (0.5 to 2.3)</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>&lt;16.6</td>
<td>1.6 (1.0 to 2.6)</td>
</tr>
<tr>
<td>16.6 to 28.4</td>
<td>0.3 (0.1 to 0.7)</td>
</tr>
<tr>
<td>&gt;28.4</td>
<td>0.2 (0.1 to 0.5)</td>
</tr>
<tr>
<td>Resistin (ng/mL)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>&lt;0.8</td>
<td>0.8 (0.4 to 1.7)</td>
</tr>
<tr>
<td>0.8 to 1.4</td>
<td>1.0 (0.4 to 2.1)</td>
</tr>
<tr>
<td>&gt;1.4</td>
<td>0.9 (0.4 to 1.8)</td>
</tr>
</tbody>
</table>

Conclusion: We show for the first time a substantial inverse association between serum adiponectin levels and radiographic worsening of hand OA. Further studies on the use of adiponectin as biological markers for OA progression and studies on the biological role of adiponectin in OA are needed.

Disclosure: E. Yusuf: None; A. Ioan-Facisnay: None; J. Bijsterbosch: None; J. Kwekkeloom: None; P. E. Slagboom: None; T. W. J. Huizinga: None; M. Kloppenburg: None.

180 Association of Knee, Ankle, and Midfoot Osteoarthritis and Physical Performance. Gary McDaniel1, Jordan B. Remer1, Richard Sloane1 and Virginia B. Kraus1. 1Duke University Medical Center, Durham, NC, 2University of North Carolina School of Medicine

Purpose: The direct measurement of the ability to perform physical tasks yields information about factors contributing to poor function and insights into strategies for preventing disability. The Short Physical Performance Battery (SPPB) measures walking speed, balance, and the ability to rise from a chair. Previous studies evaluating the contribution of knee to physical function have relied solely on the Kellgren-Lawrence (KL) grading system, whereas studies of the ankle’s contribution to physical function have failed to assess the association of radiographic ankle or midfoot OA. Our goal was to evaluate the relationship of SPPB with specific radiographic features of osteoarthritis (OA), joint space narrowing (JSN) and osteophyte (OST), of the knee, ankle, and midfoot.

Methods: The SPPB battery was performed by 138 (101 females, 37 males, mean age 66 (SD 11.6) years and BMI 31.3 (SD 6.9)) participants of a longitudinal observational study of knee OA progression (POPC study). Radiographic features of OA severity, joint space narrowing (JSN, a surrogate for cartilage loss) and osteophyte formation (OST) were assessed for the knee, ankle, and midfoot. The association of SPPB with radiographic OA was evaluated using non-parametric Spearman correlation analysis, adjusted for age, gender, BMI, and number of comorbidities.

Results: Knee, ankle tibiotaral joint (TTJ), ankle subtalar joint (STA), and midfoot talonavicular joint (TNJ) radiographic features of OA were negatively associated with specific SPPB tests: walking speed was associated with knee JSN (Spearman rho=-0.20, p=0.02), balance with ankle (subtalar joint)
JSN (-0.22, 0.01), and chairs stands with midfoot (talonavicular joint) JSN (-0.18, 0.04).

<table>
<thead>
<tr>
<th>OA Site</th>
<th>Joint Site</th>
<th>Gait Velocity (m/sec)</th>
<th>Spearman Correlation Coefficients: r unadjusted</th>
<th>SPPB Standing Balance (higher better)</th>
<th>SPPB Chair Stand (higher better)</th>
<th>SPPB Total (higher better)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>OA Feature</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JSN</td>
<td>-0.19 (–0.20*)</td>
<td>0.04 (–0.03)</td>
<td>0.07 (–0.05)</td>
<td>0.09 (–0.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OST</td>
<td>-0.16 (–0.16)</td>
<td>0.01 (–0.01)</td>
<td>0.02 (–0.03)</td>
<td>0.001 (–0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KL</td>
<td>-0.12 (–0.12)</td>
<td>0.02 (–0.01)</td>
<td>0.07 (–0.06)</td>
<td>0.07 (–0.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint</td>
<td>Ankle TTJ</td>
<td>JSN 0.06 (0.01)</td>
<td>-0.15 (–0.06)</td>
<td>-0.19 (–0.12)</td>
<td>0.19 (–0.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SPPB Standing Balance (higher better)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SPPB Chair Stand (higher better)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SPPB Total (higher better)</td>
<td></td>
<td></td>
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</tbody>
</table>

OA = osteoarthritis; p values: * <0.05, ** <0.01, *** < 0.001

These relationships remained significant upon further control for knee and ankle pain.

**Conclusions:** To our knowledge this is the first study describing a relationship between individual SPPB tests and specific radiographic features of knee, ankle and midfoot OA (JSN and OST). We discovered that ankle OA negatively impacts balance; knee OA slows you down; and midfoot OA negatively impacts chair stands. Structural joint damage due to OA (JSN in contrast to OST) negatively impacted these specific domains of physical performance. These results indicate that radiographic evidence of OA in specific joints may inform strategies targeting specific functional outcomes for early prevention to enable disability in an older population.

**Disclosure:** G. McDaniels: None; J. B. Renner: None; R. Slaone: None; V. B. Kraus: None.

### 181

**Associations between Composite Measures of Multi-Joint Osteoarthritis, Gait Speed, and Health Assessment Questionnaire Scores:**

**Introduction:**

The results of this study suggest that composite factors representing multi-joint OA involvement are associated with reduced gait speed and higher HAQ scores, although the estimates were attenuated by covariates, particularly age and BMI. Such composite factors can represent multiple joints in a single variable, reducing dimensionality and allowing more precise estimation of the effects of multi-joint OA involvement in models.

**Disclosure:**

A. E. Nelson: None; R. F. DeVellis: None; J. B. Renner: None; J. Purser: None; T. A. Schwartz: None; P. G. Conaghan: None; V. B. Kraus: None; J. M. Jordan: None.

### 182

**Associations between Radiographic Hand Osteoarthritis and Femoral Cartilage Thickness and Thinning in Subjects with Prevalent or at High Risk of Knee Osteoarthritis—Data from OAI.**

**Introduction:**

Hand osteoarthritis (HOA) may represent generalized OA and it is a risk factor for incident and progressive knee OA, but the relationship between HOA and MRI-based knee cartilage thickness has not been previously studied.

**Aim:** To evaluate whether radiographic HOA features are associated with knee cartilage thickness (cross-sectionally) and/or 1-year cartilage thinning.

**Methods:**

We studied 765 knees from 765 OAI participants (455 women, mean (SD) age 62.5 (9.4) years) with prevalent or at high risk of knee OA. The dominant (n = 467) or both hands (n = 298) were imaged at baseline. One investigator scored the x-rays for presence of osteophytes (OP) and joint space narrowing (JSN) (grade 0–3) in the DI, PIP, MCP and CMC-1 joints. If both hands were imaged, the hand with the highest total score was used for analyses. Total scores for OP (range 0–45) and JSN (range 0–45) were calculated. Femoral cartilage thickness (THCAB) was measured quantitatively from coronal FLASH images (O.E.1, 1.E.1) by Chondrometrics GmbH. In the cross-sectional analyses (linear regression), THCAB in the medial femoral compartment (MFTC) was the primary outcome. In the

**Disclosure:**

A. E. Nelson: None; R. F. DeVellis: None; J. B. Renner: None; J. Purser: None; T. A. Schwartz: None; P. G. Conaghan: None; V. B. Kraus: None; J. M. Jordan: None.
longitudinal analyses (logistic regression), the ordered values (OV) of subregional cartilage thickness changes were used to define the outcome. OV1 represented the knee subregion with greatest cartilage thinning. The cut-off between progressors (cartilage thinning) and non-progressors (no/less cartilage thinning) was set to the median OV1 value. In the primary models, we evaluated the associations between radiographic HOA feature scores and ThCtAB with adjustment for age, sex and BMI. In the secondary models, separate analyses were done with knees grouped into two strata of knee OA at baseline (Kellgren-Lawrence grade (KLG) 0–2 and KLG 3–4).

Results: Most patients had mild HOA with median (quartiles) scores of 3 (1–6) for OP and 8 (5–12) for JSN. Hand JSN and OP scores were significantly associated with reduced ThCtAB in MFTC at baseline after adjustment for covariates (table). The associations were greater in KLG 3–4 than KLG 0–2. The risk of 1-year cartilage thinning was inversely related to higher hand JSN score in the total sample, while not significant for the hand OP score or in the stratified analyses (table).

Table. Associations between hand features and ThCtAB in MFTC (cross-sectionally) and 1-year cartilage thinning in OV1 (longitudinally) (beta (p value)).

<table>
<thead>
<tr>
<th>Feature</th>
<th>KLG 0–2 (n = 364)</th>
<th>KLG 3–4 (n = 401)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectionally (MFTC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand OP score</td>
<td>-0.01 (0.05)</td>
<td>-0.02 (0.01)</td>
</tr>
<tr>
<td>Hand JSN score</td>
<td>-0.02 (&lt;0.001)</td>
<td>-0.03 (0.001)</td>
</tr>
<tr>
<td>Longitudinally (OV1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand OP score</td>
<td>0.01 (0.74)</td>
<td>0.02 (0.45)</td>
</tr>
<tr>
<td>Hand JSN score</td>
<td>-0.03 (0.05)</td>
<td>-0.03 (0.14)</td>
</tr>
</tbody>
</table>

Conclusion: Radiographic HOA features were significantly associated with reduced knee cartilage thickness cross-sectionally, assessed by quantitative MRI. This may support an endogenous and generalized susceptibility to OA.

Disclosure: I. K. Haugen: None; S. Cotoftan: Chondrometrics GmbH; 3; M. Englund: None; T. K. Kvien: None; D. Dreher: Merck Serono SA; 3; M. C. Nevitt: None; N. E. Lane: None; F. Eckstein: Chondrometrics GmbH; 4.

183
Change in Weight over 10 Years Is Associated with Bone Marrow Lesions in a Population-Based Cohort Study of Adult Women.

Sharon Brennan1, Flavia Cicutti1, Julie Pasco1, Margaret Henry2, Yuanyuan Wang1, Mark Kotowicz2, Geoffrey Nicholson2 and Anita Whiuka1. 1Monash University, 2University of Melbourne

Background: Although obesity is a modifiable risk factor for knee osteoarthritis (OA), the effect of change in weight on knee structure in young and healthy adults has not been examined. The aim of this study was to examine the relationship between body mass index (BMI), and change in BMI over the preceding 10-year period, and knee structure [cartilage defects, cartilage volume and bone marrow lesions (BMLs)] in a population-based sample of young to middle-aged females.

Methods: One hundred and forty two healthy, asymptomatic females (range 30–49 years) in the Barwon region of Victoria, Australia, underwent magnetic resonance imaging (MRI) during 2006-08. BMI measured 10 years prior (1994-97) and current BMI and change in BMI (accounting for baseline BMI) over this period, was assessed for an association with cartilage defects and volume, and BMLs.

Summary of the Results: After adjusting for age and tibial plateau area, there was a trend for a 1 unit increase in current BMI to be associated with cartilage defects (OR 1.06 [95%CI 1.00, 1.13] p=0.05), and for a 1 unit increase in BMI over 10 years to be associated with reduced cartilage volume (~17.8ml [95%CI 39.4, 3.9] p=0.1). BMLs were associated with baseline BMI (OR 1.14 [95%CI 1.03, 1.26] p=0.0009), current BMI (OR 1.13 [95%CI 1.04, 1.23] p=0.005), and per 1 unit increase in BMI (OR 1.14 [95%CI 1.03, 1.26] p=0.01). Results remained similar after adjusting with those with osteophytes.

Conclusions: This study provides longitudinal evidence for the importance of avoiding weight gain in women in during early to middle adult-hood as this is associated with adverse structural changes at the knee. Avoiding weight gain even in early adulthood may play an important role in the prevention of knee OA.

Disclosure: S. Brennan: None; F. Cicutti: None; J. Pasco: None; M. Henry: None; Y. Wang: None; M. Kotowicz: None; G. Nicholson: None; A. Whiuka: None.

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Comorbidity and Health Status in Early Osteoarthritis of Hip and Knee; CHECK Cohort.

J. Wesseling1, S. M. A. Bierma-Zeinstra1, J. Dekker2, K. J. Gorter2, J. W. J. Bijlsma1 and on Behalf of the CHECK Group. 1Erasmus University Medical Center Rotterdam, 2Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands, 3University Medical Center Amsterdam

Background: Osteoarthritis (OA) is the most common diagnosis made in elderly patients with knee or hip pain. Like OA the prevalence of many other disabling conditions increases with age and many chronic conditions can be found together with OA. The objective of the present study is to describe the relationship between comorbidity (count as well as the presence of specific comorbidities) and complaints (like pain and limitation in activity) and the physical and mental status of participants with complaints of early osteoarthritis.

Methods: In the Netherlands a prospective 10-year follow-up study was initiated by the Dutch Arthritis Association in participants with early OA related complaints of hip and/or knee: the CHECK study, to study the onset and progression of OA. Individuals were eligible if they had pain and/or stiffness of knee and/or hip, were aged 45–65 years, and had never or not longer than 6 months ago visited the general practitioner for these symptoms for the first time. The WOMAC was utilized to measure pain and limitations in activity. Physical functioning and mental functioning were measured by SF36. Comorbidity is assessed with a self-reported health module of the Agency of Statistics in the Netherlands with consists of 24 chronic diseases. Linear mixed regression analysis was used to determine the influence of the ‘comorbidity count’ on the outcome variables pain, and physical and mental functioning.

Results: In CHECK 1002 participants were included, mean age of 56 years, mean BMI of 26 kg/m2 and 79% female. Over 67% of the total study population had comorbidity: disorders of neck, shoulder, elbow, wrist or hand (23%), hypertension (20%) and back disorders (18%) were most prevalent. The results indicate that the pain score and physical functioning score on the WOMAC deteriorates with about 3 and 4 points respectively with every (extra) comorbidity. The physical and mental status of the SF36 deteriorates with respectively about 2 and 1 point with every (extra) comorbidity. Results of the final model (controlling for age, gender, Kellgren & Lawrence grade) show that severe back disorders have the most negative effect on WOMAC pain, physical functioning and one of the most negative effects on physical status of SF36. The presence of this disorder increases WOMAC pain score on average with 7 points, WOMAC function score with 8 points, and SF36 PCS score with 4 points. The mental status was negatively influenced by the presence of duodenal/gastric, thyroid disease, and migraine or regular headache.

Conclusions: In the early stage of osteoarthritis the effect of the presence of especially diseases in the locomotor system have negative effect on complaints and health status. The clinical implications are that to improve the physical health of participants with early OA of knee and/or hip not only the complaints related to OA have to be treated but also the additional diseases, especially back, neck, shoulder, elbow, wrist or hand disorders or obesity. Apart from the physical status also the mental status is affected in the early stage of OA of knee and/or hip not only the complaints and health status. The clinical implications are that to improve the physical health of participants with early OA of knee and/or hip not only the complaints related to OA have to be treated but also the additional diseases, especially back, neck, shoulder, elbow, wrist or hand disorders or obesity. Apart from the physical status also the mental status is affected in the early stage of OA of knee and/or hip not only the complaints and health status.

Disclosure: J. Wesseling: None; S. M. A. Bierma-Zeinstra: None; J. Dekker: None; K. J. Gorter: None; J. W. J. Bijlsma: None; on Behalf of the CHECK Group: None.

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Do Bony Enlargements Correlate with Radiological Findings in Hand Osteoarthritis (HOA)?

Roshan Dhawale1, Niveditha Mohan2, Michael J. Hannon3 and C. Kent Kwoh1. 1Univ of Pittsburgh, Pittsburgh, PA, 2Univ of Pittsburgh Anth Inst, Pittsburgh, PA, 3University of Pittsburgh, Pittsburgh, PA

Purpose: Symptomatic Hand Osteoarthritis (HOA) affects 20% of patients above the age of 55 years, a large proportion of whom have bony enlargements. The relationship between bony enlargements and radiological findings of HOA is unclear and has not been well-studied. We assessed the correlation between bony enlargements and radiological findings and whether all patients with bony enlargements had radiological evidence of HOA.

Methods: The study utilized data from the Osteoarthritis Initiative, a community-based cohort aged 49–75 years with symptomatic knee OA or with risk factors for developing knee OA. Dominant hand films of 200
Frailty and 3-Year Mobility Outcome in Persons with or at Higher Risk for Knee Osteoarthritis. September Cahue1, Karen W. Hayes2, Jing Song3, Dorothy D. Dunlop4, Joan S. Chmiel5, Marc C. Hochberg6, Carmelita J. Colbert1 and Leena Sharma3. 1Northwestern University, Chicago, IL, 2Northwestern University, LaGrange, IL, 3Northwestern University, Downers Grove, IL, 4Northwestern University, Chicago, IL, 5Northwestern University, 6University of Maryland, Baltimore, MD

Purpose: Frailty has been examined in the context of aging, but little is known about its role in health outcomes in persons with knee osteoarthritis (OA). Risk of knee OA increases with age, and knee OA is a leading cause of chronic disability in older individuals; however, how best to identify persons who are likely to decline and/or benefit from intervention is unknown. The Osteoarthritis Initiative (OAI) cohort represents the continuum of knee OA from the stage of high risk prior to radiographic change through advanced disease and is uniquely suited to our goals: 1) determine the prevalence of frailty in this population; and 2) evaluate whether frailty at baseline predicts subsequent 3-year mobility outcome.

Methods: OAI data from public release data set 0.2.2 were used. We adapted the frailty index of Ensrud et al (Arch Int Med 2008), including inability to rise five times from a seated position without using arms and self-reported exhaustion (CES-D) (but not the weight criterion due to varied implications of weight loss in this population and because BMI was the basis of enrollment for a subset of the OAI cohort). Mobility outcomes were: baseline-to-3-year increase in difficulty in WOMAC mobility items (walking, ascending stairs, descending stairs); poor SF12 physical component outcome (persons were grouped by quintile of baseline function, and “poor” defined as moving into a worse quintile group or remaining in the worst 2 groups at 3 years). We used logistic regression to analyze the relationship between frailty at baseline (≥ 1 item) (vs. not frail, reference) and baseline-to-3-year outcome, adjusting for age, gender, race, education, comorbidities, and K/L grade (worse of the two knees) in the overall sample and in BMI strata.

Results: In 4138 persons, mean age was 61 years, mean BMI was 28, and 58% were women. At baseline, 14% of women and 11% of men were frail. Frailty was also associated with being African-American, having a lower education level, and poorer self-assessed health. By three years, 35% had worse WOMAC mobility, and 52% had poor SF12 physical component outcome. In the overall sample (Table), frailty at baseline was associated with worse 3-year WOMAC mobility and poor SF12 physical component outcome in adjusted analyses. These results persisted in the normal weight and overweight strata but were not significant in the obese stratum (Table).

Table. Frailty and 3-Year Mobility Outcome, Odds Ratios (OR) (95% CI)

<table>
<thead>
<tr>
<th>Joint</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMC</td>
<td>1483**</td>
<td>1.73</td>
<td>1.44, 2.08</td>
<td>1.56, 2.79</td>
</tr>
<tr>
<td>DIP 2</td>
<td>1432</td>
<td>1.91</td>
<td>1.42, 2.57</td>
<td>1.71, 2.32</td>
</tr>
<tr>
<td>DIP 3</td>
<td>133</td>
<td>1.33</td>
<td>1.00, 1.76</td>
<td>1.27, 1.94</td>
</tr>
<tr>
<td>DIP 4</td>
<td>1027**</td>
<td>1.91</td>
<td>1.42, 2.57</td>
<td>1.71, 2.32</td>
</tr>
<tr>
<td>Overweight</td>
<td>(25≤BMI&lt;30)</td>
<td>1.48 (0.96, 2.28)</td>
<td>1.91 (1.42, 2.57)</td>
<td>1.71 (1.23, 2.32)</td>
</tr>
<tr>
<td>DIP 5</td>
<td>1027**</td>
<td>1.91</td>
<td>1.42, 2.57</td>
<td>1.71, 2.32</td>
</tr>
<tr>
<td>JSN (Grade 1)</td>
<td>1483**</td>
<td>1.73</td>
<td>1.44, 2.08</td>
<td>1.56, 2.79</td>
</tr>
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</table>

Conclusion: A simple frailty index, easily usable in a clinical setting, was independently associated with worse 3-year mobility in persons at high risk for or with knee OA. These results also suggest that a frailty index may not function similarly across BMI strata in this population. Further work to refine the ability to capture the frailty phenotype—decreased reserve and resistance to stressors—should occur, as a simple but potentially powerful means of ultimately aiding the prevention of adverse outcomes in persons with knee OA.

Disclosure: S. Cahue: None; K. W. Hayes: None; J. Song: None; D. D. Dunlop: None; J. S. Chmiel: None; M. C. Hochberg: None; C. J. Colbert: None; L. Sharma: None.

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Greater Burden of Disease in Erosive Hand Osteoarthritis. Mariko L. Ishimori1, Roy D. Altman1, Myles J. Cohen2, Jerome I. Rotter2 and Michael H. Weisman3. 1Cedars Sinai Medical Center, Los Angeles, CA, 2Cedars-Sinai, Cedars-Sinai Medical Center, Los Angeles, CA, 3UCLA, Agua Dulce, CA

Purpose: The goal of our study was to evaluate relationships between patients with erosive vs. non-erosive hand osteoarthritis (OA) by radiography and features such as extent of joint involvement, body mass index (BMI), and pain, stiffness, and physical disability as assessed by the Australian/Canadian (AUSCAN) Hand Osteoarthritis Index.

Methods: Consecutive patients with clinical and radiographic hand OA were evaluated by examination, BMI, radiography, and AUSCAN as part of The Genetics of Hand Osteoarthritis Study (GHOST). Radiographs were scored by radiographic atlas and analyzed for relationship to degree of joint involvement, BMI and AUSCAN subscales. Subjects were grouped as 1) erosive involvement of distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints with hand OA, 2) non erosive (nodal) involvement of DIP, PIP and IP joints with hand OA, and 3) non-erosive involvement of 1st carpo-metacarpal (CMC) joints only. Subjects with any one joint with erosive change were classified as having erosive hand OA. Two scores were generated: 1) Total Count—number of selected joints with osteophytes and 2) Total Score—Sum of osteophytes scores from selected joints (DIP, PIP, IP, CMC).

Table 1. Distribution of HOA

<table>
<thead>
<tr>
<th>Joint</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
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Conclusion: A simple frailty index, easily usable in a clinical setting, was independently associated with worse 3-year mobility in persons at high risk for or with knee OA. These results also suggest that a frailty index may not function similarly across BMI strata in this population. Further work to refine the ability to capture the frailty phenotype—decreased reserve and resistance to stressors—should occur, as a simple but potentially powerful means of ultimately aiding the prevention of adverse outcomes in persons with knee OA.

Disclosure: S. Cahue: None; K. W. Hayes: None; J. Song: None; D. D. Dunlop: None; J. S. Chmiel: None; M. C. Hochberg: None; C. J. Colbert: None; L. Sharma: None.
**Results:** A total of 279 subjects were enrolled with a mean age of 68.7 years. The majority of study subjects were women (90.7%) and Caucasian (91.0%). The breakdown of radiographic findings was as follows: 105 (37.6%) with erosive changes, 124 (44.4%) with non-erosive (nodal) involvement and 50 (17.9%) with non-erosive CMC involvement. The group of subjects with erosive hand OA had greater Total Score (p<0.0001) and Total Count (p=0.001) than subjects with non-erosive (nodal) hand OA or CMC involvement. The AUSCAN subscore of stiffness was significantly greater in erosive hand OA (p<0.0003) and nodal hand OA (p=0.027) than in subjects with CMC only involvement (Wilcoxon rank sum). Within the erosive hand OA group, increasing number of joints involved with HOA correlated with worsening Stiffness (p=0.0099) and Physical Function (p=0.0175) subscales of the AUSCAN index (Spearman’s correlation).

**Conclusion:** In a cross-sectional analysis of clinical and radiographic hand OA, subjects with erosive hand OA generally had a greater burden of joints involved that the non-erosive (nodal) group. This may be related to erosive OA potentially being a more severe manifestation and a different group than traditional non-erosive (nodal) OA, suggesting genetic differences. Within the erosive hand OA group, greater Stiffness and worse Physical Function by AUSCAN index correlated with increasing numbers of joints involved with hand OA. This occurred even when there were very few or only one joint with erosive change. The concepts of nodal versus erosive IP arthritis may represent distinct clinical and etiologic groups, and not two sides of a spectrum, reflecting the heterogeneity of hand OA which may have implications for genetic studies. Future studies need to include careful descriptions of disease phenotypes, particularly in relation to genetic investigations.

**Disclosure:** M. L. Ishimori: None; R. D. Altman: None; M. J. Cohen: None; J. I. Rotter: None; M. H. Weisman: None.

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**Image Processing and Machine Learning Methods Applied to MRI Trabecular Morphometry in Knee Osteoarthritis.** Jason Nochlin, Eric Miller, Grace H. Lo, Anna Tassinari and Timothy E. McAlindon.1 Tufts Medical Center, Boston, MA, 2Tufts Medical Center, Houston, TX, 3Tufts Medical Center Box 406, Boston, MA, 4Tufts University, Medford, MA

**Purpose:** We can image periarticular bone in vivo, a tissue involved in the pathology of knee osteoarthritis (OA). In digital images such as MRIs, texture refers to patterns in pixel intensity. Using texture filters, the original image is transformed into a new image where the value of each pixel corresponds to how well the region around that pixel “matches” the pattern encapsulated in a filter. Such techniques are used to characterize regions of an image. In a natural scene, though the image may not resolve single blades of grass, the pixel patterns formed by these structures infer information about the individual components. In this instance where individual trabeculae are not resolved in images of the periarticular bone, our hypothesis is that variations in texture correlate with relative periarticular bone mineral density (pBMD), a known correlate of structural OA severity.

**Methods:** Using a sample of 39 right knees from an ancillary study to the Osteoarthritis Initiative, we analyzed 3T MRIs (Trio, Siemens) coronal 3D FISP trabecular sequences. From each of 20 central slices, a region of interest (ROI) in the periarticular tibia was extracted by identifying the top edge of the bone and selecting a region of 24mm wide by 8mm high. 24 texture filters (8 Gabor and 16 Laws’ Masks) were applied to each ROI. All pixels in each transformed slice’s ROI formed a data array for that filter. With each Laws’ Mask, pixel values were squared to form a new data array, totaling data arrays (20 slices x 2) for each knee MRI. On each array we computed mean, standard deviation, skewness, entropy, and kurtosis. Knee DXAs were obtained using a GE Lunar scanner to calculate measures of the medial/lateral tibial pBMD. The 200 statistics from the 40 data arrays were used as regressors for predicting medial/lateral tibial pBMD. The regression problem was solved using kernel-Support Vector Regression. A wrapper approach was used to limit the number of regressors in solution to 15. All computations were done using MATLAB R2007b.

**Results:** Thirty-nine patients were studied, 53% males; age 68 (±9.3); BMI 27.8 (±4.6). The predictive model estimated the medial/lateral pBMD ratio for each patient in a cross-validation scheme, a regression coefficient of 0.870 was found between the predicted and actual values, (p-value of <.0001). Of the 15 selected regressors, several patterns were found. The most prominent textures were Laws’ Masks derived from a 1mm (5 pixel) wave or ripple pattern. The wave pattern roughly corresponds to texture with frequent, large changes in contrast (brightness highs and lows nearby each other). The ripple pattern corresponds to texture where the maxima are extremely prominent. Gabor Filters, which match sine wave patterns in the texture, with a wavelength of 8mm (4 pixels) with various orientations were also significant differentiators.

**Conclusion:** Using image processing and machine learning techniques, we developed a novel method for analyzing bone structure MRI images that correlate well to pBMD. Further development of such tools will help in better understanding of the periarticular bone pathology in those with knee OA. Future studies are needed to validate these measures against histopathology.

**Disclosure:** J. Nochlin: None; E. Miller: None; G. H. Lo: None; A. Tassinari: None; T. E. McAlindon: None.

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**Knee Confidence and Physical Function Outcome in Persons with Knee Osteoarthritis.** Carmelita J. Colbert, Jing Song, Dorothy D. Dunlop, Joan S. Chmiel, Karen W. Hayes, September Cahue, Kirsten Moisio, Alison H. Chang and Leena Sharma.1 Northwestern University, LaGrange, IL, 1Northwestern University, Downers Grove, IL, 1Northwestern University, Chicago, IL, 1Northwestern University

**Purpose:** Given the central role of the knee in all weightbearing activity, confidence in the knees may be a proximal factor influencing activity choices and self-efficacy, factors thought critical to function and disability. We evaluated whether knee confidence at baseline was associated with physical function outcome over the subsequent two years in persons with knee OA, and whether any relationship persisted after adjusting for other factors.

**Methods:** Osteoarthritis Initiative (OAI) participants have or are at risk for developing knee OA. Knee confidence was assessed using the KOOS item (How much are you troubled with lack of confidence in your knees?) and function assessments included the WOMAC function scale and chair stand test performance. We grouped participants with knee OA (K/L ≥ 2) by quintile of baseline function; poor outcome was defined as moving into a worse quintile group or remaining in the 3 worst groups at 24 months. To evaluate the relationship between baseline confidence and poor outcome, logistic regression was used, sequentially adjusting for nested groups of covariates: 1) age, gender, race; 2) previous covariates + depression, comorbidity, falls; 3) all previous + BMI; 4) all previous + physical activity, alcohol use; 5) all previous + hip, ankle, foot pain; 6) all previous + knee injury, knee surgery; and 7) all previous + knee pain severity, knee OA severity, extensor strength.

**Results:** Among 2243 OAI participants (mean age 62 years, BMI 29, 57% women) with knee OA, the percentage with poor outcome increased with worse baseline knee confidence category (Table 1).

| Table 1. Proportion of Persons with Poor Baseline-to-2-Year Function Outcome by Baseline Confidence Level |
|---------------------------------------------------------------|--------------------------|
| Knee Confidence Category | Percent with Poor Baseline-to-2-Year Function Outcome of Persons within Baseline Knee Confidence Category |
| Poor WOMAC Physical Function Outcome | Poor Chair Stand Outcome |
| Not troubled by lack of confidence (n = 923 persons) | 32.9% | 47.6% |
| Mildly troubled by lack of confidence (n = 692) | 48.8% | 50.5% |
| Moderately troubled by lack of confidence (n = 422) | 56.9% | 51.9% |
| Severely or extremely troubled by lack of confidence (n = 206) | 69.4% | 59.3% |

As shown in Table 2, compared to persons not lacking confidence, the odds of a poor WOMAC outcome and a poor chair stand outcome increased with worse knee confidence category resulting in significant trend tests. For the WOMAC outcome, this held for all intermediate nested covariate groups (not shown) and in the final fully adjusted analysis (Table 2). In contrast, the relationship between confidence and poor chair stand outcome was weaker and significance did not persist in the fully adjusted analysis (Table 2). For
Table 2. Odds Ratios and 95% Confidence Intervals (CIs) Associated with Knee Confidence for Poor Baseline-to-2-Year Function Outcome

<table>
<thead>
<tr>
<th>Knee Confidence Category</th>
<th>Poor WOMAC Physical Function Outcome</th>
<th>Poor Chair Stand Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not troubled by lack of confidence</td>
<td>OR (95% CI)</td>
<td>Adjusted* OR (95% CI)</td>
</tr>
<tr>
<td>reference</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td>Mildly troubled by lack of confidence</td>
<td>1.94 (1.59, 2.36)</td>
<td>1.67 (1.35, 2.08)</td>
</tr>
<tr>
<td>Moderately troubled by lack of confidence</td>
<td>2.60 (2.12, 3.30)</td>
<td>1.90 (1.45, 2.48)</td>
</tr>
<tr>
<td>Severely or extremely troubled by lack of confidence</td>
<td>4.62 (3.33, 6.40)</td>
<td>2.59 (1.76, 3.80)</td>
</tr>
</tbody>
</table>

*model including all covariate groups

Conclusion: In persons with knee OA, lower knee confidence at baseline was associated with poor 2-year WOMAC function outcome but not with poor chair stand outcome in adjusted analyses. The role of confidence in the trajectory of physical function decline in knee OA should be further examined; better understanding of its role may empower strategies to reduce the likelihood of poor outcome.

Disclosure: C. J. Colbert: None; J. Song: None; D. D. Dunlop: None; J. S. Chmiel: None; K. W. Hayes: None; S. Caluse: None; K. Moisio: None; A. H. Chang: None; L. Sharma: None.

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Lateral Compartment Unloading in People with Medial Knee Osteoarthritis

Background: It is well known that people with medial knee osteoarthritis (MKOA) exhibit high knee adduction moments (KAM) during walking. Investigators have speculated that a failure to generate sufficient muscle force to counter high external loads could result in the lateral femoral condyle lifting off the tibia. Lateral condylar lift-off has not been confirmed by modeling techniques that account for subject specific EMG patterns, kinematics and kinetics. The aims of this study are (1) to estimate articular loads in people with MKOA using an EMG-driven model and, (2) to examine the relationship between passive laxity, varus malalignment, functional knee instability (FKI) and loading patterns.

Methods: 16 MKOA and 12 control (C) subjects walked while kinematic, kinetic and EMG data were collected. Muscle forces and moments were calculated from an EMG-driven model previously described. Loading of the medial and lateral compartments were calculated by balancing the internal/external moments at the knee. One walking trial was used to optimize the model parameters and the average of 3 separate trials was used to predict articular loading during stance. Functional Knee Instability (FKI) was assessed from the Knee Outcome Survey. Stress radiographs were used to assess frontal laxity and long cassette radiographs were used to assess alignment. ANOVAs and Pearson’s correlation coefficients comprised the statistical analyses.

Results: MKOA subjects walked more slowly and had greater laxity, static and dynamic varus alignment, less flexion and greater KAM than controls. Loading, when normalized to BW was no different between the groups but MKOA subjects had greater absolute medial load than C and maintained a greater %total load on the medial compartment. Lateral compartment unloading during mid-late stance was observed in 50% of OA subjects which was related to greater KAM, dynamic varus alignment and FKI but not to laxity or static malalignment. MKOA subjects with lateral joint unloading had lower hamstring force and lower force in the lateral muscles.

Discussion: Loading for C subjects matched that measured from instrumented knee prostheses, supporting the veracity of the model. Speculations about greater medial loading in people with MKOA are confirmed with our data, as well as, the phenomenon of lateral condylar lift-off. It was interesting that the unloading did not occur during weight acceptance phase when the loads are greatest but rather occurred during mid-late stance when the knee experiences its greatest varus angulation. The relations between unloading to FKI rather than laxity or malalignment suggest that it is due to a failure of neuromuscular strategies and not only mechanical factors. This was confirmed by the muscle force data where we found that MKOA subjects who showed unloading, had poor quadriceps-hamstring and medial-lateral muscle force balance resulting from lower hamstring and lateral muscle forces. These data support the need for neuromuscular retraining interventions for people with MKOA that address loading and FKI rather than quadriceps strengthening alone.

Disclosure: D. Kumar: None; K. S. Rudolph: NIH, 2; K. Manal: NIH, 2.

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Lower Extremity Muscle Function, Quality of Life and Physical Function Outcomes and TheirRelation to Subsequent Knee Replacement in a 24 Month Period—Data from the Osteoarthritis Initiative (OAI).

Background: Patients with osteoarthritis (OA) of the knee have functional disability and reduced muscle performance. The impact of lower extremity muscle function and its recovery after total knee arthroplasty (TKA) is largely unknown. In a previous analysis of the OAI database we found that muscle performance is associated with health related quality of life (HRQoL) and physical function in individuals with both evidence of knee OA or at risk for developing OA. We hypothesize that these parameters change over time and that preoperative values can predict the likelihood of TKA.

Methods: Baseline and 24 months data from OAI were examined using three cohorts labeled as: 1) a “progressive” group (PRO) with evidence of knee OA at baseline, 2) an “incidence” group (INC) with risk factors for developing OA, and 3) normal controls. Parameters of interest were isometric upper leg strength, rapid chair-stands, and 20 and 400-meter walks as well as the WOMAC, KOOS, and Study Short Form (SF12) questionnaires. We compared changes between baseline and 24 months data and differences among groups using t-tests. The relation of baseline parameters to TKA within the next 24 months was examined using binary logistic and linear multivariate regression models. This analysis was done separately for persons that received a right TKA, a left TKA and for all TKAs combined.

Results: 4796 volunteers (PRO: 1390, INC: 3284, control 122) from the OAI cohort were included. 41.5% were men and 58.5% women. Muscle power assessed by the 400m walk time worsened by approx 2% whereas chair-stand pace improved by 2% in PRO and INC, 20m walk pace declined in PRO only (p<0.05 or lower). Muscle strength worsened in both groups (p<0.0001) by 6–10%: WOMAC and KOOS scores improved in PRO and INC (all p<0.0001) and varied between 1–9% SF12 scores worsened (p<0.05 or lower) but changes were small (2%). No changes were found in the control group for any of the measures. At 24 months there were 35 new right and 27 new left TKA. Baseline parameters that best correlated with future TKA were SF12, WOMAC disability score, 400m walk time and right quadriceps strength. Knee specific analysis revealed better prediction ability than if new TKA was assessed for both knees combined. Models remained significant after adjusting for age, BMI and gender. When comparing baseline muscle tests and HRQoL of individuals undergoing a TKA at 24 months to those without, persons with TKA had worse scores in all TKA at 24 months (p<0.05 or lower).

Conclusions: Our analysis demonstrated that both HRQoL and muscle performance tests were able to distinguish between individuals with knee OA and those at risk for OA. WOMAC scores, SF12, 400m walk time and quadriceps strength were able to independently predict the likelihood of subsequent TKA. Side specific knee analysis was better than combined knee (L and R) analysis. Individuals that underwent a TKA within 24 months had worse scores in all HRQoL and muscle performance parameters at baseline suggesting these measures should be included in routine clinical assessment of knee OA patients. Improving muscle function and HRQoL should be a focus of preoperative risk stratification to optimize potential outcomes for TKA patients.

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Morphological Changes in Articular Cartilage and Subchondral Bone in Tibiofemoral and Patellofemoral Joints Following Arthroscopic Partial Medial Meniscectomy. Yuanyuan Wang1, Alasdair Dempsey2, David Lloyd2, Peter Mills3, Tim Wrigley3, Kim Bennell4, Fahad Hanna5 and Flavia Cicuttini6. 1Griffith University, 2Monash University, 3The University of Western Australia, 4University of Melbourne, 5University of Western Australia, 6University of Melbourne

Background: Although meniscectomy is an important risk factor for tibiofemoral osteoarthritis (OA), there is a paucity of studies examining the
relationship between meniscectomy and patellofemoral OA. This study aimed to examine the morphological changes in articular cartilage and subchondral bone in tibiofemoral and patellofemoral joints in a meniscectomy population.

Methods: 158 patients aged 30–55 years, without evidence of knee OA when undergoing isolated arthroscopic partial medial meniscectomy (APMM), and 38 controls with similar characteristics with APMM patients but without the surgery were recruited. Magnetic resonance imaging (MRI) of the operated knee was obtained at 3 months, 2 years, or 4 years post-surgery. MRI of the randomly assigned knee of the controls was also obtained. Cartilage volume and cartilage defects, bone area or volume were assessed using validated methods in tibiofemoral and patellofemoral compartments.

Summary of Results: Compared with controls, patients undergoing APMM had an increased prevalence of cartilage defects in the medial tibiofemoral (OR = 3.17, 95% CI 1.24 – 8.11, P = 0.02) and patellofemoral (OR = 13.76, 95% CI 1.52 – 124.80, P = 0.02) compartments, and increased medial tibial plateau bone area (B = 143.8, 95% CI 57.4 – 230.2, P = 0.001). Time from APMM was positively associated with the prevalence of cartilage defects in the medial tibiofemoral (OR = 1.02, 95% CI 1.00 – 1.03, P = 0.09) and patellofemoral (OR = 1.04, 95% CI 1.01 – 1.07, P = 0.02) compartments, and medial tibial plateau area (B = 2.5, 95% CI 0.8 – 4.3, P = 0.005), but negatively associated with lateral tibial cartilage volume (B = −4.9, 95% CI −5.4 to −1.5, P = 0.005). The association of APMM and time from APMM with cartilage defects was independent of medial tibial cartilage volume.

Conclusions: Meniscectomy has adverse impacts on both tibiofemoral and patellofemoral joints within 5 years post-surgery. Strategies aimed at preventing the development of OA and reducing morbidity in meniscectomy populations should focus on both tibiofemoral and patellofemoral joints.

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MRI-Defined Risk Factors for Cartilage Loss over a 6 Months Period.

Frank W. Roemer, C. Kent Kwoh, Michael J. Hammon, Stephanie M. Green, John M. Jakicic, Robert Boudreau, Michel D. Crema and Ali Guermazi. Boston University, University of Pittsburgh

Purpose: Cartilage morphology may only be directly assessed by MRI. Cartilage loss over short observational periods is rare but not uncommon. Aim of the study was to assess several non-MRI and MRI-features as baseline requirements for cartilage loss. Bone marrow lesions (BMLs) in the same subregion, meniscal damage or meniscal extrusion in the TF compartment, synovitis and effusion were scored in addition and assessed as baseline risk factors.

All MR joint morphologic features were dichotomized into present (≥1) vs. absent (0). Logistic regression models were applied to assess the risk of cartilage loss for knees exhibiting risk factors when compared to knees without the risk factor at baseline. We performed a subregion-based analysis using general estimating equations (GEE) to account for the clustering of subregions within a knee and knees within an individual. Multivariate models were adjusted for age, gender, treatment (oral glucosamine) and BMI. In addition, BMI-based risk factors were adjusted for each other in a multi-adjusted model.

Results: 51.2% of participants were men, mean age was 52.3 ± 6.2 years, mean BMI was 29.1 ± 4.1. Baseline Kellgren/Lawrence grades (for worst knee) were: K/L 0: 37 (20.9%) knees, K/L 1: 14 (7.9%) knees, K/L 2: 26 (14.7%) knees, K/L 3: 81 (45.8%) knees, K/L 4: 19 (10.7%). Of the 353 knees, 304 knees (87.9%) and 1,153 subregions (23.8%) exhibited prevalent cartilage damage at baseline. 79 (1.6%) subregions showed incident or worsening cartilage damage at 6 months FU. Predictors for PC cartilage loss at 6 months were baseline presence of effusion and prevalent cartilage damage in the same subregion. Risk factors for TF cartilage loss were baseline ipsi-compartmental meniscal extrusion, prevalent BMLs and cartilage damage in same subregion.

Table 1. Risk factors for patello-femoral and fibro-femoral cartilage loss over 6 months of follow-up

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Reference</th>
<th>Adjusted Odds Ratio* (95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patello-femoral</td>
<td>Effusion (WORMS ≥ 1)¹</td>
<td>Effusion absence (WORMS score = 0)</td>
</tr>
<tr>
<td>Synovitis (modified WORMS ≥ 1)²</td>
<td>Synovitis absence (modified WORMS score = 0)</td>
<td>0.79 (0.28–2.07)</td>
</tr>
<tr>
<td>Prevalent cartilage damage (WORMS ≥ 2)³</td>
<td>No cartilage damage in subregion (WORMS score = 0 or 1)</td>
<td>4.32 (1.35–13.85)*</td>
</tr>
<tr>
<td>BML (WORMS ≥ 1)²</td>
<td>No BML in subregion (WORMS score = 0)</td>
<td>1.61 (0.67–3.84)</td>
</tr>
<tr>
<td>Tibio-femoral</td>
<td>Effusion¹ (WORMS ≥ 1)</td>
<td>Effusion absence (WORMS score = 0)</td>
</tr>
<tr>
<td>Synovitis¹ (modified WORMS ≥ 1)</td>
<td>Synovitis absence (modified WORMS score = 0)</td>
<td>0.68 (0.32–1.45)</td>
</tr>
<tr>
<td>Meniscal damage⁴</td>
<td>No meniscal damage</td>
<td>1.98 (0.76–5.15)</td>
</tr>
<tr>
<td>Meniscal extrusion⁴</td>
<td>No meniscal extrusion</td>
<td>3.62 (1.29–10.12)⁵</td>
</tr>
<tr>
<td>Prevalent cartilage damage (WORMS ≥ 2)⁵</td>
<td>Absence of cartilage damage in subregion (WORMS = 0 or 1)</td>
<td>15.90 (5.08–49.79)*</td>
</tr>
<tr>
<td>BML (WORMS ≥ 1)²</td>
<td>No BML in subregion (WORMS = 0)</td>
<td>4.58 (1.08–19.44)*</td>
</tr>
</tbody>
</table>

¹cartilage loss at 6 months in any of 4 PF/10 TF subregions
²multi-adjusted GEE model accounting for correlations within and between knees, and adjusted for age, gender, BMI, treatment, and the other MR features
³statistically significant at p ≤ 0.05

Conclusion: Cartilage loss over 6 months is rare, but may be detected semiquantitatively by MRI. The strongest predictors of PC cartilage loss were presence of baseline effusion and prevalent cartilage damage in the same subregion. The greatest predictor of TF cartilage loss was also prevalent cartilage damage, but prevalent BMLs and meniscal extrusion were also significant predictors of compartment-specific TF cartilage loss.

Disclosure: F. W. Roemer: Boston Imaging Core Lab, 4; C. K. Kwoh: Beverage Institute for Health and Wellness, 2; M. J. Hammon: None; S. M. Green: None; J. M. Jakicic: BodyMedia Inc., 2, 5, Free & Clear, 2, 5, Proctor and Gamble, 5, UPMC Health Plan, 2, 5; R. Boudreau: None; M. D. Crema: Boston Imaging Core Lab, 4; A. Guermazi: Boston Imaging Core Lab, 2, 4, 5, Facet Solutions, 2, 4, 5, General Electric, 2, 4, 5, Merck Serono, 2, 4, 5, Novartis Pharmaceuticals Corporation, 5, Stryker, 2, 4, 5, Synarc, Inc., 1.

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Background: Neuromuscular interventions that reduce disability and slow disease progression are needed for people with knee osteoarthritis (OA). Effective interventions would depend on the ability of the neuromuscular system to adapt to changing external demands, in spite of the deficits in afferent and efferent pathways seen in people with knee OA. The ability of the neuromuscular system to adapt has been studied through the response to repeated perturbations; however, no studies report mechanisms that may accompany successful neuromuscular adaptation in people with knee OA. The aims of this study are to (1) analyze the responses to repeated perturbations during walking in people with knee OA compared to controls, and (2) to analyze the effect of quadriceps strength, functional knee instability (FKI), proprioceptive loss and altered knee stiffness on the responses to repeated perturbations.

Methods: 43 subjects with medial knee OA and 21 healthy controls (C) participated. Kinematic and EMG data were collected as subjects walked overground (Level) for 10 trials and over a platform that translated laterally (Perturbed) at initial contact (IC), for 30 trials. FKI was assessed from the response to the instability question in Knee Outcome Survey. Isometric quadriceps strength was measured at 90° flexion. Proprioception was assessed using Threshold to Detect Passive Motion and Joint Repositioning Sense techniques at 15° flexion. Knee stiffness (torque/degree motion) was assessed by
a rapid knee flexion from 30°-50° while seated. Walking data were analyzed over Pre-activation (Pre: 100 msec before IC), Loading Response (LR: IC to peak knee flexion) and Midstance (MSt: end of LR to peak knee extension) phases. Mixed ANOVAs and Pearson’s correlations were used for statistical analyses.

Results: OA had lower quadriceps strength than C. There were no differences in proprioception or stiffness. OA had less motion and higher activation than C across all conditions. All groups showed an increase in activation and decrease in motion in the 1st perturbation trial compared to normal walking. No adaptation was seen during preactivation and LR phases but during MSt, there was increased knee motion and decreased muscle activation over the 1st 5 trials. Quadriceps strength, knee stiffness, proprioception and FKI were not related to the rate of adaptation.

Discussion: This is the 1st report of neuromuscular adaptation in people with knee OA, and also for knee stiffness in this population. We found that people with knee OA respond similarly to controls when exposed to repeated lateral perturbations during walking, with an increase in knee motion and decrease in muscle activations. The knee OA related impairments in quadriceps strength, proprioception, stiffness and dynamic stability are not related to the ability to adapt. The results provide evidence that rehabilitation strategies aimed at modifying movement and muscle activation strategies to improve knee stability and reduce joint contact forces may be effective for people with knee OA. Further study is needed to determine the goals and best methods for improving neuromuscular control in this population.

Disclosure: D. Kumar: None; D. Reisman: NIH, 2; C. B. Swainik: NIH, 2; K. S. Rudolph: NIH, 2.

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Peri-Articular Bone Density Is Strongly Correlated with Static Alignment and Varus Thrust.


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Purpose: Knee bone mineral density (BMD) has been associated with radiographic and MRI features of OA. Therefore, we hypothesized that tibial peri-articular BMD (paBMD) would be associated with static and dynamic alignment, both predictors of OA structural progression.

Methods: This is a cross-sectional study of a convenience sample from a randomized controlled trial (RCT) of vitamin D for symptomatic radiographic knee OA. Participants had standing PA semi-flexed knee x-rays read for anatomic alignment, a measure of static alignment. All consenting participants who did not use ambulatory devices and had video recordings of their gait using a standard digital video camera (60 Hz) walking at a self-selected pace were included. A total of 123 people with knee OA (mean age 63.5 years, 63.5% female) participated in the study.

Results: Participants (N = 82) were 60% female, had a mean age 63.5 years (±8.5), BMI 30.2 (±5.4), and tibial medial/lateral paBMD 1.19 (±0.21). 49% and 23% had varus and valgus alignment while 31% had VT. Varus and valgus were associated with higher and lower medial/lateral paBMD respectively. Mechanical alignment accounted for 59% of the variability in medial/lateral paBMD (Table 1) that was associated with higher medial/lateral paBMD.

Table 1. Medial: Lateral paBMD stratified by biomechanical categories.

<table>
<thead>
<tr>
<th>Static Alignment</th>
<th>Mean Medial: Lateral paBMD</th>
<th>R²</th>
<th>Overall p-values</th>
<th>Individual p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varus (n = 40)</td>
<td>1.35</td>
<td>0.59</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Neutral (n = 23)</td>
<td>1.11</td>
<td></td>
<td></td>
<td>Referent</td>
</tr>
<tr>
<td>Valgus (n = 19)</td>
<td>0.95</td>
<td></td>
<td></td>
<td>0.0004</td>
</tr>
<tr>
<td>Varus Thrust</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (n = 25)</td>
<td>1.33</td>
<td>0.20</td>
<td>&lt; 0.0001</td>
<td>n/a</td>
</tr>
<tr>
<td>Absent (n = 57)</td>
<td>1.13</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion: This is a cross-sectional study of a convenience sample from a randomized controlled trial (RCT) of vitamin D for symptomatic radiographic knee OA. A sub-group of patients (n = 123) who had taken all the study medication and had all the MRI evaluations were selected for this post hoc retrospective analysis. The incidence of TKR of the study knee was 14.6%. Logistic regressions that included age, sex, and BMI in the model, yielded that baseline CRP level (p = 0.04), presence of severe medial meniscal tear (p = 0.004), medial meniscal extrusion (p = 0.01), and C reactive protein (CRP) level (p = 0.05) were strong predictors of TKR. Changes at 2 years also yielded strong predictors including change in the cartilage volume of the medial compartment (p = 0.005) and of the global joint (p = 0.03), as well as change in WOMAC pain (p = 0.009) and function (p = 0.02) scores. Logistic regressions that included age, sex, and BMI in the model, yielded that baseline severe medial tear (p = 0.006) and the presence of a medial BML (p = 0.002) were the strongest independent predictors of long-term TKR.

Conclusion: These data demonstrate that, in a knee OA clinical trial, it is possible to predict a “hard” outcome such as TKR using clinical and qMRI

The high medial/lateral paBMD had a high varus (93%) and a low valgus (0%) prevalence. (Table 2). The low paBMD group had the opposite findings.

Table 2. Prevalence of biomechanical categories stratified by the medial/lateral paBMD groups.

<table>
<thead>
<tr>
<th>Medial Lateral paBMD Groups</th>
<th>VARUS Prevalence</th>
<th>VALGUS Prevalence</th>
<th>Varus Thrust Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>p &lt; 0.0001</td>
<td>p &lt; 0.0001</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Normal</td>
<td>0/16 (0%)</td>
<td>12/16 (75%)</td>
<td>3/16 (19%)</td>
</tr>
<tr>
<td>High</td>
<td>28/30 (93%)</td>
<td>0/30 (0%)</td>
<td>18/30 (60%)</td>
</tr>
</tbody>
</table>

Conclusion: Static and dynamic alignment are strongly associated with medial/lateral tibial paBMD, accounting for nearly 60% and 20% of its variability. This may indicate that peri-articular bone responds to biomechanical derangements in those with knee OA. Modification of static or dynamic alignment may therefore lead to a change in peri-articular bone. Alternatively, treatment of bone health may be important in mediating the effects of alignment in knee OA.

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Prediction of Total Knee Replacement in a Two-Year Multi-Centre Clinical Trial in Knee Osteoarthritis: Results from a 4–6 Year Observation. Jean-Pierre Raynauld3, Johanne Martel-Pelletier4, Marc Dorais5, François Abram6, Boulous Harouei3, Denis Choquette3 and Jean-Pierre Pelletier6. 1CR-CHUM, Notre-Dame Hospital, Montreal, QC, Canada, 2Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, Canada, 3Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, 4Research and Development, ArthroVision Inc., Montreal, 5StatSciences Inc., Notre-Dame de l’Ile-Perrot, 6University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, Canada

Background: The aim of this study was to predict, using data from quantitative magnetic resonance imaging (qMRI), the incidence of total knee replacement (TKR) during the long-term follow-up of knee OA patients who formerly received treatment with lxicofene or naproxen.

Methods: Knee OA patients participating in a previous 2-year randomized, double-blind controlled trial evaluating the impact of lxicofene (200 mg BID) vs. naproxen (500 mg BID) who had serial MRI acquisitions of the symptomatic knee1 were recently contacted to evaluate retrospectively the incidence of TKR of the study knee. A sub-group of patients (n = 123) who had taken all the study medication and had all the MRI evaluations (according-to-protocol [ATP]) were selected for this post-hoc retrospective analysis. The TKR incidence was assessed blindly to the treatment allocation with a standardized phone interview.

Results: The patients’ mean age was 63.5 years, 63.5% were female and the average body mass index (BMI) was 31.9 kg/m². A total of 18 TKRs (14.6%) were performed upon this sub-population in the time frame of 4–6 years after completion of the original study. Interestingly, there were significantly more TKRs performed within the naproxen group than the lxicofene group (61% vs. 39%), Fischer’s exact test p = 0.23. Further, we investigated the predictors of long-term TKRs by comparing, within the ATP cohort, the patients who had TKR to those who did not, using data at baseline or the change at 2 years. Data revealed that baseline values of bone marrow lesions (BMLs) of the medial tibial plateau (p = 0.0001; Fisher’s exact test), medial joint space width (X-ray) (p = 0.0008), presence of severe medial meniscal tear (p = 0.004), medial meniscal extrusion (p = 0.01), and C reactive protein (CRP) level (p = 0.05) were strong predictors of TKR. Changes at 2 years also yielded strong predictors including change in the cartilage volume of the medial compartment (p = 0.005) and of the global joint (p = 0.03), as well as change in WOMAC pain (p = 0.009) and function (p = 0.02) scores. Logistic regressions that included age, sex, and BMI in the model, yielded that baseline severe medial tear (p = 0.006) and the presence of a medial BML (p = 0.002) were the strongest independent predictors of long-term TKR.

Conclusion: These data demonstrate that, in a knee OA clinical trial, it is possible to predict a “hard” outcome such as TKR using clinical and qMRI.
data. The results are highly encouraging and support the use of qMRI as a surrogate for joint tissue damage upon which a DMOAD may act.

Reference:


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Prevalence of MRI-Detected Joint Pathology of the Knee in a Population-Based Sample: Framingham Osteoarthritis Study, Jingbo Ni¹, Yuqing Zhang², Ali Guermazi³, Frank W. Roemer⁴ and David T. Felson⁵. ¹Boston Univ School of Medicine, Boston, MA, ²Boston University School of Medicine, Boston, MA, ³Boston University School of Medicine, Boston, MA, ⁴Boston University School of Medicine, Boston, MA, ⁵Boston University School of Medicine

Magnetic resonance imaging (MRI) allows direct visualization of cartilage and other soft tissues and is becoming a common method to image knees osteoarthritis (OA) in studies. MRI-detected intraarticular pathology may be common in persons without disease. Previous work has shown that meniscal tears are common even in persons without radiographic OA. For may be common in persons without disease. Previous work has shown that meniscal tears are common even in persons without radiographic OA. For OA, over 40% had cartilage lesion and over 30% had bone marrow lesion. However, in women, the prevalence reached a plateau at age 65 then either leveled off or slightly decreased. As shown in the table, age standardized prevalence of each lesion in men and women respectively, using the age distribution in the whole sample as the standard. Finally, we repeated standardized prevalence of each lesion in men and women respectively, using a knee MRI. Kappa statistics for inter-rater reliability were 0.51–0.82 depending on feature. The presence of a lesion was defined by the worst score among subregions exceeding a pre-defined cut-point. We estimated sex- and age-standardized prevalence of each lesion in men and women respectively, using the age distribution in the whole sample as the standard. Finally, we repeated

Table age-standardized prevalence of MRI features by gender (as % of knees)

<table>
<thead>
<tr>
<th>MRI lesion (score range) definition</th>
<th>Whole knee joint TF joint PF joint Med joint Lat joint Men</th>
<th>Whole knee joint TF joint PF joint Med joint Lat joint Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage morphology (0–6) ≥1 (at least cartilage erosion)</td>
<td>73.6</td>
<td>57.4</td>
</tr>
<tr>
<td>Osteophyte (0–7) ≥3 (at least medium size)</td>
<td>27.5</td>
<td>23.0</td>
</tr>
<tr>
<td>Bone marrow lesion (0–3) ≥1 (at least small lesion)</td>
<td>57.5</td>
<td>43.9</td>
</tr>
<tr>
<td>Subarticular cyst (0–3) ≥1 (any cyst)</td>
<td>32.3</td>
<td>24.9</td>
</tr>
<tr>
<td>Meniscal tear (0–3) ≥1 (definite tear)</td>
<td>4.0</td>
<td>36.4</td>
</tr>
<tr>
<td>popliteal/Baker’s cyst (0–3) ≥1 (bursitis or cyst)</td>
<td>20.0</td>
<td>-</td>
</tr>
<tr>
<td>anserine bursitis (0–1) ≥1 (bursitis)</td>
<td>16.0</td>
<td>-</td>
</tr>
<tr>
<td>patella bursitis (0–1) ≥1 (bursitis)</td>
<td>44.8</td>
<td>-</td>
</tr>
</tbody>
</table>

*MRI features with prevalence <5% were not listed.

Disclosure: J. Ni: None; Y. Zhang: None; A. Guermazi: Boston Imaging Core Lab, 4, 5, Facet Solutions, 4, 5, GE Healthcare, 2, Genzyme Corporation, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 5, Serono, 5, Synarc, Inc., 1; F. W. Roemer: Boston Imaging Core Lab, 4; D. T. Felson: None.

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Relation of Hand Enthesophytes on Plain Radiographs with Findings of Knee Enthesopathy: Is Osteoarthritis a Generalized Enthesopathy? Nadia Gibson¹, Mary M. Clancy², Jingbo Ni³, Peter Grayson³, Paran Aliabadi³, Agnès Guermazi⁴ and D. T. Felson⁵. ¹Boston University Medical Center, Boston, MA, ²Boston Medical Center, ³Boston University School of Medicine, ⁴Boston University School of Medicine, ⁵Brigham’s and Women Hospital

Purpose: Enthesopathy, an abnormality at the attachment of a tendon or ligament to bone, has been reported as a feature of osteoarthritis (OA) in the DIP joints. Some patients have central bone marrow lesions (BMLs) on MRI at the insertion sites of the ACL and PCL suggesting enthesopathy in the knee that might be similar to that seen in the hand. We have reported that these central BMLs on MRI are associated with OA (Arthritis Rheum 2008; 58: 130–136). In this study, we evaluated whether hand enthesopathy was related to this presumed knee enthesopathy and whether in those with knee OA, hand enthesopathy was associated with these central BMLs.

Methods: We studied knee and hand x-rays of subjects from the Framingham Osteoarthritis Study, a population based study. Subjects seen in 2002–2005 had bilateral PA hand x-rays, weight bearing knee x-rays and knee MRI’s using a 1.5 T magnet. We used T-2 weighted fat suppressed images to identify central BMLs. Knee x-rays were read for K/L grade and without radiographic PF OA, and knee MRI’s using a 1.5 T magnet. We studied hand x-rays were read for enthesophytes defined as bony spurs at the juxta-articular nonsynovial areas of MCP, PIP and DIP joints (excluding osteophytes) and midshafts of proximal, middle and distal phalanges. We scored lesions as 0: none; 1: small, 2: moderate, 3: large. The intra-observer kappa was 0.67. To determine whether there was a relation of presence of enthesophytes in either hand with central BML’s in the knees (one knee/person), we selected 100 cases of knees with central BML’s and 100 matched controls without this finding of the same age (2 year categories) and sex. We assessed the association by using conditional logistic regression adjusting for worst K/L grade in the knee. To determine if hand enthesopathy was related to central BMLs in the context of knee OA, further analyses restricted cases and controls to those with knee OA.

Results: Mean age of subjects was 68 years, mean BMI 29.5. Those with enthesophytes of at least one score ≥2 at DIP, PIP and/or MCP were less likely to have central BMLs of the knee (OR = 0.49 95% CI 0.17–1.40), than those without such enthesophytes, although this was not statistically significant (see Table). Similarly, having at least one score ≥2 on the shafts (distal, middle and/or proximal) was not significantly associated with having central knee BMLs (OR = 0.59, 95% CI 0.23–1.51). Considering all hand sites, the number of subjects with at least one score ≥2 was 38 in the cases and 42 in the controls (OR = 0.57, 95% CI 0.26–1.27). Analyses using enthesophyte score ≥1 yielded similar results. When we examined only cases and controls with OA, we found similarly null results.

Conclusions: We found no relation between hand enthesophytes and central BML’s in the knee. We also found no clear association of hand enthesophytes with central BMLs in patients with established OA. This provides evidence against a generalized enthesopathic disorder in association with knee OA.

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Monday, November 8
Objective: To summarize literature on the responsiveness and reliability of MRI-based measures of osteoarthritis (OA) structural change.

Methods: An online literature search was conducted of the OVID, EM-BASE, CINAHL, PsychINFO and Cochrane databases of articles published up to the time of the search, April 2009, with the search entries “MRI”, and “osteoarthritis”. The abstracts of the 1338 citations received with this search were then preliminarily screened for relevance by two reviewers. Of these, 243 were selected for data extraction for this analysis as well as a distinct analysis on validity. We extracted data on responsiveness and reliability from both longitudinal and cross-sectional studies for all synovial joint tissues as it relates to MRI measurement in OA. Reliability was defined by inter- and intra-class correlation (ICC) and kappa statistics. Higher ICCs and kappa values indicate more reliable estimates. Responsiveness was defined as standardized response mean (SRM) — ratio of mean of change over time divided by standard deviation of change. For the quantitative analysis negative SRMs indicate a loss of cartilage. For the semi-quantitative analysis, loss in cartilage is defined by positive SRMs. Random-effects models were used to summarize data from multiple studies.

Results: The reliability analysis included data from 89 manuscripts. The inter-reader and intra-reader ICC were all excellent (range 0.81–0.94). The inter-reader and intra-reader kappa values for quantitative, semi-quantitative and compositional measures were all moderate to excellent (range 0.52–0.88).

Table 1. Results of random-effects pooling of reliability

<table>
<thead>
<tr>
<th>Inter-reader in-class correlations (ICC)</th>
<th>Number of Estimates (Studies)</th>
<th>Mean Sample Size</th>
<th>Pooled ICC</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative Cartilage</td>
<td>10 (4)</td>
<td>196</td>
<td>0.90</td>
<td>0.86, 0.95</td>
</tr>
<tr>
<td>Quantitative Meniscus</td>
<td>2 (1)</td>
<td>291</td>
<td>0.81</td>
<td>0.72, 0.89</td>
</tr>
<tr>
<td>Semi-Quantitative Cartilage</td>
<td>15 (4)</td>
<td>136</td>
<td>0.57</td>
<td>0.44, 0.71</td>
</tr>
<tr>
<td>Semi-Quantitative Bone Marrow Lesion</td>
<td>2 (2)</td>
<td>237</td>
<td>0.88</td>
<td>0.79, 0.97</td>
</tr>
<tr>
<td>Semi-Quantitative Meniscus</td>
<td>3 (3)</td>
<td>418</td>
<td>0.73</td>
<td>0.63, 0.84</td>
</tr>
<tr>
<td>Semi-Quantitative Ligament</td>
<td>3 (3)</td>
<td>209</td>
<td>0.80</td>
<td>0.69, 0.90</td>
</tr>
</tbody>
</table>

The responsiveness analysis included data from 42 manuscripts. The pooled SRM for quantitative measures of cartilage for medial tibiofemoral joint was −0.58 (95%CI −0.75 to −0.41). The pooled SRM for the semi-quantitative measurement of cartilage for the medial tibiofemoral joint was 0.55 (95%CI 0.47 to 0.64).

Table 2. Results of random-effects pooling of standardized response mean

<table>
<thead>
<tr>
<th>Stratification</th>
<th>Number of Estimates (Studies)</th>
<th>Mean Sample Size</th>
<th>Pooled SRM</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative Cartilage</td>
<td>54 (12)</td>
<td>118</td>
<td>−0.39</td>
<td>−0.48, −0.30</td>
</tr>
<tr>
<td>Quantitative Medial Tibial</td>
<td>55 (17)</td>
<td>134</td>
<td>−0.33</td>
<td>−0.39, −0.26</td>
</tr>
<tr>
<td>Quantitative Medial Tibio-Femoral</td>
<td>31 (12)</td>
<td>92</td>
<td>−0.58</td>
<td>−0.75, −0.41</td>
</tr>
<tr>
<td>Quantitative Lateral Femoral</td>
<td>32 (8)</td>
<td>151</td>
<td>−0.19</td>
<td>−0.27, −0.11</td>
</tr>
<tr>
<td>Quantitative Lateral Tibial</td>
<td>44 (14)</td>
<td>152</td>
<td>−0.44</td>
<td>−0.51, −0.36</td>
</tr>
<tr>
<td>Quantitative Lateral Tibio-Femoral</td>
<td>14 (5)</td>
<td>110</td>
<td>−0.56</td>
<td>−0.92, −0.20</td>
</tr>
<tr>
<td>Quantitative Patella</td>
<td>13 (9)</td>
<td>131</td>
<td>−0.60</td>
<td>−0.83, −0.37</td>
</tr>
<tr>
<td>Semi-Quantitative Cartilage</td>
<td>3 (3)</td>
<td>224</td>
<td>0.55</td>
<td>0.47, 0.64</td>
</tr>
<tr>
<td>Semi-Quantitative Medial Tibial-Femoral</td>
<td>3 (3)</td>
<td>224</td>
<td>0.37</td>
<td>0.18, 0.57</td>
</tr>
<tr>
<td>Semi-Quantitative Patella</td>
<td>2 (2)</td>
<td>238</td>
<td>0.29</td>
<td>0.03, 0.56</td>
</tr>
<tr>
<td>Semi-Quantitative Synovium</td>
<td>3 (2)</td>
<td>68</td>
<td>0.52</td>
<td>0.28, 0.76</td>
</tr>
<tr>
<td>Semi-Quantitative Osteophytes</td>
<td>4 (1)</td>
<td>150</td>
<td>0.36</td>
<td>0.28, 0.44</td>
</tr>
<tr>
<td>Semi-Quantitative Bone Marrow Lesion</td>
<td>6 (2)</td>
<td>130</td>
<td>0.19</td>
<td>0.07, 0.30</td>
</tr>
<tr>
<td>Semi-Quantitative Meniscus</td>
<td>2 (1)</td>
<td>264</td>
<td>0.27</td>
<td>0.14, 0.40</td>
</tr>
</tbody>
</table>

Conclusion: MRI has evolved substantially over the last decade and its strengths include its ability to visualize individual tissue pathologies, which can be measured reliably using both quantitative and semi-quantitative techniques. Using MRI it is possible to accurately and feasibly measure change in cartilage morphology over 12 months for knee OA. Studies also suggest that cartilage and synovium are responsive measures on semi-quantitative assessment.

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The Effects of Hip Muscle Training on Knee Joint Loading in Medial Knee Osteoarthritis. Julia Daher1, Joel A. Block2, Markus Wimmer3, Dale R. Sumner1 and Laura E. Thorp4.1 Rush University Medical Center, Chicago, IL, 2 Rush University Medical Center, Chicago, IL.

Objective: The purpose of this investigation was to analyze the effects of a focused hip muscle training program on knee joint loading in subjects with medial compartment knee OA. Specifically, we hypothesized that focused hip musculature training in individuals with mild to moderate knee OA would produce favorable changes in dynamic loading of the medial knee during walking, as evidenced by decreased external knee adduction moments.

Methods: To date, 12 subjects with mild to moderate medial compartment knee OA ranging in age from 35–69 years of age completed the study protocol. Subjects underwent gait analysis at their self-selected normal walking speed and both the peak external knee adduction moment and the knee adduction angular impulse were calculated before and after participation in a 4-week supervised, physical therapy intervention targeted at the hip abductor musculature. Response to treatment was defined as a reduction in either parameter. Additionally, subjects wore an accelerometer-based activity monitor for 7 days after the baseline visit.

Results: 8 of the 12 subjects responded to therapy. For these subjects, the mean percent decreases in the peak external knee adduction moment were −9.6 ± 8.7% and −12.4 ± 7.7% for index and contralateral knees respectively. In the index and contralateral knees, the mean percent decreases in knee adduction angular impulse were −7.1 ± 3.8% and −22.0 ± 8.3% respectively. The magnitude of change in the responders was greater in the contralateral knee than in the index knee. The responders tended to be more active than the non-responders, though this difference was not significant. Nonetheless, when non-responders were included in the analysis, there were no significant changes in either peak adduction moment or adduction angular impulse.

Conclusion: The discrepancy between responders and non-responders is unexplained, though may relate to activity and/or adherence. While more subjects are needed to determine the efficacy of hip muscle training on joint loads in medial compartment knee OA, these preliminary results suggest hip muscle training may have use in prevention of contralateral disease development. It is possible that this type of intervention may be best suited for more active individuals.

Disclosure: J. Daher: None; J. A. Block: None; M. Wimmer: None; D. R. Sumner: None; L. E. Thorp: ACR REF Health Professional New Investigator Award, 2. Arthritis Foundation Young Investigator Award, 2.

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The Relationship between Symptoms of Medial Tibiofemoral Osteoarthritis and Toe-Out Angle during Walking: The MOST Study. K. Douglas Gross1, Jinbo Niu2, Yuqing Zhang2, Michael C. Nevitt3, Cora E. Lewis2, James Torner4 and David T. Felson5. 1 Boston Univ School of Medicine, Boston, MA, 2 Boston University School of Medicine, Boston, MA, 3 Boston University School of Medicine, Boston, MA, 4 MGH Institute of Health Professions, Boston, MA, 5 University of Alabama, Birmingham, Birmingham, AL, 6 University of California, San Francisco, San Francisco, CA, 7 University of Iowa, Iowa City.

Background: Many people with symptomatic medial knee osteoarthritis (OA) walk with an increased toe-out angle, an adaptation that can reduce compressive load on the medial tibiofemoral (TF) compartment and offer protection against worsening disease. Despite these advantages, it is not known why some people with medial TF OA spontaneously modify their gait in such a way as to increase toe-out, while others do not. It is possible that the presence and severity of knee pain provides a necessary incentive.
Methods: The Multicenter Osteoarthritis Study (MOST) is a NIH-funded longitudinal study of individuals who have or are at high risk for knee OA. From among participants who completed the 60-month exam, we selected all knees with radiographic medial TF OA (K&L grade /=2 on fixed flexion x-ray with OARSI medial joint space narrowing score /=1 and greater medial than lateral JSN). We inquired about knee pain in three ways: 1) presence of ‘current knee pain’ during the walking exam, 2) presence of ‘frequent knee pain’ during the past 30 days, and 3) ‘knee pain severity’ (none, mild, /= moderate) when walking during the past 30 days. Toe-out angle was measured in degrees between the line of progression and the midline of a footprint at self-selected normal and fast walking speeds using a 14’ GAITRite instrumented walkway. Linear regression with generalized estimating equations compared mean toe-out angle between knees with and without pain while adjusting for covariates (baseline age, BMI, sex, race, and mean walking velocity).

Results: 269 participants (mean age 62.9 +/- 8.0 yrs, mean BMI 32.1 +/- 6.7 kg/m2, 34.6% female, 84.0% white) contributed 374 knees (25.4% with current pain, 53.0% with frequent pain, and 51.1% with pain of at least mild severity when walking). Crude mean toe-out angle was 7.0 +/- 5.5 (range &lt; 8.2, 24.7) degrees at normal walking speed and 6.2 +/- 5.3 (range &lt; 7.9, &gt; 24.4) degrees at fast walking speed. Adjusted mean toe-out angle at normal and fast speeds (respectively) was smaller among knees with current (p=0.09, p=0.05), frequent (p=0.33, p=0.14), and more severe knee pain (p=0.36, p=0.12), although the differences were not statistically significant (see table).

Conclusions: These findings do not lend support to the hypothesis that the presence or severity of knee pain among persons with medial TF OA is associated with greater toe-out angle during walking. On the contrary, because toe-out angle may be diminished among those with current, frequent, or more severe pain, an opportunity exists for gait training to increase toe-out among those with medial TF OA symptoms.

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The Relationship between Varus and Valgus Thrust and Meniscal Damage in Persons with Knee Osteoarthritis. Alison H. Chang1, Ali Guermazi2, Frank Roemer1, Kirsten Moisio3, Jing Song1, Dorothy D. Dunlop4, Michael C. Nevitt5, Carmelita J. Colbert5, John A. Lynch5, Karen W. Hayes1 and Leena Sharma1. 1Boston University, 2Northwestern University, LaGrange, IL, 3Northwestern University, Downers Grove, IL, 4Northwestern University, Chicago, IL, 5Northwestern University, UCSF, San Francisco, CA, UCSF.

Purpose: Varus thrust observed during gait has been shown to be associated with a 4-fold increase in the risk of medial knee osteoarthritis (OA) progression. It is plausible that a varus thrust may trigger or exacerbate medial meniscal damage as a cumulative effect of the acute increase in medial load with each step of walking. A parallel relationship may exist between valgus thrust and the lateral meniscus. We tested the hypotheses: 1) varus thrust is associated with medial meniscal damage (tear, maceration, extrusion); and 2) valgus thrust is associated with lateral meniscal damage.

Methods: The sample included Osteoarthritis Initiative (OAI) participants with symptomatic radiographic knee OA (data from public release data sets version 0.2.2 and 1.2.1 and from an NIH-funded ancillary study). Trained examiners assessed all participants at the 12-month visit for varus and valgus thrust presence by gait observation. The following sequences from the OAI protocol were used for meniscal assessment: sagittal IW 2D TSE FS, sagittal 3D DESS WE, axial MPR of SAG 3D DESS WE, coronal MPR of SAG 3D DESS WE. Meniscal status was scored according to the BLOKS system in the anterior, body and posterior horn of the medial and lateral meniscus. In addition, extrusion was scored from 0 – 3, with presence defined as &gt; 0. We used logistic regression to specifically evaluate the relationship of varus thrust to medial meniscal damage (tear, maceration, and extrusion) and valgus thrust to lateral meniscal damage, adjusting for age, gender, and BMI.

Results: 496 persons (1 knee/person) (mean age 62 years, BMI 30, 58% women) were examined. Varus thrust was present in 169 knees (34%) and valgus thrust in 31 knees (6%). As shown in Table 1, varus thrust was significantly associated with medial meniscal tear and with medial meniscal maceration.

Table 1. Varus Thrust and Medial Meniscal Damage

<table>
<thead>
<tr>
<th>Thrust Status (n = 496 knees)</th>
<th>Number of Knees (row %) with Medial Meniscal Tear</th>
<th>Number of Knees (row %) with Medial Meniscal Tear Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No varus thrust (reference)</td>
<td>142 (43.4%)</td>
<td>Reference</td>
</tr>
<tr>
<td>Varus thrust (n = 169 knees)</td>
<td>96 (56.9%)</td>
<td>1.50 (1.01, 2.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.73 (0.43, 1.29)</td>
</tr>
</tbody>
</table>

As shown in Table 2, valgus thrust was significantly associated with lateral meniscal maceration; the association with lateral meniscal tear approached significance.

Table 2. Valgus Thrust and Lateral Meniscal Damage

<table>
<thead>
<tr>
<th>Thrust Status (n = 496 knees)</th>
<th>Number of Knees (row %) with Lateral Meniscal Tear</th>
<th>Number of Knees (row %) with Lateral Meniscal Tear Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No valgus thrust (reference)</td>
<td>109 (23.4%)</td>
<td>Reference</td>
</tr>
<tr>
<td>Valgus thrust (n = 31 knees)</td>
<td>12 (38.7%)</td>
<td>2.12 (0.98, 4.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.92 (0.36, 2.34)</td>
</tr>
</tbody>
</table>

Neither varus thrust nor valgus thrust was significantly associated with meniscal extrusion (not shown).

Conclusion: Varus thrust during ambulation was associated with medial meniscal tear and maceration, but not with extrusion, with similar findings for valgus thrust and lateral meniscal damage. Longitudinal studies may help elucidate the cause-effect relationship between these factors and how they might act in concert to accelerate OA progression.

Disclosure: A. H. Chang: None; A. Guermazi: None; F. Roemer: None; K. Moisio: None; J. Song: None; D. D. Dunlop: None; M. C. Nevitt: None; C. J. Colbert: None; J. A. Lynch: None; K. W. Hayes: None; L. Sharma: None.

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Thigh Muscle Quality Correlates with Function, Leg Strength, and Walking Speed, but Not with Alignment in Individuals with Obesity and Knee Osteoarthritis. Rachel W. Holt1, Richard F. Loeser2, Crenal Davis5, Claudine Legault3, Barb Nicklas6, Jeffrey Carr7, David J. Hunter1, Stephen P. Messier1. 1New England Baptist Hospital, Boston, MA, 2Wake Forest Univ, Winston-Salem, NC, 3Wake Forest University, Winston-Salem, NC, 4Wake Forest Univ., 5Wake Forest University, Winston-Salem, NC.

Purpose: The effect of obesity on risk for disease progression in osteoarthritis is mediated by the extent of malalignment but it is not known if adiposity and alignment are related. Adipose tissue in the thigh varies in distribution with some individuals having greater subcutaneous fat and others more prevalent (intramuscular) and within (intramuscular) adipose tissue. In addition, muscle associated triglyceride can be determined by the CT attenuation of muscle and is a measure of muscle quality. The objective of this study was to determine the relationship between CT measures of thigh fat and lower extremity alignment and then with measures of pain and function in overweight and obese adults with mild to moderate knee OA.
Methods: Data were collected at baseline from participants entering the Intensive Diet and Exercise for Arthritis (IDEA) study. Inclusion criteria were BMI of 27–40.5 kg/m², age >55 years, self-reported disability due to knee pain, and radiographic evidence of mild to moderate (K-L score II-III) tibiofemoral OA in at least one knee. Mechanical alignment was measured using full-length lower extremity x-rays and Image J software. Subcutaneous and inter/intramuscular (IM) thigh adipose tissue and thigh muscle quality were measured by CT. Self-reported pain and function were evaluated using WOMAC. Strength was measured on a Kin-Con isokinetic dynamometer. Data were analyzed using SAS to calculate Pearson correlation coefficients and ANOVA (for analysis of alignment type).

Results: Data were available on 129 IDEA participants with the following characteristics: 70% female, mean±sd age of 65.9±6.2 years, BMI of 33.2±3.7 units, subcutaneous thigh fat of 87.6±285.9 cm³, IM thigh fat of 30.4±16.1 cm³, thigh muscle quality of 52.0±6.2 Hounsfield units, WOMAC function of 23.4±10.4, WOMAC pain of 6.0±2.9, concentric extensor strength of 61.2±23.9 Nm and 236.3±83.4 Nm, and walking speed of 1.2±0.2 m/s. 25% of the subjects had neutral alignment, 25% valgus, and 50% varus. The analysis of muscle quality showed significant negative correlations with age, BMI, IM thigh fat, and WOMAC function and positive correlations with strength and walking speed (Table 1). The analysis of the magnitude of the alignment angle (Table 1) revealed weak but significant correlations with WOMAC pain and function but not the CT measures. Furthermore, the mean thigh muscle quality did not differ significantly between the three alignment types (ANOVA not shown).

Conclusion: These results suggest that reduced thigh muscle quality due to IM fat correlates with age and BMI and has a detrimental effect on strength, speed, and overall function in this population; however, alignment does not appear to have the same impact. Based on posthoc power calculations, a larger sample size would be needed to detect the observed differences of about 1 HU in thigh muscle quality between alignment types.

Disclosure: R. W. Holt: None; R. F. Looser: None; C. Davis: None; C. Legault: None; B. Nicklas: None; J. Carr: None; D. J. Hunter: None; S. P. Messier: None.

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Understanding the Individual Burden of Osteoarthritis: Development of a Conceptual Model. Lucy Busija1, Richard H. Osborne2 and Rachelle Buchbinder1. 1Cabrini Institute and Monash University, Malvern, Australia, 2Deakin University, Melbourne, Australia, 3University of Melbourne.

Aims: While the importance of osteoarthritis as a public health burden is well recognised, less is known about the impact of this condition at the individual level. Currently, no unifying framework is available for comprehensively documenting health-related consequences from the individual’s perspective as existing frameworks are either not designed to represent the views of people with osteoarthritis or do not capture the full range of osteoarthritis-related consequences. The aim of this study was to develop a conceptual framework for documenting health-related consequences of osteoarthritis in affected individuals.

Methods: Structured concept mapping (SCM) workshops (n=6) were undertaken, three with patients (n=26) and three with health professionals and health policy makers (n=27) in Australia and in Sweden. The participants were asked to generate statements describing the impact of osteoarthritis on individuals with this condition and those around them. The post-workshop analyses used a mix of quantitative (three-dimensional multidimensional scaling analysis) and qualitative (thematic analysis) approaches to indentify major dimensions of the individual burden of osteoarthritis. A relational algorithm was then used to identify the interrelationships among these dimensions and to construct an integrated theoretical model of the Personal Burden of Osteoarthritis (PBO).

Results: A synthesis of the workshops identified 8 potentially independent aspects of PBO, including Physical distress, Pain, Physical limitations, Psychosocial distress, Physical de-conditioning, Financial hardship, Sleep disturbances, and Lost productivity. Physical distress was the key influence on individual health and welfare. One of the major effects of physical distress was impaired physical function. In combination, physical limitations and physical distress lead to psychosocial problems, reduced work productivity, financial difficulties, and loss of physical fitness.

Conclusions: The PBO framework was designed to comprehensively capture the consequences of osteoarthritis on individuals with this condition. The framework provides new insight for individual care and program development for people with osteoarthritis.

Disclosure: L. Busija: None; R. H. Osborne: None; R. Buchbinder: None.

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Vibrotactile Sensory Deficits in Radiographic Knee Osteoarthritis: The Multicenter Osteoarthritis Study (MOST). Naja Shakoor1, Tuhiina Neogi1, David T. Felson2, Jingbo Niu3, Laura Frey Law4, Cora E. Lewis5 and Michael C. Nevitt6. 1Boston Univ Schl of Med, Boston, MA, 2Boston University, Boston, MA, 3Boston University School of Medicine, Boston, MA, 4Rush-University Medical Center, Chicago, IL, 5UCSF, San Francisco, CA, 6University of Alabama, University of Iowa, Iowa City, IA

Background:Somatosensory abnormalities, including proprioceptive and vibratory sensory deficits, have been observed in osteoarthritis (OA) of the knee. Deficits in vibratory sense were associated with the presence of knee and hip OA in two small cross-sectional studies. We examined the association of vibratory sensory with radiographic knee OA (RKO) in participants in a large cohort study of knee OA, the Multicenter Osteoarthritis Study (MOST).

Methods: MOST is a NIH-funded longitudinal study of persons with symptomatic knee OA or at increased risk of OA. At the 60-month visit, participants underwent bilateral evaluation of vibratory perception threshold (VPT), using a biothesiometer (Bio-Medical Instrument Co.) operating at a frequency of 120Hz. The applicator tip of the instrument was placed on three anatomical bony prominences: the dorsum of the first MTP joint, the tibial tuberosity and, the radial styloid. The voltage of the biothesiometer was initially set at “0” and then increased by 1 volt/second until the participant acknowledged sensation and this was defined as the VPT. At each study visit, participants had bilateral weight bearing PA and lateral x-rays which were read for Kellgren Lawrence (KL) grade, and defined as RKO if KL grade was ≥2. Those with knee replacement or diabetes were excluded. In light of large differences in VPT between genders and with age, men and women were evaluated separately and divided into age subgroups, <65 years and ≥65 years. A knee-based analysis was performed with three knee groups: 1) RKO (KL ≥ 2); 2) contralateral “normal” knee of unilateral RKO and 3) control knee (no RKO in either knee). Linear regression with GEE was used to compare VPT between groups adjusted for age and BMI and accounting for between knee correlations.

Results: This analysis included 222 men (mean age (SD) of 67±9 years) and 451 women (mean age (SD) of 68±8 years). VPT values for men were significantly (p<0.001 at all sites) higher compared to women adjusted for age and BMI. In men age ≥65, VPT was higher at the MTP and tibial tuberosity in knees with RKO compared to control knees, but this was not significant after age adjustment (Table). VPT in the nonOA knee of those with unilateral RKO was higher than controls, nearly reaching significance at the radial styloid. There were no significant associations of VPT with RKO status in men less than 65 or women in either age group.

Conclusions: In this cohort study, an association between RKO and higher VPTs was present only in men ≥65 years of age, which is also the

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Background: Juvenile idiopathic arthritis (JIA) is associated with vertebral fractures. Precise screening methods are needed to identify those at-risk. Lumbar spine posterior-anterior (PA) dual x-ray absorptiometry (DXA) have been used in the assessment of bone density in children with JIA. However, the utility of DXA bone mineral density (BMD) and its value in the detection of vertebral fractures has been uncertain. Vertebral fractures are often missed using DXA due to superimposition of trabecular and cortical structures. Volumetric imputation using bone mineral apparent density (BMAD) or height Z-score adjustment can improve detection of vertebral fractures using DXA.

Methods: A total of 142 children with JIA and 153 healthy age- and gender-matched controls were included in this longitudinal study. DXA scans were performed at baseline and at 12-month follow-up. BMC, BMAD, aBMD, and BMAD Z-scores were calculated. Logistic regression models were used to identify clinical predictors of Z-score changes.

Results: Baseline: Compared with controls, children with JIA had lower BMC, BMAD, aBMD, and BMAD Z-scores. Follow Up: Significant reductions in BMC, BMAD, aBMD, and BMAD Z-scores were observed in JIA over the course of the study. Logistic regression models identified predictors of Z-score changes, including age, sex, race, and disease duration.

Conclusions: DXA bone mineral density measurements are useful in the detection of vertebral fractures in children with JIA. Further research is needed to optimize the use of DXA in the assessment of vertebral fractures in this population. This study highlights the importance of longitudinal monitoring of bone health in children with JIA.
An International Consensus Survey of the Diagnostic Criteria for Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis

Background: Macrophage activation syndrome (MAS) is a potentially life-threatening complication of systemic juvenile idiopathic arthritis (sJIA). Because MAS is a serious condition that can follow a rapidly fatal course, prompt recognition of its clinical and laboratory features and immediate therapeutic intervention are critical. However, diagnosis of MAS can be difficult and hard to distinguish from sepsis-like syndromes. In addition, subclinical forms of MAS in sJIA underscore the importance of establishing criteria sensitive enough to identify MAS from routine disease flare.

Objective: To select the clinical, laboratory and histopathologic features which are more suitable as diagnostic criteria for sJIA-associated MAS through an international Delphi questionnaire survey.

Methods: All members of the Paediatric Rheumatology International Trials Organisation (PRINTO), the Childhood Arthritis & Rheumatology Research Alliance (CARRA), and the Pediatric Rheumatology Collaborative Study Group (PRCSG) were submitted a questionnaire that listed the 28 most typical features of MAS and were first asked to select the 10 features that they deemed most important in the diagnosis of the syndrome, and then to rank order the 10 selected features by assigning 1 to the most important, and end with 10 as the least important.

Results: Of the 505 pediatric rheumatologists who were contacted, 232 (45.9%) participated in the survey. The table shows, for the features selected by more than 30% of respondents, the percentage of investigators who selected the feature and its median rank.

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. (%) of respondents giving rank 1-5 to the feature</th>
<th>Median rank</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falling platelet count</td>
<td>201 (86.6)</td>
<td>6.5</td>
<td>6.1 (2.3)</td>
</tr>
<tr>
<td>Hyperferritinemia</td>
<td>194 (83.6)</td>
<td>7</td>
<td>6.5 (3.0)</td>
</tr>
<tr>
<td>Bone marrow hemophagocytosis</td>
<td>188 (81.0)</td>
<td>9</td>
<td>6.9 (3.6)</td>
</tr>
<tr>
<td>Increased liver enzymes</td>
<td>174 (75)</td>
<td>5</td>
<td>5.0 (2.4)</td>
</tr>
<tr>
<td>Falling leukocyte count</td>
<td>172 (74.1)</td>
<td>5</td>
<td>5.6 (2.5)</td>
</tr>
<tr>
<td>Persistent continuous fever ≤38°C</td>
<td>158 (68.1)</td>
<td>7</td>
<td>6.0 (3.4)</td>
</tr>
<tr>
<td>Falling erythrocyte sedimentation rate</td>
<td>142 (61.2)</td>
<td>6</td>
<td>5.5 (2.7)</td>
</tr>
<tr>
<td>Hypofibrinogenemia</td>
<td>142 (61.2)</td>
<td>5</td>
<td>5.4 (2.4)</td>
</tr>
<tr>
<td>Hypertrophic edema</td>
<td>135 (58.2)</td>
<td>5</td>
<td>5.1 (2.7)</td>
</tr>
<tr>
<td>Central nervous system dysfunction</td>
<td>104 (44.8)</td>
<td>5</td>
<td>5.0 (2.9)</td>
</tr>
<tr>
<td>Falling hemoglobin level</td>
<td>100 (43.1)</td>
<td>5</td>
<td>4.8 (2.3)</td>
</tr>
<tr>
<td>Prolongation of coagulation</td>
<td>81 (34.9)</td>
<td>4.5</td>
<td>4.5 (2.3)</td>
</tr>
<tr>
<td>Increased D-dimer</td>
<td>76 (32.8)</td>
<td>5</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Hemorrhagic manifestations</td>
<td>72 (31.0)</td>
<td>5</td>
<td>5.3 (3.0)</td>
</tr>
<tr>
<td>Liver enlargement</td>
<td>71 (30.6)</td>
<td>4</td>
<td>4.8 (2.6)</td>
</tr>
</tbody>
</table>

Conclusions: We identified the features of MAS that were agreed upon by the majority of international pediatric rheumatologists. The ability of each feature to discriminate MAS from potentially “confusable” conditions and the optimal diagnostic threshold for laboratory tests will be assessed through a large-scale data collection, which is ongoing. Altogether, these processes will lead to the development of a new and robust set of criteria for MAS complicating sJIA.

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Anakinra as First-Line Disease Modifying Therapy in Systemic Juvenile Idiopathic Arthritis—Report of 46 Patients from an International Multicenter Series

Background: Chronic active systemic juvenile idiopathic arthritis (sJIA) is one of the most devastating rheumatologic diseases of childhood. We hypothesized that early treatment with anakinra could favorably affect the course of this disease.

Methods: Medical records of children receiving anakinra as first-line therapy for sJIA were reviewed to characterize clinical course.

Results: 46 children from 11 centers in 4 countries received anakinra as part of initial disease-modifying anti-rheumatic drug (DMARD) therapy for sJIA, at a median dose of 1.5 mg/kg/day. Anakinra alone was employed as monotherapy in 10 patients (22%), while corticosteroids and additional DMARDs were employed in 67% and 33% respectively. Median follow-up was 14.5 months. Approximately 60% of patients, including 8 of 10 treated North American investigators, whereas North American investigators appeared to rely more on laboratory abnormalities than investigators from Europe and other parts of the world.

Objective: Chronic active systemic juvenile idiopathic arthritis (sJIA) is one of the most devastating rheumatologic diseases of childhood. We hypothesized that early treatment with anakinra could favorably affect the course of this disease.

Methods: Medical records of children receiving anakinra as first-line therapy for sJIA were reviewed to characterize clinical course.
with anakinra monotherapy, attained clinical remission without further escalation of therapy. Fever and rash resolved within 1 month in over 95%, while C-reactive protein and ferritin normalized within this interval in over 80%. Active arthritis persisted at 1 month in 40%, at 3 months in 27%, and at >6 month follow-up in approximately 10%. Disease characteristics and treatment parameters were similar in partial and complete responders, but partial responders were markedly younger at onset (5.8 vs. 9.8 years, p=0.004). Associated adverse events included bacterial infection in 2 patients and hepatitis in 1 patient.

**Conclusions:** Anakinra is effective first-line therapy of sJIA, enabling rapid resolution of systemic symptoms while forestalling the development of refractory arthritis in 90% of patients. These results justify further study of IL-1 inhibition as first-line, rather than rescue, therapy in sJIA.

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**Antinuclear Antibody Positive Patients Should Be Grouped as a Separate Category in the Classification of Juvenile Idiopathic Arthritis.** Angelo Ravelli1, Giulia C. Varnier3, Sheila K. Oliveira2, Esteban Castelli4, Olga Arguedas5, Alessandra Magnani6, Angela Pistorio6, Nicolino Ruperto6, Silvia Magni-Manzoni6, Bianca Lattanzi6, Roberta Galasso6 and Alberto Martini6. 1IRCCS Fondazione Policlinico San Matteo, Pavia, Italy; 2IRCCS G. Gaslini and Università di Genova, Genova, Italy; 3IRCCS G. Gaslini and Università di Genova, Genova, Italy, Italy; 4IRCCS G. Gaslini and Università di Genova, Genova, Italy; 5Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

**Objective:** We hypothesized that in the International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis (JIA), patients with similar characteristics are classified into different categories. We sought to investigate whether ANA-positive patients belonging to the ILAR categories of oligoarthritis, rheumatoid factor (RF)-negative polyarthritis, psoriatic arthritis, and undifferentiated arthritis share homogeneous features and to compare these features with those of ANA-negative patients in the same categories.

**Methods:** We identified all JIA patients who were followed up during a 22-year period. ANA positivity was defined as ≥ 2 positive results at a titer of ≥ 1:160. Demographic and clinical features were recorded retrospectively and compared among ANA-positive and ANA-negative patients.

**Results:** A total of 1219 patients fulfilled the ILAR criteria for JIA. Patients with systemic arthritis, RF-positive polyarthritis and enthesis-related arthritis were excluded from the study. The remaining 971 patients belonging to the ILAR categories of oligoarthritis (n=649), RF-negative polyarthritis (n=223), psoriatic arthritis (n=37), and undifferentiated arthritis (n=62) were combined and classified according to their ANA status as follows: 711 (73.2%) were ANA positive, 149 (15.5%) were ANA negative, and 111 (11.4%) had a doubtful ANA status. Patients with a doubtful ANA status were excluded from the analysis. The number of ANA determinations per patient in the 860 patients who had the ANA status specified ranged from 2 to 20 (mean 5.4); the total number of determinations was 4610. All ANA-positive patients were similar in terms of age at disease presentation, female-to-male ratio, and frequency of asymmetric arthritis and iridocyclitis. Compared with ANA-positive patients, ANA-negative patients were older at disease presentation and had a lesser female prevalence, a lower frequency of iridocyclitis and asymmetric arthritis, a greater number of affected joints over time, and a different pattern of arthritis. The close relationship between the presence of ANA and younger age at disease presentation, female predilection, asymmetric arthritis, and development of iridocyclitis was confirmed by multivariate, multiple correspondence, and cluster analysis. The figure shows the 2-dimensional scatterplot of multiple correspondence analysis.

This analysis led to the identification of 2 patient groups with distinct characteristics: the circle identifies the interrelated variables that define the ANA-positive patient profile.

**Conclusion:** Our findings substantiate the hypothesis that ANA-positive patients classified into different JIA categories by current ILAR criteria constitute a homogeneous patient population, irrespective of the course of joint disease or the presence of psoriatic features.

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**Are They Ready for Adult Care? An Assessment of Variables Affecting Patient Autonomy When Transitioning from Pediatric to Adult Rheumatology.** Sharon E. Banks1, Catherine A. Bingham1 and Brandt P. Grohl.1 Hershey Medical Center, Zionsville, PA, 2Hershey Medical Center, Hershey, PA, 3Hershey Medical Center

**Background:** Transition from a pediatric to adult provider is often difficult for pediatric rheumatology patients and their families. Currently there are no criteria used to determine whom or when to transition. Physicians expect the adolescent to become motivated to be medically independent in caring for his/her own disease without parental influence. However, many adolescents are not ready to assume this role causing a lapse in medical care. We sought to identify factors which, when present, might lead to increased autonomy. Identification of these factors could be used in the clinic to determine which patients would make a more successful transition.

**Methods:** 69 pediatric and young adult rheumatology patients between the ages of 14 and 21 were surveyed independently without parental input. Information was collected by questionnaire that consisted of two types of questions. **Independence questions** included whom the patient would contact in case of worsening disease, medication refills, medical emergencies, missed appointments, and to make an appointment. **Life skills questions** included whether the patient ever had a summer job, a drivers license, current grades, scholastic level achieved, and family income. Data was analyzed to see if there was any correlation between an individual’s response to independence questions and his/her response to life skills questions. Significance was determined using Chi-square statistics and Fishers exact test where applicable. Statistically significant or near significant correlations are shown in the table below.
Results:

<table>
<thead>
<tr>
<th>Life skill question</th>
<th>Independence question</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher scores in school</td>
<td>Take meds without a reminder from parents</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Take meds which require laboratory monitoring</td>
<td>Parents give the meds</td>
<td>P = 0.07</td>
</tr>
<tr>
<td>Male gender</td>
<td>Likely to call doctor, not parent, if feel sick</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Take meds daily</td>
<td>Parent (not adolescent) phones doctor for emergency</td>
<td>P = 0.07</td>
</tr>
<tr>
<td>Increased household income</td>
<td>Parent makes doctor appointment</td>
<td>P = 0.09</td>
</tr>
<tr>
<td>Increased household income</td>
<td>Parent calls doctor for disease flare</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Increased household income</td>
<td>Parent cancels doctor appointment</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>College level</td>
<td>Cancel own doctor appointment</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Have summer job</td>
<td>Give self meds</td>
<td>P = 0.04</td>
</tr>
<tr>
<td>Have summer job</td>
<td>Call doctor (not parent) if disease flares</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Have a drivers license</td>
<td>Call doctor (not parent) if run out of meds</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Have drivers license</td>
<td>Make own doctor appointment</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Have drivers license</td>
<td>Give self meds</td>
<td>P = 0.09</td>
</tr>
</tbody>
</table>

Conclusions: Higher scores in school, college enrollment, having a summer job, and a drivers license all contributed to independence in medical care. Higher family income, taking medications which require lab monitoring, and taking medications daily were associated with less independence. Physicians could assess this information to determine which patients may need more preparation for transition to adult rheumatology versus those ready to transition.

Disclosure: S. E. Banks: None; C. A. Bingham: None; B. P. Groh: None.

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Assessment of Activity in Children with Enthesitis Related Arthritis Using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Background: Enthesitis related Arthritis (ERA), as defined by ILAR criteria, is characterized by involvement of entheses and peripheral joints; axial skeleton is affected in some patients The clinical spectrum of ERA overlaps with that of spondyloarthritis. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a score designed to determine the degree of activity in patients with Ankylosing Spondylitis. Its value as an outcome measure in children with ERA has not been tested.

Purpose: To assess disease activity using BASDAI in children with ERA. To correlate BASDAI score with disease activity markers.

Methods: Cross Sectional observational-descriptive study. Consecutive patients with ERA were included. Variables recorded were: presence of axial involvement [AI] (spinal pain and reduced spinal mobility or chest expansion), enthesitis, HLA-B27, number of active joints, number of joints with reduced mobility, duration of stiffness, ESR, physician’s global evaluation of activity (phy) [0–3], patient’s assessment of well-being (p) [0–3] and pain [0–3] measured on a 10 cm visual analogue scale (VAS), BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI) and CHAQ scores.

BASDAI score was administrated by a pediatric rheumatologist (MK) and answered by children (3–15) years. AI: 47%. Enthesitis: 57%. Presence of HLA-B27: 42%; # active joints: 2 (0–14) [median, range]; # joints with reduced mobility: 2 (0–12); duration of stiffness: 15 (0–180) minutes; Schöber test: 45 (2–7) cm; ESR = 2 (15–110) mm/h; phy VAS: 0.35 (0–1.9); pVAS: 0.48 (0–2.62); pain VAS: 0.41 (0–2.43). BASDAI >0 was recorded in 43 (86%) patients. Median BASDAI score: 1.90 (0–7.50). BASDAI correlated with: pVAS (r: 0.67; p<0.003), duration of stiffness (r: 0.65; p=0.004), phy VAS (r: 0.63; p=0.005) and ESR (r: 0.56; p=0.01). Patients with AI showed higher BASDAI score than patients with peripheral involvement. (median BASDAI score: 2.6 vs 1.7). BASDAI score corresponding to patients with AI strongly correlated with: duration of stiffness (r: 0.86; p=0.006); ESR (r: 0.86; p=0.01); phy VAS (r: 0.82; p=0.01).

Conclusion: BASDAI showed correlation with certain activity disease markers, especially in patients with AI. BASDAI score ranged in the low-medium spectrum of the scale. BASDAI should be included as a useful outcome measure in the assessment of activity in children with ERA.

Disclosure: M. M. Katsicas: None; R. A. G. Russo: None.

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Timothy Beukelman1, Timothy Beukelman2, Peter Waite2 and Randy Q. Cron1. 1Children’s Hospital of Alabama, Birmingham, AL, 2Univ of Alabama-Birmingham, 3University of Alabama-Birmingham, Birmingham, AL

Background: Temporomandibular joint (TMJ) arthritis in juvenile idiopathic arthritis (JIA) is often asymptomatic and leads to joint destruction and micrognathia. MRI is the most sensitive tool at detecting TMJ arthritis in JIA patients, with prevalence rates ranging from 63–81%. Intra-articular corticosteroid injections (IACSi) of the TMJ under CT or ultrasound guidance are reported to reduce effusion and increase maximal-incisal opening (MIO) in JIA. Herein, MRI was used to determine the prevalence of TMJ arthritis among all subtypes of a large cohort of JIA patients. The efficacy and safety of delivering TMJ IACSi under anesthesia by an oral and maxillofacial (OMF) surgeon without the need for prolonged sedation and image guidance was evaluated.

Methods: A retrospective chart review of 192 patients diagnosed with JIA (ILAR revised criteria) seen at a single children’s hospital between January 2008 and June 2010 was executed. MRI with contrast using a TMJ surface coil was performed and read by experienced pediatric radiologists. Sixty-three patients diagnosed by MRI underwent IACSi (0.5 ml of Aristospan per TMJ) by OMF surgery. Data collected included age, JIA subtype, age at diagnosis, immunosuppressive therapy, prior, MIO pre- and post-IACSi, changes on MRI, post-IACSi complications, and TMJ arthritis symptoms.

Results: MRI evidence of acute and/or chronic TMJ arthritis was noted in 46%. Of those with TMJ arthritis, 85% and 79% had received methylxatre and anti-cytokine (TNF or IL-1) therapy, respectively. All 7 JIA subtypes had relatively similar rates of TMJ arthritis (range, 40–57%). Forty-six (48%) of 95 patients with data available had MIO below mean values in age-matched normal subjects, and this was up to 61% (33 of 54 patients) in the population of patients diagnosed with TMJ arthritis and available data. Forty-two (47%) of 89 patients diagnosed with TMJ arthritis reported TMJ symptoms, particularly among 11–19-year-olds (74%). Sixty-three recorded TMJ IACSi; 66% showed MIO improvement, 27% decreased, and 7% no change. Post-IACSi MRI completed an average of 6 months post-injection (range 1.5 to 13 months) revealed improvement in 51% of patients (greatest improved opening in the systemic subtype), worsening in 34% of patients, and no change in 15% of patients. 21% reported improvement or symptom relief after IACSi. Only 3 patients (5%) reported post-TMJ IACSi complications, including localized swelling in 2, and 1 injection site hypopigmentation 10 months post-IACSi.

Conclusion: The prevalence of TMJ arthritis (46%) in this large JIA cohort was less than predicted but still substantial. Interestingly, all 7 JIA subtypes were roughly equally involved suggesting screening by MRI for TMJ arthritis in all JIA patients. No subtype had a notably worse response to TMJ IACSi, but the biggest MIO increase was in the oligoarticular subset. When using post-IACSi MRI data, similar outcomes are noted in this large JIA cohort compared to prior studies. Moreover, there is a higher frequency of MIO improvement than prior reports. Thus, TMJ IACSi by OMF surgery is similarly effective and safe as studies using radiographic guidance.

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Cancer Risk in Juvenile Idiopathic Arthritis. Sasha R. Bernatsky1, Ann E. Clarke2, Kiern G. Oen3, Ciaran M. Duffy4, Alan M. Rosenberg5, Jeremy Labrecque6, Elizabeth M. Turnbull7, Jennifer L. F. Lee1 and Rosalind Ramsey-Goldman8. 1McGill UHC/RVH, Montreal, QC, Canada, 2McGill University, Montreal, QC, Canada, 3McGill University Health Ctr, Montreal, QC, Canada, 4Montreal Children's Hospital, Montreal, QC, Canada, 5Montreal General Hospital, Montreal, QC, Canada, 6Northwestern University, Chicago, IL, 7RI McGill Univ Health Ctr, Montreal, QC, Canada, 8Royal Univ Hosp, Saskatoon, SK, Canada, 9University of Manitoba, Winnipeg, MB, Canada

Purpose: There is considerable interest in the increased risk of malignancy in adult rheumatoid arthritis, particularly for lymphoma and lung cancer. However, to date there are few assessments specifically in juvenile idiopathic arthritis (JIA). Our objectives thus were to assess the observed malignancy incidence in JIA, and compare this to the expected incidence, based on general population cancer data.

Methods: We examined cancer occurrence within JIA registries at three Canadian pediatric rheumatology centers. The subjects in the clinic registries were linked to regional tumor registries to determine the occurrence of invasive cancers over the observational interval (spanning 1974–2006). The total number of cancers expected was determined by multiplying the person-years in the cohort by age, sex, and calendar year-specific cancer rates. The standardized incidence ratio (SIR, ratio of cancers observed to expected) was generated, with 95% confidence intervals.

Results: The study sample was comprised of 1,834 patients. The female proportion was 67.6%; average age at cohort entry was 8.6 years (standard deviation, SD = 5.1). The majority of cohort members were Caucasian. Subjects contributed 22,341 patient-years (average 12.2, SD = 7.8). Within this observation interval, one invasive cancer occurred, compared to 7.9 expected (SIR 0.12, 95% CI 0.0, 0.70). This was a haematological cancer (Hodgkin lymphoma), representing a SIR for haematological malignancies of 0.76 (95% CI 0.02, 4.21).

Conclusion: Only one invasive cancer was demonstrated in this large sample of individuals with JIA, observed for an average of 12.2 years each. These data suggest that, at least in the initial years following JIA diagnosis, the risk of invasive cancers over-all is not markedly increased. However, the results do not rule out the possibility of a baseline increased risk of haematological malignancies. Potential limitations include the small number of specific minorities (e.g. blacks, Asians, Hispanics, etc.) and the difficulty in identifying risk related to specific JIA subtypes. A larger multi-center, multi-ethnic cohort study is underway, to provide more precise results for specific cancer types, and additional years of long-term follow-up.


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Childhood Idiopathic Chondrolysis: A Form of Monoarthropathy? Rafa Chaiban1 and Robert P. Sundel2. 1Children's Hospital Boston, Boston, MA, 2Children Hosp Medical Center, Boston, MA

Background: Childhood idiopathic chondrolysis of the hip is a condition characterized by substantial destruction of the articular cartilage without an identifiable cause. The incidence of this entity is low, and few pediatric cases have been reported in the literature.

Objectives: We sought to identify cases of idiopathic chondrolysis and determine whether modern diagnostic techniques offered a clearer etiopathologic explanation for this condition.

Methods: A retrospective review of all children diagnosed and treated for chondrolysis of the hip since 1988 at a single tertiary care children's hospital was conducted. Subjects were identified from a search of clinic and hospital admissions for cartilage abnormalities. Patients with no definite etiology (idiopathic) were picked for further review. Demographic data, clinical presentation and treatment were studied. Diagnostic imaging and procedures were also noted.

Results: A total of 224 patients with chondrolysis of the hip were found. Of these, seven had no known etiology (idiopathic chondrolysis of the hip). All seven patients had negative serum inflammatory markers and rheumatologic evaluation (including HLA-B27, ANA, RF). Synovial biopsy showed non-specific inflammatory changes with negative cultures for infectious organisms. Three patients were evaluated by rheumatology at the time of hospitalization for synovial biopsy, and were found to have a psoriasiform rash, dactylitis, nail pitting, or other signs of psoriatic arthritis. Two more patients had a positive family history of RA. Patients were treated for presumed inflammatory arthritis with intra-articular steroids, methotrexate, pulsed-dose methylprednisolone, and TNF inhibitors. All patients improved rapidly, and four who have been followed for a range of 4–6 years have remained well, without recurrence or progression of their chondrolysis. No patient has required joint replacement.

Conclusions: In a series of seven children at a single children's hospital diagnosed with idiopathic chondrolysis, clinical features and response to treatment were consistent with psoriatic arthritis or JIA. Aggressive therapy resulted in excellent clinical outcomes. The possibility that idiopathic chondrolysis might represent an unusually aggressive form of seronegative mono-arthritis should be considered in such patients.

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Clinical Outcomes after Withdrawal of Anti-Tumor Necrosis Factor-Alpha Therapy in Juvenile Idiopathic Arthritis: A Twelve-Year Experience. Kevin W. Baszis2, Dana Toib2, Richard Brasington1, Allison King1, Jinning Mao1, Andrew J. White2, Jane Garbutt1 and Anthony R. French1. 1Washington Unv Schl of Med, St Louis, MO, 2Washington University School of Medicine, Department of Pediatrics, St Louis, MO, 3Washington University School of Medicine, Department of Pediatrics

Objective: To determine length of time to flare and likelihood of clinical remission after discontinuation of tumor necrosis factor-alpha (TNF-α) blockers in patients with juvenile idiopathic arthritis (JIA).

Methods: This is a retrospective cohort review of 241 patients with JIA treated with TNF-α inhibitors at our center between January 1, 1998, and November 1, 2009. Primary outcomes were time to flare after withdrawal of TNF-α inhibitor and proportion of treatment episodes resulting in clinical remission after cessation of anti-TNF-α therapy. Time points of interest were based on preliminary criteria for inactive disease and remission in JIA. Inactive disease (ID) is defined by no active arthritis/uveitis, no systemic symptoms or elevated ESR/CRP attributable to JIA, and physician global assessment indicating no disease activity. Clinical remission on medication (CRM) is defined by ID for 6 months, on medication. Clinical remission (CR) is defined by ID for 12 months while off all anti-arthritis/uveitis medications. For our purposes, patients were not excluded if remaining on anti-rheumatic drugs after stopping anti-TNF-α therapy, but any further use of corticosteroids or biologic agents was cause for exclusion. Descriptive statistics, survival analyses, and hazard ratios were calculated.

Results: One hundred seventy-one patients met inclusion criteria, yielding 255 discrete episodes of anti-TNF-α treatment. Two hundred thirty-three (93.5%) episodes resulted in ID; 127 (49.8%) episodes achieved CRM. After cessation of anti-TNF-α therapy in patients with ID, 50% of episodes remained in ID at 6 months, and 32% of episodes achieved CR off of anti-TNF-α therapy.
The median duration of anti-TNF-α therapy after ID was obtained was 6.1 months; there was no correlation between this duration and time to flare \( r = 0.01, p = 0.91 \). Using hazard ratios and covariate analysis, subtype of JIA, sex, and age at diagnosis did not significantly affect risk of relapse. Median patient observation was 59.7 months.

**Conclusion:** In 171 patients with JIA achieving inactive disease on TNF-α inhibitors, 50% remained in remission at 6 months and 33% at one year. Results did not significantly vary by JIA subtype, sex, age at diagnosis, or duration of therapy. Although these results support the observation that JIA is a chronic relapsing/remitting disease, they suggest that one-third of patients can be successfully withdrawn from TNF-α antagonists for at least one year and be spared the cost and potential morbidity of treatment. Further studies are needed to identify predictive factors for those patients who successfully obtain clinical remission after anti-TNF-α cessation.

**References:**

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**Contribution of TNFα–308 and T676G TNF-RII Polymorphism to Response to Etanercept and Possibility to Discontinue Treatment.** Jelena Vojinovic1, Gordana Susić1, Jelena Basić2, Dragana Lazarević3 and Nemanja Damjanov3. 1Dept Ped Rheumatology, University Clinic Center Nis, Nis, Serbia, 2Institute of Biochemistry Faculty of Medicine Nis, Nis, Serbia, 3Institute of Rheumatology Belgrade, Belgrade, Serbia

**Background:** Genetic contribution of TNFα–308 promoter and T676G TNF-RII polymorphism on response to TNF-blocking agents in JIA is not yet well established. Primary endpoint of this study was to evaluate influence of these promoter polymorphisms, as biomarkers, in JIA patients treated with etanercept, on clinical outcome and possibility to discontinue treatment.

**Methods:** Genomic DNA was extracted and TNFα–308 promoter and T676G TNF-RII polymorphism was evaluated using the PCR-RFLP method in 60 JIA patients treated with etanercept, included in Serbian JIA registry who donated blood samples. Time cut of point for outcome data analysis was 4 years after first drug dose.

**Results:** At enrolment JIA patients mean age was 14.7±2.22, disease duration 6.59±2.76, average dose of MTX 11.91±6.68 mg/m2/week. Average duration of etanercept therapy was 34.6±12.11 months. Disease subtype distribution was 6.78% systemic, 54.24% polyRF- and extended oligo, 18.64% polyRF+ on 16.95% ERA and 3.38 Pa. The distribution of TNFα–308 and T676G genotypes was not significantly different among JIA subtypes. TNFα–308 genotypes distribution was 6.78% AA, 30.51% GG and 62.71% GA while T676G genotypes were 59.3% TT, 8.3% GG and 26.4% TG. T676G genotypic polymorphism did not significantly influence outcome. ACR Pedi 30,50,70 and 100 improvement was significantly faster and be spared the cost and potential morbidity of treatment. Further studies are needed to identify predictive factors for those patients who successfully obtain clinical remission after anti-TNF-α cessation.

**References:**

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**Effectiveness of Dexamethasone Iontophoresis in Temporomandibular Joint (TMJ)-Arthritis in Juvenile Idiopathic Arthritis (JIA).** Rina Mina1, Paula G. Melson2, Stephanie Powell3, ClaaS H. Hinze4, Joshua Penn5, Thomas B. Graham6 and Hermine I. Brunner7. 1Children’s National Medical Center, Rockville, MD, 2Cincinnati Children’s Hosp Medical Ctr, Cincinnati, OH, 3Cincinnati Children’s Hospital Medical Ctr, Cincinnati, OH, 4Cincinnati Children’s Med Ctr, Cincinnati, OH, 5Vanderbilt Children’s Hospital, Nashville, TN

**Background:** TMJ-arthritis is common in JIA and the best treatment approach is unknown. The effectiveness of dexamethasone iontophoresis, a non-invasive method of transdermal steroid administration, has not been evaluated for TMJ-arthritis in JIA.

**Objective:** Evaluate the effectiveness of dexamethasone iontophoresis for the treatment of TMJ-arthritis in JIA.

**Methods:** Medical records of all JIA patients who underwent TMJ iontophoresis at Cincinnati Children’s Hospital from 1997–2010 were reviewed. Effectiveness was assessed by comparing primary outcomes (i.e. inter-incisor distance and lateral translation) and secondary outcomes (pain, clicking and crepitus) before and after treatment using two-sided paired t-test.

**Results:** There were 28 JIA patients (all subtypes; median age ± IQR = 12 ± 8 years) who received TMJ iontophoresis. At baseline (median ± IQR) the number of active joints was 3 ± 4 and ESR was 5 ± 7. Medications included methotrexate (29%) and biologics (25%) with no clinically relevant medication-change during the treatment period. Iontophoresis was done using a standard dose of dexamethasone (6 mg) per TMJ per session (average number of sessions = 8, 45% bilateral). Statistically significant improvement was observed in the inter-incisor distance and right lateral translation (see Table). Improvement in TMJ pain (70%), clicking (80%) and crepitus (40%) were noted in those who initially presented with these findings. Side effects reported were transient and included site erythema (46%) and metallic taste (27%). Imaging with MRI was available only in select number of patients and thus not useful as study endpoint.

**Conclusion:** Dexamethasone iontophoresis appears to be effective in the management of TMJ-arthritis in JIA. Because of its ease of use and relative lack of side effects, it may be a good initial therapy for TMJ-arthritis and thus warrants prospective evaluation with focus on durability of response, imaging outcomes and optimization of treatment protocol.

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**Effectiveness of Etanercept in Juvenile Psoriatic Arthritis and in Children with Enthesitis Related Arthritis.** Marije H. Otten1, Femke H. M. Princen2, Marinka Twilt1, Nico M. Wulfraat3, Rebecca ten Cate2, Esther P. A. H. Hoppenreijis4, Yvonne Koopman-Keemink5, Simone L. W. van Rossum6 and Lisette W. A. van Suijlekom-Smit7. 1Academic Medical Centre Emma Children’s Hospital and Jan van Breemen Institute Maastricht, 2Erasmus MC Rotterdam, 3Erasmus MC Sophia Children’s Hospital Rotterdam, Rotterdam, The Netherlands, 4Erasmus MC Children’s Hospital Rotterdam, The Netherlands, 5Haga Ziekenhuis Juliana Children’s Hospital The Hague, 6Leiden University Medical Centre, 7St Lucas Andreas Hospital and Jan van Breemen Institute Amsterdam

**Background:** TMJ arthrosis is a chronic inflammatory disease that involves pain, limited mouth opening, and click and grating sounds. Dexamethasone Iontophoresis for TMJ arthrosis in JIA has been demonstrated to be effective, but this data is difficult to interpret due to limited evidence and clinical heterogeneity. Therefore, a comprehensive review is needed to evaluate the effectiveness of iontophoresis in TMJ arthrosis in JIA.

**Objective:** To evaluate the effectiveness of dexamethasone iontophoresis for the treatment of TMJ arthrosis in JIA.

**Methods:** A comprehensive literature search was conducted using PubMed, EMBASE, and Cochrane CENTRAL. Studies were included if they reported outcomes related to TMJ arthrosis in JIA and compared iontophoresis with another treatment. A total of 13 studies were included in this review.

**Results:** The results showed that dexamethasone iontophoresis was effective in reducing pain, improving mouth opening, and decreasing click and grating sounds in TMJ arthrosis in JIA. The effectiveness was comparable to other treatments, such as steroids and physical therapy, but there was a lack of evidence for long-term effectiveness.

**Conclusion:** Dexamethasone iontophoresis is an effective treatment for TMJ arthrosis in JIA. Further studies are needed to evaluate its long-term effectiveness and compare it with other treatments.

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Background: Etanercept (ETN) has proven to be effective in children with systemic and polyarticular Juvenile Idiopathic Arthritis (JIA). Experience with ETN in the treatment of Juvenile Psoriatic Arthritis (JPsA) and Enthesitis Related Arthritis (ERA) subtypes is limited. We therefore explored the effectiveness of ETN in these subtypes.

Methods: This study is embedded in the ABC-register, a since 1999 prospective ongoing multicentre, observational study of all Dutch JIA patients using biological agents. Patient and disease characteristics are collected at baseline. At start of treatment, after 3, 6, 15 months and thereafter yearly variables of the JIA disease activity score; physician’s global (VAS), Childhood Health Assessment Questionnaire (CHAQ), including global assessment of wellbeing (VAS), number of active and limited joints and ESR, are retrieved. Response was assessed by the ACR pediatric criteria, and Wallace criteria for inactive disease. We collected additional data regarding the diagnostic ILAR criteria for JPsA and ERA.

Results: Our register includes 17 JPsA and 14 ERA patients treated with ETN.

JPsA patient characteristics: 71% female, median age at onset 11.0 (range 3.3–13.3) years, 47% with psoriatic skin lesions, 41% nail psoriasis, and 24% dactylitis. Median follow-up since start etanercept of 26 (range 3–62) months.

ERA patient characteristics: 79% male, median age at onset 10.4 (range 2.3–17.0) years, presence of enthesitis in 86%, SI-joint tenderness and/or inflammatory lumbosacral pain in 57%, and HLA-B27 positivity in 79%. Median follow-up since start etanercept of 46 (range 6–110) months.

After 3 months of treatment 82% of JPsA and 86% of ERA patients achieved ACRPed30 response, increasing after 15 months to 100% and 91% resp. Of the JPsA patients reaching 39 months of follow-up (n=6) 67% achieved inactive disease and of the ERA patients (n=4) 50% (Figure 1).

In only 4 of the 8 patients with pre-existing psoriasis the skin lesions improved. Two JPsA patients and 2 additional JIA patients with other subtypes from our register developed de novo psoriasis during ETN treatment.

In both subtypes there was no ETN discontinuation because of inefficacy. Six JPsA patients and 1 ERA patient discontinued treatment after good clinical response. However, all except 1 JPsA patient flared again. They all restarted treatment with good clinical response.

Conclusion: We showed that ETN is very effective to treat the arthritis in the JPsA and ERA subtypes, with more than 90% achieving ACRPed30 response after 15 months of treatment. However the psoriatic skin lesions did not respond well and de novo psoriatic skin lesions occurred in JPsA patients and in patients with other JIA subtypes during ETN treatment. In most patients the arthritis flared after discontinuation of treatment, emphasizing the need to investigate optimal duration of therapy.

Figure 1. Improvement and inactive disease based on an intention-to-treat modus. Shown are percentages of JPsA and ERA patients that met the criteria for the ACR Pedi 30, 50 and 70 and inactive disease compared to all JIA subtypes and all non-systemic JIA subtypes (i.e. subtypes other than systemic JIA), as published from our register in 2009.

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Efficacy and Safety of Oral and Parenteral Methotrexate Therapy in Children with Juvenile Idiopathic Arthritis. Gerd Hornn2, Gerd Ganser, Ivan Foeldvari1, Andreas Urban and Ariane Klein. 1Harburg, Germany, 2Asklepios Clinic Sankt Augustin, Germany

Background: Methotrexate is widely used as first-line disease-modifying antirheumatic drug in juvenile idiopathic arthritis (JIA). Both, oral and parenteral administrations have been shown to be effective.

Methods: In the German Methotrexate Registry data concerning efficacy and safety of methotrexate treatment are collected since 2005. In a retrospective analysis we compared oral and parental methotrexate treatment regarding efficacy, adverse events and rate of and reasons for discontinuation of treatment.

Results: Between 2005 and 2009 1066 JIA patients were documented in whom treatment with methotrexate has been initiated. 612 patients received methotrexate for at least 6 months, 3 patients had to be excluded because of concomitant treatment with biologics and 198 who changed the mode of application. 259 patients (63%) received oral (0.42+/−0.24mg/kg) and 152 patients (37%) parenteral (0.43+/−0.15mg/kg) methotrexate. At start of treatment patients of the two groups did not differ in numbers for active joints, joints with limited range of motion, CHAQ score, duration of disease, MTX dosage and concomitant steroid therapy. At 6 months, comparable numbers of patients treated orally or parenterally showed a PedACR 30, 50 and 70 response (oral 75.6%/68.8%/52.8% and s.c. 76.1%/72.1%/54.4%).

In the evaluated group 151 adverse events (AE) were reported, 76 in the group of 259 patients with oral (0.3/ patient) and 75 in 152 patients with parenteral MTX (0.44/patient). Gastrointestinal AEs (40 and 25) being the most frequent, followed by infections (10 and 12) and elevated liver enzymes (7 and 8).

10 patients in the oral group and 9 patients in the parenteral group discontinued methotrexate treatment during the first 6 months of treatment. Until last observation, significantly more patients with parenteral application discontinued methotrexate because of adverse events (11 of 152 versus 6 of 259, p = 0.016). However, significantly more patients in the oral group received folinic acid (46.7%/ vs. 31.6%, p-value = 0.001).

Conclusion: In this parent group parenteral administration of methotrexate was not superior to oral administration regarding efficacy and tolerability. JIA patients treated with methotrexate did not show significantly different PedACR responses whether they received oral or parenteral MTX. These results could not argue for a possibly painful and more expensive administration mode of methotrexate especially in younger children until controlled, randomised prospective studies have been performed.


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Electronic Medical Record (EMR) Entries Can Provide a Source for Quality Improvement Projects for Juvenile Idiopathic Arthritis (JIA): Results of a Pilot Study. Michael L. Miller1, Jason Rumprecht1, George Lales, Michael L. Miller2, Jason Ruprecht1, George Lales, 1Childrens Memorial Hospital, Chicago, IL

Although EMRs have facilitated care for children with juvenile idiopathic arthritis, relevant quality improvement projects have required use of paper or manual re-entry of clinical data. To establish continuous, periodic QI activities tracking care of JIA patients, we have started EMR discrete data
entry for joint examination and related clinical parameters. This IRB approved pilot study reports successful data extraction from our EMR to Xenobase™, an application permitting cohort analysis of a clinic JIA population, stratified by disease subtype and disease severity.

Methods: During clinic visits, starting March, 2010, data were entered into flow sheet rows in EpicCare™ (Epic Systems, Verona, WI), extracted every 2 weeks, using Clarity Reports, as de-identified data. Data were de-identified and uploaded to Xenobase™. Parameters included detailed joint examination, ILAR diagnosis, MD disease activity assessment (10 = very active), Patient/Parent global assessment (10 = very good), Pain Score (10 = most severe).

Results: Data on 175 patients with JIA seen from March-May, 2010 were extracted from EMR records and analyzed in Xenobase™. Number, age, and gender distribution were: oligo (64; 52 females; 10.3 yrs); extended oligo (28; 23 females; 11.3 yrs); poly (39; 32 females; 11.8 yrs); psoriatic (13; 11 females; 12.7 yrs); psoriatic spondylitis (8; 4 females; 13.6 yrs); systemic (18; 7 females; 11.1 ± 3.9yrs); enthesitis (19; 10 females; 16.1 ± 8yrs); psoriatic (3; 2 females; 13.0 ± 4.5yrs). Patient Global assessment showed weak correlation with joint counts in active polyarticular JIA, RF positive and negative (r = 0.409), but in no other group. Conclusions: Data extraction from the EMR is feasible and useful to track JIA patients for QI projects. In this pilot study, we found data accurately reflected distribution of age, gender, and numbers typically seen in pediatric rheumatology clinics. Further data extraction and analyses (IRB approved) will compare longitudinal response to treatment. This approach may be helpful in contributing data to national disease registries.

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Gut Inflammation in Pediatric Spondyloarthritis. Matthew Stoll², Mari-lynn G. Punaro¹ and Molly Dempsey-Robertson¹. ¹Texas Scottish Rite Hospital for Children, ²UT Southwestern Med Ctr, Dallas, TX, ³UT Southwestern Medical Ctr, Dallas, TX

Purpose: Sub-clinical gut inflammation has been identified in two-thirds of adult spondyloarthritis (SpA) patients. Similar findings were observed in a study of 12 pediatric SpA patients. These studies used colonoscopy, an expensive and invasive test not well-suited for routine use in research studies. Although non-invasive tests have been studied in patients with inflammatory bowel disease (IBD), they have not been used to evaluate for sub-clinical gut inflammation among SpA patients. Our intention in this study is to evaluate whether non-invasive tests can detect gut inflammation in pediatric SpA patients.

Methods: Stool samples were obtained from children with active juvenile idiopathic arthritis (JIA). Calprotectin levels were assayed in a commercial lab (ARUP). Children with elevated calprotectin (calp) levels were offered an MRI of the intestines. Flavored sports drink containing polyethylene glycol (PEG) 3350 was used as oral contrast. Glucagon was used to arrest peristalsis. Patients were imaged in the prone position on a 1.5-T scanner. Heavily T2-weighted fat-suppressed coronal and axial images using breath-hold technique were obtained, followed by post-gadolinium fat-suppressed T1-weighted gradient echo images.

Results: Results are available on 7 children with enthesitis-related arthritis (ERA) and 5 controls with oligo-arthritic (n = 3) or poly-arthritic (n = 2) JIA. 3 of the ERA patients and none of the controls reported mild gastrointestinal (GI) symptoms. Median faecal calp levels were 171 in the ERA patients, compared to 37 in the controls (p = 0.0073; Figure 1.) The presence of GI symptoms was not associated with calp levels among ERA patients (median levels 210 in those without GI symptoms, versus 125 in those with complaints, p = 0.480). Two of the patients with abnormal calp levels underwent MRI of their intestines; one of them had evidence of terminal ileitis (Figure 2). Colonoscopy in this child was consistent with IBD primarily limited to the terminal ileum.

Figure 1. Calprotectin level in patients with ERA compared to patients with oligo-articular or poly-articular JIA.
Figure 2. Axial T1 fSPGR with fat saturation post contrast. Arrow indicates site of abnormal enhancement in terminal ileum.

Conclusions: Although preliminary, the data from this study suggest that non-invasive markers can be used to evaluate for sub-clinical gut inflammation in children with SpA. This may have both research and clinical implications.


Disclosure: M. Stoll: None; M. G. Punaro: None; M. Dempsey-Robertson: None.

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Immunogenicity and Short Term Safety of Pandemic Influenza Vaccine (Anti-H1N1) in Patients with Juvenile Idiopathic Arthritis. Nadia E. Aikawa1, Lucia M. A. Campos2, Clovis A. Silva1, Vanessa R. Guissas1, Adriana M. Salum2, Adriana A. Jesus1, Julio B. Moraes3, Cleonice Bueno1, Maria C. S. T. Timenetsky4, Alex R. Precioso1 and Claudia Goldenstein-Schambberg4. 1Adolpho Lutz Institute, University of Sao Paulo, 2Butantan Institute, 3Division of Rheumatology, Pediatric Reumatology Unit, Universidade de Sao Paulo, 4Division of Rheumatology, Universidade de Sao Paulo, 5Pediatric Reumatology Unit, Universidade de Sao Paulo

Purpose: To assess immunogenicity and safety of pandemic influenza vaccine (anti-H1N1) in patients with juvenile idiopathic arthritis (JIA).

Methods: 60 JIA patients and 55 age-matched healthy controls were vaccinated with cpea A/California/7/2009 (NYMC X-179A) anti-H1N1 vaccine. All participants received 1 dose of immunization, and those <9 yrs of age received a second dose 3 weeks apart. All subjects were evaluated before and 3 weeks after complete vaccination. Serology against H1N1 virus was performed by hemagglutination inhibition (HI) antibody (Ab) assay. Appropriate endpoints included the percentage of subjects achieving HI Ab titer \(\geq 1:40\) (seroprotection) and rates of seroconversion, defined as the percentage of subjects with either a pre-vaccination HI Ab titer \(<1:10\) and a minimum 4-fold rise in post-vaccination HI Ab titer. Demographic data, JIA onset subtype, disease duration, activity status, patient VAS and CHAQ score were analyzed. Post-vaccination adverse events (AEs) were searched. Fisher’s exact and Mann Whitney tests were used for statistical analysis considering \(p<0.05\) significant.

Results: Mean age of JIA patients and controls was 13.5±5.3yrs and 12.3±2.6yrs, \(p=0.08\); median JIA disease duration was 6.7±5.3yrs.

JIA subtypes were 48% polyarticular, 27% oligoarticular, 13% systemic and 12% others. Thirty seven patients (62%) were taking at least one DMARD and 17 (28%) were under biologic therapy (22% anti-TNF; 7% abatacept). Patient VAS, CHAQ score, ESR and CRP levels remained unchanged after immunization (\(p>0.05\)). Seroconversion rates against H1N1 influenza virus increased from 23 to 83% in JIA and from 22 to 95% in controls (\(p=0.08\)). Seroconversion rates were achieved in 78% JIA and 89% controls (\(p=0.14\)). Following vaccination, mean HI Ab titers ranged from 39±103 to 495±634 for patients and from 24±44 to 457±497 for controls (\(p=0.44\)). Seroprotection, seroconversion and mean HI Ab titers were not associated to use of DMARDs and/or biologic agents by JIA patients, although, mean HI Ab titer was significantly lower in patients <5yrs of age compared to those between 9–18yrs (217±354 vs. 628±723, \(p=0.016\)), notably, frequencies of MTX and DMARD use were higher in the former group (71% vs. 35%, \(p=0.03\) and 86% vs. 46%, \(p=0.01\), respectively). AEs were reported by 40% patients and 42% controls with rates of 2.4 AE/JIA patient and 1.6 AE/control. Most frequent AEs in patients and controls were local pain (23% vs. 29%, \(p=0.53\)), headache (18% vs. 18%, \(p=1.0\)), malaise (15% vs. 7%, \(p=0.24\)), myalgia (13% vs. 7%, \(p=0.37\)), arthralgia (13% vs. 2%, \(p=0.07\)) and fever (5% vs 3.6%, \(p=1.0\)).

Conclusions: Vaccination of JIA patients against pandemic influenza A (H1N1) generated successful protective antibody production with short term safety profile.

Disclosure: N. E. Aikawa: None; L. M. A. Campos: None; C. A. Silva: None; V. R. Guissa: None; A. M. Salum: None; A. A. Jesus: None; J. B. Moraes: None; C. Bueno: None; M. C. S. T. Timenetsky: None; A. R. Precioso: None; C. Goldenstein-Schambberg: None.

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Intra-rater Reliability of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) in Children with Spondyloarthritis. Michelle Battishill1, Alisa Rachlis, Berthu Wong, Samantha Stevens, Michelle Anderson, Brian M. Feldman1, Ronald M. Laxer1, Joanne Marcuz, Margaret Reaume, Lynn Spiegel, Kristi Whitney-Mahoney and Shirley M. L. Tse1, 1Toronto, ON, Canada, 2The Hospital for Sick Children, The University of Toronto, Toronto, ON, Canada

Background: Juvenile spondyloarthritis (JSpA), referred to as enthesis-related arthritis (ERA) sub-type under the International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis (JIA), is characterized by inflammation in the joints and entheses. Axial involvement is uncommon at presentation but may develop in the second decade of life. Several instruments assessing disease activity in ankylosing spondylitis have been validated including the BASDAI and BASFI. At this time, there are no disease activity scores for JSpA or ERA. The objective of this study is to measure the intra-rater reliability of the BASDAI and the BASFI in JSpA/ERA.

Methods: Patients diagnosed with ERA (ILAR criteria) and followed at The Hospital for Sick Children Spondyloarthritis Clinic were included in this study. Patients were excluded if they were unable to understand, speak or write English, if they were less than 6 years of age or greater than 18 years of age. Prospective subjects were consecutively enrolled (June 2009 to June 2010) and, the patient and/or one parent completed the BASDAI and BASFI at baseline and 2 weeks later (a period during which little change is expected). Intra-class correlation coefficient (ICC) was calculated and values greater than 0.6 were considered indicative of good reliability.

Results: Forty-eight patients (39 males, 81.2%) were enrolled. The average age at diagnosis was 12.5 years (range, 7.6 to 16.7 years). 41.7% were HLA-B27 positive, 18.8% had a positive family history for ankylosing spondylitis, 52% had involvement of the hip and 40% had radiographic evidence of sacroiliitis. Eight patients dropped out or were excluded due to protocol violation. 40 patients completed both sets of questionnaires. All subjects reported their overall health as “the same” when compared to their baseline visit. The mean BASDAI at baseline was 1.97 ± 1.90 and at 2 weeks was 1.69 ± 1.80 – the reliability was substantial; ICC = 0.74, Bland-Altman limits of agreement (LOA) = 2.4 to −2.8. The mean BASFI at baseline was 0.99 ± 1.49 and at 2 weeks was 0.75 ± 1.00 – likewise the reliability was excellent; ICC = 0.87, Bland-Altman LOA = 1.1 to −1.4. When examining individual questions from the BASDAI and BASFI, the following had the highest ICCs, respectively: “How long does your morning stiffness last from home or at work”, ICC = 0.88 each. Meanwhile, from the BASDAI, “How would you describe the overall level of AS neck, back or hip pain you have at home or at work”, ICC = 0.87, Bland-Altman LOA = 1.1 to −1.4. When examining individual questions from the BASDAI and BASFI, the following had the highest ICCs, respectively: “How long does your morning stiffness last from home or at work”, ICC = 0.88 each. Meanwhile, from the BASDAI, “How would you describe the overall level of AS neck, back or hip pain you have at home or at work”, ICC = 0.87, Bland-Altman LOA = 1.1 to −1.4. When examining individual questions from the BASDAI and BASFI, the following had the highest ICCs, respectively: “How long does your morning stiffness last from home or at work”, ICC = 0.88 each. Meanwhile, from the BASDAI, “How would you describe the overall level of AS neck, back or hip pain you have at home or at work”, ICC = 0.87, Bland-Altman LOA = 1.1 to −1.4.

Conclusions: There is no validated disease activity score for JSpA/ERA. Both the BASDAI and BASFI showed excellent intra-rater reliability in a cohort of ERA patients. Next steps will include the measurement of the construct validity and responsiveness of these tools in JSpA/ERA in order to determine if pediatric rheumatologists can use these as validated
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Juvenile Idiopathic Arthritis (JIA) Classification: An Audit of a Tertiary Paediatric Rheumatology Service’s Adherence to ILAR (Edmonton 2001) Classification Criteria. Angela J. Cox1, Sern Chin Lim2, Roger C. Allen3, Jonathan D. Akikusa4 and Jane Munro5. 1Royal Children’s Hospital, Melbourne, Victoria, Australia, 2Royal Children’s Hospital, Melbourne, Australia, 3Royal Children’s Hospital, Melbourne, Australia.

Background: The International League of Associations for Rheumatology (ILAR) classification criteria for Juvenile Idiopathic Arthritis are widely used in prospective and retrospective studies of chronic arthritis in childhood. They define seven subtypes of chronic arthritis based on strict inclusion and exclusion criteria involving both clinical and laboratory parameters, some of which may not appear relevant in certain clinical situations and therefore may not be tested for in daily practice. The inaccuracy in patient classification that this may produce could have a significant impact on the results of research conducted using such cohorts.

Aim: To determine whether patients newly diagnosed with JIA within a year at the Royal Children’s Hospital (RCH), Melbourne met strictly applied ILAR classification criteria for their assigned JIA subtype.

Methods: All newly diagnosed JIA patients seen in the Rheumatology Department at the RCH in 2009 were identified using the RCH rheumatology database. A retrospective review of the clinical and laboratory data collected for these patients was performed. The JIA subtype entered into the database for each patient was checked against ILAR classification inclusion and exclusion criteria. If they did not meet the designated subtype criteria or could not be classified because of incomplete data, the reason was recorded.

Results: 56 patients were included (35F, 21M). The diagnoses recorded in the database were Oligoarthritis 32 (57%), Polyarthritis 23 (41%), Septic arthritis 1 (2%), Systemic arthritis 1 (2%). 16 patients had insufficient information to allow classification using ILAR criteria. The second most common reason was an incompletely documented family history in 17 (30%) patients. If 7 (14%) patients who had not had a HLA-B27 performed or documented.

Conclusion: The strict application of the ILAR classification criteria for JIA requires information that may not be routinely collected in daily clinical practice. At our centre collection of all data required to classify children with chronic arthritis according to strictly applied ILAR criteria was uncommon, seen in less than 25% of patients. We suggest that for centres wishing to participate in research involving patients with JIA that a minimum dataset be devised and applied to all newly diagnosed JIA patients to enable accurate ILAR classification.

Disclosure: A. J. Cox: None; S. C. Lim: None; R. C. Allen: None; J. D. Akikusa: None; J. Munro: None.

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Long-Term Outcome of Patients with Juvenile Idiopathic Arthritis Treated with Etanercept – Results of the Biologic Register JuMBO. Kirsten Minden1, Martina Niewerth2, Angela E. Zink3, Eva Seipel4, Ivan Foeldvari5, Hermann Girschick6 and Gerd Hornett7. 1Asklepios Kinderklinik St. Augustin GmbH, 2German Arthritis Research Centre, Berlin, Germany, 3German Rheumatism Research Center Berlin, a Leibnitz Institute, Berlin, Germany, 4German Rheumatism Research Center Berlin, a Leibnitz Institute, 5Hamburger Zentrum für Kinder- und Jugendrheumatologie am Klinikum Eilbek, Hamburg, Germany, 6Immanuel Krankenhaus Berlin-Buch, Germany, 7Scientific Advisory Board

Purpose: To assess the outcome of patients with juvenile idiopathic arthritis (JIA) who received Etanercept in childhood.

Methods: JIA patients ≥ 18 years who were formerly included in the nation-wide child Etanercept/Methotrexate register were contacted and asked to participate in the prospective cohort study JuMBO (Juvenile arthritis Methotrexate/Biologics long-term Observation). For those included in JuMBO, clinical status, therapy, and patient-derived data, e.g. functional capacity, quality of life and socioeconomic status, were documented every 6 months. Here, data of the last available visit of patients included and treated with Etanercept at any time were analyzed.

Results: Until April 2010, 486 out of 645 (75%) patients could be relocated and contacted, 398 of them agreed to participate in JuMBO. Baseline or follow-up data were available for 285 patients ever treated with Etanercept. These patients had a mean age of 20 years (SD 2.8) and a mean disease duration of 11 years (SD 5.3). At last documentation more than 80% of the patients still received DMARDS, 58% Etanercept. Twenty four percent of the patients had an inactive disease, 45% reported no functional limitations (HAQ-score = 0). The patients rated their quality of life lower than age-matched controls, but only regarding physical functioning, vitality, bodily pain, general health, and physical role.

Three deaths occurred in this cohort, all patients died of complications connected to their rheumatic disease. Considering the years of observation of all patients contacted (2,320 patient-years), the calculated standardized mortality ratio was 6.2 (95% CI 1.04–20.48) for women and 1.4 (95% CI 0.12–11.6) for men.

Cormorbidities or serious adverse events reported over the observation period of 1,097 patient years included the following: three new-onset inflammatory bowel diseases of which two occurred under Etanercept, seven newly diagnosed uveitis cases (four in patients receiving Etanercept), and 16 medically important infections (1.5/100 patient-years). Only six of the serious infections occurred under Etanercept, one was an infection of an endoprosthetic device. No malignancy was recorded.

Conclusion: First data of the JuMBO register point to a better functional long-term outcome of patients with severe JIA treated in the biological era as compared to those treated before the year 2000. There seems to be an acceptable safety profile of Etanercept long-term use, however, more data are needed to confirm this.

Disclosure: K. Minden: Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Medac, 5, Wyeth Pharmaceuticals, 5; M. Niewerth: None; A. E. Zink: None; E. Seibel: None; I. Foeldvari: None; H. Girschick: None; G. Hornett: None.
polymarticular (26 active, 8 in remission on medication and 11 in remission off medication). The tables below show MRI findings according to JIA activity status and subtype of the disease.

<table>
<thead>
<tr>
<th>TMJ Synovial Enhancement</th>
<th>Active (n = 40)</th>
<th>Remission on medication (n = 20)</th>
<th>Remission off medication (n = 29)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>32</td>
<td>14</td>
<td>19</td>
<td>65</td>
</tr>
<tr>
<td>No</td>
<td>8</td>
<td>6</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>20</td>
<td>29</td>
<td>89</td>
</tr>
</tbody>
</table>

Conclusions: A large number (65%) of patients considered as being in remission off medication presented inflammatory TMJ alterations in MRI. Although synovial enhancement is considered the gold standard in assessing TMJ involvement, we should be cautious in interpreting this finding.

Disclosure: L. Zvir; None; S. Souza; None; M. T. Terreri; None; A S. Guimarães; None; A. Fernandes; None; M. O. Hilário; None.

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Methotrexate and Leflunomide Combination Therapy Is a Safe and Effective Alternative to Methotrexate and Etanercept in JIA. Arturo Borzutzky1, Tamy Lagunas2, David zurakowski2 and Robert P. Sundel3.

Introduction: Uveitis occurs in 10% of patients with juvenile idiopathic arthritis (JIA). Methotrexate (MTX) and corticosteroids (ST) appear to be an effective treatment for uveitis. We evaluated the occurrence of uveitis under different treatment combinations in the German Etanercept Registry.

Methods: We evaluated the prevalence of uveitis flares or new onset of uveitis in patients in the different treatment arms of the German Etanercept Registry.

Results: We reviewed the data of 868 patients. We grouped the patients in 8 therapy arms, these were: Etanercept (ETA) therapy (n = 74); ETA + glucocorticoids (ST) (n = 34); ETA + Methotrexate (MTX) (n = 246); ETA + MTX + ST (n = 290); ETA + other DMARDs (n = 45); ETA + other DMARDs + ST (n = 45); ETA + MTX + other DMARDs (n = 83); ETA + MTX + other DMARDs + ST (n = 102).

<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics of patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
</tr>
<tr>
<td>Female sex, %</td>
</tr>
<tr>
<td>Race (% white)</td>
</tr>
<tr>
<td>Diagnosis to combination therapy (months)</td>
</tr>
<tr>
<td>Duration of follow-up (months)</td>
</tr>
<tr>
<td>ILAR JIA diagnosis</td>
</tr>
<tr>
<td>Polymarticular (RF+)</td>
</tr>
<tr>
<td>Polymarticular (RF-)</td>
</tr>
<tr>
<td>Oligoarthritis</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
</tr>
<tr>
<td>Enthesitis related arthritis</td>
</tr>
<tr>
<td>Initial joint count, mean ± SD</td>
</tr>
<tr>
<td>Initial ESR, mean ± SD</td>
</tr>
</tbody>
</table>

Conclusion: A. Borzutzky; None; T. Lagunas; None; D. Zurakowski; None; R. P. Sundel; None.

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Methotrexate Gives Protection Against the New Onset of Uveitis in Combination with Etanercept. Data from the German Etanercept Registry,

Ivan Foeldvari1, Nina Thome2 and Gerd Horneff3. 1Hamburger Zentrum für Kinder- und Jugendrheumatologie, Hamburg, Germany; 2Kinder- und Jugendrheumatologie Asklepios Clinics, Sankt Augustin, Sant Augustin, Germany

Introduction: Uveitis occurs in 10% of patients with juvenile idiopathic arthritis (JIA). Methotrexate (MTX) and corticosteroids (ST) appear to be an effective treatment for uveitis. We evaluated the occurrence of uveitis under different treatment combinations in the German Etanercept Registry.

Methods: We reviewed the data of 868 patients. We grouped the patients in 8 therapy arms, these were: Etanercept (ETA) therapy (n = 74); ETA + glucocorticoids (ST) (n = 34); ETA + Methotrexate (MTX) (n = 246); ETA + MTX + ST (n = 290); ETA + other DMARDs (n = 45); ETA + other DMARDs + ST (n = 45); ETA + MTX + other DMARDs (n = 83); ETA + MTX + other DMARDs + ST (n = 102).

<table>
<thead>
<tr>
<th>Table 2. Number of patients, AE-Uveitis, Uveitis/Patient and Patient Treatment years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Etanercept (ETA)</td>
</tr>
<tr>
<td>ETA + Steroids</td>
</tr>
<tr>
<td>ETA + MTX</td>
</tr>
<tr>
<td>ETA + MTX + STs</td>
</tr>
<tr>
<td>ETA + other DMARD</td>
</tr>
<tr>
<td>ETA + MTX + other DMARD</td>
</tr>
<tr>
<td>ETA + MTX + other DMARD + STs</td>
</tr>
<tr>
<td>ETA + other DMARD + STs</td>
</tr>
<tr>
<td>All patients treated with Steroids</td>
</tr>
<tr>
<td>All patients treated with MTX</td>
</tr>
<tr>
<td>All patients treated with other DMARDs</td>
</tr>
<tr>
<td>All Patients</td>
</tr>
</tbody>
</table>

We evaluated the rate of uveitis per patient in the different groups. The lowest rate was found in the combination with MTX with ETA with 0.02. We evaluated the mean number of uveitis per 100 patient years and MTX + ETA group showed 0.9 compared to 3.5 for ETA monotherapy. ST in combination with ETA showed a protective effect too. Interestingly the other DMARDs did not have this protective effect of uveitis, the other DMARDs were mostly leflunomide or sulfasalazine.

Discussion: MTX and ST seems to be protective in this group of patients against the new onset of uveitis. Based on this data patients with a history of uveitis should receive a combination therapy of ETA and MTX to prevent flares of uveitis.

Disclosure: I. Foeldvari; Wyeth Pharmaceuticals, 5; N. Thome; None; G. Horneff; Wyeth Pharmaceuticals, 5.
Obesity and Disease Activity in Juvenile Idiopathic Arthritis. Christina F. Pelajo1, Jorge M. Lopez-Benzet2 and Laurie C. Miller1. Floating Hospital for Children at Tufts Medical Center, Boston, MA, 2Floating Hospital for Children at Tufts Medical Center

Background: Children with physical disabilities may have an increased risk of obesity. In adults, the odds of having arthritis, other than osteoarthritis, are 4.33 higher for the obese population, in comparison to the ideal weight population. Rates of obesity in patients with juvenile idiopathic arthritis (JIA) ranging from 5 to 16.7% have been reported. The aim of this study was to explore the relationship between obesity and disease activity in patients with JIA.

Methods: Body mass index (BMI) and disease activity were determined in 102 consecutive patients with JIA attending a pediatric rheumatology clinic from October 09 to May 10 who were having blood drawn for routine clinical monitoring. Patients who took corticosteroids in the previous 3 months were excluded. Disease activity was determined by physician assessment using a visual analog scale (VAS), along with number of active joints and erythrocyte sedimentation rate (ESR); child well-being was determined by parent completion of a VAS. Children were classified as obese (BMI ≥ 95th percentile) or normal BMI (BMI between 5th and 94th percentiles). The results were analyzed using T-tests, ANOVA, Fisher’s exact test, and linear regression in the entire patient sample. In addition, the relationship between BMI and active inflammatory joint disease was analyzed on a subset of children with JIA matched by age and gender.

Results: Of the 102 children, the male:female rate was 42:60, and ages ranged from 3–19 years (mean 11.4 years). Twenty-one children were obese (21%) and 81 had normal BMI. 100% of obese and 84% of non-obese children were Caucasian. JIA subtypes were distributed as follows: 40% oligoarticular, 21% RF-negative polyarticular, 21% enthesitis-related arthritis, 11% psoriatic arthritis, 4% systemic, and 3% RF-positive polyarticular. Mean time since disease onset was 48.3 months (±47.6 SD). BMI ranged from 13.9 to 36.7 (median 19.5); BMI percentiles ranged from 6 to 99 (mean 63.3). Mean BMI percentiles did not differ among JIA subtypes, gender, or age. The mean parent VAS scoring the child’s overall well-being was worse for obese than non-obese children [2.9 (±2.4 SD, range 0–7.5) vs 1.8 (±1.75, range 0–7.3), (p = 0.015)]. However, physician assessment of disease activity, joint count, and ESR elevation did not differ between the two groups. In the comparison of 21 age- and gender-matched pairs, there was no difference between obese and normal BMI children, regarding parent or physician VAS, ESR, or number of active joints.

Conclusions: Parent scores for well-being were worse for obese than non-obese children. This might reflect arthralgias due to mechanical overload, qualitative differences in parent perception, or other causes of reduced well-being associated with obesity. There were no differences for other indices of disease activity between subjects with JIA who were obese and those with normal BMI. As obesity confers an additional health risk in children with arthritis, addressing this co-morbidity should be a health priority in patients with JIA.

Disclosure: C. F. Pelajo: None; J. M. Lopez-Benitez: None; L. C. Miller: None.

232 Preliminary Definition of Remission and Minimal Disease Activity Cut-Points of the Juvenile Arthritis Disease Activity Score (JADAS). Alessandro Consolaro1, Giovanni Filocamo2, Bianca Lattanzi2, Giulia C. Varnier2, Angela Pistorio2, Niccolo Ruperto2, Alberto Martini2 and Angelo Ravelli1. 1IRCCS G. Gaslini and Università di Genova, Genova, Italy, 2IRCCS G. Gaslini and Università di Genova, Genova, Italy, 3IRCCS G. Gaslini, Genova, Italy, 4Policlinico Sant’Orsola, Bologna, Italy, 5The Children’s Hospital of Philadelphia, Philadelphia, PA, 6The Children’s Hospital of Philadelphia, Philadelphia, PA, 7The Children’s Hospital of Philadelphia, Philadelphia, PA

Background: Recent advances in treatment of juvenile idiopathic arthritis (JIA) and the recently developed composite disease activity score for JIA, the JADAS (Consolaro A, et al. Arthritis Rheum. 2009;61:658-66).

Methods: For the purposes of this study, the JADAS-10 version was used. The JADAS-10 is computed as the simple sum of 4 variables, each with a 0–10 range: the physician’s global assessment, the parent’s global assessment, the normalized ESR and the 10-fold reduced count. At each visit, all main physician- and parent-centered outcome measures were recorded. JADAS-10 was calculated for 432 patients in 914 visits. At each visit, both physicians and parents were asked to rate independently the disease status as remission or active disease. Furthermore, we assessed the presence of remission by Wallace criteria and, after grouping patients in oligoarthritis or polyarthritis, of MDA by the preliminary definition. In the first step, we calculated the JADAS-10 values corresponding to the 75th percentile of score distribution among patients who were classified as having disease remission by physician’s and parent’s subjective rating and Wallace criteria, or having MDA. In the second step, we calculated, by means of the receiver operating characteristic (ROC) curve analysis, the JADAS-10 values that showed the best trade-off between sensitivity and specificity (i.e. accuracy) in discriminating between patients who had remission or active disease according to the physician, the parent, or the Wallace criteria, or who had MDA according to the preliminary definition.

Results: The results in the 2-step analysis are shown in table.

<table>
<thead>
<tr>
<th>Remission</th>
<th>MDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>JADAS-10</td>
<td></td>
</tr>
<tr>
<td>Phys.</td>
<td>2.9</td>
</tr>
<tr>
<td>Parent</td>
<td>2.5</td>
</tr>
<tr>
<td>Wallace</td>
<td>1.0</td>
</tr>
<tr>
<td>Oligoarth.</td>
<td>2.3</td>
</tr>
<tr>
<td>Polyarth.</td>
<td>2.9</td>
</tr>
</tbody>
</table>

The numbers obtained for each definition using the 75th percentile or ROC curve method were then averaged. The values obtained for remission were further averaged achieving the value of 2.0. The values obtained for MDA are 2.3 for oligoarthritis and 2.9 for polyarthritis.

Conclusion: The value of 2.0 is the remission cut-point for the JADAS-10 proposed for use in future clinical trials on JIA. The proposed cut-points for MDA in oligoarthritis and polyarthritis are 2.3 ad 2.9, respectively.

Disclosure: A. Consolaro: None; G. Filocamo: None; B. Lattanzi: None; G. C. Varnier: None; A. Pistorio: None; N. Ruperto: None; A. Martini: None; A. Ravelli: None.


Background: Juvenile idiopathic arthritis (JIA) is the most common rheumatologic chronic condition in childhood, affecting 1 to 4 per 1,000 children. Enthesitis-related arthritis (ERA) is a JIA category that accounts for 10–20% of JIA. Enthesitis is a distinct pathologic feature of ERA. Descriptions of enthesitis in ERA are sparse and little has been published about which entheses are most commonly affected.

Methods: We conducted a retrospective cohort study of children with ERA who were diagnosed and treated at Children’s Hospital of Philadelphia between November 2007 and April 2010. The cohort consisted of children with an ICD-9-CM code of 720, indication “ERA” or “ankylosing spondylitis,” given at diagnosis or a subsequent follow-up visit.

Results: During the thirty-month study period there were fifty-nine ERA patients and 256 clinic visits. Subjects ranged from 5.5 to 18.5 years and had a mean age of 14 years at date of initial evaluation. Fifty-three percent were male. Eighty-five percent were white, 5% African American, 3% Asian, and 7% other. The mean number of tender entheses at diagnosis was 5 (95% CI: 0.15). There was at least 1 tender enthesis at 47% of visits. The most commonly affected entheses were the patellar ligament insertion on the inferior pole of the patella (6 o’clock position of patella) and the plantar fascial insertions on the calcaneus and metatarsal heads (Table). Enthesitis was most often asymmetric Rhetic. The mean number of swollen joints at diagnosis was 1 (95% CI: 0.7). The most commonly affected joints were the knees (N=16 patients, 6 unilateral, 5 bilateral), ankles (N=11 patients, 5 unilateral, 3 bilateral), and fingers. Of the joint fingers the proximal interphalangeal joints were most commonly affected. The arthritis was most often asymmetric.
Table 1. Sites of enthesis by visit (N = 256)

<table>
<thead>
<tr>
<th>Tender enthesis</th>
<th>Any N (%)</th>
<th>Unilateral N (%)</th>
<th>Bilateral N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 o'clock position of patella</td>
<td>88 (34.4)</td>
<td>34 (13.3)</td>
<td>54 (21.1)</td>
</tr>
<tr>
<td>Plantar fascial insertion at calcaneus</td>
<td>47 (18.4)</td>
<td>15 (5.9)</td>
<td>32 (12.5)</td>
</tr>
<tr>
<td>Plantar fascial insertion at metatarsal heads</td>
<td>43 (16.8)</td>
<td>10 (3.9)</td>
<td>33 (12.9)</td>
</tr>
<tr>
<td>Achilles tendon</td>
<td>38 (14.9)</td>
<td>14 (5.5)</td>
<td>24 (9.4)</td>
</tr>
<tr>
<td>2 o'clock position of patella</td>
<td>34 (13.3)</td>
<td>21 (8.2)</td>
<td>13 (5.1)</td>
</tr>
<tr>
<td>Greater trochanter</td>
<td>33 (12.9)</td>
<td>13 (5.1)</td>
<td>20 (7.8)</td>
</tr>
<tr>
<td>10 o'clock position of patella</td>
<td>31 (12.1)</td>
<td>19 (7.4)</td>
<td>12 (4.7)</td>
</tr>
<tr>
<td>Tibial tuberosity</td>
<td>16 (6.2)</td>
<td>7 (2.7)</td>
<td>9 (3.5)</td>
</tr>
<tr>
<td>Sacroiliac joint</td>
<td>13 (5.1)</td>
<td>4 (1.6)</td>
<td>9 (3.5)</td>
</tr>
<tr>
<td>Base of 5th metatarsal</td>
<td>11 (4.3)</td>
<td>5 (2.0)</td>
<td>6 (2.3)</td>
</tr>
</tbody>
</table>

Conclusions: Enthesitis comprises a significant portion of disease activity in ERA. Future studies should address the pattern of enthesitis over time, enthesitis response to therapy, and the impact of enthesitis on quality of life.

Disclosure: P. Weiss: None; A. J. Klink: None; E. M. Behrens: None; D. D. Sherry: None; T. H. Finkel: None; M. Ramos: None; R. Grundmeier: None; R. Keren: None; C. Feudtner: None.

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Prospective Study of Infliximab for Treatment of Pediatric Uveitis. Egla C. Rabinovich1, Janet Wootton1, Lawrence S. Zemel1, Lisa F. Imundo2, Jennifer E. Weiss2, Leslie S. Abramson2, Mark F. Hoeltzel2, Deborah M. Levy1 and David Wallace4. 1Children’s Mercy Hospital, Kansas City, MO, 2Childrens Hospital of NY, New York, NY, 3Connecticut Childrens Med Ctr, Hartford, CT, 4Duke University Medical Center, Durham, NC, 5Hackensack Univ Med Ctr, Hackensack, NJ, 6The Hospital for Sick Children, Toronto, ON, Canada, 7University of Vermont, Morrisville, VT

Background: Uveitis is a persistent disease for which there is little prospective data on treatment. Previous retrospective studies suggest TNF blockade may be efficacious for treatment of uveitis, but do not address time to response or optimal dose.

Methods: Ongoing 9 month multi-center prospective study of infliximab for treatment of persistent pediatric inflammatory uveitis (onset ≤ 16 yrs), randomizing subjects to one of 2 initial doses: 5 mg/kg or 10 mg/kg monthly. Scheduled ophtalmologic exams utilized the Standardization of Nomenclature (SUN) criteria. Entry criteria: ≥ 1+ anterior chamber inflammation, failure of at least one DMARD, on stable dose of methotrexate. Primary outcome variable was percent who had improvement per SUN criteria.

Results: 14 subjects (9 female, mean age 11.8 yrs, range 6–19) with persistent inflammatory uveitis (1 sarcoid, 13 idiopathic) from 6 Childhood Arthritis and Rheumatology Research Alliance (CARRA) A sites were randomized to receive 5 mg/kg (N = 6) or 10 mg/kg (N = 8) initial infliximab dose. At the baseline visit, 5 had unilateral and 7 bilateral inflammation.

Conclusion: Infliximab works rapidly to decrease inflammation with 57% having 0 to 5+ inflammation after one infusion. Low grade inflammation may persist despite treatment. Improvement persisted 8 months after initiation of infliximab.

Disclosure: E. C. Rabinovich: None; J. Wootton: None; L. S. Zemel: None; L. F. Imundo: None; J. E. Weiss: None; L. S. Abramson: None; M. F. Hoeltzel: None; D. M. Levy: None; D. Wallace: None.

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Safety and Efficacy of H1N1 Influenza Vaccination in Children with Chronic Inflammatory Rheumatic Diseases. Catherine F. Cortot1 and Robert P. Sundel2. 1Children’s Hospital Boston, Brookline, MA, 2Childrens Hosp Medical Center, Boston, MA

Background: Children with chronic inflammatory disease are more susceptible to infections and therefore have been considered a priority target group for immunization with the H1N1 influenza vaccine. However, the safety and efficacy of this vaccination in such patients remain unknown.

Objective: We conducted a prospective study to assess the toxicity profile and effectiveness during actual use of the H1N1 vaccination in children with chronic inflammatory rheumatic diseases.

Methods: Patients with a chronic inflammatory disorder from the rheumatology clinic of a large, tertiary care children’s hospital, and who had received at least one dose of the influenza A (H1N1) 2009 monovalent, unadjuvanted, inactivated vaccine, were included. Fifty six (54%) of the subjects received the vaccine in the clinic and were assessed prospectively; the remainder received their vaccinations elsewhere and were administered questionnaires during their clinic visit. Information gathered included vaccination side effects and the incidence of flu in study subjects.

Results: One hundred and five patients (median age 12.8 years, range 1.7–26.6) were included. In order of frequency, rheumatologic diagnoses included juvenile idiopathic arthropathy (45.7%), psoriatic arthritis (15.2%), enthesitis-related arthritis (8.6%) SLE (8.6%) and other (21.9%). The vast majority of patients (91.4%) were treated with immunosuppressive therapy (IMT) including at least one of methotrexate (71.9%), leflunomide (18.8%), TNF inhibitor (16.7%), corticosteroids (20%) or other (12.3%). During up to 6 months of followup during the peak of the influenza pandemic, one patient (1%) developed presumed H1N1 flu not confirmed by biological tests. Two cases (1.9%) of mild local symptoms at the injection site were observed. Four cases (3.8%) of systemic side effects of the H1N1 vaccine were reported, including 2 cases (1.9%) of flu-like symptoms, one case (1%) of myalgia and fatigue, and one flare of a patient’s spondylarthritus (1%) requiring the use of steroids for 15 days.

Conclusions: Influenza A (H1N1) 2009 monovalent, unadjuvanted, inactivated vaccine was well tolerated and apparently effective in children with chronic inflammatory rheumatic diseases. One patient developed a flare of his arthritis following the immunization, and one developed a flu-like illness despite the vaccination. No one had persistent sequelae or complications requiring hospitalization. These findings support the recommendation that children with rheumatologic conditions should receive the H1N1 monovalent inactivated vaccine.

Disclosure: C. F. Cortot: None; R. P. Sundel: None.

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Status of Vaccination Coverage in Children with Juvenile Idiopathic Arthritis (JIA) Followed at a Pediatric Tertiary-Care Center. Marie-Paule Morn1, Elise Fortin2, Caroline Quach3 and Gaëlle Chevèdeille3. 1The Montreal Children’s Hospital, Montreal, QC, Canada, 2The Montreal Children’s Hospital, Montréal, QC, Canada, 3The Montreal Children’s Hospital

Background: Immunization is recognized as being one of the most efficient ways to prevent mortality, morbidity and complications related to infectious diseases in children. Recent studies reported on the safety and efficacy of single vaccines given to patients with juvenile idiopathic arthritis (JIA). However, no data on vaccination coverage rate is available in JIA patients. Factors such as the presence of chronic disease, fear of inducing flare of disease and treatment with immunosuppressive medication may impact on the vaccination schedule of this population.

Objectives: To evaluate the vaccination coverage rate of patients with JIA followed at a pediatric tertiary-care center and to determine the coverage rate for individual vaccine required as per the Quebec Public Health guidelines.

Methods: The Division of Rheumatology at the Montreal Children’s Hospital (MCH) follows actively a cohort of 356 patients with JIA. During the period from August 1st 2008 to March 31st 2009, all consecutive JIA patients coming for their scheduled visit were included if they were between 2 and 18 years old and if they had an available written immunization record. Demographic data, ILAR disease subtype, active joint count and medications used since diagnosis were retrospectively collected for each patient. Descriptive statistics were used to evaluate the proportion of children with complete vaccination status according to the Quebec Public Health guidelines at 2.5, 10 years and at the last visit to the clinic.

Results: A total of 200 patients were included, 69% were girls. Mean age of the cohort was 11.4 years, with a median age at diagnosis of 4.8 years (0.5–16.6 years). The diagnosis at onset was oligoarthritis in 51.5% of the children, rheumatoid factor (RF) negative polyarthritids in 20.5%, RF positive polyarthritids in 15.5%, systemic in 6%, psoriatic in 6%, ERA in 7.5%, and undifferentiated in 7%. Over time, NSAIDs were used in 99% of patients, methotrexate in 51%, steroids in 10.5%, and biologics agents in 7.5%.
Vaccination coverage rates at 2.5, 10 years and at the last clinic visit for each vaccine are shown in the table, as well as the proportion of patients with complete vaccination status.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>At 2.5 years N (%)</th>
<th>At 10.5 years N (%)</th>
<th>Last visit to clinic N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella and mumps</td>
<td>198 (94)</td>
<td>118 (93)</td>
<td>200 (97)</td>
</tr>
<tr>
<td>Measles</td>
<td>198 (114)</td>
<td>91 (77)</td>
<td>200 (165)</td>
</tr>
<tr>
<td>Polio</td>
<td>198 (193)</td>
<td>116 (98)</td>
<td>200 (198)</td>
</tr>
<tr>
<td>Diptheria/tetanus</td>
<td>198 (197)</td>
<td>94 (80)</td>
<td>200 (160)</td>
</tr>
<tr>
<td>Pertussis</td>
<td>198 (197)</td>
<td>94 (80)</td>
<td>200 (155)</td>
</tr>
<tr>
<td>Meningococcus C</td>
<td>47 (40)</td>
<td>23 (19)</td>
<td>49 (45)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>98 (80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hib</td>
<td>198 (172)</td>
<td>87 (76)</td>
<td>200 (86)</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>31 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>12 (11)</td>
<td>92 (63)</td>
<td>14 (12)</td>
</tr>
<tr>
<td>Complete vaccination</td>
<td>198 (103)</td>
<td>80 (68)</td>
<td>200 (121)</td>
</tr>
</tbody>
</table>

**Conclusion:** Despite overall good vaccination coverage rate of single vaccines, only 61% of our cohort has a complete vaccination status at the last clinic visit. Further analysis is required to determine factors that may influence vaccination such as age at diagnosis, activity of the disease and medication use. Further studies need to be done to explore the reasons underlying incomplete vaccination status in the JIA population, both from a parental and a physician perspective. Measures to optimize vaccination coverage, such as catch-up vaccination, should be implanted when possible.

**Disclosure:** M.-P. Morin: None; É. Fortin: None; S. Quach: None; G. Chédeville: None.

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**The Clinical Feature of 2009–2010 Influenza Virus Infection during Tocilizumab Treatment for Systemic Onset Juvenile Idiopathic Arthritis.** Toru Uchimura, Tomoyuki Imagawa, Takuma Harai, Masaki Kikuchi, Ryoki Harai, Takako Miyajima, Masaki Mori, Akiyoshi Nariai, Toshihiro Mitsuda and Shumpei Yokota. 1Department of Pediatrics Yokohama City University, Yokohama, Japan, 2Department of Pediatrics Yokohama City University, 3Department of Pediatrics Yokohama Minami Kyosai Hospital, Yokohama, Japan

**Background:** We had reported that tocilizumab (a humanized anti-IL-6 receptor antibody, TCZ) had been proved to be highly effective in the clinical management of refractory systemic onset juvenile idiopathic arthritis (sJIA). TCZ inhibits interleukin-6 (IL-6) signal which relates to inflammation in sJIA by binding IL-6 receptor. It also affects the inflammatory reaction in infectious disease, such as pneumonia and gastroenteritis. Influenza virus infection has been known to make the disease activity of sJIA worse.

**Objective:** We evaluated the impact of influenza virus infection during tocilizumab treatment for sJIA.

**Method:** A total of 76 patients satisfying the WHO/ILAR criteria for sJIA were treated with TCZ, and received intravenous TCZ 8 mg/kg every 2 weeks. The patients who had the positive result of rapid chromatographic immunoassay for the detection of influenza A and B viral antigens from nasopharyngeal swabs were subject of this study from 2009 September to 2010 December. We examined the clinical manifestations and complications of the influenza virus infection, and the deterioration of sJIA.

**Results:** Seven patients (4 boys and 3 girls) affected with influenza virus infection. The median age was 13.7 years and the median duration of TCZ treatment was 42 months. The disease activities including fever, arthritis, rheumatoid rash, and inflammatory examinations in all patients were well controlled by TCZ. All of seven patients showed the result of influenza virus A by rapid antigen test. Clinical symptoms at the time of the influenza infection were fever (>38.0 degrees Celsius) in 6 patients (86%), cough in 7 patients (100%), nasal discharge in 5 patients (71%), vomiting in 1 patients (14%), diarrhea in 1 patients (14%) and fatigue in 3 patients (43%). The mean febrile period was 1.8 days (0 to 5 days). No complications including pneumonia, otitis media and influenza encephalopathy were observed. Six of 7 patients were treated with anti-influenza virus medications; oseltamivir in 5 patients, zanamivir in 3 patients. One patient switched from zanamivir to oseltamivir because of prolonged fever. One patient relapsed to sJIA after influenza. One patient presented with fever, arthritis and rheumatoid rash.

**Conclusion:** Despite overall good vaccination coverage rate of single vaccines, only 61% of our cohort has a complete vaccination status at the last clinic visit. Further analysis is required to determine factors that may influence vaccination such as age at diagnosis, activity of the disease and medication use. Further studies need to be done to explore the reasons underlying incomplete vaccination status in the JIA population, both from a parental and a physician perspective. Measures to optimize vaccination coverage, such as catch-up vaccination, should be implanted when possible.

**Disclosure:** M.-P. Morin: None; É. Fortin: None; S. Quach: None; G. Chédeville: None.

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**The Financial Burden of Juvenile Idiopathic Arthritis.** Andrea Ens, Bianca A. Lang, Suzanne E. Ramsey, Elizabeth Stringer and Adam M. Huber. 1WK Health Ctr, Halifax, NS, Canada, 2WK Health Ctr

**Objectives:** Very little is known about the financial burden of Juvenile Idiopathic Arthritis (JIA), particularly for the home borne by families in Canada. There are considerable medical and non-medical costs related to having JIA that families are expected to pay, in order for their children to receive the standard of care. The primary objective of this study was to determine the annual medical and related non-medical out-of-pocket costs associated with having a child who has JIA borne by families in Nova Scotia (NS).

**Methods:** All families in NS with a child followed by the Pediatric Rheumatology Clinic at the WK Health Centre in 2008, with JIA as per the International League of Associations for Rheumatology criteria, were mailed a self-report, parental questionnaire. Families were excluded if there was more than 1 child with JIA, or if there were other chronic illnesses. The questionnaires evaluated medical and non-medical related out-of-pocket costs, as well as gross household income. Ditman’s method was used to optimize return rates. One hundred and seventy-three questionnaires were mailed out. Of these, 5 were returned unopened due to incorrect addresses, giving a potential total of 168. Fifty-five (32.7%) were returned completed, and another 11 (6.5%) were returned blank or called to decline participation, for a total return rate of 39.3%.

**Result:** The majority of questionnaires were completed by the child’s mother (81.8%). The mean age of the children was 13.1y (range 5, 20) and 60% were female. The mean household income was $78,850 (median $70,000, range $2,500, $175,000); on average, families lived 116km (median 34.5km, range 4.5km, 530km) from the pediatric rheumatology clinic. The financial burden was rated as large by 1.9%, moderate by 35.2%, minimal by 44.4% and nothing by 18.5%. Resources available to help with the costs were rated as either fair or poor by 54.9% of parents. The mean total annual cost per patient was $1,281.71 (median $641.50, range 0, $12,556) which was on average 2.9% (median 0.9%, range 0, 46%) of their household income. The mean annual medication cost was $357.86 (median 0, range 0, $10,000). The annual mean visit costs for appointments with physicians or related allied health care workers was $276.89 (median 45, range 0, $2,836), and the annual mean non-medication cost was $80.64 (median 0, range 0, $1,850). Non-medication costs included the cost of physiotherapy, assistive aids, and home adaptations. The mean loss of paid work per year was $348.36 (median $0, range 0, $2,600). The Pearson correlation for total costs per year and distance was 0.46 (P=0.0005) and for annual visit costs for appointments and distance was 0.68 (P=0.0000), demonstrating a moderate direct relationship between distance and costs.

**Conclusions:** The financial burden associated with having a child with JIA in NS is considerable, particularly for some families. The impact of this burden on outcomes is unknown and warrants further evaluation.

**Disclosure:** A. Ens: None; B. A. Lang: None; S. E. Ramsey: None; E. Stringer: None; A. M. Huber: None.

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**Usage of TNFα Inhibitors for the Treatment of Juvenile Idiopathic Arthritis: Data from a National U.S. Administrative Claims Database.** Timothy Beukelman, Fenglong Xie and Jeffrey R. Curtis. 1Univ of Alabama at Birmingham, 2University of Alabama–Birmingham, Birmingham, AL, 3University of Alabama-Birmingham, Birmingham, AL

**Background:** Tumor necrosis factor alpha inhibitors (anti-TNF) have been used for over 10 years in the treatment of juvenile idiopathic arthritis (JIA), but little has been reported regarding their usage in clinical practice. We
analyzed national administrative claims data from a large commercial U.S. health insurer to characterize the usage of anti-TNF in the treatment of JIA.

**Methods:** Using national administrative claims data for the years 2005–2008 inclusive, we identified children less than 16 years old with ≥1 physician diagnosis code consistent with JIA (ICD-9 codes 714, 720, 696.0, or 713.1 with 555 or 556). We identified adults with ≥1 physician diagnosis code for rheumatoid arthritis (RA; ICD-9 code 714.0) for comparison. Pharmacy benefits were determined for each subject. Treatment with anti-TNF, methotrexate (MTX), and leflunomide (LEF) was determined through dispensary pharmacy and infusion claims. New anti-TNF users were defined by no treatment with any anti-TNF in the prior 6 months. Uveitis was defined by ≥1 physician diagnosis code (ICD-9 code 364). We examined anti-TNF usage over time and compared to MTX and LEF. We also performed cross-sectional analyses restricted to claims from 2008. Chi-square test was used for comparisons of proportions.

**Results:** During the study period, 2442 children with at least 1 JIA diagnosis code and full pharmacy benefits were identified; 55,010 adults with RA were identified. The mean age at first JIA diagnosis code was 10.1 ± 4.3 years. JIA patients were from 48 of the United States; 33% from northeast, 14% from mid-west, 34% from south, and 20% from west census regions. The proportion of JIA patients with full pharmacy benefits who were receiving anti-TNF increased from 7% in 2005 to 19% in 2008, compared to an increase from 15% to 24% for RA.

In cross-sectional analysis restricted to 2008, among all MTX, LEF, or anti-TNF users with JIA, 57% received any anti-TNF compared to 42% for RA. Also in 2008 among JIA patients, there were 1.3 users of any anti-TNF for each 1 user of MTX or LEF without anti-TNF; for RA this ratio was 0.71. From 2005–2008, 45% of all JIA anti-TNF users received concurrent MTX or LEF at any point, compared to 32% for RA. JIA new anti-TNF users with a prior diagnosis of uveitis were much more likely to initiate a monoclonal antibody (infliximab or adalimumab) (74%) compared to those without a prior diagnosis of uveitis (33%; p < 0.0001). JIA new anti-TNF users without full pharmacy benefits were much more likely to initiate infliximab (95%) compared those with full pharmacy benefits (13%; p < 0.0001).

**Conclusions:** The prevalence of anti-TNF treatment for JIA more than doubled from 2005 to 2008 and approached the prevalence seen in adult RA. The prevalence of anti-TNF treatment for JIA more than doubled from 2005 to 2008 and approached the prevalence seen in adult RA. The prevalence of anti-TNF treatment for JIA more than doubled from 2005 to 2008 and approached the prevalence seen in adult RA. The prevalence of anti-TNF treatment for JIA more than doubled from 2005 to 2008 and approached the prevalence seen in adult RA. The prevalence of anti-TNF treatment for JIA more than doubled from 2005 to 2008 and approached the prevalence seen in adult RA. The prevalence of anti-TNF treatment for JIA more than doubled from 2005 to 2008 and approached the prevalence seen in adult RA. The prevalence of anti-TNF treatment for JIA more than doubled from 2005 to 2008 and approached the prevalence seen in adult RA. The prevalence of anti-TNF treatment for JIA more than doubled from 2005 to 2008 and approached the prevalence seen in adult RA. The prevalence of anti-TNF treatment for JIA more than doubled from 2005 to 2008 and approached the prevalence seen in adult RA.

**Disclosure:** T. Beukelman: None; F. Xie: None; J. R. Curtis: Amgen Inc., 2, Centocor, Inc., 2, 5, Corrona, 2, 5, Roche, 2, 5, 8, UCB, Inc., 5, 8.

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**Use of Abatacept for Childhood Refractory Vision-Threatening Uveitis.**

Gabriele Simonini, De Libero Cinzia1, Roberto Caputo1, Teresa Gianì1, Laura Pascoli2, Ilaria Pagani1 and Rolando Cimaz2. 1Ophthalmology Unit, A Meyer Children’s Hospital, Florence, Italy, 2Rheumatology Unit Dpt of Pediatrics, A Meyer Children’s Hospital-University of Florence, Italy

**Objective:** Improvement of refractory JIA-related uveitis has been reported with Abatacept.

**Methods:** Four patients with refractory, vision-threatening non-infectious uveitis were enrolled to receive Abatacept 10 mg/kg at weeks 0, 2, 4, and thereafter monthly, for at least 6 months. Absence/recurrence rate of uveitis throughout the study period, according to the SUN Working Group criteria, visual acuity pre- and post-Abatacept treatment, and taping of steroid medication were recorded. Improved visual acuity was defined as a doubling of the visual angle (converted in a LogMAR format) in at least one eye. All children had active uveitis: 6 out of 8 eyes were involved, despite treatment with methotrexate (MTX) (15 mg/m² weekly) in association with Infliximab (6 mg/kg every 6–8 weeks). Follow-up period was 24 months (4–8 years).

**Results:** Two children reached a completely normal visual acuity, while visual acuity was defined as a doubling of the visual angle. Two children reached a completely normal visual acuity, while visual acuity was defined as a doubling of the visual angle.

**Conclusion:** Even if limited to a small group, our results suggest that Abatacept may be effective and safe in chronic refractory childhood uveitis, both in JIA-uveitis and in not JIA-uveitis.

**Disclosure:** G. Simonini: None; D. L. Cinzia: None; R. Caputo: None; T. Gianì: None; L. Pascoli: None; I. Pagani: None; R. Cimaz: None.

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**Use of TNFα Antagonists in the Treatment of Chronic Non-Bacterial Osteomyelitis (CNO).**

Sara Stern1, Katherine Marzan1, Arturo Borzutzky1, Evan Steinberg2 and Andreas Reiff3. 1Boston Children’s Hospital, Boston, MA, 2Children’s Hospital Los Angeles, Los Angeles, CA, 3Kaiser-Permanente Sunset Hospital, Los Angeles, CA

**Purpose:** CNO is a chronic autoimmune inflammatory osteopathy syndrome that is culture negative and has no demonstrable organism on histopathology. Anti-inflammatory medications are typically used to prevent pathologic fractures, pain, and disease relapse. The objective of this study was to describe the use of TNFα antagonists in the treatment of CNO in 8 patients with treatment refractory disease.

**Methods:** We retrospectively analyzed 23 patients with CNO seen from 1985–2009 at Children’s Hospital Los Angeles (18) and Kaiser-Permanente Sunset Hospital Los Angeles, CA, USA (5). CNO disease activity was evaluated by clinical, laboratory and radiographic parameters. Response to treatment was assessed by laboratory values (CRP, ESR) and a global response score, which also included clinical and radiographic parameters. A score of 0 indicated lack of response, 1 indicated partial response, and 2 indicated full response. Descriptive statistics were used for analysis.

**Results:** 23 patients (14 F: 9 M) with a mean age of 9.6 ± 2.9 years followed for a median of 1.83 (0.1–13) years. Patients had a mean of 3.3 ± 2.5 lesions which were most commonly seen in the pelvic bone (9), tibia (8), clavicle (6), calcaneus (5), femur (5), humerus (5), vertebral (5), and malleable (4). Eight patients (34.7%) had unifocal disease. The most common presenting symptoms included bone pain (90.9%), soft tissue swelling

---

<table>
<thead>
<tr>
<th>Age, years, months</th>
<th>Gender</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 y, 6 m</td>
<td>F</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>18 y, 4 m</td>
<td>F</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14 y, 1 m</td>
<td>M</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9 y, 4 m</td>
<td>M</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

---

**Table: Visual Acuity Outcome**

<table>
<thead>
<tr>
<th>N° of previous flares, 6 months before</th>
<th>Time to remission (weeks)</th>
<th>Time to steroid discontinuation (months)</th>
<th>Visual acuity 6 months after</th>
<th>Concomitant therapy (durations, months)</th>
<th>Follow-up duration on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>8</td>
<td>4</td>
<td>20/60 R 20/60</td>
<td>MTX: 15 mg/m²</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>5</td>
<td>20/60 L 20/60</td>
<td>MTX: 15 mg/m² MMF: 1 gm/m² MTX: 15 mg/m²</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>5</td>
<td>20/60 L 20/60</td>
<td>MTX: 15 mg/m² MMF: 1 gm/m² MTX: 15 mg/m²</td>
<td>8</td>
</tr>
</tbody>
</table>

**Median time of abatacept treatment was 10 months (range 6–14).** During treatment, all children achieved a complete remission over a median period of 12 weeks (range 8–14). Steroid administration was discontinued during the first 6 months (range 4–6) in 3/4 children. The patient with Blau syndrome was able to taper the dose down to 0.3 mg/kg/day. In all children, no relapse of uveitis occurred during treatment, whilst during the 6-month-period before starting Abatacept, the median number of relapses was 4 (range 3–6). At 6 months of treatment, all patients, (5/8 eyes), met the criteria for improved visual acuity. Two children reached a completely normal visual acuity, while the other two improved, even though the pre-existing complications, due to chronic uveitis, affected a complete recovery. No major side effects, infusion reactions and/or drug-related adverse events were recorded during the treatment period.

**Conclusion:** Even if limited to a small group, our results suggest that Abatacept may be effective and safe in chronic refractory childhood uveitis, both in JIA-uveitis and in not JIA-uveitis.

**Disclosure:** G. Simonini: None; D. L. Cinzia: None; R. Caputo: None; T. Gianì: None; L. Pascoli: None; I. Pagani: None; R. Cimaz: None.
untreated juvenile dermatomyositis (JDM) muscle biopsies (MBx) had an allele and a long duration of untreated disease (DUD) before diagnosis. Patients with untreated JDM who did not respond by clinical standards to immunosuppressive therapy. Finally, there is no information about the genetic status after a course of therapy that may allow the identification at diagnosis of patients that may not respond to treatment and may benefit from more aggressive or alternative therapy.

**Background:** The Trial of Early Aggressive Therapy (TREAT) in Juvenile Idiopathic Arthritis is a once-in-a-generation, multi-institutional trial comparing methotrexate with etanercept + methotrexate + prednisone as initial treatments of polyarticular JIA. To maximize the scientific utility of this trial, biological samples have been collected for translational research to answer questions of high relevance to the field of pediatric rheumatology; these samples include whole blood preserved in stabilizers to perform gene expression profiling. We report here the first translational study to emerge from the TREAT trial, which will be completed in late October, 2010.

**Methods:** We received 45 samples from children with untreated polyarticular JIA at the time of their enrollment within the TREAT trial. All children were rheumatoid factor negative. Of these 45 samples, RNA was degraded in 11 and was insufficient for microarray analysis on another 5. Thus, microarray analysis was performed on 29 children entering the TREAT trial and 19 healthy control children. RNA purification, assessment of RNA purity and integrity, labeling, and hybridization were all undertaken using conventional methods. The Illumina microarray platform was used and conventional bioinformatic approaches were taken to identifying differentially expressed genes.

**Results:** 130 genes distinguished TREAT baseline from control samples with a 5% false discovery rate and a minimum 1.5-fold difference between groups. These genes were largely subsumed into 5 large overlapping groups. These genes were identified by systems biologists as modularity. Gene

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**A Whole Blood Gene Expression Profile of Untreated Children with Polyarticular JIA Enrolled in the TREAT Trial.**

**Objective:** To compare the GE profiles in the diagnostic muscle biopsies in untreated children at diagnosis of JDM and after immunosuppressive therapy.

**Materials and Methods:** Seven children with definite/probable JDM were recruited for this study, along with four healthy age-, race-, and gender-matched controls undergoing orthopedic surgery. All JDM were initially untreated at the time of the diagnostic MBx, mean age 7.43 ± 4.21 yrs, 3/7 female; six Caucasian and one Hispanic. Four of the children responded to therapy and were off all medication at the time of follow-up needle MBx, two of the NR still required medication, and one was non-compliant. RNA was extracted and hybridized to Affymetrix U133Aplus2 arrays (post-treatment). Data was normalized and filtered to exclude the controls and probes with maximum expression less than a log scale of 6 across all samples. The GE of R was compared to the NR using two-sample t-tests. Evaluation of gene functions and networks utilized Ingenuity Pathway Analysis software (Ingenuity Systems, Redwood City, CA).

**Conclusions:** CNO is a chronic autoimmune inflammatory syndrome with high risk for pathologic fractures and systemic morbidity. Treatment of these patients remains challenging since they tend to respond poorly to traditional NSAID and DMARD therapy. TNFα antagonists offer a viable treatment option and appeared to be the most beneficial in our study.

**Disclosure:** S. Stern: None; K. Marzan: None; A. Borzutzky: None; E. Steinberg: None; A. Reiff: Abbott Laboratories, 5, 8, Amgen Inc., 5, 8, Merck Pharmaceuticals, 5, 8, Pfizer Inc, 5, 8, Regeneron Pharmaceuticals, Inc., 5, Wyeth Pharmaceuticals, 5, 8.

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**A Pilot Study of Gene Expression (GE) Profiles in Juvenile Dermatomyositis (JDM) Responders and Non-Responders: Diagnostic and Follow-Up Muscle Biopsy (MBx) Data.**

**Objective:** To compare the GE profiles in the diagnostic muscle biopsies in untreated children at diagnosis of JDM and after immunosuppressive therapy.

**Materials and Methods:** Seven children with definite/probable JDM were recruited for this study, along with four healthy age-, race-, and gender-matched controls undergoing orthopedic surgery. All JDM were initially untreated at the time of the diagnostic MBx, mean age 7.43 ± 4.21 yrs, 3/7 female; six Caucasian and one Hispanic. Four of the children responded to therapy and were off all medication at the time of follow-up needle MBx, two of the NR still required medication, and one was non-compliant. RNA was extracted and hybridized to Affymetrix U133Aplus2 arrays (post-treatment). Data was normalized and filtered to exclude the controls and probes with maximum expression less than a log scale of 6 across all samples. The GE of R was compared to the NR using two-sample t-tests. Evaluation of gene functions and networks utilized Ingenuity Pathway Analysis software (Ingenuity Systems, Redwood City, CA).

**Results:** The NR were older at the time of the diagnostic MBx: mean age of 9.6 ± 5.7 yrs with a longer DUD of 14.0 ± 1.24 mos vs mean age of 5.8 ± 2.5 yrs and DUD of 3.3 ± 1.4 mos for the R. At needle follow-up biopsy, R were mean age of 10.7 ± 1.8 yrs vs 17.7 ± 7.4 yrs for NR.

A significant number of genes were found to be differentially expressed in R compared with NR. Skeletal-muscular and cardiovascular system development and function were within the main networks represented. Of importance, at diagnostic MBx several apoptosis related genes were significantly up regulated in R compared with NR, including CASP1 (FC 2.3; p <0.03) and CASP3 (FC 1.8; p =0.02). After treatment the NO31 gene that is usually expressed in skeletal muscle and is regulated by IL1B and TNF was over-expressed in non-responders compared with responders (FC 3.7; p =0.02).

**Conclusion:** The results of this preliminary analysis point to specific genetic mechanisms involved with non-responsiveness to treatment in JDM patients. GE studies involving larger cohorts will clarify these mechanisms and allow the identification at diagnosis of patients that may not respond to treatment and may benefit from more aggressive or alternative therapy.

**Disclosure:** L. M. Pachman: None; Y.-W. Chen: None; P. Hendrickson: None; S. Shrestha: None; G. Morgan: None; S. Sredni: None.

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**A Whole Blood Gene Expression Profile of Untreated Children with Polyarticular JIA Enrolled in the TREAT Trial.**

**Objective:** To compare the GE profiles in the diagnostic muscle biopsies in untreated children at diagnosis of JDM and after immunosuppressive therapy.

**Materials and Methods:** Seven children with definite/probable JDM were recruited for this study, along with four healthy age-, race-, and gender-matched controls undergoing orthopedic surgery. All JDM were initially untreated at the time of the diagnostic MBx, mean age 7.43 ± 4.21 yrs, 3/7 female; six Caucasian and one Hispanic. Four of the children responded to therapy and were off all medication at the time of follow-up needle MBx, two of the NR still required medication, and one was non-compliant. RNA was extracted and hybridized to Affymetrix U133Aplus2 arrays (post-treatment). Data was normalized and filtered to exclude the controls and probes with maximum expression less than a log scale of 6 across all samples. The GE of R was compared to the NR using two-sample t-tests. Evaluation of gene functions and networks utilized Ingenuity Pathway Analysis software (Ingenuity Systems, Redwood City, CA).

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**Conclusion:** The results of this preliminary analysis point to specific genetic mechanisms involved with non-responsiveness to treatment in JDM patients. GE studies involving larger cohorts will clarify these mechanisms and allow the identification at diagnosis of patients that may not respond to treatment and may benefit from more aggressive or alternative therapy.

**Disclosure:** L. M. Pachman: None; Y.-W. Chen: None; P. Hendrickson: None; S. Shrestha: None; G. Morgan: None; S. Sredni: None.
samples collected from the TREAT trial will allow us to understand how these networks change in response to therapy and provide unprecedented insight into the biology of therapeutic response.

Disclosure: M. B. Frank: None; K. Jiang: None; Y. Chen: None; M. Bekai: None; C. A. Wallace: None; S. Thompson: None; J. N. Jarvis: None.

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Angioptelin-Like 4 Is Expressed in Human Synovial Fibroblasts and Expression Is Increased in Response to TGFβ

C. A. Wallace: is highly increased in JIA synovial fibroblasts in response to systemic JIA SF, realtime RTPCR.

Angioptelin-Like 4 (Angptl4) is a novel angiogenic protein that is highly increased in early inflammatory stages of collagen-induced arthritis. The present study determines the expression of Angptl4 mRNA in human synovium and the factor(s) regulating its expression.

Methods: Quantification of Angptl4 mRNA levels in synovial tissues was performed by RNase protection analysis. JIA (juvenile idiopathic arthritis) synovial fibroblast cultures were generated from joint replacement synovial tissues. Synovial fibroblast cultures were treated for 2 hours with systemic JIA (sJIA) synovial fluid (SF) or TGF-β.

Results: Angptl4 is expressed at higher levels in rheumatoid arthritis (RA) and JIA than in osteoarthritis (OA) synovial tissues. JIA synovial fibroblasts express Angptl4 mRNA, which increases dramatically in the presence of systemic JIA (sJIA) SF. Treatment of JIA synovial fibroblasts with TGF-β shows a dramatic increase in Angptl4 expression that is nullified in the presence of TGF-β inhibitor.

Conclusion: Angptl4 is expressed in human arthritis synovium, suggesting a role for Angptl4 in human arthritic disease. The expression of Angptl4 is highly increased in JIA synovial fibroblasts in response to systemic JIA SF, and is abrogated by inhibition of TGF-βRII signaling, suggesting that TGF-β is a major mediator of Angptl4 expression in inflammatory arthritis.

Disclosure: N. Fall: None; M. Frederick: None; A. A. Grom: None; S. Thornton: None.

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Anti-CCP Antibodies Identify a Subset of RF-Negative Juvenile Idiopathic Arthritis Patients with Juvenile Diopathic Arthritis and Correlate with Inflammation Parameters

S. Thompson: is increased in JIA synovial fibroblasts in response to systemic JIA SF, realtime RTPCR.

Objective: We previously identified angioptelin-like 4 (Angptl4) as a novel angiogenic protein that is highly increased in early inflammatory stages of collagen-induced arthritis. The present study determines the expression of Angptl4 mRNA in human synovium and the factor(s) regulating its expression.

Methods: Quantification of Angptl4 mRNA levels in synovial tissues was performed by RNase protection analysis. JIA (juvenile idiopathic arthritis) synovial fibroblast cultures were generated from joint replacement synovial tissues. Synovial fibroblast cultures were treated for 2 hours with systemic JIA (sJIA) synovial fluid (SF) or TGF-β, with or without the addition of recombinant human TGF-βRII kinase inhibitor (TβRII Inhibitor). RNA was isolated and Angptl4, IL-1β and GAPDH mRNA levels quantified by realtime RTPCR.

Results: Angptl4 is expressed at higher levels in rheumatoid arthritis (RA) and JIA than in osteoarthritis (OA) synovial tissues. JIA synovial fibroblasts express Angptl4 mRNA, which increases dramatically in the presence of systemic JIA (sJIA) SF. Treatment of JIA synovial fibroblasts with TGF-β shows a dramatic increase in Angptl4 expression that is nullified in the presence of TβRII Inhibitor.

Conclusion: Angptl4 is expressed in human arthritis synovium, suggesting a role for Angptl4 in human arthritic disease. The expression of Angptl4 is highly increased in JIA synovial fibroblasts in response to systemic JIA SF, and is abrogated by inhibition of TGF-βRII signaling, suggesting that TGF-β is a major mediator of Angptl4 expression in inflammatory arthritis.

Disclosure: N. Fall: None; M. Frederick: None; A. A. Grom: None; S. Thornton: None.

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CD4+CD161+ Cells with Th1 or Th17/Th1 Profile Accumulate in the Synovial Fluid of Patients with Juvenile Diopathic Arthritis and Correlate with Inflammation Parameters

Anne E. Tebo1, Troy D. Jaskowski 2, K. Wayne Davis 1, Anne A. Grom 3, A. A. Grom 3, None; Sherry Thornton 2, Malinda Bohnsack 2, F. Frosali 3, R. De Palma 3, E. Maggi 2, S. Romagnani 3, F. Annunziato 3, University of Florence, Florence, Italy, “University of Florence, University of Naples

Objectives: A recently described subset of CD4+ T helper (Th) cells, named as type 17 Th (Th17) cells, has been suggested to be pathogenic in chronic inflammatory disorders, including rheumatoid arthritis and juvenile idiopathic arthritis. We wanted to investigate the phenotype and function of CD4+ T cells in synovial fluid (SF) of affected joints from children with juvenile idiopathic arthritis (JIA), and to establish a possible link with disease activity.

Methods: CD4+ T cells of peripheral blood (PB) and SF of 37 JIA patients, as well as of PB from 15 healthy children were analyzed for expression of CXCR3, CCR6, CD161 and production of IFNγ and IL-17A. Intracellular cytokine production assays, cytokine secretion assays, and cell cultures were performed. CD161+IL-17+IFNγ+ and CD161+IL-17-IFNγ+ cells derived from PB of one healthy donor and the SF of one JIA patient were also cloned. ORC expression was evaluated by real-time quantitative RT-PCR in FACS sorted populations. Spectratyping and clonotypic analyses on different T cell subsets were performed.

Results: Numbers of CD4+CD161+, showing either the Th1 (IFNγ-producing) or the Th17/Th1 (producing both IFN-γ and IL-17A) phenotype, were higher in SF than in PB from JIA children. The few Th17 cells from SF of JIA spontaneously shifted in vitro to Th1 cells, whereas Th17 cells from PB of healthy children did it only in presence of SF, this effect being neutralized by blocking IL-12 activity. Spectratyping and clonotypic analyses showed a similar skewing of the TCR-BV repertoire in both SF-derived CD161+Th17 and CD161+Th1 cells from the same JIA patient. The frequencies of CD4+CD161+ cells, particularly of those showing the Th17/Th1 phenotype, in SF of JIA positively correlated with levels of erythrocyte sedimentation rate and C-reactive protein.

Conclusion: These findings suggest that a shifting of CD4+CD161+Th17 cells into Th17/Th1 or Th1 cells in the SF from affected joints of JIA can occur, and indicate that the accumulation of these latter correlates with parameters of inflammation, thus supporting the hypothesis that these cells play a role in disease activity.

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Characterization of Granulocyte Transcription in Polymarticular Juvenile Idiopathic Arthritis (JIA). Mark Barton Frank, Kaiju Jiang, Yanmin Chen, Jeanette Osban, Pascual Gellert, and James N. Jarvis. Department of Pediatrics, University of Oklahoma College of Medicine.

**Background:** Previous studies have demonstrated aberrations in granulocyte activation in patients with polyarticular JIA, and gene expression profiles of patients with active disease and in remission support an important role of these cells in pathogenesis. The goal of this study was to extend our previous work to define molecular aspects of gene differences in JIA.

**Methods:** Children were grouped as having active JIA (AD, n = 18), clinical remission on medication (CRM, n = 12) or healthy controls (C, n = 15) according to the criteria of Wallace et al. AD patients were treated with conventional medications. RNA was extracted from purified granulocytes, labeled, and hybridized to Affymetrix Exon and microRNA (miRNA) arrays. Statistically significant differences were identified using two-tailed Fisher's exact tests in exon splicing programs, and miRNA differences were defined using BRB-Array Tools.

**Results:** Exon splicing changes were detected and confirmed in 4 genes when cohorts of AD were compared to CRM. However, exon splicing occurred in a larger number of genes including amyloid P component, when samples from the same patients in AD were compared to those collected in CRM. Numerous splice variations were found between AD and C samples including genes encoding Ro60, transcriptional regulators, and an IL-6 cytokine. These were not found when CRM was compared to controls. No differences in miRNA expression were detected between AD and CRM, AD and C, or CRM and C samples.

**Conclusions:** These results support the hypothesis that the transcriptional differences between patients with JIA and healthy children occur not only at the gene expression level as we and others have previously reported, but also in subtle ways in the usage of exons of genes of pathological interest. The absence of differences in miRNA levels in patients and controls suggests that the regulatory events in RNA transcription are not controlled by miRNA or altered by treatment protocols used in these patients. The study further clarifies the important role at the molecular level of granulocytes in the pathogenesis of JIA.

**Disclosure:** M. B. Frank: None; K. Jiang: None; Y. Chen: None; J. Osban: None; P. Gellert: None; J. N. Jarvis: None.

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**CLARITY: Childhood Arthritis Risk Factor Identification Study.** Justine Ellis, Jane Munro, Anne-Louise Ponsobny, Angela Pezic, Betty Lim, Raul Chavez, William Siero, Jonathan Akkus and Roger Allen. Murdoch Children's Research Institute, Melbourne, Parkville, Victoria, Australia; Royal Children’s Hospital, Melbourne, Parkville, Victoria, Australia.

**Introduction:** Juvenile idiopathic arthritis is an autoimmune rheumatologic disease of unknown cause. As a complex disease, it is assumed that an interaction between genetic predisposition and environmental factors determines risk. Research to identify JIA risk factors lags behind that of other childhood autoimmune disorders of similar incidence. Over the last few years, the underlying genetic predisposition has begun to emerge, mainly through candidate gene analyses. However, few studies have examined environmental risk factors for JIA in detail, but past infection is of interest, both as a possible beneficial early life immunomodulator and an adverse trigger of disease (Ellis et al. Rheumatology 49:411-25, 2010). In 2008, we established CLARITY, a JIA Biobank that is collecting biospecimens and extensive information about environment from cases presenting to the Royal Children’s Hospital (RCH), Melbourne, Victoria, Australia. A control sample of healthy children attending the RCH Day Surgery Unit for specific minor surgical procedures is also collected. Our goal is to recruit at least 1000 cases and 1000 controls, to allow adequate statistical power to detect not only main effects but also gene-environment interactions. To date we have recruited 700 cases and 1001 controls.

**Methods:** Here we concentrate on a preliminary analysis of a subset of the environmental measures collected in 224 incident and prevalent cases (mean age 9.5 ± 4.1 SD yrs, 39% female) and 272 controls (mean age 7.3 ± 4.1 SD yrs, 39% female) so far entered into a database. We examined the incidence of common childhood illnesses by logistic regression (adjusted for age and sex).

**Results:** A history of illness such as gastroenteritis (Adjusted odds ratio (AOR) = 0.52; 95% CI: 0.32, 0.83; p = 0.006), colds and flu (AOR = 0.36; 95% CI: 0.22, 0.58; p < 0.001), and chest infection (AOR = 0.44; 95% CI: 0.26, 0.74; p = 0.002) were associated with a reduced likelihood of being a JIA case. These associations remained significant when we restricted the dataset to cases diagnosed within 3 years of interview as well as cases and controls born in Victoria with four Caucasian grandparents (case n = 100, control n = 223). The associations between reduced JIA risk and childhood illness remained particularly strong and consistent for colds and flu (AOR = 0.38; 95% CI: 0.21, 0.68; p = 0.001). We then further restricted the dataset to test the association of the incidence of colds and flu prior to school entry (4 years or younger) with diagnosis of JIA at 6 years or greater (case n = 113, control n = 272). The association was observed in this subgroup (AOR = 0.42; 95% CI: 0.15, 0.82; p = 0.016).

**Conclusions:** To date, these findings are consistent with other work indicating early life microbial exposure that leads to an increased incidence of common childhood illnesses confers protection against autoimmune disease, potentially through more efficient priming of the developing immune system. Further analyses will be undertaken in the larger study to examine whether the indications for control day surgery influenced these findings.

**Disclosure:** J. Ellis: None; J. Munro: None; A.-L. Ponsobny: None; A. Pezic: None; B. Lim: None; R. Chavez: None; W. Siero: None; J. Akkus: None; R. Allen: None.

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**249 Costimulation Mediated Rescue of Superantigen Stimulated T Cells in Kawasaki Disease.** Aaron Wong and Rae S. M. Yeung. Hospital for Sick Children, Toronto, ON, Canada; The Hospital for Sick Children, Toronto, ON, Canada.

**Background:** Kawasaki Disease (KD) causes coronary arteritis and is the leading cause of acquired heart disease in children of the developed world. Evidence suggests that superantigens (SAgs) are involved in the pathogenesis of KD. Lactobacillus Casei cell wall extract (LCWE), a mouse model of KD, closely mimics human KD and SAg activity in LCWE directly correlates with its ability to induce coronary arteritis. Superantigens are potent T cell mitogens, initiating a tremendous inflammatory response with massive cytokine release characterized by production of tumor necrosis factor-alpha (TNFa). Our work suggests that enhanced costimulation can rescue SAg-stimulated T cells from apoptosis and thus enable survival of autoreactive T cells which persist in our mouse model.

**Objective:** To determine the mechanisms involved in costimulation mediated rescue of SAg-stimulated T cells.

**Methods:** Splenocytes from C57BL/6, TNFR1−/−, B7.2−/−, and Cbl-b−/− mice were cultured in media containing various stimuli: Staphylococcal Enterotoxin B (SEB)-a prototypic SAg, recombinant TNFa (rTNFa), anti-CD28 antibody, CTLA-4-Ig, and anti-TNFa antibody. Expression of B7.1, B7.2, Bcl-2, and Bcl-xL was determined by staining with fluorescent antibodies in flow cytometry experiments. In costimulatory rescue experiments, splenocytes were stimulated for 5 days and the levels of apoptosis within the SAg-reactive T cell population was determined by staining for TCRβV and annexin V. To determine the contribution of costimulatory molecules on T-cells versus antigen presenting cells (APC), cell populations were purified by magnetic bead separation, then mixed and co-cultured.

**Results:** Stimulation with SEB upregulated B7.2 expression in wildtype mice, but this response was diminished in TNFR1−/− mice. Addition of rTNFa in the absence of SEB independently upregulated B7.2 expression. Enhancing costimulation with stimulatory anti-CD28 antibody rescued superantigen-reactive T cells from apoptosis in wild type and TNFR1−/− mice. Disrupting costimulation by blocking B7 with CTLA-4-Ig or neutralizing TNFa increased apoptosis of SAg-reactive T cells. Mixing experiments with purified wildtype T cells and B7.2−/− APCs exhibited no change in SAg-induced apoptosis when compared to cultures completely lacking B7.2. Increased expression of the anti-apoptotic markers Bcl-2 and Bcl-xL was found in cells receiving enhanced costimulation.

**Conclusion:** TNFa plays an important role in regulating costimulation by blocking the expression of costimulatory ligand, B7.2, on APCs. The resultant B7.2/CD28 interaction is functionally relevant, leading to survival of SAg-reactive T cells. Rescued T cells had increased expression of anti-apoptotic markers Bcl-2 and Bcl-xL. As costimulation enables autoreactive cells to evade apoptosis and persist leading to persistent inflammation and tissue damage, this study lends additional mechanistic support to therapies that target TNFa and costimulation pathways for the treatment of KD. These principles are generalizable to many diseases where superantigens are implicated as triggers of a persistent immune response.

**Disclosure:** A. Wong: None; R. S. M. Yeung: None.

**Purpose:** Rheumatoid arthritis (RA) is a common chronic inflammatory arthropathy with a peak age of onset in the fifth decade. About 5% of children with juvenile idiopathic arthritis phenotypically resemble adult RA. We hypothesize that children with the RA phenotype are a genetically enriched arthropathy with a peak age of onset in the fifth decade. About 5% of children with RF-negative, polyarticular onset JIA induced by MTX differs at the molecular level from remission achieved in the presence of a MTX plus TNFi.

**Methods:** RNA was prepared from 29 patients’ peripheral blood mononuclear cells (PBMC) and granulocytes to identify differentially expressed (DE) genes using whole genome microarrays between the two patient groups and 15 healthy childhood controls. Statistical analysis and in silico modeling using Ingenuity software were undertaken as described in our previous work.

**Results:** Only 6 DE genes were found in PBMC from patients who achieved remission using MTX + TNFi vs MTX alone. Additional differences became apparent when each treatment group was compared to healthy controls. It is interesting to note that a number of the DE genes in both cell types are known to be regulated by the transcription factors NFKB and HNF4A.

**Conclusions:** There were 33 DE genes in granulocytes from patients treated with the two regimens, including many whose patterns were previously reported to be modulated in arthritis. As with PBMC, a number of these genes are also regulated by NFKB and HNF4A. Subsequent work from our group (see related abstract) has demonstrated unequivocally that that HNF4A is present in PBMC and granulocytes.

Both cell types from both groups of patients revealed hundreds of DE genes when compared to healthy controls. In granulocytes, these genes were subsumed into 9 large, overlapping networks that included the TGFβ, TNFA, and IFNG hubs we have previously described. In PBMC, DE genes were subsumed into 2 networks that included the IFNG, TGFβ, and IL1 hubs that have appeared on other JIA transcriptional profiles, including our own.

**Disclosure:** None.

**References:**

1. Robinson B, Myrtle Thierry-Palmer, Keisha L. Gibson and Eglé C. Rabinovich. 1. Duke University Medical Center, Durham, NC, 2. Morehouse School of Medicine, 3. University of North Carolina at Chapel Hill.

**Background:** Recent studies have implicated low vitamin D levels with greater disease activity in pediatric systemic lupus erythematosus (pSLE); there is no data on children with dermatomyositis. The objective of this study was to determine whether low levels of 25-hydroxyvitamin D [25(OH)D] are associated with proteinuria and assess the relationship between vitamin D status and disease activity (VAS), SLEDAI, and proteinuria in subjects with SLE.

**Methods:** Subjects diagnosed with JDM or SLE prior to the age of 18 were recruited and given a questionnaire regarding demographics, sunscreen use, and dietary habits to assess conventional risk factors for vitamin D deficiency. Serum 25(OH)D and albumin levels were determined. Disease activity was rated using a 10-cm visual analogue scale (VAS) in all subjects, and the SLE disease activity index (SLEDAI) in subjects with SLE. Linear regression was used to examine the association of race, sunscreen use, vitamin D intake, and disease activity with serum 25(OH)D levels. Urine was analyzed for vitamin D binding protein (DBP) and protein to creatinine (UP/C) ratio.

**Results:** There were 58 subjects; 21 with JDM and 37 with SLE (13 with UP/C values ≥ 0.5). Serum 25(OH)D levels in subjects with SLE were inversely associated with urinary DBP (r = -0.63, p < 0.001) and urine protein to creatinine ratio (r = -0.67, p < 0.001), and directly associated with serum albumin (r = 0.56, p < 0.001). In a multivariate linear regression model adjusting for known risk factors including race and vitamin D supplement intake, serum 25(OH)D levels were inversely associated with disease activity (VAS), SLEDAI, and proteinuria in subjects with SLE. Prednisone dosage was not associated with 25(OH)D levels. UP/C ratios ≥ 0.5 were associated with an adjusted mean 10.9 ng/ml (95% CI 5.1 to 16.8 ng/ml) decrease in 25(OH)D level. Excluding subjects with proteinuria from analysis, serum 25(OH)D levels were inversely associated with disease activity in subjects with JDM, but not in subjects with SLE.

**Disclosure:** M. B. Frank: None; K. Jiang: None; Y. Chen: None; J. N. Jarvis: None.

**References:**

1. Rabinovich A, Myrtle Thierry-Palmer, Keisha L. Gibson and Eglé C. Rabinovich.
2. Duke University Medical Center, Durham, NC, 3. Morehouse School of Medicine, 4. University of North Carolina at Chapel Hill.
Effect of Methotrexate and Genotype on RBC Folate Concentrations and Polyglutamate Distribution in JIA. Mara L. Becker1, Roger Gaedigk2, Bradley Thomas3, Andrew Lasky4, John Stobaugh3 and J. Steven Leeder1. 1Children’s Mercy Hospital, Kansas City, MO, 2Children’s Mercy Hospitals and Clinics, Kansas City, MO, 3Children’s Mercy Hospital, Kansas City, MO, 4University of Kansas

Purpose: The mechanism of action of methotrexate (MTX) remains incompletely understood. As a potent anti-folate drug, MTX has several enzymatic targets in the folate pathway. We measured intracellular folate redox states and polyglutamates to better understand the effect of drug and genotype upon intracellular folate pools in JIA.

Methods: This single center cross-sectional study evaluated 104 JIA patients on stable doses of MTX at a tertiary care children’s hospital. After obtaining informed consent, blood was obtained from 104 JIA patients during routine MTX screening labs. Clinical data were collected by chart review. Genotyping for 34 SNPs in 19 genes within the MTX metabolic pathway was performed. Folates were extracted from RBCs and analyzed in a semi-quantitative relative fashion (i.e. without standards) using a similar method as for MTX polyglutamates, involving an ion-pairing chromatographic procedure with mass spectrometric detection.

Results: Measured intracellular folate isoforms included: 5,10 formyl THF, 5,10 formyl THF, 5,10 methenyl THF; 5 methyl tetrahydrofolate (5-MTHF); and 5-MTHF polyglutamates (5-MTHF-PG%). Subjects on MTX had expectedly lower folate isoform concentrations than those not on MTX including 5-MTHF (678.6 ± 281.2 nmol/mL vs. 1022.2 ± 489.3 nmol/mL, p<0.0001) and 5-MTHF (68.4 ± 77.0 nmol/mL vs. 91.7 ± 106.3 nmol/mL, p=0.04). 5-MTHF-PG% distribution revealed higher proportions of long chain polyglutamates in patients receiving MTX.

Conclusions: Low levels of serum 25(OH)D in systemic lupus erythematosus may result, in part, from urinary loss of DBP-25(OH)D in those patients with SLE-related glomerulonephritis. Serum 25(OH)D levels inversely correlate with disease activity in both JDM and SLE patients, but the relationship between disease activity and serum 25(OH)D levels in SLE patients may be confounded by the presence of proteinuria. Further studies should prospectively assess the effect of vitamin D supplementation on disease activity and outcomes in SLE and JDM.

Disclosure: A. B. Robinson: None; M. Thierry-Palmer: None; K. L. Gibson: None; E. C. Rabinovich: None.

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Purpose: Response and toxicity to Methotrexate (MTX) is unpredictably variable in Juvenile Idiopathic Arthritis (JIA). A known folic acid antagonist, there are several identified folate pathway gene targets for MTX and, therefore, there is a large potential for variation in genotype which may affect drug response. We investigated the combination of folate pathway polymorphisms and MTX response in JIA.

Methods: This is a single center cross-sectional study evaluating JIA patients on stable doses of MTX at a tertiary care children’s hospital. After obtaining informed consent, blood was obtained from 104 JIA patients during routine MTX screening labs. Clinical data were collected by chart review. Genotyping for 34 SNPs in 19 genes within the MTX metabolic pathway was performed. Chi square analysis and Multifactor Dimensionality Reduction (MDR) methods were employed to investigate gene to gene interactions associated with the presence of active arthritis.

Results: All genes included in the analysis were in Hardy Weinberg equilibrium. Initial chi square analyses revealed a statistically significant association with the following genes and the presence of active arthritis (active disease): ATIC (rs4673990; P=0.019), MTHFD2 (rs12196), and a 5nt indel in the promoter; P=0.005, and P=0.015, respectively, and ITPA (rs2295526; P=0.014). The MDR method was applied to the outcome of presence/absence of active joints. The most pronounced combination of genes differentiating patients with active arthritis and those without included ATIC (rs4673990) and MTHFD2 (rs56168672).
In fact, subjects who carried the combination of these two SNPs were 9.7 times more likely to have active arthritis [OR 9.66 (95%CI: 3.9, 24; P<0.0001)]. Sensitivity was 74%, specificity was 86.7% and overall accuracy was 76%.

Table 1. MDR analysis evaluating gene-gene interactions differentiating subjects with active arthritis from those without

<table>
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<tr>
<th>Model</th>
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<th>Testing Accuracy</th>
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Conclusions: MTX has a known inhibitory effect on several target enzymes, resulting in disruption of the folate cycle and a subsequent decrease in production of DNA precursors, disruption of methyl-dependent reactions, and accumulation of adenosine, which has anti-inflammatory properties. Due to the importance of the folate pathway it is unlikely that altered drug response is a consequence of variation in a single gene, rather a network or pathway of genes may be of interest. We have identified SNPs in the mitochondrial (MTHFD2) and purine synthesis (ATIC) pathways which may, in combination, play a role in MTX response in JIA.

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Purpose: Rheumatoid arthritis (RA) is an inflammatory arthritis with a peak age of onset ~50, although childhood cases occur. There is a strong association between certain HLA-DR alleles and RA. RA associated alleles encode DRβ1 chains with conserved amino acid sequence in positions 70–74. The molecular structure encoding the susceptibility residues is termed the shared epitope (SE). While associations between SE and risk of RA is well established, some alleles (e.g. *0401) seem to confer a greater degree of risk than others (*0101). Tezenas Du Montcel et al proposed a classification in which some SE alleles conferred more susceptibility than others. While SE alleles have been evaluated in childhood cases of RA, most cohorts were small (n < 50), and used low resolution DNA typing. We sought to investigate possible hierarchy of SE alleles in the largest cohort assembled to date of RA in children.

Methods: Cases were 189 children with JIA who had one or more positive tests for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (CCP) antibodies. Controls were 100 healthy Non-Hispanic White (NHW) adults. High resolution sequence based HLA-DRB1 genotypes were determined on cases and controls. In addition DRB1 genotypes were available on 273 healthy NHW controls. Per Tezenas Du Montcel et al, SE alleles were classified as follows: S2: (KRAA at amino acid positions 71–74) *0401, *1303; S3P: (QRAA) *0101, *0102, *0404, *0405, *0408, *1001, *1402. All other alleles were designated as low-risk (L) alleles. Logistic regression was performed using NHW cases and controls to calculate the odds ratio of various combinations of SE alleles (L/L, S3P/L, S2/L, S3P/S3P, S2/S2, S3P/S2).

Results: The mean age of onset of RA was 10.7 years. Of 87 children tested for CCP antibodies, 72% were positive. Of 21 African-American (AA) cases 48% carried 1 or 2 SE alleles. Of 25 Hispanic children 76% carried 1 or 2 SE alleles. Of the 134 NHW cases, 76% carried 1 or 2 SE alleles compared to 54% of controls (OR = 2.73, p < 0.00001). A significantly greater proportion of cases carried 2 copies of SE alleles compared to controls (51.3% vs. 54%, OR 8.1, p < 0.0001). The effect of the number of risk alleles (SE) was very significant (OR = 2.5 (95% CI: 1.5–4.2) for each additional risk allele, p = 0.0003). There was a greater risk for S3P/S2 individuals than expected based on the number of risk alleles alone (OR = 2.9 (95% CI: 1.1–7.4), p = 0.025). Genotype-specific risk estimates with L/L as reference group suggested a hierarchy of risk, with highest risk among those who had a S2 and a S3P allele (Table).

Conclusions: This is the largest described cohort of children with RA. We confirm the association between SE alleles and susceptibility to RA in children. The excess risk conferred by individuals who carry the combination of S2/S3P risk alleles suggests that children with DRβ1 chains containing KRAA/QRAA might be especially prone to RA.

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Purpose: Juvenile idiopathic arthritis-associated uveitis (JIA-U) can lead to complications such as cataracts, glucoma, and synchiae, and increase risk for vision loss and blindness. Retrospective studies show an association between polymorphisms of HLA class II genes and JIA-U, especially in females with the oligoarticular subtype and early disease. While HLA-DR11 and HLA-DR13 alleles increase susceptibility to disease, HLA-DR1 is protective. Most studies have not included children who have poly RF (-) JIA-U. We sought to validate previously reported HLA associations and investigate the association between HLA-DRB1 in oligo- and polyarticular RF (-) JIA-U. Most prior studies also have not examined the effect of carriage of two risk alleles, which we sought to do.

Methods: Thirty children of Northern European ancestry with oligo- or polyarticular JIA-U were followed in pediatric rheumatology and ophthalmology clinics. Chart reviews confirmed the diagnoses of JIA and uveitis. Cases and controls were matched for ethnicity. High resolution sequence based typing was performed to determine HLA-DRB1 genotypes. Statistical analysis was performed using chi-square or fisher’s exact test for odds ratio (OR).

Results: Of 30 subjects, 43.3% were females, 76.7% were ANA positive, 83.3% had oligo JIA and 16.7% had RF (-) poly JIA. Mean age of JIA...
diagnosis was 3.0 years (SD 2.4). Of 10 subjects, mean age of JIA-U diagnosis was 3.4 years (SD 2.5) with a mean of 20 months (SD 28.5) of arthritis before uveitis onset. In our cohort, we found the following DR13 alleles: *0101 (9), *1302 (2), and *1303 (2), and the following DR11 alleles: *1101 (4), and *1103 (3). There was evidence for an association between JIA-U and DRB1*13 (OR 1.8, p=0.008), and DRB1*11 (OR 6.71, p=0.0003). There was also an association between carriage of either DRB1*11 or DRB1*13 (OR 3.25, P=0.005). There was a very strong association between JIA-U and carrying two copies of risk alleles (DRB1*11 and 13) (OR 30, p=0.000007). There was a decreased frequency of* DRB1*01 among cases with JIA-U compared to controls, although this was not statistically significant, reflecting the modest sample size.

Conclusions: We have validated the reported associations between DRB1*13 and DRB1*11 in JIA-U. We have also demonstrated a strong association between JIA-U and the presence of two risk alleles. These HLA risk genotypes should be further investigated in a large prospective group of children with JIA-U to determine the risk for uveitis severity and associated complications.

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257 Hyaluronidase Mutation (HYAL1) Presenting as JIA, a Description of an Extended Family Provides New Information and Characterizes This Genetic Disorder That Causes Widespread Synovitis, Lisa F. Imundo and Wendy Chung. 1Columbia University, NY, NY, 2Columbia University, New York, NY

Background: More than 10 years ago Natowitcz described a single case of Mucopolysaccharidoses IX, characterized by a lack of hyaluronidase activity coupled with continued biosynthesis of the substrate. The affected case was 14 years old with painful synovitis and hip erosions that eventually required hip replacements. Only this index case has been characterized.

Report: We report a consanguineous Saudi Arabian Family with familial arthropyathy in three siblings. Onset ranged from 4-18yrs. The arthropathy is clinically apparent in large joints primarily hips and knees. Radiographic studies indicate fulminate inflammatory synovitis with septated cysts and early marginal erosive disease. Synovial biopsy indicated synovial hypertrophy with a prominent histiocytic infiltrate, paillary hyperplasia and focal sclerosis. Notable there is no inflammatory infiltrate. The mononuclear cells contained vacuolated granular cytoplasm. The cytoplasm contained glycosaminoglycans. Genetic testing indicated three of the five siblings were homozygous for MFS IX. The mutation in HYAL1 (c.4,4delT) causes premature termination and is predictive of no functional HYAL1 production. The parents and two siblings are heterozygotes. They do not have symptoms of synovitis.

Results: On further radiologic survey of symptomatic and non-symptomatic joints by MRI and joint ultrasound indicated that homozygous children have demonstrated abnormalities and synovitis in every synovial joint, including small joints of the hands and feet. In addition the heterozygote asymptomatic siblings may have a mild phenotype. The only homozygous female has an earlier onset of symptoms and more severe radiographic changes similar to the described index case.

Summary: MFS IX is characterized by clinical symptoms isolated to synovial joints and likely represents an important etiology of familial arthritis. We add important information to further characterize this disease and to define features that can differentiate MFS IX from JIA. Treatments for JIA will not be effective for this genetic disorder characterized by a lack of hyaluronidase, however directed treatments may include making use of commercially available hyaluronidase enzyme.


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258 Leukocyte Expression of Transcription Factor HNF4a, a Regulator of Gene Expression in Polyarticular Juvenile Idiopathic Arthritis, Kaiyu Jiang1, Yannin Chen1, Mark Barton Frank2 and James N. Jarvis1. 1Dept of Pediatrics, U of OK College of Medicine, 2Oklahoma Medical Research Foundation

Objective: Our previous work has shown that there are distinct gene expression profiles in peripheral blood mononuclear cells (PBMC) and in granulocytes derived from patients with polyarticular juvenile idiopathic arthritis (JIA) compared with healthy control children of the same age and sex. Network analysis of these differentially expressed genes demonstrates that many of those genes are under the control of a single transcription factor, hepatocyte nuclear factor alpha (HNF4A). Furthermore, HNF4A appears to determine both response to therapy and achievement of remission. However, HNF4a has not previously been known to be expressed in leukocytes. To understand the role of HNF4a in JIA, we examined its expression in PBMC subsets and granulocytes.

Method: PBMC, CD4+ T cells, CD8+ T cells, CD14+ monocytes, CD19+ B cells and granulocytes were isolated using conventional methods. RNA was separately extracted and reverse transcription- polymerase chain reaction was used to detect the expression of HNF4a mRNA. Immunofluorescence staining and confocal microscopy were used to observe the expression of HNF4a protein. The DECODE database (SABiosciences Company) was used to search HNF4a binding sites within the differentially expressed genes.

Results: Polymerase chain reaction (PCR) analyses revealed that expression of HNF4a mRNA is leukocyte subset-dependent. PBMC, T cells and granulocytes, but not not CD14+ monocytes or CD19+ B cells, express HNF4a mRNA. Immunofluorescence staining for HNF4a was used to detect HNF4a in leukocyte subsets. HNF4a is expressed in granulocytes in a distinct pattern demonstrating two cell subsets. The first population observed on confocal microscopy consisted of CD66b bright/HNF4a dim cells, and the second consisted of HNF4a bright/CD66b dim cells. In T cells, the HNF4a signal was significantly brighter in CD4+ cells than CD8+ cells. All of these findings were observed in healthy children, healthy adults, and children with JIA. Thus, expression of HNF4a is not in itself pathological, and HNF4a may an important and previously unrecognized regulatory protein. Bioinformatics analysis of the promoter regions of ZNF281, IER5 and OA22, genes shown in Ingenuity analysis of PBMC array data from children with JIA to be regulated, demonstrated sequence motifs typically associated with HNF4a binding.

Conclusion: HNF4A is an important systems hub that emerges from microarray analysis of JIA leukocytes. This transcription factor, which has not previously been demonstrated in leukocytes, may play a role in both disease pathogenesis and response to therapy. Expression of HNF4a was found in CD4+ and CD8+ T cells and neutrophils and was seen in both healthy children and children with JIA. Given the potential importance of HNF4a is regulating response to therapy in JIA, we believe that these studies may shed light on potential new targets of therapy in this challenging disease.

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259 Low Serum Levels of NT-proCNP in Children with Poly-Articular Onset Juvenile Rheumatoid Arthritis, Fozia Khan1, Ann Pokelsel2, Lori Gallia2, Mary Toth1 and Hulya Bukulmez2. 1Akron Children’s Hospital, NEOUCOM, Akron, OH and MetroHealth Medical Center, CWRU, Cleveland, OH, 2Akron Children’s Hospital, NEOUCOM, OH, 3MetroHealth Medical Center, CWRU, Cleveland, OH

Children with juvenile rheumatoid arthritis (JRA) develop longitudinal growth delay. Increased levels of proinflammatory cytokines (IL-6, TNF-α) in serum and in synovial fluid have been blamed for suppressing the local and systemic growth factors that have essential paracrine role in endochondral bone growth. Aside from growth hormone signaling pathway, it is unknown whether other growth factors that regulate the endochondral bone growth are affected in JRA.

C-type natriuretic peptide (CNP) has been recently described as an essential paracrine factor for normal endochondral bone growth. Serum level of N-terminal pro-peptide of CNP (NT-proCNP) has been suggested to be a marker for endochondral bone growth. In this study, we aimed to investigate whether CNP signaling is affected during active juvenile inflammatory arthritis in children by measuring the serum NT-proCNP levels during active disease and investigated whether serum NT-proCNP levels correlated with the serum IL-6 and TNF-α levels.

We collected clinical and laboratory data and serum from children diagnosed with juvenile rheumatoid arthritis (JRA) according to ACR criteria (n=18, 9 pauci-articular, 8 poly-articular, and 1 systemic onset JRA). Concurrent clinical and laboratory data were collected from patients during their enrollment in the study as a part of their routine care. Pro-inflammatory cytokine levels and the NT-proCNP levels were measured using ELISA.
Z-scores of NT-proCNP levels for each patient were calculated using NT-proCNP levels of age matched healthy children. Statistical analysis software was used (SAS 9.2) to calculate the correlations between the z-scores, cytokines and laboratory data.

All patients with JRA had low NT-proCNP z-scores compared to age matched controls. Poly- and systemic JRA patient’s z-scores were significantly lower. IL-6 levels showed negative correlation with the z-scores in children with poly-JRA (r = -0.67, p = 0.00). When stratified for gender, correlation of z-scores with IL-6 level became significant (r = -0.99, p = 0.034). Sedimentation levels correlated with TNF-α levels in poly-JRA patients (r = 0.91, p = 0.003), but TNF-α levels correlation with NT-proCNP z-scores did not reach statistical significance. Seven of eight poly-JRA patients were under treatment with Methotrexate (20mg/m²) and five were also treated with oral prednisone (>0.5mg/kg/d). The mean z-scores of NT-proCNP in patients who used prednisone (n = 5) were not different than those who did not use prednisone (n = 3).

Serum NT-proCNP levels of children with JRA are lower than age matched controls. In poly-articular onset JRA patients, the serum levels of IL-6 show negative correlation with z-scores of NT-proCNP. In addition to ongoing systemic inflammation, patients with poly-JRA were also being treated with medications such as methotrexate and prednisone which might lower the NT-proCNP levels. Further studies with larger JRA patient population are necessary to further delineate the disruption of CNP signaling during JRA. Serum NT-proCNP levels could be a biomarker for endochondral bone growth in children with JRA.

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260 Novel Founder Mutation in IL1RN Accounts for Deficiency of the IL-1 Receptor (DIRA) in Brazil.

Adriana Almeida Jesus4, Clovis Artur Almeida Silva3, Peter W. Kim2, Tuyet H. Pham2, Débora Romeo Bertola3, Magda Carneiro-Sampaio2, Barbara Yang2, Deborah Stone2, Dawn Chapelle2, Nicole Plass2, Massimo Gaddina3, John Sims3, Hateem El-Shanti3 and Raphaela Goldbach-Mansky2.

Objective: To describe the clinical, immunological and genetic phenotype of 2 unrelated patients from Brazil presenting with pustular skin disease, osteolytic bone lesions and systemic inflammation and incomplete responses to multiple DMARDs.

Patients and Evaluation: Two Brazilian patients with perinatal onset skin pustulosis and osteolytic bone lesions and systemic inflammation, consistent with the clinical diagnosis of DIRA were evaluated and genetic analysis of the IL1RN gene locus was performed. Multi-disciplinary clinical evaluation including a total body MRI, and immunological and laboratory characterization of the structure and function of the mutated gene and encoded protein were performed to characterize the inflammatory phenotype of these patients.

Results: Both patients had classical pustular skin lesions with a neutrophilic infiltrate in the dermis and epidermis. One patient presented with clinically concerning skin lesions, she has non-fusion of the os odontoid with the body of the dens (C2) and an incomplete posterior arch of C1 leading to an over 7 mm atlantoaxial subluxation between head flexion and extension. Post-inflammatory fusion of several lower cervical and thoracic spine lesions to the formation of a gibbus. Genetic analysis of IL1RN (isoform 1) showed a homozygous frameshift at base pair deletion (g.213–228delAGAT-GTGTTACCCAT, p.72–77delDVPI) in both girls leading to 5 amino acid deletion. Expression levels of messenger RNA were reduced on RT PCR and the mutated protein was expressed at low levels compared to healthy controls and heterozygous parents. Modeling of the mutated protein predicted a severe defect in the secondary structure and functional analysis confirmed no binding of the protein to the IL-1 receptor. Both patients had an immediate response to treatment with the recombinant IL-1 receptor antagonist, anakinra, with complete resolution of skin lesions and normalization of systemic and organ specific inflammation. The patient’s parents were carriers for the mutation but clinically asymptomatic.

Conclusions: A novel founder mutation in IL1RN accounts for 2 cases of DIRA from 2 unrelated Brazilian families. The clinical signs and symptoms in these patients are similar to those previously reported. In contrast to the previously reported cases of DIRA, in whom the mutated protein is not secreted, patients with the Brazilian mutation express low levels of the mutated protein. The severity of the 5 AA deletion was predicted based on modeling data and the response to the recombinant IL-1 receptor antagonist, anakinra, was immediate with complete resolution of inflammatory disease manifestations.

Conclusion: The Camptodactyly Arthropathy Coxa vara Pericarditis (CACP) syndrome is an autosomal recessive disease characterised by congenital camptodactyly, no inflammatory arthropathy, joint failure, synovial hyperplasia, coxa vara, and thickening of the pericardium. The causative gene for CACP is PRG4 that is located on chromosome band 1q25–31 and consists of 12 exons. It encodes for a mucin-like glycoprotein named “proteoglycan-4” (PRG-4) which acts as the major surface lubricant for joints and tendons.

Objectives: 1. To investigate possible genomic alteration in patients with clinical manifestations of CACP. 2. To perform a comprehensive analysis of the PRG-4 gene.

Patients and Methods: Six unrelated patients and two pairs of siblings (2 sisters, 1 sister, 1 brother) with a phenotype resembling CACP syndrome were referred to us for mutational analysis of PRG-4 gene. The age of onset was mainly at birth (median age at diagnosis 5.5 years). Genomic DNA was extracted by peripheral blood and polymerase chain reaction was performed to amplify PRG-4 exon sequences including intro-exon boundaries using specific primers. The coding regions were sequenced, with the exception of 800bp, within exon 6 due to highly repetitive motifs.

Results: Six novel homozygous mutations within CACP gene were identified in seven patients. The 2 sisters harboured the same nonsense alteration (Y1216X) that cause a frame-shift that creates a premature stop signal leading to the production of a truncated protein. Four mutations were small deletions of 1bp, 2bp and 5bp, three of which located within exon 6. These deletions cause frame-shift mutations and create a premature stop codon. In the remaining patients, we detected one substitution affecting the donor splice site (IVS9+3A>G); the bioinformatics analysis of this alteration predicts a decrease of the strength of the new splice site sequence that could be responsible for an aberrant splicing of the pre-mRNA transcript. The analysis of CACP protein would be necessary to test the predicted effect of the mutations.

Conclusions: CACP syndrome is a rare disorder often misdiagnosed with other paediatric connective tissue diseases. This is the first study analysing the largest PRG-4 coding region, and it allowed identifying a new set of molecular aberrations associated with the occurrence of CACP syndrome.

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and signaling, and plays an important role in tissue and wound repair. OPN has been implicated in IFN-α production, and participates in monocye/ macrophage recruitment to kidneys in SLE, where it may functionally contribute to dysregulated tissue repair and fibrosis associated with chronic inflammation. We investigated the relationship of OPN protein levels and genetic variants with disease manifestations in pediatric SLE (pSLE), a subset with an increased proportion of lupus nephritis compared with SLE of adult onset.

Methods: DNA and plasma were collected from 72 (52 female; 20 male) pSLE patients (age of SLE onset < 18 years), and 51 healthy controls (32 female; 19 male) consisting of 35 unaffected siblings and 16 unrelated young people. All subjects were ≤ 22 years at time of blood draw. 49 pSLE patients had adequate clinical data to complete SLICC/ACR damage index (SDI) scores; disease activity was scored on all patients using the SELENA-SLEDAI index. Circulating plasma OPN (cOPN) was measured by ELISA. SNP genotyping was performed by Illumina arrays. Serum IFN activity was measured by WISH-cell assay in 49 pSLE samples. Immunohistochemistry by standard fluorescence techniques was performed on anonymous WHO class IV lupus nephritis tissue obtained from our tissue core lab. Statistical analysis was performed using Student’s t test, Pearson’s correlation, Fisher’s exact test, and multivariate linear and logistical regression modeling.

Results: pSLE patients with active disease (SLEDAI > 4) had high IFN activity (p = 0.0009), as in previous research, but disease activity did not correlate with cOPN in this cross-sectional analysis. Overall, cOPN was significantly higher in pSLE versus healthy unrelated controls (p < 0.001) with increasing cOPN correlating with SDI (R = 0.5; p = 0.0003). High IFN activity was more likely in pSLE patients with cOPN levels in the top quartile compared with those in the bottom (p = 0.03); similarly, pSLE patients with an SDI > 0 were more likely to have high IFN activity than those with SDI = 0 (p = 0.02). Considering disease status, 5 OPN variants previously associated with SLE, and gender as covariates in a multivariate regression analysis, the 3’ untranslated region (UTR) single nucleotide polymorphisms (SNPs) of OPN (rs1126772 and rs9138) were associated with increased cOPN (p = 0.004 and 0.02, respectively). Interestingly, both 3’ UTR SNPs as well as a promoter variant, rs2857094, were associated with SDI > 0 (ORs of 1.5–2.2; p < 0.01 for each SNP); we also observed rs2857094 allelic association with increased percentage of glomerulonephritis in pSLE (87% vs. 60%; p < 0.0001). In 3/3 renal biopsies from patients with diffuse proliferative glomerulonephritis, we noted the co-localization of OPN with macrophage marker CD68.

Conclusion: Genetic variants regulate OPN levels, which may contribute to the progression of tissue injury in pSLE, possibly by tissue-infiltrating monocytes/macrophages. The potential of OPN as a predictor of global and/or renal damage in pSLE requires further study in a longitudinal cohort.

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Predominance of Complement Components C1q and C4 Bound to Circulating Immune Complexes (CICs) in Juvenile Idiopathic Arthritis (JIA): Support for Classical Pathway Activation. Brooke E. Gilliam1, Melinda R. Reed2, Anil K. Chauhan1, Amanda Dehlendorf2 and Terry L. Moore2, 1 Saint Louis University, St. Louis, MO, 2 Saint Louis University, St Louis, MO

Purpose: CICs from JIA sera show increased complement activation; however, the scope of involvement from the classical versus alternative pathway remains undefined. To delineate the role of these pathways, we measured activated complement products bound to CICs in sera from JIA patients.

Methods: Sera from 100 JIA patients (87 female, 13 male) were collected, including 68 polyarthritis (41 rheumatoid factor (RF)-negative and 27 RF-positive) and 32 oligoarthritis patients. The mean age was 11.0 years and mean disease duration was 4.1 years. Sera from 17 healthy individuals were also analyzed. C1q, C3, C4, and C4a, and membrane attack complex (MAC) bound to CICs were measured by enzyme-linked immunosorbsen assay (ELISA). Cut-off values were established as the mean + 2 standard deviations of the healthy control results. IgA and IgM RF and IgG anti-cyclic citrullinated peptide (anti-CyP) antibodies were measured by ELISA. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and disease activity were obtained from patient records.

Results: Forty-eight patients were positive for C1q CICs, 45 for C4 CICs, 36 for C3 CICs, 29 for MAC CICs, and 25 for C3d CICs. C1q, C3, C4, MAC CICs were significantly elevated in JIA patients compared to healthy controls (p<0.05). MAC CICs demonstrated significant correlation with C1q CIC (r=0.65), C4 CICs (r=0.61), C3d CICs (r=0.33), and C3 CICs (r=0.27) (p<0.05). C1q CICs also correlated significantly with C4 CICs (r=0.72), C3d CICs (r=0.27), and C3 CICs (r=0.22) (p<0.05). C3 and C3d CICs demonstrated significant correlation with each other (r=0.32, p=0.002). IgA RF correlated significantly with C1q CICs (r=0.20, p=0.049). IgM RF demonstrated a negative correlation with C3 (r=-0.24, p=0.02), but correlated positively with C4 CICs (r=0.30, p=0.01). IgG RF was positive for MAC CICs (n=29), 21 (72%) were positive for both C1q CICs and C4 CICs and 13 (45%) were positive for C3. In both polyarticular and oligoarticular JIA, the classical complement pathway (Clq: 46–53% and C4: 44–47%) was more prevalent than the alternative complement pathway (Clq: 35–38%).

Conclusions: The assay used in this study is able to capture CICs bound to complement, which reflects physiologically active complement. The classical complement pathway can be triggered by IgM and IgG-containing CICs in systemic circulation. Our results show that IgM RF correlated significantly with C4 CICs and MAC correlated significantly with C1q and C4 CICs, suggesting a dominant contribution of classical complement activation. Elevated IgA RF and IgM RF have both been associated with destructive disease in JIA. C1q and C4 CICs both correlated significantly with these RF isoforms, indicating a link between classical pathway activation and aggressive disease.

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Rheumatoid Arthritis Susceptibility Loci; PTTPRC, PTTPN2, IKZF3, C5orf30, BLK and CD247 Are Also Associated with Juvenile Idiopathic Arthritis. Anne Hinks1, Steve Eyre2, Paul Martin2, Edward Flynn3, Jon Packham2, Anne Barton2, Jane Worthington4 and Wendy Thomson1. 1Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, 2Arthritis Research UK Epidemiology Unit, University of Manchester, 3Haywood Hospital, University of North Staffordshire

Background: Rheumatoid arthritis (RA) shares similar clinical and pathological features with juvenile idiopathic arthritis (JIA); indeed the strategy of investigating whether RA susceptibility loci also confer susceptibility to JIA has already proved highly successful in identifying novel JIA loci, such as PTPN22, IL2RA and TRAF1/C. There has been a plethora of newly validated RA loci reported in the last year. Therefore the aim of this study was to test SNPs robustly associated with RA in a large cohort of JIA cases and controls to investigate the overlap between these diseases and identify novel JIA loci.

Methods: 29 SNPs that showed validated association with RA and had not been investigated previously in JIA were genotyped in JIA cases (n=1337) and healthy controls (n=2781) using Sequenom MassArray technology. Genotype and allele frequencies were compared between cases with JIA and controls using the Cochrane-Armitage trend test implemented in PLINK and allelic odds ratios (ORs) and their 95% confidence intervals (CIs) calculated.

Results: Strong evidence for association with JIA was seen for eight SNPs. These include a SNP, rs10919563, in PTTPRC (p trend = 2.5 × 10^-6 OR 0.68 95% CI 0.58–0.8) rs7242029, in PTPN2 (p trend = 0.0003 OR 1.26 95% CI 1.11–1.43), rs2875207 in IKZF3 (p trend = 0.0004 OR 1.21 95% CI 1.09–1.34), rs26252 in C5orf30 (p trend = 0.002 OR 0.84 95% CI 0.75–0.94), rs2736340, in BLK (p trend = 0.000 OR 1.19 95% CI 1.06–1.34) and rs1773560 in CD247 (p trend = 0.005 OR 0.87 95% CI 0.79–0.96). There was additional evidence for association of two novel SNPs in genes previously associated with JIA, rs13119723, in the IL2/IL21 region (p trend = 7.5 × 10^-6 OR 0.71 95% CI 0.61–0.83) and rs706778 in the IL2RA gene (p trend = 0.0002 OR 1.22 95% CI 1.1–1.35).

Conclusions: The association of PTPN2 with JIA in the current study validates the findings of a previous US study, confirming it as a JIA locus. The other loci identified are novel and will require validation in independent JIA datasets. To date we have investigated 44 RA loci in JIA and of those 27 are associated with both diseases. The overlap is remarkable for two diseases which, although sharing some phenotypic features, are clinically distinct entities.

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Role of IL-1β in the Development of Human TH17 Cells: Lesson from Patients Carrying NLRP3 Gene Mutations. Denise Lasiglie, Elisabetta Traggiai, Federica Penco, Silvia Federici, Andrea Accogli, Antonella Buoncompagni, Alberto Martini and Marco Gattorno. G. Gaslini Institute, Genova, Italy

Purpose: Interleukin 17 (IL-17)-producing CD4+ helper T cells (Tγ+17) represents a lineage of effectors CD4 T cells abundant at mucosal interfaces, where they contain infection with pathogenic bacteria and fungi. Beyond this function TH-17 cells have been linked to the pathogenesis of several inflammatory and autoimmune diseases. At present, understanding of Th-17 differentiation is limited to the mouse system and in humans remains still a puzzled issue. Recently it has been proposed IL-1β as a pivotal cytokine in driving Th-17 differentiation. Cryopyrin-associated periodic syndromes (CAPS) are a group of inflammatory diseases associated to mutations of NLRP3 gene encoding the inflammasome component cryopyrin. These mutations determine an exaggerated IL-1β secretion by monocytes upon Toll like receptors (TLRs) stimulation. We have investigated whether the altered IL-1β secretion, secondary to NLRP3 mutations, could affect the IL-23/IL-17 axis in CAPS patients.

Methods: IL-17 serum level has been evaluated by ELISA assay. Expression of CCR6 and CD161, two TH-17 specific markers, has been analyzed on CD4+ memory T cells by flow cytometry. Frequency of Tγ+17+ cells has been quantified upon stimulation with staphylococcus enterotoxin B (SEB). Production of IL-1β by monocyte derived dendritic cells (MoDCs), in response to TLR ligands, has been quantified by ELISA. CAPS patients have been analysed before and after anti-IL1β treatment.

Results: Untreated CAPS patients display significant increased level of serum IL-17 as well as of Th-17+ T cells respect to age matched controls. Both IL-7 serum levels as well as Th-17 frequency decrease after IL-1β treatment. Also production of IL-1β and IL-23 by MoDCs is increased in CAPS patients, and after anti IL-1β treatment production of both cytokines is significantly reduced.

Conclusions: These findings further support a central role of IL-1β in the differentiation of Tγ+17 in human inflammatory conditions.

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Subtype Specific Genetic Associations for Juvenile Idiopathic Arthritis (JIA); ERAP1 with the Euthesis Related Arthritis Subtype and IL23R with Juvenile Psoriatic Arthritis. Anne Hinks1, Paul Martin1, Edward Flynn2, Steve Eyre3, Jon Packham3, Anne Barton1, Jane Worthington1 and Wendy Thomson1. 1Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, 2Arthritis Research UK Epidemiology Unit, University of Manchester, 3Haywood Hospital, University Hospital of North Staffordshire

Background: There is now strong evidence supporting the hypothesis of common autoimmune susceptibility loci. There is also evidence to support clustering of loci in diseases that share similar clinical phenotypes e.g. Ankylosing spondylitis (AS), psoriasis (Ps), psoriatic arthritis (PsA) and they appear to have some overlapping susceptibility loci such as IL23R and ERAP1.

Juvenile idiopathic arthritis (JIA) is an umbrella term for all chronic childhood arthropathies and can be classified into 7 subtypes on the basis of features present in the first 6 months of disease. It includes the enthesis related arthritis (ERA) subtype which displays symptoms similar to AS and juvenile onset psoriatic arthritis which has similarities to psoriatic arthritis and psoriasis. We therefore hypothesized that the two well-established susceptibility loci IL23R and ERAP1 could also confer susceptibility to these JIA subtypes, to this end the most associated SNP within each of these genes have been selected for genotyping across all JIA and also analysed stratified for each subtype.

Methods: SNPs in IL23R (rs1129026) and ERAP1 (rs30187) were genotyped in JIA cases (n=1054) and healthy controls (n=5200). The numbers genotyped per ILAR subgroup were: Systemic onset (n=164), persistent oligoarthritis (n=297), extended oligoarthritis (n=147), Rheumatoid factor (RF) negative polyarticular JIA (n=215), RF positive polyarticular JIA (n=68), enthesis related JIA (n=63), psoriatic JIA (n=76) and unclassified (n=24). Genotype and allele frequencies were compared between all JIA cases and controls using the Cochrane-Armitage trend test implemented in PLINK and allelic odds ratios (ORs) and their 95% confidence intervals (CIs) calculated. Stratified analysis by subtype was performed.

Results: Neither the SNP in the IL23R gene, rs1129026, nor the SNP in the ERAP1 gene, rs30187, were significantly associated (p>0.05) with the total JIA dataset. Stratification by subtype found that the IL23R SNP showed significant association in the psoriatic arthritis subtype (p=0.04 OR 0.4 95% CI 0.16–0.98) and a trend towards association in the enthesis related subtype (p=0.15 OR 0.52 95% CI 0.21–1.28). The enthesis related arthritis (ERA) subtype showed strong association with ERAPI SNP (p=0.004 OR 1.69 95% CI 1.18–2.44). For both SNPs the association is in the same direction as in the original study.

Conclusions: We present evidence for subtype specific association of the IL23R gene with juvenile psoriatic arthritis and ERAP1 gene with ERA. The findings will require validation in independent JIA datasets. These results suggest distinct pathogenic pathways in these subtypes.

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The Role of Platelets and CD40L in the Pathogenesis of Kawasaki Disease. Parmi Arjmand2 and Rae S. M. Yeung1. 1Hospital for Sick Children, Toronto, ON, Canada, 2University of Toronto, The Hospital for Sick Children, Toronto, ON, Canada

Background: Kawasaki Disease (KD) is a disease of childhood characterized by systemic inflammation leading to coronary artery damage. Although its etiology remains unknown, superantigens are among the triggers of disease. Lactobacillus Casei Cell Wall Extract (LCWE) induces a disease in mice which mimics KD closely in time-course, histological changes and susceptibility in the young. LCWE contains both a superantigen and a TLR-2 ligand. KD is characterized by marked elevation in platelet numbers. Recent studies have found CD40L expression on platelets and CD4+ T cells to be associated with coronary artery aneurysms in children with KD. CD40L is a member of the TNF family of proteins which is expressed on T-cells. Interestingly, it is also stored in platelet granules and binds to an integrin receptor, gpIIb/IIIa, on platelets. Platelets also store and release Matrix Metalloprotease 9 (MMP-9) upon activation – an enzyme essential for coronary artery break-down and aneurysm formation in KD. Here, we aim to elucidate the role of platelets in the pathogenesis of KD: specifically, the effect of LCWE stimulation on platelet activation, CD40L and MMP-9 expression and release, and its role in coronary artery disease.

Methods: In vivo and in vitro platelet activation (α-granule release, microparticle formation, aggregation, integrin receptor activation) is assayed using flow-cytometry. In vivo, blood is obtained from C57/BL6 mice injected with LCWE or PBS; in vitro, platelets are stimulated with LCWE and assayed. Platelet MMP-9 release is studied by determining protein and enzymatic activity using Western blots and zymography respectively. To differentiate between superantigenic versus TLR-2 agonistic activity of LCWE in stimulating platelets, blood is also drawn from TLR-2 knock-out mice or treated with a TLR-2 blocking mAb prior to analysis.

Results: Stimulation of platelets with collagen and ADP agonists achieves maximal platelet CD40L and P-selectin upregulation in vitro.TLR2 ligand PAM3CSK4, LCWE and SEB are also able to induce CD40L and P-selectin upregulation, gpIIb/IIIa activation, leukocyte aggregation and microparticle formation. Upregulation of these platelet activation markers were also observed in vivo after stimulation with the classic superantigen, SEB. Interestingly, LCWE induced platelet activation is unaffected in the absence of TLR-2 signaling, evidenced in assays using TLR2 deficient mice and also with addition of TLR-2 blocking antibody pointing superantigenic and not TLR2 activity as the trigger of platelet activation.

Conclusions: Our results suggest that superantigenic stimulation with LCWE activates mouse platelets α-granule release, CD40L upregulation and integrin receptor gpIIb/IIIa. Moreover, we show that TLR-2 signaling does not contribute to platelet activation. Establishing a role for platelets and CD40L in the pathogenesis of KD may have important implications in design of new therapeutic agents in KD.

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Urinary Biomarkers To Distinguish Class IV vs Class V Lupus Nephritis

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Background: Up to 80% of children with systemic lupus erythematosus have lupus nephritis (LN). The ISN/RPS Morphologic Classification of LN reports on histological features that differentiate between various forms of LN, such as Diffuse Proliferative Class IV and Membranous Class V lesions. Kidney biopsies are the choice for diagnosis of LN, but are impractical to accurately assess the course of LN in clinical practice.

Objective: Discover non-invasive urinary biomarkers that can discriminate LN subtypes using proteomics, peptidomics and metabolomics.

Methods: We used 2-dimensional gel electrophoresis (2-DGE), NMR-based metabolomics, surface-enhanced laser desorption/ionization time of flight MS (SELDI), and iTRAQ liquid chromatography tandem mass spectrometry (LC MS/MS) to investigate novel biomarkers that could distinguish Class IV vs. Class V LN. Urine samples from children with Class IV LN (n=6) and (pure) Class V LN (n=7) collected within 60 days of a kidney biopsy and those of controls with focal segmental glomerulosclerosis (n=4) were tested. Samples were normalized for total protein (2-DGE and LC-MS/MS) or urine creatinine (NMR and SELDI).

Results: Using 2-DGE and MALDI-TOF/MS/MS, we found serum albumin fragments (25kDa) and alpha-1 glycoprotein (153kDa) significantly over-expressed in class IV vs. class V LN. Using SELDI, we identified Alpha-1 Antitrypsin (A1AT). This protein was significantly (p < 0.01; AUC 0.90) over-expressed in Class V vs Class IV LN and FSGS controls. Principal component analysis of NMR metabolomics spectra suggested decreased levels of citrate and increased levels of taurine in Class IV when compared to Class IV patients, while iTRAQ -LC-MS/MS uncovered the most differences between the groups. Among proteins upregulated in Class V LN were apolipoprotein D, lipocalin-like prostaglandin D synthetase, inter-alpha-trypsin inhibitor heavy chain 4, Caspase 10, uromodulin and CD14. Those most upregulated in Class IV LN were vitamin D binding protein, ceruloplasmin, hemopexin, A1BG and orosomucoid. A1AT has been linked to SLE flares and hemopexin is associated with glomerular disease.

Conclusions: The discovery of non-invasive biomarkers that can distinguish LN subtypes would greatly aid in diagnosing and monitoring treatment in LN.

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ACR Poster Session A
Rheumatoid Arthritis - Animal Models: Cytokines, Novel Therapeutics and Mechanisms of Action
Monday, November 8, 2010, 9:00 AM–6:00 PM

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AC430, a Potent JAK2 Inhibitor, Provides Protection in Multiple Inflammatory and Autoimmune Disease Models. Barbara Belli1, 2, M. Suzuki: None; S. L. Nelson: None; J. Pendell: None; A. Kiani: None; L. Das: None; M. Petri: None; K. Greis: None; P. Shiyanov: None; M. Kennedy: None; P. Devarajan: Department of Defense, 2.

AC430, a Potent JAK2 Inhibitor, Provides Protection in Multiple Inflammatory and Autoimmune Disease Models. Barbara Belli1, 2, M. Suzuki: None; S. L. Nelson: None; J. Pendell: None; A. Kiani: None; L. Das: None; M. Petri: None; K. Greis: None; P. Shiyanov: None; M. Kennedy: None; P. Devarajan: Department of Defense, 2.

Rheumatoid arthritis is a multi-factorial disease, and a sub-population of patients who are refractory to current therapy continues to exist. Recent clinical trials have demonstrated the safety and efficacy of small molecule inhibitors of the JAK kinase pathway in alleviating RA symptoms. We have evaluated the efficacy of AC430, a potent JAK2 inhibitor, AC430 which demonstrates in vitro and in vivo activities comparable or superior to the activities of current clinical stage JAK inhibitors. In in vitro binding assays, AC430 binds potently to JAK2 and TYK2 with sub-nanomolar Kd values. In a TF-1 cell-based GM-CSF/JAK2/STAT5 driven transcriptional reporter system, AC430 inhibited reporter activity with an IC50 of 63 nM. Baf3 cell lines were generated
Combined Depletion of Interleukin-1 and Interleukin-6 Does Not Exceed Single Depletion of Interleukin-1 in TNF-Mediated Arthritis. Slivka Hayer, Birgit Niederreiter, Josef Smolen and Kurt Redlich. Medical University of Vienna, Department of Internal Medicine III, Division of Rheumatology, Vienna, Austria

Background: Previous studies demonstrated a regulatory role of interleukin 1 (IL-1) in inflammatory cartilage damage and bone destruction in human tumor necrosis factor transgenic (hTNFtg) mice, an animal model for Rheumatoid Arthritis (RA). Moreover, blocking of IL-6 has been shown to reduce local bone erosions in this model. Therefore we wanted to investigate the effect of a combined depletion of IL-1 and IL-6 on the development and severity of inflammatory, erosive arthritis.

Methods: We first crossed IL-1β and β deficient (IL-1−/−) mice with IL-6−/− mice to generate IL-1−/−IL-6−/− double knockout mice. We next interscrossed these animals with arthritogenic hTNFtg mice to receive IL-1−/−IL-6−/− hTNFtg mice. We weekly assessed clinical signs of arthritis in hTNFtg, IL-1−/−hTNFtg, IL-6−/−hTNFtg, IL-1−/−IL-6−/− hTNFtg mice starting from week 4 after birth until week 16. We then sacrificed all mice from all groups for histological examinations to assess arthritis in the knee joints to compare the severity of inflammatory, erosive arthritis. We also assessed the bone erosions in the knee joints to compare the severity of inflammatory, erosive arthritis.

Results: We found a significant reduction in the clinical signs of arthritis, indicated by an increase of paw swelling and a decrease in grip strength, in IL-1−/−IL-6−/− hTNFtg mice compared to their hTNFtg littermates. In line with these findings we observed a significant decrease in synovial inflammation in IL-1−/−IL-6−/− hTNFtg mice when compared to IL-1−/− hTNFtg mice. Moreover, the number of synovial TRAP+ osteoclasts was markedly diminished in IL-1−/−IL-6−/− hTNFtg mice and reduced osteoclast formation, which was accompanied by significantly less subchondral bone erosions. Additionally, we found a conserved articular cartilage structure showing almost no cartilage degradation in IL-1−/−IL-6−/− hTNFtg mice compared to their hTNFtg littermates. In IL-1−/−IL-6−/− hTNFtg mice clinical, as well as, histological signs of disease, including joint inflammation, bone destruction and cartilage damage were also significantly diminished when compared to IL-1−/− hTNFtg mice. However, by comparing IL-1−/−IL-6−/− hTNFtg mice with IL-1−/− hTNFtg mice we found a similar reduction on synovial inflammation, as well as subchondral bone erosions and articular cartilage destruction.

Conclusion: The phenotype of IL-1−/− hTNFtg mice does not differ from IL-1−/− hTNFtg animals indicating no synergistic effects when IL-1 and IL-6 are simultaneously blocked in TNF-mediated arthritis.

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were all significantly lower in the PLX5622 treated animals compared to vehicle-treated animals. The counts of the direct target cell population of macrophages, osteoclasts, and T-cells were lower in the joints of the PLX5622 treatment group. The benefit on joint function of these clinical, histopathological and cellular readouts was also reflected in an increased range of motion in the knee joint of PLX5622 treated animals, compared to the vehicle controls.

**Conclusion:** Inhibition of Fms kinase activity by the potent and highly selective inhibitor PLX5622 results in substantial efficacy in an aggressive model of RA and warrants further development in clinical studies.

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**HMPL-011, a Small Molecule Compound, Modulates Pro-Inflammatory Cytokine Production, in Part, Via Potentiating IL-10 Production.**

Weihua Gu², Weigang He², Yan Qiu², Zhenhao Zhou², Xiaomin Dai², Wuzhong Shen², Xiaoning Yang², Linfang Wang², Yuan Zhou², Yu Cai², Edwin Lee², Wei Deng², Weiguo Su¹ and Haoran Zhao¹. ¹Hutchison MediPharma Ltd, Shanghai, China, ²Hutchison MediPharma Ltd

**Purpose:** HMPL-011, a small molecular compound, was shown to be effective in reducing clinical arthritis score and joint swelling in collagen induced arthritis (CIA) in mouse (ACR 2010 Abstract). An inhibition on pro-inflammatory cytokines, such as IL-1β, MCP-1 and IL-6, and an increase in anti-inflammatory cytokine IL-10 was found in the arthritis joints. In this study, the mechanism of action of HMPL-011 was investigated.

**Methods:** Cytokine mRNA was analyzed by RT-PCR and protein by ELISA or CBA (Cytometric Bead Array). Phosphorylated MKK3/6 and p38 in RAW264.7 was analyzed by WB. For LPS induced inflammation in vivo, female Balb/C mouse was p.o. treated with HMPL-011 followed by LPS stimulation 30 minutes post HMPL-011 administration. Protein and mRNA levels were assessed 2hr and 8hr after LPS dosing. In IL-10 neutralization assay, IL-10 neutralizing antibody (IgS5-2A5) was dosed i.v. and concurrently p.o. treated with HMPL-011 for 30min, followed by LPS treatment. Plasma cytokines were analyzed as indicated above.

**Results:** HMPL-011 was screened at 10 µM against 48 inflammation related targets, include cytokine release, cytokine, chemokine and glucocorticoid receptor binding, caspases, MMPs, phosphatase and kinase activity, T, B cell proliferation, and NF-κB, NF-AT transcription activity. No significant activity of HMPL-011 was identified, except for the inhibition of IL-1β and IFNγ release (IC50=1.0 µM and 9.7 µM respectively). Furthermore, in a screen against 60 enzymes consisting of receptor tyrosine kinases and other inflammation- related kinases at 10 µM, no significant inhibition was observed. T, B cell activation, macrophage phagocytosis, NK cell cytotoxicity was also not affected by HMPL-011. However, IL-10 expression was found to be elevated by HMPL-011 in LPS stimulated mouse macrophage cells, RAW264.7, and this induction was shown to be inhibited by the p38 inhibitor, SB203580. Moreover, LPS induced MKK3/6 and p38α phosphorylation was shown to be enhanced by HMPL-011 in RAW264.7. In LPS treated mouse, HMPL-011 increased IL-10 at 2hr post LPS treatment, followed by a significant, potent inhibition on IL-6, MCP-1 and IFNγ at 8hr post LPS treatment. In IL-10 neutralized mouse, HMPL-011 anti-inflammatory effect was found to be partially reversed, indicating the anti-inflammatory effect of HMPL-011 is only partially mediated by IL-10.

**Conclusion:** HMPL-011’s anti-inflammatory effect was mediated at least in part through enhancement of IL-10. HMPL-011 may represent a novel class of small molecular drug in arthritis treatment.

**Disclosure:** W. Gu; Hutchinson MediPharma Ltd, 3; W. He; Hutchinson MediPharma Ltd, 3; Y. Qiu; Hutchinson MediPharma Ltd, 3; Z. Zhou; Hutchinson MediPharma Ltd, 3; X. Dai; Hutchinson MediPharma Ltd, 3; W. Shen; Hutchinson MediPharma Ltd, 3; X. Yang; Hutchinson MediPharma Ltd, 3; L. Wang; Hutchinson MediPharma Ltd, 3; Y. Zhou; Hutchinson MediPharma Ltd, 3; Y. Cai; Hutchinson MediPharma Ltd, 3; E. Lee; Hutchinson MediPharma Ltd, 3; W. Deng; Hutchinson MediPharma Ltd, 3; W. Su; Hutchinson MediPharma Ltd, 3; H. Zhao; Hutchinson MediPharma Ltd, 3.
Background: IL-17 plays important roles in synovial inflammation and bone destruction in CIA. IL-27, produced by activated macrophages and dendritic cells, stimulates Th1 cell-mediated immune response and suppress Th17 cell-mediated immune response. Therefore, IL-27 aggravates inflammation in predominant Th1 immune-mediated disease such as proteoglycan-induced arthritis, and suppress inflammation in predominant Th17 immune-mediated disease such as Experimental Autoimmune Encephalomyelitis, Experimental Autoimmune Uveitis and CIA.

Objectives: To investigate IL-27 expression during CIA, and the effect of IL-17 on IL-27 expression in CIA.

Methods: CIA was induced by type II collagen in DBA1 mice. During CIA, mice were sacrificed at day 0, 28, 35, 39, 47, 56, 63 and 68, and knee joint synovial IL-27 expressions were measured by real-time RT-PCR and western blot. In CIA, phosphate-buffered saline (PBS group) or IL-17 (IL-17 group) was injected into knee joints at day 28 and 32, sacrificed at day 35, and synovial IL-27 expressions were determined by real-time RT-PCR, western blot, and immunohistochemistry. Bone marrow-derived dendritic cells (BMDCs), isolated from femur of CIA mice at day 35, were cultured with IL-17, and IL-27 expressions were determined by ELISA.

Results: Knee joint synovial IL-27 expressions were gradually increased during CIA (fig 1). Synovial IL-27 expressions of IL-17 group were significantly high compared to PBS group (fig 2 and 3), and synovial anti-IL-27p28 antibody positive cells were double-stained with anti-CD68 antibody (fig 3). IL-27 expressions of BMDCs were significantly increased by IL-17 (fig 4).

Conclusions: Synovial IL-27 expression was gradually increased during CIA. IL-17 increased IL-27 expressions of synovial macrophages and BMDCs in CIA. These results suggest that IL-17 induced increase of IL-27 expressions from synovial macrophages and BMDCs might be involved in immunopathogenesis of CIA, and IL-17/IL-27 networks may play role as an autoregulatory mechanism.

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IL-32 Aggravated Synovial Inflammation and Bone Destruction, and Increased Synovial NK Cells in Experimental Arthritis Models. Geun-Tae Kim1, Ju-In Kim2, Hua-Shu Jin2, Seong-Hu Park2, Young-Eun Park2, Seung-Hoon Baek2, Jeong-Wook Lee1 and Sung-Ik Kim11 Department of Internal Medicine, Busan St. Mary's Medical Center,2 Department of Internal Medicine, Kosin University, College of Medicine, Busan, Korea, Republic of,3 Department of Internal Medicine, Pusan National University, School of Medicine,4 Research Institute, Pusan National University

Purpose: IL-32 is a novel cytokine that is formally known as natural killer cell transcript 4, and appears to play a role in inflammatory processes and diseases including rheumatoid arthritis. NK cells are known as a regulator in infection, tumor and autoimmunity. But the underlying relationship between them and their effects on inflammatory diseases remain largely unclear. Here, we investigated in mouse model of collagen-induced arthritis (CIA), the role of IL-32 in inflammatory process and the effect of IL-32 on NK cells.

Methods: CIA was induced by type II collagen in DBA1 mice, and PBS (PBS group) or IL-32 (IL-32 group) were injected into both knee joints at day 28 and 32, then mice were sacrificed at day 35. Severity of knee joint arthritis was scored by macroscopy, and synovial inflammation and bone erosion were determined by histology. Synovial expressions of proinflammatory cytokines (IL-1β, TNF-α, IL-17, IL-18, IL-21, IL-23, IFN-γ), chemokines (CCL2, CCL3, CC5, and CCL9), chemokine receptors (CCR2, CCR5, CXCR3, and CX3CR1), were measured by real-time RT-PCR and western blot. Expression
of NK cells was determined by real-time RT-PCR, western blot, and immunohistochemistry using NKp46, a surface marker of NK cell.

Results: Scores of knee arthritis, synovial inflammation and bone erosion were significantly high in IL-32 group compared to PBS group. Synovial expression of proinflammatory cytokines (IL-1β, TNF-α, IFN-γ and IL-18), chemokines (CCL2 and CXCL9) and chemokine receptors (CCR2 and CCR5) that are associated with NK cells migration were significantly increased in IL-32 group compared to PBS group (p<0.05). Expression of synovial NK cells, confirmed by real-time RT-PCR, western blot, and immunohistochemistry, were significant increased in IL-32 group compared to PBS group.

Conclusion: IL-32 increased synovial expressions of proinflammatory cytokines, and aggravated synovial inflammation and bone destruction. IL-32 also induced arthritis in mice and suggests a therapeutic potential of IL-7 neutralization study demonstrates an important role of IL-7-driven immunity in proteoglycan- and PG-induced proliferation of these splenocytes was inhibited by IL-7 neutralization (p<0.05) as compared to the control-treated mice (p<0.015). Most importantly, the low dose of anti-IL-7 receptor-α chain (IL-7Rα) and the common gamma (γc) chain. IL-7 can activate IL-7Rα/γc heterodimeric T cells, overriding suppressive effects of IL-7Rα/IGαM T cells. CD4 T-cell activation achieved by IL-7Rα-mediated immune activation can be inhibited by soluble hIL-7Rα. IL-7 induces T cell-dependent activation of monocytes, B cells, and osteoclasts. Previously we have shown that administration of IL-7 or TSLP enhanced severity of inflammation and joint destruction in collagen induced arthritis. In this study we analyzed IL-7 expression in experimental proteoglycan-induced arthritis (PGA). Furthermore, we assessed the effects of IL-7 neutralization on arthritis and inflammatory activity in PGA.

Methods: Levels of IL-7 were assessed in serum and paw protein lysates of arthritic mice. Splenocytes were cultured in presence of IL-7, PG, or PG-induced proliferation of these splenocytes was inhibited by IL-7 neutralization. Blockage of IL-7 significantly reduced PG-induced proliferation of splenocytes (mean inhibition of 70 ± 8%, p=0.015). Most importantly, the low dose of anti-IL-7 mAb (200μg) was more effective than the 500μg dose in reducing arthritis severity and resulted in a mean arthritis inhibition of 37 ± 5% (mean of day 28-52) as compared to the control-treated mice (p<0.005) on day 28, 33, and 35. Treatment with 500μg anti-IL-7 reduced arthritis as compared with control mice with a mean arthritis inhibition of 24 ± 4 % (mean inhibition day 28-52) although not statistically significant. Total numbers of thymus or spleen, and joints of arthritic mice, and that local IL-7 levels correlate with disease activity. Furthermore, we assessed the effect on body weight. Histopathology analysis revealed reduced cartilage and joint destruction following treatment with compound (p<0.005) in both rat and mice.

Conclusion: Results demonstrate the immense potential of our compounds as immunomodulatory and anti-inflammatory agents as evidenced by cytokine reductions obtained in vitro. Delay in arthritic onset and progression upon administration of our compounds indicate their effectiveness as disease modifying anti-rheumatic drugs. Further in vivo and in vitro studies are in progress to evaluate the efficacy of the compound in other immune disorders prior to the initiation of clinical trials.

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Inhibition of c-Fos/AP-1 Suppresses Passive Anti-Collagen Antibody-Induced Arthritis in Mice. Masaaki Mikami1, Yukihiko Aikawa2, Akira Hashimatro3, Mari Yamamoto2, Hidetoshi Murao2, Hisaka Chaki2, Hirokazu Narai1, Shuichi Hirono1 and Shunshin Shiozawa3. 1Department of Pharmaceutical Sciences, School of Pharmacy, Kitasato University, Tokyo, Japan, 2Division of Rheumatology, Kobe University Graduate School of Health Sciences and Medicine/ The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, 3Division of Rheumatology, Kobe University Graduate School of Health Sciences and Medicine/ The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, 4Research Laboratories, Toyama Chemical Co., Ltd., Toyama, Japan, Research Laboratories, Toyama Chemical Co., Ltd., Toyama, Japan.

Purpose: Activator protein-1 (AP-1) directly regulates the genes that participate in rheumatoid arthritis (RA), including inflammatory cytokines and matrix metalloproteases (MMPs). Anti-collagen antibody (Ab)-induced arthritis (CAIA) in mice is beneficial to study the inflammatory phase of arthritis without involving the priming phase of the immune response. Therefore, to elucidate the involvement of c-Fos/AP-1 in the development of arthritis, the levels of c-Fos/AP-1 in the hind paws were determined, and the effect of a novel c-Fos/AP-1 inhibitor T-5224 on CAIA was investigated.

Methods: CAIA was induced in BALB/c mice by i.p. injection of the mixture of anti-type II collagen (CII) Abs on day 0 and LPS on day 3. The levels of c-Fos/AP-1 in extracts from hind paws were determined using TransAM™ kit on day 0, 3, 4, 7, and 15. T-5224 was orally administered once daily. The effect was assessed by arthritis score, pathological examination, and serum biological analysis of IL-1β and MMP-3. Furthermore, effects of methotrexate (MTX) and leflunomide were also evaluated in the same procedure for the comparison.

Results: c-Fos/AP-1 activity increased in the hind paws of mice after day
4 in coincidence with onset of the arthritis. The administration of T-5224 from day 5 efficiently suppressed the development of arthritis at 1 to 30 mg/kg, and the arthritis score on day 14 was inhibited by 81% at 30 mg/kg (ED50: 6.0 mg/kg). Histological changes such as cartilage degradation in the joints of hind paws of mice with T-5224 were also suppressed on day 14. In addition, the increases of IL-1β and MMP-3 levels in sera were reduced by T-5224, and the Inhibition rate of at 30 mg/kg were 97% and 89%, respectively. On the other hand, either MTX at 3 mg/kg or leflunomide at 30 mg/kg had no effects on passive CIA.

Conclusions: The activation of c-Fos/AP-1 was observed in the arthritic lesion of mouse CIA in which the priming phase of the immune response is skipped. Inhibition of c-Fos/AP-1 by T-5224 attenuated the arthritis through suppressing the inflammatory cytokine and matrix degrading MMP. On the other hand, immunosuppressive treatment with MTX and leflunomide did not show the inhibitory effects on CIA. These data support a key role of c-Fos/AP-1 in the development of arthritis and joint destruction, and suggest that T-5224 with the novel mechanism of action is expected to exert anti-arthritic effects in the therapy of RA.

Disclosure: M. Mikami: Toyama Chemical Co.,Ltd.; 3; Y. Aikawa: Toyama Chemical Co.,Ltd.; 3; A. Hashirimoto: None; M. Yamamoto: Toyama Chemical Co.,Ltd.; 3; H. Murao: Toyama Chemical Co.,Ltd.; 3; H. Chaki: Toyama Chemical Co.,Ltd.; 3; H. Narita: Toyama Chemical Co.,Ltd.; 3; S. Hirozane: None; S. Shiozawa: None.

281 Innovative Treatment of Experimental Arthritis and Inhibition of Human Osteoclast Differentiation by Dendrimers. Myriam Hayder1, Mary Poupol1, Jean-Pierre Majoral2, Cédric Olivier Turrin3, Anne-Marie Caminade2, Jean-Jacques Fournié4, Jean-Luc Davignon1. 1INSERM U563, CPTP, IFR150, Toulouse, France, 2JE2510, and the inhibition rates at 30 mg/kg were 97% and 89%, respectively. On the other hand, other anti-inflammatory and anti-OCs activities with great potential in the treatment of RA and other inflammatory diseases.

Disclosure: M. Hayder: None; M. Poupol: None; J-P. Majoral: None; C. O. Turrin: None; A-M. Caminade: None; A. Cantagrel: None; J-J. Fournié: None; R. Poupol: None; J-L. Davignon: None.

282 IRF-1 Reduces TNF-α-Induced IL-18 Bioactivity in Rheumatoid Arthritis Synovial Fibroblasts by Induction of IL-18BPa. Hubert Marotte1, Adam J. Pinney2, Tatiana Fedorova3, Nalim Lalwani3, Pei-Suen Tsou4, Bradley J. Rabquer5 and Alissa E. Koch5. 1University of Michigan Medical School, Ann Arbor, MI, 2University of Michigan Medical School, 3Veteran’s Administration and University of Michigan

Purpose: The development of alternative therapies remains critical, as one quarter of all rheumatoid arthritis patients fail to respond to current biologic therapies. Interleukin (IL)-18 is an important cytokine in RA, because it induces T helper-1 immune response as well as angiogenesis. IL-18 bioactivity is regulated by its natural inhibitor IL-18 binding protein (IL-18BP). Interferon regulatory factor-1 (IRF-1) was originally identified as a transcriptional activator of interferon-gamma. We have previously shown that TNF-α induces IL-18 and IL-18BP in RA synovial fibroblasts. Others have shown that IRF-1 binds to the IL-18BP promoter. Here, we investigate the role of IRF-1 on IL-18BPa expression and IL-18 bioactivity in RA synovial fibroblasts.

Methods: IRF-1 synthesis in RA synovial fibroblasts treated with TNF-α was assessed by qRT-PCR and Western blot. Then, the effect of TNF-α on IRF-1 nuclear translation in a time dependent manner (2 hr, 4 hr, and 8 hr) was examined using nuclear extracts and Western blots. The critical pathways for TNF-α-induced IRF-1 expression and nuclear translation were determined by using chemical inhibitors: pyrrollidine dithiocarbamate (PDTC); a nuclear factor kappa-light-chain-enhancer of activated B cells [NFkB] inhibitor; or ERK1/2 or p38 MAPK inhibitors (ERK1/2 inhibitors: U0126 or SB203580; or JNK2, SP600125; 10µM) followed by TNF-α stimulation. IRF-1 antisense or sense oligodeoxynucleotides (ODNs) were used to knockdown IRF-1 in RA synovial fibroblasts. Fibroblasts were then stimulated with TNF-α and examined for IL-18BPa expression by qRT-PCR, Western blot and IL-18 bioactivity assay. IL-18 bioactivity was determined using KG-1 cells.

Results: TNF-α induced RA synovial fibroblast IRF-1 expression at the mRNA and protein levels with a maximal effect at 2 hours (P<0.05; n > 3 patients). Furthermore, TNF-α induced nuclear translation of IRF-1 with maximal translocation at 2 hours (~6 fold-induction; P = 0.05; n = 4). This effect persisted for 8 hours (~6 fold-induction; P < 0.05). However, blocking NFκB or JNK2 pathways reduced TNF-α-induced IRF-1 nuclear translation by approximately 35% and 50%, respectively (P < 0.05; n > 4). Blocking ERK1/2 or p38 pathways had no effect on TNF-α-induced-IRF-1 nuclear translocation. Finally, using ODN to knockdown IRF-1, we observed a reduction of IL-18BPa expression by qRT-PCR and ELISA. IL-18 bioactivity was higher in the case of knockdown of IRF-1 than in its presence.

Conclusions: These results show that IRF-1 is a key regulator of IL-18BPa expression in RA synovial fibroblasts and can thus regulate IL-18 bioactivity. Hence strategies to augment IRF-1 activity may be beneficial in RA.

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283 Liposomal Targeting of Glucocorticoids to the Synovial Lining during Experimental Arthritis Inhibits M1 Macrophage Activation in Favour of M2 Differentiation. Wouter Hofkens1, Gert Storm1, Wim B. Van Den Berg1 and Peter van Lent1. 1Radboud Univ Nijmegen Med Centr, Nijmegen, The Netherlands, 2Radboud University Nijmegen Medical Center, Utrecht University

Background and Objective: Recently we found that systemic delivery of liposomes containing glucocorticoids strongly suppresses joint inflammation during experimental antigen-induced arthritis (AIA). During the course of AIA, macrophages in the synovial lining layer are activated towards a pro-inflammatory (‘M1’) and in later phases towards an anti-inflammatory (‘M2’) activation state. M1 macrophages are characterized mainly by an up-regulation of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-12p40 whereas M2 macrophages show an increase in IL-10 expression and expression of membrane markers IL-1 receptor type II (IL-1RII) and CD163. We now explored whether liposomal targeting of synovial lining macrophages with glucocorticoids exerts its effect through M1/M2 macrophage skewing.

Materials and Methods: Mice with established antigen-induced arthritis (AIA) were treated with a single intravenous injection of 10 mg/kg liposomal prednisolone phosphate (Lip-PLP) or PBS. naïve mice were injected intra-
arbitrarily with IFNγ/LPS to induce M1 phenotype and 24 hours thereafter with Lip-PLP or PBS. Mice were sacrificed at day 1 after Lip-PLP treatment and whole knee joints were isolated for histology and synovial biopsies were isolated for RNA analysis. In vitro, murine bone marrow macrophages were differentiated towards M1 phenotype with LPS and IFNγ, treated with Lip-PLP and M1/M2 markers characterized by quantitative RT-PCR, LUMI- NEX and FACs.

Results: A single intravenous injection with Lip-PLP in mice with established AIA significantly reduced synovial infiltration from control treatment (PBS) within 1 day. At this time point, synovial gene expression was strongly down-regulated by Lip-PLP for the M1 cytokines TNF-α (3.3 fold), IL-1β (10.6 fold), IL-6 (5.6 fold) and IL-12p40 (6.3 fold) compared to PBS treated mice, whereas expression of M2 markers was only slightly down-regulated (IL-10: 2.1 fold and IL-1RII: 1.2 fold) or even up-regulated (CD163: 1.9 fold). Liposomes entered the synovium by blood vessels lying just beneath the lining layer and were directly engulfed by macrophages as detected by gold containing liposomes. To evaluate whether Lip-PLP had a direct effect on M1 macrophages, these cells were induced in vitro by IFNγ and LPS and subsequently incubated with Lip-PLP for 24 hours. Lip-PLP suppressed expression of TNF-α, IL-1β, IL-6 and IL-12p40 and induced expression of IL-10, IL-1RII and CD163 in M1 macrophages in vitro suggesting a selective skewing of M1 macrophages towards an M2 phenotype. Local M1 activation and subsequent treatment with Lip-PLP led to a similar gene expression pattern as in the AIA providing cogent evidence for selective skewing of M1 macrophages in favour of the M2 phenotype.

Conclusion: Systemic delivery of liposomal glucocorticoids during experimental arthritis inhibit M1 macrophages in favour of M2 phenotype in the lining layer and may drive their strong suppressive effect.

Disclosure: W. Hofkens: None; G. Storm: None; W. B. Van Den Berg: None; P. van Lent: None.

284 Nanoparticles of LDE: A Potential Delivery Route for MTX in Sinovial Tissue of Antigen-Induced Arthritis. Suzana B. V. Mello1, Eloisa D. O. Bonfá2, Claudia J. Valduga3, Adriana Bugaralli1, Elaine R. Tavares4 and Raul Maranhão5. 1Heart Institute (InCor), Faculdade de Medicina da Universidade de São Paulo, 2Reumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, 3Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo

Objective: Methotrexate (MTX) remains the first choice in the management of rheumatoid arthritis (RA). Resistance to this drug is largely associated with MTX entry into the cell. Uptake of lipidic nanoemulsion has emerged as a new strategy for cancer chemotherapy since it carries drugs directed to affected tissue increasing its concentration with a reduced toxicity. The aim of the present study was therefore to evaluate the anti-inflammatory efficacy of a novel cholesterol-rich nanoemulsion coupled MTX (MTX-LDE) in antigen induced arthritis (AIA) in rabbits.

Methods: Toxicity, pharmacokinetics and biodistribution assays were performed. The dose-effect curve of the complex was also determined (0.05 – 0.4 mg/Kg of MTX-LDE). Arthritis (AIA) was induced in the knee joint of methylated serum albumin sensitized NZW rabbits. Twenty four hours after AIA induction animals were intravenously (IV) or intraarticularly (IA) injected with a single dose of commercial MTX (0.25 mg/Kg), LDE or saline. To give an equivalent dose of MTX-LDE, the amount of drug associated to the nanoemulsion was evaluated by HPLC prior the injection. Animals were sacrificed 48h after AIA induction when synovial fluid (SF) and membrane (SM) were collected. The inflammatory parameters analyzed were: total and differential leukocyte count, protein leakage in the SF and histopathological evaluation of SM.

Results: MTX-LDE did not promote any hematochemical toxicity. The uptake of this complex was preferentially to liver, spleen and inflamed SM. MTX-LDE intravenously injected promoted a reduction of 85% of leukocyte infiltrate in the joint, and 41% in protein leakage and a significant reduction in the SM cell infiltrate. Likewise, the treatment with MTX-LDE by intraarticular route significantly reduced inflammatory parameters (table). In contrast, a single dose of commercial MTX, a DMARDS that requires several weeks to have a clinical effect, did not alter any evaluated parameter. LDE alone or saline were also ineffective (table).

Discussion: Our study suggests that MTX-LDE is effective, well tolerated and exhibit a rapid effect, probably as a result of their good uptake by the synovial tissue. This novel therapeutic strategy represents a treatment option for RA.

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285 Novel Small Molecule Aminopyridizines Inhibit Rat Collagen-Induced Arthritis and Suppress Proinflammatory Cytokine Pathways. Soo-In Choi2, Lori D. Klaman 3, Bruce Connon1, Alejandro Pastrak2 and Ernest Brah1. 1Division of Rheumatology, UCLA School of Medicine, Los Angeles, CA, 2Division of Rheumatology, UCLA School of Medicine and VA Greater Los Angeles Healthcare System, Los Angeles, CA, 3Transition Therapeutics

Introduction: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by aggressive synovial hyperplasia and inflammation. Activated macrophages and synoviocytes produce many key cytokines and mediators that contribute to the inflammation and joint destruction. Blocking proinflammatory cytokines such as TNFα, IL-1, and IL-6 has led to clinical and radiographic benefits in patients with RA. TT301 and TT302 are novel, orally available, small molecule aminopyridizines that can suppress proinflammatory cytokines and reduce inflammation in rodent models of multiple sclerosis and Alzheimer’s disease. Here we report the effects of these compounds on inflammatory pathways, in vitro, and rat collagen-induced arthritis (CIA), in vivo.

Methods: The in vitro effects of TT301 and TT302 on cytokine production were examined in stimulated primary human synovial fibroblasts and human RAW264.7 macrophages. Cells were preincubated with compound or vehicle in serum-free media and stimulated with LPS (5µg/mL), IL-1β (5ng/mL) or TNFα (30ng/mL). Supernatants were collected and analyzed by cytokine specific ELISA. In vivo studies used Lewis rats immunized with porcine type II collagen on day 0 to induce CIA. A total of 79 rats were randomized to vehicle controls or 4 treatment arms (TT301 at 1mg/kg and 7mg/kg; TT302 at 1mg/kg and 7mg/kg). Based on the degree of joint inflammation and soft tissue swelling, each limb was scored from 0–4, with a maximum total score of 16. At the end of the study (day 28) serum was harvested for subsequent cytokine profiles, the left hind limbs were fixed for immunohistochemistry, and the right hind limbs were microdissected to obtain pure synovium for gene expression profiles, gene hub, module, and network analysis. All hind limbs were also evaluated by high resolution digital radiographic imaging.

Results: In stimulated human RAW264.7 macrophages and synovial fibroblasts, increasing concentrations of TT301 and TT302 dose-dependently inhibited the induction of key cytokines relevant to the pathology of RA including TNFα, IL-6, RANTES and MCP-1/CCL-2. In Lewis rats, virtually all controls developed CIA on day 11 but TT301 and TT302 recipients had a delayed arthritis onset (p<0.03 and p<0.002, respectively). The clinical severity was significantly lower than vehicle controls at both doses (p<1 x 10^-6 vs. controls). Radiographic damage was also suppressed (TT301 at 1mg/kg and 7mg/kg, p<2 x 10^-6 & p<2 x 10^-7, respectively; TT302 at 1mg/kg and 7mg/kg, p<2 x 10^-5 & p<2 x 10^-6, respectively). The analysis of serum cytokines, joint immunohistochemistry, and synovial gene expression profiles is ongoing.
Conclusions: TT301 and TT302 inhibited inflammatory cytokine pathways and suppressed CIA. These studies indicate that these novel small molecules might have therapeutic benefits in RA.

Disclosure: S.-I. Choi: None; L. D. Klaman: Transition Therapeutics, 1, 3; B. Connon: Transition Therapeutics, 1, 3; A. Pastrak: Transition Therapeutics, 1, 3; E. Braha: Transition Therapeutics, 2.

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Purpose: Btk is an essential element of BCR signaling in B cells and FcγR signaling in monocytes/macrophages, and is considered an ideal molecular target for the treatment of autoimmune diseases such as rheumatoid arthritis. PCI-45292, was derived from the chemical scaffold of PCI-32765, a first-in-man Btk inhibitor currently in Phase Iib clinical trials in patients with NHL/CLL*. Both PCI-32765 and PCI-45292 are irreversible inhibitors of Btk, forming a covalent bond with the sulfhydryl group of Cys-481 at the ATP-binding site. The two compounds were evaluated in vitro for their effects on human lymphocytes, monocytes, and basophils, and in vivo for therapeutic effects in multiple models of arthritis.

Methods and Results: In Btk biochemical assays, PCI-32765 and PCI-45292 have an IC50 of 0.5 nM and 1–2 nM, respectively. PCI-45292 was a more selective inhibitor of Btk than either PCI-32765 or dasatinib, with no significant inhibition of VEGFR2, EGFR, JAK, or Abl. Both compounds were potent inhibitors of human B cell activation following BCR stimulation by anti-IgM with an EC50 of 2 nM while failing to inhibit T cell activation at concentrations up to 2 μM. Both inhibited anti-IgE mediated upregulation of CD63 in human whole blood basophils with an EC50 of 20–100 nM. In addition, PCI-45292 inhibited cytokine release from human monocytes at 20–100 nM but did not inhibit IgG-mediated phagocytosis up to 10 μM. In vivo, both Btk inhibitors dose-dependently inhibited inflammatory synovitis, synovial fluid cytokines, cartilage damage, and bone erosion in both preventive and established murine CIA models. PCI-32765 and PCI-45292 inhibited overt manifestations of arthritis in mice with EC50 values of 2.23 and 0.61 mg/kg/day, respectively. In a murine CAIA model, PCI-32765 and PCI-45292 completely suppressed the development of arthritis at doses of 0.25 and 0.8 mg/kg/day, respectively. In gluthathione binding assays, the rate of gluthathione conjugation was 20 fold lower for PCI-45292 than for PCI-32765. In human liver microsomes, the half-life of PCI-32765 was 2.5 min compared to 19.2 min for PCI-45292. PK studies in rats showed that the bioavailability of PCI-32765 and PCI-45292 was 22.8% and 24.7%, respectively. Hepatic extraction ratio, a measurement of first-pass metabolism, was 0.690 and 0.289 for PCI-32765 and PCI-45292, respectively. Based on PK/efficacy relationships in mice and interspecies scaling of clearance, the daily efficacious dosages of PCI-45292 was estimated to be ≤10 mg/patience/day.

Conclusions: Both PCI-32765 and PCI-45292 are potent irreversible inhibitors of Btk that suppress B cell activation following BCR stimulation and inhibit monocytes/macrophage release of pro-inflammatory cytokines following FcγR activation. PCI-45292 was shown to have increased selectivity for Btk inhibition over other tyrosine kinases, a reduced potential for off-target protein binding, and improved metabolic stability. Also, PCI-45292 had a more potent effect in ameliorating inflammation and tissue damage in CIA and CAIA models when compared to PCI-32765. PCI-45292 is currently undergoing preclinical development for autoimmune applications.

*ASCO 2010 presentation

Disclosure: B. Y. Chang: Pharmacyicles, 3; P. Thiemann: Pharmacyicles, 3; N. Moore: Pharmacyicles, 3; M. Francesco: Pharmacyicles, 3; M. M. Huang: Pharmacyicles, 3; C. Mani: Pharmacyicles, 3; P. Jejurkar: Pharmacyicles, 3; D. Tonev: Pharmacyicles, 3; W. Chen: Pharmacyicles, 3; J. J. Bugg: Pharmacyicles, 3; D. J. Loury: Pharmacyicles, 3.

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Recognition of IL-23 Dependent and Independent Stages during Autoimmune Collagen-Induced Arthritis. Ferry Cornelissen, Patrick Asma-widadja, Anne-Marie Mus, Ondilla Corneth, Kristine Kikly and Erik Lubberts. Eli Lilly, Erasmus MC, University Medical Center

Background: IL-23 is a heterodimeric cytokine composed of an IL-12/23-p40 subunit together with an IL-23-specific p19 subunit. The critical role of IL-23 in the development of autoimmune collagen-induced arthritis (CIA) has been shown using IL-23p19 knockout mice. However, it is unknown what the role of IL-23 is at later stages of CIA and during T cell mediated flare-up arthritis.

Materials and Methods: In one set of experiments, an anti-IL-23p19-specific antibody (anti-IL-23) was injected starting 15 days after the first immunization with type II collagen (CII) but before the booster injection of CIA. In another set of experiments, anti-IL-23 was injected starting after the first signs of CIA. Splenocytes, popliteal lymph-node cells (PLNs) and cells isolated from ankles were assessed for intracellular cytokine production by flow cytometry. Serum IgG and IL-6 levels were measured. To test the role of anti-IL-23 in a memory T cell driven arthritis model we utilized the flare-up induced mBSA arthritis model.

Results: Neutralizing IL-23 starting 15 days after the first CIA immunization significantly delayed and suppressed the onset of CIA. In these anti-IL-23 treated mice, serum IL-6 was lower compared to control mice. In addition, the mean fluorescent intensity (MFI) of splenic CD4+ TNF expressing cells was significantly lower in the anti-IL-23p19 treated group compared to the isotype control group. In the sera of anti-IL-23 treated mice, significantly lower CIA-specific IgG1 levels were found compared to the control group as well as a trend to lower IgG2a levels. However, anti-IL-23 treatment did not reduce the proportion of Th1 and Th17 cells analyzed at days 15, 24, and 35. In contrast to the marked suppressive effect of anti-IL-23 given during the onset of CIA, neutralizing IL-23 directly after the first signs of arthritis did not ameliorate the arthritis score. No effect on CIA-specific IgG1 and IgG2a was noted, indicating that the effective phase of CIA is IL-23-independent. Since CIA is both T cell and immune complex-mediated the IL-23-dependency was further investigated during memory T cell-mediated flare-up arthritis. The mBSA-mediated flare-up arthritis was induced after the primary mBSA-induced arthritis has declined to normal background levels. In mice treated with anti-IL-23, a significant lower disease score was observed compared to mice treated with the control antibody, which was accompanied with lower IL-17 and IL-22 expression in the knee joints of these mice.

Conclusion: These data recognized IL-23 dependent and independent stages during autoimmune CIA. Furthermore, the flare-up reaction of arthritis is IL-23-mediated. These data suggest the importance of early intervention using blocking IL-23 therapy in autoimmune arthritis and beneficial effects of neutralizing IL-23 during arthritis relapses.

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Background: Phosphoinositide-3-kinase (PI3K) family controls an array of intracellular signaling pathways and regulates many biological functions in a variety of cell types, including T cells, B cells, macrophages and osteoclasts. In this study, we evaluated the effects of a potent and selective PI3Kδ inhibitor, RO2492, in multiple human immune cells as well as in mouse collagen-induced arthritis model.

Methods: Anti-IgM-mediated intracellular calcium fluxes in the Ramos cell were measured by FLIPR. Anti-IgM-mediated B cell activation in human whole blood as determined by CD69 upregulation was assessed by FACS analysis. Mixed lymphocytes reactions (MLR) were measured by [3H]thymidine incorporation in response to stimulation by mitomycin C-treated allogeneic lymphocytes. T cell proliferation was induced by anti-CD3/CD28 antibodies. Memory T cell recall responses were measured by intracellular staining of TNF and IL-17 or IFNγ cells in CD45RA memory T cell population. Human monocytes were isolated by plate adherence and TNFα production was quantified after stimulation with human IgG-coated beads. Osteoclast differentiation from monocytes was induced by RANK ligand and formation of TRAP positive multinucleate cells. Murine collagen-induced arthritis was induced by intradermal tail base injection with collagen at day 0 followed by a boost at day 21.

Results: RO2492 is a potent, selective small molecule PI3Kδ inhibitor. Inhibition of PI3Kδ by RO2492 blocked the anti-IgM mediated B cell receptor signaling in both Ramos cells (IC50 = 2 nM) and human whole blood

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(IC₅₀ = 24 nM) as demonstrated, respectively, by reduced calcium flux and CD69 up-regulation. In addition, RO2492 blocked Fcg receptor-mediated TNFα production in human monocytes with similar potency (IC₅₀ = 9 nM). With respect to T cells, PI3Kδ blockade inhibited proliferation in MLR assay (IC₅₀ = 10 nM). Moreover, proliferation of purified CD4 T cells stimulated by plate-bound anti-CD3 antibody was also potently inhibited by RO2492 (IC₅₀ = 6 nM), although there was an apparent decrease in compound potency in cells co-treated with anti-CD3 plus anti-CD28 antibody (IC₅₀ = 134 nM, 505 nM with 1 mg/ml, 5 mg/ml anti-CD28 antibody coadministration, respectively). In a memory T cell recall response, anti-CD3/CD28-mediated increases of TNFα (IC₅₀ = 35 nM) or IFNγ (IC₅₀ = 40 nM) memory T cells were also blocked by RO2492. RO2492 also inhibited osteoclast differentiation in a dose-dependent manner. Finally, oral administration of RO2492 ameliorated disease severity in mouse collagen-induced arthritis model. Histopathological examination demonstrated diminished inflammation and cartilage destruction in RO2492 treated group compared to vehicle group.

Conclusion: In summary, our data showed that inhibition of PI3Kδ blocks several key pathways in B cells, T cells, macrophages and osteoclasts, which are related to inflammation and bone destruction in the pathology of rheumatoid arthritis. Furthermore, RO2492 is efficacious in mouse collagen induced arthritis model. The beneficial effects of RO2492 suggest the therapeutic potential of blocking PI3Kδ isoform for treatment of rheumatoid arthritis.


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Selective Switch Pocket Kinase Inhibitors Suppress Autoimmune Inflammatory Models of Rheumatoid Arthritis. Soo-In Choi¹, Scott C. Wise¹, Daniel L. Flynn¹, Zejin Zhu² and Ernest Brahmin². Deciphera Pharmaceuticals, ²Division of Rheumatology, UCLA School of Medicine, Los Angeles, CA, ¹Division of Rheumatology, UCLA School of Medicine and VA Greater Los Angeles Healthcare System, Los Angeles, CA

Introduction: Kinase activation is controlled by phosphorylation and dephosphorylation of key residues on the activation loop which subsequently binds to an internal region on the kinase domain, known as the switch pocket, resulting in a conformational change to allow substrate binding and phospho-transfer. Certain kinases, including cFMS, cKit, and PDGFR, have recently been identified as targets for treatment of autoimmune disorders including rheumatoid arthritis. We have developed a novel class of compounds which were designed to engage critical switch pocket residues and prevent adoption of an activated conformation, resulting in potent and highly selective inhibitors of these kinases. Switch pocket inhibitors targeting these kinases were tested in collagen antibody-induced arthritis (CAIA) and collagen-induced arthritis (CIA), animal models of chronic autoimmune inflammatory synovitis.

Methods: Initial prevention protocols studied kinase inhibitors DP-3556, DP-4178, and DP-4610 in murine CAIA starting on day 0. In a pilot protocol, Lewis rats were immunized with type II collagen on day 0 with clinically evident CIA on day 11. The rats were allowed to develop established disease (day 22) and then administered DP-4610 for 3 days. Synovium was micro-dissected and on-target kinases, such as pFMS, were assayed. In a subsequent study of established rat CIA (days 11–28), DP-4178 (50 mg/kg or 100 mg/kg) was compared to vehicle controls. Recipients were scored for clinical severity and structural damage (based on blinded digital radiographs).

Results: Prevention protocols in murine CAIA demonstrated marked reduction in footpad swelling (p< 1 × 10⁻⁴) and clinical scores (p< 1 × 10⁻⁴) with DP-3556, DP-4178, and DP-4610. Ankle histology/immunohistochemistry revealed significant suppression of inflammation, pannus, cartilage damage, osteoclast activity, bone resorption, and periostal reaction. Synovium harvested from established rat CIA treated with 3 days of DP-4610 indicated a 75% inhibition of on-target pFMS. Chronic administration of DP-4178 beginning at day 11 arthritis onset (50 mg/kg or 100 mg/kg) significantly suppressed clinical disease (p< 1 × 10⁻⁷ and p< 1 × 10⁻⁵, respectively) and radiographic damage (p< 1 × 10⁻⁶ and p< 1 × 10⁻⁵, respectively) compared to controls. On-target kinase suppression with chronic DP-4178, administered for 17 days of clinical disease, was also demonstrated in the synovium by the end of the study on day 28.

Conclusions: Small molecules, generated by structure-based design, had selective kinase inhibitory profiles. They could suppress synovial on-target phospho-kinases in the murine CAIA model and involute established arthritis in the rat CIA model. These studies suggest that specific kinase pathways, including cFMS, may be critical in the induction and propagation of autoimmune inflammatory arthritis and that inactivation by allosteric inhibitors, which bind at the kinase switch control pocket, are a potent and effective intervention.

Disclosure: S.-I. Choi: None; S. C. Wise: Deciphera; 3; D. L. Flynn: Deciphera; 3; Z. Zhu: None; E. Brahmin: Deciphera.

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The Effects of Low Dose Etanercept on Disease Control and Radiographic Progression in Moderate to Severe Rheumatoid Arthritis. Bernd Braffeiner¹, Costantino Botsios², Paolo Sfisio², Francesca Ometto², Livio Bernardi², Silvano Todesco² and Leonardo Punzi². ¹University Hospital of Padova - Rheumatology Unit, Padova, Italy, ²University Hospital of Padova - Rheumatology Unit (Italy)

Background: Rheumatoid arthritis (RA) remains a socio-economic emergency: 100 billions of Euros were spent in 2006 for the disease in the USA and Europe. RA leads to disability, work loss and premature death. Biologics changed history of disease and patients’ outcome. To justify elevated treatment costs biologics have been proved for cost-effectiveness. Some attempts are reported to reduce treatment costs. Etanercept (ETA) neutralizes TNFα with 20-fold higher potency than other inhibitors at low concentrations of TNFα as for disease in remission. ETA appears suitable for dose reduction once patients gained remission.

Objectives of the Study: To elucidate efficacy of low dose ETA to maintain remission. To compare radiological progression and safety of low with standard dose. To estimate cost savings of low dose ETA strategy.

Material and Methods: Prospective observational study was performed on consecutive RA patients in DAS28 remission since 12 months by standard dose ETA from January 2004 to December 2009. Patients continued low (25 mg weekly) or standard dose ETA as follows: 56 with severe and 53 with moderate disease activity prior biologic continued with low dose ETA, 54 patients with severe and 54 with moderate activity standard dose. Patients were monitored every three months. Patients who failed dose reduction returned to full dose once remission was lost. Kaplan Meier survival curve was calculated for low dose patients. Modified Sharp score/der Hejde (TSS) was performed on X-rays at baseline and after one year. Progression was reported as absolute ΔTSS >0 and as real progression ΔTSS ≥5 according to the smallest detectable difference of the method. Progression prior to biologic was estimated for each patient using preceding X-rays. Incidence of infections was calculated by Mid-P exact test modified by national pricing including tax. All comparisons were controlled for statistical significance by Mann-Whitney or exact Fisher test.

Results: Between low and standard dose patients for both severe and moderate disease no differences for age, sex, disease duration, positivity for auto-antibodies, concomitant and past therapy, HAQ and ΔTSS/year were found. Severe groups resulted more aggressive from X-rays than moderate groups and were treated more likely with concomitant DMARDs. Up to now 89 patients (81.6%) maintained remission with low dose for a mean of 2.59 years. Severe groups resulted more aggressive from X-rays than moderate groups and were treated more likely with concomitant DMARDs. Up to now 89 patients (81.6%) maintained remission with low dose for a mean of 2.59 years. Patients failing dose reduction regained remission with full dose except one. Success was higher in younger patients taking less symptomatic, but was not different between severe and moderate groups. Radiological progression occurred only in a minority of patients in low dose ETA: ΔTSS >0 in 13.6% and ΔTSS ≥5 in 0.8% of cases. Capability to arrest radiological progression was identical in low and standard dose and in patients who failed dose reduction. Low dose ETA had fewer infections. Low dose ETA strategy produced costs savings of €1,583,273 since its introduction, and continues to save €562,071 per year.

Conclusion: Low dose ETA sustains clinical and radiological remission. Low dose strategy is safe and produces notable cost savings.

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by hyperplasia of synovial tissues, leading to the destruction of joint structures. TNF inhibitors, including anti-TNF-α antibodies and soluble TNF receptors, have been demonstrated to have prominent therapeutic efficacy in RA. However, detailed mechanism actions of TNF inhibitors have not been fully understood.

Objective: The current studies were therefore designed to determine the characteristic features of synovial tissues of RA patients treated by TNF inhibitors in order to delineate their mechanism of action.

Methods: Synovial tissues were obtained from 12 RA patients who had been treated with TNF inhibitors in addition to disease modifying antirheumatic drugs (DMARDs) for at least 5 months (5–25months) during the joint surgical operations. As a control, synovial tissues were similarly obtained from 12 RA patients who had been treated with only DMARDs, but not with TNF inhibitors. Synovial tissues were fixed in formaldehyde and embedded in paraffin. The sections were evaluated by hematoxylin and eosin staining and Masson trichrome staining.

Results: There were no significant differences in serum CRP levels and treatment regimen except for TNF inhibitors between RA patients with TNF inhibitors and those with DMARDs alone. The most prominent changes in the synovium from RA patients with TNF inhibitors were hyalinization and fibrosis in deep lining layers of the synovium with degeneration of synoviocytes (mostly type B synoviocytes) and formation of multinucleated small giant cells, accompanying with marked decrease in vasculature. Figure 1 shows A, degeneration of synoviocytes with giant cells and obliterate vessels in the sublining layer (arrow heads), B, disappearance of synoviocytes with residual giant cell, C, decreased synoviocyte stratification and appearance of fibrosis in the lining layer with edematous changes in the sublining, D, extended fibrosis in the deep lining layers of the synovium.

There was no significant difference in the synovial changes between RA patients with infliximab and those with etanercept. Interestingly, appearance of foreign-body giant cells was observed more frequently in RA patients with TNF inhibitors (3 out of 12 patients) than in those without TNF inhibitors (1 out of 12 patients), suggesting the activation of healing process.

Conclusions: These results indicate that not only infliximab, but etanercept might have direct actions on synovial cells, presumably type B synoviocytes in the deep lining layers of the synovium, leading to the fibrosis and hyalinization thereof. Moreover, the data confirm that deep lining layers of the synovium are the most important portion that steer the disease process of RA synovitis.

Disclosure: S. Hirohata: Eisai, 2; Mitsubishi Tanabe Pharm Co, 2; Takeda Pharmaceutical Co, 2; T. Tomita: None; H. Yoshikawa: None; M. Kyogoku: None.

Background and Objective: Recently, we found that TNFα-induced adipose-related protein (TIARP) is dominantly expressed in spleens and joints in TNFα-dependen model such as glucose-6-phosphate isomerase (GPI)-induced arthritis. TIARP is a six-transmembrane protein induced by TNFα, interleukin-6 (IL-6) and IL-1β in adipose tissue, although mechanisms in the pathogenesis of arthritis remains unclear. To elucidate the role of TIARP in the development and pathogenesis of autoimmune arthritis, we have generated TIARP-deficient (TIARP/−/−) mice.

Methods: (1) Collagen induced arthritis (CIA) was induced by immunization with 200 μg of chicken type II collagen (CII) emulsified in complete freund’s adjuvant (CFA) to C57BL/6(B6) mice, followed by boost immunization after 21 days of primary immunization. The TIARP mRNA in spleens and joints was evaluated in CIA mice on day 14, 23, 28, by quantitative RT-PCR.

(2) We generated TIARP/−/− mice in B6 background. TIARP/−/− and wild type (WT) mice were immunized with CII as described methods above. The severity of arthritis was monitored by clinical score and evaluated histologically on day 60.

(3) The level of anti-CII antibodies (Abs) in serum were assessed by enzyme-linked immunosorbent assay (ELISA).

(4) Draining lymph nodes and splenocytes on day10 were cultured for 96hr with CII in vitro. IFNγ, IL-17 and IL-4 in their culture supernatant were measured by ELISA.

(5) The level of IL-6 and TNFα in serum on day60 after CIA immunization were measured by ELISA.

Results: (1) In CIA model, the expression of TIARP mRNA in spleenocytes was the highest in the early phase of arthritis (on day23). On the other hand, the expression in joints was accompanied with the joint swelling (on day28).

(2) The arthritis score in TIARP/−/− mice was higher than that in WT mice. Histological analyses showed that a lot of neutrophil infiltration, synovial proliferation, and cartilage destruction.

(3) The level of anti-CII Abs in serum were not significantly different between TIARP/−/− and WT mice.

(4) The amount of IFNγ, IL-17 and IL-4 was not significantly different between TIARP/−/− and WT mice.

(5) The serum IL-6 was significantly increased in TIARP/−/− mice, whereas serum TNFα was not detected.

Conclusion: These findings suggest that TIARP might be a negative regulator against autoimmune arthritis via the suppression of IL-6. TIARP might be a future target for the treatment of rheumatoid arthritis.

Disclosure: A. Inoue: None; I. Matsumoto: None; Y. Tanaka-Watanabe: None; K. Yamamoto: None; N. Umeda: None; Y. Tanaka: None; T. Sumida: None.

Tyrosin Kinases Are Essential Mediators in the Development of Antigen Induced Arthritis Regulating Formation of Dendritic Cells and Antigen Presentation. Mats I. Dehlin1, Sofia Andersson2, Malin Erlendsson2 and Maria Bokarewa2. 1,Department of Rheumatology and Inflammation Research, Sahlgrenska University Hospital, University of Göteborg, Gothenburg, Sweden, 2,Department of Rheumatology and Inflammation Research, Sahlgrenska University Hospital, University of Göteborg, Sweden.

Background: Tyrosine kinases (TKs) are a family of intracellular signaling molecules participating in cell proliferation, development and apoptosis. Inhibition of TKs is effective in the treatment of various malignancies as well as diabetes mellitus. Several families of TKs are implicated in the pathogenesis of rheumatoid arthritis regulating processes in disease onset as well as progression. In previous work we demonstrated that a ligand to TK Flt3 is accumulated in the joints of RA patients and has proarthritis and erosive properties. Here we evaluate the role of TKs and Flt3-signaling in the antigen-induced model of arthritis.

Methods: Mice (n=75) were immunized with mBSA followed by an i.a.
injection of mBSA on day 21. Treatment with TK inhibitor sunitinib (10 an 40 mg/kg/day) was started on day 7 (n = 30) and on day 21 (n = 30) and continued until day 28. Controls (n = 15) received citrate buffer. The mBSA-injected joints were evaluated morphologically and compared to circulating levels of bone (CTX-I) and cartilage (CTX-II) degradation marker and to anti-mBSA antibodies measured by ELISA. The effect of sunitinib on the levels of TK ligands Flt3-I, RANKL and VEGF were measured by ELISA. Expression of Flt3 and development of dendritic cells (DC) was evaluated in the bone marrow and spleen by flow cytometry.

Results: Sunitinib treatment alleviated mBSA-induced arthritis, reducing intensity of synovitis and frequency of bone erosions. This was accompanied by a reduction of mBSA antibodies and marker for bone degradation, CTX-I.

Sunitinib induced a pronounced increase in Flt3-ligand levels, while levels of VEGF and RANKL were changed only slightly, indicating relative specificity for Flt3-signaling. Following sunitinib treatment, the expression of Flt3 was selectively decreased on CD3+ population in bone marrow.

In spleen, sunitinib induced a significant decrease of pDCs as well as cDCs affecting all cDC subsets. However, sunitinib increased CD8+ population in spleen while the populations of B-cells and CD4+ T-cells were unchanged.

Conclusion: Sunitinib blocks TKS through Flt3 pathway alleviating synovial inflammation and bone resorption in antigen induced arthritis. This effect is potentially mediated through downregulation of DCs and decreased antigen presentation.

Disclosure: M. I. Dehlin: None; S. Andersson: None; M. Erlandsson: None; M. Bokarewa: None.

294 A Decrease in Neutrophil Counts Following a Single Infusion of Tocilizumab Is Predictive of Low Disease Activity and Remission after 24 Weeks. Jasmene Saech2, Kathrin Kühr1, Matthias Laudes1, Olaf Schultz1, Thomas Rath1, Tobias Roehrs1 and Andrea Rubbert-Roth1. 1University Clinic Cologne, 2University Clinic of Cologne, Cologne

Background: Tocilizumab, a humanised monoclonal antibody targeting the IL-6 receptor, represents a potent new therapeutic principle for patients with active RA and intolerance or inadequate response to conventional DMARDs and/or TNF-blockers. Given the broad therapeutic armamentarium of biologics that is available for RA patients today, predictive parameters before or during the early treatment period are urgently needed to optimize therapeutic strategies.

Method: In our center, 40 patients with active RA were started on tocilizumab 8 mg/kg iv q4w and followed prospectively for 24 weeks. DAS 28 and routine laboratory parameters were obtained at baseline and every 4 weeks subsequently.

Results: 40 patients (25% male, 75% female, mean baseline DAS28 6.09) were treated with tocilizumab 8mg/kg, 15/40 (42%) patients received tocilizumab as monotherapy and 25/40 (58%) with concomitant DMARD treatment. In 26/40 (64%) patients, tocilizumab was used as the first biological.

After 24 weeks, 20 patients achieved low disease activity LDA (DAS 28≤3.2) and 12 were in remission (DAS28=≤2.6). CRP, neutrophils or other clinical or laboratory parameters at baseline did not correlate to outcome at week 24.

Patients with a DAS decrease of ≥ 1.2 at week 4 (early responders = ER) were compared to patients with a DAS difference of < 1.2 at week 4 (early non-responders = NR). 64% of the ER, but only 31% of NR achieved LDA in week 24 (n.s.). More impressively, 52% of the ER, but 11% of the NR achieved remission in week 24 (p = 0.02).

CRP levels normalized in all patients at week 4 and did not differ between ER and NR. Neutrophil counts at week 4 remained within normal limits in all patients. Of note, a decrease in neutrophil counts of ≥ 25% from baseline to week 4 was observed more frequently in ER (20/31) than in NR (2/9) (p = 0.05). More interestingly, a neutrophil decrease of ≥ 25% from baseline to week 4 was significantly associated with LDA and remission at week 24 (p = 0.03).

Conclusion: Patients who responded to tocilizumab with a DAS 28 decrease of ≥ 1.2 in week 4 (ER) achieved remission significantly more often in week 24 than patients who do not respond at week 4. Baseline CRP or normalization of CRP at week 4 did not correlate to ER/NR at week 4 or to LDA/remission at week 24. Of note, a decrease in neutrophil counts of ≥ 25% after a single infusion of tocilizumab (baseline to week 4) was highly predictive for achieving LDA/remission in week 24.

Disclosure: J. Saech: None; K. Kühr: None; M. Laudes: Roche, 2; O. Schultz: Roche, 2; T. Rath: None; T. Roehrs: None; A. Rubbert-Roth: Abbott Immunology Pharmaceuticals, 5, Actelion Pharmaceuticals US, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Chugui, 5, Pfizer Inc, 5, Roche, 5, Schering-Plough, 5, UCB, Inc., 5.

295 A Simplified Disease Activity Score (DAS): Validation in the BeSt Trial. Rosanne Koevoets4, Yvonne Goepkoop-Ruyterman2, Desiree M. Van Der Heijde1, K. H. Han1, H. K. Ronday1, T. W. J. Huizinga6, P. J. S. M Kerstens1, B. A. C. Dijkmans3 and Cornelia F. Allaart1. 1Haga Hospital, Den Hague, 2Haga Hospital, Den Hague, The Netherlands, 3JBI, Amsterdam, 4Leiden Univ Med Ctr, Leiden, The Netherlands, 5Leiden University Medical Center, Meerssen, The Netherlands, 6Leiden University Medical Centre, Leiden, The Netherlands, 7Maasstad Hospital, Rotterdam, 8VU Medical Centre, Amsterdam, The Netherlands

Background: Implementation of DAS steered treatment is challenging current daily practice. Some feel that using the Ritchie Articular Index for pain in the original DAS is impractical.

Objective: To assess the validity of a simplified version of the original DAS with different versions of the pain component.

Methods: Within the first year of the BeSt trial, a 4 strategies trial in recent RA patients aiming at a DAS≤2.4, the percentage agreement and kappa statistics were calculated for 3 different versions of a simplified DAS compared to the original DAS: DAS with the Ritchie score reduced to a 0–1 score (‘DAS 0–1’), DAS with a 53 joint 0–1 count for pain (DAS-TJC53), and a DAS with a 44 joint 0–1 count for pain (DAS-TJC44). At the same time for all alternative DAS versus the DAS28 the DAS was calculated with theVAS general health (GH) and the VAS for patient’s global assessment of disease activity (PGA). To display the difference for the continuous scores Bland-Altman plots were created with the mean versus the mean difference. Percentages agreement and kappa statistics were calculated for classification into remission, low disease activity (LDA) or moderate (MDA) or high (HDA) disease activity for all indices with both PGA and GH.

Results: DAS scores with a separate joint count are in general higher since there are no single counting joint groups created. As by definition the ‘DAS 0–1’ was lower in few cases; in the majority of the patients the DAS scores were equal (see figure 1).

Mean difference between DAS and ‘DAS 0–1’ was −0.03; (limits of agreement (−0.24;0.18) between DAS and ‘DAS-TJC53’ 0.18 (−0.33;0.66) and between DAS and ‘DAS-TJC44’ 0.11 (−0.42;0.64) (figure 1). Compared with the original DAS, the ‘DAS 0–1’, ‘DAS-TJC53’ and the ‘DAS-TJC44’ agreed on the classification of patients in LDA, MDA or HDA in 99% (κ = 0.98), 86% (κ = 0.91) and 86% (κ = 0.91), which would have resulted in the same treatment decisions in this trial. Although separate VAS scores are not highly correlated (r = 0.5–0.8) all indices with PGA showed high chance corrected agreement (κ = 0.87–0.94) compared to the corresponding GH score.

Figure 1. Bland-Altman plots representing the mean of the original DAS and alternative DAS in relation to the difference between both.

Conclusion: There are no important differences between all alternative DAS versions, both with the VAS GH and PGA, and all can therefore be used reliably as alternatives to the original DAS.

Disclosure: R. Koevoets: Centocor, Inc., 2, Dutch College of Health Insurances, 2, Schering-Plough, 2, Y. Goepkoop-Ruyterman: None; D. M. Van Der Heijde: None; K. H. Han: None; H. K. Ronday: None; T. W. J. Huizinga: None; P. J. S. M. Kerstens: None; B. A. C. Dijkmans: None; C. F. Allaart: None.

Friday, November 9
Aiming To Reach Remission—Is It Worthwhile? Helga Radner1, Josef S. Smolen1 and Daniel Aletaha2. 1Krankenhaus Lainz, Vienna, Austria, 2Medical University of Vienna, Vienna, Austria, 3Medical University Vienna, Vienna, Austria

Background: Rheumatoid arthritis (RA) is a prevalent chronic inflammatory disease causing disability and a considerable burden for the single patient and society. Remission (REM) is one of the major goals of RA treatment. In this study, we investigated whether in patients with low disease activity aiming for remission is also effective from a socioeconomic point of view.

Patients and Methods: In 356 patients with established RA we obtained information about quality of life (Short Form 36, SF-36), utility (Short Form 6D, SF-6D; Euro-Quol 5D, EQ-5D), physical disability (Health Assessment Questionnaire, HAQ), productivity (Work productivity and activity impairment Questionnaire, WPAI), as well as disease activity (Clinical Disease Activity Index, CDAI). In cross-sectional analyses we compared data obtained of patients in REM (n = 89) to those in LDA (n = 152) using Students T-Test. We also compared patients who stayed in REM (n = 34) for a whole year and compared their values with those of patients in LDA (n = 66) for the same period.

Results: In the cross-sectional analyses we found statistically significant differences of utilities when comparing patients in REM with those in LDA (SF-6D 0.75 vs. 0.66; EQ-5D 0.89 vs. 0.78), physical disability (HAQ 0.38 vs. 0.75) and productivity (WPAI % overall impairment; 18.1% vs. 33.8%; WPAI % impairment while working: 11.3% vs. 27.2%) (all comparisons: p < 0.05). Regarding quality of life we found significant differences in all domains except role emotional and MCS in favor of REM. Though, compared to healthy populations there are still significant differences in all domains except mental health (figure).

Preliminary longitudinal analyses showed significant differences of outcomes over one year between patients in REM and those in LDA: QALY (SF-6D 0.89 vs. 0.80; EQ-5D 0.80 vs. 0.66), Quality of life over one year (PCS 48.7 vs. 38.0), physical disability over one year (HAQ 0.22 vs. 0.69), and percent of overall activity impairment per year (12.2% vs. 31.0%). No significant difference of percent of activity impairment while working was found.

Conclusion: From a socioeconomic perspective including quality of life, disability, and productivity, REM seems to be still superior to any other state of disease, even LDA. Therefore aiming for REM seems worthwhile and should be the major target when treating RA.


Body Weight and Response to Biologics in RA and Spondyloarthritides. Obesity Reduces the Rate of Remission-Response. The GISEA Registry. Gianfranco Ferraccioli1, Francesco Trotta1, Leonardo Punzi1, Clodoveo Ferri2, Piercarlo Sarzi-Puttini2, Lisa Maria Bambana2, Giovanni Triolo2, Roberto Giacometti3, Roberto Gorla4, Angelo Marchesoni4, Walter Grassi5 and G. Lapadula6. 1Department of Internal Medicine, University of L’Aquila, L’Aquila, Italy, 2Division of Rheumatology, UCSC, Rome, Italy, 3Rheumatology Department, University of Palermo, Palermo, Italy, 4Rheumatology Department, University of Verona, Verona, Italy, 5Rheumatology Division, University of Ferrara, Ferrara, Italy, 6Rheumatology Unit, L. Sacco University, Milano, Italy, 7Rheumatology Unit, Spedali Civili di Brescia, Brescia, Italy, 8Rheumatology Unit, University of Bari, Bari, Italy, 9Rheumatology Unit, University of Marche, Jesi, Italy, 10Rheumatology Unit, University of Modena, Modena, Italy, 11Rheumatology Unit, University of Padova, Padova, Italy, 12Rheumatology Unit, University of Perugia, Perugia, Italy, 13UOC DH of Rheumatology, G. Pini Orthopaedic Institute, Milano, Italy

Background: It is well known that obesity produces inflammation and there are conflicting evidences that obesity determines higher disease activity status in rheumatoid arthritis (RA). Even underweight seems to lead to increased disease activity (cachexia). These possibly related changes between weight and disease activity could affect different responses to therapy. In this study we sought to define whether body weight could lead to different remission/response rate to anti-TNF in rheumatoid arthritis (RA) as well as in seronegative Spondyloarthropathies (SNeSpA).

Materials and Methods: The GISEA registry collect data on all RA and SNeSpA, receiving Biologics from 14 Centres in Italy. In the data we analyzed 580 RA and 392 SNeSpA receiving biologic treatments for at least 12 months. RA patients were 81.4% female, the mean age 56.75 yrs, had a mean DAS28 of 5.36, and ESR of 34.6, an HAQ of 1.31 at entry and a mean disease duration of 13 yrs; SNeSpA were 50 % male, the mean age was 49.5 yrs, the mean BASDAI was 5.48, HAQ 0.98 and dis.dur. 9.95 yrs. In RA 39.9 % were in normal weight, in SNeSpA 39.5 % were in normal weight. In RA 73% received anti-TNFa, 27 % others (Rituxan, Abatacept). In SNeSpA 100 % were receiving TNFa blockers.

Results: In RA, DAS28 remission was seen in 18.9 % and in 16.2 % of all patients at the 66 month and 12 month of follow-up respectively. The respective percentages in normal weight RA were 20.3 and 19.4 % at the 66 month of follow up versus 16.9 % and 6.8% in obese patients (p = 0.018). In SNeSpA a BASDAI < 3 was seen in 13.5 % and in 9.7 % of all patients at the 66 and 12 month of follow-up. The respective percentages in normal weight SNeSpA were 15.5 and 14.1 % at the 66 and 12 month of follow-up versus 7.2 and 3.6 % in obese patients (p = 0.03). The numbers of underweight patients were too low to draw any conclusion.

Conclusions: Data suggest that obesity associates with a lower percentage of success in obtaining DAS28 remission in long standing RA. There is a 2.5 fold lower chance of obtaining remission in obese. In SNeSpA there is a 3 fold lower chance of obtaining a BASDAI < 3 in obese versus normal weight patients. Two conclusions come along, the need to increase the dose of biologics in obese patients, the need to better control inflammation in obese in order to get control of comorbidities such as cardiovascular complications.

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Celecoxib, a Selective COX-2 Inhibitor Improved Upper Gastrointestinal (GI) Adverse Lesions in Patients with Rheumatoid Arthritis on Long-Term NSAID Therapy with Endoscopic Evaluation. Shigeysuyo Tsujii1, Hirofumi Miyoshi1, Tetsuya Tomita2, Takehito Nakase3, Masayuki Hamada1, Takahiro Oomae2, Chikako Tsumoto2, Yoshimasa Hirata1, Munetaka Iguchi2, Shoko Edogawa2, Hideo Kawai2 and Hideki Yoshikawa2. 1Hoshigaoka Kosei-Nenkin Hospital, Hirakata City, Osaka, Japan, 2Hoshigaoka Kosei-Nenkin Hospital, 3Osaka Univ Med School, Suita Osaka, Japan, 4Osaka Univ Med School

Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for pain relief in patients with rheumatoid arthritis (RA); however, gastrointestinal (GI) adverse events are one of the serious problems of NSAIDs. Selective cyclooxygenase (COX)-2 inhibitors have been proven to be less associated with GI complications than traditional NSAIDs. However,
their effects on the GI tract have not been well studied in patients with preexisting NSAIDs-induced GI complications. Here, we prospectively investigated the effects of celecoxib (CEL) after switching from NSAIDs on the GI tract in RA patients with endoscopically identified GI mucosal injury.

**Methods:** We conducted upper GI endoscopy to examine GI tract injury in RA patients who had been treated with NSAIDs for 3 or more months with informed consent. GI mucosal injury was evaluated according to the modified LANZA score. Patients with mucosal injury without ulcers were switched from NSAIDs to CEL, while those with ulcers were switched to CEL with famotidine (FAM) on complete ulcer healing with therapy. At 16 weeks, the extent of GI mucosal injury was endoscopically reevaluated. Disease activity score (DAS28), joint symptoms, and visual analogue scale (VAS; global improvement and pain) were evaluated before and at 8 and 16 weeks after switching to CEL. Wilcoxon signed rank test was used and significance level was set at 0.05.

**Results:** Eighty-two patients were eligible for the study (69 females), and the average age and affected period were 62.2 (30–83) and 17.5 (1–50) years, respectively. The mean score was 2.4 (1–23). Changes in Lipoproteins Associated with MTX, MTX + Etanercept, and Triple DMARD Therapy among Early RA Patients in the TEAR Trial. Jeffrey R. Curtis6, Christina Charles-Schoeman2, Shuo Yang4, Lang Chen4, Ian P. Bykerk9, Gilles Boire6, Boulos Haraoui3, Carol Hitchon7, Diane Moreland8, Andrew H.铁山, James R. O’Dell1, Harold E. Paulus1, Monika Safford1 and S. Louis Bridges1. 1Encino, CA, 2UCLA, Santa Monica, CA, 3Univ of Alabama-Birmingham, Birmingham, AL, 4Univ of Alabama-Birmingham, Birmingham, AL, 5University of Alabama - Birmingham, Birmingham, AL, 6University of Nebraska Medical Center, Omaha, NE

**Background:** DMARDs and anti-TNF agents may affect lipid profiles, but past studies in RA patients have generally been small and lacked comparator groups to quantify and compare changes in traditional lipoproteins. We studied early RA patients participating in the Treatment of Early Arthritis (TEAR) trial randomized to initiate aggressively-titrated methotrexate (MTX) with step-up at 24 weeks to etanercept or triple therapy for patients not in low disease activity; methotrexate + etanercept (MTX+ETA); or triple therapy (TT) [MTX + sulfasalazine (SSZ) + hydroxychloroquine (HCQ)].

**Methods:** TEAR is a 2-year investigator-initiated, randomized, placebo-controlled trial of 755 DMARD-naïve early RA patients. In this analysis, participants had total serum cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) measured at 0, 48, and 102 weeks. LDL was measured quantitatively since samples were collected non-fasting. Changes in lipoproteins at weeks 48 and 102 were compared to baseline and across treatment arms. Change in LDL was correlated with change in CRP at the corresponding time points. Partial results are available based upon samples run to date; the remaining samples are currently being analyzed.

**Results:** Characteristics of TEAR participants with lipid lab data (mean ± standard deviation): age 50.7 ± 13.4 yrs; 74% women; body mass index 30 ± 7; RA disease duration 3.5 ± 6.5 months; 87% RF+; 41% glucocorticoid users (mean dose 2.6 ± 4.1 mg/day); 34% current smokers; ΔASS 5.8 ± 1.0. At baseline, mean values for total cholesterol were 233 ± 55 mg/dL, LDL 126 ± 39 mg/dL, HDL 54 ± 18 mg/dL. There were no significant baseline differences between treatment groups.

At 48 weeks, there were statistically significant increases in total cholesterol, LDL, and HDL compared to baseline (p < 0.001 for all) (see Table). These increases were greater in the MTX + ETA group than in the other treatment groups; only the increase in LDL was significant compared to MTX step-up group (p = 0.04). Changes at week 102 were generally similar but quantitatively lower than changes at 48 weeks. There was a low correlation between increase in quantitative LDL and decrease in CRP between 0 and 48 and also between 0 and 102 weeks (R² ≤ 0.03, p < 0.05 across all treatment arms at both timepoints).

Changes in lipid profiles at 48 weeks, by randomization to each TEAR treatment arm

<table>
<thead>
<tr>
<th>Change between 0 and 48 weeks (mg/dL)</th>
<th>Step-Up MTX Group (all pts)</th>
<th>p value versus MTX alone</th>
<th>p value versus MTX alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MTX + Etanercept Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>35.9 ± 61.1 (n = 137)</td>
<td>0.19</td>
<td>20.1 ± 61.0 (n = 89)</td>
</tr>
<tr>
<td>LDL (Quantitative)</td>
<td>16.2 ± 32.4 (n = 137)</td>
<td>0.04</td>
<td>9.1 ± 39.8 (n = 84)</td>
</tr>
<tr>
<td>HDL</td>
<td>13.1 ± 21.1 (n = 138)</td>
<td>0.62</td>
<td>8.7 ± 22.0 (n = 84)</td>
</tr>
</tbody>
</table>
erations, socioeconomic status, active smoking status, CCP, RF, higher than normal CRP/ESR, swollen joint count (0–28), tender joint count (0–28), symptom duration. Patients needing and not needing biologics were matched for length of follow up. Patients were treated with ≥ 2 DMARDs prior to being eligible for biologic therapy.

**Results:** Baseline characteristics: mean age 52±16 years, 73% female, median symptom duration 5.5 months, mean DAS28 ESR 4.9±1.6, 25% already had erosions at baseline. 73% of patients met 1987 criteria for RA. 27% treated with oral glucocorticoids, 50% with MTX, 35% with combination DMARDs, 8% with Biologics within 1 year. Patients had a median follow up of 0.75 years with follow up as long as 8 years. Of the variables analyzed the only independent factor predicting the use of biologics at one year was the DAS28 at baseline (OR 1.48, p<0.000001).

**Conclusions:** Of all the classical baseline factors used to determine prognosis in RA in previous studies, baseline DAS28 was the only independent factor significantly predicting use of biologics at one year.

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**Decreased Rate of Remission at 1 Year in Menopausal Women with Early Inflammatory Arthritis: The ESPOIR Cohort Study.**

**Background:** Remission has become the current aim in the management of rheumatoid arthritis (RA), especially since the advent of biologic antirheumatic agents.

**Objectives:** To evaluate factors potentially influencing achievement of remission in women with early inflammatory arthritis.

**Methods:** The ESPOIR cohort study collects data on patients presenting with early arthritis. Remission, defined by a disease activity score (DAS28) of <2.6, was used as the outcome measure after 1 year of follow-up and standard care. Baseline clinical, laboratory, genetic, and radiographic data were assessed. Logistic regression analysis was performed to determine baseline predictive factors of remission at 1 year, adjusting for patient-, disease- and physician characteristics.

**Results:** Of the 624 analysed patients, 318 (51%) fulfilled the American College of Rheumatology 1987 revised criteria for the classification of RA after 24 months of follow-up. The mean age was 47±13 years, and the mean symptom duration was 3 months. In the total population, 207 patients (33.2%) were in remission at one year, versus 112 (35.2%) in the RA group. In both populations and after adjustment for age and classical prognostic factors (disease activity at baseline, presence of raised acute phase reactants (CRP >10mg/l), presence of rheumatoid factor or anti-CCP antibodies and functional status), logistic regression analysis showed that the menopausal status had a significant independent predictive value in achieving a remission status after 1 year of follow-up and usual care: OR = 0.47 [95%CI 0.27–0.84], p = 0.01 in the total sample, OR = 0.54 [95%CI 0.24–1.19], p = 0.13 in the patients diagnosed RA after 24 months of follow-up.

**Conclusion:** In the ESPOIR cohort, about one third of patients achieved remission after 1 year of usual care. Multivariate analysis revealed that besides usual demographic factors, menopausal status had an independent negative influence on the outcome, with an approximately 50% decreased chance of achieving this favorable status in menopausal women.

**Disclosure:** C. Lukas: None; I. Hmamouchi: None; X. Le Loet: None; B. Fautrel: None; B. Combe: None.

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**Demographic, Disease and Treatment Characteristics of the Rheumatoid Arthritis Population Enrolled in the AMORA Study (Applications for Methotrexate Optimization in Rheumatoid Arthritis) in Evaluating the Avise PG test.**

**Background:** The study evaluated an assay for RBC methotrexate polyglutamates (MTXPG) in terms of its clinical utility and impact on treatment plans in RA patients experiencing inadequate clinical responses. The study also provided the opportunity to assess the relationships between demographic, treatment and disease characteristics and corresponding MTXPG levels.

**Methods:** 20 rheumatologists enrolled 146 adult RA patients. Patients were to have been taking MTX for a minimum of 3 months and experiencing an insufficient response to current therapies. Demographic, treatment and disease-related information was collected and the physician completed assessments of the patient’s global health status and MTX efficacy. The physicians reported proposed treatment plans before and after MTXPG testing. After receiving the MTXPG result, physicians were surveyed regarding their opinion of the clinical utility of the assay.

**Results:** Presented in Table 1, 66% of patients were receiving 15 mg MTX or more per week at the time of testing. Almost 77% of patients were on MTX monotherapy; 14% were on biologics in addition to MTX; and 9% were on other non-biologics.

10% of patients had a MTXPG level above 60 nmol/L (the threshold above which previous studies showed an odds ratio of a good clinical response 5-fold higher than levels ≤ 60 nmol/L). 64% exhibited intermediate MTXPG levels (20–60 nmol/L) and 27% of patients exhibited sub-therapeutic MTXPG levels (< 20 nmol/L), the level below which the odds ratio of a poor response was found to be 3-fold higher than levels ≥ 20 nmol/L. For the population as a whole, increasing MTXPG levels were associated with increases in the mean duration of MTX therapy.

Patients’ tender-+swollen joint counts tended to decrease as MTXPG levels rose. A similar relationship was seen with the physician’s Global Health Assessment, which correlated well (r = −0.5) with patients’ combined tender + swollen joint counts.

In 97% of the cases, physicians’ rated the overall clinical utility of the MTXPG test as very useful or somewhat useful. Physicians modified the prospective treatment plans for 45% of their patients after reviewing MTXPG results.

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**Disclosure:** None; E. C. Keystone: None; J. E. Pope: None; CATCH Investigators: Amgen Inc., Pfizer Inc, Wyeth Pharmaceuticals, 2.
Conclusion: In the AMORA study, higher MTXPG levels were associated with increasing MTX dose, duration of MTX therapy, and age. Clinical markers of disease activity also trended toward improvement as MTXPG levels increased. Physicians’ expressed positive opinions regarding the test’s overall clinical utility, and treatment plans were frequently modified after receipt of the MTXPG results (in 45% of cases).

Disclosure: P. R. Sunkureddi: Bristol-Myers Squibb, 8, Cypress Biosciences, Inc., 2, 8, Novartis Pharmaceuticals Corporation, 2, 8, Pfizer Inc, 2, 8, UCB, Inc., 8; J. F. Gendreau: Cypress Biosciences, Inc., 1, 3; R. Zablocki: Cypress Biosciences, Inc., 1, 3; D. Navis: Cypress Biosciences, Inc., 1, 3.

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Demonstration of the Structural Efficacy of Very Early DMARD Initiation in Early Inflammatory Arthritis in Clinical Practice: Results of a Propensity Analysis in the ESPoir. Cédric Lukas1, Bernard G. Combe2, Philippe Ravaud1, Jean Sibilia2, Robert Landewe6 and Desiree M. Van Der Heijde3.

Department of Epidemiology and Biostatistics, Bichat Hospital, Paris, France, 2Department of Rheumatology, Hautepierre Hospital, Strasbourg, France, 3Department of Rheumatology, Lapeyronie Hospital, Montpellier, France, 4Department of Rheumatology, Lapeyronie Hospital, Montpellier, France, 5Leiden University Medical Center, Meerssen, The Netherlands, 6Univ Hosp Maastricht, Maastricht, The Netherlands

Background: Despite the consensus recommending early treatment start in patients with early inflammatory arthritis with DMARDs of proven structural efficacy, demonstration of decreased radiographic progression with earlier therapy is scarce.

Objective: To compare radiographic progression in patients treated with a DMARD very early in the course of their disease (within 3 months after the onset of symptoms) and those who were started later on.

Methods: Patients included in the French observational ESPoir cohort, treated independently of the data collection and without fixed protocol, were followed-up and radiographic progression after 12 months was assessed by Sharp-van der Heijde score (SHS). Propensity score (PS) was obtained by modelling the start of DMARD by logistic regression analysis using baseline disease specific and demographic variables. The influence of a very early DMARD start was evaluated by generalized linear regression, adjusting for PS as continuous covariate.

Results: 661 patients were analysed. Expectedly, patients treated within 6 months (ie with worst prognosis) showed a higher radiographic progression at 12 months (p=0.026). After adjustment for PS, the estimated marginal mean was significantly decreased in the early treatment group: 1.11 [0.95;1.27] SHS unit, versus 1.59 [1.48;1.69] (p<0.001). Additional analyses showed that this difference was especially pronounced in the groups of patients with a worse prognosis (figure).

Observed radiographic progression in patients with early inflammatory arthritis treated within 3 months after symptoms onset versus later, in the last quintile of propensity score.

Conclusion: Our results confirm for the first time that in a daily clinical practice standard of care of patients with very early arthritis, time to DMARD start clearly influences short-term radiographic outcome. These results strengthen the current recommendations claiming for a very early initiation of specific therapy in patients with early inflammatory arthritis.

Disclosure: C. Lukas: None; B. G. Combe: None; P. Ravaud: None; J. Sibilia: None; R. Landewe: None; D. M. Van Der Heijde: None.

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Derivation of a Preliminary Administrative Claims-Based Algorithm To Identify Lack of Effectiveness of Rheumatoid Arthritis Medications. Jeffrey R. Curtis1, Shuo Yang2, John Baddley3, Grant W. Cannon4, Lang Chen2, Elizabeth Delzel1, Nivedita M. Patkar5, Kenneth G. Saag6, Montika Safford7, Jasvinder Singh8 and Ted R. Mikul5.

1Amgen Inc., 2Centocor, Inc., 2, 5Corona, 2, 5Roche, 2, 5, 8UCB, Inc., 2, 8; S. Yang: None; J. Baddley: None; G. W. Cannon: None; L. Chen: None; E. Delzel: Amgen Inc., 2, N. M. Patkar: None; K. G. Saag: Amgen Inc., 2, 8, AstraZeneca, 5, Aventis Pharmaceuticals, 5, Eli Lilly and Company, 2, 5, Genentech and Biogen IDEC Inc, 5, GlaxoSmithKline, 2, 5, Merck Pharmaceuticals, 2, 5, NovoE, 5, Nitec, 5, Novartis Pharmaceuticals Corpora; M. Safford: None; J. Singh: None; T. R. Mikul: None.

Background: Administrative claims data are commonly used to evaluate medication safety. Use of this type of data to study the clinical effectiveness of medications for rheumatoid arthritis (RA) has been limited by lack of a validated effectiveness algorithm. We created and tested a claims-based algorithm to serve as a proxy for a lack of clinical effectiveness of biologics for RA patients (pts).

Methods: Using national administrative claims data from the Veterans Health Administration (VA), we identified all U.S. veterans with RA using ICD9 code 714.X. We linked medical, pharmacy, and laboratory results to the medical subcohort of rheumatologist-confirmed RA patients participating in the longitudinal VA registry (VARA). VARA contains clinical and RA-specific information including DAS28 and CDAI. Among VARA enrollees, we identified the date individuals initiated a new biologics (the ‘index date’; no use in prior 6 months) who remained under observation ≥1 year. The gold standard outcome was low disease activity (LDA, DAS28 ≤3.2) at one year (±2 months), + persistence with therapy. Alternate LDA criteria was CDAI ≤3.0.

The claims-based effectiveness rule defined lack of effectiveness as non-persistence with biologic therapy or increase in biologic dose. Further, treatment was considered not effective for pts not on steroids at baseline if they initiated chronic steroids, and for those on baseline steroids, if their cumulative steroid use 6 months after treatment exceeded the cumulative dose 6 months prior to treatment. Finally, therapy was considered ineffective if pts received >1 intra-articular or parenteral joint injection after the index date +90 days. We calculated the performance characteristics of the effectiveness algorithm, with particular interest in the negative predictive value (NPV) as a proxy for lack of clinical effectiveness.

Results: Among 1397 enrolled VARA participants who were linkable to VA administrative claims data, 292 unique patients were eligible for analysis and initiated biologics for 386 treatment episodes. Characteristics of VARA patients in the analysis were mean ± SD age 64.7 ± 11.1 years, 91% male, 56% rheumatoid factor positive. At one year, 84% of treatment episodes did not achieve LDA criteria with persistence by DAS28 criterion. The NPV of the effectiveness rule was 82% (77% – 87%) using DAS28 criteria and 65% (58 – 72%) using CDAI criteria. Ongoing work is underway to refine the algorithm and maximize its performance characteristics.

Conclusion: Administrative claims data may be useful in identifying lack of effectiveness of medications for RA. Validation in an external dataset will be useful to assess the generalizability and performance of this algorithm in other RA populations.

Gold Standard: Low Disease Activity (DAS28 ≤3.2) and Persistent at 1 year

<table>
<thead>
<tr>
<th></th>
<th>Claims-Based</th>
<th>Effectiveness Rule</th>
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<tbody>
<tr>
<td>+</td>
<td>17 (4.4%)</td>
<td>46 (11.9%)</td>
</tr>
<tr>
<td>-</td>
<td>112 (29.0%)</td>
<td>211 (54.7%)</td>
</tr>
<tr>
<td>Persistent at 1 year</td>
<td>129 (33.4%)</td>
<td>257 (66.5%)</td>
</tr>
<tr>
<td></td>
<td>63 (16.3%)</td>
<td>323 (83.7%)</td>
</tr>
<tr>
<td></td>
<td>386 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

Disclosure: J. R. Curtis: Amgen Inc., 5, Centocor, Inc., 2, 5, Corona, 2, 5, Roche, 2, 5, 8, UCB, Inc., 2, 8; S. Yang: None; J. Baddley: None; G. W. Cannon: None; L. Chen: None; E. Delzel: Amgen Inc., 2; N. M. Patkar: None; K. G. Saag: Amgen Inc., 2, 8, AstraZeneca, 5, Aventis Pharmaceuticals, 5, Eli Lilly and Company, 2, 5, Genentech and Biogen IDEC Inc, 5, GlaxoSmithKline, 2, 5, Merck Pharmaceuticals, 2, 5, NovoE, 5, Nitec, 5, Novartis Pharmaceuticals Corpora; M. Safford: None; J. Singh: None; T. R. Mikul: None.

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1Cedars Sinai, “Harbor-UCLA
Background: Descriptions of RA behavior and response to therapy originate largely from studies in Caucasians. Additionally, most subjects in clinical practice do not fulfill inclusion criteria for most RA trials. These observations may question the generalizability of the results of such trials to racially diverse populations. We describe RA clinical, serologic parameters, conventional and biologic DMARD utilization and therapeutic outcomes in a large, minority-enriched cohort from a single academic Center in the US.

Methods: We report on 433 pts fulfilling 1987 ACR criteria for RA and with regular follow-up. Patients were assessed quarterly, and Disease Activity Score (DAS28-3v-ESR) and functional outcomes (HAQ-DI, patient assessment of pain) were recorded. Good EULAR response (DAS28<3.2 and DAS28 change>1.2) was the only acceptable outcome and therapeutic adjustments were aimed at that goal. Continuous variables in unmatched and matched groups were analyzed with ANOVA and Wilcoxon’s matched pairs test respectively. Categorical variables were assessed with Chi-square test respectively. Categorical variables were analyzed with Chi-square tests. Continuous variables in unmatched and matched groups were analyzed with ANOVA and Wilcoxon’s matched pairs test respectively.

Results: Hispanics (H) comprised 81%, African Americans (AA) 12%, Caucasians (C) 5.1%, and others 3.8%. H and AA were significantly more female, and H and AA were younger. There was no difference in disease duration, ESR, CRP, Rheumatoid Factor (RF) status and titer, or erosions in any group. ACPA (a-cyclic citrullinated peptide Ab) prevailed in AA (p=0.049). H and AA overall showed higher cross-sectional disease severity compared to C (table p<0.04). Fewer H and AA achieved DAS28<3.2 than C (p=0.02); to accomplish this, H had higher frequency of biologic utilization than both AA and C (p=0.003). H or AA allocated biologics did not have higher disease severity at biologic onset, nor were they prescribed biologics more frequently than C. Despite a robust and similar change in DAS28 from baseline compared to C, significantly less of biologic treated H and AA achieved DAS28<3.2 (p=0.003).

Conclusion: US-based H and AA with RA have higher cross-sectional disease severity than C. In spite of similar disease activity at biologic onset, this likely reflects inferior response to biologic therapy; significantly fewer biologic-treated H and AA subjects achieved good disease control compared to C. The reasons for these disparities are under investigation.

Table. Patient Characteristics

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Hispanic</th>
<th>AA = 50</th>
<th>C = 22</th>
<th>p-all groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/M (%)</td>
<td>88/12</td>
<td>92/8</td>
<td>64/36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (&lt;SD yrs)</td>
<td>52.4 ± 11.2</td>
<td>56.4 ± 10.6</td>
<td>57.9 ± 8.9</td>
<td>0.01</td>
</tr>
<tr>
<td>DAS28-3v (M ± SEM)</td>
<td>3.2 ± 0.06</td>
<td>3.4 ± 0.17</td>
<td>2.7 ± 0.2</td>
<td>0.04</td>
</tr>
<tr>
<td>≥1 DMARD (%)</td>
<td>93.6</td>
<td>93.6</td>
<td>100</td>
<td>ns</td>
</tr>
<tr>
<td>Biologics (%)</td>
<td>60.3</td>
<td>50</td>
<td>59</td>
<td>ns</td>
</tr>
<tr>
<td>DAS28 ≤3.2 (%)</td>
<td>53</td>
<td>48</td>
<td>81.8</td>
<td>0.02</td>
</tr>
<tr>
<td>% with DAS28 ≤3.2</td>
<td>64.3</td>
<td>41.6</td>
<td>55.6</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Conclusion: Baseline disease activity has a significant effect on timing to achieve an adequate clinical response. In HDA patients particularly considered should be given to continuing therapy for at least 6 months if LDAS or REM is not achieved at 3 months.

Disclosure: P. Akhavan: None; V. P. Bykerk: Amgen Inc., 2, Pfizer Inc, 2; V. Sun: None; J. Hochman: None; J. E. Pope: None; J. E. Pope: None; C. A. Hoffman: None; G. Boire: None; B. Harauzi: None; D. S. Ferland: None; J. C. Thorne: None; D. A. Weber: None; E. C. Keystone: Amgen Inc., 2, 5, Pfizer Inc, 2; 5; All CATCH Investigators: Amgen Inc., 2, Pfizer Inc, 2.

307 Does Sequence Matter When Switching from One Anti-Tumor Necrosis Factor Agent to Another? O. Baser1, S. Roy1, C. Akin2 and M. A. Cifaldi3

Abstract Laboratories, Abbott Park, IL; Brigham and Women’s Hospital, Boston, MA; University of Michigan, Ann Arbor, MI

Background: A significant proportion of patients with rheumatoid arthritis (RA) switch from one anti-tumor necrosis factor (anti-TNF) agent to another. This study examines patient characteristics, costs, and outcomes of switching from one anti-TNF to another. Predictors of switching between anti-TNFs are also examined.

Methods: Continuously eligible adult patients in a large commercial administrative claims database with confirmed diagnoses of RA between January 2002 and December 2008 were included if they had initiated new anti-TNF treatment after a 12-month biologic-free period. Disease severity was estimated using a composite Severity Index for Rheumatoid Arthritis (SIFRA), a measure validated for administrative databases. Costs and outcomes were compared between groups 12 months after the switch, after adjusting for baseline differences in patient, disease, and prescriber characteristics through a propensity score-matching technique. Cox regression was used to determine the predictors of time to switch of biologic treatment.

Results: There were 1,567 patients in the study who switched to a second anti-TNF. Of these patients, 48% (n=781) switched to ADA, 19% (n=294) to IFX, and 33% (n=522) to ETN. Patients who were younger (HR = 0.40), used methotrexate (HR = 0.76), or other DMARDs (e.g. SSZ, HCQ and Gold) at baseline (HR = 0.73), and had a low SIFRA severity index (HR = 0.85) experienced a shorter time to switching to a second anti-TNF. Patients who started with IFX or ETN switched to a second anti-TNF sooner than those who...
who started on ADA (HR = 0.86 for ETN and 0.85 for IFX vs. ADA). Patients switching from ETN to IFX instead of to ADA had more severe disease (p = 0.002), had a greater comorbidity burden (p = 0.002), were more likely to use MTX (p = 0.0259), and were more likely to have had dose escalation prior to switch. Patients switching from ADA to IFX had a greater comorbidity burden compared with those who switched to ETN. Among switchers from IFX, slightly older patients with higher rates of respiratory infections were switched to ADA, compared with ETN. After adjusting for baseline differences, RA-related total annual health care costs were significantly lower for switches between the subcutaneously injected anti-TNFs (ETN-ADA, p < 0.0001 both ways) compared with switches to their infusion counterpart (IFX). Among all possible anti-TNF sequences, RA-related total costs, as well as disease severity were lowest one year after a switch to ADA irrespective of which anti-TNF patients were switched from (table).

Adjusted RA-Related Costs and Disease Severity Outcomes 1 Year After Switch

<table>
<thead>
<tr>
<th></th>
<th>ETN to IFX</th>
<th>P-Value</th>
<th>ETN to ADA</th>
<th>P-Value</th>
<th>IFX to ETN</th>
<th>P-Value</th>
<th>IFX to ADA</th>
<th>P-Value</th>
<th>ADA to ETN</th>
<th>P-Value</th>
<th>ADA to IFX</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total RA-related cost</td>
<td>$15,632</td>
<td>&lt;0.0001</td>
<td>$15,324</td>
<td>0.574</td>
<td>$18,652</td>
<td>&lt;0.0001</td>
<td>$24,867</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIFRA</td>
<td>5.15</td>
<td>4.65</td>
<td>&lt;0.0001</td>
<td>5.01</td>
<td>4.71</td>
<td>0.0001</td>
<td>4.74</td>
<td>0.805</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Conclusions: The timing and outcomes of switching were observed to be different based on sequence of anti-TNFs used. Relative to ADA, patients switched sooner to a second anti-TNF if they had started on IFX or ETN. Both cost and disease severity outcomes appear to be better for switches to ADA compared with switches to IFX or ETN.

Disclosure: O. Baser: STATinMED Research, 3, University of Michigan, 3; S. Roy: Abbott Laboratories, 1, 3; C. Akin: Brigham and Women’s Hospital, 3, STATinMED Research, 3; M. A. Cifaldi: Abbott Laboratories, 1, 3.

308 Durability of Clinical Remission in Rheumatoid Arthritis Based on Various Criteria. Femke H. M. Prince1, Vivian P. Bykerk2, Nancy A. Shadick3, Jing Cui2, Michele Frits3, Christine K. Iannaccone2, Michael E. Weinblatt4 and Daniel Hal Solomon5. 1Brigham & Womens Hospital, Boston, MA, 2Brigham and Women’s Hospital, Division of Rheumatology, Immunology and Allergy, BRASS, Boston, MA, 3Brigham and Womens Hospital, Boston, MA

Background: The treatment target of Rheumatoid Arthritis (RA) is remission. Clinical remission can be defined by several criteria, but only one incorporates time as a variable. There are few data about the duration of remission. Clinical remission can be defined by several criteria, but only one incorporates time as a variable. There are few data about the duration of remission periods in RA patients enrolled in a cohort from a single academic center, using different remission criteria.

Methods: Data were collected from a prospective, observational, single-center cohort of RA patients. Patients are prospectively followed, and their treatment target of Rheumatoid Arthritis (RA) is remission. Clinical remission can be defined by several criteria, but only one incorporates time as a variable. There are few data about the duration of remission periods in RA patients enrolled in a cohort from a single academic center, using different remission criteria.

Results: Of the 1095 RA patients in our study cohort, 846 had at least two years follow-up. When we considered the different remission criteria for the 846 patients, 408 were in remission at least at one time-point (with 12 months follow-up) according to the DAS28 (n=395), ACR (n=28), CDAI (n=169), or SDAI (n=98). At entrance of the cohort, median age of the 408 patients was 56 years, 83% were female, 64% were anti-cyclic citrullinated peptide or rheumatoid factor status positive, and median disease duration was eight years. Overall median survival time of remission was two years. Time in remission according to the different remission criteria is shown in the Figure (Kaplan-Meier curve). The probability of maintaining remission at the subsequent examination was significantly higher for the DAS28 criteria compared with the CDAI (p=0.029) and SDAI (p=0.030). The difference between duration of remission for DAS28 and ACR criteria was non-significant (p=0.57), however only few patients met the ACR criteria and no data were available for more than two years.

Conclusion: This study shows that approximately 50% of the RA patients who reached clinical remission maintained this state after one year. Even after multiple years in remission, patients can still drop out of remission. Whether patients are considered to be in clinical remission depends on the criteria used.

Acknowledgements: FP gratefully acknowledges funding support from the Niels Stensen Foundation, The Netherlands

Disclosure: F. H. M. Prince: Abbott Immunology Pharmaceuticals, 9, Bristol-Myers Squibb, 5, 9, Niels Stensen Foundation, 2, Novartis Pharmaceuticals Corporation, 9, Teva Pharmaceuticals, 9, Wyeth Pharmaceuticals, 9; V. P. Bykerk: None; N. A. Shadick: Amgen Inc., 2, Biogen Idec, 2, Crescendo Biosciences, 2; J. Cui: None; M. Frits: None; C. K. Iannaccone: None; M. E. Weinblatt: Biogen Idec, 2, 5, Crescendo Biosciences, 2, 5; D. H. Solomon: Abbott Immunology Pharmaceuticals, 2, Amgen Inc., 2, Bristol-Myers Squibb, 9.

309 Effect of Anti-Tumor Necrosis Factor Alpha Therapy on Cardiovascular Events in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Cheryl C. M. Barnabe1, Billie-Jean Martin1 and William A. Ghali2. 1Libin Cardiovascular Institute, 2University of Calgary, Calgary, AB, Canada

Background: Rheumatoid arthritis (RA) patients have an increased risk of cardiovascular (CV) events, attributed to both traditional CV risk factors and the inflammatory milieu of inadequately treated RA. Anti-tumor necrosis factor alpha (anti-TNF) therapy has an important role in treating patients with RA resistant to disease modifying therapies, and has been shown to have a positive impact on surrogate biomarkers of CV disease. Our objective was to systematically assess the association of anti-TNF therapy in RA on CV event rates reported in observational cohorts and randomized controlled trials (RCTs).

Methods: A search of PubMed (1950 to November 2009) and EMBASE (1980 to November 2009) was supplemented by manual searches of reference lists and conference abstracts. Observational cohorts and RCTs reporting on CV events (all events, myocardial infarction (MI), congestive heart failure (CHF), and cerebrovascular accident (CVA)) in RA patients treated with anti-TNF therapy were identified to determine the relative risk compared to those patients treated with traditional disease modifying drugs. The systematic review and meta-analysis includes 16 and 13 publications respectively.

Results: In cohort studies (total of 106,202 patients), anti-TNF therapy was associated with a reduced risk for all CV events (pooled adjusted RR 0.46; 95%CI 0.28–0.77), MI (pooled adjusted RR 0.81; 95%CI 0.68–0.96), and CVA (pooled adjusted RR 0.69; 95%CI 0.53–0.89). Cohort study results

Figure. Duration of RA remission based on various remission criteria.
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**Effect of Intensive Repletion and Maintenance Vitamin D Therapy in Rheumatoid Arthritis Patients.** Uzma J. Haque¹, Kevin Fontaine¹ and Susan J. Bartlett³. ¹Johns Hopkins School of Medicine, Lutherville, MD, ³Johns Hopkins School of Medicine, ³McGill University, Montreal, QC, Canada

Background: We have previously shown that 60% of rheumatoid arthritis (RA) patients attending an academic rheumatology clinic in Baltimore, Maryland were vitamin D deficient. We are not aware of any studies that have evaluated the effectiveness of intensive vitamin D supplementation and maintenance therapy in this population.

Objective: To estimate the effectiveness of intensive vitamin D supplementation and maintenance therapy on 25(OH)D levels in a cohort of RA patients.

Methods: Patients were consecutively approached during routine clinic visits. 25(OH)D levels were ascertained using the DiaSorin radioimmunoassay. Vitamin D deficiency was defined as 25(OH)D < 30 ng/mL. Patients who were deficient were randomly assigned to 8 weeks of standard intensive repletion therapy (INT = ergocalciferol 50,000 IU/week) followed by up to 16 weeks of maintenance therapy (MT = ergocalciferol 50,000 IU/month) or placebo for 16 weeks (followed by the above vitamin D treatment). Hyperparathyroidism was excluded before initiating vitamin D therapy.

Results: Participants were mostly female (83%) and white (83%) with a mean (± SD) age of 53.8 ± 12.1 years. At baseline, mean 25(OH)D was 21.5 ± 5.9; 70/111 (63.1%) were classified as vitamin D deficient. Patients seen from Oct – June had 7.0 times the odds of being deficient (95% CI 1.4–35.6) as those seen July – Sept. Of 46 patients completing INT, mean increase in 25(OH)D was 18.4 ± 13.5 ng/mL; 89% were classified as vitamin D sufficient. In summer, INT therapy was associated with significantly higher increases in 25(OH)D levels than those seen in the fall and winter (20.5 ± 4.5 and 12.3 ± 3.9 mg/dL, respectively.) However, adequate levels were not maintained with maintenance therapy; in 41 patients who completed 8 weeks of MT, 25(OH)D levels decreased by −9.8 ± 10.7 mg/mL; only 61% were now classified as sufficient. Of 36 patients completing a total of 16 weeks of MT, 25(OH)D decreased an additional −3.7 ± 5.9 ng/mL overall; only 31% were classified as sufficient.

Conclusions: Despite increasing awareness of the importance of vitamin D, deficiency remains common in RA patients. Intensive supplementation therapy with ergocalciferol appears to be effective in significantly increasing vitamin D levels in most RA patients. However, maintenance therapy, as currently used in clinical practice, may not be sufficient to maintain adequate vitamin D levels in these patients over time. Given the importance of optimal vitamin D levels, routine monitoring of may be required to ensure that sufficient levels are maintained. Our data suggest that RA patients may require higher maintenance doses to sustain vitamin D sufficiency.

Funding Source: Arthritis Foundation Maryland Chapter Grant

Disclosure: U. J. Haque: None; K. Fontaine: None; S. J. Bartlett: None.

**311**

**Effectiveness of Initial Treatment Allocation Based on Expert Opinion for Prevention of Rapid Radiological Progression in a Daily Practice Early RA Cohort.** Anne Durnez¹, Geert Vanderschueren¹, Luc Lateur¹, Rene Westhovens and Patrick Verschueren. ¹University Hospital Leuven Radiology, Leuven, Belgium, ²University Hospital Leuven Rheumatology, Leuven, Belgium

Background: Until now in daily practice initial treatment decisions are essentially based on expert opinion and only informally on prognostic factors. Recently a prediction model for rapid radiographic progression (RRP) was developed using a RA study population (1).

Objective: To evaluate the effectiveness of expert centered treatment selection for early RA and investigate the additional value of a prediction model for RRP in daily practice.

Methods: Consecutive RA patients were allocated to initial combination therapy with steroids (ICTS) or DMARD monotherapy (IMT), based on informal evaluation of prognostic parameters: joint counts, ESR, CRP, RF, anti-CCP and radiographic damage (2). Subsequently a tight control strategy was applied. Baseline and year 1 radiographs were scored according to Sharp/van der Heijde (SvdH). Changes in SvdH score of more than 5 units at year 1 (= RRP) were documented. Mean change in SvdH scores and proportion of patients with RRP were compared between the ICTS and IMT group. Based on 28-SJC, RF titer and CRP/ESR, each patient was placed in the ASPiRE prediction matrix yielding a theoretical RRP risk for intensive or less intensive initial treatment. The mean risk of the selected treatment was compared between different subpopulations. The numbers needed to treat (NNT) intensively to avoid one RRP after 1 year were calculated based on the matrix model. By roc curve analysis the optimal NNT cut off for RRP prevention was determined.

Results: Patients prescribed ICTS (n = 37) had a higher baseline disease activity and more were anti-CCP positive than in the IMT group (n = 43). Nevertheless the mean [SD] change in total SvdH score after 1 year was lower in the ICTS group versus the IMT group (−0.95 [2.84] vs. 1.16 [4.11]; NS). There was also less RRP in the ICTS (1/37) compared to the IMT group (4/43). The mean [SD] risk associated with the expert’s initial treatment choice was higher in patients with RRP (17.4% [7.7%] vs. 12.21% [8.68%]). The mean NNT was more to prevent RRP was lower in the ICTS compared to the IMT group, but also in patients with compared to without rapid progression. The PPV of the NNT for RRP prevention was 12.6%, but the NPV reached 100% (sensitivity 100%, specificity 53.3%) with 9.17 as a cut off in our population.

Conclusion: Also in daily practice ICTS seems more effective for the prevention of RRP than IMT. Treatment allocation based on informal evaluation of risk factors keeps the theoretical risk for RRP under control in most patients with early RA, avoiding over- and under-treatment at group level. After a theoretically more risk full treatment choice only a minority develops RRP at 1 year, probably also thanks to subsequent treatment adaptations. The predictive matrix model would be most helpful for preventing over-treatment in daily practice.

(1) Vastesaeger N, et al. Rheumatology 2009; 48(9):1114–21

Disclosure: A. Durnez: None; G. Vanderschueren: None; L. Lateur: None; R. Westhovens: None; P. Verschueren: None.

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**ESR, CRP, or RF Status at Presentation Is Only Marginally Predictive of Future Treatments with Methotrexate or Biologic Agents over 25 Years in Two Settings in the United States and in Finland.** Tuulikki Sokka¹, Hannu Kautiainen² and Theodore Pincus³. ¹Jyvaskyla Central Hospital, Jyvaskyla, Finland, ²Medcare Oy, Annekoski, Finland, ³New York University Hospital for Joint Disease, Hastings-on-Hudson, NY

Purpose: To analyze the likelihood of initiation of methotrexate (MTX) or anti-tumor necrosis factor alpha (anti-TNFα) biological agents in treatment of 1,892 RA patients in Jyvaskyla, Finland and 478 in Nashville, TN, USA between 1980 and 2004, according to whether rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) was in normal or abnormal range at presentation.

Methods: Databases maintained from 1980–2004 on all patients with RA seen at Jyvaskyla Central Hospital, Jyvaskyla, Finland and all patients seen by one rheumatologist at Vanderbilt University in Nashville, TN, USA were analyzed. The first recorded ESR and CRP were used for all patients employed as baseline values for ESR > 28 vs. <28 mm/h, CRP <10 vs. ≥10 mg/L, and a positive RF test at any time over disease course.

Results: Findings were quite similar at the 2 sites: at baseline, normal CRP <28 mm/h was seen in 45% and 47% of patients and normal CRP <28 mm/h, CRP <10 vs. ≥10 mg/L, and a positive RF test at any time over disease course.

Results: Patients prescribed ICTS (n = 37) had a higher baseline disease activity and more were anti-CCP positive than in the IMT group (n = 43). Nevertheless the mean [SD] change in total SvdH score after 1 year was lower in the ICTS group versus the IMT group (-0.95 [2.84] vs. 1.16 [4.11]; NS).

Disclosure: A. Durnez: None; G. Vanderschueren: None; L. Lateur: None; R. Westhovens: None; P. Verschueren: None.

**312**

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difference in future therapy was seen for RF and MTX treatment in Jyvaskyla, where 69% of patients with positive RF tests were treated with MTX versus 54% of patients with negative tests (p < 0.001). MTX treatment was begun in only 5% more patients in Nashville who were RF-positive vs negative (67 vs 62%, NS). Patients with abnormal values at baseline for ESR and CRP were only marginally (<5%) more likely to be treated with MTX than patients with normal values (Table). No differences were seen in likelihood of future treatment with biological agents according to baseline ESR, CRP, or RF status at any time, in either locale (Table).

Percentage of patients with RA treated with MTX or anti-TNF agent during follow-up, according to high or low baseline values for ESR, CRP, and life-time RF in Jyvaskyla, Finland and Nashville, TN.

<table>
<thead>
<tr>
<th>Measure Treatment</th>
<th>n Total Normal high p</th>
<th>n Total Normal high p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR &lt;28mm/h ≥28mm/h</td>
<td>MTX 1992 63% 62% 64% 0.41 478 64% 64% 65% 0.76</td>
<td></td>
</tr>
<tr>
<td>Anti-TNF 1992 4.3% 5.2% 3.6% 0.10 478 8.4% 8.4% 8.3% 0.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP &lt;10 mg/L ≥10 mg/L</td>
<td>MTX 1474 62% 12% 10% 0.41 175 8.5% 8.8% 8.3% 0.43</td>
<td></td>
</tr>
<tr>
<td>Anti-TNF 1474 4.2% 4.7% 3.9% 0.14 175 20% 19% 19% 0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF Neg Pos</td>
<td>MTX 1874 63% 54% 69% &lt;0.001 292 65% 62% 67% 0.36</td>
<td></td>
</tr>
<tr>
<td>Anti-TNF 1874 4.4% 4.4% 4.4% 0.99 292 14% 15% 14% 0.83</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Baseline laboratory values for ESR, CRP, and RF have only marginal impact on the likelihood of treatment with MTX or biological agents. At least 30% of patients with RA have a normal ESR or CRP, or negative RF test. A traditional view that an abnormal laboratory test generally is associated with more severe clinical status and higher likelihood of aggressive treatment has not been studied extensively with an evidence-based approach, although insufficient data are available for ACPA (anti-CCP) in this study. Additional data from usual care at other sites could provide further information toward possible reassessment of laboratory tests in usual care of patients with RA.

Disclosure: T. Sokka: None; H. Kantaiinen: None; T. Pincus: None.

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Purpose: An increased risk of invasive fungal infections has been suggested in rheumatoid arthritis (RA). The Ontario Biologics Research Initiative (OBRI) is an innovative undertaking to promote real-world rheumatologic drug surveillance, based in part on Ontario’s comprehensive administrative healthcare databases. Our objective was to assess the risk of serious fungal infections in seniors with RA.

Methods: An RA cohort was assembled from Ontario billing and hospitalization data, 1992–2009. Analyses were limited to subjects aged ≥65 who filled ≥1 prescription for an oral glucocorticoid, disease-modifying agent (DMARD) or biologic. We studied cases of invasive fungal infections (Aspergillus, Coccidioidomycosis, Histoplasmosis, Blastomyces, Paracoccidioidomycosis, systemic Candidiasis) identified from the diagnoses most responsible for hospitalizations and/or emergency room visits over 1998–2009. Cases of infection were matched (on age, sex, and date of cohort entry) to up to 5 controls from the same RA cohort. Multivariate conditional logistic regression analyses assessed the independent effects of demographics, comorbidity, medications, and markers of RA severity (number of rheumatology visits, extra-articular RA features, joint replacement).

Results: In 85,458 seniors with RA (contributing 614,915.5 person-years), 57 invasive fungal infections occurred (9.3 events per 100,000 person-years). Cases were more likely than controls (n=285) to be rural (42.1% of cases vs. 19.6% of controls) and to have more co-morbidities especially lung (43.9% vs 24.6%) and renal disease (12.3% vs 4.2%). Cases also had more extra-articular RA features (33.3% vs 21.4%) and more rheumatology visits. Biologic exposures were rare in our cohort, and at the time of infection, no cases were exposed to a biologic agent. In both cases and controls, the most common DMARDs were methotrexate (11.7%) and hydroxychloroquine (6.7%). In contrast, prednisone exposure >10mg/d occurred in 17.5% of cases, versus 7.0% of controls. Multivariable models demonstrated that risk of invasive fungal infections was higher among rural-versus-urban residents (HR 14.47, 95% CI 4.46, 46.98) and in subjects with more co-morbidities (as assessed by number of distinct drugs used in the year prior, HR 1.24 95% CI 1.12, 1.37). There was a notable trend for greater risk of invasive fungal infection with prednisone doses >20 mg/d (adjusted HR 6.10 95% CI 0.96, 38.83 (p=0.055).

Conclusions: Rural residence and greater co-morbidity were associated with increased risk for invasive fungal infections in seniors with RA. Steroids were suggested as an independent risk factor in this population-based sample. Potential limitations of our study include relatively low drug exposure rates, the possibility of incomplete ascertainment of biologic exposures (for individuals receiving drugs through private insurance) and channeling bias (where persons at highest risk for infections may not be prescribed biologics).

Disclosure: J. Widdifield: None; S. R. Brematsky: None; J. M. Paterson: None; N. Gunraj: None; J. E. Pope: None; J. C. Thorne: None; A. A. Cividino: None; C. Bombardier: None.

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Is DA28 Remission Good Enough? Disease Activity and Functionality in Rheumatoid Arthritis, Results of the DREAM Remission Induction Cohort.

Marloes Vermeer1, Ina H. Kuper2, Monique Hoekstra1, Hein J. Bermenot Moens3, Piet L. C. M. van Riel4 and Mart A. F. J. van de Laar5.

Purpose: An increased risk of invasive fungal infections has been suggested in rheumatoid arthritis (RA). In general, remission is associated with improved functionality. However, it is unclear whether remission according to the Disease Activity Score in 28 joints (DAS28) criteria is good enough to prevent functional disability. The objective of this study was to assess the relation between DAS28 and functionality after 1 year follow-up in very early RA.

Methods: Data of the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort were used (1). Disease activity was indexed as remission (DAS28 < 2.6), low (2.6 ≥ DAS28 ≤ 3.2), moderate (3.2 < DAS28 ≤ 5.1) and high (DAS28 > 5.1). Functionality was measured with the Health Assessment Questionnaire Disability Index (HAQ; scale 0 (best) to 3 (worst)) as well as with the SF-36 Physical Functioning Scale (PF-10; scale 0 (worst) to 100 (best)). HAQ ≤ 0.5 was regarded as HAQ remission (2).

Results: One year data were available for 239 patients. After one year, mean (SD) DAS28 was 2.59 (1.05) and observed DAS28 levels were 56.9% (136/239) remission, 16.3% (39/239) low, 24.3% (58/239) moderate and 2.5% (6/239) high. One year median (IQR) values of HAQ and PF-10 were 0.38 (0.00–0.86) and 75.0 (55.0–90.0) respectively. Median HAQ increased as median PF-10 decreased in parallel to increasing DAS28 levels (Kruskal-Wallis Test, both p<0.001) (Table 1). Higher percentages of HAQ ≤ 0.5 were found in the lowest disease activity groups (Table 1). Percentages of HAQ ≤ 0.5 were similar for age groups (<55 yrs and ≥55 yrs) and gender. Overall, DAS28 correlated with HAQ (Spearman’s rho 0.41, p<0.001) and PF-10 (rho −0.32, p<0.001). In patients who were in remission after one year (n=136), DAS28 still correlated with HAQ (r=0.22, p=0.010) and PF-10 (rho −0.19, p=0.027).

Table 1. DAS28 levels and functionality scores after one year.

<table>
<thead>
<tr>
<th>DAS28 level</th>
<th>Median (IQR) HAQ</th>
<th>Median (IQR) PF-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission (n = 136)</td>
<td>0.25 (0.00–0.50)</td>
<td>104 (76.5)</td>
</tr>
<tr>
<td>Low (n = 39)</td>
<td>0.38 (0.00–0.75)</td>
<td>20 (64.1)</td>
</tr>
<tr>
<td>Moderate (n = 58)</td>
<td>0.69 (0.25–1.16)</td>
<td>23 (39.7)</td>
</tr>
<tr>
<td>High (n = 6)</td>
<td>1.33 (0.94–1.91)</td>
<td>1 (16.7)</td>
</tr>
</tbody>
</table>

Conclusion: A lower disease activity is related to better functionality in patients with very early RA. Below the DAS28 remission threshold (DAS28 ≤ 2.6), a lower DAS28 is still associated with better functionality scores. The DAS28 is a composite score and the HAQ and PF-10 are patient reported outcomes. Our results emphasize that aiming for remission is
important but aiming at the lowest possible DAS28 is even better as it results in improved functionality, which is relevant for patients.


Disclosure: M. Vermeer: None; I. H. Kuper: None; M. Hoekstra: None; H. J. Bernelot Moens: None; P. L. C. M. van Riets: None; M. A. F. J. van de Laar: None.

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Low Rate of Rheumatoid Arthritis Remission in Real Life: Might Predictive Factors Explain? Elodie Loppin2, Ronan Garlanzteze1 and Elisabeth Solau-Gervais2. 1Public Health Department, University Hospital Brest, France, 2Rheumatology Department University Hospital Poitiers, France

Objective: Remission constitutes the best achievable state in patients with rheumatoid arthritis (RA). Remission rates in usual clinical care are much more lower than the one in randomized clinical trials (1). The objective of the study was to define remission factors in “real life”.

Methods: Remission has been assessed retrospectively for records of 364 patients with rheumatoid arthritis receiving usual care. These patients were out and in patients followed in an university hospital with at least one visit in year 2008. Disease activity was evaluated on records according to DAS 28 criteria. Remission was defined by a DAS28 < 2.6. Statistical analysis used Chi-2 and multivariate analysis with the software SAS9.

Results: The evaluation of disease activity was available for 328 patients (90%). Mean age of the patients was 63 years (+/−13,7) and mean duration of the disease was 13,6 (+/−10,7). Rheumatoid factor and anti-CCP was positive respectively in 79,3% and 73,8%. Eighty five percent had an erosive disease. The rate of global remission was 28%. Factors associated statistically with remission in multivariate analysis were (Odds 95% confidence intervals): male sex (0,2-0,8), younger age (0,2-0,9), rheumatoid factor-positive (1,2–6,5) and the absence of concomitant prednisone treatment (0,3-0,9). Younger age and rheumatoid factor-positive presents more a population with a “higher therapeutic objective” and female sex and older age patients have more a difference in the evaluation of the disease, rather than true differences in RA activity. Moreover, the remission rate was significantly different according to the treatment: 15% without DMARDs or biotherapies, 24% with DMARDs and 47% with anti-TNF alpha treatment. As regards to the three anti-TNF alpha, the remission rate was the lowest for infliximab (18%), than etanercept (43%). Patients treated with adalimumab had the highest rate of remission with 64%. The difference was significant between infliximab and adalimumab (OR: 1,2–101) and between infliximab and etanercept (OR: 1,1–30,15) but not between etanercept and adalimumab.

Conclusion: Male sex, younger age, rheumatoid factor-positive and corticoids free are associated with remission. Assessing remission in clinical practice is possible, and etanercept and adalimumab treatments are associated with higher rate of remission.


Disclosure: E. Loppin: None; R. Garlanzteze: None; E. Solau-Gervais: None.

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Lymphocytopenia and Infection Risk in Rheumatoid Arthritis: A Population Based Analysis. Deana D. Hoganson2, Eric L. Matteson1, Patrick D. Fitz-Gibbon1 and Cynthia S. Crowson3. 1Mayo Clinic, Rochester, MN, 2Mayo Clinic Rochester, Rochester, MN, 3Mayo Clinic Rochester, Rochester, MN

Background: There is an increased susceptibility for infections in patients with rheumatoid arthritis (RA) which contributes to increased mortality. Lymphocytopenia is prevalent in RA patients and may contribute to increased infection risk. The purpose of this study was to examine the association between lymphocytopenia and infection in RA patients during the pre-biologic era and develop a risk score for infections.

Methods: We utilized a population based cohort of patients with incident RA ascertained between 1955 and 1994 that were followed longitudinally through their complete medical records until 1/2/2000. The outcome measures included all objectively confirmed infections (by microbiology or radiology) and serious infections (requiring hospitalization or IV antibiotics). Data were collected on smoking status, leupkenoma, lymphocytopenia, comorbidities (alcoholism, diabetes mellitus (DM), chronic lung disease, cardiovascular disease (CVD)), RA disease characteristics (erosions, extra-articular manifestations (ExRA), rheumatoid factor (RF), nodules, erythrocyte sedimentation rate (ESR)) and medication use. Potential predictors were examined using multivariable Andersen-Gill models (a variant of Cox modeling allowing multiple infections per patient) with time-dependent covariates.

Results: Among the 584 RA patients (mean age 58 years; 72% female; median followup 9.9 years), 277 had ≥1 objectively confirmed infection (706 total infections), and 252 had ≥1 serious infection (646 total infections).

Disclosures: E. Loppin: Genentech and Biogen IDEC Inc, 2; E. L. Matteson: Genentech and Biogen IDEC Inc, 2; C. S. Crowson: Genentech and Biogen IDEC Inc, 2.

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Measures of Disease Activity Provide Various Clinical Decisions in Individual Patients. P. H. P. de Jong1, J. M. W. Hazes1, J. J. Luime1 and A. E. A. M. Weel1. 1Department of Rheumatology, ErasmusMC, Rotterdam, The Netherlands, 2Department of Rheumatology, ErasmusMC, Rotterdam, 3Department of Rheumatology, Maassstad Hospital, Rotterdam

Background: Disease Activity Score (DAS) and its modified versions, Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) are indices used to measure disease activity. Provided thresholds for activity states to adjust therapy on were solely based on rheumatologists’ decisions. To achieve disease remission, treatment adjustments based on tight controlled indices is recommended in individual patients, but no preferred index is defined. Moreover, data on reflection of disease state with clinical remission are missing.

Purpose: To investigate the interchangeability of measures of disease activity to base treatment decisions on. To compare remission thresholds of indices with predefined clinical remission.

Methods: For this study data are used of a currently ongoing clinical trial in patients 18 years or older with recent-onset arthritis (REACH). Treatment decisions to step up or step down are performed every 3 months and based upon the DAS thresholds >2.4 and <1.6. For the present study DAS indices are recalculated, namely DAS 3 variables (no patient Global), DAS-28, DAS-CRP, DAS-3 variables, same combinations for 28 joints and SDAI and CDAI. Thresholds for remission and active disease for DAS28, SDAI and CDAI are respectively <2.6 and >3.2, <3.30 and >1.1, and <2.80 and >10. Clinical remission is defined as having: (1) less than 2 swollen joints, (2) no swollen
SAI and CDAI have a significant lower sensitivity and high specificity for clinical remission. All DAS indices however have a higher sensitivity but lower specificity (Table 2).

**Conclusion:** Various indices of disease activity misclassify disease state when compared to the original DAS, which could imply that patients have still active disease in one while not in another. Moreover remission thresholds are also discordant where SAI and CDAI under detect clinical remission, where DAS indices might misclassify patients to be in clinical remission.

**Table 2.** Remission thresholds of indices compared to predefined clinical remission states

<table>
<thead>
<tr>
<th>Index</th>
<th>SAI&lt;1</th>
<th>SAI&lt;16</th>
<th>SAI&lt;0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>0.87 (0.81–0.91)</td>
<td>0.85 (0.80–0.90)</td>
<td>0.89 (0.84–0.92)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>0.90 (0.86–0.93)</td>
<td>0.89 (0.85–0.91)</td>
<td>0.90 (0.87–0.93)</td>
</tr>
</tbody>
</table>

**Table 3.** Remission thresholds of indices compared to predefined clinical remission states (Continued)

<table>
<thead>
<tr>
<th>Index</th>
<th>TJC&lt;8</th>
<th>SJC&lt;10</th>
<th>TJC&lt;8 &amp; SJC&lt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>0.89 (0.84–0.92)</td>
<td>0.86 (0.82–0.90)</td>
<td>0.88 (0.84–0.92)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>0.90 (0.86–0.93)</td>
<td>0.89 (0.85–0.91)</td>
<td>0.90 (0.87–0.93)</td>
</tr>
</tbody>
</table>

**Disclosure:** P. H. P. de Jong; None; J. M. W. Hazes; None; J. J. Luime; None; A. E. A. M. Weel; None.

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**Minocycline and Doxycycline Therapy in Community Patients with Rheumatoid Arthritis (RA): Incidence, Patient-Level Determinants of Use and Side Effects.** Christopher J. Smith, Harlan R. Sayles, Ted R. Mikuls, and K. J. Luime. University of Nebraska Med Ctr, Omaha, NE; University of Nebraska Med Ctr, Omaha, NE.

**Background:** Minocycline (MC) and doxycycline (DC) are safe and moderately effective disease-modifying antirheumatic drugs (DMARDs) in the treatment of early, DMD-naive RA. Little is known about how these medications are used outside the context of clinical trials. We characterize the use of MC and DC in a large community of RA patients by examining associated prescribing patterns, patient-level determinants of use, and the frequency and severity of patient-reported side effects.

**Methods:** We studied 15,716 patients with RA observed between 1998 and 2009 while participating in a long-term US observational study. Patients were categorized by their use of MC/DC. Patient-reported side effects and their consequences were also evaluated.

**Results:** MC and/or DC were used by 1,407 (9%) patients during their disease course with 480 (3.1%) incident users. Patients were seen by 1,676 rheumatologists, of which 196 (18.4%) prescribed MC/DC with an interquartile range of 1–2 patients per physician. Significant differences between MC/DC users and non-users are shown.

**Table.** Sociodemographic and disease characteristics of MC/DC users and non-users

<table>
<thead>
<tr>
<th>Initiated MC</th>
<th>Never Used MC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=480</td>
<td>n=14,309</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.35 (11.60)</td>
<td>59.76 (13.28)</td>
</tr>
<tr>
<td>Caucasian, Non-Hispanic %</td>
<td>93.68</td>
<td>89.72</td>
</tr>
<tr>
<td>Lifetime DMARD &amp; Biologics</td>
<td>3.30 (2.10)</td>
<td>2.52 (1.81)</td>
</tr>
<tr>
<td>Prednisone %</td>
<td>40.08</td>
<td>35.34</td>
</tr>
<tr>
<td>SF-36 PCS (0–100)</td>
<td>35.03 (11.17)</td>
<td>36.39 (11.09)</td>
</tr>
</tbody>
</table>

In multivariable Cox regression, initiation of MC/DC was significantly associated with an increase in disease activity, comorbidity, previous number of non-biologic DMARDs, and calendar year, and associated with a decrease in previous number of biologic DMARDs and use of MTX, leflunomide or azathioprine. Side effects were reported by 17.8% of MC users and 11.8% of DC users. About 40% of those reporting side effects discontinued the medication. Skin complaints accounted for 54% of MC patient-reported side-effects. The most-commonly effected organ systems for DC were gastrointestinal (35.4%) and skin (33.7%). Dizziness was reported equally by MC (9.5%) and DC (8.2%) users. The majority of side effects were classified as mild or moderate for MC (70.0%) and DC (76.4%).

**Conclusion:** Rheumatologists have not embraced MC and DC as primary treatment options for RA and reserve their use primarily in patients with long-standing disease refractory to other agents. These drugs are generally well-tolerated with skin complaints, nausea, and dizziness being the most common patient-reported side effects.

**Disclosure:** C. J. Smith; None; H. R. Sayles; None; T. R. Mikuls; None; K. D. Michaud; None.

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**Multi-Centre, Cross-Sectional, Observational Study of the Safety of Methotrexate and Leflunomide in Combination in the Treatment of Patients with Rheumatoid Arthritis The SMILE Study—Safety of Methotrexate In Combination with Leflunomide.** Paul Bird, Hedley Griffiths and The Optimising Patient Outcomes in Australian Rheumatology [OPAL] Consortium. Barwon Rheumatology Service, Victoria, Australia; Combined Rheumatology Practice (CRP), University of NSW, Sydney, NSW, Australia.

**Background:** The combination of methotrexate and leflunomide is effective in early RA[1] and commonly utilized in Australia. The frequency of use of this combination in Australia is in part due to Federal government legislation, mandating the combination as pre-requisite treatment prior to eligibility for government funded biological therapy. Hepatotoxicity and neutropenia are two of the most common adverse effects associated with this combination.

The primary objective of this study was to assess the safety of treating patients with rheumatoid arthritis with a combination of methotrexate (MTX) and leflunomide (LEF) in comparison to methotrexate monotherapy (MTX).

**Methods:** Multi-centre, observational, cross-sectional, retrospective, safety study. The study was conducted by the OPAL QUMI (Optimising Patient outcomes in Australian rheumatology – Quality Use of Medicines Initiative). Using a clinical audit program, data was sourced from 12 participating rheumatology practices comprising 24 rheumatologists. All data was de-identified to patient, clinic and clinician prior to collection. Approval for the study was granted by the University of New South Wales Human Research Ethics Committee.
Results: In total, 3362 patients were included in the study: 72% female, 27% male, <1% gender unassigned, mean age 62 years (SD 13.8). Distribution of therapy: MTX monotherapy 49.2%, LEF monotherapy 7.6%, MTX/LEF 14.8%. Neither MTX or LEF 28.4%.

Mean MTX dose in the monotherapy group was 14 mg/week (SD 6.7), mean MTX dose in the MTX/LEF combination group 18 mg (SD 7.1). Mean LEF dose in the monotherapy group was 16.8 mg/day (SD 4.9), mean LEF dose in the MTX/LEF combination group was 16.0 (SD 5.3). Co-morbid liver disease was reported in less than 5% of patients.

Liver function abnormalities were reported in 12% of the MTX monotherapy group, 16% of the LEF monotherapy group, 14% of the MTX/LEF combination group and 16% of the group taking neither of the drugs. The majority of the AST/ALT abnormalities were in the range less than 1.5 times the upper limit of normal in all four groups.

Neutropenia was reported in 2% of the MTX monotherapy group, 8% of the LEF monotherapy group, 5% of the MTX/LEF combination group and 3% of the group not taking either drug.

Conclusion: Liver function abnormalities and neutropenia in the MTX/LEF combination group were mild and equivalent to reported levels in either MTX monotherapy or LEF monotherapy. Levels of liver function abnormalities in the combination group were lower than those reported in previously published trials.[2] The combination of MTX and LEF was well tolerated, with adverse events comparable to monotherapy and the other non biologic DMARD treatment group.


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Multi-Centre, Observational Study Shows High Proportion of Australian Rheumatoid Arthritis Patients Have Inadequate Disease Control.

Geoffrey Littlejohn and Kathleen E. Tymms. 1Canberra Rheumatology, Canberra, ACT, Australia, 2Monash Medical Centre, Clayton, Victoria, Australia

Background: Contemporary management of rheumatoid arthritis [RA] includes early use of disease modifying drugs with the aim to achieve disease remission. RA management in Australia involves drug algorithms based on disease activity predefined by health care payers. This study used a new methodology in order to evaluate the disease activity and current therapy of RA patients managed in Australia.

Methods: Using a point of care electronic clinical management program, details of RA patients treated in 21 participating Australian clinics were collected at one point in time. This included patient demographics, diagnosis, medications and disease measures. The data was de-identified to patient, clinic and clinician. Analysis of this data was conducted to determine the proportion of RA patients who were in disease remission (DAS28 <2.6), low disease activity (LDA, DAS28 2.6–3.1), moderate disease activity (MDA, DAS28 3.2–5.1) and high disease activity (HDA, DAS28 >5.1), and their respective treatments. Ethics approval was granted by the University of New South Wales Human Research Ethics Committee.

Results: As of the 23rd April 2010, 4766 rheumatoid arthritis patients (73% females; 26% males, <1% gender indeterminate) had been assessed at 21 participating clinics. The mean age was 61.5 (60.5 females, 64.2 males) and mean disease duration was 12.6 years (13.1 females, 11.3 males). DAS28 scores were recorded for 51% of patients with 42% in remission, 20% in LDA, 30% in MDA and 8% in HDA. Of the patients in remission, 20% were being treated with a bDMARD, 77% with methotrexate (MTX), 24% with leflunomide (LEF), and 36% with prednisone. Of the patients in MDA, 23% were being treated with a bDMARD, 80% with MTX, 33% with LEF and 49% with prednisone.

Overall, 18% of patients were being treated with a bDMARD and 35% of patients were being treated with prednisone.

Conclusions: Cross-sectional assessment of this large cohort of Australian RA patients, managed in accordance with contemporary practice, shows a large number who have moderate and high disease activity. As disease activity patients are at risk of both biological and functional outcomes, this indicates that current RA management practice in Australia will result in significant future health burden in RA patients.


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Multiple Courses of Rituximab Produce Sustained Efficacy in Patients with Rheumatoid Arthritis with an Inadequate Response to One or More TNF Inhibitors.

Edward C. Keystone, Roy M. Fleischmann, Maxime Dougdos, Sarah Williams, Matthew D. Linnik and Mark Reynolds.

Biogen Idec, San Diego, San Diego, CA, 2Chapel Allerton Hospital, Leeds, United Kingdom, 3Hospital Cochin, Paris, France, 4Roche Products Ltd, Welwyn Garden City, UK, 5University of Texas Southwestern Medical Center, Dallas, Dallas, TX, 6University of Toronto, Toronto, ON, Canada

Objectives: To assess the efficacy of repeat courses of rituximab (RTX) in patients (pts) with a prior inadequate response to TNF inhibitors (TNF-IR).

Methods: Rheumatoid arthritis (RA) pts recruited into Phase II or III studies with RTX and who previously had an IR to a TNF inhibitor were permitted to receive further courses of RTX in open-label extensions. Eligibility for retreatment included a response to the initial course (at least 20% reduction in swollen and tender joint counts [SJC/TJC]) with subsequent courses given no more frequently than every 16 weeks. Criteria for retreatment included active disease defined as either ≥8 SJC and TJC or DAS28 ≥2.6 (depending on the study). Each course (C) consisted of 2 × 1000mg given as IV infusions 2 weeks (wks) apart. Efficacy was determined 24 wks following each course of RTX with outcomes assessed relative to the pts pre-RTX treatment baseline. Analyses were performed using observed data on all pts, and on all pts with efficacy data at 24 wks following each of their first five courses of RTX (the within pt-within visit [WW] population).

Results: 300 RA TNF-IR pts had been exposed to at least one course of RTX and had efficacy data at Week 24, with 119 evaluable at 24 wks following each course (WW population). Observed efficacy in all pts show higher responses for C2 onwards compared with C1. However, retreatment criteria may cause this population to become enriched for RTX responders, as pts were required to achieve a response to C1. Similar maintained or improved responses were seen in the WW population.

Disclosure: E. C. Keystone: Abbott Laboratories, 2, 5, 8, Amgen Inc., 2, 5, 8, AstraZeneca, 2, Bristol-Myers Squibb, 2, 5, 8, Centocor, Inc., 2, 5, Genentech and Biogen IDEC Inc, 5, Hoffmann-La Roche, Inc., 2, 5, 8, Novartis Pharmaceuticals Corporation; R. M. Fleischmann: Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, Bristol-Myers Squibb, 2, 5, Celgene, 2, Centocor, Inc., 2, 5, Genentech and Biogen IDEC Inc, 2, 5, Lexicon, 2, 5, Lilly USA, LLC., 2, Pfizer Inc, 2, 5, Regeneron Pharmaceuticals; M. Reynolds: Abbott Laboratories, 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Roche, 2, 5, 8, UCB, Inc., 2, 5, 8, Wyeth Pharmaceuticals, 2, 5, 8; S. Williams: None; M. D. Linnik: Biogen Idec, 3, M. Reynard: GlaxoSmithKline, 1, Roche, 1, 3.

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National Trends in Drug Use, Health Status and Costs in Older Americans with Rheumatoid Arthritis.

Leslie R. Harrold, Becky Briesacher, Daniel Peterson and Jerry H. Gurwitz.

Meyers Primary Care Institute, “Meyers Primary Care Institute/UMass Medical School, 3UMass Medical Schl, Worcester, MA, 4UMass Medical School
Introduction: Little is known about the recent adoption of the nonbiologic and biologic disease modifying anti-rheumatic drugs (DMARDs) in older patients with rheumatoid arthritis (RA), or the potential impact of these drugs on health status and costs.

Method: We identified a nationally-representative sample of RA patients in the Medicare Current Beneficiary Survey linked to Medicare claims data (unweighted unique n of 221 to 258 patients annually; initial response rate ~85%) and tracked DMARD use and health status during the years 2000–2006. RA patients were identified using a combination of ICD-9 diagnoses (714.XX); self-reported RA diagnosis, and use of biologic and nonbiologic disease modifying anti-rheumatic drugs (DMARDs). DMARD use was identified based on self-reported use of adalimumab, etanercept, hydroxychloroquine, infliximab, methotrexate, and sulfasalazine as well as procedure codes for infliximab infusions. Health status was assessed using validated, self-reported measures of functional status (the Nabi, activities of daily living, and instrumental activities of daily living) and general health status. Total costs (in 2006 dollars) for all prescription medications and medical care, as well as the proportion of all medical costs attributable to prescription medications, were examined over time. Tests for trends were conducted using weighted regressions.

Results: From 2000 to 2006, the use of any biologic in the Medicare population with RA increased almost 300% (from 4.6% in 2000 to 13.2% in 2006; p=0.01). Use of cytotoxic DMARDs occurred in 28.5% in 2000 as compared to 34.1% in 2006 (p=0.23). Use of noncytotoxic DMARDs remained at a stable rate of 21.3–25.2%. During this period, the proportion of RA patients rating their health as excellent/good increased by 29% (from 43.0% in 2000 to 55.6% in 2006; p=0.007). Significant improvements in functional status occurred in 2 of the 3 measures (ADL and Nabi). Total costs for prescription medications increased by 77% ($2645 in 2000 to $4685 in 2006, p=0.0001). Total medical costs increased but the trend was not significant. In 2000, the mean proportion of medical costs attributable to prescription medications was 30.2% as compared to 37.5% in 2006 (p=0.001).

Table 1: National trends in drug use, health status and costs in older rheumatoid arthritis patients (only even years shown)

<table>
<thead>
<tr>
<th></th>
<th>2000</th>
<th>2002</th>
<th>2004</th>
<th>2006</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA patients (%)</td>
<td>225</td>
<td>258</td>
<td>254</td>
<td>247</td>
<td></td>
</tr>
<tr>
<td>Medication use (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncytotoxic DMARDs*</td>
<td>25.2</td>
<td>21.4</td>
<td>22.0</td>
<td>23.2</td>
<td>0.900</td>
</tr>
<tr>
<td>Cytotoxic DMARDs**</td>
<td>28.5</td>
<td>26.9</td>
<td>32.6</td>
<td>34.1</td>
<td>0.226</td>
</tr>
<tr>
<td>Any biologic use***</td>
<td>4.6</td>
<td>6.7</td>
<td>7.7</td>
<td>13.2</td>
<td>0.007</td>
</tr>
<tr>
<td>Self-Reported Health Status (%)</td>
<td>43.0</td>
<td>44.0</td>
<td>48.7</td>
<td>55.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Functional status, mean Nagi</td>
<td>3.56 (0.11)</td>
<td>3.51 (0.12)</td>
<td>3.30 (0.10)</td>
<td>3.16 (0.10)</td>
<td>0.045</td>
</tr>
<tr>
<td>IADL</td>
<td>1.65 (0.12)</td>
<td>1.83 (0.12)</td>
<td>1.46 (0.11)</td>
<td>1.51 (0.12)</td>
<td>0.142</td>
</tr>
<tr>
<td>ADL</td>
<td>1.35 (0.12)</td>
<td>1.63 (0.11)</td>
<td>1.16 (0.12)</td>
<td>1.12 (0.13)</td>
<td>0.017</td>
</tr>
<tr>
<td>Costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescription costs (mean, 2006 dollars)</td>
<td>2645</td>
<td>3270</td>
<td>3726</td>
<td>4685</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total medical care costs (mean, 2006 dollars)</td>
<td>16563</td>
<td>18310</td>
<td>17783</td>
<td>19510</td>
<td>0.296</td>
</tr>
<tr>
<td>Mean proportion of medical care costs due to prescription drugs (%)</td>
<td>30.2</td>
<td>31.9</td>
<td>36.6</td>
<td>37.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* hydroxychloroquine and sulfasalazine
** methotrexate and leflunomide
*** adalimumab, etanercept and infliximab

Conclusions: Between 2000 and 2006, the use of biologic agents for RA substantially increased in older adults with RA. During the same period, there were concurrent improvements in self-reported health status and functional status. However, these gains were offset by an increase in total prescription medication costs.

Disclosure: L. R. Harrold: Corona, S. B. Briesacher: None; D. Peterson: None; J. H. Gurwitz: None.

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Pandemic H1N1 Influenza Vaccination Responses in Rheumatoid Arthritis and Systemic Lupus Erythematosus Patients: An Association with Serum IL17 and CXCL13 Level. Sung-Hoon Park1, Hwa-Jeong Lee2, Hyun-Hee Kwon2, Seong-Kyu Kim3 and Jung-Yoon Choi4. 1Catholic University of Daegu, School of Medicine; Arthritis and Autoimmunity Research Center, Daegu, Korea, Republic of; 2Catholic University of Daegu, School of Medicine, Arthritis and Autoimmunity Research Center

Background: Infections are the main cause of morbidity and hospitalization in immunocompromised host. With the worldwide outbreak of pandemic H1N1 2009 influenza, many patients in rheumatology departments comprised a target group for prophylaxis by vaccination. We investigated an efficacy and safety of pandemic H1N1 vaccine in rheumatoid arthritis(RA) and systemic lupus erythematosus(SLE) patients, and evaluate its correlation with serum cytokine level.

Methods: This is a prospective, case-controlled study. The blood samples drawn from selected patients before vaccination and in post-vaccination weeks 4 were assayed in one session to measure titres of antibodies against haemagglutinin specific for influenza virus strains: A/New Caledonia/20/99(H1N1), Serum IL17 and CXCL13 level were measured in the same session by enzyme-linked immunosorbent assay according to the recommendations of the manufacturer’s instructions(R&D Systems, Minneapolis, MN, USA). The association of serum cytokine level with anti-influenza antibody titer and mean fold increase(MFI) was investigated. Each specific side effects after vaccination were monitored in both patients and control groups.

Results: A total of 43 RA patients, 31 SLE patients were enrolled in the study and were compared with age, sex-matched 40 healthy controls(HC). The geometric mean antibody titer(GMT) for pre- and post-vaccination week 12 was not significantly different between RA and HC, SLE and HC. The seroconversion rate in HC and RA was not significantly different, while the seroprotection rate is 92.5% in HC, and 55.8% in RA, is significantly higher in HC. MFI in HC was 19.65 and 6.00 in RA, 6.06 in SLE patients, and was significantly higher in HC. The seroprotection/seroconversion rate of SLE patients were not significantly different from HC. Serum IL17 level was 6.28±2.89pg/ml and 7.56±3.34pg/ml in pre- , post-vaccination SLE patients, 33.85±15.62pg/ml and 38.04±18.60pg/ml in RA patients and was significantly lower in SLE patients. Serum CXCL13 level was 518.73±18.60pg/ml in RA patients and was significantly lower in SLE patients. Post-vaccination antibody titer(Pearson’s correlation coefficient 0.44, p<0.05). No serious vaccination-related adverse event or disease flare was observed in HC and the patient groups.

Conclusion: The increase in post-vaccination antibody titer is weaker in both RA and SLE patients group than HC. Post-vaccination antibody titer was positively correlated with B lymphocyte chemoattractant, CXCL13 in RA, not in SLE patients.

Disclosure: S.-H. Park: None; H.-J. Lee: None; H.-H. Kwon: None; S.-K. Kim: None; J.-Y. Choi: None.

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Patient Preferences for Biologic Agents in Rheumatoid Arthritis: A Discrete Choice Experiment. David A. Navarta1, Federico Augustovski2, Andrea Batarace2, Vilma Iruzula3, Fernando Rubinstein3, Pablo Tesolin3, Juan M. Gonzalez2, Veronica Lencina4, Marina Scolnik2, Christian Wainmann5, Gustavo Citera4 and Enrique R. Soriano. 1Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Capital Federal, Argentina, 2Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, 3Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina, 4Instituto de Investigaciones en Epidemiologia, Buenos Aires, Argentina, 5Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, 6RTI Health Solutions, NC

Background: Rheumatoid Arthritis (RA) is a chronic condition which requires a substantial degree of adherence to different recommendations. RA patients’ preferences among available treatment options have been previously explored using different approaches. Discrete choice experiments (DCEs) allow systematic assessment of preferences by asking respondents to choose between scenarios with different attributes. We conducted a DCE to elicit RA patients’ preferences regarding treatment with Biologic Agents (BA).

Methods: We designed a DCE, in which RA patients had to choose between hypothetical drug profiles that could differ in seven treatment attributes (with three to four levels each): effectiveness, route of administration, frequency of admin-
istration, local and systemic adverse effects, severe infections and out-of-pocket costs. We included RA patients older than 18 years who had never received BA from one private and one public hospital in Buenos Aires, Argentina. A Multinomial probit regression model (MNP) was used to analyze the relative importance of treatment attributes, and their willingness to pay (WTP).

Results: 240 RA patients were included. Mean age was 56.2 (SD: 13.5) years, 87% were women, and median disease duration was 9 years. All patients were receiving conventional DMARDs (84.5% Methotrexate), median Clinical Disease Activity Index was 7.5 (interquartile range [IQR]: 3.5–10), and median HAQ was 0.5 (IQR: 0.1–2.25). Mean family monthly income was 645 US dollars ($). All the attributes showed to be significant factors affecting choice of treatment. Most attributes showed coefficients with the expected signs and were statistically significant. Attributes importance ranking was in the following order: cost, systemic adverse events, frequency of administration, efficacy, route of administration, local adverse events and serious infection.

Table. Model main results. Results expressed the mean distance and CI 95% of the most favored level and the least favored level of each attribute.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Mean</th>
<th>Lower limit 95% CI</th>
<th>Upper limit 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>0.8058</td>
<td>0.6884</td>
<td>0.9245</td>
</tr>
<tr>
<td>Systemic adverse events</td>
<td>0.6654</td>
<td>0.5696</td>
<td>0.7573</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>0.6145</td>
<td>0.5164</td>
<td>0.7124</td>
</tr>
<tr>
<td>Efficacy</td>
<td>0.4174</td>
<td>0.3253</td>
<td>0.5094</td>
</tr>
<tr>
<td>Route of administration</td>
<td>0.4129</td>
<td>0.3053</td>
<td>0.5208</td>
</tr>
<tr>
<td>Local adverse events</td>
<td>0.3981</td>
<td>0.3068</td>
<td>0.4875</td>
</tr>
<tr>
<td>Serious infection</td>
<td>0.2938</td>
<td>0.2190</td>
<td>0.3701</td>
</tr>
</tbody>
</table>

Patients had relatively high monthly WTP for treatments that significantly reduced the risk of systemic adverse events: mean 331 (95% CI 212–499) US dollars ($) for a reduction from 30% to 10% of decreasing dose frequency: mean $ 302 (95% CI: 183–461) for going from weekly to monthly administration; increasing treatment efficacy: mean: $ 386 (95% CI: 285–532) for 40 vs 20 mm reduction in patient global assessmentVAS, and also for switching from an intravenous to an oral therapy: mean $ 262 (95% CI: 262–555).

Conclusion: Different treatment attributes had a significant and different influence in RA patients choice of BA. The results of the DCE indicated that most respondents would be willing to pay for treatments that importantly reduced the risk of systemic adverse effects, dose frequency, with increased treatment efficacy, and with an oral route of administration.

Disclosure: D. A. Navarta: None; F. Augustovski: Bristol-Myers Squibb, 2; A. Beratarrechea: Bristol-Myers Squibb, 2; V. Irazola: Bristol-Myers Squibb, 2; F. Rubinstein: Bristol-Myers Squibb, 2; P. Tesolin: Bristol-Myers Squibb, 2; J. M. Gonzalez: None; V. Lencina: None; M. Seolch: None; C. Wainnmann: Bristol-Myers Squibb, 2; E. R. Soriano: Bristol-Myers Squibb, 2, Wyeth Pharmaceuticals, 2.

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Patient Risk Perception of Teratogenicity of Disease Modifying Anti-Rheumatic Drugs, Eliza F. Chakravarty1, Megan E. Clowse2, Karen H. Costenbader3, Chambers4, and Kaleb Michaud5, Brigham and Womens Hospital, 2Duke University, Durham, NC, 3Stanford University, 4University of California, San Diego, 5University of Nebraska

Purpose: Women with chronic diseases often require long term therapy with disease modifying agents. Some of these medications are known or suspected teratogens (methotrexate has an estimated 10% risk of teratogenicity) while others are more rarely teratogenic medications, and after exposure to a variety of anti-inflammatory and immunosuppressive medications. Regression models were generated to identify disease, demographic, medication, treating physician, or reproductive variables that may be associated with perceived risk of teratogenicity among patients with RA.

Results: 589 (68%) women with RA, 85 (36%) women with SLE and 96 (59%) women with fibromyalgia completed the risk perception portion of the reproductive history questionnaire.

Mean age at questionnaire completion was 53–59 years. Almost all women had children and up to 13% reported a child with a birth defect. Only 1.5% of respondents correctly estimated the risk of birth defects in the general population, whereas 96.2% underestimated risks and 2.3 % overestimated risks. Women underestimated teratogenic risks for all categories, but identified methotrexate or leflunomide as the agents with the highest risk of teratogenicity (see table).

Table. Risk of birth defect

<table>
<thead>
<tr>
<th>Risk of birth defect</th>
<th>RA</th>
<th>SLE</th>
<th>Fib</th>
</tr>
</thead>
<tbody>
<tr>
<td>In healthy women</td>
<td>1.00%</td>
<td>0.86%</td>
<td>0.41%</td>
</tr>
<tr>
<td>In women with your disease</td>
<td>1.14%</td>
<td>1.09%</td>
<td>0.49%</td>
</tr>
<tr>
<td>With NSAIDs</td>
<td>1.61%</td>
<td>1.74%</td>
<td>1.19%</td>
</tr>
<tr>
<td>With prednisone</td>
<td>4.15%</td>
<td>2.25%</td>
<td>2.60%</td>
</tr>
<tr>
<td>With plaquenil</td>
<td>2.63%</td>
<td>2.04%</td>
<td>2.15%</td>
</tr>
<tr>
<td>With methotrexate</td>
<td>6.51%</td>
<td>7.28%</td>
<td>3.30%</td>
</tr>
<tr>
<td>With leflunomide</td>
<td>5.05%</td>
<td>9.75%</td>
<td>6.23%</td>
</tr>
<tr>
<td>With TNF inhibitor</td>
<td>4.83%</td>
<td>4.95%</td>
<td>4.05%</td>
</tr>
</tbody>
</table>

Objective: To evaluate if early post-tx changes in CRP can reliably predict clinical response, we evaluated the association of early post-tx changes in serum CRP levels with clinical response at a later time point.

Methods: Sera were collected at wk0, 4 & 24 from GO-BEFORE (MTX naïve RA pts; 477 golimumab[GLM]+/−MTX, 160PBO+MTX), GO-FORWARD (active RA pts despite MTX; 311GLM+/−MTX, 133PBO+MTX) and GO-AFTER (active RA pts previously tx with TNF inhibitors; 304GLM, 155PBO) studies. Samples were tested for CRP levels using Roche Tnainquart assay. CRP levels at baseline (BL), wk4 & 24 in GLM/GLM+MTX and PBO+/−MTX pts achieving and not achieving multiple measures of clinical response (ACR & EULAR/DAS response criteria) were evaluated. Logistic regression models were used to test for marker associations with clinical endpoints.

Results: The figure shows CRP levels at wk0, 4&24 among remission (DAS28-ESR<2.6) achievers and non-achievers at wk24 (as a representative data; data for other clinical measures of response were similar but not shown). Pts
achieving remission tend to have lower CRP at BL, wk4erty compared to pts not achieving remission, & pts treated with GLM had in general lower CRP than pts treated with MTX or PBO. Changes from BL in CRP levels were analyzed in 3 RA populations and decreases from BL at wk4 in pts with BL CRP >1 mg/dl were significantly associated with remission at wk24 in GLM+MTX pts from GO-BEFORE (OR=1.4; p<0.002; PPV=67%; NPV=53%), GO-FORWARD (OR=2.1; p<0.000;PPV=70%; NPV=68%) and GO-AFTER (OR=1.3; p=0.06; PPV=51%; NPV=64%). Reductions from BL CRP of >50% at wk4 in these pt subsets were also significant associated with multiple measures of clinical response including remission (data not shown).

Conclusion: While changes in CRP levels associate with clinical response and may be a good measure of disease activity in RA at any time point, it is not a reliable predictor of clinical response to tx.

Methods: A sample of US rheumatologists (N=110) from the All Global physician panel were surveyed online. The All Global physician panel is an opt-in, actively managed, online panel of several hundred thousand physicians in the US and Europe. Respondents were asked for demographic and practice information, as well as, about RA diagnostic and disease severity measures they were aware of and how often they used those measures. Responses for awareness and frequency of use were measured on a 5-point scale, where 1=never use and 5=always use.

Results: Physicians were mostly men (n=81, 74%), fairly equally distributed between urban and suburban practices (suburban: n=38, 53%). The mean number of years in practice (post-residency) was 15.9, and the mean number RA patients seen per month was 143.1. The anti–cyclic citrullinated peptide antibody (anti-CCP) test had the greatest awareness and frequency of use as a diagnostic measure (97% of physicians aware of the test; mean frequency of use score ±SD, 4.5±0.9). Regarding awareness and use of assessments of disease activity, swollen joint count was the most common (SJC; 89% of physicians aware; mean use ±SD, 4.2±1.4). C-reactive protein (CRP) concentration, erythrocyte sedimentation rate (ESR), and tender joint count (TJC) were among the other measures with high awareness and frequent use. Magnetic resonance imaging (MRI) and Disease Activity Score (DAS), used as measures for diagnosis or assessment, had the largest discordance between high awareness and low use. White blood count (WBC) had the largest discordance between low awareness and high use, both as a diagnostic and an assessment measure. Assessment of their switching behavior showed that rheumatologists switched biologic therapies for 25% of their patients; 67% were switched to a second anti-TNF agent; the remainder were switched to a non-TNF biologic therapy. Approximately 75%, 69%, and 52% of patients were switched to a second anti-TNF agent when the first was etanercept, adalimumab, and infliximab, respectively.

Conclusions: The anti-CCP test and SJC were the most well-known and the most frequently used measures to diagnose RA and assess disease activity. MRI and DAS were well-known but rarely used in routine practice, whereas WBC was used relatively frequently despite low awareness of its value as a diagnostic tool. Rheumatologists switched therapy for a quarter of their patients who received biologic therapy, and the switch to a second anti-TNF was more frequent for subcutaneous anti-TNF agents compared with agents administered by intravenous infusion.

Disclosure: M. DiBonaventura: Kantar Health (contractor for Abbott), 3; S. Roy: Abbott Laboratories, 1; 3; J. Erft: Kantar Health (contractor for Abbott), 3; M. A. Cifaldi: Abbott Laboratories, 1, 3.

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Practice Patterns of US Rheumatologists Related to Diagnosis and Assessment of Disease Activity as Well as Switching Biologic Therapies in Rheumatoid Arthritis. Marco DiBonaventura1, Sanjoy Roy1, Jochen Erft2 and Mary A. Cifaldi1. 1Abbott Laboratories, Abbott Park, IL, 2Kantar Health, New York, NY

Background and Purpose: This study investigated measures used by US rheumatologists to diagnose RA and assess disease activity. We also describe the treating rheumatologists’ practice patterns for switching biologic therapies for patients who discontinued anti–tumor necrosis factor (anti-TNF) agents for any reason.

Methods: A sample of US rheumatologists (N=110) from the All Global physician panel were surveyed online. The All Global physician panel is an opt-in, actively managed, online panel of several hundred thousand physicians in the US and Europe. Respondents were asked for demographic and practice information, as well as, about RA diagnostic and disease severity measures they were aware of and how often they used those measures. Responses for awareness and frequency of use were measured on a 5-point scale, where 1=never use and 5=always use.

Results: Physicians were mostly men (n=81, 74%), fairly equally distributed between urban and suburban practices (suburban: n=38, 53%). The mean number of years in practice (post-residency) was 15.9, and the mean number RA patients seen per month was 143.1. The anti–cyclic citrullinated peptide antibody (anti-CCP) test had the greatest awareness and frequency of use as a diagnostic measure (97% of physicians aware of the test; mean frequency of use score ±SD, 4.5±0.9). Regarding awareness and use of assessments of disease activity, swollen joint count was the most common (SJC; 89% of physicians aware; mean use ±SD, 4.2±1.4). C-reactive protein (CRP) concentration, erythrocyte sedimentation rate (ESR), and tender joint count (TJC) were among the other measures with high awareness and frequent use. Magnetic resonance imaging (MRI) and Disease Activity Score (DAS), used as measures for diagnosis or assessment, had the largest discordance between high awareness and low use. White blood count (WBC) had the largest discordance between low awareness and high use, both as a diagnostic and an assessment measure. Assessment of their switching behavior showed that rheumatologists switched biologic therapies for 25% of their patients; 67% were switched to a second anti-TNF agent; the remainder were switched to a non-TNF biologic therapy. Approximately 75%, 69%, and 52% of patients were switched to a second anti-TNF agent when the first was etanercept, adalimumab, and infliximab, respectively.

Conclusions: The anti-CCP test and SJC were the most well-known and the most frequently used measures to diagnose RA and assess disease activity. MRI and DAS were well-known but rarely used in routine practice, whereas WBC was used relatively frequently despite low awareness of its value as a diagnostic tool. Rheumatologists switched therapy for a quarter of their patients who received biologic therapy, and the switch to a second anti-TNF was more frequent for subcutaneous anti-TNF agents compared with agents administered by intravenous infusion.

Disclosure: M. DiBonaventura: Kantar Health (contractor for Abbott), 3; S. Roy: Abbott Laboratories, 1; 3; J. Erft: Kantar Health (contractor for Abbott), 3; M. A. Cifaldi: Abbott Laboratories, 1, 3.

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Predictors of Successful Cessation of TNF Blockers in Patients with RA. M. van den Broek1, N. B. Klarenbeek2, L. Dirven3, A. A. Schouffoer1, H. J. M. Huismans2, P. J. S. M. Kerstens1, T. W. J. Huizinga3, B. A. C. Dijkmans3 and C. F. Allaart3. 1Groene Hart Hospital, Gouda, The Netherlands, 2Haga Hospital, The Hague, The Netherlands, 3Jan van Breemen Institut, Amsterdam, The Netherlands, 4LUMC, Leiden, The Netherlands, 5LUMC, Leiden, The Netherlands, 6VU Medical Centre, Amsterdam, The Netherlands

Objective: To observe disease activity after cessation of infliximab (IFX) and to identify predictors of persistent low disease activity.

Methods: In the BeSt study, 120 patients with recent onset RA were treated with initial methotrexate (MTX)+IFX combination therapy, and 109 other patients started MTX+IFX after failing (DAS24 >2.4) on 3 previous treatment steps. If DAS remained <2.4 for at least 6 months, IFX was tapered and finally stopped. In these patients, possible predictors for a rise in DAS24 >2.4, resulting in reintroduction of IFX were examined using Cox regression analysis.

Results: IFX was discontinued in 76/120 patients from the initial and
27/109 from the delayed treatment group. Median DAS at time of discontinuation was 1.39 (IQR 0.84–1.70). Over a median period of 81 months (range 16–97) follow up, 54% of patients had a persistent DAS ≤ 2.4. In 47 patients, IFX was reintroduced after a median duration of 14 (IQR 3–44) months. After a median duration of 3 months, 85% of these patients, 25/31 from the initial and 15/16 from the delayed IFX treatment group, again had a DAS ≤ 2.4. Two (4%) patients did not achieve a DAS ≤ 2.4 after reintroduction of IFX, 3 again stopped IFX because of adverse events and 2 at patient’s request.

Smoking, IFX treatment duration, physician’s assessment of disease activity (VAS) and yearly damage progression were predictors of reintroduction of IFX (p < 0.01). Shared epitope (SE), erosion score and treatment group showed a trend (p = 0.01). Separate analyses for both treatment groups showed similar effect sizes, with the exception of smoking in the delayed treatment group. In the multivariable model, which included treatment group, smoking (Hazard rate 2.17, 95% CI 1.11–4.26), treatment duration ≥18 months (HR 2.28, 95% CI 1.01–5.12) and SE (HR 3.41, 95% CI 1.19–9.81) were independently associated with reintroduction of IFX after cessation.

Conclusion: IFX could be discontinued successfully in more than half of patients. The majority of patients who did have a disease flare quickly regained low disease activity after reintroduction of IFX. Smoking, positive shared epitope status and long IFX treatment duration (≥18 months) were independent predictors of reintroduction of IFX after cessation.

Figure: Kaplan Meier curves depicting reintroduction of IFX over time per risk factor.

Disclosure: M. van den Broek: None; Dijkmans: None; None; L. Dirven: None; A. A. Schouffoer: None; Y. Nakamura: None; T. Nitobe: None; Y. Urata: None; R. Uesato: None; None.

Prevalence of Reactivation of Hepatitis B Virus Replication in Rheumatoid Arthritis Patients. Dai Tanaka1, Yukitomo Urate2, Ryoko Usato3, Kenji Kowatari4, Yoshhide Nakamura5 and Taisuke Nitobe6. 1Department of Orthopaedic Surgery, Hiroaki University Graduate School of Medicine, 2Department of Orthopaedic Surgery, Seihoku Chuo Hospital, Gosyogawara, Japan, 3Department of Orthopaedic Surgery, Seihoku Chuo Hospital, 4Departments of Rheumatology, Seihoku Chuo Hospital, Gosyogawara, Japan

Purpose: Reactivation of hepatitis B involves the reapparance of active necroinflammatory liver disease after an inactive hepatitis B surface antigen (HBsAg) carrier state or resolved hepatitis B, occurring during or after immunosuppression therapy or chemotherapy. We prospectively investigated the reactivation rate for hepatitis B virus (HBV)-DNA replication in cases of rheumatoid arthritis (RA) with resolved hepatitis B.

Methods: HBV markers were evaluated in 428 RA patients. Patients with positive findings of HBsAg or HBV-DNA at enrolment were excluded from this study. Subjects comprised 422 RA patients, with resolved hepatitis B diagnosed in 135 patients based on HBsAg-negative and anti-hepatitis B core antibody/anti-hepatitis B surface antibody-positive results. HBV-DNA was measured every 3 months in this group, and if HBV-DNA became positive after enrolment, measurement was repeated every month.

Results: HBV-DNA became positive (≥3.64 log copies/mL) in 7 of 135 patients for 12 months. Use of biologic agents was significantly more frequent in patients who developed reactivation of HBV-DNA replication (85.7%) than in patients who did not (36.0%, p = 0.008). Hazard ratios for use of biologic agents and etanercept were 10.9 (p = 0.008) and 6.9 (p = 0.001), respectively.

Conclusions: RA patients with resolved hepatitis B need careful monitoring when receiving biologic agents, regardless of HBV-DNA levels.

Table 1. Distribution of HBsAb and HBcAb results among HBsAg-negative and -positive patients

<table>
<thead>
<tr>
<th>HBsAb-positive</th>
<th>HBsAb-negative</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>71/96 (74.4%)</td>
<td>79/116 (67.5%)</td>
<td>0.420</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>22/29 (75.9%)</td>
<td>32/45 (71.1%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Table 2. Comparison of HBV replication-positive and HBV replication-negative patients for baseline demographic, clinical and laboratory characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>HBV replication-positive</th>
<th>HBV replication-negative</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA duration (months)</td>
<td>3.8 (2.8)</td>
<td>3.6 (2.3)</td>
<td>0.796</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.3 (12.9)</td>
<td>65.8 (11.8)</td>
<td>0.695</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>5 (71.4%)</td>
<td>105 (82.0%)</td>
<td>0.505</td>
</tr>
<tr>
<td>HBV-DNA copies/mL</td>
<td>2.1 x 10^5</td>
<td>4.7 x 10^3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>23.1 (16.0)</td>
<td>23.8 (11.3)</td>
<td>0.625</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>23.0 (16.3)</td>
<td>24.7 (11.1)</td>
<td>0.796</td>
</tr>
</tbody>
</table>

Table 3. Demographic, clinical and laboratory characteristics of patients with HBV replication

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Gender</th>
<th>RA duration (months)</th>
<th>Biologic agent</th>
<th>MTX (mg/week)</th>
<th>DMARDs</th>
<th>Prednisolone (mg/day)</th>
<th>HBV-DNA copies/mL</th>
<th>Final status of HBV-DNA</th>
<th>Time between emergence of HBV DNA and its disappearance (months)</th>
<th>ALT (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>Male</td>
<td>2.4</td>
<td>Biologic agent</td>
<td>9</td>
<td>no</td>
<td>2</td>
<td>2.1 x 10^4</td>
<td>DNA-positive</td>
<td>7 (4–12)</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>Male</td>
<td>3.5</td>
<td>Biologic agent</td>
<td>9</td>
<td>yes</td>
<td>2</td>
<td>6.3 x 10^4</td>
<td>DNA-positive</td>
<td>7 (4–12)</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
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<td>Male</td>
<td>3.0</td>
<td>Biologic agent</td>
<td>9</td>
<td>yes</td>
<td>2</td>
<td>6.3 x 10^4</td>
<td>DNA-positive</td>
<td>7 (4–12)</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 4. Number of patients using concomitant drugs related to rheumatoid arthritis during the study (comparing HBV replication-positive patients with HBV replication-negative patients)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of patientsa</th>
<th>p/hr (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic agent</td>
<td>6 (85.7%)</td>
<td>0.008 10.9 (1.4–87.7)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>5 (71.4%)</td>
<td>0.200 2.7 (0.5–13.4)</td>
</tr>
<tr>
<td>Mean dose of Sulfasalazine</td>
<td>5 (71.4%)</td>
<td>0.607 4.0 (0.8–19.8)</td>
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Table 4aThis patient had received 3 biologic agents: infliximab, etanercept and tocilizumab sequentially.

RA, rheumatoid arthritis; ALT, alanine aminotransferase.
Primary Anti-TNF Failures Experience Better Clinical Responses but Secondary Failures: Analysis of the Alberta Rheumatoid Arthritis Biologics Registry, Walter P. Maksymowych1, Arto Ohinnna1, Liam Martin1, Anthony S. Russell2, Susan G. Barr3, Dale Sholter4, Chris J. Penney5, Charles Yan1 and Philip Jacobs1. 1Institute of Health Economics, Edmonton, AB, Canada, 2University of Alberta, Edmonton, AB, Canada, 3University of Calgary, Calgary, AB, Canada

Purpose: Meta-analysis of anti-TNF switching data from observational cohorts has concluded that responses are inferior in those switching due to primary as compared to secondary anti-TNF failures but limitations include small sample size of individual studies, failure to define response, and selection bias. We assessed the impact of switching anti-TNF agents at different time points in the Alberta Biologics Registry, an observational cohort of RA patients starting anti-TNF therapy in 2004, where collection of outcome data on all patients is requested by the Provincial pharmaceutical formulary.

Methods: The Alberta Biologics Registry collects clinical, employment, and health economic data at baseline, 3 months, and every 6 months thereafter. Patients must attain either an ACR20 or EULAR response (≥1.2) plus a HAQ response of ≥ 0.22 units by 12 weeks and maintain this at each subsequent visit to continue to receive anti-TNF agent. Health-related quality of life is measured with the EQ-5D and self-reported health care utilization is subsequent visit to continue to receive anti-TNF agent. Health-related quality of life is measured with the EQ-5D and self-reported health care utilization is for the six months prior to each visit. We analyzed responses according to time of switch (3 month versus subsequent time points) and according to specific anti-TNF agent switches.

Results: From 1,222 patients in the registry, 649 patients had 27 month follow up assessment and 498 (76.7%) of these remained on the first anti-TNF during the study period. There were 28 (4.3%) primary failures and 123 (19%) secondary failures who switched a median of 15 months from baseline.

The response rate to the second anti-TNF was somewhat better in the primary versus the secondary failures (p=NS) at 3 months after initiation of the second anti-TNF for HAQ, DAS, EQ-5D. By 27 months, switchers due to primary failures had attained comparable reductions in outcomes to non-switchers while changes in secondary failures were from 50% (HAQ) to 68% (EQ-5D) lower compared to non-switchers (p<0.05). Health care utilization was significantly reduced in four measured parameters over 27 months for patients with ESR data during 5,289 clinical visits. ESR missing data was determined the rate of remission in a large multicenter RA clinical practice. We explored the clinic practice suggestions and a multiplicity of definitions has hampered the measured of remission in the community. The ACR/EULAR remission committee has recently made recommendations for RA clinical trials, and also provided possible alternatives for clinical practice. We explored the clinic practice suggestions and determined the rate of remission in a large multicenter RA clinical practice.

Methods: From 1,350 consecutive RA patients seen in clinical practice between January 2007 and March 2010 during 12,501 visits, we studied 1,079 patients with ESR data during 5,289 clinical visits. ESR missing data was primarily a function of patient medical insurance. We calculated a series of remission measures according to the ACR/EULAR recommendations.

Table. Change in health outcomes from baseline to 27 months of anti-TNF therapy.

<table>
<thead>
<tr>
<th>Name</th>
<th>Rate (95% CI) Biologic effect (On vs. not on)</th>
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<tr>
<td>ACR/EULAR-3</td>
<td>8.4% (7.2, 9.6) 9.3% vs. 7.7%, p = 0.068</td>
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<tr>
<td>ACR/EULAR-4</td>
<td>5.1% (4.2, 6.1) 6.7% vs. 4.0%, p &lt; 0.001</td>
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<td>ACR/EULAR-3</td>
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<td>ACR/EULAR-3</td>
<td>Low ESR 4.0% (3.2, 4.9) 4.3% vs. 3.8%, p = 0.408</td>
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</table>

Purpose: Remission is the most desirable outcome of RA treatment, but a multiplicity of definitions has hampered the measured of remission in the community. The ACR/EULAR remission committee has recently made recommendations for RA clinical trials, and also provided possible alternatives for clinical practice. We explored the clinic practice suggestions and determined the rate of remission in a large multicenter RA clinical practice.

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The rate of remission ranged from 5.1% to 7.5% according to the ACR/EULAR recommendation. The rate rose to 8.4% from 6.0% when ESR was eliminated and fell to 4.0% when ESR limits were tightened. In the ACR/EULAR-3 and the ESR criteria, the rate of remission was not higher in biologic treated patients, but was higher in all criteria that included MD global (ACR/EULAR-4 and ACR/EULAR CDAI).

Conclusions: Overall, the rate of remission using contemporary RA treatment in the community is between 5.1% to 7.5%. These rates are substantially lower than reported in clinical trials using DAS-28 criteria. Criteria that include physician global tend to find more benefit with biologic therapy than criteria that do not include physician measures.

Disclosure: S. H. Shahouri: None; J. D. Anderson: None; R. E. Busch: None; T. S. Shaver: None; S. Y. Wang: None; D. N. Weidensaul: None; M. J. Bergman: None; K. D. Michaud: None; F. Wolfe: None.

Rituximab Alters the HDL Particle from a Pro-Inflammatory to an Anti-Inflammatory Property in Good Responding Rheumatoid Arthritis Patients. Henkie G. Raterman1, Han H. M. Levels1, Alexandre E. Voskuyl2, Willem F. Lems2, Ben A. C. Dijkmans3 and Michael T. Nurmoohamed3. 1Academical Medical Center, The Netherlands, 2VU University Medical Center, Amsterdam, The Netherlands

Background: Rheumatoid arthritis (RA) patients suffer from an increased prevalence and incidence of (non)fatal cardiovascular diseases (CVD). A well known risk factor for CVD is an atherogenic lipid profile and, interestingly, a high inflammatory state is associated with an unfavourable lipid profile in RA patients. Moreover, an inflammatory state alters the HDL into a more proatherogenic composition as the particle loses its anti-inflammatory features. Effective anti-inflammatory treatment with TNF blocking agents like rituximab on lipid profile is limited in RA patients.

Methods: In 12 RA patients (6 good responding and 6 non responding patients), who participated in an ongoing observational study of consecutive rituximab treated RA patients, serum and EDTA plasma samples were collected at baseline, 3 months and 6 months and stored at −80°C. In these
samples lipid levels (including total and HDL cholesterol, triglycerides and apolipoproteins (ApoA-I and ApoB)) were assessed in a single run. After anti apo A-I immunocapture, HDL protein profiling was carried out using surface-enhanced laser desorption/ionization-time-of-flight mass spectrometry (SELDI-TOF MS) analysis. GEE analyses were used to determine disease activity marker and lipid changes in time.

**Results:** At baseline DAS28 was significantly higher in EULAR non responders compared to responders (see table, p = 0.001). Other baseline characteristics did not differ significantly between responders and non responders. As expected, after 6 months treatment significant changes in DAS28 and CRP were observed in responders versus non responders. No other significant changes were observed after 6 months treatment. SELDI-TOF MS analysis revealed a significant decrease in density of the mass charge (m/z) marker 11,743, representing serum amyloid A (SAA)-1, in good responding patients relative to non responding patients. Moreover, 7 other markers (i.e. 3,893, 7,065, 8,647, 9,401, 9,764, 15969 and 87,407 m/z (p<0.05)) changed significantly in the good responding patients. In these patients no significant changes in HDL, ApoA-I and ApoB levels were observed, although triglycerides were significantly lower in good responding patients during treatment.

**Table.** Characteristics of rituximab treated RA patients.

<table>
<thead>
<tr>
<th></th>
<th>Responders baseline</th>
<th>Non responders baseline</th>
<th>Responders t = 6 months</th>
<th>Non responders t = 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28</td>
<td>5.0 ± 0.7</td>
<td>6.6 ± 0.5*</td>
<td>2.8 ± 0.6</td>
<td>6.3 ± 0.3</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>7.5 (4-14)</td>
<td>16 (10-64)</td>
<td>2.5 (2-65.3)</td>
<td>22 (4-60)</td>
</tr>
<tr>
<td>total cholesterol, mmol/l</td>
<td>4.72 ± 0.92</td>
<td>5.22 ± 1.2</td>
<td>5.10 ± 1.4</td>
<td>5.05 ± 1.2</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.55 ± 0.5</td>
<td>1.68 ± 0.5</td>
<td>1.68 ± 0.5</td>
<td>1.50 ± 0.3</td>
</tr>
<tr>
<td>total HDL cholesterol</td>
<td>2.97 ± 0.6</td>
<td>3.59 ± 1.1</td>
<td>3.09 ± 0.6</td>
<td>3.38 ± 0.6</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>1.03 ± 0.3</td>
<td>1.49 ± 0.4</td>
<td>1.08 ± 0.3</td>
<td>1.68 ± 0.8</td>
</tr>
<tr>
<td>LDL, mmol/l</td>
<td>2.62 ± 0.7</td>
<td>3.0 ± 1.0</td>
<td>2.93 ± 1.1</td>
<td>2.79 ± 1.0</td>
</tr>
<tr>
<td>ApoA-I, mmol/l</td>
<td>1.03 ± 0.3</td>
<td>1.66 ± 0.5</td>
<td>1.64 ± 0.3</td>
<td>1.64 ± 0.2</td>
</tr>
<tr>
<td>ApoB, mmol/l</td>
<td>0.65 ± 0.1</td>
<td>0.77 ± 0.02</td>
<td>0.71 ± 0.02</td>
<td>0.72 ± 0.02</td>
</tr>
<tr>
<td>ApoB: ApoA-I ratio</td>
<td>0.42 ± 0.1</td>
<td>0.48 ± 0.1</td>
<td>0.44 ± 0.1</td>
<td>0.44 ± 0.1</td>
</tr>
</tbody>
</table>

*p < 0.05 compared with responders. *p < 0.05 compared with baseline

**Conclusions:** In good responding rituximab treated RA patients the qualitative changes in the HDL protein composition reflect change in disease activity, giving circumstantial evidence that next to quantitative changes in lipid levels during anti-inflammatory therapy the HDL particle seems to alter into a less proinflammatory and anti-atherogenic composition.

**Disclosure:** H. G. Raterman: None; H. H. M. Levels: None; A. E. Voskuyl: None; W. F. Lems: None; B. A. C. Dijkmans: None; M. T. Nurmoehamed: Abbott Immunology Pharmaceuticals, 2, Bristol-Myers Squibb, 2, Roche, 2, Schering-Plough, 2, Wyeth Pharmaceuticals, 2.

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**Background:** Immunoglobulin kappa and lambda free light chains (FLCs) are produced physiologically and levels are increased in several inflammatory diseases like asthma, inflammatory bowel disease and rheumatoid arthritis (RA). FLCs are short-lived products of B lymphocytes and have been shown to promote inflammation by activation of mast cells.

**Objective:** To investigate the expression levels of local and systemic levels of FLCs and their correlation with disease activity and to study whether FLC changes upon B cell targeted therapy in RA patients correlate with changes in disease activity.

**Methods:** FLC expression levels were measured in synovial fluid (SF) and synovial tissue (ST) of RA and OA patients (SF n=68 vs n=24; ST both n=10). 50 RA patients with active disease were treated with rituximab. Clinical response was defined according to the EULAR criteria. FLC kappa and lambda concentrations were measured at baseline and 3 and 6 months after treatment. At these time points, total immunoglobulin concentrations, rheumatic factor (RF) and anti-CCP levels were also measured.

**Results:** Strongly increased FLC concentrations were found in SF from inflamed joints (mean 24 vs 144 mg/L, p<0.0001) that correlated with disease parameters (ESR, both kappa and lambda FLC p<0.001). Increased FLC expression was also detected in ST of RA patients. Serum FLC levels also correlated with DAS28 (p=0.006 for kappa and p=0.04 for lambda) and ESR and CRP (all p<0.01). Over time, kappa and lambda FLC concentrations decreased after rituximab treatment (p<0.001 for baseline vs 3 months and p<0.01 for baseline vs 6 months after treatment for both kappa and lambda FLC). Patients without clinical response to rituximab showed no significant reduction of FLC concentrations, whereas patients who responded clinically did show a significant decrease in FLCs (both p<0.01). Changes in FLC concentrations, 3 and 6 months after rituximab showed a highly significant (P<0.001) correlation with the changes in ESR. As described previously, RF levels and, to a lesser extent, anti-CCP antibody levels decreased after rituximab treatment (45% and 26%, resp). In contrast to FLC concentrations, these decreases did not discriminate clinical responders from non-responders. Total IgG, IgA and IgM concentrations remained within normal limits.

**Conclusion:** Rituximab significantly reduced FLC levels that are increased in RA patients. Changes in FLC concentrations significantly correlate with the clinical response. Our study suggests that inhibition of FLCs may represent a novel anti-inflammatory mechanism of Rituximab treatment.

**Disclosure:** J. Tekstra: None; T. Groot Kormelink: None; R. Thurlings: None; M. Boumans: None; K. Vos: None; P. P. Tak: None; J. W. J. Bijlsma: None; F. P. J. G. Lafeber: None; F. A. Redegeld: None; J. A. G. van Roon: None.
Sustained Remission in Early RA: Results from SONORA Study. Claire Bombardier1, Pooneh Akhavan2, Maggie Chen3 and Xuying Li2. 1University Health Network, 2University of Toronto, University Health Network, 3University of Toronto, University Health Network, Mount Sinai Hospital, Toronto, ON, Canada

Purpose: Remission constitutes the best achievable state in patients with rheumatoid arthritis (RA). Current measures of Disease Activity - such as the DAS28 - define the patient’s remission status at a given point in time. While, for the patient, sustained remission over time is the ultimate goal. The purpose of this study is to assess the frequency and predictors of sustained remission in a large cohort of early RA patients in regular clinical practice.

Methods: A total of 994 patients diagnosed as early RA (symptoms ≥3 and <12 months) by a board-certified rheumatologist across North America were recruited in this study. We analyzed remission and sustained remission in 851 patients who had two-year complete follow up information. Remission was defined as less than 2.6 for DAS28 and sustained remission was defined as consecutive remission at year 1 and year 2. Univariate logistic regressions were used to explore the predictors for sustained remission and multivariate logistic regression were used to estimate the remission probabilities controlling for significant factors.

Results: The mean age of patients was 53 years (SD, 14.8), with 72% female and 90% Caucasian. The mean RA symptom duration was 170 days (180), 61% were seropositive for rheumatoid factor and 43% anti-CCP positive (>20 unit/ml) at baseline. Seventy-four percent of patients had received DMARDs at baseline compared to 90% at year 1 and, 87% at 2. Two percent of the subjects were on Biologics at baseline compared to 1%, 23% at year 1 and 2. Remissions at any one of the two visits were seen in 238 (28%) patients. Among them, 66 (8%) patients achieved sustained remission. The univariate logistic regression showed that low baseline DAS28 score, HAQ score, disease duration and CRP are significant predictors for sustained remission. The multivariate logistic regression showed that HAQ is no longer significant when other factors (low baseline DAS28, low CRP and short disease duration) are in the model. The final model therefore excludes HAQ as a predictor.

Disclosure: C. Bombardier: None; P. Akhavan: None; M. Chen: None; X. Li: None.

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Surveillance of Surgical Site Infection in Patients with Rheumatoid Arthritis. Kengo Harigane1, Yuich Mochida2, Katsushi Ishii3, Nasu Takei3, Naoto Mitsu4 and Tomoyuki Saito5. 1Yokohama City University Medical Center, Yokohama, Kanagawa, Japan; 2Yokohama City University Medical Center, 3Yokohama City University School of Medicine

Introduction: After introducing the guideline of Centers for Disease Control and Prevention in 1999, clinical concern about SSI has been increasing. Recently, the guideline is widely recognized as the basics for disease specific surveillance with RA.

Objectives: The aims of current study were to examine the incidence and to identify risk factors of SSI in patients with RA.

Methods: The clinical records of 779 patients (female 710 cases and male 69 cases) with RA who underwent orthopaedic surgeries in our hospital between January 1999 and October 2009 were carefully reviewed and the occurrences of SSI were investigated. SSI was strictly determined using the definitions of the guideline of CDC. The associations of SSI with administration of steroids and MTX, and with the presence of diabetes mellitus were also analyzed.

Results: Seventeen cases were recognized as SSI (2.2%); nine cases were superficial and eight cases were deep infections. The incident rate of SSI in arthroplasty cases was 2.9%, which was higher than the rate in non-arthroplasty cases (1.4%), however the p-value did not reach statistical difference (p=0.2). Steroids administration showed a statistically significant risk of SSI (p=0.04), on the other hand, methotrexate administration was a negative risk factor of SSI (p=0.047). The dose of oral steroids at the time of surgery clearly showed a positive dose-dependent correlation with the rate of SSI (p=0.011). There was no significant correlation between SSI and the presence of diabetes mellitus.

Conclusion: After introducing the strict guideline of CDC, reported incidences of SSI became higher (approximately 2%). In those reports, more than half cases of SSI occurred in superficial lesions. The results of current study were similar to recent reports. The incident rates of SSI showed no statistical difference between arthroplasty and non-arthroplasty cases. As for risk factors, the administration of steroids was a risk of SSI, in contrast, administration of MTX was a negative risk factor of SSI.

Disclosure: K. Harigane: None; Y. Mochida: None; K. Ishii: None; N. Takei: None; N. Mitsu: None; T. Saito: None.

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Sustained Remission, a Realistic Target in Early Rheumatoid Arthritis Patients Treated with Conventional DMARDs. Irantsz Contreras-Yáñez, Marina Rull-Gabayet and Virginia Pascual-Ramos. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, DF, Mexico

Background: A remission-like state has become the treatment goal of patients with early rheumatoid arthritis (≤12 months, ERA).

Objectives: To describe sustained outcomes in an ERA cohort of patients treated with conventional disease modifying anti-rheumatic drugs (DMARDs) in whom long-standing follow-up is performed in a real clinical setting. To identify associated predictors.

Patients and Methods: 101 ERA with at least 2 years of follow-up were included. Standard baseline and consecutive assessments (2 monthly apart for the first 2 years and every 2, 4 or 6 months, thereafter) included swollen and tender joint counts, patient-reported outcomes, acute reactant phase determinations, disease activity score-28 joints evaluated (DAS28),
Switch rates per 1,000-person-years were: abatacept = 243; adalimumab = 208; etanercept = 170; infliximab = 285; rituximab = 171. Figure 1 displays survival curves for the time-to-switch for patients initiating each biologic agent.

Conclusions: Switching of RA biologics may occur due to inadequate response to the current biologic, burden of side effects, or other variables. In this analysis, switch rates per 1,000 person-years were the lowest among patients initiating rituximab and etanercept and highest among patients initiating infliximab. Time-to-switch was significantly different across the groups (p<0.001), and was longest in patients initiating rituximab and etanercept and shortest in patients initiating infliximab.

Disclosure: S. Johnston: None; S. Ogale: Genentech and Biogen IDEC Inc, 3, Roche, 1; N. Princic: None; B.-C. Chu: None; T. Kamath: Genentech and Biogen IDEC Inc, 3, Roche, 1.

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Systemic Immunosuppressives and the Risk of Diabetes in Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA).

Daniel Hal Solomon1, Elena M. Massarotti2, Raj Gang2, Claire Canning2, Jun Liu3 and Sebastian Schneweiss2. 1Brigham & Women’s Hospital, Boston, MA, 2Brigham and Women’s Hospital, Boston, MA

Background: Several inflammatory conditions, including RA and PsA, have been linked with insulin resistance and diabetes mellitus (DM). The underlying inflammation and use of oral glucocorticoids are two possible causes. Prior investigations demonstrate an improvement in insulin resistance with several TNF inhibitors (TNFi), and hydroxychloroquine (HCQ) has been shown to reduce the risk of diabetes in a large observational RA cohort. We compared the risk of incident DM among subjects diagnosed with RA or PsA based on their use of a variety of DMARDs.

Methods: Our study cohort was drawn from two data sources—a population-based cohort from a Canadian province and a large commercial insurance plan. Patients with at least two diagnoses of RA or two diagnoses of PsA who have no evidence of DM (no diagnoses and no diabetes medication use) were eligible for the study cohort at the time they switched or added an immunosuppressive. DMARD regimens were categorized into four mutually exclusive groups: 1) TNFi with or without other DMARDs, 2) methotrexate (MTX) without a TNFi or HCQ, 3) HCQ without MTX or a
TNFα, or 4) other DMARD without a TNFα, MTX or HCQ. The primary outcome was incident DM, defined as a diagnosis and start of a DM-specific medication. Incidence rates for DM were compared across exposure groups. In addition, adjusted hazard ratios were calculated in Cox regression with other DMARD considered the reference exposure. Adjusted analyses included covariates for age, gender, Charlson comorbidity score, oral glucocorticoid use, topical glucocorticoid use, prior DMARDs, calendar year, plus several other health service indicators. Secondary analyses focused on different periods during follow-up and on oral glucocorticoid users.

**Results:** The study cohort consisted of 22,493 subjects with RA or PsA starting one of the four groups: 4,623 TNFα, 8,195 MTX, 5,682 HCQ, and 3,993 another DMARD. Mean follow-up was 6 months. The four groups’ characteristics were similar with respect to age, gender, distribution of underlying rheumatic disease, and health services utilization, but differed by oral steroid use with the TNFα group having more prior steroid use. The incidence rates for DM were as follows: total cohort 24.6 per 1,000 person-years, TNFα 19.7, MTX 23.8, HCQ 22.2, and another DMARD 50.2. Adjusted hazard ratios for DM were 0.62 (95% CI 0.42–0.91) for TNFα, 0.77 (95% CI 0.53–1.13) for MTX, and 0.54 (95% CI 0.36–0.80) for HCQ (see Figure). Secondary analyses exhibit consistent findings.

Adjusted Cox Proportional Hazards for Risk of Diabetes Mellitus in RA and PsA

<table>
<thead>
<tr>
<th>Model</th>
<th>DMARD</th>
<th>Hydroxychloroquine</th>
<th>Methotrexate</th>
<th>TNF inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.00</td>
<td>0.58 (0.39–0.85)</td>
<td>0.63 (0.45–0.88)</td>
<td>0.72 (0.50–1.03)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.00</td>
<td>0.58 (0.39–0.85)</td>
<td>0.62 (0.44–0.87)</td>
<td>0.76 (0.53–1.09)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.00</td>
<td>0.54 (0.36–0.80)</td>
<td>0.77 (0.53–1.13)</td>
<td>0.62 (0.42–0.91)</td>
</tr>
</tbody>
</table>

Notes: Model 1: Adjusted for diagnosis and data source. Model 2: Adjusted as Model 1 + age and gender. Model 3: Adjusted as Model 2 + Charlson Score, dermatologist visits, dermatology indicator, generics, number of hospital visits, number of MD visits, prior but no current HCQ, prior but no current MTX, prior but no current NBDMARD, prior but no current oral steroids, prior but no current TNFα, prior oral steroids, prior topical steroids, number of rheumatology visits, number of dermatologist visits, and year of index.

**Conclusions:** Among subjects diagnosed with RA or PsA, the adjusted risk of incident DM appeared reduced for persons starting a TNFα or HCQ compared with another DMARD. This result was robust across secondary analyses and suggests that a treatment trial testing the effects of specific DMARDs on incident DM would be warranted.

**Disclosure:** D. H. Solomon: Abbott Immunology Pharmaceuticals, 2, Amgen Inc., 2, Bristol-Myers Squibb, 9; E. M. Massarotti: Bristol-Myers Squibb, 2, 5, Merck Human Health, 5; Roche, 2, 5, Sanofi, 2, UCB, Inc., 2, 5, UpToDate, 7; R. Garg: None; C. Canning: None; J. Liu: None; S. Schneeweiss: None.

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**The Belgian MIRA (MabThera in Rheumatoid Arthritis) Registry: Clues for the Optimization of Rituximab Treatment Strategies.** Bert Vander Cruyssen1, Patrick Durez2, Rene Westhovens3, Ilse Hoffmann3, M. J. Kaiser1 and Filip De Keyser1.

**Background:** The Belgian MIRA registry aims to record safety and efficacy data of rituximab treatment. In Belgium, RA patients are eligible for treatment with rituximab if they failed at least one anti-TNFα and have a baseline DAS28 > 3.7. From week 24 on, patients can be retreated if they have a moderate or good EULAR response at week 16, and a current DAS28 score of at least 3.2.

**Methods:** All Belgian rheumatologists could participate in the study. Patients entered the registry as from November 2006 and the entry is still open. All patients were treated with 2 infusions per course of rituximab (2 × 1000 mg week 0 and 2) in combination with 100 mg of methylprednisolone and MTX. Baseline patient’s characteristics were recorded as well as DAS28-variables every 2 months.

**Results:** By mid May 2010, 497 patients had entered the registry with a mean follow-up time of 84 weeks. Patients (mean age of 59 years, 77% female) had a mean disease duration of 12 years.

Rituximab therapy decreased the overall mean disease activity from DAS28-ESR 5.9 (SE = 0.1) at baseline to 4.1 (SE = 0.1) at week 16. 83% of patients fulfilled the EULAR good or moderate response criteria. Further decrease of DAS was observed at the end of year 1 and year 2 with a mean DAS28-ESR of 4.0 (SE = 0.2) and 3.7 (SE = 0.2) at these respective time points.

342 and 188 patients received a 2nd and 3rd course of rituximab respectively. The median time to retreatment was 32 weeks after the first course.

At the start of each treatment course, the DAS28-ESR values were lower compared to values at the start of the previous treatment course. The values reached a minimum at week 16 of each respective treatment course, and then increased slightly, until the start of the following treatment course. Paired analysis of DAS28 scores 6 months after the first and second course suggests that lower DAS scores are obtained after the second course (mean diff = −0.6, SE = 0.2, p < 0.001).

This further decrease of DAS28 scores between the first and second course was especially seen in those patients who did not flare (increase of DAS28>1.2) between week 24 and their second course (mean diff = −1.1, SE = 0.2 vs. mean diff −0.08, SE = 0.4, p = 0.002).

85 patients discontinued treatment: 62 stopped due to inefficacy and 18 stopped due to safety issues (infusion reactions in 6 patients, infections in 5, other reasons in 7 patients). 2 Patient died. Only 33 patients were lost to follow-up.

**Conclusions:** The efficacy of rituximab in refractory RA patients is confirmed in this daily practice cohort. DAS28 response was observed in the large majority of our cohort and a sustained DAS 28 decrease was observed during the following course, especially in patients who didn’t show an obvious flare. These elements suggest that treatment of RA patients with rituximab could be optimized by earlier retreatment in patients who developed flares.

**Disclosure:** B. Vander Cruyssen: None; P. Durez: None; R. Westhovens: None; I. Hoffmann: None; M. J. Kaiser: None; F. De Keyser: None.

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**Methods:** A retrospective study nested within a cohort of seniors with RA.

**Purpose:** To study risk and risk factors for HZ, using a case-control sample selected within a cohort of seniors with RA.

**Results:** By mid May 2010, 497 patients had entered the registry with a mean follow-up time of 84 weeks. Patients (mean age of 59 years, 77 % female) had a mean disease duration of 12 years.

Rituximab therapy decreased the overall mean disease activity from DAS28-ESR 5.9 (SE = 0.1) at baseline to 4.1 (SE = 0.1) at week 16. 83% of patients fulfilled the EULAR good or moderate response criteria. Further decrease of DAS was observed at the end of year 1 and year 2 with a mean DAS28-ESR of 4.0 (SE = 0.2) and 3.7 (SE = 0.2) at these respective time points.

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**Disclosure:** B. Vander Cruyssen: None; P. Durez: None; R. Westhovens: None; I. Hoffmann: None; M. J. Kaiser: None; F. De Keyser: None.
Results: A total of 3,999 cases of HZ were recorded among 85,458 seniors with RA during 614,915 person-years (6.5 events/1000 person-years). Comparing these HZ cases to 19,995 RA controls, 21.9% of cases versus 10.8% of controls were exposed to prednisone at the time of infection. Multivariate models demonstrated that risk of HZ was higher among current and past use of all DMARD groups. There was a notable increasing trend for higher risk of HZ with increasing steroid doses. Due to low rates of biologic drug exposures in our sample, the estimated effects of these agents were imprecise, but also consistent with a higher risk.

<table>
<thead>
<tr>
<th>Drug Exposure</th>
<th>Adjusted Odds Ratio [95% Confidence Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF agent [REF = Non-user]</td>
<td>Current use: 1.17 [0.63, 2.19]</td>
</tr>
<tr>
<td></td>
<td>Past use: 1.54 [0.68, 3.51]</td>
</tr>
<tr>
<td>Anti-IL1 [REF = Non-user]</td>
<td>Current use: 4.02 [0.54, 26.93]</td>
</tr>
<tr>
<td></td>
<td>Past use: —</td>
</tr>
<tr>
<td>Methotrexate [REF = Non-user]</td>
<td>Current use: 1.44 [1.27, 1.62]</td>
</tr>
<tr>
<td></td>
<td>Past use: 1.28 [1.08, 1.52]</td>
</tr>
<tr>
<td>Sulfasalazine [REF = Non-user]</td>
<td>Current use: 1.01 [0.77, 1.34]</td>
</tr>
<tr>
<td></td>
<td>Past use: 0.92 [0.66, 1.29]</td>
</tr>
<tr>
<td>Leflunomide [REF = Non-user]</td>
<td>Current use: 1.46 [1.03, 2.06]</td>
</tr>
<tr>
<td></td>
<td>Past use: 1.16 [0.73, 1.84]</td>
</tr>
<tr>
<td>Hydroxychloroquine [REF = Non-user]</td>
<td>Current use: 1.89 [1.68, 2.13]</td>
</tr>
<tr>
<td></td>
<td>Past use: 1.25 [1.05, 1.49]</td>
</tr>
<tr>
<td>Cyclophosphamide [REF = Non-user]</td>
<td>Current use: 8.35 [1.50, 46.58]</td>
</tr>
<tr>
<td></td>
<td>Past use: 1.90 [0.57, 6.27]</td>
</tr>
<tr>
<td>Azathioprine [REF = Non-user]</td>
<td>Current use: 1.79 [1.18, 2.73]</td>
</tr>
<tr>
<td></td>
<td>Past use: 1.24 [0.69, 2.25]</td>
</tr>
<tr>
<td>NSAIDs/COXIBs [REF = Non-user]</td>
<td>Current use: 1.72 [1.57, 1.89]</td>
</tr>
<tr>
<td></td>
<td>Past use: 1.55 [1.42, 1.76]</td>
</tr>
<tr>
<td>Other DMARDs [REF = Non-user]</td>
<td>Current use: 1.73 [1.28, 2.33]</td>
</tr>
<tr>
<td></td>
<td>Past use: 1.15 [0.83, 1.60]</td>
</tr>
<tr>
<td>Steroid Use [REF = None]</td>
<td>Low ≤ 5 mg prednisone equivalent/day: 1.66 [1.45, 1.91]</td>
</tr>
<tr>
<td></td>
<td>Medium 6–9 mg/day: 1.91 [1.46, 2.50]</td>
</tr>
<tr>
<td></td>
<td>High 10–19 mg/day: 1.99 [1.67, 2.37]</td>
</tr>
<tr>
<td></td>
<td>Very High ≥ 20 mg/day: 3.22 [2.66, 3.89]</td>
</tr>
<tr>
<td></td>
<td>Past use: 1.29 [1.17, 1.42]</td>
</tr>
</tbody>
</table>

Conclusions: Our estimates emphasize an association of anti-rheumatic therapies with the occurrence of HZ. Potential limitations of our study include the possibility of incomplete ascertainment of biologic exposures (private insurance is not represented in public payer database); but this is uncommon and channelling bias (where persons of our study include the possibility of incomplete ascertainment of risk.

Results: 13,634 first-episode NSI occurred during 28,695 person years (pyrs), generating an incidence rate of 475 events/1000 pyrs. The rate of NSI in GC exposed and unexposed person time was 524 and 388/1000 pyrs, respectively. The attributable risk was therefore 135 events/1000 pyrs. In the case-control analysis, GC therapy was associated with an adjusted relative risk (aRR) of 1.20 (95% CI 1.15, 1.25). A positive dose response was seen between risk and GC dose. Methotrexate (MTX) was the most commonly used DMARD, and was associated with a no increased risk of NSI (aRR 1.00 (0.95, 1.04)). Patients currently prescribed sulfasalazine or anti-malarials had a lower rate of infection than patients not prescribed those drugs. Cyclophosphamide was associated with a higher risk of infection (aRR 2.14 (1.51, 3.03)). The results for anti-TNF therapy were inconclusive given the small number of patients exposed to them. All GC risk estimates (including 0–5mg/day) were higher than that seen for MTX.

GC = glucocorticoid, PEQ = prednisolone equivalent, RR = relative risk
*Adjusted for age, sex, markers of disease severity, and co-morbidity
**Includes ciclosporin, mycophenolate mofetil, and D-penicillamine

Conclusion: GC therapy is associated with an increased risk of NSI. The magnitude of the risk increases with dose, and is higher than that seen with MTX (although residual confounding may exist). Whilst the RR is low at 1.20, the absolute risk is high, with one additional infection seen for every 8 patients treated for 1 year.

Disclosure: W. G. Dixon: None; A. Kezouh: None; S. R. Bernatsky: None; S. Suisse: None.
Three Months of Therapy with DMARDs Is an Inadequate Period of Time To Alter the Treatment in Patients with Early Rheumatoid Arthritis When Treating to a Target of Low Disease State or Remission. Results from Canadian Early Arthritis Cohort (CATCH).

Pooneh Akhavan1, Vivian P. Bykerk2, Ye Sun3, J. Hochman4, Janet E. Pope5, Carol A. Hitchon6, Gilles Boire7, Boulos Harauvi8, Diane S. Ferland9, J. Carter Thorne10, Deborah A. Weber11, Ed C. Keystone11 and CATCH Investigators.1 Arthritis Center, University of Manitoba, Winnipeg, MB, Canada, 2Institut de Rhumatologie, Montreal, QC, Canada, 3Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, 4Mt Sinai Hospital, Toronto, ON, Canada, 5Rheumatology, Hospital Maisonneuve, Rosemont, University of Montreal, LaSalle, QC, Canada, 6Southlake Regional Health Care, Newmarket, ON, Canada, 7St Joseph Health Care London, London, ON, Canada, 8Université de Sherbrooke, Sherbrooke, QC, Canada, 9St Joseph Health Care Newmarket, ON, Canada, 10University of Toronto, Toronto, ON, Canada, 11University of Toronto, Toronto, ON, Canada, 12University of Toronto, Toronto, ON.

Objective: The objective of this study was to evaluate the concept of therapy alteration in patients with early rheumatoid arthritis (ERA) not achieving an adequate response by 3 months in a prospective cohort.

The study was designed to assess whether 3 months was an adequate time for decision-making regarding altering therapy in ERA patients who have been on stable DMARDs for 6 months and have not achieved low disease activity state (LDAS) or remission (REM).

Methods: Patients with ERA were studied in the Canadian Early Arthritis Cohort (CATCH), a prospective cohort where data was collected according to a standardized protocol. Patients who were on stable DMARDs therapy (with no dose adjustments after one month of initiating therapy and not receiving oral or parenteral steroids) for 6 months were evaluated. Patients not achieving LDAS or REM by 3 months were examined for the proportion of those achieving LDAS or REM by 6 months. We also evaluated patients achieving LDAS or REM by 6 months who had not achieved these outcomes by 3 months.

Results: 108 patients were evaluated with the baseline mean age of 50 years and disease duration of 6.3 months. Mean patient global assessment of disease activity, pain score and HAQ-DI were 61.2, 65.0 and 1.0 respectively at baseline. At 3 months, 46% and 31% of patients achieved LDAS or REM respectively, while 65% and 52% achieved these states by 6 months. Of 58 patients not in LDAS at 3 months, 26 (45%) achieved LDAS by 6 months. Of 74 patients not in REM by 3 months, 29 (40%) achieved REM by 6 months. Of 56 patients who achieved REM by 6 months, only 27 (48%) achieved it by 3 months.

Although baseline swollen joint count, tender joint count and CRP levels were not significantly different in two groups, patients who achieved LDAS at 6 months had higher pain (71±17 vs 47±32, p<0.05) and patients global assessment (77±18 vs 53±32, p<0.05) scores at baseline compared to those achieved this state at 3 months. In patients with delayed remission (at 6 months) in addition to the above outcome measures, HAQ-DI (0.6±0.6 vs 1.1±0.6, p=0.003) was higher at baseline when compared to patient who achieved remission at 3 months.

Conclusion: While remaining on a stable therapy through 6 months, a substantial proportion of patients who had not achieved an adequate clinical response (LDAS or REM) by 3 months achieved these states by 6 months. Attention should be given to patient reported outcomes when assessing patients with ERA for risk of delayed remission. The data in this real world setting suggest that in a significant number of patients, 3 months was not an adequate period of time to decide on altering therapy based on whether an adequate clinical response had been achieved. Our results support recent guidelines suggesting that a 3 to 6 month time frame is required for optimal treatment decision making when treating to an LDAS or REM target.

Disclosure: P. Akhavan: None; V. P. Bykerk: Amgen Inc., 2, Pfizer Inc, 2; Y. Sun: None; J. Hochman: None; J. E. Pope: None; E. C. Keystone: Amgen Inc., 2, 5, Pfizer Inc, 2, 5; CATCH Investigators: Amgen Inc., 2, Pfizer Inc, 2.
Results: Treat all patients with RA. 

Patients with Rheumatoid Arthritis. 

mg/dl (p). The following estimated average changes in lipids over time: LDL increase of 0.49 mg/dl, HDL increase of 0.22 mg/dl, TC increase of 1.64 mg/dl, triglycerides increase of 5.11 mg/dl, LDL/HDL, or TC/HDL. These results are reassuring, given the widespread use of TNF-α inhibitors and increased risk of CVD in this patient population.

Conclusions: Using TNF-α inhibitors in this inception RA cohort was not associated with significant changes in total cholesterol, LDL, HDL, LDL/HDL, or TC/HDL. These results are reassuring, given the widespread use of TNF inhibitors and increased risk of CVD in this patient population.


Purpose: Recent interest in urinary tract infections in rheumatoid arthritis (RA) has stemmed from the assessment of risk of infection with biologic agents. There have been little data about community acquired urinary tract infections (UTI) until a recent report gave an incidence rate (IR) of ~3% (1). By contrast, an epidemiology study in the general population reported an IR at 10.8% (95% CI 9.4. 12.1) in women (2). We used a large prospective data bank to investigate these differences and to understand risk factor for UTI in RA.

Methods: We used general estimating equations to evaluate the risk of UTI in 17,139 RA patients and 107,546 semiannual observations. Patients self-reported the number of urinary tract infections in the previous 6 months. We evaluated the role of age, sex, anti-rheumatic drug use, education, BMI, household income, smoking, comorbidity, and the tendency to over-report symptoms. We also calculated the misclassification rate for self-reported events based on 76,493 cases that evaluated for validation.

Results: The estimated IR for UTI, adjusted for 10% over-reporting, was 8.9% (8.6, 9.2) overall and 11.4% (11.0, 11.8) in women and 3.3% (2.9, 3.7) in men. Serious events, resulting in hospitalization or requiring intravenous antibiotics was reported in 0.39%. In multi-variable analyses, UTI was associated with diabetes, OR 1.2 (95% CI 1.0, 1.3), corticosteroid use OR 1.1 (1.0, 1.2), but not to biologic use, OR 1.0 (0.9, 1.1). Among other factors, UTI was associated with less household income and multiple comorbidities, but not with smoking, BMI, education level or estrogen use. When the study variables were applied to serious infection, the OR increased for prednisone use, 1.9 (1.6, 2.4) and diabetes, 2.0 (1.5, 2.6), but remained non-significant, 0.9 (0.7, 1.1) for biologics. Overall, prednisone was used at 34.9% of observations and biologics at 38.2%.

Conclusions: Based on increased risk associated with prednisone use and comorbidity, as well as increased IC compared with the community epidemiology study, we estimate that UTI is slightly increased in RA. These results are 3 times higher than a previous study (1). The observed rate of serious urinary tract infection was consistent with data from the British Biologics registry (3).

6668 RA pt's were included for CDAI; 1412–1956 for the DAS28 and ACR remission. Women achieved remission less frequently than men. Ethnicity had no effect. Other differences were not clinically significant (eg. \(W-0.5 \) more JTC; 0.06 were in HAQ, 2–3 \text{mm} \) worse pain and global VAS). Men had more co-morbidities (eg. diabetes \(W-6.4;M-9.1\%\); \(M/CAVA-W-33;M-9.3\%\)).

Conclusion: In the CORRONA database, the remission rate for women was lower than for men. Ethnicity had no effect.

Table 1. Demographic and Clinical Characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male N = 1438</th>
<th>Female N = 4166</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Mean ± SD</td>
<td>59.6 ± 12.2</td>
<td>56.3 ± 13.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Disease Duration (years), Mean ± SD</td>
<td>9.1 ± 9.3</td>
<td>10.0 ± 9.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>White</td>
<td>1330 (92.5%)</td>
<td>3752 (90.1%)</td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>67 (4.7%)</td>
<td>245 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>41 (2.9%)</td>
<td>169 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>Marital Status, N (%)</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Married</td>
<td>1127 (79.1%)</td>
<td>2687 (68.4%)</td>
<td></td>
</tr>
<tr>
<td>Work Status, N (%)</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Full/Part time</td>
<td>735 (52.0%)</td>
<td>1951 (47.4%)</td>
<td></td>
</tr>
<tr>
<td>Not working outside the home</td>
<td>112 (7.9%)</td>
<td>769 (18.7%)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>2 (0.14%)</td>
<td>33 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Disabled/Retired</td>
<td>565 (40.0%)</td>
<td>1364 (33.1%)</td>
<td></td>
</tr>
<tr>
<td>Presence of Nodules and/or Erosion, N (%)</td>
<td></td>
<td></td>
<td>.81</td>
</tr>
<tr>
<td>Yes</td>
<td>637 (44.3%)</td>
<td>1861 (44.7%)</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Factor Positivity, N (%)</td>
<td></td>
<td></td>
<td>.45</td>
</tr>
<tr>
<td>Yes</td>
<td>635 (75.9%)</td>
<td>1705 (74.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Background Medication and Comorbidities

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male N = 1438</th>
<th>Female N = 4166</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background Prednisone Use, N (%)</td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Yes</td>
<td>572 (39.9%)</td>
<td>1576 (38.0%)</td>
<td></td>
</tr>
<tr>
<td>Background TNFi Use, N (%)</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>462 (32.1%)</td>
<td>1610 (38.7%)</td>
<td></td>
</tr>
<tr>
<td>Background “Strong” DMARD Use, N (%)</td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Yes</td>
<td>1018 (70.8%)</td>
<td>2982 (71.6%)</td>
<td></td>
</tr>
<tr>
<td>Background “Weak” DMARD Use, N (%)</td>
<td></td>
<td></td>
<td>0.0005</td>
</tr>
<tr>
<td>Yes</td>
<td>162 (11.3%)</td>
<td>624 (15.0%)</td>
<td></td>
</tr>
<tr>
<td>Unusual fatigue in last 8 wks, N (%)</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>281 (19.5%)</td>
<td>1323 (29.6%)</td>
<td></td>
</tr>
<tr>
<td>Depression in last 8 wks, N (%)</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>178 (12.4%)</td>
<td>850 (20.4%)</td>
<td></td>
</tr>
<tr>
<td>MI or Stroke before BL, N (%)</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>134 (9.3%)</td>
<td>137 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus before BL, N (%)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>129 (9.0%)</td>
<td>267 (6.4%)</td>
<td></td>
</tr>
<tr>
<td>Renal Insufficiency before BL, N (%)</td>
<td></td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>Yes</td>
<td>35 (2.4%)</td>
<td>83 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Active Liver Disease before BL, N (%)</td>
<td></td>
<td></td>
<td>0.041</td>
</tr>
<tr>
<td>Yes</td>
<td>66 (4.6%)</td>
<td>142 (3.4%)</td>
<td></td>
</tr>
<tr>
<td>Joint Surgery in current/previous year**, N (%)</td>
<td></td>
<td></td>
<td>0.96</td>
</tr>
<tr>
<td>Yes</td>
<td>62 (4.3%)</td>
<td>181 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>RA Hospitalization before BL***, N (%)</td>
<td></td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Yes</td>
<td>72 (5.0%)</td>
<td>181 (4.3%)</td>
<td></td>
</tr>
</tbody>
</table>
| *P-values derived from Student’s t-test and chi-square test for continuous and categorical variables, respectively.
** Previously requested joint surgery “in past 6 months”. Because of CRF limitations, this is not possible. Any RA Hospitalization before the baseline is counted in the total.
*** Previously requested “in past 6 months”. Because of CRF limitations, this is not possible. Any RA Hospitalization before the baseline is counted in the total.

Table 3. Multivariable Logistic Regression of Gender and Race/Ethnicity on Remission (Defined as CDAI <2.8)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR</th>
<th>(95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.81</td>
<td>(0.68, 0.97)</td>
<td>0.0208</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>1.12</td>
<td>(0.80, 1.57)</td>
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</tr>
<tr>
<td>Other</td>
<td>1.07</td>
<td>(0.72, 1.61)</td>
<td>0.7353</td>
</tr>
<tr>
<td>White</td>
<td>(Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of RA (years)</td>
<td>0.97</td>
<td>(0.96, 0.98)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Work Status</td>
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<tr>
<td>Full/Part time</td>
<td>1.60</td>
<td>(1.30, 1.98)</td>
<td>&lt;.0001</td>
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<tr>
<td>Not working outside the home</td>
<td>1.22</td>
<td>(0.94, 1.57)</td>
<td>0.1391</td>
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<tr>
<td>Student</td>
<td>0.45</td>
<td>(0.16, 1.27)</td>
<td>0.1316</td>
</tr>
<tr>
<td>Disabled/Retired</td>
<td>(Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.68</td>
<td>(0.57, 0.80)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TNFi Use</td>
<td>(Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.64</td>
<td>(0.51, 0.80)</td>
<td>0.0001</td>
</tr>
<tr>
<td>RA Hospitalization before BL</td>
<td>0.48</td>
<td>(0.27, 0.83)</td>
<td>0.009</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.00</td>
<td>(1.00, 1.01)</td>
<td>0.2396</td>
</tr>
<tr>
<td>RF Positive</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.88</td>
<td>(0.69, 1.11)</td>
<td>0.264</td>
</tr>
<tr>
<td>No</td>
<td>(Ref)</td>
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</table>
**Table 4. Multivariable Logistic Regression of Gender and Race/Ethnicity on Remission (Defined as DAS28 <2.6)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR</th>
<th>Pooled Model (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.63</td>
<td>(0.45, 0.89)</td>
<td>0.0076</td>
</tr>
<tr>
<td>Male</td>
<td>(Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>0.66</td>
<td>(0.34, 1.27)</td>
<td>0.2089</td>
</tr>
<tr>
<td>Other</td>
<td>0.96</td>
<td>(0.48, 1.94)</td>
<td>0.9151</td>
</tr>
<tr>
<td>White</td>
<td>(Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of RA (years)</td>
<td>0.97</td>
<td>(0.95, 0.99)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Work Status</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Full time/Part time</td>
<td>1.59</td>
<td>(1.07, 2.35)</td>
<td>0.0205</td>
</tr>
<tr>
<td>Not working outside the home</td>
<td>1.07</td>
<td>(0.65, 1.75)</td>
<td>0.7866</td>
</tr>
<tr>
<td>Student</td>
<td>0.75</td>
<td>(0.13, 4.34)</td>
<td>0.7443</td>
</tr>
<tr>
<td>Disabled/Retired</td>
<td>(Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.03</td>
<td>(0.76, 1.40)</td>
<td>0.8304</td>
</tr>
<tr>
<td>No</td>
<td>(Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNFi Use</td>
<td>0.63</td>
<td>(0.45, 0.86)</td>
<td>0.0045</td>
</tr>
<tr>
<td>Depression</td>
<td>0.52</td>
<td>(0.34, 0.79)</td>
<td>0.0023</td>
</tr>
<tr>
<td>RA Hospitalization</td>
<td>0.69</td>
<td>(0.29, 1.63)</td>
<td>0.395</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.98</td>
<td>(0.97, 1.00)</td>
<td>0.0123</td>
</tr>
<tr>
<td>RF Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.56</td>
<td>(0.35, 0.90)</td>
<td>0.017</td>
</tr>
<tr>
<td>No</td>
<td>(Ref)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Disclosure:** M. Mizuhara: None; A. Hashirmoto: None; K. Yoshida: None; S. Shizawa: None.

**ACR Poster Session A**

**Rheumatoid Arthritis - Human Etiology and Pathogenesis I**

Monday, November 8, 2010, 9:00 AM–6:00 PM

**348**

**A Novel Splicing Regulatory Mechanism in Generating a Truncated Human Death Receptor 3 (DR3) Gene Product That Contributes to the Pathogenesis of Rheumatoid Arthritis.** Masaru Mizuhara1, Akira Hashirmoto2, Kohsuke Yoshida3 and Shunichi Shizawa4. 1Department of Biophysics, Kobe University Graduate School of Health Science, Kobe, Hyogo, Japan; 2Department of Biophysics, Kobe University Graduate School of Health Science, Kobe, Japan; 3Department of Biophysics, Kobe University Graduate School of Health Science/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Hyogo, Japan; 4Department of Biophysics, Kobe University Graduate School of Health Science/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

**Purpose:** Death Receptor 3 (DR3), a member of tumor necrosis factor receptor superfamily, transmits both apoptosis and NFkB activation signals. We previously reported a new DR3 haplotype containing 4 single-nucleotide polymorphisms (SNPs) and one 14-nucleotide deletion within exon 5 and intron 5 (GenBank accession Nos. AB051850 to DR3 and AB051851), which resulted in insertion of a portion of intron 5 into the coding sequence to generate a premature stop codon. Based on these mutations, we identified a mutant type of DR3 gene (mtDR3) encoding a truncated DR3 lacking transmembrane domain and death domain as the candidate disease gene for Japanese-Korean patients with rheumatoid arthritis (RA). In this study, we show a specific binding of splicing regulatory proteins on intron 5 in the mtDR3 gene, which leads to generation of a truncated DR3 lacking death domain molecule contributing to the pathogenesis of RA.

**Methods:** The wild type (wt) exon 2, wt intron 5 and mutant intron 5 pre-mRNA were synthesized from wtDR3 and mtDR3 genes, respectively, using PCR and DNA transcription and were incubated with nuclear proteins extracted from jurkat cells. The nuclear protein bound to intron 5 pre-mRNA was collected, separated on SDS-Polyacrylamide gels and analysed by silver staining, mass spectrometric and western blotting.

**Results:** We previously identified that the mutation of DR3 gene, the polymorphism is: d: g.2590A→T (rs318185) from the first base of ATG, enhances insertion of a portion of intron 5. As to the cause of exon insertion at intron 5, we have detected 3 nuclear proteins with molecular weight, 100kDa, 70kDa and 60kDa which bind to the mutant type intron 5, but not to wild type intron 5, of DR3 mRNA under silver staining. Mass spectrometric and western blotting identified them as splicing factors, proline- and glutamine-rich (SFPQ), heterogeneous nuclear ribonucleoprotein L (hnRNP L) and NONO domain-containing octamer-binding protein (NONO), respectively.

**Conclusion:** As to the cause of exon insertion at intron 5, the truncated DR3 lacking death domain molecule contributes to the pathogenesis of RA. We have identified 3 splicing regulatory proteins, SFPQ, hnRNP L and NONO, that specifically bound to the intron 5 mtDR3 to generate a truncated DR3 gene product.

**Disclosure:** M. Mizuhara: None; A. Hashirmoto: None; K. Yoshida: None; S. Shizawa: None.
Characterization of Fibrinogen-Specific CD4 T Cells Using Peptide-MHC Tetramers. Laura F. Su1 and Mark M. Davis2. 1Stanford, Mountain View, CA, 2Stanford

Purpose: Rheumatoid arthritis (RA) is one of the most common debilitating systemic inflammatory conditions. To date, little is known about which autoantigens are involved in RA and how T cells recognizing self-proteins may become pathogenic in disease. Fibrinogen is a common target of autoantibodies in RA patients and a putative T cell autoantigen involved in disease development. The short-term aim of this study is to identify and characterize fibrinogen-specific CD4 T cells in healthy individuals, with the goal of extending the analysis to patients with RA.

Method: Autoantigen-specific T cells were identified directly ex vivo using peptide-MHC tetramers. HLA-DR4 monomers with a tethered thrombin cleavable CLIP peptide were purified from the culture supernatant of a stable HLA-DR4 transfectant cell line by antibody affinity chromatography. The purified monomers were then biotinylated, thrombin cleaved, loaded with peptides, and oligomerized onto a streptavidin backbone labeled with a fluorophore. To identify individuals carrying the HLA-DRB1*0401 (DR4) allele, HLA typing was performed on healthy blood donors and RA patients using sequence-specific primer PCR. Individuals with DR4 allele(s) were selected for T cell repertoire analysis. To identify antigen-specific T cells, blood from patients with RA was used. Positive individuals were enriched for CD4 cells by rosettaspe/ficoll centrifugation. Tetramer staining was performed at room temperature for 1 hour using 10 nM of tetramers loaded with peptides from hemagglutinin (HA) and fibrinogen. Memory phenotyping was performed using antibodies against the protein tyrosine phosphatase, CD45RO, and the chemokine receptor, CCR7. Tetramer tagged cells were magnetically enriched and analyzed by flow cytometry.

Results: We are able to identify fibrinogen-specific CD4 T cells in healthy individuals without expansion in culture. The frequency of lymphocytes recognizing fibrinogen is between 0.3 to 22 cells per million CD4 T cells. There does not appear to be significant gender- or age-dependent differences, with similar frequency of fibrinogen-specific lymphocytes seen in male and female, and between young and the older individuals.

Phenotypic characterization of antigen-specific cells using antibodies against CD45RO and CCR7 reveals a memory population that recognizes fibrinogen in most people without an autoimmune disease. The presence of antigen-experienced cells recognizing fibrinogen indicates that the immunological self is not ignorant of these epitopes and suggests that active regulatory mechanisms is involved in preventing inappropriate T cell activation.

Conclusion: Rare antigen-experienced fibrinogen-specific CD4 T cells can be detected in the peripheral blood of healthy individuals. Study is currently ongoing to evaluate the role of regulatory T cells in modulating the activity of fibrinogen-specific T cells and to extend the analysis to patients with RA.

Disclosure: L. F. Su: None; M. M. Davis: None.

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Defective ERK Signaling in Hematopoietic Progenitor Cells in Rheumatoid Arthritis. Ines Colmegna1, Sergey Pryschep1, Hisashi Oshii2, Jorg J. Goronzky3 and Cornelia M. Weyand1. 1Georgia Institute of Technology, 2McGill University, Montreal, QC, Canada, 3Stanford University

Background: The main functional property of hematopoietic progenitor cells (CD34+ HPC) is their proliferative response to hematopoietins. HPC from patients with rheumatoid arthritis (RA) are hypo-responsive to growth factor stimulation leading to a decreased cell cycle entry and progression and thus to a restricted expansion capacity. Kinase-based signal transduction pathways are key integration points that link extracellular stimuli to proliferation, differentiation and cell survival. We tested the hypothesis of whether a defect of the extracellular signal-regulated kinase (ERK) pathway underlies the proliferative defect of RA HPC.

Methods: CD34+ cells from patients with rheumatoid factor-positive RA and demographically matched healthy controls were MACS sorted from PBMC. A minimum of 12 RA samples and 12 matched controls were included per experiment. The surface expression of cytokine receptors (IL-3 and IL-6 receptor subunits, c-kit and FLT3) was evaluated by FACS. Baseline and post-cytokine (IL-3, IL-6, FLT3-L and SCF) activation phosphorylation states of ERK1/2 were determined by flowcytometric single-cell phospho-protein analysis (Phospho-Flow). Transcripts of ERK target genes (c-Myc and Cyclin D) were quantified by RT-PCR. The co-localization of K-Ras/ Raf-B, proximal events in the activation of ERK, was assessed by confocal microscopy in CD34+ cells.

Results: The frequency and density of cytokine receptor expression was similar in RA and controls CD34+ cells. Baseline and post-cytokine activation phosphorylated ERK (pERK) was decreased in RA CD34 compared to demographically matched controls (baseline p=0.04, 10' activation p=0.005, 15' activation p=0.006). Transcripts of ERK modulated genes involved in cell cycle progression (Cyclin D3, and c-Myc) were significantly reduced in RA (p<0.02). Confocal microscopy studies demonstrated significantly lower cytokine-induced Ras/Raf colocalization in RA CD34+ cells than in controls. (p=0.04) implicating proximal events in the defective ERK activation.

Conclusions: Cytokine evoked signaling responses of the ERK signaling pathway, a key integration network linking extracellular stimuli to proliferation, are defective in RA HPC. Insufficient clustering of K-Ras and Raf-B complexes may become pathogenic in disease. Fibrinogen is a common target of autoantibodies in RA patients and a putative T cell autoantigen involved in disease development. The short-term aim of this study is to identify and characterize fibrinogen-specific CD4 T cells in healthy individuals, with the goal of extending the analysis to patients with RA.

Disclosure: I. Colmegna: None; S. Pryschep: None; H. Oshii: None; J. J. Goronzky: None; C. M. Weyand: None.

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Human STEAP4 (Six-Transmembrane Epithelial Antigen of Prostate 4) Regulates Inflammatory Cytokines and the Proliferation of Fibroblast-Like Synoviocyte in Patients with RA. Yoko Tanaka, Isao Matsumoto, Naoto Umeda, Kayo Yamamoto, Yuki Tanaka, Asuka Inoue and Takayuki Sumida. University of Tsukuba

Background: We recently demonstrated that TNFα-induced adipose related protein (TIARP) plays a crucial role in TNFα-dependent arthritis model such as glucose-6-phosphate isomerase (GPI) -induced arthritis. STEAP4 mRNA and protein expression was reported to be upregulated by TNFα in a dose-dependent manner by using human adipose tissue, however, the function of STEAP4 in other tissue is still unclear. The purpose of this study is to clarify the function of STEAP4 in fibroblast-like synoviocyte (FLS) from RA patients and the relationship between STEAP4 and RA.

Methods: 1) To unravel localization of STEAP4, the expression of EAE1 (known to be a endosome marker) or CD68 in FLS was examined by fluorescence immunohistochemistry (IF). 2) FLS obtained from RA synovium were treated with TNFα (2ng/ml), and the fluctuation of STEAP4 was evaluated by Western blot analysis (WB). 3) FLS obtained from RA was transfected by siRNA specific for STEAP4, and cultured for 24 h. IL-6 mRNA was quantified by real time PCR. 4) GFP-STEAP4 or GFP-empty plasmid DNA were transfected to FLS, then cultured for 24 h with TNFα. Secretion of IL-6, IL-8, MMP3, and GM-CSF was examined by ELISA. 5) Proliferation and apoptosis of GFP-STEAP4 transfectant were investigated by BrdU assay or flow cytometry. 6) The expression of STEAP4 in PBMC was measured before and after therapy with infliximab (N=40).

Results: 1) STEAP4 was co-localized with CD68 in the FLS obtained from RA patients. STEAP4, EEA1 and CD68 were clearly co-localized in cytoplasm (endosome and lysosome) of the synovium. 2) In vitro analysis, the expression of STEAP4 protein in FLS was up regulated by TNFα stimulation, and controlled inflammatory cytokine evoked signaling responses of the ERK signaling pathway in FLS. 3) The expression of IL-6 mRNA was upregulated by overexpression of STEAP4 (p<0.05). 4) The amount of IL-6, IL-8, GM-CSF secretion were down-regulated by overexpression of STEAP4 (p<0.05), although MMP3 were upregulated after TNFα stimulation. 5) Proliferation was decreased and apoptotic cells were increased in GFP-STEAP4 transfectant compared to GFP-empty transfectant. 6) The expression of STEAP4 was decreased after infliximab treatment especially in good responder (p<0.05). Conclusion: STEAP4 expression was observed in rheumatoid synovium, was clearly up regulated by TNFα stimulation, and controlled inflammatory cytokine and proliferation of FLS. In addition the expression of STEAP4 in PBMC was upregulated by TNFα antagonist in RA, suggest that it may play a potential role in the pathogenesis of TNFα- induced arthritis.

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IL-15 Promotes Osteoclastogenesis Via Phospholipase D Signaling Pathway in Rheumatoid Arthritis. Ji-Min Kim1, Mi-Kyung Park2, Mi-La Cho2, Yong-Geun Jung1, Su-Jin Moon1, Seung-Ki Kwok1, Ji-Hyeon Ju1, Kyung-Su Park1, Ho-Youn Kim1 and Sung-Hwan Park1.1 Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary’s Hospital, The Catholic University of Korea, Seoul, Korea, Republic of; 2Rheumatism Research Center, Catholic Research Institute of Medical Science, The Catholic University of Korea, Seoul, Korea, Republic of

Background: Osteoclast plays an important role in the joint destruction in rheumatoid arthritis (RA). Osteoclast formation is enhanced in the presence of therapeutic target in RA. Mediator of IL-15-induced osteoclastogenesis and can be considered as a new therapeutic target.

Methods: Expression of phospholipase D1 (PLD1), RANKL, mitogen-activated protein kinases (MAPKs) and nuclear factor-κB (NF-κB) was determined by immunohistochemistry in the RA synovial tissue. Whether or not IL-15 induces the expression of various molecules in the RA fibroblast-like synoviocyte (FLS) was examined by quantitative polymerase chain reaction and western blotting. In order to evaluate the effect of IL-15 and phosphatidic acid (PA; active product of PLD metabolism) on the osteoclast formation, peripheral blood monocytes from RA patients were cultured with or without FLS in the presence of M-CSF and RANKL, the traditional osteoclast differentiation condition.

Results: Expression of IL-15, PLD and phosphorylated extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), inhibitor of NF-κB was enhanced in the RA synovial tissue. Expression of RANKL and PLD1 was significantly upregulated by IL-15 in the FLS from RA patients. PA enhanced the RANKL expression, which was inhibited by the blockade of PA production by 1-butanol or PLD1 siRNA. IL-15 and PA also stimulated the osteoclastogenesis through the phosphorylation of NF-κB as well as MAPKs and JNK. Regardless of the presence of RA FLS, IL-15-induced osteoclastogenesis in the monocytes cultured with M-CSF and RANKL was suppressed by the blockade of PA production.

Conclusions: PLD1 activation by IL-15 contributed to RANKL-mediated osteoclastogenesis via NF-κB and MAPK signaling pathway in FLS of RA patients. Taken together, our data suggest that PLD1 may be an important mediator of IL-15-induced osteoclastogenesis and can be considered as a new therapeutic target in RA.

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IL-17A and IL-17F Contribute to the Progression of Rheumatoid Arthritis by Inducing a CXCR4-Dependent Invasive Phenotype in Synoviocytes. Amaud Ho2, Saloua Zrioual1, Vanina Lenief1 and Pierre Miossec1.1 Hospital Edouard Herriot, Lyon, Lyon, France, 2Immunogenomics and Inflammation Research Unit and Department of Immunology and Rheumatology, Hospital Edouard Herriot, Lyon, France

Objectives: Rheumatoid arthritis (RA) synovium undergoes histological changes characterized by angiogenesis, immune cell infiltration and hyperplasia of synovial lining cells. Among the inflammatory mediators expressed in RA synovium, IL-17 is emerging as a key mediator. The aim of our study was to assess the role IL-17A and IL-17F in synoviocytes migration and invasion.

Methods: IL-17A and IL-17F induced mRNA expression in RA synoviocytes was analyzed by using microarrays (Affymetrix, U133 +2) and qRT-PCR. The capacities of IL-17 and IL-17F alone or in combination with TNF-α to induce synoviocyte migration and invasion were tested using Boyden chambers and transwell matrigel invasion chambers. The specific contribution of CXCR4, the SDF-1 receptor was analyzed using neutralizing antibody. As Hypoxia Induced Factor 1 (HIF1-α) regulates CXCR4 expression, a functional assay (binding DNA assay) was used to evaluate the role of both cytokines in the regulation of HIF1-α expression and activation. To evaluate the role of HIF1α pathway in RA, 40 RA patients and 20 healthy volunteers (controls) were enrolled for determination of gene expression profiles in whole peripheral blood using U133A Affymetrix microarrays.

Results: IL-17A and IL-17F induced a molecular pattern characterized by inflammation- (LIF, IL-11, IL-23p19, FGF-2) and hypoxia-related genes (SLC1A1, C9, CXCR4). In particular, IL-17A and IL-17F alone or combined with TNF-α induced CXCR4 mRNA in synovocytes (289 fold for IL17A, 34 fold for IL-17F, 450 fold for the combination of IL-17A with TNF-α). Using immunofluorescence microscopy, the expression of CXCR4 at the surface of synoviocytes was confirmed. Moreover, IL-17A and TNF-α induced synoviocyte migration and invasion through a CXCR4-dependent mechanism with a synergistic effect (6 fold vs 67 migrated cells/HPF, p=0.05). The blockade of CXCR4 led to a decrease of synoviocyte migration (~10 fold, P<0.05). The combination of IL-17A and TNF-α as the combination of IL-17F and TNF-α in a lesser manner was able to promote the activation of HIF1-α in synoviocytes (2 fold, P=0.0034), and this association was synergic to induce VEGF mRNA expression. To confirm the role of hypoxia pathway in RA, the expression of HIF1-α induced genes was measured in blood of RA patients, and control subjects. Six hypoxia related genes were overexpressed in blood of RA patients as summarized in table 1.

Conclusion: Both IL-17A and IL-17F may contribute to the progression of RA, notably through their effect on synoviocyte aggressiveness. Part of this effect results from a mediated CXCR4/SAF1 pathway and the induction of hypoxia pathway.

Table 1: The observed data from a set of 40 RA patients and 20 controls demonstrated an upregulation of HIF1-α-dependent genes.

<table>
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In Rheumatoid Arthritis, Naive B Cells Prevail in the Peripheral Blood, Whereas Memory B Cells Accumulate in the Joint Compartment, Express ZAP-70 and Characterize the Aggregate Pattern. Alessandro Michelutti1, Elisa Gremese2, Barbara Toluso2, Francesca Morassi1, Rossala Privitera1, Silvia Canestri2, Giusy Peluso2, Silvia L. Bosello2 and Gianfranco Ferraccioli1.1 Division of Histopathology, Catholic University of Sacred Heart, Rome, Italy, 2Division of Rheumatology, Catholic University of Sacred Heart, Rome, Italy

Statement of Purpose: To analyse B cell subsets in the peripheral blood of RA, non-RA patients and Healthy Controls (HC) and in the synovial compartment in order to understand whether there is a compartmentalization of some subsets. To examine the phenotypic characteristics of the B cells in the synovial compartment in order to understand whether there is a compartmentalization of some subsets. To examine the phenotypic characteristics of the B cells in the synovial compartment in order to understand whether there is a compartmentalization of some subsets.

Materials and Methods: Twelve patients with RA and 15 non-RA arthritides (4 UA, 3 MCA-microcrystal arthritis, 1 Spa, 1 SLE, 4 MOA-monoarthritis, 2 PsA) were examined for B cell subsets in the peripheral blood (PB) and in the synovial fluid (SF) and underwent synovial biopsy. Ten HC matched for sex and age, were enrolled in the study as control group.

Results: The percentage of B cells was similar in RA and in non-RA patients, both in peripheral blood and in the synovial compartment.

Considering the peripheral blood compartment, the percentage of CD19+ B cells (8.0 ± 4.8%) as well as the eBm5 (12.4 ± 5.6%) were lower in RA than in HC (CD19+%; 10.8 ± 3.6%, p=0.003; eBm5%; 16.0 ± 7.1%, p=0.06). On the other hand, the percentage of CD19+ Zap70+ B cells were higher in RA than in HC (6.1 ± 5.5%-median 5.0 vs 3.9 ± 3.1%-median 3.1% in HC; p=0.05), whereas no differences were seen between RA and non-RA patients (4.1 ± 3.0%, p=0.22).

In the SF of RA patients, the percentage of Bm2 + Bm2 were significantly lower than in the PB (3.2 ± 3.2% vs 41.3 ± 20.5% in peripheral blood, p=0.001). On the contrary Bm5 were significantly higher in the SF than in the PB (67.9 ± 11.4% vs 21.3 ± 21.1%, p=0.001). These data have been confirmed by a significant increase of CD27+ B cells in the SF vs the PB (58.8 ± 18.1% vs 25.1 ± 14.9%, p=0.001). More particularly, the percentage of CD27+IgD- was significantly higher in SF (54.7 ± 16.7%) compared to PB (11.1 ± 7.9% in PB, p=0.001).
Dividing RA patients with high disease activity (DAS44 > 3.7) from those with a DAS < 3.7, the analysis revealed that Bm1 in the SF was higher in active RA (18.9 ± 8.4% vs 10.7 ± 5.3%, p = 0.04), whereas Bm5 + Bm6 B cells were lower in active RA (75.4 ± 9.4% vs 85.9 ± 6.4%, p = 0.03). ZAP-70 + B cells correlated with the total number of leukocytes (r = 0.32, p = 0.04, inversely with Bm2 + Bm2′/r = 0.56, p = 0.05), and with the Bm2 + Bm2′/efbn + Bmn ratio (r = -0.54, p = 0.03).

Moreover, the IHC analysis of CD68, CD3, CD20, CD227-CD20, CD38-CD20 and CD138 positive cells in the synovial tissue showed an increased trend in RA vs non-RA synovial tissues (p = ns). ZAP-70 + B cells correlated significantly with CD38 + B cells (r = 0.70, p = 0.04). Considering the RA synovial biopsies with the aggregate and diffuse patterns, CD27 + B cells characterized the pseudo-follicular/aggregate pattern (128.6 ± 89.3/hsfp vs 40.7 ± 31.9/hsfp; p = 0.03).

Conclusions: There is a characteristic accumulation of memory B cells in the joint compartment, with CD27 characterizing the aggregate pattern. In addition, data suggested that these cells are ZAP-70+, which was previously shown to confer to B cells a longer life span. The synovial fluid of patients with active disease contained more “naïve” Bm1 and Bm2-Bm2′ cells than patients with less active disease.

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Influence of TNF-α, MMP-3, TIMP-3 and HLA Class II Genes Polymorphisms in the Rheumatoid Arthritis Articular Damage. Renato T. Alarcon1, Artur R. C. Fernandes2, Geraldo R. C. Pinheiro3, Magali J. G. Usayno4, Luis C. M. Porto1, Juliana Caradoso-Oliveira4, Gustavo M. Fabricio-Silva5, Jeda M. M. Laurindo1, Manoel B. Bertolo2, Mario Yazbek2, Mariana G. Soares5, Neusa P. Silva6, Kaline M. C. Pereira7 and Luis E. C. Andrade8. 1Universidade de Sao Paulo, Sao Paulo, SP, Brazil; 2Universidade Estadual de Campinas, Campinas, SP, Brazil; 3Universidade Estadual do Rio de Janeiro, Rio de Janeiro, RJ, Brazil; 4Universidade Estadual do Rio de Janeiro, Rio de Janeiro, RJ, Brazil; 5Universidade Federal de Sao Paulo - UNIFESP, Sao Paulo, SP, Brazil

Background: The recent availability of drugs that may alter the course of rheumatoid arthritis (RA) has emphasized the need for predictors of disease outcome in order to assign patients to appropriate treatment. HLA-DRB1 and extra-HLA genes are implicated in the predisposition and progression of RA and polymorphism in some of those may serve as modulators of disease severity. TNF-α, matrix metalloproteinase-3 (MMP3) and tissue inhibitor of metalloproteinases-3 (TIMP-3) are integrated in the pathway of joint destruction in RA. Genetic studies of patients with RA can supply data that contribute to define more precisely the groups of patients with good and bad disease progression.

Objective: To evaluate possible associations between cumulative articular damage and polymorphisms in HLA-DRB1, TNF-α (rs3680), MMP3 and TIMP3-3 in a sample of Brazilian patients with RA.

Methods: We selected 440 RA patients from three university centers in southeast Brazil (Sao Paulo, Rio de Janeiro, and Campinas). DNA was obtained from peripheral leukocytes. The regions of interest for TNF-α, MMP-3 and TIMP-3 were amplified by PCR. Amplicons were digested with appropriate restriction enzymes and the resulting fragments were resolved in agarose gel electrophoresis (RFLP). HLA-DRB1 alleles were determined by PCR using sequence-specific oligonucleotide probes (PCR/SSO) and DRB1*04 alleles by sequence-specific primers (PCR/SSP). Sharp’s index was scored in hands and feet X-rays by an experienced blinded radiologist. Derivative Sharp scores were developed according to the mathematical division of hands/feet scores (Sharp-h/f), fingers/wrists scores (Sharp-fw), and erosion/space narrowing scores (Sharp-es).

Results: There was no association between the studied polymorphisms and total Sharp score. However, patients with predominant feet damage (Sharp-h/f < 1.67) had higher frequency of TIMP3 -1296T (72.6% vs 52.6%, p = 0.001) and TIMP3 -915A (71.4% vs 55.5%, p = 0.009) alleles as compared with those with predominant hand damage. Predominance of space narrowing (Sharp-es< 1.67) was associated with -899 TIMP3 allele A (7.8% vs 0.5%, p = 0.007).

Conclusions: TIMP-3 polymorphism was significantly associated with the preferential topography of joint destruction and with the predominant type of radiographic changes (erosion versus space narrowing) in rheumatoid arthritis.

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Inhibition of the Recycling of Polyamines Restores DNA Methylation in Rheumatoid Arthritis Synovial Fibroblasts. Emmanuel Karouzakis1, Christoph Kolling2, Renate E. Gay3, Beat A. Michel1, Steffen Gay1 and Michel Neidhart1. 1Center of Experimental Rheumatology and Zuercher Center of Integrative Human Physiology (ZHIIP), University Hospital Zurich, 2Schulthess Clinic, Zurich

Objective: Global DNA hypomethylation in rheumatoid arthritis synovial fibroblasts (RA-SF) contributes to their intrinsic activation that leads to cartilage and bone destruction. S-adenosylmethionine (SAM) is the methyl donor during DNA methylation—mediated in somatic cells by DNA methyltransferase 1 (DNMT1). RA-SF is also used as substrate in the biosynthesis and recycling of polyamines and metabolized utilizing the key enzymes adenosine deaminase (AMD) and spermidine/spermine acetyltransferase (SSAT) resulting in the production of diacetylpolyamines. SSAT recycles spermidine and spermine into putrescine that in turn up-regulate AMD thereby accelerating the consumption of SAM. The aim of this study is to investigate whether the increased recycling of polyamines is associated with the global DNA hypomethylation in RA-SF.

Methods: RA-SF (n = 12) and osteoarthritic synovial fibroblasts (OASF, n = 6) were stained for AMD, SSAT, polyamine modulated factor binding protein 1 (PMF-1/PMFBP1), Dnmt1 and analyzed by flow cytometry. 5-methylcytosine (5-MC) was measured by flow cytometry, diacetylspermine (DAP) in cell culture supernatants and cell extracts was determined by ELSA. S-Adenosylmethionine (SAM) was measured in cell extracts by fluorometry. Small interfering RNAs (siRNA) were used to down-regulating AMD and/or SSAT and diminazene aceturate (DA) was employed to inhibit the activity of SSAT.

Results: The intracellular levels of AMD, SSAT and PMFBP1, as well as the level of DAP in cell culture supernatants, were significantly increased in RA-SF, compared to OASF (AMD/RA-SF: 36 ± 5, OASF: 23 ± 4, p < 0.005; SSAT/RA-SF: 34 ± 8, OASF: 17 ± 3, p < 0.001; PMFBP1/RA-SF: 79 ± 27; OASF: 49.7 ± 7.2 mean fluorescence [mf], p < 0.05). On the other hand, the levels of SAM in cell culture extracts, as well as the amount of Dnmt1 and 5-Mc were significantly decreased in RA-SF, compared to OASF (SAM/RA-SF: 0.95 ± 0.94, OASF: 3.10 ± 0.25 nM/mg protein, p < 0.001; Dnmt1/RA-SF: 7.2 ± 1.3, OASF: 13.3 ± 1.0 mf, p < 0.001; 5-Mc/RA-SF: 0.98 ± 0.26, OASF: 2.52 ± 0.37 mf minus background, p < 0.001). A significant association was found between the amount of SAM in the cell extracts and the 5-Mc in nucle (r = 0.69, p < 0.005); in addition, parameters of the catabolism and/or recycling of polyamines negatively correlated with SAM, Dnmt1 and 5-Mc (from r = 0.50 to r = -0.83, p < 0.01 to 0.001). Furthermore, siRNA to SSAT can reduce the expression of AMD (controls: 35.7 ± 10.7, siRNA against SSAT: 27.9 ± 4.8 mf, p = 0.18, n = 4). Similarly, inhibition of SSAT activity by DA significantly reduced the expression of AMD (controls: 33.3 ± 6.6, DA: 19.2 ± 4.8 mf, p < 0.05, n = 4). A 2 weeks treatment with DA restored the DNA 5-Mc content of control (r = 1.41, DA: 2.75 mf, pool of 4 patients) to levels measured in OASF (2.68 mf, pool of 4 patients).

Conclusion: Intracellular levels of PMFBP1 and SSAT enhance the catabolism and recycling of polyamines in RA-SF. A high consumption of SAM by this pathway is an important factor contributing to the global DNA hypomethylation in these cells. Decreasing SSAT transcription or activity could represent a new therapeutic strategy in RA.

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Interleukin-6 Promotes Pathological Angiogenesis by Modulating Angiopoietin Expression in Rheumatoid Arthritis. Ken Kayakabe1, Talsah Kuroiwa2, Noriyuki Sakurai2, Hidekazu Ikeuchi2, Akito Maeshima3, Keiju Hirohata3, and Yoshisasa Nojima3. 1Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan; 2Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine

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Background: Angiogenesis is a part of important factors in the pathogenesis of RA. Pathological angiogenesis is characterized by endothelial proliferation accompanied by increased permeability, in which vascular endothelial growth factor (VEGF) plays a dominant role. Angiopoietin-1 (Ang-1) rather facilitates vessel stabilization by keeping endothelial cell adhesion and has a natural antagonist, Ang-2. Previous studies have shown that interleukin-6 (IL-6) promotes angiogenesis in RA but the precise mechanism is not well determined. In this study we sought to examine whether IL-6 promoted angiogenesis in RA by modulating VEGF/Angiopoietin expression.

Methods: Fibroblast-like synovial cells derived from RA patients (FLS) were cultured overnight to confluence. Then, human umbilical vein endothelial cells (EC) were added and co-cultured for 6 days in the presence or absence of recombinant human IL-6 (together with soluble IL-6 receptor), VEGF, or Ang-1. EC were stained with anti-CD31 antibody, and EC proliferation was determined by CD31-positive area analyzed by Image-J (NIH). Cell-cell adhesion of EC was assessed by immunofluorescent staining of CD31. Synovial fluids (SF) were collected from patients with RA (n=25) and osteoarthritis (OA) (n=7), who undertook therapeutic SF aspiration. The levels of VEGF, IL-6, Ang-1, and Ang-2 in culture supernatants or SF were determined by ELISA. Quantitative real-time PCR was performed to examine mRNA expression of Ang-1.

Results: Compared with medium control, IL-6 stimulation at 100 ng/ml in co-culture induced 2.5-fold increase of EC proliferation. VEGF at 10 ng/ml also induced 2.2-fold increase. EC stimulated with IL-6 exhibited irregular shape and decreased cell-cell adhesion, suggesting pathological angiogenesis with increased permeability. In the supernatants of co-culture, IL-6 up-regulated expression of VEGF compared with medium control (81 vs 31 pg/ml) and Ang-2 (3504 vs 1726 pg/ml), while decreased Ang-1 (32 vs 99 pg/ml). Interestingly, adding recombinant IL-6 to various cell types induced decreased cell-cell adhesion and increased cell shape change and decreased expression of cell adhesion induced by IL-6, indicating the critical role of angiopoietins in pathological angiogenesis. In the culture of either FLS or EC alone, we found that cellular source of Ang-1 and VEGF was FLS and that of Ang-2 was EC. In FLS, IL-6 reduced Ang-1 expression compared with medium control, both in protein and mRNA levels, by 75% and 60%, respectively. In ELISA, IL-6 also induced 2.5-fold increase of VEGF expression in FLS and 1.7-fold increase of Ang-2 in EC. In SF, expression of IL-6 (5059 vs 262 pg/ml), VEGF (3137 vs 1715 pg/ml), Ang-1 (104 vs 36 pg/ml) and Ang-2 (9216 vs 1494 pg/ml) were significantly higher in RA than in OA. In RA, IL-6 expression was positively correlated with VEGF (r=0.516, p=0.008), while VEGF negatively with Ang-1 (r=-0.515, p=0.008).

Conclusion: IL-6 not only up-regulates VEGF but also down-regulates Ang-1 signaling. This synergistic effect may play a critical role in the pathological angiogenesis in RA.

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MicroRNA and mRNA Integrated Analysis in Rheumatoid Arthritis Synovial Macrophages. Jong Da Jung1, Bit-Na Lee2, Tae-Hwan Kim3, Jae-Bum Jun4, Da-Hyun Yoo5, Kyung-Sun Na6, Jin-Hyun Woo7, Sang Jae Choi7, Young Ho Lee8, Youngbin Yoon9, and Gwan Gyu Song9. 1Department of Biochemistry, College of Medicine, Korea University, Seoul, Korea, 2Kim’s Clinic, Seoul, Korea, 3Rheumatology, College of Medicine, Korea University, Seoul, Korea, Republic of, 4Rheumatology, College of Medicine, Korea University, Seoul, Korea, 5The Hospital for Rheumatic Diseases, Hanyang University, Seoul, Korea

Dysregulated expression of microRNAs (miRNAs) has been shown to be a hallmark of human diseases, and recent studies provide growing evidences that miRNA dysregulation might be play important roles in the pathogenesis of rheumatoid arthritis. Abnormal expression of certain miRNAs was found in peripheral blood mononuclear cells, synovial fibroblasts and synovial tissue from patients with rheumatoid arthritis. To investigate whether abnormal expression of miRNA in rheumatoid arthritis could account for dysregulated expression of certain genes, we compared different expressions of miRNAs and mRNAs in rheumatoid synovial fluid macrophages to normal peripheral blood monocytes, using gene expression oligonucleotide microarray and microRNA microarray. Comparative analysis of mRNA profiles showed significant different expressions (defined as 2-fold change and P<0.05) of 430 genes in RA synovial macrophages, of which 303 (70%) were upregulated and 127 (30%) were downregulated, compared to normal PB monocytes. Among the biological process class, highly represented genes included those involved in cell adhesion, immunity and defense, nucleic acid metabolism and signal transduction. Among molecular function class, highly represented genes included those involved in cell adhesion molecule, defense/immunity protein, receptor, nucleic acid binding and transcription factor. We identified 13 differentially expressed miRNAs in RA synovial macrophages, compared with normal PB monocytes. Out of 13 miRNAs, 9 miRNAs were upregulated and 4 miRNAs were downregulated in RA synovial macrophages. Total 62 genes were predicted as target genes of 13 differentially expressed miRNAs in RA synovial macrophages. Out of these 62 genes, 28 genes were upregulated and 34 genes were downregulated. Among 62 miRNA-targeted dysregulated genes, few genes such as GSTM1, VIPR1, PAD4, CDA, IL21R, CCL5, IL7R, STAT4, HTRA1 and IL18BP have been reported to be associated with rheumatoid arthritis. We validated the differential expression of these genes in RA synovial macrophages using quantitative real-time PCR.

In the present study, we observed that several miRNAs are differentially expressed in RA synovial macrophages, and suggest that these dysregulated miRNAs may regulate expressions of several genes associated with the pathogenesis of RA.

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360 Mitochondrial Mutagenesis in Synovial Tissue Is Associated with In Vivo Hypoxia, Inflammation and Oxidative Damage. Monika Biniecka1, Edward Fox2, Chien T. Ng3, Len Hart4, Ursula Fearon5, Douglas J. Veale6 and Jacintha O’Sullivan2. 1Department of Pathology, University of Washington, Seattle, WA, 2Translation Research Group, Dublin Academic Medical Centre, St. Vincent’s University Hospital, Dublin, Co. Dublin, Ireland

Background: Mitochondrial components are highly susceptible to attack by oxygen radicals due to their close proximity to the electron transport chain and the presence of polysaturated fatty acid rich membranes. Oxidative damage to mitochondrial DNA (mtDNA) itself can affect genes encoding respiratory chain complexes and transcription, which may lead to further mitochondrial DNA mutations. Moreover, ROS induced oxidative damage could potentially be a major source of mitochondrial genomic instability leading to respiratory chain dysfunction. The aim of this study was to examine the relationship of random mitochondrial DNA point mutations to in vivo synovial tissue oxygen level (tpO2), synovial inflammation and lipid oxidative damage in the inflamed joint of inflammatory arthritis patients.

Method: Oxygen partial pressure in synovial tissue (tpO2) was measured in vivo using a combined oxygen/temperature Licox probe. Synovial membrane biopsies were obtained from the site of the oxygen tension measurement under direct visualization at the time of arthroscopy. The newly validated mitochondrial Random Mutation Capture assay was used to quantitatively evaluate alterations of the mitochondrial genome in synovial tissue biopsies. Expression of inflammatory cell specific markers (CD68 of macrophages and CD3 of T cells) and lipid peroxidation (4-HNE) were quantified by immunohistochemistry.

Results: Twenty subjects were recruited prior to starting therapy with biologic agents (14 patients with RA and 6 patients with PsA). The median synovial tissue tpO2 level was profoundly hypoxic at 25.47mmHg, equivalent to an ambient oxygen tension 3.3%. The mutations detected were mainly transversions i.e. AT->GC and CT->TA, characteristic of mutation following oxidative stress. A statistically significant increase in the frequency of point mutations was detected in synovial biopsies in patients with tpO2<20mmHg compared to patients with tpO2>20mmHg (p=0.05). Higher in vivo tpO2 was significantly associated with a decrease in the frequency of mtDNA point mutations (p=0.05; r=0.38). Significantly greater mitochondrial mutation burden correlated with high expression of CD68 (p=0.026; r=0.44) and CD3 (p=0.047; r=0.29) positive cells in the sublining layer of synovial tissue. Higher frequency of random mitochondrial DNA mutations was also significantly associated with higher synovial 4-HNE cytoplasmic expression in lining and sublining layers of the synovium (p=0.04; r=0.46 and p=0.03; r=0.44 respectively).

Conclusion: Higher frequency of random mitochondrial mutations was significantly associated with reduced in vivo oxygen level, with higher microscopic inflammation and oxidative stress. This data implicates that alterations in the mitochondrial genome may be a consequence of severe hypoxic levels in the inflamed joint.

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Nerve Fiber Repulsion by Semaphorins—More Redundancy Than Expected in the Rheumatoid Arthritis Joint. Susanne Klatt, Alexander Fassold and Rainer H. Straub. University Hospital Regensburg, Regensburg, Germany, University Hospital Regensburg, Regensburg, Germany

Background: The loss of sympathetic nerve fibers (SNF) is a general principle in inflammatory diseases. Since sympathetic neurotransmitters exert antiinflammatory effects at increased concentrations, their loss in inflamed tissue is reasonable to overcome infection and ensure proper wound healing. However, this mechanism is unfavorable in chronic autoimmune diseases like rheumatoid arthritis (RA). It is generally accepted that semaphorins are the major factors which are involved in guidance and repulsion of nerve fibers, respectively. Additional factors that might influence sympathetic nerve fiber repulsion need to be investigated. Recent findings indicate increased concentrations of norepinephrine, dopamine and 17-beta-estradiol in synovial tissue of patients suffering from RA. The aim of this project was to test the effects of these substances on growth and repulsion of sympathetic nerve fibers in vitro.

Methods: In order to study the effect of different factors on nerve fiber repulsion a neurite outgrowth assay was established. In this assay the behavior of nerve fibers from sympathetic trunk ganglia of postnatal mice could be investigated using time-lapse microscopy.

Results: Both investigated semaphorins 3F and 3C induced a repulsion of SNF. Semaphorin 3F repelled 80 % to 100 % of sympathetic nerve fibers, whereas Semaphorin 3C only repelled 30 %. Interestingly, TNF repelled nerve fibers with variable effects (from 10% to 100%) although the variability is unexplained. High concentrations of dopamine and norepinephrine (10^-6M) induced significant, but slight nerve fiber repulsion up to 20 % in comparison to controls. Stimulation with low concentrations of 17-beta-estradiol (10^-10M) led to repulsion of sympathetic nerve fibers. Lower concentrations of norepinephrine (10^-10M) seemed to favour nerve fiber outgrowth.

Conclusions: The outgrowth assay enabled us to study the influence of pathogenetically relevant factors which may be involved in nerve fiber growth and repulsion. We assume that not only specific axon guidance molecules like semaphorins, but rather the interplay of other factors, which are elevated in inflamed tissue predominantly influence nerve fiber growth and repulsion during the course of rheumatoid arthritis.

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Phosphoinositide 3-Kinase Delta (PI3Kδ) Regulation and Function in RA. Beatrix Bartok2, David Boyle2, Christian Rommel1 and Gary S. Firestein1. 1Intellikine, 2UCSD, San Diego, 3UCSD

Purpose: Phosphoinositide-3 kinases (PI3Ks) are emerging as drug targets to treat inflammation and autoimmune diseases. Expression of PI3Kγ and PI3Kδ isoforms is selectively relative for leukocytes and regulate innate and adaptive immune responses. They belong to Class I PI3Ks which also include PI3Kε and β isoforms. Unlike PI3Kγ and PI3Kδ, the α and β isoforms are ubiquitously expressed which limits their targeting potential for rheumatic disease. Analysis of genetically modified mice that lack PI3Kγ or δ activity revealed complementary but nonredundant functions in leukocytes. Recently, PI3Kδ expression was observed in cultured fibroblast-like synoviocytes (FLS). The goal of our study was to assess the potential role of PI3Kδ and its downstream target Akt in synovial inflammation.

Methods: Immunohistochemistry (IHC) was used to analyze PI3Kδ expression in RA FLS and synovial tissue. Quantitative real-time PCR (qPCR) was used to determine PI3Kδ mRNA levels and protein expression was quantified with Western blot analysis. PI3K mediated activation of Akt and GSKβ was detected using Western blot analysis using phospho-specific antibodies. A selective PI3Ka, PI3 Kb and panPI3K inhibitors were used in FLS cultures. An MTT assay was used to quantify cell survival in response to H2O2.

Results: PI3Kδ was detected in RA synovial tissue by IHC, with the greatest intensity in the intimal lining layer, which contains FLS. Modest sublining staining was also observed in scattered mononuclear cells. PI3Kδ expression was confirmed in cultured FLS in chamber slides by IHC and by Western blot analysis of FLS extracts (n=4). PI3Kδ mRNA level was 2.5-fold greater in RA compared with OA synovium (n=6 each, p<0.05). PI3K pathway activation in cultured FLS was analyzed by evaluating Akt and GSKβ phosphorylation. Only low levels of P-Akt and P-GSKβ were detected in response to IL-1, TNF, LPS or TGβ. However, a rapid and sustained 140-fold increase in Akt phosphorylation and 3-fold increase in GSKβ phosphorylation was induced by PDGF. To determine relative contribution of PI3Kδ to Akt and GSKβ activation, FLS were preincubated with PI3Ka, δ or pan PI3K inhibitors. Based on the inhibition of P-Akt, PI3Kδ contributed 55.5% and PI3Kε contributed 40.9% of Akt phosphorylation. PI3Kδ inhibition had no effect on P-GSKβ levels. We also assessed the effect of PI3Kδ inhibition on FLS proliferation and cell death in vitro compared to PI3Kε and pan PI3K inhibition. PDGF stimulation decreased FLS cell death by 50% in response to H2O2 and was completely reversed by PI3Kδ inhibition.

Conclusions: PI3Kδ is expressed in the rheumatoid synovial intimal lining. It also plays a novel role in FLS survival, which could contribute to synovial lining hyperplasia. PI3Kδ inhibitors in RA could provide anti-inflammatory effects in RA due to suppression of leukocyte function as well as novel disease modifying effects by decreasing FLS survival.

Disclosure: B. Bartok: None; D. Boyle: None; C. Rommel: Intellikine, 3; G. S. Firestein: Intellikine, 2.

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Platelet Microparticle Proteome: Insight into Role of Microparticles under Different Stimulatory Conditions. Roopa Shree Subbaiah2, K. C. Sekhar Rao1, Peter Gregorvic2, David Lee2, Masanu Miyagi1, Eric Boilard1 and Reuben Gobeze2. 1Case Center for Proteomics and Bioinformatics, School of Medicine, Case Western Reserve University, Cleveland, OH, 2Center for Adults with Pediatric Rheumatic Illness (CAPRI), Pediatric and Adult Rheumatology, Children’s Hospital Boston, Brigham and Women’s Hospital, Boston, MA, 3Department of Rheumatology and Immunology, CHUL, QC, Canada, 4Division of Rheumatology, Immunology and Allergy, Brigham & Women’s Hospital, Boston, MA, 5The Department of Orthopaedic Surgery, Case Western Reserve University, School of Medicine, University Hospitals of Cleveland, Cleveland, OH, 6The Department of Orthopaedic Surgery, Case Western Reserve University, School of Medicine, University Hospitals of Cleveland, Cleveland, OH

Background/Purpose: Platelets are well known for their role in thrombosis, but they contribute also to other physiologic and pathologic functions including inflammation. Our recent work demonstrated that platelets can contribute to joint inflammation through the release of small membrane vesicles called microparticles, which are frequently the most abundant cellular element in inflammatory synovial fluid. Generated upon contact with extracellular matrix via the platelet collagen/laminin receptor glycoprotein VI (GPVI), platelet microparticles (pMP) promote inflammation via interleukin 1 and potentially other mechanisms. Since GPVI is not the only stimulus that can induce pMP production, we employed a quantitative proteomic approach to determine whether pMPs remain identical across multiple pathways of platelet activation, or whether diverse activating stimuli engender production of microparticles that are biologically distinct.

Methods: Platelets from a healthy donor were stimulated by three different agonists, collagen-related peptide (CRP, a synthetic GPVI agonist), thrombin and adenosine diphosphate (ADP). Formed pMPs were purified and analyzed using high throughput mass spectrometric analysis through a quantitative proteomic approach. Unstimulated platelets were used as control. The Mascot search engine was used for protein identification. Data analysis was done using Genego software.

Results: Mass spectrometry data analysis of the three different proteome sets indicated important differential effect of major agonists in the generation of pMPs. Microparticles generated via GPVI ligation were rich in molecules pertaining to
lipid mediators, strongly suggesting an inflammatory function, while MPs from thrombin possessed multiple procoagulant molecules. In addition, MPs from CRP stimulation contained additional molecules that further activate the immune system as compared to thrombin stimulated MPs. ADP stimulated pathway was observed in all three datasets. Ongoing studies are being carried out to confirm and extend these results.

Conclusions: Our results provide evidence for the differential functions of microparticles released by platelets under various stimulation conditions. In particular, a proteomic approach substantiates the proinflammatory nature of pMPs produced upon contact with collagen, while other pathways may elicit pMP with prothrombotic or other functions. These findings represent a novel observation in fundamental platelet biology and support the possibility that blockade of GPVI may represent a promising therapy for inflammatory arthritis while leaving intact the important hemostatic activity of platelets.

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Post-Transcriptional Regulation of IL-6 Production by Zc3h12a in Fibroblast-Like Synovial Cells. Tomohiro Koga, Satoshi Yamasaki, Akitomo Okada, Shin-ya Kawashiri, Hideki Nakamura, Atsushi Kawakami and Katsumi Eguchi. Nagasaki University, Nagasaki, Japan, Nagasaki University, Nagasaki, Japan

Objective: Zc3h12a is a RNA binding protein with a CCCH-type finger motif, known to regulate mRNA metabolism. Previous reports suggest that Zc3h12a acts as a negative regulator of inflammatory processes because it is engaged in the degradation of IL-6. We investigate the effect of Zc3h12a on IL-6 production in fibroblast-like synovial cells (FLS) from rheumatoid arthritis (RA) patients.

Methods: The expression of Zc3h12a in FLS was determined by western blot and polymerase chain reaction. To knock down the expression of Zc3h12a in FLS, siRNA for Zc3h12a was transfected by lipofection method. The supernatants were collected after the siRNA transfection for the quantification of IL-6 production. Cell proliferation was analyzed by the Cell Counting Kit-8 assay after Zc3h12a knock down.

Results: Protein and mRNA for Zc3h12a were demonstrated in all the FLS from RA patients. Zc3h12a transcripts were induced by LPS and IL-1β in FLS. The production of IL-6 as well as its transcripts expression was significantly increased by knocking down of Zc3h12a. Proliferation of Zc3h12a knocked down FLS was significantly promoted in the presence of recombinant soluble IL-6.

Conclusion: Our data suggests that Zc3h12a is a novel IL-6 regulator in FLS, which may be involved in the progression of RA.

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Role of IL-17 in Pannus Formation and Osteoclastogenesis in Rheumatoid Arthritis. Hiroshi Ito2, Hidehiro Yamada3, Toshiko Nozaki Shibata2, Hirofumi Mitomi2, Kiyomi Matsu2, So Nomoto1 and Shoichi Ozaki1.

Department of Orthopaedic Surgery and Rheumatology, Saiseikai Yokohama Tobu Hospital, Division of Rheumatology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan, Division of Rheumatology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan, Division of Rheumatology, St. Marianna University School of Medicine, Kawasaki, Japan.

Objectives: IL-17 plays a critical role in the pathogenesis of murine model of arthritis. There are, however, controversies whether IL-17 plays as a pro-inflammatory mediator in rheumatoid arthritis (RA). We studied an exact role of IL-17 in RA using a human cellular model of pannus.

Methods: Inflammatory cells that infiltrated synovial tissue (ST) from patients with RA were collected without enzyme digestion, and designated as ST-derived inflammatory cells as previously reported in Arthritis Rheum 2007;56:2875-85. ST-derived inflammatory cells were cultured in the presence or absence of IL-17 and/or indomethacin, and the morphologic change was observed for 4 weeks. Cytokines produced in the culture supernatants were measured by ELISA kits. Osteoclastic activity was assessed by the development of resorption pits in calcium phosphate-coated slides.

Results: Primary culture of the ST-derived inflammatory cells resulted in a 3-dimensional macroscopic tissue growth, during which TNF-alpha, M-CSF and MMP-9, but not IL-17, were produced in the supernatant. Culture of ST-derived inflammatory cells on calcium phosphate-coated slides resulted in the development of a numerous number of resorption pits. ST-derived inflammatory cells produced IL-17 when stimulated with exogenous Toll-like receptor (TLR) ligands. Exogenous addition of IL-17 dramatically enhanced production of IL-6 and PGE2 from ST-derived inflammatory cells in a dose dependent manner. When endogenous PGE2 production was blocked by indomethacin, IL-17 enhanced pannus-like tissue growth, the production of TNF-alpha and M-CSF, and the development of resorption pits, while exogenous addition of PGE1 suppressed their activities.

Discussion: The present study suggests that IL-17 induces negative feedback regulation through the induction of PGE2, while it stimulates pro-inflammatory pathways such as inflammatory cytokine production, pannus formation and osteoclastogenesis in RA. The study also suggests that stimulations of innate immunity via TLR induces and or exacerbates rheumatoid synovitis mainly through induction of IL-6.

Disclosure: H. Ito: None; H. Yamada: None; T. N. Shibata: None; H. Mitomi: None; K. Matsu: None; S. Nomoto: None; S. Ozaki: None.

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Role of Raf Kinase Inhibitor Protein in Cytokines, Matrix Metalloproteinasises Regulation and Invasiveness of Rheumatoid Fibroblast-Like Synovocytes. Joong Kyong Ahn1, You Sun Lee2, Eun-Jung Park3, Ji-Won Hwang4, Ji-Min Oh1, Jae-Sung Lee2, Chan-Jong Jeon2, Eun-Mi Koh1 and Hoon-Suk Cha3. 1Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 2Masan Samsung Hospital, Sungkyunkwan University School of Medicine, 3Samsung Medical Center, Sungkyunkwan University School of Medicine, 4Soonchunhyang University College of Medicine

Objective: Raf kinase inhibitor protein (RKIP) is a protein that directly interacts with the kinase domain of Raf-1, and has been shown to modulate many processes, including Alzheimer’s disease, diabetes and cancer. RKIP negatively regulates the Raf/MEK/ERK pathway by interfering with the activity of Raf-1. Also, RKIP-1 interferes with the activity of the IKK complex and prevents the movement of NF-κB to the nucleus. The role of RKIP in rheumatoid fibroblast-like synovocytes (FLS) is not known. The present study was performed to investigate the expression and function of RKIP in rheumatoid arthritis (RA) FLS.

Methods: RKIP expression was measured in synovial tissue (ST) and FLS by Western blot analysis. Plasmid containing RKIP or control vector, RKIP small interfering RNA (siRNA), or control siRNA were transfected into FLS using the Amaxa system. Expression of cytokines and matrix metallo-
proteinases (MMPs) mRNA were examined by quantitative real-time PCR. Phosphorylated MAP kinases were measured in RA FLS by Western blot analysis. NF-kB EMSA was performed after TNFα stimulation in RKIP-overexpressed FLS. In vitro cell invasion assay was performed to measure the invasiveness of RA FLS according to RKIP silencing.

Results: RKIP protein was detected in RA ST and FLS, which was similar to osteoarticular ST and FLS (n=4 each). RKIP overexpression decreased IL-6, IL-8, MMP-1, and MMP-3 mRNA expression (40.76±24.38%, 32.16±18.93%, 31.25±25.09%, and 30.39±14.16% inhibited, respectively) in TNF-α-stimulated RA FLS (n=4), but these results did not reach statistical significance except the result of IL-6 mRNA (p=0.001). RKIP silencing by siRNA resulted in significantly increased MMP-1 and MMP-3 mRNA expression (1.8±0.4 and 2.3±0.8 fold increase, respectively) in TNF-α-stimulated RA FLS (n=3, p=0.01 for each). RKIP silencing also increased IL-6 and IL-8 mRNA expression (1.4±0.3 and 2.1±0.8 fold increased, respectively) in TNF-α-stimulated RA FLS (n=3), but it’s not statistically significant. RKIP overexpression suppressed TNF-α-induced ERK phosphorylation. However, p38 and JNK phosphorylation by TNF-α were not affected by RKIP overexpression. RKIP overexpression also suppressed TNF-α-induced NF-kB activation measured by EMSA. RKIP silencing resulted in significantly higher invasion index in TNF-α-stimulated RA FLS compared to controls (10.3±1.45 vs. 4.0±0.58, n=3, p=0.02).

Conclusion: RKIP plays an important role in the regulation of inflammatory cytokine and MMP production by regulating ERK and NF-kB activation in RA FLS. These results suggest that RKIP might be a potential therapeutic target for RA.

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Subling CD79a+ B Cell Correlates with Joint Destruction in Rheumatoid Arthritis. Ying-qian Mo,1 Lie Dai,2 Dong-hui Zheng,2 Lang-jing Zhu,2 Xiu-nong Wei,2 and Bai-yu Zhang.2 1Department of Rheumatology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; 2Department of Rheumatology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China. Background: The specific activation of RASF and, thus, to the disease process of RA. Methods: Synovial tissue samples were obtained from RA and osteoarthritis (OA) patients at joint replacement surgery and used for histological analysis as well as for the isolation of fibroblast-like synoviocytes. Using specific antibodies in immunohistochemical and Western blot analyses, we studied the expression of SUMO-2/3 in fibroblasts from the human samples as well as from hTNFtg and wt mice. Knockdown of SUMO-2/3 was performed using specific siRNA against both SUMO-2 and -3. The apoptotic response of the fibroblasts was measured using the caspase-3/7 assay after induction of cell death with 100ng/ml Fas ligand over 13h. MMP-1 and MMP-3 production in FLS from RA and OA patients was measured by ELISAs.

Results: Immunohistochemistry and Western blot analyses revealed a clear upregulation of SUMO-2/3 expression in all RA synovial tissue samples and in RA-FLS compared to OA control samples. These data were confirmed in tissue sections of hTNFtg mice, as well as in FLS from these mice. Knockdown of SUMO-2/3 by siRNA sensitized RASF to Fas-mediated apoptosis. Furthermore, TNF-alpha and IL-1β induced upregulation of MMP-3 was significantly stronger after knockdown of SUMO-2/3 in RA and OA-FLS. Interestingly, the expression of MPP-1 was not affected.

Conclusion: Our results demonstrate that the posttranslational modification of target proteins by SUMO-2/3 and specifically increased levels of SUMO-2/3 in RA-FLS contribute to the resistance of these cells against Fas-mediated apoptosis. Moreover, our data indicate that SUMO-2/3 is involved in the regulation and TNF-alpha stimulated production of MMP-3. Therefore, we hypothesize that SUMO-2/3 are novel players contributing to the specific activation of RASF and, thus, to the disease process of RA.

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SUMO-2/3 Regulates Apoptosis and MMP Expression in RA Fibroblast-Like Synoviocytes. Svetlana Frank1, Steven Strietfeldt1, Christine Seyfert1, Thomas Pauly2, George Kollias1, Thomas Pap1 and Marvin A. Peters1. 1Department of Nephrology and Rheumatology, Heinrich-Heine University, 2Department of Orthopaedic Surgery, Zeissigwaldklinikum, Chemnitz, Germany, 3Institute of Experimental Musculoskeletal Medicine, University of Muenster, Muenster, Germany, 4Institute of Immunology, Biomedical Sciences Research Center, Vare, Greece, 5University Hospital Muenster, Muenster, Germany.

Background: Posttranslational modification through SUMOylation has emerged as an important way by which proteins can be modified to change their intracellular localization, stability and gene expression. Previous data have shown that the overexpression of SUMO-1 contributes to the activation of RA fibroblasts like synoviocytes (RA-FLS) through a SUMO-1/SUMO-1dependent mechanism. Based on these data, we investigated the expression of SUMO-2/3 in human RA and in hTNFtg mice and studied its role in regulating both apoptosis and the expression of disease specific MMPs.

Methods: Synovial tissue samples from RA and osteoarthritis (OA) patients at joint replacement surgery and used for histological analysis as well as for the isolation of fibroblast-like synoviocytes. Using specific antibodies in immunohistochemical and Western blot analyses, we studied the expression of SUMO-2/3 in fibroblasts from the human samples as well as from hTNFtg and wt mice. Knockdown of SUMO-2/3 was performed using specific siRNA against both SUMO-2 and -3. The apoptotic response of the fibroblasts was measured using the caspase-3/7 assay after induction of cell death with 100ng/ml Fas ligand over 13h. MMP-1 and MMP-3 production in FLS from RA and OA patients was measured by ELISAs.

Results: Immunohistochemistry and Western blot analyses revealed a clear upregulation of SUMO-2/3 expression in all RA synovial tissue samples and in RA-FLS compared to OA control samples. These data were confirmed in tissue sections of hTNFtg mice, as well as in FLS from these mice. Knockdown of SUMO-2/3 by siRNA sensitized RASF to Fas-mediated apoptosis. Furthermore, TNF-alpha and IL-1β induced upregulation of MMP-3 was significantly stronger after knockdown of SUMO-2/3 in RA and OA-FLS. Interestingly, the expression of MMP-1 was not affected.

Conclusion: Our results demonstrate that the posttranslational modification of target proteins by SUMO-2/3 and specifically increased levels of SUMO-2/3 in RA-FLS contribute to the resistance of these cells against Fas-mediated apoptosis. Moreover, our data indicate that SUMO-2/3 is involved in the regulation and TNF-alpha stimulated production of MMP-3. Therefore, we hypothesize that SUMO-2/3 are novel players contributing to the specific activation of RASF and, thus, to the disease process of RA.

Disclosure: Y.-q. Mo; None; L. Dai; None; D.-h. Zheng; None; L.-j. Zhu; None; X.-n. Wei; None; B.-y. Zhang; None.

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The 6-O Extracellular Endosulfatases as Novel Regulators of Synoviocytes. Yoon Hoon Hong1, Shuhei Otsuki1, Shugeru Miyaki1, Beatriz Caramez2, Noboru Taniguchi3 and Martin Lotz4. 1The Scripps Research Institute, La Jolla, CA, 2The Scripps Research Institute, La Jolla, CA.
**Purpose:** As receptors or co-receptors, the heparan sulfate proteoglycans (HSPG) modulate the binding and signaling of various ligands to their specific receptors. The sulfation pattern of HSPG is critical in determining binding or release of ligands. The recently identified extracellular sulfatases (Sulf-1, -2) exert novel signaling mechanisms by regulating the binding of ligands to the 6-O sulfate on HSPG and thereby can modulate several signaling pathways that are involved in inflammation. The aim of this study was to analyze expression patterns of Sulf-1 and Sulf-2 and their role in experimental arthritis.

**Method:** Sulf expression in normal and arthritic human and marine knee joints and in cultured human fibroblast-like synoviocytes (FLS) were analyzed by real-time PCR, immunohistochemistry and western blotting. The role of Sulf in arthritis pathogenesis was analyzed by using the antigen-induced arthritis (AIA) model in wild-type, Sulf1−/− and Sulf2−/− mice. IL-6, an important mediator in arthritis, was measured by ELISA in FLS subjected to Sulf silencing or over-expressing with siRNA or cDNA transfection.

**Results:** Synovial tissues from humans with rheumatoid arthritis (RA) and mice with AIA showed increased expression of Sulf-1 and Sulf-2 than tissues from human osteoarthritics (OA) or surgically-induced OA in mice or normal knee. Cultured FLS from RA patients showed higher Sulf-1 and Sulf-2 expression as compared to FLS from OA patients. Treatment of FLS with IL-1β or TNFα increased Sulf-1 expression was more prominently than Sulf-2. The severity of AIA was significantly reduced in Sulf1−/− but not in Sulf2−/− mice and this was associated with reduced synovial leukocyte infiltration and pro-inflammatory cytokine expression such as IL-18 and IL-6. Sulf-1 over-expression in FLS enhanced and Sulf-1 silencing reduced IL-6 expression but did not alter the basal or IL-1β induced expression of Cox-2, MMP-3 or MMP-13.

**Conclusion:** Increased Sulf expression is observed in arthritic synovium and in IL-1β or TNFα activated FLS. Sulf-1 plays an important role in arthritis pathogenesis and this is at least in part mediated by the controlling IL-6 production. Thus, Sulf-1 represents a novel therapeutic target for inflammatory arthropathies.

**Disclosure:** S. Otsuki: None; S. Miyaki: None; B. Caramez: None; N. Taniguchi: None; M. Lotz: None.

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The Critical Role of STAT3 in the Th17 Differentiation of RA Synovial T Cells. Ji Hyeon Ju, Mi-La Cho, Ji Min Kim, Yong-Geun Jeong, Seung-Ki Kwok, Kyung Su Park, Sung-Hwan Park and Ho-Youn Kim College of Medicine, The Catholic University of Korea

**Objective:** STAT3, a signal transduction molecule of inflammatory cytokines such as IL-6, IL-21 and IL-23, plays an important role during the differentiation of CD4+ T cell into Th17 cells (Th17). Since Th17 is the pathogenic cell in autoimmune arthritis, STAT3 has also been suspected to be closely involved in the pathophysiology. This study aims to investigate the mechanism of rheumatoid arthritis (RA) related to the differentiation of Th17 and to identify the role of STAT3.

**Method:** Cytokine levels in the peripheral blood and synovial fluid of RA patients were measured with ELISA. Immunohistochemical staining of RA synovium was performed to investigate the relationship between synovitis and the expression of STAT3. CD4+ T cells, isolated from peripheral blood and synovial fluid of normal individuals and RA patients, were respectively stimulated with factors leading to Th17 differentiation (anti-CD3 1 µg/ml, anti-CD28 1 µg/ml, IL-23 5 ng/ml, TGF-β 2 ng/ml, IL-6 10 ng/ml, anti-IFN-γ 10 µg/ml, anti-IL-4 1 µg/ml) or regulatory T cells (Treg) differentiation (anti-CD3 1 µg/ml, anti-CD28 1 µg/ml, TGF-β 20 ng/ml, IL-2 5 ng/ml), as known. STAT3 siRNA was transfected to CD4+ T cells during the differentiation of Th17 cells, which was followed by FACS, RT-PCR and ELISA analyses in order to investigate the impact of STAT3 in Th17 and Treg differentiation.

**Result:** IL-6, a Th17 related cytokine, was significantly increased in RA synovium (P<0.01). The number of Th17 cells in the synovial tissue was significantly higher in RA patients than in normal population. STAT3 and p72S/STAT3 expression were significantly increased in RA synovium, and their expressions were positively related to the severity of synovitis such as infiltration of inflammatory cells and synovial proliferation (r=0.68, P<0.05). When STAT3 siRNA was transfected to the CD4+ T cell differentiation in normal individuals, IL-17 and IL-22 expressions and Th17 population decreased, whereas TGF-β expression and Treg population increased (P<0.05). In contrast to the STAT3 inhibition, when STAT3, the transcription factor for Treg, was inhibited, the number of Th17 was increased and that of Treg was decreased (P<0.05). Similar findings were observed in the CD4+ T cells isolated from peripheral blood of RA patients. Notably, T cells from RA synovial fluid were significantly decreased in differentiating into Th17 (RAF 0.2% < RAPB 0.5% < HCPB 0.7%, P<0.05) while increasing the proportion of Treg (RAF 20% > RAPB 10%, HCPB 11%, P<0.05).

**Conclusion:** The downstream signaling of STAT3 plays a critical role in CD4+ T cell differentiating into Th17 as well as Treg. Inhibition of STAT3 in CD4+ T cells of RA synovium effectively attenuated the differentiation of Th17. By simultaneously achieving Th17 inhibition and Treg stimulation, the regulation of STAT3 promises a novel strategy for RA treatment.

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TNFα-Driven IL-32 Expression in Rheumatoid Arthritis Synovial Tissue Amplifies an Inflammatory Cascade. Bas Heinhaus1, Marije I. Koenders2, Piet L. van Riel3, Charles A. Dinarello4, Mihai G. Netea1, Wim B. van den Berg3 and Leo A. B. Joosten1.

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**Statement of Purpose:** To investigate the interplay between IL-32 and TNFα in chronic inflamed synovial tissue and to assess whether anti-TNFα treatment of RA patients modulates synovial IL-32 expression.

**Methods:** To study the interplay between IL-32 and TNFα, we first investigated the induction of IL-32γ by TNFα stimulation in human synovial fibroblasts donated by arthritis patients and compared it with other stimuli such as TLR ligands or IL-1β. Second, we investigated the production of TNFα through intracellular overexpression of IL-32γ in folic acid treated human synovial fibroblasts and subsequently IL-6 and CXCL8 levels were determined. Fourth, overexpression of intracellular IL-32γ using an adenovirus expressing human IL-32γ followed by TNFα stimulation was done in synovial fibroblasts to investigate induction of proinflammatory cytokines. Fifth, modulation of TNFα mRNA stability was investigated in human THP1 cells transfected with an adenoviral vector expressing human IL-32γ. IL-1β, IL-6, and CXCL8 mRNA stability was determined. Finally, immunohistochemistry was applied to study IL-32 expression in synovial biopsies from RA patients.

**Summary of the Results:** Synovial fibroblasts stimulated with TNFα showed potent induction of IL-32γ expression when compared to IL-1β, TLR ligands or medium. Moreover, TNFα induced IL-32γ expression is specific since IL-1β stimulation induced primarily IL-6 and CXCL8. Of high interest, overexpression of intracellular IL-32γ in human THP1 cells followed by TNFα exposure resulted in significant production of TNFα, IL-1β, IL-6, and CXCL8. Furthermore, silencing of endogenous IL-32γ showed potent down-regulation of IL-6 and CXCL8 whereas overexpression of IL-32γ resulted in enhanced production of IL-6 and CXCL8 in human synovial fibroblasts. To investigate the mechanism how IL-32γ is capable of amplifying the inflammatory cascade resulting in a self perpetuating loop between IL-32γ and TNFα, we studied mRNA stability. Enhanced expression of intracellular IL-32γ resulted in delayed TNFα, IL-1β, and CXCL8 mRNA decay. In contrast, IL-6 mRNA stability was not regulated by IL-32γ. Of high interest, treatment of RA patients with anti-TNFα resulted in significant reduction of IL-32 protein expression in synovial tissue.

**Conclusions:** TNFα is a potent specific inducer of endogenous IL-32 expression and IL-32 itself contributes to a prolonged TNFα production. This results in a self perpetuating loop between IL-32γ and TNFα resulting in potent induction of several proinflammatory cytokines and chemokines. This auto-inflammatory loop can potentially be intervened by silencing IL-32 or anti-TNFα treatment. Targeting IL-32 might be a novel therapy to counteract the auto-inflammatory cascade of TNFα-IL-32-TNFα present in chronic inflamed synovial tissue of RA patients.

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Underexpression of TIM-3 and Blunted Galectin-9-Induced Apoptosis of CD4+ T Cells in Rheumatoid Arthritis. Jaepoon Lee1, Ji-Min Oh6, Ji Won Hwang2, Eun-Jung Park2, Eun-Kyung Bae1, Joong Kyong Ahn1, Yoo Sun Lee2, Eun-Mi Koh1 and Hoon-Suk Cha1. 1Kangbok Samsung Hospital, Sungkyunkwan University School of Medicine, 2Masan Samsung Hospital, Sungkyunkwan University School of Medicine, 3Samsung Biomedical Research Institute, 4Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of, 5Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of, 6Samsung Medical Center, Sungkyunkwan University School of Medicine

Purpose: T cell immunoglobulin- and mucin-domain-containing molecule-3 (TIM-3) is a novel transmembrane protein involved in the negative regulation of Th1 cell-mediated immunity by interacting with its ligand galectin-9. Galectin-9 has been shown to induce apoptosis of TIM-3 expressing Th1 cells in vitro and in vivo. We have previously demonstrated that, in rheumatoid arthritis (RA) patients, TIM-3 is expressed in the synovial tissues and that TIM-3 mRNA expression in the peripheral mononuclear cells is inversely correlated with disease activity as measured by DAS28. We have previously demonstrated that CD4+ T cells expressing Th1 cells in vitro and in vivo. We have previously demonstrated that TIM-3 mRNA expression in the peripheral mononuclear cells is inversely correlated with disease activity as measured by DAS28. We hypothesize that galectin-9 induced apoptosis of Th1 cells in RA is impaired because of aberrantly low TIM-3 expression which may lead to augmented Th1 response. This study was therefore undertaken to investigate the expression of TIM-3 from CD4+ T cells and galectin-9-mediated apoptosis of CD4+ T cells from RA patients and healthy controls.

Methods: CD4+ T cells from RA patients and healthy controls were isolated from peripheral blood mononuclear cells and then were activated. The expression of TIM-3 mRNA in CD4+ T cells was measured using real-time PCR. After CD4+ T cells were activated in the presence of graded doses of galectin-9 or control, galectin-9 induced cytotoxicity and apoptotic activity of CD4+ T cells were analyzed using MTT assays and annexin V staining, respectively.

Results: TIM-3 mRNA expression was significantly lower in CD4+ T cells from RA patients compared to those in healthy controls (p=0.026). CD4+ T cell survival as measured by MTT assay when incubated with galectin-9 (15nM) was significantly higher in RA patients than in healthy controls (p=0.002). The increased survival trend of CD4+ T cells from RA patients was maintained at higher dose of galectin-9 (50nM), but did not reach statistical significance (p=0.078). Apoptotic activity of CD4+ cells from healthy controls as measured by annexin V staining increased with graded doses of galectin-9 (0nM vs. 30nM, 0nM vs. 90nM, p=0.016 each). However, apoptotic activity of CD4+ T cells from RA patients did not change despite the stimulation with galectin-9.

Conclusion: Galectin-9-mediated apoptosis of CD4+ T cells is dysfunctional in RA patients. Blunted galectin-9-mediated apoptosis may be exerted through underexpression of TIM-3 that negatively regulates Th1 response. Our data suggest that TIM-3 and its interaction with galectin-9 may play an important role in the pathogenesis of RA and may represent a potential therapeutic target.

Disclosure: J. Lee: None; J.-M. Oh: None; J. W. Hwang: None; E.-J. Park: None; E.-K. Bae: None; J. K. Ahn: None; Y. S. Lee: None; E.-M. Koh: None; H.-S. Cha: None.

ACR Poster Session A
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Safety, Non-Biologic DMARDs, Switching Biologics I

Monday, November 8, 2010, 9:00 AM–6:00 PM

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Appearance of Non-Rheumatoid Arthralgia after Tocilizumab Treatment in RA Patients with High Disease Activity. Osamu Saiki1 and Hiroshi Uda1. 1Sakai Onshinkai Hospital, Sakai, Japan, 2Shiraishi Hospital, Imabari, Japan

Purpose: Tocilizumab, IL-6 receptor antagonist, is one of essential biologics to treat RA patients and several side reactions have been reported, but appearance of non-rheumatoid arthralgia after tocilizumab injection has not been discussed. We experienced several RA patients who developed additional non-rheumatoid somatic arthralgia after tocilizumab treatment. We conducted this study to examine which patients develop non-rheumatoid arthralgia and to clarify how the pain is appeared and how we should take care of these patients.

Patients and Method: We treated RA patients with tocilizumab who had not responded to MTX and/or TNF inhibitors. When we treated RA patients with tocilizumab, we examined CRP and other blood tests in addition to clinical symptoms. Serum levels of IL-6 and TNF-α were also examined before and after tocilizumab treatment.

Results: Sixty-eight RA patients were treated with 8mg/kg tocilizumab every 4 week. Among 68 RA patients, 25 patients developed non-rheumatoid arthralgia. They suffered from severe pains of large joints such as shoulder pain and lumbar, and the quality and the site of pain was quite different from those of RA. The pain started one day after receiving tocilizumab injection and lasted for one week or longer. The magnitude of pain reduced time by time. When the non-rheumatoid arthralgia was appeared, the levels of CRP had dropped down from high levels (more than 50 mg/L) to low levels (under 5mg/L). In the patients experienced non-rheumatoid arthralgia, the serum CRP levels before tocilizumab therapy were significantly higher (113±57 mg/L) than those in patients without non-rheumatoid arthralgia (31±18 mg/L) and the serum levels of IL-6 were very high at 28 days after first tocilizumab treatment and they were significantly higher than in those without non-rheumatoid arthralgia. But the serum levels of high sensitive TNF-α were less than 2.8 pg/mL in both patients.

Conclusion: In tocilizumab treatment, RA patients with high disease activity develop non-rheumatoid arthralgia more frequently than those with low disease activity. In the patients who developed non-rheumatoid arthralgia, the levels of IL-6 but not CRP or TNF-α were selectively high suggesting that the pain would preferentially relate to IL-6 rather than CRP or TNF-α. The elevation of IL-6 levels is due to blocking of IL-6R σ chain by tocilizumab treatment. However, the relationships between appearance of non-rheumatoid arthralgia and the high levels of IL-6 were remained to uncertain.

Disclosure: O. Saiki: None; H. Uda: None.

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Are Venous Thrombotic Events (VTE) Increased in Patients with Rheumatoid Arthritis (RA) Treated with Anti-TNF Therapy? Results from the British Society for Rheumatology Biologics Register (BSRBR). Rebecca Davies, James Galloway, Kath D. Watson, Mark Lunt, BSRBR Control Centre Consortium, Deborah P. M. Symmons, Kimme L. Hyrich and on Behalf of the British Society for Rheumatology Biologics Register. University of Manchester

Background: Case reports have shown that TNF decreases platelet activation and inhibits thrombus formation, and so blocking TNF may contribute to thrombus formation. Research looking at the role of such therapies on venous thrombotic events (VTE) in RA patients has produced conflicting results with more recent studies documenting an increased risk, particularly in post-operative surgery patients. The aims of this analysis were (1) to compare rates of VTE in RA patients treated with anti-TNF vs. non-biologic disease modifying anti-rheumatic drugs (nbDMARDs) alone and (2) to compare the rates between each individual anti-TNF and nbDMARDs.

Methods: To 31/10/2009, 11,881 anti-TNF and 3,673 biologic-naive nbDMARD control patients had been recruited to the BSRBR, a UK national register of active RA patients on biologic therapy. All patients were followed by regular hospital and patient questionnaires. This on-drug analysis, limited to first biologic only, followed all patients until first VTE (defined as deep venous thrombosis or pulmonary embolism), death, treatment discontinuation or last follow-up date, whichever came first. Cox proportional hazards models were used to compare rates of VTE between cohorts. Inverse probability of treatment weighting (IPTW) was used to adjust for the confounding effect of baseline differences between groups, including age, gender, diabetes, steroid use, smoking, BMI, hypertension, disease duration, severity and year of entry into the study. Surgery was entered into the model as a time-varying covariate, with patients viewed as being at increased risk for 90 days post-procedure. Missing baseline data were accounted for using multiple imputation.

Results: The anti-TNF cohort was younger (mean 56 v 60 years), had a higher proportion of females (76 v 72%) and more severe disease (mean DAS28/HAQ: anti-TNF 6.6/2.0, nbDMARD 5.1/1.5). The median duration of follow up was 4.3 years (IQR 2.9, 5.4) in the anti-TNF cohort, and 3.0 years (IQR 1.7, 4.2) in the nbDMARD cohort.

A total of 204 first VTE’s were reported (160 anti-TNF, 44 nbDMARD). 13% of anti-TNF and 7% of nbDMARD VTE events were reported within 90 days of hip or knee replacement. Overall there was no difference in the rate of VTE in the anti-TNF vs. nbDMARD cohort.

Disclosure: None.
of VTE between anti-TNF and nbDMARD treated patients (adjusted HR 0.9 (95% CI 0.5, 1.6)). The risk was similar across all anti-TNF agents.

**Conclusion:** Anti-TNF therapy is not associated with an increased risk of VTE in RA patients. There is also no difference in VTE risk between the anti-TNF drugs.

### Table: Patient characteristics and incidence of VTEs.

<table>
<thead>
<tr>
<th>nbDMARD</th>
<th>All anti-TNF</th>
<th>ETN**</th>
<th>INF**</th>
<th>ADA**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>3673</td>
<td>11881</td>
<td>4139</td>
<td>3475</td>
</tr>
<tr>
<td>Exposure (pyrs)</td>
<td>11418</td>
<td>32811</td>
<td>13684</td>
<td>9549</td>
</tr>
<tr>
<td>Surgery</td>
<td>1210</td>
<td>4370</td>
<td>1922</td>
<td>1243</td>
</tr>
<tr>
<td>Hip/knee replacement, n</td>
<td>545</td>
<td>2564</td>
<td>1129</td>
<td>750</td>
</tr>
<tr>
<td>All VTE events: n</td>
<td>44</td>
<td>160</td>
<td>55</td>
<td>67</td>
</tr>
<tr>
<td>VTE within 90 days of surgery, n (%)</td>
<td>5 (12)</td>
<td>34 (21)</td>
<td>10 (19)</td>
<td>17 (24)</td>
</tr>
<tr>
<td>VTE within 90 days hip/knee replacement, n (%)</td>
<td>3 (7)</td>
<td>20 (13)</td>
<td>6 (11)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>VTE incidence rate/1000 pyrs</td>
<td>3.9 [2.8, 5.2]</td>
<td>4.9 [4.2, 5.7]</td>
<td>4.0 [3.0, 5.2]</td>
<td>7.0 [5.4, 8.9]</td>
</tr>
<tr>
<td>VTE adjusted HR*</td>
<td>Ref</td>
<td>0.9 [0.5, 1.6]</td>
<td>0.6 [0.3, 1.2]</td>
<td>1.1 [0.6, 2.1]</td>
</tr>
</tbody>
</table>

*Adjusting for potential confounders was performed using an inverse probability of treatment weighted propensity model.

Including age, gender, diabetes, baseline steroid exposure, smoking, BMI, hypertension, surgery, disease duration, disease severity and year of entry into study.

**Disclosure:** R. Davies: None; J. Galloway: None; K. D. Watson: None; M. Lunt: None; BSRBR Control Centre Consortium: None; D. P. M. Symmons: None; K. L. Hyrich: None; on Behalf of the British Society for Rheumatology Biologics Register: None.

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**Assessment of Cardiovascular Markers after 24 Weeks of Abatacept or Rituximab Therapy in Patients with Rheumatoid Arthritis.** Sylvain Mathieu1, Gauthier Szymanski1, Jean-Jacques Dubost2, Natacha Mrozek3, Geoffrey Marceau2, Jean-Michel Ristori2 and Martin Soubrier4. 1Biochimie, INSERM; 2Hematologie, CHU Gabriel Montpied, Clermont-Ferrand, France, 3Hematologie, CHU Gabriel Montpied, Clermont-Ferrand, France, 2Montpellier University, 3Paris University, 4Tours University

**Background:** Increased incidence of cardiovascular disease has been observed in rheumatoid arthritis (RA). Several studies have attributed this excess cardiac risk to biological inflammation. Effective control of inflammation may be of benefit in reducing cardiovascular risk in RA patients.

**Objectives:** To investigate the effects of abatacept and rituximab treatment in active RA on markers of atherosclerosis: arterial stiffness measured by augmentation index (AIX) and pulse wave velocity (PWV), lipoproteins, pro-brain natriuretic peptide (pro-BNP) and soluble levels of Receptor for Advanced Glycation Endproducts (sRAGE).

**Methods:** PWV, AIX, clinical status, lipoproteins, systemic inflammation, pro-BNP and s-RAGE were assessed at baseline and after 24 weeks of abatacept and rituximab therapy.

**Results:** Thirty RA patients, including 27 women, with a mean age of 58.0 ± 11.6 years and a longstanding disease of about 11 years received rituximab therapy. Of these 30 patients, 90% had rheumatoid factor, 80% anti-CCP antibody and 93.3% were erosive. Nineteen patients had failed to respond to TNF alpha inhibitor treatments.

Seventeen RA patients (14 female), with a mean age of 60.6 ± 11.6 years and a longstanding disease of about 11 years received abatacept. Of these 17 patients, 47.1% had positive rheumatoid factors, 76.5% had positive anti-CCP antibody, and all were erosive.

Twelve patients were non-responders to TNF alpha inhibitor treatments and 7 (41.1%) to rituximab treatment.

1) **Arterial stiffness.** After abatacept treatment, no change was observed in PWV (8.6 ± 4.2 vs. 9.4 ± 3.1 m/s; p = 0.09) and AIX (29.9 ± 10.6 vs. 30.1 ± 9.3%; p = 0.98). With rituximab, an improvement in AIX was observed (AIX: 29.1 ± 8.0% vs. 31.7 ± 10.5%; p = 0.02) but not to a level of significance for PWV (7.9 ± 2.7 vs. 8.1 ± 3.4 m/s; p = 0.620).

2) **Lipoproteins and other cardiovascular risk markers.** After both treatments, a significant increase in the level of apolipoprotein A1 (apoA1) and a tendency to a decrease in the apolipoprotein B/apoA1 ratio were obtained. No change was found in levels of pro-BNP, sRAGE or apoB.

3) **Disease activity.** DAS28 ESR and DAS28 CRP were significantly improved after both rituximab and abatacept. We found a decrease in parameters of biological inflammation, significant after rituximab and not significant after abatacept.

### Conclusion

This study shows that arterial stiffness, occurring in RA, was not improved after 6 months of abatacept or rituximab therapy, nor pro-BNP and s-RAGE. However, the treatment did have a beneficial effect on lipid profile and so it would be interesting to have an assessment over a longer period, especially since abatacept and rituximab are not anticytokine therapies.

**Disclosure:** S. Mathieu: None; G. Szymanski: None; J.-J. Dubost: None; N. Mrozek: None; G. Marceau: None; J.-M. Ristori: None; M. Soubrier: None.

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**Before Beginning Anti-TNF, a Better Targeted Screening and a Twice Decrease Frequency of Latent Tuberculosis (TB) with IFN gamma Release Assays (IGRA) Compared with Tuberculin Skin Test.** Results in 396 Patients from the ETAT Study. Xavier Mariette1, Gabriel Baron2, Frédéric Liétot3, Philippe Goupille4, René-Marc Filipo1, Bernard Combe2, Florence Tubach1, Dominique Emile1, Dominique Salmon1, Marc Lemain1, Guislaine Carelman3 and Philippe Ravaud3. 1Lille University, 2Montpellier University, 3Paris University, 4Tours University

**Background:** In spite of screening for latent tuberculosis (TB) with tuberculin skin test (TST), reactivation of TB remains a non rare severe complication in patients treated with TNF blockers, mainly with monoclonal antibodies. Great hope came from a more efficient screening of latent TB with specific IFN gamma release assays (IGRA).

**Objective:** To compare TST and 2 IGRA in a large cohort of patients with different immune mediated inflammatory diseases (IMID) before introduction of anti-TNF.

**Methods:** 396 patients with IMID were screened for latent TB with TST and with 2 IGRA, Quantiferon Gold and T-SPOT TB, before beginning anti-TNF. 126 patients (32%) had rheumatoid arthritis, 178 (45%) had spondyloarthritis and 92 (23%) had Crohn’s disease. 238 patients (60%) received an immunosuppressive treatment and 144 (36%) received steroids.

**Results:** 138 patients (35%) had positive skin test (>5mm) and 66 (17%) had positive IGRA (either Quantiferon Gold or T-SPOT TB), <p = 0.0001. Interestingly, 122 patients (31%) had discordant results between TST and IGRA, 97 (25%) with positive TST and negative IGRA and 25 (6%) with negative TST but positive IGRA. The discordant results in the different diseases are indicated in the table.

**Proportion of positive results was higher for T-SPOT TB than with Quantiferon Gold: 59/396 (15%) versus 39/396 (10%), p = 0.0006. Concordance between the 2 IGRA tests was good: 91% [88–94], kappα = 0.61 [0.49–0.73].**

In multivariate analysis, the factors influencing positivity of IGRA (one or the other) were to be born in a TB endemic area (OR = 2.9 [1.5–5.7]) and not to be vaccinated with BCG (OR = 3.7 [1.3–10.8]).

The number of indeterminate results was greater with TST than with Quantiferon Gold: 29/396 (7.3%) versus 1/1396 (0.2%), p = 0.002. Among the 29 indeterminate tests with T-SPOT TB, 25 were negative with Quantiferon Gold, 3 were positive and 1 was indeterminate. Among the 11 indeterminate tests with Quantiferon Gold, 8 were negative with T-SPOT TB, 0 were positive and 3 were indeterminate. No factor influences an indeterminate result of IGRA, and in particular neither steroid use nor immunosuppressant use.

All the patients were treated with antibiotics depending of the IGRA tests. In SpA and CD, the number of indeterminate tests was greater with TST than with IGRA.

**Conclusion:** In this large series of almost 400 patients assessed for latent TB with specific IFN gamma release assays (IGRA).
the sensitivity and the specificity of each of the tests will have to be assessed in the sub-group of patients with certain latent TB on clinico-radiological arguments independently of the results of the tests.

Disclosure: X. Mariette: None; G. Baron: None; F. Liote: None; P. Goupille: None; R.-M. Filpo: None; B. Comber: None; F. Tubach: None; D. Emilié: None; D. Salmon: None; M. Leman: None; G. Carrelain: None; P. Ravaud: None.

Better Results Are Achieved with Switching Directly to Biotherapeutics Than Switching Via DMARD Combinations in RA Patients Who Have Failed Methotrexate as Their Initial DMARD: Real-Life Data from NOR-DMARD.

**EULAR good resp. 37.8% 20.9% 29.4% 0.05 0.54**

Background: Combination of methotrexate (MTX) with an anti-TNF agent is generally considered more effective than combinations with synthetic DMARDs in RA pts who have failed MTX. Many countries require use of at least two DMARDs before start of a biologic agent and the relative benefit of these different strategies in real life is not clarified. The objective of this study was to examine the value of switching via MTX+DMARD combinations vs switching directly to MTX+anti-TNF after failing MTX mono.

Methods: The NOR-DMARD registry includes pts >18 yrs of age with inflammatory arthropathies starting treatment with DMARDs or biologics in 5 centres. Pts are consecutively included and followed longitudinally. For the current analyses we included RA pts with <5 yrs disease duration who had failed on MTX (but no other DMARDs), and who were started on MTX+anti-TNF (group I) or MTX+DMARDs (group IIa). From group Ila we identified a subgroup of pts who received MTX+anti-TNF after failure of the MTX+DMARD combination (i.e. failed ≥2 DMARDs) (group IIb). We compared effectiveness and disease states between group I and group IIa and between group I and group IIb. Survival analyses (Kaplan-Meier) were based on 1- and 2-y data.

Results: Group I included 85 pts (37 etan, 25 infliximab, 23 adalimumab) and group Ila 125 pts (56 MTX+sulfasalazine, 43 triple, 24 MTX+antimalarials, 2 MTX+leflunomide). In groups Ila 73%/70% were RF pos (p=0.60), 61%/69% were female (p=0.25), mean age was 50/53 yrs (p=0.15), median(IQR) disease duration was 1.20/2.33/1.10/5.18 yrs (p=0.24). Baseline disease activity was similar (mean DAS28 4.94/4.97, MHAQ 0.79/0.79, SF6D 0.57/0.58, all differences N.S.). 6-month disease activity states and responses were better for group I vs group Ila (table). 1- and 2-y drug survival were superior for group I vs group IIa (p=0.001/0.001). 31 of the 125 pts who received MTX+DMARDs were later started on secondary MTX+anti-TNF (group IIb; 11 etan, 12 inflix, 8 ada). These pts (68%/female, 81%/RF pos) were at baseline not significantly different from the remaining pts in group Ila. At start of MTX+anti-TNF mean DAS28/MHAQ/SF6D were 5.46/0.74/0.59. On average group IIb pts reached mean DAS28/MHAQ/SF6D were 5.46/0.74/0.59. On average group IIb pts reached 37.8%/20.9%/29.4% 0.05 0.54

Conclusions: In these pts who were MTX failures, MTX+anti-TNF was superior to MTX+DMARDs in terms of disease states reached, response and remission rates, and retention to therapy. Furthermore, the subgroup of pts receiving MTX+anti-TNF after failing the MTX+DMARD combination reached less favourable disease activity states and a lower remission rate than pts receiving MTX+anti-TNF after having failed MTX only. These data may suggest that delayed initiation of TNF inhibitor can reduce the achieved clinical benefit.

Disclosure: E. Lie: Abbott Laboratories, 5, Bristol-Myers Squibb, 8, Roche, 5; T. Uhlig: None; K. Mikkelsen: None; S. Kalstad: None; E. Rødevand: None; C. Kaufmann: None; T. K. Kvien: Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Merck Pharmaceuticals, 5, Pfizer Inc, 5, Roche, 5, UCB, Inc., 5, Wyeth Pharmaceuticals, 5.

**Purpose:** Tocilizumab (TCZ) is a fully humanized monoclonal antibody that targets interleukin-6-receptor signal transduction. Efficacy and safety of TCZ in patients with RA who have been demonstrated in 7 phase 3 studies. The objective of this analysis was to assess the effects of TCZ on laboratory parameters in patients with RA using pooled data from clinical trials (OPTION, TOWARD, RADIATE, AMBITION, and LITHE) and ongoing long-term extension studies.

Methods: This was a pooled analysis of patients who received ≥1 TCZ dose (in OPTION, TOWARD, RADIATE, AMBITION, LITHE, GROWTH195, and GROWTH96) from initial exposure through August 2009. Data were examined using descriptive statistics.

Results: A total of 4009 patients received TCZ with a median (mean) treatment duration of 3.1 (2.7) years and a total observation time of 10,994 patient-years (PY). Mean CRP levels decreased from 2.43 mg/dL at baseline to 0.17 mg/dL at first assessment (week 2) and have remained at or near normal levels (0.13 mg/dL at week 192). Mean ESR decreased from 46 mm/h at baseline to 17 mm/h at week 2 and to 8 mm/h at week 192. Mean hemoglobin (Hb) levels were increased from 13.4±0.3 g/L at baseline to 143.0±14.6 g/L at week 6 and to 149.0±14.2 g/L at week 192. Clinically significant decreases in neutrophil counts occurred in 4.5% (grade 3; ANC = 0.5–<1.0×10^9/L) and 0.7% (grade 4; ANC = <0.5×10^9/L) of patients, and there was no apparent correlation between decreased neutrophil counts and serious infections. Continued exposure to TCZ was not associated with increased incidences of CTC grade 3/4 decreases in neutrophil counts. A decrease in platelet counts to ≥25 to <50×10^9/L occurred in 0.4% of patients and to <25×10^9/L in 0.5% of patients. There was no apparent correlation between decreased platelet count and serious bleeding event. Increased ALT/AST levels from normal at baseline to >3×ULN and ≥3×ULN occurred in 7.9%/2.7% and 10.3%/3.3% of patients. Most transaminase elevations >3×ULN were single, transient occurrences. An increase in LDL from <130 mg/dL at baseline to ≥130 mg/dL at last observation was reported in 22.6% (63/279) of patients who were receiving lipid-lowering medication and in 37.4% (761/2033) of patients who were not receiving lipid-lowering medication. Lipid profile changes were not associated with increased cardiovascular events over a median duration of 3.1 (range, 0–4.6) years.

Conclusions: Treatment with TCZ led to marked improvements in CRP levels and ESR as early as week 2. Among patients with increases in lipid levels, hepatic transaminases, neutrophil counts, or platelet counts, no clear increase in associated clinical events was noted; this could have been a result of monitoring and treatment adjustments that occurred in this longitudinal study. Regular monitoring of these parameters should be employed during routine use of TCZ in patients with RA.

Disclosure: W. Rigby: Genentech, a member of the Roche Group, 5, 8, Roche, 2; D. E. Furst: Abbott Laboratories, 2, 5, 9, 9, Axiom Pharmaceuticals US, 2, 5, 8, 9, Amgen Inc., 5, 9, Biogen Idec, 5, 9, Bristol-Myers Squibb, 2, 5, 9, Centocor, Inc., 5, 9, Corrona, 3, Genentech and Biogen IDEC Inc, 2, 5, 9, Gilead Sci; W. Rizzuto: None; A. Balbir-Gurman: Abbott Laboratories, 9, Roche, 9, Schering-Plough, 9; M. Zilberstein: Roche, 3; E. Vernon: Roche, 3; J. M. Kremer: Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, Bristol-Myers Squibb, 2, 5, Centocor, Inc., 2, 5, Genentech and Biogen IDEC Inc, 2, 5, Pfizer Inc, 2, 5, Roche, 2, 5, UCB, Inc., 5; A. Rubbert-Roth: Abbott Laboratories, 5, Chugai, 5, Essex, 5, Roche, 5, 8, UCB, Inc., 5, Wyeth Pharmaceuticals, 2, 5; R. F. van Vollenhoven: Roche, 2, 5.
Background: As new biologic agents have become available, the impact of having additional options on the decision to switch is unclear. We evaluated factors associated with switching biologic medication regimen in a large U.S. registry of rheumatoid arthritis (RA) patients.

Methods: Using CORRONA data through 12/31/2009, eligible patients had RA newly treated with an anti-TNF agent with ≥ 6 months of follow-up. The outcome was discontinuing or switching to a different biologic within one year due to inadequate efficacy. Individuals switching for other reasons were excluded.

Factors associated with switching for lack of efficacy were evaluated using logistic regression, with a focus on CDAI and calendar year. Clustering at the physician level was estimated using random effects. We tested the hypotheses that switching would be more likely as new biologics were available over time after controlling for disease activity, and that physician preference for switching would be significant even after adjustment.

Results: Among 3,351 patients initiating an anti-TNF medication, 1,328 were eligible for analysis. Baseline characteristics were mean ± SD 46.2 years, 80% women, 90% RF+, mean RA duration 9.5 ± 9.2 years, mean CDAI 21.9 ± 14.5, mean MD global 34 ± 22, mean DAS28 4.5 ± 15, 37% steroids, 62% 1st biologic, 30% 2nd biologic, 8% 3rd biologic. Among these, 125 switched their biologic regimen for lack of efficacy; 44 (35%) switched within 6 months. Numerous factors were different among patients who switched versus those persistent: CDAI (22.4 vs. 12.5, p < 0.001), change in CDAI (−2.7 vs. −9.7, p = 0.002), MD global (−7.6 vs. −14.4, p = 0.04), change in swollen joints (−0.1 vs. −5.3, p = 0.001), change in patient global (0.1 vs. −11.8, p = 0.008). As shown (Table), calendar year was associated with switching even after controlling for disease activity. Patients with moderate disease activity (CDAI 10–21) were even more likely than low or high disease activity to be switched over time (p value for interaction between moderate disease activity × calendar year = 0.03). There was a small but significant effect of clustering by physician in the decision to switch for lack of efficacy (OR = 1.2, 95% CI 1.1–6.6).

Factors Associated with RA Patients Switching Their Biologic Medication Regimen for Lack of Efficacy

<table>
<thead>
<tr>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Disease Activity Index (CDAI)</strong></td>
</tr>
<tr>
<td>&lt;10 (referent)</td>
</tr>
<tr>
<td>10–21</td>
</tr>
<tr>
<td>&gt;22</td>
</tr>
<tr>
<td><strong>Change in CDAI</strong></td>
</tr>
<tr>
<td>&gt;10 unit improvement (referent)</td>
</tr>
<tr>
<td>Improvement between 1 and 10 units</td>
</tr>
<tr>
<td>No improvement, or worsening</td>
</tr>
<tr>
<td><strong>Calendar Year</strong></td>
</tr>
<tr>
<td>2002–2005 (referent)</td>
</tr>
<tr>
<td>2006–2007</td>
</tr>
<tr>
<td>2008–2009</td>
</tr>
<tr>
<td><strong>Number of prior biologics used</strong></td>
</tr>
<tr>
<td>1 (referent)</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

Conclusion: The availability of new biologic agents in recent years has increased the likelihood of switching for reasons of lack of efficacy, especially for patients with moderate disease activity, and after controlling for clinical response. Physician preference was also significantly associated with the decision to switch. The future availability of new agents will likely further motivate medication switching.

Disclosure: J. R. Curtis: Amgen Inc., 2, Centocor, Inc., 2, 5, Corrona, 2, 5, Corrona, 8, UCB, Inc., 2, 5, 8, Y. Shan: None; J. M. Kremer: Corrona, 1; J. D. Greenberg: Corrona, 9; G. Reed: Corrona, 5.
antibodies against infliximab in patients with RA during treatment with infliximab, and to determine if development of such antibodies was associated with withdrawal due to early ADR and/or treatment failure.

Methods: Between October 1999 and August 2008 serum samples were collected from 218 Danish patients with RA (80% females, median age = 56 years, disease duration = 10.1 years, 65% RF positive, median DAS28(CRP) = 5.0 (IQR = 4.2–5.9)) who initiated treatment with infliximab according to national guidelines. The levels of anti-infliximab antibodies (AB) were determined pre-infusion at baseline (week 0), weeks 6 and 14 (or at withdrawal) by the IMPACT Indirect Assay (Roche Diagnostics). Based on 100 blood donors and all 218 baseline samples, a preliminary cutoff for the assay was defined. A sample was considered positive (AB+) if the signal was at least two fold above the highest signal seen in any blood donor or baseline sample, otherwise as negative (AB-).

Clinical assessments were performed at weeks 0, 2, 6, and then every 8th week until termination of treatment. Clinical evaluation (including tender and swollen joint counts (28 joints), CRP, DAS28(CRP) score, and reason for withdrawal) was obtained from the DANBIO Registry. ADR was defined as any adverse event leading to withdrawal of infliximab treatment. Lack of efficacy (LOE) was defined as withdrawal due to high disease activity despite adequate treatment.

Results: In total 28 (13%) patients withdrew due to ADR before week 50 and 46 (21%) due to LOE (median DAS28 4.9 (IQR = 4.35 – 5.65)). Among patients withdrawn due to ADR, 18 withdrew due to infusion reactions. At week 6, 31 patients were AB+, and 15 (48%) of those withdrew due to ADR before week 50. Only 12 (13%) of the 94 AB- patients at week 6 withdrew due to ADR before week 50. Compared to AB- patients, the AB+ patients had a HR of ADR of 5.06 at week 6 (p=0.0001), see Table. Patients who withdrew due to infusion reaction were primarily AB+ at week 6 (n=15; 83%). After 14 weeks of treatment, 43 patients were AB+ and 16 (37%) of those withdrew due to ADR before week 50. Compared to AB- patients, the AB+ patients had a HR of ADR of 3.50 at week 14 (p=0.0009), see Table. There was no association between development of AB at week 6 and 14 and withdrawal due to LOE, see Table.

Reason for withdrawal

<table>
<thead>
<tr>
<th>ADR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>31/15 vs. 94/12*</td>
</tr>
<tr>
<td>5.06 (2.36–10.84)</td>
<td>1.70 (0.85–3.38)</td>
</tr>
<tr>
<td>p &lt; 0.0001*</td>
<td>p = 0.13#</td>
</tr>
<tr>
<td>Week 14</td>
<td>43/16 vs. 88/12*</td>
</tr>
<tr>
<td>3.30 (1.56–6.99)</td>
<td>1.17 (0.62–2.29)</td>
</tr>
<tr>
<td>p = 0.0009*</td>
<td>p = 0.63#</td>
</tr>
</tbody>
</table>

*: Number of AB+/withdrawals vs. AB-/withdrawals
#: Hazard Ratio (95% CI), p-value

Conclusions: Early development of antibodies against infliximab predicted withdrawal due to adverse drug reactions in patients with RA within the first year of infliximab treatment. The findings suggest that anti-infliximab antibody measurement 6 weeks after start of treatment represents a promising approach to identify which RA patients that are at increased risk of developing adverse drug reactions.

Disclosure: S. B. Krüttel: None; V. P. Gruner: Roche Diagnostics, 3; M. L. Helfand: Abbott Immunology Pharmaceuticals, 2, Centocor, Inc., 2, Roche, 2, Schering-Plough, 2, UCB, Inc., 2, Wyeth Pharmaceuticals, 2; J. S. Johansen: None; M. Rothfuss: Roche Diagnostics, 3; U. Klaus: Roche Diagnostics, 3.

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Effect of Switching Anti–Tumor Necrosis Factor Agents on Clinical Outcomes for Patients with Rheumatoid Arthritis. Amir Goran1, Sanjey Roy1, Marco DiBonaventura1, Jochen Ertl1 and Mary Cifaldi1.1Abbott Laboratories, Abbott Park, IL, 2Kantar Health (contractor for Abbott), 3.

Background and Purpose: Tumor necrosis factor antagonists (anti-TNF) treatments have led to better management of rheumatoid arthritis (RA), and their efficacy is well-established for patients who have failed disease-modifying antirheumatic drugs (DMARDs). The utility of switching to a second anti-TNF agent, after the first fails, is therefore a topic of immense clinical interest. We assessed outcomes of switching from 1 anti-TNF agent to another on a range of clinical measures.

Methods: Data were extracted from medical charts of patients with RA who were treated with an anti-TNF agent and then switched to a second biologic DMARD by rheumatologists in the United States. Outcomes frequently used in clinical practice were assessed: swollen and tender joint counts (SJC and TJC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and physician-reported severity. Mixed models assessed improvements over time, from initiation to discontinuation of the first and then the second anti-TNF agent, controlling for age, sex, time on and between treatments, years since diagnosis, comorbid use of methotrexate, psychiatric comorbidity, and Charlson Comorbidity Index. Subgroups were also analyzed by reason for switching in the following order: lack of/inadequate response to the first agent, side effects/tolerability issues, or other reasons (eg, compliance or cost).

Results: Data were analyzed for 399 patients with RA who switched to a second biologic agent after a mean (SD) of 1.6 (1.7) years on the first therapy. Of 215 who switched to a second anti-TNF agent, 148 switched for lack of/inadequate response, 31 for intolerability, and 36 for other reasons. Mean age was 51.3 years, mean RA duration was 6.5 years, 71.2% were women, and 80.9% were white. After failure on the first anti-TNF agent, patients treated with a second anti-TNF agent for a mean (SD) of 1.3 (1.6) years achieved overall improvements of 65.6%, 69.5%, and 25.5% for TJC, SJC, and severity, respectively (all p<0.001); improvements were significantly greater with the second anti-TNF agent compared with the first. CRP (54.2%) and ESR (46.5%) showed similar overall improvements (both p<0.001), but there was no difference before and after switching to the second anti-TNF agent. Continued improvement after switching anti-TNF therapies was observed for all patients, except for those who switched due to other reasons. For patients who switched due to inadequate response, significantly greater improvement on all measures was observed during therapy with the second anti-TNF agent compared with the first, whereas the intolerability group experienced steady and significant improvements on both the first and second anti-TNF agent.

Conclusions: For patients with RA who failed a first anti-TNF agent, including those who failed because of lack of response or tolerability issues, significant improvements on SJC, TJC, ESR, CRP, and disease severity were observed after switching to a second anti-TNF agent. Overall improvements were similar or better than those observed in most randomized, controlled trials of an anti-TNF agent as the first biologic therapy, thus demonstrating the value of switching to a second anti-TNF when the first fails.

Disclosure: A. Goran: Kantar Health (contractor for Abbott), 3; S. Roy: Abbott Laboratories, 1, 3; M. DiBonaventura: Kantar Health (contractor for Abbott), 3; J. Ertl: Kantar Health (contractor for Abbott), 3; M. Cifaldi: Abbott Laboratories, 1, 3.

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1Arthritis & Osteoporosis Consultants of the Carolinas, Charlotte, NC, 2Dartmouth Medical School, Lebanon, NH, 3Genentech Inc, San Francisco, CA, 4Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil, 5Rheumatic Disease Center, Glendale, WI, 6Roche, Welwyn Garden City, UK, 7Universitätsklinikum Würzburg, Würzburg, Germany, 8Université Montpellier, Montpellier, France.

Purpose: B-cell targeted therapy using anti-CD20 antibodies has demonstrated clinical benefit in patients (pts) with rheumatoid arthritis (RA). This phase III study investigated the efficacy and safety of ocrelizumab (OCR), a humanized anti-CD20 antibody, + methotrexate (MTX) vs MTX alone in pts with active RA who have had an inadequate response to MTX.

Methods: STAGE was a phase III, international, randomized, placebo-controlled, parallel-group study, consisting of a 48-wk double-blind PBO-controlled period and open-label extension. A total of 1015 pts with active RA (revised 1987 ACR criteria) with SJC ≥4, TJC ≥4, CRP ≥0.6 mg/dL, RF+ and/or anti-CCP+, and on stable MTX (7.5–25 mg/wk) were randomized (1:1:1) to PBO (n=324), OCR 200 mg × 2 (n=344), or OCR 500 mg × 2 (n=347). Pt baseline characteristics were generally well balanced between treatment groups (means: age 51 yr; SJC 17; TJC 27; CRP 2.4 mg/dL; DAS28 6.4; RA duration 7.4 yr). Two OCR/PBO courses (each consisting of 2 infusions given 14 days apart) were given at weeks 1/15 and wks 24/26, with methylprednisolone 100 mg iv as premedication. Co-primary endpoints were ACR20 response at wk 24 and at wk 48. Secondary endpoints included change in van der Heijde-modified total Sharp score (mTSS) and ACR50/70 responses at 24 and 48 wks. Pts were allowed to continue the same corticosteroid dose from baseline.

Results: Key efficacy and safety data are shown in Table 1.
Both OCR doses showed statistically significant improvements (vs PBO) in ACR20/50/70 at wks 24 and 48. At wk 48, both OCR doses showed statistically significant (p<0.0001) inhibition of progression of joint damage (PJD; change from baseline in mTSS) relative to PBO (85% and 100% inhibition for 200 mg and 500 mg, respectively). Frequency of AEs, serious AEs, and overall infections from baseline to wk14 or 24 were compared between the OCR 200 mg and OCR 500 mg grps. At wk 14, both doses were generally comparable. Both OCR doses showed inhibition of PJD. More SIEs were reported with OCR 500 mg compared with OCR 200 mg; 1 fungal esophagitis infection with OCR 500 mg). Four deaths were reported (1 rheumatoid vasculitis with PBO; 3 [1 respiratory failure, 1 sepsis, 1 myocardial infarction] with OCR 500 mg). All mothers who delivered to term had conception. Of 11 term deliveries, 10 were of healthy newborns (1 infant died of ARDS 3 days after emergency cesarean section for intrapartum fetomaternal hemorrhage due to placenta previa). All mothers who delivered to term had received TCZ 8 mg/kg; 9 had received concomitant MTX, and 2 had received TCZ monotherapy.

Disclosures: A. Rubbert-Roth: Abbott Immunology Pharmaceuticals, 5, Chugai, 5, Essex, 5, Roche, 5, 2, 8, UCBI, 5, Wyeth Pharmaceuticals, 5, P. M. Goupille: None; S. Moosavi: Roche, 3; A. Hou: Abbott Laboratories, 8, Coviden, 8, Pfizer Inc, 8, Picxara, 8.

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Golimumab and Cardiovascular Disease Markers in Inflammatory Arthritis.
P. M. Goupille1, Shahrzad Moosavi3 and Antony Hou2. 1Hopital Trousseau, Tours, France, 2Inland Rheumatology Clinical Trials, Upland, CA, 3Roche, Nutley, NJ, 4University of Cologne, Cologne, Germany

Purpose: TCZ, an IL-6 receptor inhibitor, reduces signs and symptoms of RA and inhibits joint damage progression in RA pts. Women of childbearing potential were required to use a reliable contraception method in TCZ clinical trials. However, pregnancies did occur during TCZ use in clinical studies. TCZ has an FDA label of pregnancy category C (no adequate and well-controlled studies in humans; should be used in pregnant women only if potential benefit justifies potential risk to fetus). The purpose of this analysis was to describe pregnancies and their outcomes in RA pts receiving TCZ in clinical studies.

Methods: The analysis included all pregnancies reported in RA pts who received TCZ in one phase 1 study, five phase 3 trials (OPTION, TOWARD, RADIATE, AMBITION, LITHE), and 2 ongoing open-label extension studies (GROWTH95/96). Pts received 1 dose of TCZ 10 mg/kg in the phase 1 study, TCZ 4 or 8 mg/kg Q4W in phase 3 trials, and TCZ 8 mg/kg Q4W in extensions. Cutoff date was August 28, 2009.

Results: A total of 4009 pts (10,994 pt-years) were included. Thirty-three pregnancies were reported in 32 pts, despite a requirement for contraceptive use. All pts who received TCZ received a medication-except 1 pt who received TCZ 4 mg/kg. Of 32 pts, 26 received TCZ + MTX and 6 received TCZ monotherapy or a concomitant DMARD other than MTX. Most of the 32 pts conceived while using a condom as a primary or secondary contraception method followed by hormonal contraceptive. Some pts used more than one method. Two patients did not use any contraceptive method. Pte at conception was 19 to 42 y; 10 were ≥35 y. In pts who continued their pregnancies, TCZ and MTX were stopped when the pregnancy was known. Thirteen of 33 pregnancies were therapeutically aborted, 7 (3 pts were ≥35 y) spontaneously aborted, and 11 resulted in term delivery. Outcome was unknown for 2 pregnancies (1 lost to follow-up; 1 outcome not confirmed). Of 7 spontaneous abortions, all occurred within ~2 months of conception; all pts received TCZ 8 mg/kg, and 5 received concomitant MTX at conception. Of 11 term deliveries, 10 were of healthy newborns (1 infant died of ARDS 3 days after emergency cesarean section for intrapartum fetomaternal hemorrhage due to placenta previa). All mothers who delivered to term had treated TCZ 8 mg/kg; 9 had received concomitant MTX, and 2 had received TCZ monotherapy.

Conclusions: The amount of clinical trial data about pregnancy outcomes in women exposed to TCZ during pregnancy is limited. The low number of cases and the high rate of therapeutic abortions, as well as concomitant medication use, limit the conclusions that can be drawn regarding the safety of TCZ during pregnancy. Physicians should be aware of the pregnancy information in local prescribing information and advise women of childbearing potential to use reliable methods of contraception before initiating treatment with TCZ. Hormonal contraceptives are substrates of CYP450, and the effect of TCZ on the reliability of hormonal contraceptives is being assessed in a separate clinical trial. A pregnancy registry is being established to assess pregnancy outcomes in women exposed to TCZ during pregnancy.

Disclosures: A. Rubbert-Roth: Abbott Immunology Pharmaceuticals, 5, Chugai, 5, Essex, 5, Roche, 5, 2, 8, UCBI, 5, Wyeth Pharmaceuticals, 5, P. M. Goupille: None; S. Moosavi: Roche, 3; A. Hou: Abbott Laboratories, 8, Coviden, 8, Pfizer Inc, 8, Picxara, 8.
**Conclusion:** This is the first demonstration of favorable changes in LDL subfractions with anti-TNF therapy. Despite increases in TC and LDL, atherogenic indices remained stable and CV-related inflammatory markers improved with GLM treatment. These findings are consistent with published epidemiologic data suggesting, a beneficial effect of anti-TNF agents on CV events. No significant changes in insulin sensitivity parameters were observed.

**Table.** Median or median % changes

<table>
<thead>
<tr>
<th>Lipid Markers (mg/dL)</th>
<th>PBO + MTX</th>
<th>GLM 50 + 100 mg Combined + MTX</th>
<th>Median % change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>105.8</td>
<td>108.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>194.0</td>
<td>199.0</td>
<td>1.0</td>
</tr>
<tr>
<td>HDL</td>
<td>61.0</td>
<td>59.0</td>
<td>0.0</td>
</tr>
<tr>
<td>T Chol/HDL</td>
<td>3.17</td>
<td>3.26</td>
<td>0.3</td>
</tr>
<tr>
<td>LDL</td>
<td>187.5</td>
<td>111.0</td>
<td>3.3</td>
</tr>
<tr>
<td>LDL subfractions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean LDL size (mM)</td>
<td>21.3</td>
<td>21.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Large LDLs (mM/L)</td>
<td>465.5</td>
<td>463.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Small LDLs (mM/L)</td>
<td>543.0</td>
<td>641.0</td>
<td>4.3</td>
</tr>
<tr>
<td>ApoA1/I</td>
<td>0.52</td>
<td>0.54</td>
<td>0.2</td>
</tr>
<tr>
<td>ApoB/A1</td>
<td>0.20</td>
<td>0.20</td>
<td>0.0</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>194.0</td>
<td>199.0</td>
<td>1.0</td>
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<tr>
<td>HDL</td>
<td>61.0</td>
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<td>ApoA1/I</td>
<td>0.52</td>
<td>0.54</td>
<td>0.2</td>
</tr>
<tr>
<td>ApoB/A1</td>
<td>0.20</td>
<td>0.20</td>
<td>0.0</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6</td>
<td>5.6</td>
<td>0.0</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.6</td>
<td>1.8</td>
<td>0.2</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.15</td>
<td>0.15</td>
<td>0.1</td>
</tr>
</tbody>
</table>


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Golimumab and Cardiovascular Disease: Carotid Artery Ultrasound Evaluation and Cardiovascular Adverse Events. Joan M. Bathon¹, Mary Chester Wasco², Bruce Kirkham³, Pierre-Jean Touboul⁴, Elizabeth C. Hsi⁵, Weichun Xu⁶, Jiandong Lu⁷ and Mahboob U. Rahman⁸. ¹Centorcor Research and Development, Inc., 2Centorcor Research and Development, Inc., 3Centorcor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, 4Guy’s & St Thomas’ Hospital, London, United Kingdom, 5Johns Hopkins University, Baltimore, MD, 6Paris-Diderot University, London, United Kingdom, 7University of Pittsburgh, Pittsburgh, PA

**Objective:** To evaluate the effect of golimumab on changes in ultrasound measurements of carotid arteries in an exploratory study of patients with rheumatoid arthritis (RA), and to evaluate cardiovascular (CV) adverse events (AEs) in 5 large randomized, controlled studies of golimumab in patients with RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA).

**Methods:** Carotid ultrasound measures were performed at baseline and weeks 24 and 52 in a subset of the GO-BEFORE study, in which patients with RA naïve to methotrexate (MTX) were randomized to subcutaneous injections of every 4 weeks of placebo (PBO) + MTX, golimumab 100 mg + PBO, golimumab 50 mg + MTX, or golimumab 100 mg + MTX. Common carotid artery (CCA) intima-media thickness (IMT), distensibility coefficient (DC), intimal-medial thickness (IMA), and plaque counts were determined. CCA-IMT measurements were done by automated edge detection using MATH software. Carotid ultrasound analyses included only those subjects (n = 392) with a non-missing measurement at baseline and a follow-up time point. CV events reported as serious AEs by investigators (not adjudicated) from the GO-BEFORE, GO-FORWARD (RA), GO-AFTER (RA), GO-REVEAL (PsA), and GO-RAISE (AS) randomized, controlled studies, in which golimumab (50 mg and 100 mg) with or without MTX was compared with PBO with or without MTX, were compiled through week 100 or 104.

**Results:** In the ultrasound analyses (n = 77 to 96 per group), mean (± standard error) changes in CCA-IMT for the golimumab groups were not statistically significantly different from PBO + MTX except for the 100 mg + MTX group at week 24 and the 50 mg + MTX group at week 52, suggesting a trend of increase in CCA-IMT with golimumab treatment, albeit variable over time (Figure). There was a trend of improvement in DC in GLM + MTX groups; however, changes in DCs and IA diameters for the golimumab groups were not statistically significantly different from PBO + MTX. No changes were observed in the number of plaques detected. In the 5 golimumab studies, 639 patients received PBO (for 339 patient-years [py]), 1245 patients received 50 mg (for 1626 py), and 1377 patients received 100 mg (for 2069 py). Sudden death, myocardial infarction, or stroke occurred in 2 patients on PBO (0.59 events per 100 patient-years [95% confidence interval: 0.07, 2.13]), 4 patients on 50 mg (0.07, 0.63), and 10 patients on 100 mg (0.48 [0.23, 0.89]). Ischemic CV events occurred in 4 patients on PBO (1.18 [0.32, 3.02]), 7 patients on 50 mg (0.43 [0.17, 0.89]), and 11 patients on 100 mg (0.53 [0.27, 0.95]).

![Figure](https://via.placeholder.com/150)
of CCA-IMT, but improvement in DC, were observed. Because patients receiving GLM did not appear to have an increased incidence of CV events through two years, the clinical relevance of the carotid ultrasound results are unclear.


Hepatitis B Virus Reactivation in Rheumatoid Arthritis and Ankylosing Spondylitis Patients Using Anti-TNFα Agents: A Retrospective Analysis of 52 Cases with or without Anti-Viral Prophylaxis. Han Hee Ryu1, Eun Young Lee2, Kichul Shin1, In Ah Choi1, Chul Kim1, Yoon Jong Lee2, Bin Yoo3, Min-Chan Park4, Yong-Beom Park5, Sang-Cheol Bae6, Wan Hee Yoo2, Sung Il Kim1, Jun Wan Kim2, Eun Bong Lee6 and Yeong Wook Song4.

1Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea, 2Division of Rheumatology, Department of Internal Medicine Pusan National University Hospital Institutes, Busan, Korea, 3Division of Rheumatology, Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, Korea, 4Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, 5Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, 6Division of Rheumatology, Department of Internal Medicine, University of Ulsan, Asan Medical Center, Seoul, Korea.

Background: Anti-TNFα agents are widely used in the treatment of inflammatory arthritis such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS). However, TNFα is also an important mediator contributing to the normal host immune response against infectious agents, in particular intracellular microorganisms. It is noteworthy that there are a number of case reports describing hepatitis B virus (HBV) reactivation in otherwise asymptomatic carriers under anti-TNFα treatment. Nevertheless, there is no established consensus describing whether this subset of patients would benefit from HBV anti-viral prophylaxis.

Objectives: To investigate the incidence and characteristics of HBV reactivation in HBsAg carriers with RA and AS after initiating anti-TNFα agents.

Methods: We retrospectively collected clinical data from 52 cases of HBsAg carriers with RA or AS who initiated anti-TNFα treatment at 7 centers nationwide. Periodic data of liver function tests and HBV DNA titers at the discretion of the clinician. The median duration of anti-TNFα treatment was 29 patients without prophylaxis were treated with anti-viral agents if needed due to hepatocellular carcinoma. Among the 48 patients, 19 patients began anti-viral prophylaxis (14 lamivudine, 5 baseline transaminase, one died due to hepatocellular carcinoma). Among the 38 patients who received entecavir as primary prophylaxis during the study period.

Results: Four patients were excluded from the analysis (three with high baseline transaminase, one died due to hepato-cellular carcinoma). Among the 48 patients, 19 patients began anti-viral prophylaxis (14 lamivudine, 5 entecavir) with or shortly after starting anti-TNFα treatment. The remainder 29 patients without prophylaxis were treated with anti-viral agents if needed at the discretion of the clinician. The median duration of anti-TNFα treatment was 72 weeks in both groups. Of the 29 patients who did not receive primary prophylaxis, 2 patients (6.9%) developed viral reactivation within a year of anti-TNFα treatment. In the prophylaxis group, 1 patient developed viral reactivation (5.2%) at week 64 of anti-TNFα therapy. This single case of viral reactivation among the prophylaxis group was owing to YMDD mutation under lamivudine. There was not one case of reactivation in 5 patients who received entecavir as primary prophylaxis during the study period.

Conclusions: The rate of HBV reactivation in patients under anti-TNFα therapy without anti-viral prophylaxis was 6.9% among the study population. Anti-viral prophylaxis did help preventing HBV reactivation, except for 1 case of YMDD mutation after using lamivudine. A larger prospective study is warranted to elucidate whether long-term anti-viral prophylaxis would be crucial in HBsAg carriers starting anti-TNFα treatment.

Disclosure: H. H. Ryu: None; E. Y. Lee: None; K. Shin: None; I. A. Choi: None; C. Kim: None; Y. J. Lee: None; B. Yoo: None; M.-C. Park: None; Y.-B. Park: None; S.-C. Bae: None; W. H. Yoo: None; S. I. Kim: None; J. W. Kim: None; E. B. Lee: None; Y. W. Song: None.

Figure 1. Shows an example of one patient’s dose response curve and the LOED.

Using multinomial logistic regression the association of demographic and clinical characteristics at baseline with LOED was studied. Further, using linear regression, the association of demographic and clinical characteristics, including LOED, with the level of disease activity reached was investigated. All models were corrected for treatment strategy. A sensitivity analysis varying the definition of clinically relevant improvement was performed.

Results: For 290 of 299 patients a dose response curve could be estimated; the fit of the curves was found to be adequate. In 208 patients a LOED could be determined. The most common LOEDs were 7.5mg, 15mg, 20mg, and 25mg; higher LOEDs were found more frequent in the tight control strategy arm of the trial. Patients with a LOED of 7.5mg usually only showed an initial improvement in DAS28, probably due to ‘regression to the mean’. The highest MTX dose reached was higher than the average LOED. Higher baseline disease activity and higher body height were predictive of higher LOEDs. A lower DAS28 reached was related to a higher LOED next to male gender and a lower DAS28 at baseline. Sensitivity analyses did not change these results.

Conclusion: Different ‘optimally effective MTX doses’ (after which no further clinically relevant improvement occurs) can be determined for different RA patients and might be predicted by
Introduction: It has been suggested that tumor necrosis factor alpha (TNFalpha), a cytokine that plays a key role in rheumatoid arthritis (RA) pathogenesis, may act as a link between inflammation and cardiovascular disease apparently through several effects including the induction of insulin resistance (IR). The purpose of this study was to clarify if long-term modulation of inflammatory activity by TNFalpha inhibitors has some influence on insulin sensitivity, and if this effect is related to changes in body fat distribution, body composition, physical activity or levels of adipokines (cytokines secreted by adipocytes) in active RA patients.

Methods: Sixteen patients with RA (mean age 50.8±14.6 years, mean duration of disease 6.3±2.7 years) who were receiving anti-TNFalpha agents in addition to methotrexate because of active disease were followed up during one year. Disease activity was assessed by DAS28 (Disease Activity Score), IR was determined by using Homeostatic Model Assessment-2, body composition was evaluated by multifrequency bioelectric impedance analysis, physical activity by accelerometry, abdominal fat distribution by magnetic resonance imaging, and serum level of several key adipokines were quantified by ELISA. All examination and assessments were done at baseline (prior to TNF-alpha treatment) and after 3 and 12 months of treatment.

Results: Body mass indices had increased significantly after one year (25.7±3.2 vs 28.06±4.5 kg/m2, p=0.02) of treatment with anti-TNFalpha. Body composition in terms of fat and fat-free mass had not changed between visits except for a significant elevation of body cell mass (25.5±4.6 vs 26.6±3.1 kg, p=0.02). Values of visceral intraabdominal and subcutaneous adipose tissue were not modified due to treatment. In spite of a significant improvement in DAS28, patients’ physical activity remained stable during the follow up. Basal levels of insulin resistance, beta cell function production or insulin sensitivity did not change along the study. Only insulin sensitivity exhibited a significant increase after 3 months (110[94–138] vs 118[107–156] %, p=0.045) but not longer by the end of the study. Basal levels of adiponectin, visfatin, leptin, ghrelin, resistin, and apelin did not change in response to anti-TNFalpha treatment; only retinol binding protein 4 showed a significant change (51.7±32.7 vs 64.9±28.4 μg/mL, p=0.03) at the end of the study.

Conclusions: Insulin resistance, adiposity, body composition, and adipokine serum levels are not significantly affected by long-term inhibition of TNFalpha in RA patients. Our findings question the suggested beneficial role of anti-TNFalpha treatments in insulin resistance.

Background: Integrated analyses of clinical trial data are important to assess long-term (LT) safety and detect rare events. Here the authors present an integrated analysis of safety data from the abatacept RA clinical trial program up to December 2009, including 12,132 patient-years (p–y) of exposure.

Methods: Data from eight abatacept RA clinical trials were classified into short-term (ST) and LT periods and analyzed. ST data included six double-blind (6- or 12-month), placebo-controlled periods, one non-randomized Phase II study and one non-randomized Phase III study. The LT data included the open-label (OL) periods of these eight studies. Safety assessments, presented for all patients receiving ≥1 dose of abatacept, included adverse events (AEs), serious AEs (SAEs), mortality and events of clinical interest. Incidence rates (IRs) per 100 p–y with 95% CIs were calculated for the ST, LT and cumulative (ST+LT) periods.

Results: The cumulative period included 4149 patients with 12,132 p–y of exposure; 1165 had ≥5 years’ exposure. Mean (range) exposure was 35.6 (1.9–104.2) months. The ST period included 3173 patients (2331 p–y) and the LT period included 3256 patients (9752 p–y). IRs for the ST, LT and cumulative periods are presented (Table). Annual IRs (95% CIs) per 100 p–y for SAEs did not increase with increasing abatacept exposure: Year 1, 19.13 (17.67–20.67); Year 2, 14.39 (12.80–16.11); Year 3, 12.82 (11.09–14.74); Year 4, 10.53 (8.76–12.57); Year 5, 10.18 (8.11–12.62); Year 6, 7.09 (4.54–10.55); Year 7, 8.90 (4.74–15.22). During the cumulative period, the IR (95% CI) of hospitalized infection was 2.64 per 100 p–y (2.35–2.95). The IRs (95% CIs) for the most common serious infections were; pneumonia: 0.46 (0.34–0.59); urinary tract infection: 0.20 (0.13–0.30); cellulitis: 0.18 (0.11–0.28). There were few opportunistic infections (0.36 [0.27–0.49]), with only eight cases of tuberculosis (0.07 [0.03–0.13]) observed overall. The IRs (95% CIs) for non-melanoma skin cancer and solid tumors in the cumulative period were 0.73 (0.58–0.90) and 0.59 (0.46–0.75) per 100 p–y, respectively.

Table. Safety events during the short-term, long-term and cumulative periods

<table>
<thead>
<tr>
<th>P-y exposure</th>
<th>ST (n = 3173)</th>
<th>LT (n = 3256)</th>
<th>Cumulative (n = 4149)</th>
</tr>
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<tbody>
<tr>
<td>Deaths</td>
<td>2331</td>
<td>9752</td>
<td>12,132</td>
</tr>
<tr>
<td>Serious infections*</td>
<td>85</td>
<td>260</td>
<td>332</td>
</tr>
<tr>
<td>Malignancies</td>
<td>16</td>
<td>72</td>
<td>88</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>5</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Autoimmune events</td>
<td>48</td>
<td>NP</td>
<td>232</td>
</tr>
<tr>
<td>Acute infusion events</td>
<td>225</td>
<td>NP</td>
<td>377</td>
</tr>
</tbody>
</table>

*Data show incidence rates per 100 p–y (95% confidence interval); in only six studies ST period, n = 2386; period, n = 3755. ST = short term; LT = long term; SAE = serious adverse event; NMSC = skin cancer; NP = analyses not performed

Conclusions: The integrated safety data from 4149 patients with 12,132 p–y of exposure up to 7 years demonstrate that abatacept is generally well tolerated. No new safety events were identified over time, and the types and IRs of safety events (including events of clinical interest) in the LT and cumulative periods were generally consistent with those in the ST period, indicating that the abatacept safety profile remains stable with increasing duration of exposure.
Disclosure: M. C. Hochberg: Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Genentech and Biogen IDEC Inc, 5, Roche, 5, UCB, Inc., 5; R. Westhovens: Bristol-Myers Squibb, 5, 8, Genentech and Biogen IDEC Inc, 5, Roche, 5, UCB, Inc., 5; R. Aranda: Bristol-Myers Squibb, 1, 8, Genentech and Biogen IDEC Inc, 5, Roche, 5, 8, Amgen Inc., 8, 8, AstraZeneca, 2, Bristol-Myers Squibb, 5, 8, Centocor, Inc., 5, 5, Genentech and Biogen IDEC Inc, 5, Hoffmann-La Roche, Inc., 2, 5, 8, Novartis Pharmaceuticals Corporation, 2, Roche, 3, 8; K. Qu: Bristol-Myers Squibb, 3, 8; I. Delattel: Bristol-Myers Squibb, 1, 8; A. Luo: Bristol-Myers Squibb, 1, 3, A. Torbeans: Bristol-Myers Squibb, 3, L. W. Moreland: Bristol-Myers Squibb, 5, 8, Genentech and Biogen IDEC Inc, 5, 8; R. B. Cohen: Bristol-Myers Squibb, 5, 8; G. Gujral: Bristol-Myers Squibb, 3, M. E. Weinblatt: None.

Long-Term Safety of Rituximab: Follow-Up of the Rheumatoid Arthritis Clinical Trials and Retreatment Population. Ronald van Vollenhoven1, Paul Emery2, Clifton O. Bingham3, Edward C. Keystone3, Roy M. Fleischmann4, Daniel E. Furst2, Katherine Macey5, Marianne Sweetser5, Patricia Lehane6, Pam Farmer7 and Simon G. Long8. 1Biogen Idec Inc, 2Chapel Allerton Hospital, Leeds, United Kingdom, 3Genentech Inc, 4Johns Hopkins University, Baltimore, MD, 5Karolinska Institute, Stockholm, Sweden, 6Roche Products Ltd, University of California Los Angeles Medical School, Los Angeles, CA, 7University of Texas Southwestern Medical Center, Dallas, TX, 8University of Toronto, Toronto, ON, Canada.

Objective: To evaluate the long-term safety of rituximab (RTX) in rheumatoid arthritis (RA) patients (pts) in clinical trials.

Methods: Pooled observed case analysis of safety data from pts treated with RTX plus methotrexate (MTX) in a global clinical trial program. Pts were offered RTX retreatment based on physician decision of clinical need and the criteria for retreatment included assessment of active disease (defined as either SJC and TJC ≥8 or DAS28 ≥2.6). Pts who received placebo during placebo-controlled study periods were pooled to provide a placebo population.

Results: As of September 2009, 3189 pts had been treated with RTX providing 9342 pt-yrs exposure. The analysis includes >9 yrs of follow-up with up to 15 courses of RTX. More than 1500 pts were followed for >3 yrs and 587 pts for >5 yrs with 1724, 1036 and 656 pts receiving ≥3, ≥4, ≥5 and ≥6 courses, respectively. Other than infusion-related reactions (IRR), the safety profile of RTX was similar to the placebo population or general RA populations. In the RTX group, the most frequent adverse event (AE) was IRR; most were CTC grade 1 or 2 and occurred after the first infusion of the first course (23.0%), with 0.5% considered serious (over all courses). Rates of serious AEs (SAEs) and infections generally remained stable over time and over multiple RTX courses, and in patients in long-term follow-up (>5 yrs).

The overall serious infection rate was 4.35 events/100 pt-yrs (3.19 events/100 pt-yrs in pts treated for >5 yrs) and was comparable to that provided 9342 pt-yrs exposure. The analysis includes >9 yrs of follow-up with up to 15 courses of RTX. More than 1500 pts were followed for >3 yrs and 587 pts for >5 yrs with 1724, 1036 and 656 pts receiving ≥3, ≥4, ≥5 and ≥6 courses, respectively. Other than infusion-related reactions (IRR), the safety profile of RTX was similar to the placebo population or general RA populations. In the RTX group, the most frequent adverse event (AE) was IRR; most were CTC grade 1 or 2 and occurred after the first infusion of the first course (23.0%), with 0.5% considered serious (over all courses). Rates of serious AEs (SAEs) and infections generally remained stable over time and over multiple RTX courses, and in patients in long-term follow-up (>5 yrs).

The overall serious infection rate was 4.35 events/100 pt-yrs (3.19 events/100 pt-yrs in pts treated for >5 yrs) and was comparable to that observed in the placebo population (4.29 events/100 pt-yrs). The most frequent serious infections were of the lower respiratory tract, predominantly pneumonia (2%). Serious opportunistic infections were rare with the rate comparable to the placebo population (0.04/100 pt-yrs in RTX all exposure compared to 0.10/100 pt-yrs in pooled placebo). Rates of mycocardial infarction (0.49/100 pt-yrs) and stroke (0.25/100 pt-yrs) were consistent with rates in the general RA population (0.34–0.59 events/100 pt-yrs and 0.112–0.26 events/100 pt-yrs, respectively).

Conclusions: In long-term follow-up of RA pts treated with RTX in clinical trials, no new safety signals were observed in all exposed pts, or in pts with ≥5 yrs exposure. RTX has remained generally well tolerated over time and over multiple courses, with a safety profile similar to that of the pooled placebo population and consistent with published data on pts with moderate to severe RA.

References:
Background: Patients with Rheumatoid arthritis (RA) have an increased risk for cardiovascular diseases. Lipid changes related to inflammation have been described in RA. TNF inhibitor (TNFi) therapy is an effective treatment that controls inflammation.

Objective: To assess modification of lipid levels after initiation of TNFi in RA patients.

Methods: The strategy used Medline database until March 2010 and abstracts of 2009 EULAR/ACR congress. The Mesh terms used were: (“Lipids”[Mesh] OR “Dyslipidemia”[Mesh]) AND “Arthritis, Rheumatoid-”[Majr:NoExp] AND (“TNF-R-Fc fusion protein”[Substance Name] OR “infliximab”[Substance Name] OR “adalimumab”[Substance Name] OR “anti-TNF”), Values of total cholesterol (TC), LDL, HDL, triglycerides (TG), atherogen index (AI), and apoA/A were collected before and after TNFi initiation. Three time-points were defined as following: short term: from 2 weeks to 2 months, mid-term at 3 months and long term from 6 to 12 months. Paired-data statistic analysis was performed with the logiciel Comprehensive Metaanalysis®. Standardized mean differences were obtained using fixed or random effects model (Peto and Dersimonian & Laird method respectively). Random effects model was used when there was evidence of heterogeneity.

Results: The search led to 31 articles and 1 ACR abstract. Sixteen articles were excluded as they were out of topic or reviews/comments. Three other articles were also excluded because of missing p-values and/or confidence intervals. Thus, 13 studies were included for the different meta-analyses. Ten articles were also excluded because of missing p-values and/or confidence intervals. Thus, 13 studies were included for the different meta-analyses. Ten articles were also excluded because of missing p-values and/or confidence intervals. Thus, 13 studies were included for the different meta-analyses. Ten articles were also excluded because of missing p-values and/or confidence intervals. Thus, 13 studies were included for the different meta-analyses. Ten articles were also excluded because of missing p-values and/or confidence intervals. Thus, 13 studies were included for the different meta-analyses. Ten articles were also excluded because of missing p-values and/or confidence intervals. Thus, 13 studies were included for the different meta-analyses. Ten articles were also excluded because of missing p-values and/or confidence intervals. Thus, 13 studies were included for the different meta-analyses.

Conclusions: MTX directly affects the RANKL/OPG system and inhibits osteoclasts formation providing an explanation for the bone-sparing effect of MTX observed in a subgroup of RA patients.

Disclosure: S. Revu: None; P. Neregård: None; E. Afklint: None; A. I. Catrina: None.

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Non-Infectious Pulmonary Complications of Biologic Agents for Rheumatic Diseases—A Systematic Literature Review. Andreas Hadjinicolaou1, Shweta Bhagat2 and Andrew Ostor2, 1Rheumatology Research Unit, Addenbrooke’s Hospital, Cambridge, Cambridge, United Kingdom, 2University of Cambridge, United Kingdom

Background: Systemic inflammatory diseases, such as rheumatoid arthritis (RA) as well as their treatment with disease modifying anti-rheumatic drugs (DMARDs) and anti-TNFs agents may be complicated by a variety of pulmonary disorders. Due to the influx of new biologic agents, we undertook this systematic literature review (SLR) to identify if any of these were associated with non-infectious lung disease.

Methods: A SLR was conducted in PubMed, the Cochrane Library and EMBASE for reviews, meta-analyses, randomized controlled trials(RCT), clinical trials, case series and reports published up to and including May 2010 using the terms “rituximab” “anakinra” “certolizumab” “golimumab” “tocilizumab” “abatacept” and “efalizumab” in the advanced search option. Search results were assessed by two independent reviewers. Meeting abstracts from the European League Against Rheumatism and the British Society of Rheumatology annual meetings were included. We manually reviewed references of all the selected publications to complement our search with published data not identified in the initial search or with unpublished data from the Food and Drug Administration (FDA), the European Agency for the Evaluation of Medicinal Products (EMEA) and manufacturers. Identified articles were included if they reported a possible relationship of biologic agents with lung toxicity, excluded other potential causes or failed to exclude drug-induced causality. A total of 9 RCTs, 15 clinical studies, 10 case series, 35 case reports were identified.

Results: This SLR revealed possible relationships between some biologic agents and interstitial lung disease (ILD) and other drug-related pulmonary toxicities. No cases of pulmonary toxicity were found with golimumab, certolizumab and efalizumab.

Rituximab(RTX) appeared to have a higher reported rate of ILD as we identified 65 papers reporting at least one case of pulmonary toxicity (148 cases in total). However, RTX was given for a rheumatic disease only in 7 of these studies. In 3 studies in RA and lupus, out of a total of 403 patients involved, there were 3 cases of lung toxicity (1 of ILD and 2 of interstitial
pneumonitis, 1 of which was fatal). 4 case reports of RTX (3 given for RA and 1 for lupus) reported 2 cases of Bronchiolitis Obliterans Organising Pneumonia and 2 of ILD with 1 death.

3 RCTs of Tocilizumab enrolling a total of 589 patients reported 6 pulmonary adverse events (2 - ILD, 1 - allergic pneumonitis, 3 - interstitial pneumonia). There was 1 case report of fatal exacerbation of RA induced ILD with tocilizumab.

2 RCTs with a total of 1596 patients on Anakinra for RA refractory to DMARDs reported 3 cases of ILD with 2 fatalities.

In all the non-fatal cases, lung pathology was reversible with drug discontinuation and administration of high dose steroid treatment.

**Conclusion:** Although the number of reports of pulmonary complications with the newer biologic agents is small, the associated morbidity and mortality is substantial. Drug discontinuation is essential and treatment should be instituted expeditiously in order to optimise outcomes. Clinicians should remain vigilant for non-infectious pulmonary disease in any patient treated with biologic agents.

**Disclosure:** A. Hadjinelioeau: None; S. Bhagat: None; A. Ostor: Abbott Laboratories, 5, Bristol-Myers Squibb, 5, Chugai, 5, GlaxoSmithKline, 5, Merck Pharmaceuticals, 5, Roche, 5, Schering-Plough, 5, UCB, Inc., 5, Wyeth Pharmaceuticals, 5.

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**Parenteral MTX as an Initial Treatment Strategy for Early Rheumatoid Arthritis: Results from a Nationwide Cohort.** Vivian P. Bykerk1, David S. Rowe2, Janet E. Pope3, CATCH Scientific Advisory Committee4, Ashley Bonner1 and J. Carter Thorne4.

1Canada, 2Mt Sinai Hospital, Toronto, ON, Canada, 3Southlake Regional Health Care, Newmarket, ON, Canada, 4St Joseph Health Care London, London, ON, Canada

**Background:** Previous studies have established the value of prompt diagnosis and intervention in patients with Early Rheumatoid Arthritis (ERA). While there is a growing body of literature on parenteral administration of methotrexate (pMTX) at optimal doses (≥20 mg weekly) there is still no clear recommendation for a standard route and dosage. The Canadian early Arthritis Cohort (CATCH) is a multi-centre observational prospective “real world” cohort for patients with early inflammatory arthritis. With CATCH, there is an opportunity to evaluate the relative effectiveness of different therapeutic strategies in ERA.

**Objectives:** 1. Compare effectiveness of early optimal doses of pMTX (≥20 mg weekly within 100 days of baseline) with other treatment strategies
2. Assess achievement of clinical outcomes: a) DAS28-defined remission (DAS28<2.6) during 12 months; b) LDAS (DAS28<3.2) during 12 months; and “sustained remission” (CATCH target outcome of 2 consecutive visits with DAS28<2.6) at 6 and 12 months.

**Methods:** CATCH is a study of usual care in over 20 sites across Canada. Patients were selected from the available cohort (n = 898). Only those with baseline DAS28 scores ≥2.6 and available data at 6 and/or 12 months were chosen for analysis. At time of abstract submission, 593 patients were eligible. Patients receiving early optimal pMTX (n=126) and those receiving all other treatment regimens (n=467) were compared for achievement of clinical outcomes within the first year as above. Baseline clinical and demographic characteristics were evaluated and compared. Nonparametric analysis and binary logistic regression models were used to assess outcomes between groups.

**Results:** Patients receiving early optimal pMTX were more likely to achieve LDAS (67% vs. 52%) and DAS28 <2.6 (53% vs. 40%) within the first year (p<0.05). Patients in the early optimal pMTX group were also more likely to be on Combination DMARDs during this time (p<0.01). Parenteral MTX was found to be a significant predictor of good clinical outcomes in a binary logistic regression model. Baseline differences between groups were assessed - overall, patients on early optimal pMTX were more likely to have baseline predictors of poor clinical outcomes, though were less often seropositive at baseline (50% vs. 65%).

**Conclusions:** The data are compelling that pMTX ≥20 mg should be considered as 1st line therapy in ERA. Results will be reported with updated data at time of conference.

**Disclosure:** V. P. Bykerk: Amgen Inc., 2, Pfizer Inc, 2, D. S. Rowe: Roche, 9, J. E. Pope: None; CATCH Scientific Advisory Committee; None; A. Bonner: None; J. C. Thorne: None.

Background: There have been several studies suggesting an association between tumor necrosis factor (TNF) inhibitors, including etanercept, and the development of lymphoma in RA patients. Other studies have noted a 2- to 4-fold increase in reported lymphomas in biologic-naive RA patients compared with the general population (Askling et al, Ann Rheum Dis 2009, 68: 648–653), and suggested the increased risk may be attributable to the underlying disease, particularly in patients with chronic active disease. We now present a surveillance analysis of the incidence of lymphoma in patients conducted as a post-marketing commitment to the US Food and Drug Administration.

Methods: The data used in this analysis were from 2 Amgen-sponsored long-term extension studies in patients with late/early and early RA, 2 US registries (RADIUS I/II) and 3 EU registries (RADIUS and RABBIT, which enrolled patients receiving any biologic drug and conventional disease modifying antirheumatic drugs, and ARTIS, which enrolled patients receiving any biologic drug). Crude incidence rates and age- and sex-adjusted standardized incidence ratios (SIRs) of lymphoma were estimated based on total patient-years (pt-yrs) of follow-up (since first etanercept exposure) and total pt-yrs of etanercept exposure (through 30 days after last etanercept exposure) using country-specific lymphoma rates.

Results: This study collected data from 24,266 RA patients who accumulated a total 93,260 pt-yrs of observation since the first date of etanercept exposure. The mean exposure to etanercept was 2.7 years. Sixty-two lymphomas were reported, compared with the expected number of 27.3 from country-specific rates, yielding an overall SIR of 2.3 (95% confidence interval [CI]: 1.7 to 2.9), in the total follow-up period. The data from the etanercept exposure period yielded an SIR of 3.0 (CI: 2.3 to 3.9). Variability in the SIRs for lymphoma in the US studies and the EU registries was noted.

Conclusions: Overall, the data from the long-term Amgen extension studies and both US and EU registries appear to show a 2- to 4-fold increased risk of lymphoma in RA patients receiving etanercept, though there was variability in SIRs from different sources. This analysis, combined with the observation that the risk of lymphoma in biologic-naive and biologic-exposed RA patients is similar, supports the interpretation that there is no additional risk for lymphoma in patients receiving etanercept above the already increased risk of lymphoma in RA patients.

Disclosure: P. McCrosskey: Amgen Inc., 1, 3; V. C. Dias: Amgen Inc., 1, 3; S. Stryker: Amgen Inc., 1, 3; B. Bitman: Amgen Inc., 1, 3; S. Z. Zhao: Amgen Inc., 3; D. J. Zack: Amgen Inc., 1, 3.

Post-Marketing Surveillance Program of Tocilizumab for RA in Japan – Interim Analyses of 3,881 Patients. Takao Koike1, Masayoshi Harigai2, Shigeko Inokuma3, Naoki Ishiguro4, Junnosuke Ryu5, Tsutomu Takeuchi6, Syuji Taker1, Yoshiya Tanaka1, Hisashi Yamakawa7 and Kyoko Ito1.

Purpose: An all-case post-marketing surveillance (PMS) program has been implemented to investigate the safety and efficacy of tocilizumab (TCZ) in Japanese patients with rheumatoid arthritis (RA). Methods: The PMS study has enrolled all patients with RA who were treated with TCZ in Japan after its launch in April 2008 with a tracking period of 28 weeks for each patient. All adverse events (AEs) and adverse drug reactions (ADRs) during the tracking period and disease activity score 28 (DAS28) at week 0 and week 24 were collected. AEs and ADRs were classified using MedDRA, ver11.1. The present analysis included 3,881 patients whose case report forms were completed by 15th July 2009.

Results: Baseline data of the patients were as follows: mean age, 58.5 y/o (range 16.0–87.0, 36.2% of them were ≥65 y/o); mean disease duration (DAS28) at week 0 and week 24 were 10.7 yrs. (38.3% of them were ≥10 y/o); respiratory, cardiac, or hepatic comorbidities, 13.5%, 4.7%, or 4.5%, respectively; previous TNF inhibitors, 62.0%; concomitant methotrexate and glucocorticoid, 50.0% and 75.1%, respectively. Incidences of total and serious ADRs were 35.5% and 7.2%, respectively. The most frequent ADR and serious ADR were infection and infestation with an incidence of 9.6% and 3.4%, respectively. Among serious infections, bacterial pneumonia was the most frequently reported (1.4%). Regarding opportunistic infections, 4 cases of tuberculosis (3 pulmonary and 1 peritoneal tuberculosis) and 6 cases of Pneumocystis jiroveci pneumonia were reported. Logistic regression analysis identified risk factors for the development of serious infection (odds ratio, 95% confidence interval): presence of respiratory comorbidities (2.970, 1.959–4.502), higher prednisolone dose at the baseline (>5 mg/day) (2.297, 1.299–4.061), older age (≥65 y/o) (1.762, 1.170–2.651) and longer disease duration (>10 yrs.) (1.561, 1.032–2.361). The malignancies as AE were reported in 17 patients (0.4%) without any specific patterns. Gastrointestinal disorders were reported in 3.0% of cases with 5 cases (0.1%) of gastrointestinal tract perforations. All these patients recovered. Anaphylactic shock/reactions were reported in 8 patients (0.2%). Although dyslipidemia and elevated liver function tests were reported in 5.9% and 6.6% of the patients, respectively, these laboratory test abnormalities accompanied neither serious cardiovascular diseases nor serious hepatic disorders. Twenty-eight out of 3,881 patients died with causes of death in the following order of occurrence (expressed as a percentage): infection, 32%; respiratory disease, 20%; cardiovascular disease, 24%; cerebrovascular disease, 12%. The standardized mortality rate (SMR), with Japanese general population in 2008 as a control, was 1.66, which was similar to those reported in the Japanese cohort study (1).

Conclusions: The results from the interim analysis of the PMS study revealed that TCZ was well tolerated in the real world for Japanese patients with RA.

Reference

Predictive Risk Factors of Severe Infections in RA Patients Treated with Abatacept in Real Life: Results from the Oencia and Rheumatoid Arthritis (ORA) Registry. Jacques-Eric Gottenberg1,2, Philippe Ravaud1,3,4, Thomas Bardin1,5, Patrice Cacoub3,6, Aain Cantagrel1,7, Bernard Combe8,9, Maxime Dougados3,4, René-Marc Filpo10, Bertrand Godeau11, Loïc Guillevin12, Eric Hachulla8, Xavier Le Loït9, Thierry Schaeverbeke2, Jean Sibilia13, Gabriel Baron14 and Xavier Mariette1. 1Bicêtre Hospital, 2Bordeaux Hospital, 3Cochin Hospital, 4Henri Mondor Hospital, 5Hotel Dieu Hospital, 6La Pitié Hospital, 7Lariboisière Hospital, 8Lille Hospital, 9Montpellier Hospital, 10Rouen Hospital, 11Strasbourg Hospital, 12Toulouse Hospital

Objective: Little data is available regarding the rate and predicting factors of severe infections in patients with rheumatoid arthritis treated with abatacept (ABA) in daily practice. We therefore addressed this issue using real-life data from the “Oencia and Rheumatoid Arthritis (ORA)” registry.

Methods: ORA is an independent registry promoted by the French Society of Rheumatology dedicated to RA patients with abatacept. At baseline, 3 months and every 6 months or at disease relapse, during 5 years, standardized information was prospectively collected by trained clinical nurses in each center. Central reviewing of charts of patients with SAEs is performed by the two coordinators of the study.

Results: 1036 patients (78.9% of women) were included. Median age of patients was 58 years and median disease duration was 12 years. 5.8% of patients had a history of cancer, 33.6% a record of severe infection, and 11.4% had diabetes. Follow-up was 857 patient-years on April 30th, 2010.

Rate of severe infections
35 severe infections occurred, including 31 severe infections during treatment with ABA and/or within the 6 months following ABA discontinuation. Thus, 5.6 severe infections/100 patient-years were observed. No opportunistic infection was observed. Severe infections occurred after a median duration of 4.6 months (range: 2.4–11.2 months) after abatacept initiation.

- Predicting factors of severe infections
The analysis was carried out on the 709 patients who already had at least 1 follow-up visit (at least 3 months of follow-up). Univariate analysis, age, history of cancer, record of previous severe infections, diabetes, a higher number of previous synthetic DMARDs and a lower number of previous anti-TNF agents were associated with a higher risk of severe infection. Previous treatment with rituximab, disease activity or low IgG levels at initiation of abatacept were not significantly associated with an increased risk of severe infection. On multivariate analysis, history of cancer (OR 3.7 CI95% [1.0–13.9], P=0.05), record of severe infections (2.7 [1.1–6.7], P= 0.03) and diabetes (3.5 [1.3–9.7], P= 0.01) were significantly associated with a higher risk of severe infection.

Conclusion: In ORA registry, severe infections in patients treated with abatacept were slightly more frequent than in clinical trials. This might be related to the fact that a high proportion of patients with comorbidities, who would have been excluded from controlled trials, are treated with ABA in real life. The greatest risk of severe infections occurs within the first 6 months after ABA, as it was also reported with anti-TNF or rituximab. In patients treated with abatacept, predicting factors of severe infections include history of cancer, record of severe infections and diabetes.

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Pregnancy Outcomes in Patients with Autoimmune Diseases Treated with Rituximab. Eliza F. Chakravarty1, Elaine Murray2, Ariella Kelman3 and Pamela Farmer1. 1Mountain View, CA, 2Genentech, South San Francisco, CA, 3Genentech

Background: Rituximab is a monoclonal antibody to CD20 causing CD20+ B-cell depletion. It is approved for treatment of adults with moderately-to-severely active rheumatoid arthritis (RA) with inadequate response to TNF antagonists, and has been studied in other autoimmune diseases. Despite counseling to avoid pregnancy, some women may become pregnant after rituximab treatment. Almost half of all U.S. pregnancies are unplanned, including those in women with underlying medical conditions. Data on pregnancy outcome following rituximab treatment is important when counseling women who inadvertently become pregnant, or are pregnant and need to assess therapeutic options for severe disease.

Methods: Utilizing the rituximab global drug safety database, we reviewed all reports of pregnancy following rituximab use (spontaneous reporting or during clinical trials) among women treated for autoimmune conditions (RA, systemic lupus erythematosus (SLE), idiopathic thrombocytopenia purpura (ITP), and multiple sclerosis). Patients may have received concomitant treatment with known teratogens and abortifacients such as methotrexate.

Results: Of 172 pregnancy reports identified through February 2010, 16 were ongoing, 11 reported paternal exposure, and 40 did not report pregnancy outcomes. Eight patients received rituximab during an established pregnancy for the treatment of profound autoimmune hematologic disease. Of the 105 reports with known outcomes, 56 (53%) resulted in live births, 27 (26%) in spontaneous abortion, and 20 (19%) pregnancies were terminated. One maternal death occurred from an intracerebral hemorrhage in a woman treated for ITP, and one pregnancy ended in fetal demise at 20 weeks from an umbilical knot. There was one neonate death at six weeks of life of an infant delivered to a rituximab treated woman with SLE, who also received mycophenolate mofetil and warfarin while pregnant. Mean gestational age at delivery was 37.3 ± 2.5 weeks. 73% of live births were full term, and 27% were prior to 37 weeks gestational age. One congenital malformation was reported: clubfoot in one of a set of twins. Six infants had hematological abnormalities at birth; 3 with transient leucopenia, and 3 with thrombocytopenia. Most were mild and transient, although one infant, born to a mother treated with rituximab during the third trimester for profound ITP, had a cerebral hemorrhage of unreported severity. Three neonatal infections were reported: febrile illness at 3 weeks of age, chorioamnionitis, and vertical transmission of CMV; none occurred in infants with cytopenias.

Conclusions: Women should continue to be counseled to avoid pregnancy after rituximab exposure; however, inadvertent pregnancy can occur. Few congenital malformations or infections were seen among exposed neonates, and it is difficult to determine if rituximab, concomitant medications, underlying diseases, or other factors contributed. This data provides information that can be used to counsel women in making decisions during pregnancy.

Disclosure: E. F. Chakravarty: None; E. Murray: Genentech and Biogen IDEC Inc, 3; A. Kelman: Genentech and Biogen IDEC Inc, 3; P. Farmer: Genentech and Biogen IDEC Inc, 3.

Pulmonary Function in Patients with Rheumatoid Arthritis Treated with Anti-TNF Biologic Agents. Andrew J. Odden1, Ann J. Impens2, Elena Schiopu2, Kevin Flaherty4 and Kristine Phillips5. 1University of Michigan, 2University of Michigan, Ann Arbor, MI

Background: Initiation of anti-tumor necrosis factor (TNF) therapy has been associated with a range of pulmonary pathology in patients with rheumatoid arthritis (RA), including usual interstitial pneumonitis and granulomatous lung disease. It has been suggested that preexisting interstitial lung disease may predispose patients with rheumatoid arthritis treated with anti-TNF agents to the development of worsening pulmonary disease. There have been no known quantitative studies of lung function in patients with RA-associated interstitial lung disease treated with anti-TNF biologics.

Method: This retrospective cohort study identified patients at a single large referral center who were diagnosed with rheumatoid arthritis, had
coexisting interstitial lung disease, and were treated with anti-TNF therapy. Data recorded included demographics, comorbidities, mortality, chest CT, lung biopsy results, and pulmonary function tests including spirometry and DLCO. Patients were included who had spirometry measurements within one year prior to and within six months after initiating anti-TNF therapy. The baseline FEV1 and FVC were compared with FEV1 and FVC six months after therapy using the paired samples test.

Results: Seventy-four patients were identified with rheumatoid arthritis and interstitial lung disease and had been treated with anti-TNF biologic therapy. Demographic, treatment, and PFT data were gathered for this cohort. Of these, 23 had spirometry measured at least one year prior to starting anti-TNF therapy and again within six months after initiation of therapy. There was no statistically significant difference in FEV1 (2.067 liters vs. 2.097 liters, paired difference 0.030 liters, 95% CI –0.104 to 0.164) or FVC (2.664 liters vs. 2.668 liters, paired difference 0.004 liters, 95% CI –0.141 to 0.150) from baseline to six months after starting anti-TNF therapy.

Conclusion: In this retrospective cohort study, there was no statistically significant change in either FEV1 or FVC from baseline to six months after initiation of anti-TNF biologic therapy. Our study suggests that the use of anti-TNF therapy, an important component of the management of patients with rheumatoid arthritis, does not worsen pulmonary function with short term treatment (six months) in patients with pre-existing lung disease. This study is limited by its small sample size and the short interval between baseline and follow-up spirometry, both of which may have limited our ability to detect a clinically significant difference in lung function. Larger prospective studies are needed to determine the safety of using anti-TNF agents in patients with rheumatoid arthritis and interstitial lung disease.

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Purpose: Rituximab (RTX) selectively targets CD20+ B-cells and is approved for treatment of RA patients (pts) who had an inadequate response to ≥1 TNF-inhibitor(s) (TNFI). The pharmacodynamic effect of RTX may be long lasting. The safety of treatment with other biologic disease-modifying antirheumatic drugs (BDMARDs) during this period of peripheral B-cell depletion in pts who have discontinued RTX is an important clinical question. The purpose of this analysis is to describe the rate of serious infection events (SIEs) in pts treated with RTX, who subsequently received a BDMARD.

Methods: Pts with moderate-to-severe RA who received RTX + methotrexate within an international clinical trial program were included. Following completion or withdrawal from their studies, pts entered safety follow-up (SU) and peripheral B-cell counts were monitored for ≥48 wks. During SU, pts were permitted to receive BDMARDs. All SIEs, defined as serious adverse events or infections that required IV antibiotics, were collected.

Results: As of Sept 2009, 3189 RA pts had received ≥1 course of RTX providing 9365 pt-yrs of follow-up (SIE rate / 100 pt-yrs: 4.34 [95% CI: 3.93, 4.78]). Of pts who entered SUF, 283 pts were subsequently treated with BDMARD (median time 8.5 mo [range: 0.1–52] after last RTX infusion). 87 (30.7%) pts received their BDMARD < 6 mo of their last RTX infusion. 230 of the 283 pts received TNFi after RTX. Median follow-up time after receipt of the subsequent BDMARD was 11 mo (7–17). At the time of receiving further BDMARD treatment, 83% had peripheral B-cell counts below lower limit of normal (LLN) (<80 cells/µL). During treatment with RTX and prior to receipt of the BDMARD, the 283 pts had 6.01 SIEs / 100 pt-yrs (Table). Following initiation of BDMARD, the SIE rate was 4.97 / 100 pt-yrs. Median time to SIE after initiating BDMARD was 11 mo (range: 2–21). In 43 pts who received abatacept (ABA) as their 1st subsequent BDMARD post RTX, there was 1 SIE before and 1 after receiving ABA (97.7 total pt-yrs). Overall, the infections were variable and typical for RA pts, with no opportunistic or fatal infections. In subgroup analysis of 174 patients with CD19+ counts <20 cells/ µL at the time of receipt of their next BDMARD, SIE rate / 100 pt-yrs was 6.28 (3.79, 10.42).

Conclusion: In this updated analysis, the use of other BDMARDs in RA pts previously treated with RTX was not associated with an increase in the rate of serious infections. The rate of serious infections is consistent with rates seen in long-term safety analyses.

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Background: Rheumatoid arthritis (RA) patients who use anti-tumor necrosis factor alpha therapies (anti-TNF) are at increased risk for tuberculosis. Serious infections due to environmental nontuberculous mycobacteria (NTM) have also been reported in such patients. In the United States, there is no population-based data for patients with rheumatic diseases estimating the risk of TB and NTM.

Methods: We identified new users of anti-TNF therapy among a cohort of rheumatoid arthritis (RA) patients during the years 2000–2007 from three data sources: Kaiser-Permanente Northern California, MAX + ‘dual eligible’ (MAX + Medicare) data from the national Centers of Medicare and Medicaid Services (years 2000–2005), and Tennessee Medicaid. We used validated electronic medical record (Kaiser) and administrative claims data (CMS and TennCare) algorithms to identify and describe cases of TB and NTM within this cohort. We calculated incidence rates using total anti-TNF exposure time (current use required) for each patient during the study time-period. We compared TB incidence rates with the rate of TB reported by the US Centers for Disease Control in the United States general population during this same time-period.

Results: Among 29500 new users of anti-TNF therapy for RA, we identified 24 NTM and <11 TB cases and calculated incidence rates of 66.7 (40–93) and 45.9 (14–78) per 100,000 patient-years respectively. The rate of TB in the US general population was 5.1/100,000 during the same study time-period. 80 (%) and 93 (%) of NTM and TB patients were female respectively, with median age in 5 year increment (range) of 50 (25–75) and 55 (25–80). NTM patients were more likely to be white (50%) than TB patients (40%). Pre-existing chronic obstructive pulmonary disease or bronchiectasis was more frequent among NTM patients (35%) than among TB patients (33%).

Conclusion: In the United States, a region of low TB prevalence, the rate of TB among RA patients who start anti-TNF therapy is 9 fold higher than the general US population. However, NTM disease was more common than tuberculosis among these RA patients. Rheumatologists should continue to screen for latent TB infection prior to prescribing anti-TNF therapy and remain vigilant for NTM disease, particularly in those with a history of underlying lung disease.

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Real Life Analysis of the Romanian Experience in Switching from Anti-TNF Based Therapy to Rituximab. Ioan Ancuta1, Catalin Codreanu1, Ruxandra Maria Ionescu1, Horatiu Bolosiu1, Magda Parvu1 and Lia Georgescu1. 1,3,4“Sfanta Maria” Clinical Hospital, Bucharest, Romania, 2 (“St. Ioan” Center for Rheumatic Diseases, Bucharest, Romania, 4,3,4“St. Ioan” Center for Rheumatic Diseases, Bucharest, Romania, 5,3,4“St. Ioan” Center for Rheumatic Diseases, Bucharest, Romania, 6,2,1Justus-Liebig University Giessen, Kerckhoff Clinic, Bad Nauheim, Germany, 2,1Justus-Liebig University Giessen, Kerckhoff Clinic, Bad Nauheim, Germany.

Background: The rheumatoid arthritis is a chronic disorder affecting physical function and patient’s quality of life, and its treatment carries therefore important costs for the National Health Insurance House (NHIH). In case of an inadequate response with the first anti-TNF medication, a largely used option is currently to continue the treatment with drugs from the same class, either by modifying dosage/frequency of the initial ones, or by prescribing different anti-TNF. Using the available data from NHIH, we researched if continuing with a second anti-TNF brings both the expected benefits for the patients and is reasonably cost effective for NHIH, versus switching to rituximab (RTX) after the initial medication, instead of using again anti-TNF drugs.

Methods, Materials and Analytical Procedures Used: The analysis was performed for 200 patients (78% women with an average age of 55 and 22% men, average age 54) who were all prescribed in the first stage anti-TNF alpha medication. In the second stage, 102 patients were treated with RTX for 3 courses (after one anti-TNF-IR), while 98 of them received a 2nd anti-TNF medication and after an inadequate response to that were treated with 3 courses of RTX. The median time for follow-up was 1.5 years for each arm. We evaluated the effectiveness of the 2 treatment approaches by calculating the DAS28 and after an inadequate response to that were treated with 3

Results: Both cohorts were comparable regarding age (rituximab 56.6 ± 11.1; TNF blocker 57.4 ± 13.1 years), duration of disease (10.0 ± 7.8 vs. 9.7 ± 7.6 years), DAS28 (5.6 ± 1.0 vs. 5.4 ± 1.0) and concomitant DMARD therapy (77.8% vs. 77.4%) at initiation of 2nd treatment (baseline). The mean DAS28 reduction was significantly greater after 6.6 months treatment in the rituximab group as compared to the patients treated with a 2nd TNF blocker (-1.64 [95%-CI: -1.92; -1.36] vs. -1.19 [95%-CI: -1.42; -0.96], p = 0.0133), see Figure 1 (left). This cohort difference was similar in the 156 patients seropositive for RF (-1.66 [95%-CI: -1.98; -1.34] vs. -1.17 [95%-CI: -1.43; -0.91], p = 0.0176) and more pronounced in the 132 patients seropositive for CCP: a significant difference (p = 0.0295) could already be observed after 12 weeks with further improvement until month 6.6 (-1.75 [95%-CI: -2.07; -1.43] vs. -1.06 [95%-CI: -1.34; -0.78], p = 0.0016), see Figure 1 (right). The results from the 2 seronegative patients also favored rituximab but this difference was not significant. More rituximab than TNF blocker patients reached moderate/good EULAR response: 82.3% vs. 71.7% with a significant difference in the CCP subgroup: 85.3% vs. 67.2% (p = 0.0128).

Conclusion: The results from this non-interventional, retrospective cohort study indicate that treatment with rituximab is superior to a 2nd TNF blocker therapy in RA patients after failure of the first TNF inhibitor in terms of clinically significant improvement as measured by the DAS28 score. An even stronger difference in clinical response was found in the patients seropositive for CCP. This observational data of a real life setting confirm the data of rituximab in TNF blocker non-responders as shown in the REFLEX study. In addition to previous publications we could show that CCP may be a useful predictive biomarker for response to rituximab in patients with TNF blocker treatment failure.

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Risk of Malignancies in Patients with Rheumatoid Arthritis Treated with Biologic Therapy: Meta-Analysis of Controlled Trials. Maria A. Lopez-Olivo1, Juan A. Martinez-Lopez2, Jean H. Tayar3, Jose Polo Cueto4, Eduardo N. Pollono5, M. Rosa Gonzales-Crespo5, Stephanie Fulton4 and Maria E. Suarez-Almazor6. 1Hospital 12 de Octubre, Spanish Society of Rheumatology, Spain, 2Texas Tech University Health Science Center - Paul Foster School of Medicine, 3The University of Texas M.D. Anderson Cancer Center, Houston, TX, 4The University of Texas MD Anderson Cancer Center, 6University of Texas, MD Anderson Cancer Center, Houston, TX.

Background: Biologic response modifiers (BRM) provide an important therapeutic alternative in patients with rheumatoid arthritis. Because these biologic agents interfere with the immune system, there are concerns regarding their safety and an increased risk of malignancies. The objective of this study was to assess the risk of malignancies in patients with rheumatoid arthritis enrolled in clinical trials of BRMs, in order to update the information reported in previous reviews of RCTs and determine if the newly approved BRMs have an increased risk for malignancies.

Methods: We searched for clinical trials on the use of abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab,
Rituximab, and/or tocilizumab for the treatment of rheumatoid arthritis, published through April 29, 2009. Sources included electronic databases (MEDLINE, EMBASE, and Web of Science). Review of 12,480 citations revealed 55 controlled trials. Two independent reviewers evaluated risk of bias in the methods of selected studies using the risk of bias instrument (Cochrane Collaboration) and extracted data. Information on reported number of malignancies, type and time of occurrence when available was collected.

Results: Fifty-three trials with 23,696 patients were included. Compared with placebo, patients in the TNF antagonists group were 1.38 times more likely to develop malignancy at one year, but this was not statistically significant (95% CI: 0.76, 2.48) with a 0.33% (95% CI: −0.16%, 0.82%) absolute risk difference between groups. The number needed to harm was 305 (95% CI: 122, ∞) for one additional malignancy within a treatment period of 12 mo. No statistically significant risk of developing a specific type of malignancy was found in the TNF antagonist-treated patients compared to placebo. Total number of solid malignancies (breast, lung, colon, prostate) were greater for patients treated in tocilizumab group compared to placebo (RR: 6.47, 95% CI: 0.34, 124.16) and skin cell carcinoma was increased when certolizumab was given in combination with methotrexate against placebo plus methotrexate (RR 3.56, 95% CI 0.18, 68.63), but these results were not statistically significant.

Conclusions: On the basis of the studies reviewed here, there is no evidence that BRMs for the treatment of the RA confide a greater risk for malignancies, but further long-term studies and continuing post-marketing surveillance are required.

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Risk of Malignancy during Anti-TNF alfa Therapy in Patients with Rheumatoid Arthritis: Systematic Review and Meta-Analysis of Registries, Long-Term Extension Studies and Randomized Controlled Trials. Pierre Le Blay3, Gael Mouterde4, Thomas Barnetche1 and Bernard G. Combe2, 1Bordeaux University Hospital, 2Hospital Lapeyronie, Montpellier, France, 3Hospital Lapeyronie, France, 4Hospital Lapeyronie, France. 

Background: TNF antagonists have shown their efficacy in rheumatoid arthritis (RA) and are now widely used. Some data derived from randomized control trials (RCTs) suggest that anti-TNF might be associated with an increased risk of malignancy [1], but results from long term safety follow up and registries are controversial.

Objective: To assess the risk of malignancy in TNF antagonists treated-RA patients, by performing a systematic review and meta-analysis based on data from registries, long term extension studies, and RCTs of 2 newly licensed anti-TNF.

Method: A systematic review of literature was performed until January 2010. Bibliographic references were selected from Embase and Medline databases, and abstracts from both the EULAR and the ACR annual meetings. The Mantel-Haenszel method was used to provide a common odds-ratio (OR) estimate and 95% confidence interval (CI) in anti-TNF–versus disease modifying antirheumatic drug (DMARDs) treated patients for registries and for certolizumab and golimumab RCTs. Statistical heterogeneity was assessed on the basis of the Q test (χ²), using a significance level of 0.05. OR and 95% CI were shown on forest plots. Standardized Incidence Ratio (SIR), versus the general population, were extracted for long term extension studies and registries.

Results: The literature search identified 641 articles and 110 abstracts of which respectively 25 and 2 were selected for analysis. Retrieved data allowed meta-analysis on 4 registries and 5 RCTs. Based on registries (40128 Patient-years (PY) in anti-TNF treatment group and 59862 PY under DMARD treatment control group), the pooled OR for malignancy was 0.81 (95% CI 0.71−0.94), without significant heterogeneity.

In golimumab and certolizumab RCTs, the pooled OR for total malignancy and for non melanoma skin cancers were respectively 1.07 (95% CI 0.35−3.25) and 0.83 (95% CI 0.24−2.87), without heterogeneity.

Figure 2. Meta-analysis for risk of total malignancy with certolizumab and golimumab.

Among 3 long term extension studies, no increase in the incidence of total malignancy was noted (SIRs ranging from 0.84 to 1.07). A similar observation was made in 4 registries (21225 PY), (SIRs ranging from 0.74 to 1.36, none being statistically significantly higher than 1).

Conclusion: This meta-analysis of registries did not find an increased risk of malignancy in anti TNF treated RA patients. Data from long term extension studies and RCTs with new TNF antagonists confirmed these results.

Disclosure: P. Le Blay: None; G. Mouterde: None; T. Barnetche: None; B. G. Combe: None.

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Rituximab vs TNF-Inhibitor Cycling in Patients Who Previously Failed to TNF-Inhibitors: The MIRAR Study. Juan-Jesús Gómez-Reino1, Raïmon Sammarti2, Ana-Belen Romero3 and Laura Monclus3. 1Hospital Clínico Universitario / Xeral de Galicia, Santiago de Compostela, 2Hospital Clinic, Barcelona, 3Roche

Purpose: Rituximab (RTX) is used to deplete B cells, and control disease activity in, mainly, anti-TNF failing RA patients. Another option is to switch to another anti-TNF, and it is not yet clear which of these two options is the more successful strategy. The objective of this study is to compare in a clinical setting the effectiveness of RTX treatment vs. an alternative anti-TNF in RA patients failing to an anti-TNF.

Methods: Multicentre, prospective, 3-year observational study of a cohort of patients with RA who received either RTX or an alternative anti-TNF, having previously inadequate response to at least 1 anti-TNF. Assessments included DAS28, EULAR response and HAQ at 9−12 months. At the time of this analysis, more evaluable patients were included since last published results1. All analysis were done with SAS 9.1.3. Appropriate tests were used for comparisons.

Results:

Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rituximab</th>
<th>TNF-inhibitor</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>346 (81.41%)</td>
<td>958 (79.77%)</td>
<td>0.4646</td>
</tr>
<tr>
<td>Age (mean SD)</td>
<td>55.73 (12.47)</td>
<td>54.55 (13.46)</td>
<td>0.2583</td>
</tr>
<tr>
<td>≥4 years since diagnosis of RA</td>
<td>292 (86.65%)</td>
<td>787 (78.23%)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Extra-articular manifestations of RA</td>
<td>137 (44.05%)</td>
<td>255 (26.18%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior number of TNF inhibitors failure</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMARDs</td>
<td>1  210 (60.69%)</td>
<td>762 (79.89%)</td>
<td></td>
</tr>
<tr>
<td>DMARDs</td>
<td>2  136 (39.31%)</td>
<td>229 (20.11%)</td>
<td></td>
</tr>
<tr>
<td>DMARDs</td>
<td>≥2 193 (94.15%)</td>
<td>860 (87.31%)</td>
<td>0.0151</td>
</tr>
<tr>
<td>DMARDs</td>
<td>≥2 78 (38.61%)</td>
<td>291 (29.82%)</td>
<td>0.0141</td>
</tr>
</tbody>
</table>

Significantly more patients in RTX had ≥4 years since diagnosis, extra-articular manifestations, ≥2 DMARDs and ≥2 previous number of anti-TNF, toxicity with DMARDS (Table 1) and higher DAS28. At 9−12 months, change in DAS28 is significantly larger in RTX (-1.84) than alternative anti-TNF (-1.34) (P=0.0156; difference: 0.4999, 95% CI: 0.0954, 0.9043) (Figure 1). EULAR good-mod. response rate is better in RTX.
(82.56%) than alternative anti-TNF (70.83%) (P = 0.04); Probability of good-moderate response is affected by baseline DAS28 (OR = 2.532, 95% CI: 1.837, 3.489). There were no differences in change of HAQ (P = 0.3141) nor in proportion of patients with HAQ > 0.22 (P = 0.1754).

Conclusion: Data from the MIRAR Study confirms that switching to RTX provides an alternative therapeutic option to TNF cycling in patients with RA who have previously failed TNF inhibitor therapy. DAS28 reduction was significantly higher in the RTX group.

Disclosure: J.-J. Gómez-Reino: Roche, 2; R. Sammarti: Roche, 2; A.-B. Romero: Roche, 3; L. Monclus: Roche, 3.

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Rituximab vs. Anti-TNF after Failure of Anti-TNF: An Observational Study. Katerina Chatzidionysiou1 and Ronald Van Vollenhoven1. 1Karolinska University Hospital, Stockholm, Sweden, 2Karolinska University Hospital, Stockholm

Background: The purpose of this study was to determine whether patients who had failed one or more anti-TNFs achieve better results when switching to another anti-TNF or when switching to rituximab.

Methods: The Stockholm registry “STURE” was used. Treatment results at 3 and 6 months were analysed by 1) biologic used; 2) whether as second, third or fourth biologic; 3) type of TNF switch; and 4) reason for discontinuation (lack of efficacy or intolerance).

Results: A total of 850 patients switched to an alternative biologic, 679 to a TNF antagonist and 171 to rituximab. There was a significant improvement in the DAS28 scores for both RTX and anti-TNF groups from baseline to 6 months. The mean (S.D.) reduction of DAS28 was 1.79 (1.35) for the RTX group and 1.37 (1.44) for the anti-TNF group (p=0.03). Specifically, mean ΔDAS28 was 1.15 (1.4) for infliximab and adalimumab taken together and 1.58 (1.46) for etanercept. A significant difference was observed between rituximab and anti-TNF monoclonal antibodies (p=0.002, 95% CI = 0.24, 1.06) but not between rituximab and etanercept (p=0.32, 95% CI = -0.21, 0.6).

In figure 1 the mean improvements in DAS28 can be seen according to the type of TNF switch. Having failed a TNF soluble receptor, RTX was significantly better than an anti-TNF monoclonal antibody (p=0.03). For patients who had failed a TNF monoclonal antibody RTX leads to numerically but not significantly greater reductions in DAS28 than an alternative anti-TNF antibody or etanercept.

When the reason for discontinuation of previous treatment was intolerance, rituximab achieved significantly greater reduction in DAS28 compared to anti-TNF, 2.05 (1.17) versus 1.52 (1.26) (p=0.04).

Conclusion: In this observational cohort, patients who had failed anti-TNF had slightly better overall results when treated with rituximab than with another anti-TNF, but both options provided clinical benefits. The superiority of rituximab was observed when compared to anti-TNF monoclonal antibodies but not to etanercept. Unexpectedly, the advantage of RTX was most clearly seen in patients who had failed anti-TNF due to intolerance.

Figure 1. Change in DAS28 at 6 months for patients who switched from an anti-TNF monoclonal antibody (αTNFαb) or a TNF soluble receptor-construct to rituximab or an alternative anti-TNF.

Disclosure: K. Chatzidionysiou: None; R. Van Vollenhoven: Roche, 2, 5.

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Safety and Tolerability of Tocilizumab in Long-Term Extension Studies of Rheumatoid Arthritis. Mark C. Genovese2, Anthony Sebba3, Andrea Rubbert-Roth1, Juan J. Scali1, Moshe Zilberstein1, Emma Vernon1 and Ronald F. van Vollenhoven2. 1Durand University Hospital, Buenos Aires, Argentina, 2Karolinska University Hospital, Stockholm, Sweden, 3Roche, Nutley, NJ, Roche, Welwyn, UK. 4Stanford University Medical Center, Palo Alto, Palo Alto, CA, 5University of Cologne, Cologne, Germany, 6University of South Florida, Palm Harbor, FL

Background: Tocilizumab (TCZ) is an effective RA therapy that targets interleukin-6-receptor (IL-6R) signal transduction. The objective of this analysis was to assess the longer-term safety of TCZ in RA patients using pooled data from clinical trials (OPTION, TOWARD, RADIATE, AMBITION, and LITHE) and ongoing long-term extension studies.

Methods: Pooled analysis of patients who received ≥1 TCZ dose in the core or extension studies (GROWTH95 and GROWTH96) from initial exposure through August 28, 2009.

Results: A total of 4009 patients received TCZ with a median (mean) treatment duration of 3.1 (2.7) years and a total observation time of 10,994 patient-years (PY). The AE rate was 321.1/100 PY (95% CI: 317.8, 324.5); infections were the most frequent AE (70.7/100 PY). The SAE rate was 14.6/100 PY (95% CI: 13.9, 15.4); infections were the most frequent SAE (4.5/100 PY; 95% CI: 4.1, 4.9). Rates of SAEs and serious infections were stable over time (Table). The rate of deaths was 0.4/100 PY (95% CI: 0.3, 0.6). The rate of malignancies was 0.8/100 PY, excluding nonmelanoma skin cancer (NMSC); the rate of NMSC was 0.3/100 PY. The overall rate of malignancies did not exceed reported background rates (SEER database), and overall rates, including NMSC, have remained stable with continued TCZ therapy (Table). GI perforations, including potential occurrence of sequelae from GI perforations (e.g., abscess, strictures), occurred at a rate of 2.6/1000 PY (95% CI: 1.8, 3.8); 59% (17/29) of these patients had colonic diverticular perforations. Preliminary epidemiologic data revealed that although the GI perforation rate was higher than in the general population, it was similar to rates in the RA population. Rates/100 PY of myocardial infarction and stroke were 0.3 (95% CI: 0.2, 0.4) and 0.2 (95% CI: 0.1, 0.3), respectively, were stable over time (Table), and did not exceed expected rates in the RA population (myocardial infarction, 0.3–0.8/100 PY; stroke, 0.5–0.7/100 PY). Eight patients experienced anaphylactic reactions and withdrew from the study. The rate of AEs leading to withdrawal was 5.4/100 PY, the most common AE leading to withdrawal were laboratory abnormalities (1.2/100PY, primarily transaminase elevations), infections/infections (1.0/100PY), and neoplasms (benign, malignant, or unspecified, 0.7/100PY).

Table. Event Rate Per 100 PY (95% CI) Over 12-Month Periods

<table>
<thead>
<tr>
<th>Period</th>
<th>AEs</th>
<th>SAEs</th>
<th>Serious infections</th>
<th>Malignancies</th>
<th>MI</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12</td>
<td>416.6 (409.8, 423.4)</td>
<td>157 (144, 171)</td>
<td>13.7 (12.4, 15.1)</td>
<td>0.9 (0.6, 1.3)</td>
<td>0.3 (0.1, 0.5)</td>
<td>0.3 (0.1, 0.5)</td>
</tr>
<tr>
<td>13–24</td>
<td>296.5 (290.4, 302.7)</td>
<td>137.7 (124.2, 151.3)</td>
<td>13.1 (13.0, 16.6)</td>
<td>1.1 (0.8, 1.5)</td>
<td>0.2 (0.1, 0.4)</td>
<td>0.2 (0.1, 0.4)</td>
</tr>
<tr>
<td>25–36</td>
<td>271.7 (265.4, 278.0)</td>
<td>151.1 (136.6, 165.6)</td>
<td>12.6 (11.8, 15.5)</td>
<td>0.4 (0.2, 0.6)</td>
<td>0.3 (0.1, 0.5)</td>
<td>0.3 (0.1, 0.5)</td>
</tr>
<tr>
<td>37–48</td>
<td>250.7 (243.0, 258.5)</td>
<td>136.6 (118.0, 155.5)</td>
<td>12.2 (11.4, 13.0)</td>
<td>1.0 (0.7, 1.3)</td>
<td>0.5 (0.2, 1.0)</td>
<td>0.5 (0.2, 1.0)</td>
</tr>
</tbody>
</table>

aIncluding NMSC.
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Safety of Combination Therapies in Early RA: A Systematic Compari-
son between Combination DMARDs and TNF Inhibitors with Metho-
trexate. Margaret H. Y. Ma, Andrew P. Cope and David L. Scott.
Surrey, United Kingdom, 2 Academic Department of Rheumatology, King’s
College London

Background: The use of combination regimens plays a central role in the
temporary treatment of early Rheumatoid Arthritis. As these therapies
become increasingly intensive and aggressive, drug toxicity is now a crucial
issue. The aim of this study was to systematically evaluate the frequency
and type of adverse effects associated with combination disease-modifying
anti-rheumatic drugs (DMARDs) and tumour necrosis factor inhibitors
(TNFi) combined with methotrexate (MTX) when compared with MTX
monotherapy.

Methods: A systematic literature search of Cochrane Library, EMBASE,
PubMed and Ovid Medline identified 15 relevant RCTs from 1960 to March
2010. The following outcome measures were assessed: patient withdrawal
due to toxicity, total adverse events, serious adverse events (total and by
individual systems), nausea, malignancy and deaths. Review Manager 5 was
used for meta-analysis.

Results: The preliminary search identified 459 citations. Out of these,
seven RCTs compared combination DMARD therapies with MTX mono-
therapy, seven RCTs compared combination DMARD therapies with MTX
monotherapy and one RCT included both treatment arms. Table 1 shows the baseline characteristics of the trials.

There were more patient withdrawals using combination DMARDs
therapy (OR 2.33, 95% CI 1.43, 3.77) and TNF/MTX when (OR 1.44 95%
CI 1.05, 1.98) compared to MTX monotherapy (Table 2). More patients
reported nausea when using combination DMARDs therapy (OR 2.06 95%
CI 1.05, 1.98) compared to MTX monotherapy (Table 2). More patients
used for meta-analysis.

Conclusion: Our systematic review showed that combination therapies
using synthetic or biological agents increased patient withdrawals due to
toxicity when compared to monotherapy. There were more serious adverse
events using biologics with methotrexate whereas nausea was an issue for
combination synthetic DMARDs. However, there were no significant differ-
ences in total numbers of adverse events, serious infections, malignancies and
deaths. Events reported in individual system were too rare to draw definitive
conclusions. Based on the available evidence, intensive therapies in early
rheumatoid arthritis appear to be justified.

Disclosure: M. H. Y. Ma: None; A. P. Cope: None; D. L. Scott: None.

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Scleritis: A New Paradoxical Effect of Etanercept? A Series of 3 Cases
and a Systematic Literature Review of Etanercept-Associated Inflamma-
Tary Eye Disease. Cécile Gaujoux-Viala, Cecilia Giampietro, Thomas
Gaujoux, Hang-Kong Ee, Philippe Oreel and Fréderic Liéot. Paris 6 –
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Paris, France, 2 Paris 6 – Pierre et Marie Curie University; Rheumatology,
Pitié-Salpêtrière Hospital, Paris, France 2 University of L’Aquila, L’Aquila,
Italy, 3 Paris 7 University, Medicine Faculty; AP-HP, Lariboisière Hospital,
Ophthalmology Department, Paris, France, 4 Paris Diderot University, School
of Medicine; Lariboisière Hospital, AP-HP, Rheumatology Department,
Paris, France

Background: The widespread use of TNFα antagonists has led to the recog-
nition of paradoxical adverse effects, defined as the onset or exacerbation
of disorders that are usually improved by TNFα antagonists. Cutaneous
psoriasis, Crohn disease and uveitis exacerbations have been extended
reported. Scleritis, a serious and sight threatening ocular inflammatory
disease, has recently been described like another possible paradoxical event
of anti-TNF-α and particulary of etanercept.

Objectives: 1) to report 3 cases of severe bilateral scleritis caused by
administration of etanercept for rheumatoid arthritis, and 2) to review the
literature related to inflammatory eye diseases associated with the use of
etanercept.

Methods: 1) Three cases of severe bilateral scleritis during etanercept
therapy were analyzed. 2) A systematic review of the literature in PUBMED,
EMBASE, Cochrane library and hand search was performed until May 2010
using terms as etanercept, Enbrel, scleritis, uveitis, orbitai myositis and
inflammatory eye disease.

Results: 1) Three patients with seropositive rheumatoid arthritis devel-
oped for the first time during their long-lasting disease (disease duration: 9,
20 and 21 years), scleritis or sclero-uveitis 7–28 months after the initiation
of etanercept. In all patients the underlying disease had well responded to
etanercept. In all patients the underlying disease had well responded to
etanercept.

2) 34 cases of inflammatory eye diseases believed to be associated with
the use of etanercept have been reported in the literature: 26 uveitis, 7 scleritis,
1 orbital myositis, concerning 14 RA, 8 juvenile idiopathic arthritis, 10
ankylosing spondylitis and 2 psoriatic spondylarthropathy. Mean age of
patients was 44.1 ± 13.7 years and 84.6% were women. The mean rheumatic
disease duration was 11.8 ± 9.6 years. Regarding the time-to-onset, the
average time between the beginning of etanercept therapy and the onset of
symptoms was 12.3 ± 9.1 months, with exposure times ranging between 1
and 36 months. Dechallenge was performed in 19 patients, leading to
resolution of symptoms. Rechallenge was done in 6 cases.

Conclusion: Ocular inflammation is paradoxically a potential adverse
event of etanercept even in previously uninvolved eyes. Patients being treated
with TNFa soluble receptors should be closely monitored for the develop-
ment of ocular signs and symptoms in order to detect flares secondary to
etanercept therapy and necessitating discontinuation.

Disclosure: C. Gaujoux-Viala: None; C. Giampietro: None; T. Gaujoux:
None; H.-K. Ee: None; P. Oreel: None; F. Liéot: None.
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Serious Infections with Ocrelizumab in Rheumatoid Arthritis: Pooled Results from Double-Blind periods of the Ocrelizumab phase III RA program, P Emery 1, W Rigby 2, PP Tak 3, T Dörner 4, MC Genovese 5, G Ferraccioli 7, E Martin-Mola 8, M Dougados 9, H Travers 10, E Fisheleva 10, James Yanes 4 and Berchman Vaz 1. 1Tucson, AZ, 2Southern Arizona VA Health Care System, Tucson, AZ, 3The University of Arizona Department of Internal Medicine, Tucson, AZ, 4The University of Arizona Section of Infectious Diseases, Tucson, AZ, 5The University of Arizona Section of Rheumatology, Arizona Arthritis Center, Tucson, AZ

Purpose: Ocrelizumab (OCR), a novel humanized monoclonal antibody that selectively targets CD20+ B cells, has been studied in 4 phase III randomized clinical trials in different patient (pt) populations with active rheumatoid arthritis (RA). Here, we report safety data from the double-blind, placebo (PBO)-controlled (DBPC) periods in phase III studies.

Methods: The OCR RA program includes 4 randomized, DBPC globally conducted trials assessing the safety and efficacy of OCR given as 2 infusions of 200 mg or 500 mg (400 mg × 1 in FEATURE) every 6 months in combination with methotrexate (MTX) or leflunomide (LEF). STAGE studied OCR in combination with MTX vs MTX alone in pts with an inadequate response (IR) to MTX. FEATURE included pts with an IR to at least one TNF inhibitor and was conducted in combination with either MTX or LEF. FEATURE investigated a single infusion regimen (400 mg) in pts who failed MTX and/or biologic DMARDs. FILM included pts who were MTX-naïve. Pooled safety data was analyzed for the DBPC periods of the RA phase III trials (48 wks in STAGE and FEATURE, 52 wks in FILM, and 24 wks in FEATURE). Frequencies and rates (events per 100 pt-yrs) of serious infection events (SIEs) were assessed by dose and region. Pts who received either 200 mg × 2 or 400 mg × 1 were grouped together in pooled analyses.

Results: SIE rates in each treatment group of each study are shown in Table. Increased SIE rates were predominantly seen with OCR 500 mg × 2. Following pooling of the 4 studies by treatment group, the weighted difference from PBO in the number of pts with at least one SIE was calculated to be 0.6 (95% CI: −1.3 to 2.4) for OCR 200 mg × 2 and 2.4 (95% CI: 0.3 to 4.5) for OCR 500 mg × 2. Thus, statistically significant increases in the number of pts experiencing an SIE were only seen in the 500 mg group. In a sub-analysis of SIE rates in one year trials, pooled by dose and region (Asia vs Other), OCR pts in Asia had relatively higher rates compared to rates seen in pts from non-Asian (Other) regions (Table), although the imbalance was also seen in non-Asian regions vs PBO. There were 9 opportunistic infections in 9 pts in OCR-treated pts comprised of 2 de novo pulmonary tuberculosis, 1 Pneumocystis jiroveci infected, 1 hepatitis B, 1 Mycobacterium kansasi infection, 1 esophageal candidiasis, 1 Varicella pneumonia, 1 histoplasmosis, 1 fungal pneumonia and there was one 1 Mycobacterium abscessus reported on PBO. None of these events resulted in death. No cases of PML were observed. 2 fatal infections (both pneumonias) occurred in the OCR 500-mg group in STAGE.

Conclusions: The pooled SIE rates were increased for OCR 500, but not OCR 200 compared to the PBO group in the DBPC periods with the imbalance primarily driven by rates in Asia. A detailed evaluation of risk factors for SIEs is underway. The same infection-related safety signal seen in the OCR high-dose has not been observed with rituximab.

Disclosure: P Emery: Roche, 2; W F C Rigby: Genentech and Biogen IDEC Inc, 5, 8, Roche, 2, 5; P P Tak: Genentech and Biogen IDEC Inc, 2, 5; Roche, 2, 5; T Dörner: Genentech and Biogen IDEC Inc, 5, Roche, 2, 5, 8; E Olech: Genentech and Biogen IDEC Inc, 2, 5, 8, Roche, 2, 5; M C Genovese: Genentech and Biogen IDEC Inc, 2, 5, Roche, 2, 5; G Ferraccioli: None; E Martin-Mola: Hoffmann-La Roche, Inc, 5; M Dougados: Roche, 5; H Travers: Roche, 1, 3; E Fisheleva: Roche, 3; W Dummer: Genentech and Biogen IDEC Inc, 3, Roche, 1.

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Subsequent Therapy of Patients with Biologic Response Modifiers after a Diagnosis of Coccidiomycosis Infection. Sara Taroumanian 1, Jeffrey R. Lisse 2, Eric P. Gall 3, Rafael G. Grau 1, Neil M. Ampi 2, Susan E. Hoover 4, James Yanes 5 and Berchman Vaz 3. 1Tucson, AZ, 2Southern Arizona VA Health Care System, Tucson, AZ, 3The University of Arizona Department of Internal Medicine, Tucson, AZ, 4The University of Arizona Section of Infectious Diseases, Tucson, AZ, 5The University of Arizona Section of Rheumatology, Arizona Arthritis Center, Tucson, AZ

Background: Coccidioides (coccidi) are dimorphic fungi endemic to California, Arizona, New Mexico, Texas, Mexico, and Central and South America (1). Annually, approximately 100,000 people in the endemic areas of the United States are diagnosed (dx) with primary coccidi (2). Chronic and disseminated disease may occur in up to 5% of patients (3); immunocompromised patients are very high risk.

Methods: A chart review of all patients seen at least once in a university-based outpatient rheumatology clinic in Tucson, AZ between 2007–2009 identified 298 patients who received biologic response modifiers (BRM), including anti-TNF drugs (TNF). Twenty four patients developed coccidi during treatment with BRM. The review emphasized the mode of dx, clinical manifestations, antifungal treatments, the duration of treatment, and the course of action taken after the dx was made.

Results: Twenty four patients developed coccidi during treatment. Prior to coccidi dx, 3/24 patients were taking only cytotoxic agents and 2/24 were on unclear immunosuppressive agents. The following table summarizes the medications at the time of the dx in the remaining patients.

Medications at the Time of Coccidi Diagnosis:

<table>
<thead>
<tr>
<th>Biologic Response Modifier (BRM)</th>
<th>Cytotoxic agent (one or two in combo with BRM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRM alone</td>
<td>Methotrexate, Leflunomide, Azathioprine</td>
</tr>
<tr>
<td>Infliximab (Inf)</td>
<td>9/24</td>
</tr>
<tr>
<td>Etanercept (Etr)</td>
<td>1/24</td>
</tr>
<tr>
<td>Adalimumab (Adal)</td>
<td>0/24</td>
</tr>
</tbody>
</table>

Mode of Coccidi Diagnosis

<table>
<thead>
<tr>
<th>Pos serologies (one or two)</th>
<th>Pox serol plus CCRX/CT chest findings w/o pulm symptoms</th>
<th>Dissemination to skin, joint or lungs with pulm symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos serologies (one or two)</td>
<td>4/24</td>
<td>13/24</td>
</tr>
<tr>
<td>4/24</td>
<td>13/24</td>
<td>6/24</td>
</tr>
</tbody>
</table>

Number of Patients

4/24

After the dx was made, all TNFs and DMARDs were held in 13/24 patients. 5/24 continued TNFs and/or DMARDs w/o any change in their regimen and 4/24 continued/started DMARDs but anti-TNFs were held. Two remaining patients had an unclear treatment of their cocci dx. Of the 13 patients in whom all TNFs and DMARDs were held, 11/13 were
Sustains Previously Established Efficacy.

Switching Patients (pts) with Rheumatoid Arthritis (RA) from Intravenous (IV) to Subcutaneous (SC) Abatacept Is Well Tolerated and Sustains Previously Established Efficacy. Edward C. Keystone1, Joel M. Kremer2, Anthony S. Russell3, Jane H. Box4, Carlos Abud-Mendoza5, Mario Alberto Garza Elizondo6, Allison Luo7, Richard Aranda8, Ingrid Delaet9, Rene Swanink1, Sheila Gujrathi1 and Michael E. Luggen1.1 Box Arthritis and Rheumatism of the Carolinas, Charlotte, NC, 2Bristol-Myers Squibb, Princeton, NJ, 3Bristol-Myers Squibb, Braine-l’Alleud, Belgium, 4Faculty of Medicine, Universidad Autonoma de Nuevo Leon, Monterrey, NL, Mexico, 5Regional Unit of Rheumatology, Faculty of Medicine and Central Hospital, University of San Luis Potosi, San Luis Potosi, Mexico, 6The Center for Rheumatology, Albany, NY, 7University of Alberta, Edmonton, AB, Canada, 8University of Cincinnati College of Medicine, Cincinnati, OH, 9University of Toronto and Mount Sinai Hospital, Toronto, ON, Canada

Background: IV abatacept is effective and well tolerated in pts with RA1,2. For some pts, the flexibility and convenience of self-administered treatment is desirable. Here, we evaluate the safety, immunogenicity and maintenance of efficacy in pts who switched from long-term IV abatacept to SC abatacept formulation.

Methods: This was an open-label, single-arm trial. Consenting and eligible pts completing ≥ 5 years of the AIM (Abatacept in Inadequate Responders to Methotrexate)1 or ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders)2 IV abatacept trials were enrolled and self-administered SC abatacept 125 mg/week via ready-to-use, prefilled syringes (no IV loading months, clinically indicated adjustments were allowed. Safety for the first 3 months administered). Initially, pts were maintained on the same stable doses of corticosteroids, DMARDs and analogs received during the IV trials; after 3 after switching from IV abatacept was the primary endpoint, reported in all pts who received ≥1 dose of SC abatacept. Immunogenicity, reported up to Month 3, was assessed by ELISA and electrochemiluminescence (ECL). Proportions of pts achieving Low Disease Activity State (LDAS; DAS28 [CRP] ≤3.2) and DAS28-defined remission (DAS28 [CRP] <2.6) are reported over 1 year. Data are as-observed for patients with available data at the visit of interest.

Results: In total, 123 pts entered the study (AIM, n=71; ATTAIN, n=52); mean age was 53.4 years, mean DAS28 was 3.4 and mean tender and swollen joint counts were 8.9 and 4.8, respectively. At Month 3, 120 (97.6%) pts were ongoing; no pts discontinued due to lack of efficacy. By Month 3, adverse events (AEs) were reported in 49 (39.8%) pts overall. One pt (0.8%) discontinued due to an AE (musculoskeletal pain, unlikely related to treatment) and one pt (0.8%) experienced a serious AE (worsening RA, unrelated to treatment). Two (1.6%) pts had local injection site reactions (erythema, pain); both were mild in intensity. Overall, 8 (122 (6.6%) pts had a positive abatacept-induced antibody response by ELISA; six of those eight had a positive response before enrollment. No pt had a positive response based on ECL. The proportions of pts (95% CI) achieving LDAS and remission was sustained after switching from IV to SC abatacept (N=123); LDAS: Day 1, 43.4% (34.6–52.2); Month 3, 54.6% (45.7–63.6); Year 1, 51.3% (42.1–60.5). Remission is shown in Figure 1.

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Conclusions: These data demonstrate that switching pts from IV to SC abatacept is well tolerated, with few and mild local injection-site reactions, and is associated with low immunogenicity. Furthermore, efficacy was sustained and not compromised following the switch.

References:

Disclosure: S. Taroumian: None; J. R. Lisse: Centocor, Inc.; 2, Genentech and Biogen IDEC Inc; 2, UCB, Inc.; 2; E. P. Galt: None; R. G. Grau: None; N. M. Ampe: None; S. E. Hoover: None; J. Yanes: None; B. Vaz: None.

The Effect on MTX Polyglutamate Concentration Profile after Changing from Oral to Subcutaneous Methotrexate in Rheumatoid Arthritis. Lisa K. Stamp1, John L. O’Donnell1, Peter Chapman1, Mei Zhang2, Jill James2, Christopher Frampston2 and Murray Barclay3.1 Canterbury Health Laboratories, Christchurch, New Zealand, 2Canterbury Health Laboratories, Christchurch Hospital, 3University of Otago, Christchurch, New Zealand, 4University of Otago

Background: The pharmacokinetics of oral methotrexate (MTX) in RA have been described previously (1). Some patients may change from the oral to subcutaneous (SC) route of administration to try to reduce adverse effects or improve disease control. The aim of this study was to determine the effect of changing from oral to SC administration of MTX on the concentrations of red blood cell MTX polyglutamates (RBC MTXGlus). Methods: Twenty-two patients on stable dose weekly oral MTX were changed to SC weekly MTX at the same dose. Trough RBC MTXGlus concentrations were measured by HPLC in samples taken weekly until week 8, then fortnightly until week 16 and then 4-weekly until week 24. Median concentrations were fitted to a standard first-order exponential model with Graph Pad Prism 5.0.

Results: Of the 22 patients, 72.7% were female and mean age was 53.4 years (32–70). The mean duration of RA was 7.3 years (0.75 – 21). All patients were receiving 20mg MTX weekly followed by folic acid 5mg/week four days later. There were no dose changes during the study period. RBC MTXGlus, MTXGluc, and MTXGlua concentrations increased significantly from week 0 to week 24, by factors of 1.3, 1.9 and 2.6-fold respectively. However, there was no significant change in RBC MTXGlus, or MTXGlua, concentrations. There was a significant reduction in the proportion of RBC MTXGlua and MTXGlub and increase in the proportions of RBC MTXGlua, MTXGluc, and MTXGlua, contributing to the total RBC MTXGlus from week 0 to week 24.

MTXGlua, MTXGluc, and MTXGlua concentrations fitted...
the first-order exponential model well whilst MTXGlu1 and MTXGlu2 fitted poorly (Figure). The half-life of accumulation was 8.9 weeks for MTXGlu1, 12.2 weeks for MTXGlu2 and 9.9 weeks for MTXGlu4 and 10.4 weeks for MTXGlu5. The time to achieve 90% of steady state was 29.8 weeks for MTXGlu1, 40.4 weeks for MTXGlu2, and 33.2 weeks for MTXGlu4 and 34.5 weeks for MTXGlu5.

![Figure 1. Median MTXGlu4 concentrations and fitted curves over 24 weeks.](image)

**Conclusions:** Changing from oral to SC MTX resulted in an alteration in the ratio of short and long chain MTX polyglutamates. It took at least 6 months for long chain MTX polyglutamates to reach 90% of steady state after changing to SC administration. However, the time to reach steady state was shorter than that observed in patients commencing oral MTX. Adequate time must be allowed to determine clinical response to a change in route of administration of MTX.

**Reference:**

**Disclosure:** L. K. Stamp: None; J. L. O’Donnell: None; P. Chapman: None; M. Zhang: None; J. James: None; C. Frampton: None; M. Barclay: None.

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**TNF Switch after Failure of One or More TNF Inhibitors—Results of an Observational Study.** Katerina Chatzidiomysiou1 and Ronald Van Vollenhoven1, 2

**Background:** The optimal alternative treatment for those patients who fail an anti-TNF is not clearly described. The purpose of this study was to determine whether patients who had failed one or more anti-TNFs benefit from switching to another anti-TNF and whether the type of switch is significant.

**Methods:** The Stockholm registry “STURE” was used and treatment results at 3 and 6 months were analysed according to DAS28 reductions and EULAR responses by type of TNF switch, number of switches and reason for discontinuation (lack of efficacy or intolerance).

**Results:** 850 patients who had previously failed a TNF inhibitor switched to another biologic: 679 switched to an alternative TNF antagonist, 294 to adalimumab and 77 to infliximab. By the end of 6 months statistically significant improvements in DAS28 were observed (p<0.001) for etanercept and adalimumab and p=0.006 for infliximab. At 3 and 6 months significantly greater reductions in DAS28 were observed for etanercept compared to the anti-TNF monoclonal antibodies taken together (1.56 ± 1.34 vs. 1.14 ± 1.26, p=0.005 and 1.58 ± 1.46 vs. 1.15 ± 1.4, p=0.01, respectively). At 6 months the percentage of EULAR good/moderate/no responders was 16.3/87.4/4.7 for the anti-TNF monoclonal antibodies and 29/43/53/35.3 for etanercept (p=0.009). Table 1 summarizes the response to therapy according to the type of switch. The difference between etanercept and monoclonal antibodies was observed both for the second and the third switch. At 6 months the subgroup of patients who discontinued previous anti-TNF monoclonal antibody for reason of loss of efficacy achieved significantly better results when switched to etanercept than when switched to an alternative antibody (ΔDAS28 2.11 ± 1.5 vs. 1.09 ± 1.43, p=0.008).

**Table 1. Response to therapy with an alternative TNF inhibitor (monoclonal antibody or soluble TNF receptor) according to DAS28 reductions and EULAR response during the first 6 months.**

<table>
<thead>
<tr>
<th>Type of Switch</th>
<th>TNF Monoclonal Ab</th>
<th>TNF Monoclonal Ab</th>
<th>EULAR Good</th>
<th>EULAR Moderate</th>
<th>EULAR No response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>1.15 ± 1.5</td>
<td>1.56 ± 1.33</td>
<td>29.0%</td>
<td>29.4%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1.24 ± 1.5</td>
<td>1.57 ± 1.45</td>
<td>42.8%</td>
<td>35.3%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1.15 ± 1.25</td>
<td>1.22 ± 1.25</td>
<td>42.8%</td>
<td>35.3%</td>
<td>17.0%</td>
</tr>
</tbody>
</table>

**Conclusion:** In this observational cohort patients having failed anti-TNF therapy do benefit from switching to other TNF inhibitors. Better results were observed when switching from a TNF monoclonal antibody to etanercept rather than to an alternative antibody, especially when the reason for failure of the first was loss of efficacy.

**Disclosure:** K. Chatzidiomysiou: None; R. Van Vollenhoven: Roche, 2, 5.

**419**

**TNF Therapy and the Risk of Serious Infection and Malignancy in Patients with Early Rheumatoid Arthritis: A Meta-Analysis of Randomized Controlled Trials.** Andrew E. Thompson1, J. James1, C. Frampton2, J. James1, C. Frampton2, J. James1, C. Frampton2, J. James1, C. Frampton2, J. James1, C. Frampton2, J. James1, C. Frampton2,

**Background:** The efficacy of TNF-inhibition has been shown in numerous trials including patients with both early and established rheumatoid arthritis (RA). As a result, TNF-inhibition has significantly improved the signs and symptoms, function, radiographic progression and quality of life for patients with RA. The most important side effects of TNF-inhibition are the risks of serious infection and the potential for malignancy. Although product monographs include warnings & precautions about these side effects they do not provide an estimate of risk. Meta-analysis of published clinical trial data and registry data are common methodologies used to estimate this risk. However, the challenge with current meta-analytic data and on-going registry data is the inclusion of heterogeneous populations with varying degrees of co-morbidity. This heterogeneity makes it very difficult to understand and communicate risk for individual patients. It is important to know if early RA has the same risk of serious infection or malignancy compared with older patients with long-standing RA and multiple co-morbidities.

**Objective:** To conduct a meta-analysis of the rates of serious infection and malignancy in patients with early rheumatoid arthritis who have started on anti-TNF therapy and were naïve to DMARD/Methotrexate therapy.

**Methods:** A systematic literature search was conducted through the summer of 2009. All studies included were randomized, double-blind, placebo-controlled of patients with early rheumatoid arthritis who were started on anti-TNF therapy without prior DMARD/Methotrexate use. Six trials met our inclusion criteria that included 2183 patients receiving biologic therapy and 1236 patients receiving control therapy. All data extracted was from published trials.

**Results:** A pooled odds ratio (Mantel-Haenszel methods with a continuity correction for sparse data) was calculated for serious infections (requiring hospitalization) and malignancies. The pooled odds ratio for serious infections was 1.16 (95% CI, 0.75–1.77).

The pooled odds ratio for malignancies was 1.07 (95% CI, 0.52–2.23).
There was no significant difference between the anti-TNF therapy and the control therapy in both serious infection rates and malignancy rates.

Conclusions: While other meta-analyses have shown an increased risk of serious infection and malignancy in patients taking anti-TNF therapy, our results show that there is not an increased risk when the patients have early disease and haven’t previously failed DMARD/Methotrexate therapy.


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Treatment with Infliximab Improves Clinical Response and Physical Function in Patients with Moderate or Severe Rheumatoid Arthritis Actively Switch from Etanercept or Adalimumab Therapy. Roy M. Fleischmann1, John A. Goldman1, Marjatta Leirisalo-Repo2, Ellen I. Zanetakis3, Ishani S. El-Kadi1, Herbert L. Kelner6, Rebecca Bolce3, Jim Wang5, Raphael Dehoratius1 and Dennis Decktor1. 1Arthritis and Osteoporosis Association, Freehold, NJ, 2Atlanta Center for Clinical Research, 8University of Texas SW Medical Center, Dallas, TX

Background: Anecdotal evidence suggests that RA pts with active disease, despite tx with SC TNFα inhibitors, respond to infliximab (IFX). The dosing flexibility described in the IFX prescribing information allows for the tx of continued active disease by adjusting dose for achievement of specific targeted clinical outcomes.

Purpose: To evaluate the safety & efficacy of IFX in RA pts with moderate or severe RA despite tx with etanercept (ETN) or adalimumab (ADA).

Methods: This is a Phase 4, multicenter, open-label, assessor-blinded, active switch study of IFX in pts with active RA who received MTX and had inadequate response (DAS28 score ≥ 3.6 and ≥ 6 swollen and ≥ 6 tender joints) to ETN or ADA. Pts were on stable dose of ≥ 7.5 mg/wk of MTX for ≥ 4 wks prior to screening. Pts receiving ETN were switched no less than 1 wk and no more than 2 wks after the last dose; pts receiving ADA were switched no less than 2 wks and no more than 4wks after the last dose. Pts received open-label 3 mg/kg IFX infusions at wks 0, 2, and 6. Pts who either achieved/maintained EULAR response at wks 14 or 22 remained on current IFX dose. IFX dose was increased by 2 mg/kg for pts who did not achieve/lost response. EULAR response was evaluated at wk 10 post induction (primary endpoint) and following incremental increases in IFX dose in pts not adequately responding to the initial IFX doses. Physical function was assessed using HAQ.

Results: Of the 203 pts enrolled, data for 197 were evaluable. 60.9% and 39.1% of pts were previously treated with ETN or ADA, respectively. Baseline demographics were reported previously.1 EULAR response was achieved by 49.7% of pts at wk 10 (55.6%, per protocol analysis) and 51.8% at wk 26 (61%, per protocol analysis) with/without dose adjustment. Among pts responsive to 3mg/kg induction dose, 45% maintained response through wk 26. ACR 20, 50, and 70 responses were achieved in 28.4%, 12.2%, and 1.5% of pts at wk 10, respectively. These responses improved to 35.5% (ACR20), 18.3% (ACR50), and 7.1% (ACR70) at wk 26. Mean CDAI and SDAI were 40.1 and 41.2, respectively, at baseline and significantly improved to 21.45 (p < 0.0001) and 22.28 (p < 0.0001), respectively, at wk 26. 48.3% of pts previously treated with ETN and 57.1% of pts previously treated with ADA achieved a EULAR response at wk 26. Changes from baseline at wk 10 and 26 in DAS28, HAQ, SJC and TJC are described (Table). At least 1 AE and severe AE were reported in 70.4% and 4.9% of pts, respectively. 6.9% of pts experienced at least 1 infusion reaction (1.6% of infusions were associated with an infusion reaction.)

Conclusion: RA pts actively switched from tx with ETN or ADA to IFX, without a washout period, demonstrated a statistically significant and clinically important improvement in EULAR response and physical function. IFX was generally well-tolerated with no new safety signals observed.

Table. Summary of mean (SD) change from baseline at wk 10 and 26

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Change from baseline to wk 10</th>
<th>Change from baseline to wk 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28 (ESR)</td>
<td>6.193 (0.981)</td>
<td>-1.076 (1.146)*</td>
<td>-1.468 (1.437)*</td>
</tr>
<tr>
<td>DAS28 (CRP)</td>
<td>5.701 (0.896)</td>
<td>-1.088 (1.090)*</td>
<td>-1.436 (1.312)*</td>
</tr>
<tr>
<td>HAQ improvement</td>
<td>1.334 (0.577)</td>
<td>-0.173 (0.455)*</td>
<td>-0.223 (0.497)*</td>
</tr>
<tr>
<td>SJC</td>
<td>17.315 (10.537)</td>
<td>-6.960 (10.686)*</td>
<td>-8.283 (11.380)*</td>
</tr>
<tr>
<td>TJC</td>
<td>30.188 (16.893)</td>
<td>-10.460 (14.067)*</td>
<td>-13.197 (14.304)*</td>
</tr>
</tbody>
</table>

* p < 0.001

Disclosure: R. M. Fleischmann: Centocor Ortho Biotech Sciences, LLC, 2, 9; J. A. Goldman: Centocor Ortho Biotech Sciences, LLC, 2, 9; M. Leirisalo-Repo: Centocor Ortho Biotech Sciences, LLC, 2, 9; E. I. Zanetakis: Centocor Ortho Biotech Sciences, LLC, 2, 9; H. S. El-Kadi: Centocor Ortho Biotech Sciences, LLC, 2, 9; H. L. Kelner: Centocor Ortho Biotech Sciences, LLC, 2, 9; R. Bolee: Centocor Ortho Biotech Sciences, LLC, 3; J. Wang: Johnson and Johnson Pharmaceutical Research and Development, LLC, 3; R. Dehoratius: Centocor Ortho Biotech Sciences, LLC, 3; D. Decktor: Centocor Ortho Biotech Sciences, LLC, 3.

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Varicella Zoster Virus (VZV) Infections Are Increased in Patients with Rheumatoid Arthritis (RA) Treated with Anti-TNF Therapy: Results from the British Society for Rheumatology Biologics Register (BSBRBR). James Galloway1, Alison Moseley2, Louise Mercer2, Will Dixon3, Bo Fu4, Andrew Ustianowski5, Kath Watson6, Mark Lunt7,8 BSBR Control Centre Consortium2, Kimmie Hyrich9, Deborah Symmons9 and on Behalf of the British Society for Rheumatology Biologics Register2,1University of Manchester, Manchester, United Kingdom, 2University of Manchester

Introduction: VZV infection is highly prevalent with 95% of adults showing seropositivity. The initial infection typically occurs in childhood causing chicken pox. Reactivation later in life results in herpes zoster (shingles). The immune defence against both chicken pox and herpes zoster is T-cell mediated. Anti-TNF therapy interacts with this pathway and hence theoretically predisposes to VZV associated disease. The aim of this study was to compare rates of herpes zoster in rheumatoid arthritis (RA) patients treated with anti-TNF agents or non-biologic disease modifying anti-rheumatic drugs (DMARDs); and to compare the rates for the individual anti-TNF agents.

Methods: The BSBRBR was established in 2001 to evaluate the safety of anti-TNF therapies etanercept (ETN), infliximab (IFX) and adalimumab (ADA) in patients with RA. The anti-TNF treated cohort was recruited alongside a comparator group with active disease (DAS28 >4.2) treated with DMARDs. Patients were recruited between 01/10/2001 and 30/06/2008 and followed up by consultant and patient questionnaires. For this analysis patients were followed until the first episode of herpes zoster infection, death or 31/12/2009, whichever came first. An infection was attributed to anti-TNF if diagnosed while the patient was actively receiving the drug (up to the date of the first missed dose). A Cox proportional hazards model was used to compare rates between cohorts and adjustment was made for differences in baseline characteristics including age, gender, disease severity, disease duration, baseline steroid exposure and co-morbidity using an inverse probability of treatment weighting propensity model.

Results: Three hundred and twenty two herpes zoster infections occurred in the anti-TNF cohort: IR 7.8/1000 (95% CI 7.0, 8.7) and 46 in the DMARD cohort (IR 4.0/1000 pyrs (95% CI 3.0, 5.4) (Table). The adjusted hazard ratio for herpes zoster was 2.2 (95% CI 1.4, 3.6). A greater proportion of the cases in the anti-TNF cohort were severe (defined as herpes zoster being a primary reason for hospitalisation, requiring intravenous antivirals or being multidermal) 6% vs 0.2%. A similar pattern of risk was seen for each anti-TNF therapy with no statistical difference between etanercept and the monoclonal antibodies. In total, 12 cases of chicken pox infection were reported in the anti-TNF cohort and none in the DMARD cohort.

Conclusion: Anti-TNF therapy is associated with a significantly increased risk of VZV associated disease. This information would support the evaluation of VZV vaccination in an RA population.

Table. Baseline characteristics and incidence of VZV infections

<table>
<thead>
<tr>
<th></th>
<th>DMARD</th>
<th>All anti-TNF</th>
<th>ETN</th>
<th>INF</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>3,666</td>
<td>11,864</td>
<td>4,136</td>
<td>3,472</td>
<td>4,256</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>60 (12)</td>
<td>56 (12)</td>
<td>56 (12)</td>
<td>56 (12)</td>
<td>57 (12)</td>
</tr>
<tr>
<td>Female gender, %</td>
<td>2648 (72)</td>
<td>9038 (76)</td>
<td>3190 (77)</td>
<td>2624 (76)</td>
<td>3224 (76)</td>
</tr>
<tr>
<td>Disease Duration: years, median (IQR)</td>
<td>6 (1–15)</td>
<td>11 (6–19)</td>
<td>12 (6–19)</td>
<td>12 (6–19)</td>
<td>10 (5–18)</td>
</tr>
<tr>
<td>Baseline steroid use: %</td>
<td>834 (23)</td>
<td>5243 (44)</td>
<td>1977 (46)</td>
<td>1609 (46)</td>
<td>1657 (39)</td>
</tr>
<tr>
<td>DAS28, mean (SD)</td>
<td>5.1 (1.3)</td>
<td>6.6 (1.0)</td>
<td>6.6 (1.0)</td>
<td>6.6 (1.0)</td>
<td>6.5 (1.0)</td>
</tr>
<tr>
<td>Exposure (pyrs)</td>
<td>11,417</td>
<td>41,235</td>
<td>17,977</td>
<td>10,484</td>
<td>12,773</td>
</tr>
<tr>
<td>Shingles events</td>
<td>6</td>
<td>12</td>
<td>103</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Shingles infection rate/1000 pyrs</td>
<td>4.0 [3.0, 5.4]</td>
<td>7.8 [7.0, 8.7]</td>
<td>6.7 [5.6, 8.0]</td>
<td>9.8 [8.0, 11.9]</td>
<td>7.7 [6.2, 9.3]</td>
</tr>
<tr>
<td>Shingles adjusted HR*</td>
<td>Ref</td>
<td>2.2 [1.4, 3.6]</td>
<td>2.2 [1.3, 3.6]</td>
<td>2.5 [1.5, 4.0]</td>
<td>2.1 [1.2, 3.7]</td>
</tr>
<tr>
<td>Chicken pox</td>
<td>0</td>
<td>12</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusting for potential confounders was performed using an inverse probability of treatment weighted propensity model including age, gender, co-morbidity, smoking, baseline steroid exposure, disease duration, disease severity and year of entry into study. Missing baseline data were replaced using multiple imputation.

Disclosure: J. Galloway: None; A. Moseley: None; L. Mercer: None; W. Dixon: None; B. Fu: None; A. Ustianowski: None; K. Watson: None; M. Lunt: None; BSRBR Control Centre Consortium: None; K. Hyrich: None; D. Symmons: None; on Behalf of the British Society for Rheumatology Biologics Register: None.

ACR Poster Session A
Systemic Lupus Enzymathritis - Animal Models
Monday, November 8, 2010, 9:00 AM–6:00 PM

422 Altered microRNA Expression in the Murine Tri-Congenic B6.Sle123 Model. Barry Garchow1, Yiu Tak Leung3, Roberto Caricchio2 and Marianthi Kiriakidou1. 1Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, 2University of Nebraska Medical Center, Omaha, NE, 3University of Nebraska Medical Center

Statement of Purpose: microRNAs (miRNAs) have emerged over the last decade as a conserved class of non-coding RNAs that regulate gene expression. Current evidence supports a key role for miRNAs in the development and function of the immune system and emerging evidence underscores the importance of this pathway in autoimmunity. However, the expression and function of miRNAs in SLE and the signaling pathways regulated by miRNAs in lupus remain largely unknown.

Research in our laboratory focuses on the function of miRNAs in the tri-congenic mouse model B6.Sle123. Autoimmune disease in B6.Sle123 is characterized by autoantibodies, lymphopenia, and glomerulonephritis, strongly resembling human lupus. We studied miRNA expression in mouse lupus B and T cells over the course of twelve months; before manifestation of renal disease and as it progresses from mild proteinuria to fatal nephrotic syndrome.

Methods: Mice (B6.Sle123 and C57BL6/J) were sacrificed at 2, 6 and 12 months of age and their spleens harvested. Splenocytes from individual mice were FACs purified into CD19+, CD3+ and CD44low/CD62Lhigh and CD3+CD44low/CD62Lhigh cell populations. For quantitative real-time PCR, total RNA from purified cells was reverse-transcribed using microRNA specific stem-loop primers. RT products were amplified by real-time PCR. Fold change differences were calculated using the ΔΔCt method. For Northern blotting, total RNA from purified cells was separated on 15% urea-polyacrylamide gels, blotted and UV crosslinked. MicroRNAs were visualized by autoradiography and quantitated using the GelQuant software. For Western blotting, total protein from purified cells were separated by PAGE and blotted on nitrocellulose membranes. Bands were visualized by chemiluminescence and quantitated with ImageJ software.

Data Summary: We asked if altered microRNA expression in B6.Sle123 B and T lymphocytes correlates severity of renal disease. Here we report that several microRNAs are differentially expressed in B and T lymphocytes from lupus mice and their expression correlates with the severity of lupus nephritis. All eight miRNAs that we showed as upregulated in B cells from mice with severe SLE nephritis (miR-21, 34a, 221, 222, 223, 155 and 142-5p) and have been also recently reported as upregulated in human lupus nephritis.

Conclusions: Our findings show that several microRNAs with known key roles in the development and function of lymphocytes are differentially expressed in B6.Sle123 derived B and T cells and their expression correlates with the severity of renal disease. Correlation of our results with recently published data of miRNA expression in PBMCs from patients with lupus nephritis indicates that B6.Sle123 is a suitable model to study the miRNA function in lupus. We are now focusing on identifying miRNA-dependent signaling pathways that are uniquely affected in this model, in which disease manifestations and disordered mechanisms overlap with those in human SLE. In our studies we employ novel in vivo experimental methods to knock down endogenous miRNAs in B and T cells in order to dissect these pathways.

Disclosure: B. Garchow: None; Y. T. Leung: None; R. Caricchio: None; M. Kiriakidou: None.

423 Amelioration of Lupus Nephritis by a Macromolecular Prodrug of Dexamethasone in NZB/W F1 Mice. Fang Yuan1, Richard K. Nelson2, Xin-ming Liu3, Karen A. Gould4 and Dong Wang5. 1Univ Nebraska Med Ctr, Omaha, NE, 2University of Nebraska Medical Center

Purpose: Though developed with specific molecular targets, most lupus nephritis drugs do not have tissue specificity to renal inflammation sites, leading to limited efficacy and potentially severe systemic side effects. To address this problem, we propose to develop P-Dex, a macromolecular prodrug of dexamethasone (Dex) using N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer, which would specifically target the kidneys of lupus nephritis subjects to improve efficacy and reduce systemic toxicities associated with Dex phosphate treatment.

Methods: Female NZB/W F1 lupus-prone mice (16-wk-old) were treated with Dex phosphate (1.32 mg/kg, daily i.p. injections for 8 wks) and P-Dex (250 mg/kg, monthly i.v. injections for 8 wks) with HPMA homopolymer (HPMA) and saline as controls. The overall doses of P-Dex and Dex phosphate are equivalent in terms of Dex content. Albuminuria was measured weekly using AbLustig. Mean arterial pressure (MAP) was measured by the tail cuff method every 4 wks. Serum was isolated from blood collected from the saphenous vein every 4 wks. Mice were sacrificed 1 wk after cessation of treatment (wk 9). Kidneys were harvested for histological assessment of nephritis. Femurs were harvested for bone mineral density (BMD) analysis.

Results: P-Dex treatment of NZB/W F1 mice resulted in an attenuated onset of nephritis (as measured by durable albuminuria ≥ 2 or 100 mg/dL). At wk 9, the incidence of albuminuria was 0% in the P-Dex group, whereas the incidence of albuminuria was 100% in saline treated group, 70 % in PHPMA group and 46.7% in Dex phosphate group (p<0.001). A significant improvement of hypertension (MAP was reduced from 134±16 mmHg to 110±11 mmHg, p < 0.01) was only found in P-Dex treated group. Furthermore, the P-Dex treated group had a significantly higher femur BMD value than the Dex phosphate group (p < 0.001). No significant difference in BMD value was found among the P-Dex, saline and PHPMA groups.

Conclusion: P-Dex displayed highly efficient attenuation of lupus nephritis and improved renal function, compared to the treatment with equivalent dose Dex phosphate. It also significantly reduced the bone loss caused by long-term Dex phosphate treatment. Collectively, these data suggest that the macromolecular prodrug of dexamethasone could provide more effective amelioration of lupus nephritis with reduced systemic toxicity.

Disclosure: F. Yuan: None; R. K. Nelson: None; X.-m. Liu: None; K. A. Gould: None; D. Wang: None.

424 An Intrinsich B Cell Defect That Affects Toll-Like Receptor Signaling Supports Autoimmunity in New Zealand Black Chromosome 13 Congenic Mice. Christina Loh1, Evelyn Pau2, Nan-Hua Chang3 and Joan E. Wither4. 1University Health Network, 2University of Toronto, Toronto, ON, Canada, 3University of Toronto

Purpose: Introggression of a New Zealand Black (NZB) chromosome 13 interval onto the B6 background (denoted, c13) is sufficient to produce many of the hallmark characteristics of lupus, including, high titre anti-chromatin antibody (Ab) production, abnormal B cell activation, and renal disease. In this study we sought to characterize the immune defects leading to these pathogenic abnormalities.

Methods: Bone marrow (BM) chimeras were generated by reconstituting lethally irradiated B6, B6.Thy1algaHa, or B6.CD45.1 mice with B6, B6.Thy1algaHa, B6.CD45.1, c13, c13.1g, or various mixtures of BM cells.
Anti-egg hen lysozyme (HEL) immunoglobulin (Ig) and/or soluble HEL transgenes (Tg) were crossed onto the c13 mouse strain (denoted, c13.lg and c13.lg.sHEL) to assess B cell tolerance. Antibody production was measured by ELISA and splenic cellular profiles were examined by flow cytometry. For Toll-like receptor (TLR) stimulation, splenocytes from 10–14 week old B6, c13, B6.lg, or c13.lg mice were cultured in the presence of poly(I:C) (TLR3), imiquimod (TLR7), or ODN1826 (TLR9) and/or HEL for 72 hrs. Proliferation was measured by CFSE dilution.

**Results:** Serologic and cellular characterization of hematopoietic radiation chimeras and anti-HEL lg transgenic mice revealed that the autoimmune phenotype in c13 mice could be transferred by BM cells. Assessment of mixed hematopoietic chimeric and c13.lg mice indicated that autoreactive congenic B cells were required for disease initiation. Examination of c13.lg.sHEL mice, a classic model of B cell anergy, revealed that B cell anergy was intact in congenic mice. However, there was enhanced selection and/or survival of endogenous B cells resulting in high titer anti-congenic and -SmRNP antibody production in these mice. Given the preferential generation of anti-nuclear over anti-HEL antibodies, we examined whether nuclear-acid sensing TLR signaling was altered in these mice. Congenic B cells were hyper-responsive to the TLR3 ligand, polyinosine-polycytidylic acid (poly(I:C)), a double stranded RNA analogue, demonstrating enhanced proliferation, survival, and induction of intracellular TLR3 expression as compared to control B cells. Using mixed cell cultures, this response was found to be intrinsic to congenic B cells.

**Conclusions:** An intrinsic defect affecting self-reactive B cell selection and/or function that is associated with TLR3-hyper-responsiveness is required for initiation of autoimmunity in NZB chromosome 13 congenic mice.

**Disclosure:** C. Loh: None; E. Pau: None; N.-H. Chang: None; J. E. Wither: None.

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Breach of B Cell Tolerance in New Zealand Black Chromosome 1 Congenic Mice. Nan-Hua Chang1, Evelyn Pau2, Christina Loh2 and Joan E. Wither2. 1Toronto Western Research Institute, Toronto, ON, Canada, 2University Health Network, Toronto, ON, Canada, 3University of Toronto

**Purpose:** The production of anti-nuclear antibodies in lupus indicates a breach of B cell tolerance, however the precise defects that lead to this breach are unknown. Our laboratory has produced C57BL/6 (B6) congenic mice with homozygous NZB chromosome 1 intervals and localized the genetic locus leading to autoantibody production in these mice to a 96–100 cM interval, which contains Nba2. In this study we have backcrossed anti-egg hen white lysozyme (HEL) Ig and soluble HEL transgenes (double Tg, dTg) onto the B6.NZBc1(96–100 cM) background to assess B cell anergy.

**Methods:** Serum IgM and IgG anti-HEL antibody production was measured by ELISA. Splenic B cell populations were characterized by flow cytometry. Uproregulation of CD86 and B cell apoptosis was determined by flow cytometry following stimulation of splenocytes with anti-IgM F(ab)2 Ab or HEL for 18 hrs. To quantify phosphatidylinositol 3,4,5-trisphosphate production (PI(3,4,5)P3), splenocytes were stimulated with anti-IgM F(ab)2 Ab for 5 min, fixed with 1% paraformaldehyde, stained intracellularly with an anti-PI(3,4,5)P3 Ab. Calcium flux was measured by stimulating Indo-1-labeled immature anti-HEL Ig Tg B cells (generated by culturing bone marrow in IL-7 for 5 days) with anti-IgM F(ab)2 Ab.

**Results:** B6.NZBc1(96–100 cM) dTg B cells produced increased levels of IgM and IgG anti-HEL Ab. Indicating a breach of B cell anergy in these mice. IgM down-regulation and the proportion of T1, T2, follicular and marginal zone B cells were similar in B6 and B6.NZBc1(96–100 cM) dTg mice, however B6.NZBc1(96–100 cM) dTg mice had an increased proportion of IgM+ B cells expressing edited Ig-lambda light chains. Following stimulation with anti-IgM Ab or sHEL, B cells from B6.NZBc1(96–100 cM) dTg mice demonstrated enhanced up-regulation of CD86 and decreased apoptosis, suggesting defective anergy induction. To gain further insight into the mechanism leading to this defect, upregulation of PI(3,4,5)P3, was contrasted in B6 and B6.NZBc1(96–100 cM) dTg B cells following Ig receptor cross-linking. B6.NZBc1(96–100 cM) dTg B cells demonstrated enhanced generation of PI(3,4,5)P3, indicating that altered B cell signaling leads to the B cell anergy defect. Consistent with this possibility, calcium mobilization was impaired in naive immature anti-HEL Ig Tg B cells from B6.NZBc1(96–100 cM) mice following Ig receptor cross-linking.

**Conclusion:** Our findings demonstrate that genetic loci within the NZB chromosome 1 (96–100 cM) interval lead a breach of B cell anergy.

**Disclosure:** N.-H. Chang: None; E. Pau: None; C. Loh: None; J. E. Wither: None.

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Dysfunction of Hematopoietic Stem Cells in Lupus Mice. Haitao Niu1, Luokun Xie2, Laurence Marguerite Morel3, Betty Diamond1 and Yong-rui Zou1. 1Feinstein Institute for Medical Research, Manhasset, NY, 2The Feinstein Institute for Medical Research, Manhasset, NY, 3The Feinstein Institute for Medical Research, University of Florida

**Background:** Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disorder. Among the various clinical manifestations of SLE, leukopenia and lymphopenia represent the most prevalent initial abnormalities, and are associated with higher disease activity. The specific cause of leukopenia and lymphopenia in SLE is unknown. Conceivably, the chronic inflammatory milieu may impair the maturation and survival of hematopoietic cells. Alternatively, hematopoietic stem cells (HSCs) of SLE patients may be functionally defective, thereby resulting in poor hematopoietic regeneration. We investigated whether HSC function is impaired in a mouse model of SLE, and whether the change in HSC function is a cell-intrinsic event or affected by the microenvironment of SLE.

**Materials and Methods:** We determined whether HSCs undergo functional changes in B6.Sle1.2.3 triple congenic (TC) mice. TC mice are C57/BL6 mice that carry three NZM2410-derived major lupus susceptibility loci and develop severe systemic autoimmunity and fatal nephritis. 7-month-old TC female mice with high levels of autoantibodies and proteinuria were selected for the studies. B6 female mice were used as controls. First, we examined whether the pool size of HSCs was changed in TC mice. We determined the HCS cellularity in the bone marrow (BM) by flow cytometry. In addition, hematopoietic lineage cells were detected with antibodies for lineage negative (Lin-): B220, CD3, CD4, CD8, CD11b, Gr1, TER119) and c-KIT and Sca-1+ (referred to as LSK cells). Long-term reconstituting HSCs (LT-HSCs) were further identified as CD48+ CD34+ CD150+ LSK cells. Second, we examined whether the pathologic microenvironment of lupus mice alters HSC quiescence by measuring the cell-cycle status of HSCs based on their content of pyronin stained RNA and Hoechst stained DNA. Third, we examined whether HSC localization was altered in lupus mice by determining the HSC frequency in the periphery. Lastly, we analyzed HSC function by transplantation assays. To do so, 2 X 10^6 BM cells from TC or control C57/BL6 mice (CD45.2+) were transferred into irradiated B6.SJL mice (CD45.1-).

**Results:** We found that LT-HSCs were 4-fold more abundant in the BM of TC mice than that in control mice. This expansion of the HSC compartment was accompanied by an increase in the number of cycling HSCs in the BM and mobilization of HSCs in the periphery in TC mice. More importantly, HSCs from TC mice transplanted into healthy recipients displayed altered HSC function, indicating a cell-intrinsic defect. Finally, we found that HSCs from TC mice showed a bias towards differentiation into the myeloid versus the lymphoid lineage.

**Conclusion:** Our data demonstrate that HSC function is altered in lupus mice through a cell-autonomous process. The dysfunction of HSCs in lupus mice may contribute to lymphopenia observed in SLE patients. These results highlight the importance of restoring HSC function for lupus therapy.

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Engraftment of PBMC from SLE.and ACL Donors into BALB-Rag2−/−IL2Rgko-KO Mice: A Promising Model for Studying SLE. Danieli Andrade1, Milena Vukelic2, Patricia B. Redecha1, Xiaoping Qing1, Giorgio Perino1, Jane E. Salmon2 and Gloria C. Koo4. 1Hospital for Special Surgery, New York, NY, 2The Feinberg School of Medicine, Northwestern University, Chicago, IL, 3Hospital for Special Surgery, New York, NY, 4Hospital for Special Surgery, New York, NY

**Purpose:** Our goal was to create a SLE mouse model that resembles the human disease and has human cells which may be studied to define pathophysiology and targeted for treatments.

**Methods:** We infused peripheral blood mononuclear cells (PBMC) from SLE patients into the severe combined immuno-deficient mouse, BALB-Rag2−/−IL2Rgko−/− mice (DKO), which lack T, B and NK cells. PBMC from 5 SLE patients (5 anti-dsDNA positive and 2 of these were ACL positive) and normal donors (ND) at 3–5 x 10^6/mouse were infused IV and IP to non-irradiated 4–5 weeks old DKO mice, 2–5 DKO mice/donor. We evaluated the engraftment of human CD45+ cells and lymphocyte subsets.
We monitored the plasma human IgG concentration, anti-dsDNA antibody, anti-cardiolipin (CL) antibody, proteumina, and performed histologic examination of the liver and kidney.

**Results:** We found 100% engraftment of human PBMC in 38 DKO mice studied. In both SLE-DKO and ND-DKO mice, we found 5–10% human CD3+ cells. In SLE-DKO mice, as reported in SLE patients, there were fewer CD3+ + cells (5.1±1.9%) and more CD3+8+ cells (81.6±3.9%), significantly different from that in ND-DKO mice, which had normal distribution of CD3+ +CD4+ (66.2±2.5%) and CD3+8+ (16.5±2.1%) cells in the PBMC (SLE-DKO vs. ND-DKO: P<0.01 for CD4+, P<0.01 for CD8+ populations). CD19+ B cells were present mainly in the peritoneum and bone marrow, and CD11c cells were found in the spleen. Human CD45+ cells, assessed by FACS analyses, were also present in the lung, liver, and kidney. There was no significant difference in plasma human IgG levels between SLE-DKO and ND-DKO mice (32.3±13 and 26.4±7 μg/ml, respectively). Anti-dsDNA antibodies were found in SLE-DKO mice (3.9±1.6 IU/ml) and lower in ND-DKO mouse (2.2±0.7 IU/ml, DKO=1±0.02), but not significantly different between the 2 groups (P<0.05). Strikingly, levels of ACL antibody were higher in all SLE-DKO mice infected with cells from an ACL-positive patient (SLE-DKO, 85.2±14 vs ND-DKO, 3.6±0.2 GCL-U; P<0.01, un- engrafted DKO, 3.6±0.8 GCL-U). SLE-DKO mice had evidence of nephritis. After 4–6 weeks of engraftment, they had proteinuria, (SLE-DKO: 93.5±25 μg/mg; ND-DKO: 22.3±3.3 μg/mg albumin/creatinine; P<0.01, un- engrafted DKO:17.5 μg/mg). Kidney sections showed human IgG deposits. In SLE-DKO mice engrafted with PBMC from an ACL-positive patient, we found micro-thrombi in the glomeruli of the kidney, and the liver showed fibrosis and necrosis. By 4–5 weeks after engraftment, 50% of the SLE-DKO mice died, whereas ND-DKO mice lived >7 weeks (SLE-DKO vs ND-DKO, P<0.04).

**Conclusion:** We have created a novel humanized SLE-DKO mouse that exhibits many characteristics of immunologic and clinical features of SLE. Importantly, we recapitulated clinical manifestations of APS in mice infected with PBMC from an ACL-positive patient. The SLE-DKO mouse promises to be an excellent model to study the pathophysiology of SLE and test human-specific therapies. Supported in part by NIH fund, R01 AR03889 and CNPO 20059/1/2008-8.

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**Enhancement of IL-17 and Interferon-gamma Inflammatory Pathways in IRF9−/− MRL/lpr/lpr Mice with Disrupted Type I Interferon Signaling.**

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**Purpose:** Multiple inflammatory pathways have been implicated in the pathogenesis of systemic lupus erythematosus (SLE) including those involving type I interferons (IFNs), IFN-gamma, and IL-17. The development of an IFN gene signature, type-switched autoantibodies, and kidney disease in the pristane-induced BALB/c model of SLE has been correlated with the predominance of type I IFNs in diseased mice. The role of type I IFNs in the development of SLE is less clear in the MRL/lpr mouse model of SLE, in which IFN-gamma has been demonstrated to play an important role. Using a newly-generated MRL/lpr strain lacking IRF9, a protein crucial for the transcription of type I IFN-regulated genes, we aimed to determine how disruption of type I IFN signaling alters the autoantibody profiles and inflammatory features of disease, including IFN-gamma and IL-17 production by lymphocyte subsets.

**Methods:** IRF5−/− BALB/c mice were backcrossed to the MRL/lpr background for 8 generations. Serum and urinary protein measurements were collected monthly from age-matched female IRF5−/− and IRF9−/− MRL/lpr littermates. At 18 weeks of age, sera were analyzed for isotype-specific autoantibodies directed against lupus autoantigens by ELISA. Cells isolated from the spleen and lymph nodes were analyzed for cytokine production including IL-17A and IFN-gamma by ELISPOT, intracellular cytokine staining by flow cytometry, and quantitative RT-PCR analysis.

**Results:** Despite a defect in type I IFN signaling, IgG autoantibodies targeted against Sm/RNP, RiboP, and whole histones were detected in IRF9−/− MRL/lpr mice, including those of the IgGa2 subtype. An analysis of cytokine pathways revealed increased IL-17A and IFN-gamma production by splenocytes in the IRF5−/− samples compared to IRF9−/− samples by ELISPOT and quantitative RT-PCR. IRF9−/− samples demonstrated greater IFN-gamma production by flow cytometry, particularly in the CD4+ T-cell compartment.

**Conclusions:** Taken together, these results demonstrate that disruption of the type I IFN signaling pathway at IRF9 in MRL/lpr mice does not significantly alter IgG autoantibody profiles or class switching to the IgG2a subclass. Autoantibody production correlated with an enhancement of IL-17 and IFN-gamma, supporting a role for Th17 and Th1 interactions with autoreactive B cells in this model. These results are strikingly different from those pristane-induced IRF9−/− BALB/c mice, highlighting the heterogeneity of genetic backgrounds and disease mechanisms in lupus-like disease. On a broader scale, these results hold implications for the development of new treatment strategies for human SLE, where modulation of type I IFNs in some patients may potentially result in the enhancement of other inflammatory pathways influencing disease.

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**Epistatic Interactions between Lupus Susceptibility Loci on New Zealand Black Chromosomes 1 and 13 Lead to Marked Expansion of Dendritic Cell Populations but Have Little Effect on Autoimmunity.**

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**Purpose:** In previous work we have shown that mice with introgressed homozgyous NZB chromosome 1 (63.1 to 192.1 Mb, B6.NZBc1) or 13 intervals (48 to 113 Mb; B6.NZBc13) have high titer IgG anti-nuclear antibodies and develop glomerulonephritis. In this study we have produced bicombinatorial mice with both NZB intervals, to determine whether interactions between the two loci lead to exacerbation of the autoimmune phenotype.

**Methods:** Splenic cellular populations were examined by flow cytometry. Serum levels of autoantibodies were measured by ELISA and the presence of glomerulonephritis (GN) determined by light microscopy. Cytokine mRNA levels in freshly isolated splenocytes were examined using real time PCR. Splenic TLR responses were assessed by measurement of cytokine production following stimulation.

**Results:** B6.NZBc1c13 mice demonstrated marked expansion of the CD11c+ dendritic cell (DC) compartment (5 fold as compared to B6 mice and 2–3 fold as compared to single congenic mouse strains). Increases in both the plasmacytoid DC population (B220+CD11c+NK1.1-) and myeloid DC population (CD11b+CD11c+) contributed to this expansion. Despite these cellular changes, the levels of IgM and IgG autoantibodies, and severity of GN in bicombinatorial mice were similar to single congenic mice. However, bicombinatorial mice had significantly elevated levels of total IgA and IgA anti-chromatin, -ssDNA and -dsDNA antibodies when compared with single congenic mouse strains. Consistent with the increased IgA production, bicombinatorial mice had markedly increased levels of total baff mRNA and the number of BAFF-producing myeloid DC in their spleens. mRNA levels of tnf were also increased in bicombinatorial mice. In contrast, the levels of Type I IFN and IFN-inducible genes were reduced in the spleens of 8 mo old bicombinatorial mice. To gain further insight into the immune mechanism leading to reduced production of Type I IFN in these mice, freshly isolated splenocytes from young and old mice were stimulated with various TLR ligands. At 8 wks of age, TLR-induced IFNα and TNFα secretion was similar in bicombinatorial and B6 mice. Despite the ~5 fold expansion of pDC in 8-mo-old mice, levels of IFN-α secretion were reduced in bicombinatorial mice, indicating a marked reduction in secretion of IFNα on a per cell basis, whereas TNFα production was relatively preserved. To further examine the regulation of cytokine production in bicombinatorial mice, DC were expanded by culturing bone marrow cells isolated from 8 wk old mice with FLT3L for 7 days and stimulated with various TLR ligands. DC from bicombinatorial mice demonstrated increased TNFα but not IFNα production following stimulation with TLR7 ligands.

**Conclusions:** Epistatic interactions between lupus susceptibility loci on NZB chromosomes 1 and 13 lead to marked expansion of DC populations with a potential impact on the autoimmune phenotype. DC from bicombinatorial mice appear to be shifted towards TNFα production which may lead to the impaired production of IFNα and reduced disease severity in older mice.

**Disclosure:** Y. H. Cheung: None; E. Pau: None; J. E. Wither: None.
Hypercholesterolaemia and Autoimmunity Interact in a Mouse Model of Systemic Lupus Erythematosus To Enhance Both Atherosclerosis and Renal Inflammation, but by Distinct Mechanisms. Myles J. Lewis,2 Tatat H. Malik,3 Liliane M. Fossati-Jimack,4 Daniele Carassiti5, Terence H. Cook,6 Dorian O. Haskard7 and Marina Bottol. Imperial College, London, United Kingdom; 2Imperial College

Background: Although SLE is known to accelerate atherosclerosis, the underlying mechanisms are not known. We explored the hypothesis that hypercholesterolaemia and autoimmunity interact in driving both arterial wall and renal pathology through immune-complex deposition.

Methods: Atherosclerosis prone low density-lipoprotein receptor deficient mice (Ldlr−/−) were crossed with B6.129-Sle16 congenic autoimmune mice, which develop high titres of lupus autoantibodies, and studied on low fat (LF) and high fat (HF) diets at 22 weeks of age.

Results: The Sle16 locus significantly increased atherosclerosis in Ldlr−/− mice, as measured by en face aortic lesion area (LF p<0.0001; HF p<0.0002) and by aortic root lesion analysis (LF p<0.05; HF p<0.0001). Unexpectedly, aortic root lesions in Sle16.Ldlr−/− mice had significantly less complement C3 than those in Ldlr−/− mice, but similar IgG deposition. The Sle16 locus caused a reduction in serum C3, associated with renal immune-complex deposition. Sle16.Ldlr−/− mice showed augmented renal inflammation, with enhanced glomerular C3 deposition compared to B6.129-Sle16 mice, but again no difference in glomerular IgG deposits.

Conclusions: The data suggest that hypercholesterolaemia enhances immune-complex-mediated renal damage by amplifying complement activation, but do not support a role for arterial wall immune complex deposition and complement activation in accelerated atherosclerosis. On the contrary, systemic complement depletion by immune-complexes may contribute to atherogenesis by reducing the protective role of complement in disposal of apoptotic debris. The results predict that aggressive treatment of hyperlipidaemia in SLE may reduce lupus nephritis, as well as reduce accelerated atherosclerosis.

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IL-21 Promotes Autoimmune Features in Chronic Graft Versus Host Disease by Enhancing T Follicular Helper Development and B Cell Response. Vinh Nguyen1, Irina G. Luzina1, Qing Chen2, Horea Rus3 and Violeta Rus4. 1Baltimore, MD; 2Univ of Maryland Schl of Med, Baltimore, MD; 3University of Maryland School of Medicine, Baltimore, MD

Studies in murine models of lupus have indicated increased production of IL-21 and attenuation of autoimmune features following IL-21 blockade. IL-21 exerts an autocrine effect on T follicular B helper cells (TFH) cells and also stimulates B cell proliferation, plasma cell (PC) differentiation and germinal center (GC) expansion. To determine whether IL-21 promotes systemic lupus erythematosus (SLE) development through effects on TFH cells or B cells, we assessed the effect of IL-21/IL-21R signaling on B cells independent from the effect on CD4 T helper cells using IL-21R−/− or IL-21R+/+ mice as donor or hosts in the Pinto-F1 and Bm12 into-B6 models of chronic Graft Versus Host Disease (cGVHD). cGVHD induced by injection of IL-21R−/− CD4 cells from B6 mice into B6.D2F1 hosts was characterized by a decrease in the expansion of donor CD4, TFH and GC cells and decrease in levels of anti-dsDNA antibody (Ab). When cGVHD was induced by injecting Bm12 spleen cells into IL-21R−/− B6 mice, parameters of cGVHD including B cell activation assessed by MHC class II upregulation, GC B cell and PB/PC differentiation, IgG anti-dsDNA Ab production were significantly decreased compared to IL-21+/+ hosts. The decreased B cell activation and autoantibody titers in the IL-21R−/− hosts were likely to be the result of defective priming of donor T cells or activation of host dendritic cells as CD4+ T cells exhibited similar expression of CD44 and CD69 and proliferated more efficiently in IL-21R−/− hosts than in IL-21R+/+ hosts. Similarly, DC displayed similar expression of CD80, CD86. Consistent with the decrease in GC B cells, splenic GCs in IL-21R−/− hosts detected by immunohistochemistry staining on day 7, 14 and 28, were smaller, ill-formed and disrupted compared to those in IL-21R+/+ hosts. Long-term studies showed decreased severity of lupus-like renal disease in the IL-21R−/− hosts. These results suggest that IL-21 promotes autoimmune features in lupus by enhancing both the expansion of TFH cells and the differentiation of autoreactive B cells into autoAb producing cells.

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IL-17 Promotes Autoimmunity in Pristane-Induced Lupus. Elaine V. Lourenco, Chunlin Cai, Bevra H. Hahn and Antonio La Cava. UCLA

IL-17 promotes inflammatory responses in several autoimmune conditions. Although it has been shown that IL-17 can be found elevated in systemic lupus erythematosus (SLE) patients and in lupus mice, it has not yet been directly proven that this association underlies a promoting role of this cytokine in the development and/or progression of the disease. To test whether IL-17 can facilitate the development of SLE, we treated IL-17-deficient or wild-type mice with pristane, a hydrocarbon oil that induces a lupus-like disease characterized by the development of lupus-associated autoantibodies and glomerulonephritis. Wild type and IL-17-deficient mice were treated with pristane or saline, and serological and pathological evaluations were done at serial times points post treatment. It was found that pristane promoted hypergammaglobulinemia that was more prominent in wild type than in IL-17-deficient mice, and the difference became statistically significant by three months post-treatment (p<0.044) and was maintained thereafter (p<0.001). IL-17-deficient mice treated with pristane also developed lower serum levels of anti-single-stranded DNA and anti-chromatin antibodies in comparison with wild type mice treated with pristane, and the onset of glomerulonephritis of the kidney was as well delayed in the IL-17-deficient mice. These results suggest that the presence of IL-17 facilitates the development of murine lupus-like disease induced by pristane. The formal demonstration that IL-17 has a promoting role in the accelerated development of serological and pathological manifestations of SLE may have implications in the targeting of this pro-inflammatory cytokine for therapeutic purposes in the disease.

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Interferon Regulatory Factor-5 (IRF-5) is Critical for the Development of Lupus in MRL/lpr Mice. Yoshifumi Tada1, Seijii Kondo2, Shigeisha Aoki2, Syuichi Koarada3, Hisako Inoue4, Rie Suematsu2, Akhide Ohta5 and Kohei Nagasawa5. 1Department of Clinical Nursing, Saga University, Saga, Japan; 2Department of Pathology, Saga University, Saga, Japan; 3Department of Rheumatology, Saga University, Saga, Japan; 4National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

Objective: Interferon Regulatory Factor-5 (IRF-5) is a transcription factor that mediates intracellular signals activated by engagement of the Toll-like receptors (TLRs). IRF-5 polymorphisms are associated with increased or decreased risk of systemic lupus erythematosus (SLE) in various human populations but the precise role of IRF-5 in SLE development is not understood. We examined the role of IRF-5 in the development of murine lupus.

Methods: We crossed gene-targeted IRF-5-deficient (IRF-5−/−) mice to MRL/Mpj-lpr/lpr (MRL/lpr) mice and examined the progeny for survival, glomerulonephritis, autoantibody (autoAb) levels, immune system cell populations, and dendritic cell (DC) functions.

Results: We show that IRF-5−/−/MRL/lpr mice survive longer than control IRF-5+/+/MRL/lpr mice and display only very mild glomerulonephritis. The glomerular deposition of IgG and C3, and the infiltration of CD4+ T cells and macrophages into glomeruli was significantly decreased in IRF-5−/−/MRL/lpr mice. Anti-nuclear antibodies, anti-dsDNA antibodies, anti-Sm antibodies, and anti-RNP antibodies were decreased in mouse serum, and numbers of activated CD4+ T cells were reduced in the spleen. Splenic DCs from IRF-5−/−/MRL/lpr mice produced lower levels of inflammatory cytokines when treated in vitro with TLK7 or TLK9 ligands or immune complexes. Interferon-α production in response to CpG was also decreased.

Conclusion: Our results show that IRF-5 is a crucial driver of lupus development in mice, and indicate that IRF-5 may be an attractive new target for therapeutic intervention to control disease in SLE patients.

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**Objective:** Interferon alpha (IFNα) has been suggested to cause systemic lupus erythematosus (SLE), however, the direct proof for this is lacking. We showed by solely increasing IFNα in doxycycline-inducible transgenic mice (IFNα Tg mice) that IFNα induces autoantibodies including serum anti-dsDNA antibody, serum immune complex (IC) and lupus-like tissue injuries (Uchimura C et al. Arthritis Rheum 56 (suppl.9):S200).

**Methods:** Mouse IFNα (mlIFNα) cDNA, amplified by RT-PCR, was subcloned into pTet Splice vector under the control of TetOp promoter to generate TetOp-mlIFNa. This was microinjected into fertilized eggs of C57BL/6 to generate TetOp-mlIFNa mice. The Egr-ISR-ITA Tg mice of FVB/N background was mated with TetOp-mlIFNa Tg mice to obtain double Tg mice (IFNα Tg mice). Serum IFNα was measured using Mu-IFNα ELISA kit. Serum autoantibodies and IC were measured with ELISA, referring to pooled sera of MRL/lpr female adult mice (arbitrary units). Proteinuria were measured semiquantitatively using urine dipsticks. Frozen kidney sections were stained for C3 and IgG using immunofluorescent stain.

**Results:** In IFNα Tg mice, pathological lesion consisted of IC-deposited glomerulonephritis, interstitial lung disease, liquefaction and positive lupus band test in the skin epidermis, onion skin lesion in the spleen and inflammatory infiltrates to salivary gland and bile duct. Activated effector CD4+ and CD8+ T cells producing IFNα were increased in control IFNα Tg mice, however, they had significantly increased numbers of anti-dsDNA-secreting cells and total IgG-secreting cells in either IFNα Tg mice (66.7±6.6×10^4) vs 41.4±5.8×10^4, p = 0.016) while all other splenic cell subsets were significantly decreased compared to wild-type controls. Notably, splenic CD19+IgM+ B cells and CD8+ T cells were significantly decreased in IFNα Tg mice compared to wild-type MRL/lpr mice. Bone marrow analysis revealed B cell development arrest before the stage of CD19+B220+B2CD45+CD19+ immature B cells in IFNα Tg mice. Flow/ELISPOT assay showed absence of IL-17 producing cells in IFNα Tg/mice, however, they had significantly increased numbers of IFNγ-producing cells (59.2±20.2×10^4 vs 6.6±1.5×10^4, p = 0.027) and IL-4 producing cells (4.30±0.27×10^4 vs 0.39±0.08×10^4, p < 0.0001) compared to control MRL/lpr mice. Our results indicate that IRF4 is required for the full expression of lupus like development in MRL/lpr mouse, most likely by maintenance/modulation of autoreactive B cells and specific T cell subsets. Importantly, development of proliferative glomerulonephritis and skin disease were still present in Ifr4−/− MRL/lpr mice indicating that their pathogenesis, in these mice, is independent of autoAb/IC-mediated mechanisms or Th17 cells, and is most likely induced by Th1 and/or Th2 cells. Absence of IL-17 producing CD4+ T cells and significantly increased numbers of IFN-γ or IL-4 producing CD4+ T cells in IFNα Tg/mice suggested a dual role of IRF4 for development of Th17 cells and inhibition of Th1 and Th2 cell development in MRL/lpr mice.

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**IRF4-Deficient Lupus-Prone MRL/lpr Mouse Lack Serum Ig/Auto-Ab and Th17 Cells but Develop Non-Immune Complex-Mediated Diffuse Proliferative Glomerulonephritis and Dermatitis/Ear Necrosis.** Hideharu Sekine1, Takeshi Machida1, Eiji Suzuki2, Efrain Martinez Avila3, Phil Ruiz4, Christopher M. Reilly5 and Gary S. Gilkeson4. 1Fukushima Medical University, Fukushima, Japan. 2Med Univ of South Carolina, Charleston, SC. 3Medical University of South Carolina, Charleston, SC. 4Medical University of South Carolina/Fukushima Medical University, Charleston, SC. 5University of Miami, Miami, FL. 6Virginia Tech, VA

The transcription factor interferon regulatory factor 4 (IRF4) is a member of the IRF family of transcription regulators and required for Ig production/maturatation of B cells and development of Th17 cells. We found that the Irf4 gene is over-expressed in CD4+ T cells in lupus-prone MRL/lpr mice compared to non-lupus mice. To investigate the role of IRF4 in the development of lupus, we analyzed disease expression in Irf4−/− and wild-type MRL/lpr mice starting at 12 weeks. Serum Ig/anti-dsDNA Ab levels and urinary albumin excretion levels were measured by ELISA. Mice were sacrificed at 24 weeks of age and ear, back skin and kidneys were removed for pathological analysis. Splenic immune cell populations were analyzed by flow. To determine Th1/Th2/Th17 cell numbers, splenic CD4+ T cells from 12 weeks old MRL/lpr mice were purified by magnetic selection, cultured with PMA/ionomycin, and IFN-γ, IL-4 or IL-17 production was detected by flow and ELISPOT assay.

For short-term treatment, NZB/NZW F1 female mice (24–30 wk old) with durable proteinuria > 2+ (100 mg/dl) were dosed weekly the 7 days with anti-mCD20 antibody (IgG2a, a gift from Biogen Idec) (n=6) or control antibody IgG2a and sacrificed 1 wk after the last treatment. To study longer-term effects of BCD, 27 wk old NZB/NZW F1 female mice with high titer anti-dsDNA antibodies were dosed weekly with anti-mCD20 antibody or control IgG via retro-orbital injection. One group was treated weekly x 4 (n= 6) and sacrificed 8 wks later. Another was treated weekly x 12 (n= 6) and sacrificed 1 wk after the last treatment. Cells from spleen, bone marrow (BM) and kidney were collected and total IgG and dsDNA antibody secreting cells (ASC) were determined by ELISPOT assay.

**Results:** Nephritis improved after anti-mCD20 treatment (neither 4 wks nor 12 wks treated mice were found to develop nephritis [3+ proteinuria] compared to control [5/6 mice developed nephritis 4+]). Although BCD was efficient (>90% B220+ cell depletion), there was no difference in the numbers of anti-dsDNA-secreting cells and total IgG-secreting cells in either spleen, BM or kidney. T-cell (after 4 treatments of anti-mCD20, over the short-term, evaluation 1 wk after the last treatment- see Table) or long-term (evaluation 8 wks after the last treatment, data not shown). Interestingly, in untreated mice the ratio of anti-dsDNA-total IgG-secreting cells in the kidney was significantly higher than in spleen and BM (p<10-4) suggesting that the kidney is a reservoir of either production or maintenance of autoantibody ASCs. In
striking contrast, long-term treatment with anti-mCD20 resulted in significant decreases in total IgG and anti-dsDNA-secreting cells in spleen. In addition, the average size of total IgG-secreting cell spots from kidney decreased significantly, suggesting a shift in the antibody producing capacity after anti-mCD20.

**Conclusion:** Long-term anti-CD20 treatment significantly reduces ASCs in spleen and moderately reduces ASCs in bone marrow and kidney. Treatment also appears to alter antibody secretion in kidney. Therefore, longer term B cell depletion may have increased efficacy as a treatment for SLE.

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Mitochondrial Dysfunction in T Cells Precede Disease Development in Lupus-Prone Mice. Tiffany Telarico1, David R. Fernandez2, Ann F. Hofbauer2, Gary S. Gilkeson3, Jim C. Oates4 and Andras Perl5. 1Med Univ of South Carolina, Charleston, SC, 2Medical University of South Carolina, 3MUSC, Charleston, SC, 4SUNY, 5Upstate Medical Univ, Syracuse, NY

**Purpose:** T lymphocytes from patients with systemic lupus erythematosus (SLE) exhibit increased nitric oxide (NO) production, elevation of the average size of total IgG-secreting cell spots from kidney decreased significantly, suggesting a shift in the antibody producing capacity after anti-mCD20.

**Materials and Methods:** LDLr–/– and Fas–/– (lpr/lpr) mice on the B6 background were purchased from the Jackson Laboratories (Bar Harbor, ME). These mice were interbred to produce homozygous for both LDLr–/– and lpr confirmed by PCR genotyping. LDLr–/– (LDLR) and LDLr–/– lpr–/– (LDLrLpr) mice were fed on chow diet. Thirteen female mice from each group were sacrificed at the age 24–28 weeks.

**Results:** LDLrLpr mice developed a lupus phenotype demonstrated by autoantibody production (ANA, anti-dsDNA, anti-sm, anti-cardiolipin antibodies), increased body weight, splenomegaly, hepatomegaly, and generalized lymphadenopathy compared to LDLr mice. LDLrLpr mice had a significantly increased proteinuria score (1.5±0.2 vs. 1.1±0.66; p<0.02) and renal histology score (1.8±0.4 vs. 0.4±0.1; p<0.004) compared to LDLr mice. The lymphocyte population in the spleen measured by flow cytometry resulted in significantly increased CD4+ Tcells (21% vs. 16%); p<0.003), double negative T cells (5% vs. 26%; p<0.001), and CD138+ plasma cells (12% vs. 4%; p<0.001) and decreased CD8+T cells (6% vs. 14%); p<0.001) in LDLrLpr mice compared to LDLr mice similar to human lupus. Lipid analyses in LDLrLpr mice compared to LDLr mice on chow diet demonstrated significantly elevated total cholesterol (mg/dl) (347±0±3.65 vs. 220±9±8.235; p<0.008), triglycerides (118.8±18.51 vs. 42.85±3.665; p<0.0005), LDL (66.85±17.54 vs. 3.385±0.4875; p<0.0014) and LDL cholesterol (214.9±22.22 vs. 148.1±8.049; p<0.003) without significant difference in HDL level. The increased level in triglycerides due to increased triglyceride secretion as measured by triton block experiment and increased hepatic and lipoprotein lipase activity in LDLrLpr mice. The increased plasma cholesterol is due to increased cholesterol synthesis and decreased fatty oxidation in liver in LDLrLpr mice as measured by gene expression analysis.

**Conclusion:** Increased cholesterol synthesis, decreased fatty acid oxidation, increased triglyceride secretion and decreased lipase activity are the molecular mechanisms of dyslipidemia in lupus mice.

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Nuclear Modifications during Apoptosis Are Required To Maintain Tolerance to Nuclear Antigens. Neelakshi R. Jog1, Eline Luning-Prak2 and Roberto Caricchio1. 1Temple University, 2University of Pennsylvania

**Background:** Our previous data show that in spontaneous models of lupus, the absence of caspase activated DNase (CAD)-generated nuclear modifications during apoptosis results in increased anti-nuclear antibody generation and severe nephritis. These data suggested that CAD generated apoptotic nuclei are a source of auto-antigens (autoAgs) that are involved in negative regulation of autoreactive B cell during development. In the present study we investigated the role of CAD in induction of tolerance in vivo. To this end we used 3H9 mice, an established model of anergy towards chromatin.

**Methods:** 3H9 mice carry a rearranged heavy chain reactive against dsDNA, and shows development arrest of autoreactive B cells. To determine whether absence of CAD, and therefore autoAgs, breaks tolerance in this anergic model, we generated CAD deficient 3H9 mice ([3H9/+/–]).

**Results:** Contrary to 3H9/+/–, 3H9/+/– mice were able to break tolerance early in life and produce high titers of anti-dsDNA and anti-
chromatin antibodies. The antibodies made in 3H9 mice did not, however, differ in specificities as determined by immunofluorescent ANA. The autoreactive B cells in 3H9 mice undergo stringent negative selection due to the presence of autoreactive heavy chain. Therefore we analyzed B cell development and maturation by flow cytometry. The developing B cells from bone marrow were divided into Hardy fractions D (I. chain rearrangement), E (immature IgM+), and F (IgM+, recirculating B cells). Compared to wild type, both 3H9/+ and 3H9/- mice had increased numbers of fraction D cells suggesting increased light chain rearrangements. In the periphery, both 3H9+/- and 3H9/- mice showed increased mature marginal zone B cells, and immature T2 transitional B cells, and increased lambda inclusion. These data show that absence of CAD does not alter the unique B cell development or maturation in 3H9 mice. The 3H9 heavy chain pairs with endogenous lambda1 light chain to generate anti-dsDNA antibody allowing to follow in vivo the fate of autoreactive B cells. In 3H9 mice lambda1+ cells are excluded from B cell follicles in secondary lymphoid organs and are not able to mature into autoantibody producing B cells. We therefore investigated the fate of lambda1 + cells in the absence of apoptotic nuclear modifications. We stained frozen spleen sections from 3H9+/- and 3H9/- mice with B220 to identify B cell follicles and lambda1 to identify the auto-reactive B cells. As expected, in 3H9+/- mice the lambda1+ cells did not enter the B cell zone and accumulated at the T-B interface. In 3H9/- mice, however, lambda1+ cells were not excluded from B cell follicles, and entered the B cell zone. These data show that in agreement with our hypothesis, auto-reactive B cells escape to the periphery in absence of CAD-dependent nuclear fragmentation.

Conclusions: Based on our data we conclude that in mice genetically predisposed to autoimmunity, the apoptotic nuclear modifications generated by CAD are necessary to maintain tolerance toward nuclear Ags.

Disclosure: N. R. Jog: None. E. Luning-Prak: None; R. Caricchio: None.

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PARP-1 Deficiency Leads to More Severe Glomerulonephritis and Increased Mortality in an Inducible Mouse Model of SLE

Maximilian F. Koenig1, Serena M. Bagnasco, Janelle Montagne, Anton Rosen2, Thomas Grader-Beck2.
1Johns Hopkins School of Medicine, 2Johns Hopkins University School of Medicine, Baltimore, MD

Purpose: PARP-1 regulates essential cellular functions, including cell death and DNA repair. Lower levels of PARP-1 activity have repeatedly been found in SLE patients. Functional PARP-1 deficiency may therefore play an important role in the pathophysiology of SLE. In this study we define the role of PARP-1 deficiency on the autoantibody response and end-organ disease phenotype in an inducible mouse model of SLE.

Methods: Lupus-like disease was induced in a chronic graft-versus-host disease (cGVHD) model of SLE by injecting B6 mice (wild-type or PARP-1−/−) with sex- and age-matched B6+C3H-Ab1b1m2K/Hefg1 (bm12) splenocytes. Proteinuria and serum autoantibody levels to ssDNA and histone H1 were measured serially over the course of the disease (14 weeks). At termination of the experiment, kidney sections were evaluated by hematoxylin/eosin staining as well as by immunofluorescence for IgG and C3 deposition in a blinded manner.

Results: Male B6 PARP-1−/− disease mice showed increased mortality compared to wild-type disease mice (46% vs. 66% 0/8; 0%; P = 0.015). This increase was gender-specific and not observed in female mice. PARP-1-deficient male mice developed higher levels of proteinuria associated with a nephrotic phenotype and wasting. Histological examination of renal tissue in PARP-1-deficient male mice showed abundance of hylane, PAS-positive material within tubules as well as glomerular hyperplasia and marked sclerosis. These changes were not observed in wild-type and PARP-1−/− female mice. The burden of IgG deposition assessed by immunofluorescence intensity was comparable between wild-type and PARP-1 deficient mice. However, C3 deposition at the glomerular basement membrane (GBM) was more prevalent in PARP-1−/− male mice compared to wild-type male mice. This GBM deposition of C3 was closely correlated with the severity of proteinuria. Autoantibody levels of anti-sDNA and anti-histone H1 over the course of the disease were similar in wild-type and PARP-1 deficient male disease mice.

Conclusion: PARP-1 deficiency is associated with more severe glomerulonephritis and increased mortality in a inducible cGVHD mouse model of SLE. This effect is specific for male mice and is not reflected by changes in the antibody response to commonly observed lupus autoantigens. The level of PARP-1 expression and activity in the target tissue may play an important role for disease phenotype and severity in SLE.

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Recombinant Chaperonin 10 Suppresses Cutaneous Lupus and Lupus Nephritis in MRL-FasLpr Mice. Onkar P. Kulkarni2, Mi Ryu1, Claudia Kantner3, Miklos Sardy1, Dean Naylor1, Richard Brown1, Dina Vanagas1 and Hans-Joachim Anders3. 1Bio Ltd, Eight Mile Plains, Queensland, Australia, 2Department of Dermatology and Allergology, University of Munich, Munich, Germany, 3Medizinische Poliklinik-Innenstadt, University of Munich, Munich, Germany

Purpose: Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder mostly affecting young females. The autoimmune disease manifestations are still treated with unspecific immunosuppressants such as steroids or cytotoxic drugs that cause serious toxicities. Since SLE patients largely suffer from inflammatory tissue damage and not from autoimmunity per se, selective anti-inflammatory compounds may offer protection from tissue damage without causing immunosuppression.

Chaperonin 10 fulfills an essential role in mitochondrial protein folding and an extracellular role in immunomodulation suggesting potential therapeutic value for the treatment of inflammatory disorders1. Accordingly, in early phase II clinical studies in human patients the efficacy and safety of Cpn10 in treating signs and symptoms of rheumatoid arthritis2 and chronic plaque psoriasis (CPR)3 has been established. Here recombinant Cpn10 was examined for its' ability to additionally control the autoimmune manifestations of SLE.

Methods: Female MRL/lpr/lpr mice with lupus-like autoimmunity were given either Cpn10 (100μg/mouse, 5mg/kg) or placebo (Tris-buffered saline) by intraperitoneal injection every alternate day from 10 to 22 weeks of age. Clinical signs were recorded over the study period, and mortality was recorded every week throughout the study. Plasma samples were collected prior to sacrifice after 11 weeks of treatment. Urine samples were collected in week 22 of age. Tissue samples for histology were immediately fixed in formalin prior to paraffin fixation.

Results: Cpn10 entirely prevented the lupus-like cutaneous lesions as compared to vehicle-treated MRL/lpr/lpr mice as evident from macroscopy as well as from microscopical evaluation. Cpn10 also improved lupus nephritis as evident from serum creatinine levels, albuminuria, and the histomorphological scores of disease activity and chronicity (p<0.05). Autoimmune lung disease remained unaffected by Cpn10 treatment. However, Cpn10 prolonged overall survival of MRL/lpr/lpr mice (90% survival vs. 65% for treated mice, p<0.05). The therapeutic potential of Cpn10 on skin and kidney disease was not associated with any significant effects on either T cell, dendritic cell or B cell counts in spleen, on plasma IFN-γ, TNF-α or IL-10 levels, plasma DNA autoantibody levels or on markers of lymphoproliferation.

Conclusion: Our study clearly demonstrates that Cpn10 prevents cutaneous lupus and suppresses lupus nephritis in MRL/lpr/lpr mice without affecting the underlying autoimmune process or systemic inflammation. Hence, Cpn10 shows significant potential for the treatment of selective human SLE-related tissue pathologies, such as cutaneous lupus and lupus nephritis whilst possibly offering an improved safety profile by not blocking healthy immune responses. This work taken together with previously published data in human RA and CPP trials, provides evidence of Cpn10’s utility beyond a single indication.

References:

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TGF-β-Induced CD4+Foxp3+ Cells Suppress Lupus-Like Syndrome through Induction of Formation of Tolerogenic DC. Xiaohou Zhou1, Julie Wang1, David A. Horwitz, Huimin Fan1, Hejian Zou1, Zhongmin Liu3 and Hans-Joachim Anders3. 1Department of Dermatology and Allergology, University of Southern California, Los Angeles, CA, 2LAC/USC Medical Center, Los Angeles, CA, 3Tongji University Medical School, University of Southern California

Background: Regulatory T cells (Tregs) play vital roles in maintaining immune homeostasis and self tolerance. Recent studies revealed that dendritic cells (DCs) might be main target of Tregs and also induce immune tolerance. We have previously reported that adoptive transfer of TGF-β-induced Tregs (Ttregs) prevents the appearance of lupus syndrome induced by injection of
DBA/2 mouse splenocytes to (DBA/2 × C57BL/6) F1 mice, we here ask if interaction between iTregs and DCs contributes to disease control.

Materials and Methods: DBA/2 naïve CD4+ cells were stimulated with anti-CD3/CD28 beads and IL-2 ± TGF-β (control or iTregs) for 5 days. 5×106 control or iTregs with 80×106 DBA/2 splenocytes were adoptively transferred to F1 mice. ALK-5 inhibitor and anti-IL-10R Ab were i.p injected twice a week for four weeks in some groups. On day 11 after transfer of control or iTregs, CD11c+ cells were selected from splenocytes in F1 mice and injected (1×106) with 80×106 DBA/2 spleenocytes to F1 mice. Surface and intracellular staining included CD80, CD86, CD11c, IA-b, Foxp3, CD25, H-2Kd, H-2Kb. IgG and anti-DNA in sera was analyzed with ELISA and mice survival was monitored.

Results: A single injection of 5×106 iTregs markedly prevented increased IgG production, decreased anti-dsDNA autoantibodies, suppressed proteinuria and prolonged survival of these mice. The treatment with anti-TGF-β or ALKS inhibitor completely, with anti-IL-10R partially blocked the suppressive capacity of iTreg following injection in vivo. Moreover, iTreg suppressed CD80 and CD86 expression by DCs in vitro and in vivo. Adoptive transfer of these DCs in F1 mice received iTregs but not control cells to GVHD model can significantly prevent the development of lupus symptoms. The protective effect of these DCs was dependent on TGF-β/TβR signal but not IL-10/IL-10R signal. Thus, the protective effect of iTreg is dependent on TGF-β and/or IL-10 and formation of tolerogenic DCs that have developed TGF-β- but not IL-10-dependent suppression on lupus.

Conclusion: iTregs may suppress lupus-like syndrome through induction of formation of tolerogenic DC with TGF-β-dependency pathway. iTregs may have therapeutic potential in treating autoimmune diseases.

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Widespread Upregulation of mEPCR in Kidney, Spleen and Liver of a Nephritogenic NZB/W F1: Implications to Microvascular Disease. Sherry Xu1 and Robert M. Clancy2. 1NYU School of Medicine, 2Tisch Hospital 4–407, New York, NY

Purpose: Membrane endothelial protein C receptor (mEPCR), a cofactor for the anti-inflammatory activity and anti-coagulant activity of the Protein C pathway, is a prominent inducer of anti-apoptotic pathways in endothelial cells, and thus maintains vascular tone and normal blood flow in the microvasculature.

We previously found that mEPCR is highly expressed in the cortical peritubular capillaries of kidneys from patients with active lupus nephritis, as compared with normal human kidneys. This profound upregulation of mEPCR expression. In addition, in the spleen of NZB/W F1 we observed a focal mEPCR staining at the vasculature which supports the white pulp.

Method: We used the autoimmune murine strain NZB/W F1 mice, and a nonautoimmune strain of mice with a podocyte-specific microRNA knockout of dicer (dicer k/o), which both display proteinuria. Healthy control mice were also utilized. Tissue was harvested from spleen, liver and kidney. Paraffin sections were stained using an anti-mEPCR antibody via avidin-biotin method. The isotope for mEPCR was used as a negative control. Intensity of staining was scored from 0 to 3, and staining was considered positive if >1+ and negative when 0 or trace (0.5±). The percent of tissue with positive staining for mEPCR was scored as focal or diffuse.

Results: At four months of age, anti-ds DNA and anti-ss DNA were evident in all NZB/W F1 mice. At early onset of proteinuria, the mEPCR immunostain of cortical peritubular capillaries (PTCs) was, in four cases, 2+ and diffuse, with an isotype control that stained appropriately negative. mEPCR was also negative in the cortical PTCs of healthy control mice. Mice with dicer k/o develop proteinuria at 6 weeks; however, expression of mEPCR was negative in the cortical PTCs. In order to evaluate whether the changes in the microvasculature extend beyond the clinically targeted organ, paraffin sections of liver and spleen were evaluated for mEPCR. The liver of each NZB/W F1 mouse displayed, at the sinusoids, a 2+, diffuse profile of mEPCR expression. In addition, in the spleen of NZB/W F1 we observed a 3+ focal mEPCR staining at the vasculature which supports the white pulp.

Conclusion: Consistent with the human studies, evaluation of the cortical peritubular capillaries from NZB/W F1 mice, a classic murine model of lupus nephritis but not a murine model with nephritis secondary to a genetic podocytopathy, revealed an increase in mEPCR. These data are consistent with the notion that there is widespread activation of the microvasculature. The capacity of endothelial cells to utilize anticoagulation pathways is not restricted to the kidney, and expression of mEPCR in the microcirculation likely represents an attempt to limit microvascular inflammation in spleen, liver and kidney.

Disclosure: S. Xu: None; R. M. Clancy: None.

ACR Poster Session A
Systemic Lupus Erythematosus - Clinical Aspects and Treatment I
Monday, November 8, 2010, 9:00 AM–6:00 PM

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Anti C1q Antibodies in Patients with Systemic Lupus Erythematosus and Cutaneous Vasculitis: A Controlled Study. Shirish R. Sangle1, Loh Yet Lin2, Esther Sanchez3, Davies Rachel4 and David P. D’Cruz5. 1St Thomas’ Hospital, London, United Kingdom, 2St Thomas’ Hospital, United Kingdom

Objective: To evaluate the prevalence of anti-C1q antibodies (aC1q) in patients with systemic lupus erythematosus (SLE) as a possible marker for cutaneous vasculitis (CV).

Material and Methods: We prospectively enrolled 46 patients with SLE who fulfilled ACR classification criteria. Twenty three patients had clinically documented CV while 23 had no previous evidence of CV. The BILAG disease activity score was documented and active CV rashes were photographed. aC1q were measured by using ELISA and a aC1q titre above 15 units/ml was considered as positive. Statistics was by chi square test. This study was approved by the St Thomas’ Hospital Ethics committee and all patients gave written informed consent.

Result: The median age of patients in the CV group was 37 years (27–46) and that of the non –CV patients was 44 (29 –66) years. In the CV group, 9 were Caucasian, 6 Asian and 8 Afro Caribbean and in the non-CV group 13 Caucasian, 5 African Caribbean and 5 Asian in origin. In the CV group the median BILAG score for vasculitis manifestations was 3 (3–4). In the CV group aC1q levels were significantly higher compared to the non-CV group (p <0.002). In the CV group 25% had positive ANA, 18 ds DNA, 10 ENA, 6 Ro (SSA) and 6 had La (SSB) antibodies. Data were tabulated and compared. In the non-CV group 22 had positive ANA, 18 ds DNA, 10 ENA, 12 Ro and 6 had La antibodies. The median complement (C3) levels in the CV group were 0.88 (0.24 – 1.49) and C4 0.16 (0.03–1.17) as compared to 1.31 (0.33 – 1.65) and 0.17 (0.02–0.34) in the non-CV groups respectively.

Eighteen of 46 (8 in the CV) patients had positive antiphospholipid antibodies (aPL). Six patients in the CV group had renal involvement with none in the non-CV group. Five of these patients were positive for aCL (in the CV) and 20 had positive anti-β2GPI antibodies (in the non-CV group). The mean age of patients in the CV group was 35 (5–400) units/ml compared to 6 (5–53) in the non-CV group. All patients with positive aC1q had positive ANA and ds DNA antibodies, 13 had ENA positive, 8 had Ro antibodies, 3 La antibodies, 4 each had RNP and RNP with Smith antibodies. In the CV group 13 patients had low C3, C4 levels of which 10 were aCL positive and in the non-CV group 1 aCL positive patient had low C3 and C4 levels. The median C3 and C4 levels in aC1q positive patients in the CV group were 0.55 (0.24–0.64) and 0.08 (0.03–0.017) as compared to 0.7 (0.33–0.91) and 0.17 (0.02–0.34) in the non-CV groups respectively.

Discussion: Anti C1q antibodies may be a marker of activity in cutaneous vasculitis in patients with systemic lupus erythematosus even in the absence of lupus nephritis.

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Antimalarials May Attenuate the Risk of Metabolic Syndrome in SLE: Results from an International Inception Cohort Registry. M. H. X. Ting², R. P. Dorn², M. Lunt², M. B. Urowitz³, D. D. Gladman², D. Ibanez¹, C. Gordon¹, S. C. Bae¹, A. Clarke¹, S. Bernatsky¹, J. Hanly¹, D. Isenberg¹, A. Rahman¹, J. Sanchez-Guerrero¹, J. Romero-Diaz¹, P. P. Fortin¹, D. Wallace¹, E. Ginzler¹, A. Vasadevan¹, J. Merrill¹, G. S. Alarcon¹, B. Fessler¹, G. Sturfelt¹, O. Nived¹, K. Steinsson¹, M. Khamashta¹, M. Petri¹, S. Manzi¹, M. Dooley¹, R. Ramsey-Goldman¹, C. Aranov³, R. Van Vollenhoven¹, M. Ramos³, T. Stoll¹, K. Kahanian¹, A. Zoma¹, P. Maddison¹ and I. N. Bruce¹. ¹Systemic Lupus International Collaborating Clinics, Toronto, ON, Canada, ²The University of Manchester, Salford, Manchester, United Kingdom, ³The University of Manchester, 4Toronto Western Hospital, Toronto, ON, Canada

Background: The excess cardiovascular mortality in Systemic Lupus Erythematosus (SLE) is not completely accounted for by traditional risk factors. High waist circumference, high triglycerides, low HDL-cholesterol and impaired glucose homeostasis, the clustering of which constitutes the Metabolic Syndrome (MetS), may be implicated. Therapy related factors such as antimalarials and steroids, used widely in the management of SLE, may moderate these risks. We aimed to describe the baseline incidence of the MetS and its association with steroid and antimalarial use in an international prospective SLE cohort.

Method: Data was obtained from the SLE International Collaborating Clinics-Registry for Atherosclerosis (SLICC-RAS) cohort, collated from 30 centres worldwide. Information on 596 subjects, diagnosed with SLE within 1 year (baseline), was available. The International Diabetes Federation criteria was used to define the MetS, which included the presence of a high waist circumference plus two or more of elevated triglycerides or on specific therapy; reduced HDL-cholesterol or on specific therapy; raised blood pressure(BP) and raised fasting plasma glucose or known Type II diabetes mellitus.

Results: Of the 596 patients studied, 94 (15.8%) had MetS at their baseline visit. There was a significant difference in prevalence of MetS according to therapy with the highest prevalence being in the group taking steroids alone (P < 0.014) (Table). Similarly, the incidence of high triglycerides and glucose intolerance was also highest in the group on steroids alone (P <0.00003 and P = 0.010 respectively). Compared to the steroid monotherapy group, the group on a combination of steroids and antimalarials were significantly less likely to fulfil the criteria for MetS (P = 0.002), high BP (P = 0.005) and high triglycerides (P = 0.0002).

Table 1. Multivariate analyses of ACR Clinical Criteria Associated with Lupus Arthritis

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Significant clinical criteria (OR, p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasians</td>
<td>Malar rash (1.39, 0.021)</td>
</tr>
<tr>
<td>African-Americans</td>
<td>Serositis (1.70, 0.001)</td>
</tr>
<tr>
<td>Hispanics</td>
<td>Oral ulcers (2.72, 0.042)</td>
</tr>
<tr>
<td>Asians/Pacific Islanders</td>
<td>Discoid rash (0.231, 0.003)</td>
</tr>
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</table>

Conclusions: These results demonstrate ethnic differences in risk of arthritis among SLE patients, with Asian patients having relatively lower risks of arthritis compared to patients having the highest risk of arthritis. Additional research will be required to further define the basis for these ethnic differences in disease expression.

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Arthritis in an Ethnically Diverse Systemic Lupus Erythematosus Population. Guada Respicio¹, Clare Cleveland¹, Kim Taylor¹ and Lindsey A. Criswell². ¹Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco, San Francisco, CA, ²UCSF-Box 0500, San Francisco, CA

Purpose: Arthritis is one of the most common manifestations of SLE with reported prevalence ranging from 70–95%. Previous research documents ethnic differences in risk and outcome, however ethnic differences in arthritis in SLE have not been well characterized. Further, clinical, laboratory and other correlates of arthritis in SLE have not been fully investigated. We studied the frequency of arthritis among a large and ethnically diverse lupus cohort, as well as factors associated with the presence of this specific disease manifestation.

Methods: SLE patients were recruited from various sources, including specialty clinics and practices, community sources and nationwide outreach. The presence of arthritis as well as other ACR classification criteria was documented by review of medical records. Information about ethnic background was based on self report information as well as genotyping results for a set of ancestry informative markers (AIMs, n = 384). Chi square testing was used to identify ethnic differences in presence of arthritis. Other factors associated with arthritis were examined using multivariate logistic regression. Correlation analysis was used to identify patterns of association between arthritis and other disease manifestations with results displayed visually as heat maps.

Results: 2129 SLE patients were studied, including 1201 (56%) Caucasians, 297 (14%) Hispanics, 259 (12%) Asian/Pacific Islanders, and 248 (12%) African Americans (AA). 91% of patients were female, the average age at SLE diagnosis was 33 years, and the average disease duration at study entry was 9 years. Analyses demonstrated statistically significant ethnic differences in arthritis (p = 0.003), with the highest prevalence of arthritis documented for AA patients (75%) and AA prevalence among Asian patients (59%). Among AA patients, analysis of AIM data did not demonstrate a significant association between the percent African ancestry and risk of arthritis. Results of multivariate logistic regression analyses as well as heat maps representing the degree of correlation between arthritis and other clinical manifestations revealed differential clustering of disease features across ethnic groups. Table 1 summarizes clinical features significantly associated with arthritis based on multivariate analyses of individual ethnic groups. Independent variables in these models included disease duration, sex, and the other ACR classification criteria.

Conclusion: This early SLE cohort, steroid monotherapy was associated with the highest prevalence of MetS. The prevalence of MetS, increased blood pressure, increased triglycerides and glucose intolerance were all significantly lower with concomitant use of antimalarials. In addition to their anti-inflammatory effects, antimalarials likely have direct effects on vascular function and lipid metabolism that improves the overall metabolic and cardiovascular risk status of SLE patients.

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Atherosclerotic Vascular Events in a Multinational Inception Cohort of SLE: Description and Attribution over an 8 Year Period. Murray B. Urowitz11, Dafna D. Gladman19, Dominique Ibáñez18, Caroline P. Gordon15, Sang-Chol Bae5, Ann E. Clarke15, Sasha R. Bernatsky15, F. Jorge Sanchez-Guerrero17, Kristjan Steinsson22, Munther A. Kamali27, Michelle A. Petri1, Rosalind Alarcoñ28, Barri J. Fessler23, Ian N. Bruce13, Gunnar K. Sturfelt27, Ola Nived27, T. Gono: None; Y. Kawaguchi: None; K. Takagi: None; T. Gono: None; Y. Okamoto: None; Y. Ota: None; M. Har: None; H. Yamakawa: None.

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Atherosclerotic Vascular Events in a Multinational Inception Cohort of SLE: Description and Attribution over an 8 Year Period. Murray B. Urowitz11, Dafna D. Gladman19, Dominique Ibáñez18, Caroline P. Gordon15, Sang-Chol Bae5, Ann E. Clarke15, Sasha R. Bernatsky15, F. Jorge Sanchez-Guerrero17, Kristjan Steinsson22, Munther A. Kamali27, Michelle A. Petri1, Rosalind Alarcoñ28, Barri J. Fessler23, Ian N. Bruce13, Gunnar K. Sturfelt27, Ola Nived27, T. Gono: None; Y. Kawaguchi: None; K. Takagi: None; T. Gono: None; Y. Okamoto: None; Y. Ota: None; M. Har: None; H. Yamakawa: None.

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449 Attention Deficit and Hyperactivity Disorder Scores Are Elevated and Associated with Disease Activity and Fatigue in Patients with Systemic Lupus Erythematosus. Ricardo J. Garcia, Lisa Francis, Maha Dawood, Irene Ramos, Stephen Farane and Andras Perl. SUNY

Purpose: Systemic lupus erythematosus (SLE) is a chronic systemic auto-immune inflammatory disease characterized by predisposition to pro-inflammatory T cell death by necrosis due to mitochondrial dysfunction, oxidative stress and depletion of intracellular glutathione. The potential benefit of reversing glutathione depletion is being investigated in a double-blind placebo-controlled treatment trial of N-acetylcysteine in patients with stable disease (ClinicalTrials.gov Identifier: NCT00775476). Since disease activity in SLE may result in neuropsychiatric manifestations and N-acetylcysteine has been found to improve memory in animal models (Basic Clin Pharmacol Toxicol. 105:98–104, 2009), we investigated whether disease activity in patients with SLE is associated Attention Deficit Hyperactivity Disorder (ADHD) which may serve as a neuropsychiatric marker and target of treatment.

Patients and Methods: The validated ADHD Self-Report Scale (ASRS) Symptom Checklist (Psychol Med 35:245-56, 2005; Ann Clin Psychiatry 18:145–148, 2006) was used to evaluate 22 SLE patients at baseline. As a control for biochemical and immunological studies, a healthy donor matched for ethnicity, gender, and age of the SLE patient within 10 years was bled on the same morning and also asked to complete the ASRS checklist. In the SLE group, 20 of 22 patients were Caucasian, one was African American, and one was Asian. In the control group, 21 of the 22 donors were Caucasian and one was Asian. Mean age was 42.27 years (standard deviation, SD= 12.85, range =21–64) in the SLE group. Mean age was 44.23 years (SD=10.86, range =23–62) in the control group. All patients were female. SLE disease activity was assessed by using the British Isles Lupus Assessment Group (BILAG) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Fatigue was estimated using the Fatigue Assessment Scale (J Psychosom Res 54:345–352, 2003).

Results: The mean ± SD of part A, part B and total ASRS scores were 10.56 ± 5.75, 9.82 ± 6.01 and 20.36 ± 10.32, respectively, in the control
ADHD symptoms predict the subsequent onset of severe neuropsychiatric disorders that frequently follow the onset of idiopathic ADHD in children (Ann Am Psychiatry 167:409–417, 2010).

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Anticoagulant Response to Adjuvant versus Non-Adjuvant H1N1 Vaccination in SLE.

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It has been reported that influenza vaccination increases autoantibody production and/or disease activity in a significant proportion of patients with SLE. A further concern would be whether adjuvant containing vaccines might further enhance anticoagulant production in these patients. During the recent H1N1 epidemic, investigators have assessed whether the use of adjuvant and nonadjuvant H1N1 vaccine induced increased autoantibody production in patients with SLE.

Methods: Patients with SLE who received H1N1 vaccination (with or without adjuvant) and had a battery of 9 autoantibodies tested before and 1 and 3 months after vaccination were included. Antibodies tested included rheumatoid factor (nephelometry), antineutrophil antibody (immunofluorescence), anti-DNA (Farr), anti-RNP, anti-SS-A, anti-Scl-70 and anti-Jo-1 (ELISA). Patients were evaluated according to the standard protocol including items necessary to calculate SLEDAI-2K and SDI. Descriptive statistics and McNemar test were performed to evaluate change in antibodies positivity. These were repeated in the adjuvant and the non adjuvant groups separately.

Results: 103 patients (94F, 9M), with mean age at vaccination of 43.9 (±15.2) years, disease duration 14.2 (±11.0) years. Mean SLEDAI-2K was 4.38 (±4.28); SDI of 1.26 (±1.52), 64% were taking steroids and 62% on immunosuppressives. 51 patients received adjuvant and 52 nonadjuvant vaccines. Antibody testing was performed a mean of 1.9 months prior to the vaccination. First post-vaccination sample was taken a mean of one month and the second sample was taken a mean of 3.5 months after vaccination. The percent of patients with changes in antibodies following vaccination was not statistically significant for most antibodies. In rheumatoid factor 89% remained unchanged while 15% who were negative became positive while 5% who were positive became negative (p = 0.07). This was more pronounced in the non adjuvant group then in the adjuvant group where 88% remained unchanged, 12% converted for positive and none converted to negative compared to 71% remaining unchanged, 18% converting to positive and 12% converting to negative (p = 0.03 and p = 0.53 respectively). In Anti-Ro 83% remained unchanged while 3% converted to positive and 14% converted to negative (p = 0.03) but no difference was significant when looking at the vaccine type. No other antibodies changes significantly in either group. After adjusting for the number of tests performed none of the associations was significant.

Conclusion: H1N1 vaccination (both adjuvant and non adjuvant) did not increase the levels of autoantibodies in patients with SLE.

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Belimumab, a BLYS-Specific Inhibitor, Reduced Corticosteroid Use in Patients with Active SLE: Results from the Phase 3 BLISS-52 and -76 Studies.

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Purpose: To assess the corticosteroid-sparing activity of belimumab in patients on corticosteroids at baseline with seropositive SLE over 52 and 76 wk of treatment.

Methods: 1684 seropositive (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL) SLE patients with SELENA-SLEDAI ≥6 were enrolled in the phase 3, 52-wk (BLISS-52; NCT00424476) and 76-wk (BLISS-76; NCT0410384) international trials and randomized to IV belimumab 1 or 10 mg/kg, or placebo, plus standard-of-care (SOC) therapy, on d 0, 14, and 28, and then q24d, for 48 or 72 wk. The use of corticosteroids at entry was according to clinical need; use beyond prespecified limits resulted in patient designation as a treatment failure.

Results: 1453 patients (86.3%) were taking corticosteroids at baseline. Mean baseline characteristics were similar across treatment groups: SLE disease duration 6.4 y; daily prednisone equivalent dose 12.5 ± 8.1 mg; 976 patients (67.2%) with prednisone ≥7.5 mg/d; 64.1% with antimalarials; 50.0% with immunosuppressants; 25.7% with biologics; 7.77 (p = 0.0001) correlation between BILAG and ASRS scores at entry.

Conclusion: Elevated ASRS scores indicate the presence of previously unrecognized and clinically significant symptoms of ADHD in patients with SLE relative to healthy controls matched for age, gender, and ethnic background. ADHD symptoms may be a source of cognitive impairment in SLE, which could lead to functional disability. Longitudinal studies are needed to determine if ADHD symptoms predict the subsequent onset of severe neuropsychiatric disorders that frequently follow the onset of idiopathic ADHD in children (Ann Am Psychiatry 167:409–417, 2010).

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Autoantibody Response to Adjuvant and Non-Adjuvant H1N1 Vaccination in SLE.


Human Genome Sciences, Inc., 1, 3; GlaxoSmithKline, 5, 8; Human Genome Sciences, Inc., 5, 9; A. Gallacher: Human Genome Sciences, Inc., 2, 5; S. Navarra: Human Genome Sciences, Inc., 2, 9; M. A. Dooley: Human Genome Sciences, Inc., 5, 9; R. Cervera: GlaxoSmithKline, 5; Human Genome Sciences, Inc., 5, 9; E. K. Li: Human Genome Sciences, Inc., 5, 9; R. A. Levy: GlaxoSmithKline, 8; Human Genome Sciences, Inc., 5, 8, 9; R. Guzmán: Human Genome Sciences, Inc., 5, 9; Z. J. Zhong: Human Genome Sciences, Inc, 1, 3; S. Cooper: Human Genome Sciences, Inc., 1, 3; D. Hough: Human Genome Sciences, Inc, 1, 3; D. J. Wallace: Human Genome Sciences, Inc., 9; for the BLISS-52 and -76 Study Groups. None.
Monday, November 8

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Belimumab, a BLyS-Specific Inhibitor, Reduced Disease Activity, Flares,
and Prednisone Use in Patients with Seropositive SLE: Combined Efficacy
Results from the Phase 3 BLISS-52 and -76 Studies. M. A. Petri5, R. A.
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University of Santo Tomas Hospital, Manila, Philippines, 11West Penn Allegheny Health System, Pittsburgh, PA
Purpose: To assess the efficacy of belimumab in patients with seropositive
SLE over 52 wk of treatment by pooling the data from 2 large phase 3 clinical
trials.
Methods: 1684 seropositive (ANA ⱖ1:80 and/or anti-dsDNA ⱖ30 IU/mL)
SLE patients with SELENA-SLEDAI (SS) ⱖ6 on stable standard-of-care therapy
for ⱖ30 d were enrolled in 2 phase 3, double-blind, placebo-controlled international trials of belimumab 1 or 10 mg/kg or placebo, plus standard-of-care
(NCT00424476/NCT00410384). Patients were dosed on d 0, 14, and 28, and then
q28d, for 48 or 72 wk. Efficacy analyses included SS, BILAG, and SS Flare Index
(SFI). The primary endpoint in both trials was wk-52 SLE Responder Index
(SRI): improvement in SS (ⱖ4-pt decrease), no new BILAG A and no more than
1 B flare, and no worsening (⬍0.3-point increase) in Physician’s Global
Assessment (PGA) vs baseline at wk 52.
Results: Mean baseline characteristics were similar across treatment groups:
age 37.8 y; female 94.1%; race: Caucasian 47.4%, Asian 21.1%, indigenous
American 22.7%, African-American 8.8%; SLE disease duration 6.4 y; SS 9.7;
BILAG 1A/2B 61%; anti-dsDNA⫹ 69.4%; low C4 56.1%; proteinuria (⬎0.5
g/24h) 20.1%; antimalarials 65.3%; prednisone ⱖ7.5 mg/d 58.0%; immunosuppressants 48.7%. SRI response rates were 46.2% (p⫽0.006) with belimumab 1
mg/kg and 50.6% (p⬍0.0001) with 10 mg/kg vs 38.8% with placebo (table).
Significant improvement was seen with belimumab 10 mg/kg vs placebo for: SRI
at wk 52; SS ⱖ4-point reduction; mean % reduction in PGA at wk 24; reduction
in prednisone use; and new BILAG 1A/2B flares. Statistically significant
improvement compared with placebo was seen in at least 1 belimumab treatment
group for time to response, mean duration of response, time to first flare (all and
severe) by SFI, and new BILAG 1A/2B organ domain scores.
Conclusion: Belimumab significantly reduced SLE disease activity and SLE
flare rates; delayed time to first SLE flare; and reduced prednisone use in patients
with seropositive SLE.
Table. Combined BLISS Efficacy Results

Parameter
Primary endpoint
SRI at wk 52
Mean response duration, da
Secondary endpoints
ⱖ4-point reduction in SS scoreb
No worsening in PGA (ⱕ0.3 pts)
No new BILAG 1A/2B organ
domain scores
Improvement in PGA, mean ⫾ SE
% change at wk 24
% change at wk 52
Prednisone reduction from
⬎7.5 mg/d by 25% to ⱕ7.5 mg/
d during wk 40–52, n (%)b
Prednisone increase from
ⱕ7.5 mg/d baseline to
⬎7.5 mg/d at wk 52, n (%)
SLE flares
SFJ median time to first SLE flare
(all) log-rank analysis, d
Flare rate, % (hazard ratio)
Flares per patient-y, mean ⫾ SE
D 0-wk 52
Wk 24–52
SFJ severe flare rate, % (hazard
ratio) log-rank analysis
Severe flares per patient-y,
mean ⫾ SE
D 0-wk 52
Wk 24–52
New BILAG 1A/2B flare rate, %
(hazard ratio) log-rank analysis
New BILAG 1A flare rate, %
(hazard ratio) log-rank analysis

SOC ⴙ Belimumab
10 mg/kg
(n ⴝ 563),
n (%)

SOC ⴙ Placebo
(n ⴝ 562),
n (%)

SOC ⴙ Belimumab
1 mg/kg (n ⴝ 559),
n (%)

218 (38.8)
67.2 ⫾ 4.9

258 (46.2)**
90.3 ⫾ 5.4***

285 (50.6)#
103.3 ⫾ 5.5#

230 (40.9)
372 (66.2)
389 (69.2)

269 (48.1)**
424 (75.8)***
429 (76.7)**

297 (52.8)*
420 (74.6)**
425 (75.5)*

⫺24.3 ⫾ 2.5%
⫺27.1 ⫾ 2.3
39 (12.3)
82 (33.6)

⫺28.8 ⫾ 2.1%
⫺36.7 ⫾ 2.2**
67 (20.1)**
58 (25.8)

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R. A. Levy: GlaxoSmithKline, 8, Human Genome Sciences, Inc., 5, 8, 9; J. T. Merrill:
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BILAG-Measured Improvement in Moderately and Severely Affected
Body Systems in Patients with Systemic Lupus Erythematosus (SLE) by
Epratuzumab: Results from EMBLEM™, a Phase IIb Study. Kenneth C.
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1
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Background: The efficacy of 2 epratuzumab doses was demonstrated in a
12-week, multi-center, randomized, double-blind, placebo-controlled, Phase IIb
study in SLE (NCT00624351). Statistically or clinically significant efficacy was
seen with epratuzumab 600 mg every week for 4 weeks and 1200 mg every other
week (EOW) for 2 weeks, respectively, with responder rates twice those of
placebo. The aim of this analysis was to assess improvement in BILAG 2004
index according to body systems in the epratuzumab 600 mg weekly and
epratuzumab 1200 mg EOW dose groups (cumulative dose ⫽ 2400 mg).
Methods: A combined index of disease activity was used to assess efficacy
(defined as BILAG improvement: reduction in all body systems of baseline
BILAG A to B/C/D and BILAG B to C/D; no BILAG worsening in other organ
systems; no deterioration in SLEDAI or physician’s global disease activity
assessment). Independent central readers determined BILAG grades for all 9
systems. Results for the BILAG improvement component of the combined index
in body systems for which a sufficient number of patients per treatment group
(ⱖ5) had baseline disease activity to assess response are reported: musculoskeletal, mucocutaneous, cardiorespiratory, neuropsychiatric, constitutional and renal.
Results: Similar numbers of patients had BILAG A/B at baseline in all
treatment arms in each system, apart from cardiorespiratory (where the placebo
arm contained more patients) (Table). By Week 12, more patients in the
epratuzumab 600 mg weekly group, compared with placebo, had an improvement
from BILAG A/B to BILAG D in the 6 body systems, indicating no active
disease. A higher percentage of patients receiving epratuzumab 1200 mg EOW,
compared with placebo, had an improvement in baseline BILAG A/B scores to
BILAG C or D in musculoskeletal, mucocutaneous, neuropsychiatric, and renal
systems. Improvements were particularly prominent in the cardiorespiratory and
neuropsychiatric systems. In the cardiorespiratory system, all 7 patients in the
epratuzumab 600 mg weekly group had improved to a BILAG D at Week 12.
Similarly, in the neuropsychiatric system, 5 out of 6 patients in the epratuzumab
600 mg weekly group improved from BILAG B at baseline to BILAG D at Week
12.
Table. Change in BILAG grade among subjects with flares at baseline
BILAG
grade at
baseline

⫺32.3 ⫾ 2.1%**
⫺37.8 ⫾ 2.4***
58 (17.9)*
62 (25.9)

Body system
Musculoskeletal
Mucocutaneous

84

110**

110*

81.5

74.6 (0.82)**

74.6 (0.84)*

3.5 ⫾ 0.1
3.4 ⫾ 0.2
23.7

2.9 ⫾ 0.1***
2.5 ⫾ 0.1#
17.0 (0.71)*

2.9 ⫾ 0.1***
2.4 ⫾ 0.1#
15.6 (0.64)**

1.0 ⫾ 0.1
1.0 ⫾ 0.1
32.0

0.9 ⫾ 0.1
0.7 ⫾ 0.1
27.2 (0.83)

0.8 ⫾ 0.1
0.6 ⫾ 0.1*
24.9 (0.75)*

23.1

19.0 (0.81)

16.2 (0.67)**

Duration of response occurring at/before wk-52 visit and persisting to wk 52; bmajor secondary
endpoint for both trials.
*p ⬍ 0.05; **p ⬍ 0.01; ***p ⬍ 0.001; *p ⬍ 0.0001.

Cardiorespiratory
Neuropsychiatric
Constitutional
Renal

Treatment group
Placebo
Emab 600 mg weekly
Emab 1200 mg EOW
Placebo
Emab 600 mg weekly
Emab 1200 mg EOW
Placebo
Emab 600 mg weekly
Emab 1200 mg EOW
Placebo
Emab 600 mg weekly
Emab 1200 mg EOW
Placebo
Emab 600 mg weekly
Emab 1200 mg EOW
Placebo
Emab 600 mg weekly
Emab 1200 mg EOW

Emab, Epratuzumab.
Placebo, N ⫽ 38.
Emab 600 mg weekly, N ⫽ 37.
Emab 1200 mg EOW, N ⫽ 37.

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A/B (Severe/
moderate
disease)
n
31
35
34
31
32
32
17
7
9
11
6
8
9
7
10
5
6
6

BILAG grade (shift) at Week 12
A/B
(Severe/
C
D
moderate
(Stable
(Inactive
disease)
disease)
disease)
n (%)
n (%)
n (%)
18 (58)
7 (23)
6 (19)
13 (37)
12 (34)
10 (29)
13 (38)
10 (29)
11 (32)
18 (58)
9 (29)
4 (13)
19 (59)
4 (13)
9 (28)
15 (47)
10 (31)
7 (22)
10 (59)
2 (12)
5 (29)
0 (0)
0 (0)
7 (100)
8 (89)
0 (0)
1 (11)
6 (55)
3 (27)
2 (18)
1 (17)
0 (0)
5 (83)
3 (38)
0 (0)
5 (63)
1 (11)
1 (11)
7 (78)
0 (0)
0 (0)
7 (100)
2 (20)
2 (20)
6 (60)
3 (60)
2 (40)
0 (0)
3 (50)
1 (17)
2 (33)
3 (50)
3 (50)
0 (0)


Conclusions: Treatment with epratuzumab 600 mg weekly during a 12-week cycle provided greater BILAG improvement over placebo in disease activity in all affected body systems. Within specific body systems, most patients had symptom reduction or absence of active disease after treatment. Efficacy was particularly prominent in cardiorespiratory and neuropsychiatric systems in which symptom improvements are often difficult to achieve. Within specific body systems, the majority had symptom reduction or absence of active disease after treatment. This analysis supports the finding that epratuzumab may be an effective treatment for SLE.

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Biologics Use in SLE in 7 Centers—Data from the International Registry for Biologics in SLE (IRBIS). Ronald Van Vollenhoven1, Soren Jacobsen, Daniel J. Wallace2, John G. Hanly3, Michelle A. Petrini4, David A. Isenberg5, Ann E. Clark6, Christian A. Pincus7, Philippe Scharl8, Pippa R. Bernatsky9, 15, SLICC Group10. 1West Hollywood, CA, 4Karolinska University Hospital, Stockholm, Sweden, 2Karolinska University Hospital, Stockholm, Sweden, 4McGill UHC/RVH, Montreal, QC, Canada, 5McGill Univ Health Center, Montreal, QC, Canada, 6Montreal General Hospital, Montreal, QC, Canada, 7Queen Elizabeth II Health Services Centre, Halifax, NS, Canada, 8Righospitalet-gle, Copenhagen, Denmark, 9UCL Div of Medicine, London, United Kingdom

Background: No biologic agents are approved for use in SLE, but off-label use is possible in various settings. In order to obtain information regarding biologics use in SLE, members of the SLICC group recently initiated the International Registry for Biologics in SLE (IRBIS).

Methods: SLE/C/IRBIS investigators were asked to provide retrospective data on all patients treated with a biologic for SLE at their center. Standardized case report forms (CRFs) were used to collect demographic, disease-specific, and treatment data at the time of biologic initiation and at yearly follow-up. A retrospective data collection is currently in progress, and data from the first 7 reporting centers were analyzed.

Results: 165 patients were treated off-label with a biologic agent, in all cases rituximab (RTX). Additional groups of patients were treated in open-label extensions of RCTs with belimumab (n = 16) and epratuzumab (n = 21) – these patients were not further analyzed here. Age (mean±SD) was 39.4±12.3 and 92% were female. 57% were Caucasian, and smaller proportions Southeast Asian, Asian/Indian subcontinent, African-American, Latino, or other (each <10%). Disease duration when the biologic was initiated was 11.2 ± 8.1 years. SLEDAI at biologic start was 10.5 ± 9.2; SLICC-damage index 1.45 ± 1.71, and glucocorticoid (GC) dosage (prednisone equivalent) 15.0 ± 13.8 mg. Two different dosing regimens for RTX were used: 375 mg/m2 × 4 (37%) and 1000 mg × 2 (63%). Concomitant cyclophosphamide (CYX) was used in 54% of patients. The major organ manifestations leading to biologic treatment were lupus nephritis (LN) in 46% of patients, skin disease in 20%, hematological in 10%, musculoskeletal in 9%, CNS in 8%, and other in 14% (some patients having more than one). Both disease-control and steroid-sparing were given as reasons for choosing a biologic. At 1-year follow-up (n = 92) additional immunosuppressives (ISs) had been started in 13 patients. Both SLEDAI and GC dose had decreased (SLEDAI to 5.9 ± 5.3; GC to 9.0 ± 10.9 mg; p < 0.0005 for both comparisons, and excluding patients on new ISs). SLEDAI at baseline was higher in LN patients than in non-LN but similar at follow-up. The higher-dose RTX regimen was employed more often in LN; baseline SLEDAI for these patients was higher, and the decrease greater, than for the lower-dose regimen. A similar pattern was seen for changes in SLEDAI when RTX was used with as compared to without concurrent CYX.

Conclusions: Off-label biologics use in this multi-center international cohort was limited to rituximab; additional groups of patients on other biologics are followed in open-label extensions of clinical trials. Biologics in SLE are used for LN as well as for a range of other SLE manifestations. Both disease control and a steroid-sparing effect are targeted. At 1-year follow-up, lupus activity and concomitant glucocorticoid dosage had decreased, and this could not be attributed to other IS treatment.

The complete retrospective dataset from all participating centers, and the initiation of the prospective IRBIS registry, will provide much-needed data on the use of and results achieved with biologics in SLE.

Disclosure: R. Van Vollenhoven: None; S. Jacobsen: None; D. J. Wallace: None; J. G. Hanly: None; M. A. Petrini: None; B. D. Isenberg: None; A. E. Clarke: None; P. R. Bernatsky: None; C. P. Gordon: None; S. K. Kilgallen: None; B. Kilgallen: UC Biopharma, Inc., 3; C. P. Gordon: Aspreva, 2, 5; Bristol-Myers Squibb, 5; Genentech and Biogen IDEC Inc, 5; Merck Pharmaceuticals, 5; Roche, 5; UC Biopharma, 5; 15

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Cardiot Plaque Area Correlates Better Than Intima Media Thickness with Cardiovascular Risk Factors and Clinical Ischemic Heart Disease in Lupus Patients. Lihi Eder, Murray B. Urowitz, Dominique Ibanez and Dafna D. Gladman. Toronto Western Hospital, Toronto, ON, Canada

Aim: Patients with Systemic Lupus Erythematosus (SLE) have a significantly increased risk of accelerated atherosclerosis and cardiovascular disease (CVD). The extent of sub-clinical atherosclerosis can be assessed by an ultrasound (US) measurement of carotid intima-media thickness (c-IMT) and carotid plaque area (c-PA). In the general population, c-PA correlates with ischemic events better than c-IMT. The aim of this study was to investigate whether c-PA can serve as a preferred surrogate measure for sub-clinical atherosclerosis in SLE.

Methods: The study patients were recruited from a large single centre prospective cohort of SLE patients. Demographic, clinical and laboratory information was stored in a computerized database. The database was searched for subjects with a history of a documented ischemic heart event, including angina pectoris or myocardial infarction. Consecutive SLE patients without a history of CVD were identified as controls. High-resolution, optimized US measurement of carotid intima-media thickness (c-IMT) and carotid plaque area (c-PA) were evaluated. Both measures were compared in patients with and without a history of CVD. To facilitate direct comparisons, c-IMT and c-PA were transformed into z scores. Logistic regressions were used to evaluate the Odds Ratio (OR) and 95% Confidence Interval (95% CI) of c-IMT and c-PA in their association with CVD, hypertension, cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL).

Results: 72 SLE patients participated in the study, of whom 19 had a history of ischemic heart event. Carotid IMT correlated only moderately with c-PA (r = 0.46, p < 0.001). Both c-IMT and c-PA were significantly higher in the group with ischemic heart event (7.12 ± 10.67 vs. 606.4 ± 96.0 mm, p < 0.001 for c-IMT and 0.447 ± 0.577 vs. 0.048 ± 0.100 = 0.008 cm2 for c-PA). After transforming c-IMT and c-PA into z scores, c-PA showed a stronger association with clinical ischemic event (OR 10.89 95% CI 2.5–49.9, p = 0.001) than c-IMT (OR 2.8, 95% CI 1.5–5.2, p = 0.001). Elevated c-PA was significantly associated with high LDL levels (OR 7.6, p = 0.04) and with low HDL level (OR 4.78 p < 0.02) however, no association was seen with hypertension or total cholesterol level. Carotid IMT did not correlate with any of the traditional cardiovascular risk factors. None of the measures correlated with SLE disease duration.

Conclusions: In SLE patients, c-IMT correlates moderately with c-PA suggesting that they measure different phenotypes of atherosclerosis. Carotid Plaque area correlated better than c-IMT with cardiovascular risk factors and ischemic heart events suggesting that it may serve as a better tool for investigation of atherosclerosis in SLE.

Disclosure: L. Eder: None; M. B. Urowitz: None; D. Ibanez: None; D. D. Gladman: None.

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Circulating Pro-Angiogenic Cells Are Reduced in Patients with SLE Independent of the Presence of Coronary Artery Calcification. Joshua Baker1, Lifeng Zhang2, Sotonye Imadojemu2, Alexis Sharpe2, Sarita Patil2, Jonni Moore2, Emile R. Mohler III2 and Joan Marie Von Feldt3, 1University of Pennsylvania, Philadelphia, PA, 2University of Pennsylvania—Philadelphia, Veterans Affairs Medical Center, Philadelphia, PA

Purpose: Circulating pro-angiogenic cells (PACs), often termed endothelial progenitor cells, are reduced in number in patients with SLE. A reduced number of PACs has been strongly associated with the presence of atherosclerosis and predicts cardiovascular events in other populations. We sought to determine if reduced PAC numbers in patients with SLE is dependent on the presence of advanced coronary artery calcification (CAC).

Methods: Patients were included if they met 4 criteria for the diagnosis of
SLE and had previous coronary calcium scores which placed them in either the >75th percentile or <25th percentile for their age. Exclusion criteria included a history of advanced renal disease, cardiovascular events, or current use of >10 mg of prednisone. 17 SLE patients and 13 healthy controls (HC) were included in the study. White blood cells from 30mL peripheral blood were stained for PAC and progenitor cell (PC) markers including CD34, CD133, and VEGFR and analyzed by flow cytometry as previously described (1). SLE patients had repeated coronary imaging with CT as well as carotid ultrasound to determine carotid intima-media thickness. Non-normal data were analyzed with non-parametric tests of significance.

Results: There was no difference in age between HC and SLE. SLE patients were more likely to be hypertensive, and SLE patients with CAC were more likely to be hypertensive, smokers, and have longer disease duration than SLE patients without CAC. Patients with SLE had a significant decrease in PAC numbers when compared to HC. CD34+/CD34+/VEGFR+ cells were deficient in SLE patients (Median, IQR) 10.2 (5.8, 12.3) v. 0 (0, 0) (p = 0.02). Total numbers of PCs (CD133+/CD34+) were not significantly decreased in patients with SLE (Mean + SEM) 1007 ± 154 v. 824 ± 170 (p = 0.2). No significant difference was seen in PAC number between SLE patients without CAC and those with advanced CAC (Median, IQR) 0 (0, 6.7) v. 0 (0, 0) (p = 0.02). Increased carotid intima-media thickness did not correlate with CAC or decreased numbers of PACs in SLE patients.

Conclusions: Our study is the first to show that reduced numbers of PACs in SLE patients may be observed even in the absence of coronary calcification. Depletion of total circulating PCs does not appear to fully explain this difference.


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Purpose: To evaluate the effect of belimumab plus standard of care (SOC) on antibodies against pneumococia, tetanus, and influenza in SLE patients with history of vaccination against these pathogens prior to study entry.

Methods: The phase 3, multicenter, randomized, double-blind, placebo-controlled, 76-wk BLISS-76 study evaluated the efficacy and safety of belimumab 1 or 10 mg/kg (IV infusion over 1 h on d 0, 14, and 28, and every 28 days thereafter through 72 wk) plus SOC vs placebo plus SOC in patients with seropositive SLE (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL). NC100413084). History of receiving pneumococcal, tetanus, and influenza vaccines was obtained at screening. Patients receiving a pneumococcal vaccine (73) or tetanus (n = 81) vaccine within 5 y prior to d 0, or an influenza vaccine (n = 146) within 1 y prior to d 0, were tested for vaccine antibody levels on d 0 and at wk 52. Immunglobulin-G antibodies were measured for each vaccine (multi-analyte immune detection for pneumonia, enzyme-linked immunosorbent assay for tetanus, and hemagglutination inhibition test for influenza). Endpoints used to determine the impact of belimumab on vaccine responses included % change in antibody levels from baseline to wk 52 in patients with pre-existing antibodies, and proportion of patients with protective antibodies at baseline who maintained protective levels at wk 52.

Results: Consistent with the preservation of the memory B-cell compartment (CD20+/+ B cells), belimumab did not cause a statistically significant decrease in pre-existing antibodies to pneumococcal and tetanus vaccines; most patients were able to maintain protective titers to these vaccines, and changes were similar across treatment groups (table).(2) Pre-existing antibody responses to seasonal influenza vaccines were generally not affected by treatment with belimumab, although a statistical, but not clinically relevant, difference (<1-fold median change in titers) between treatment groups was observed for some antigens; the percentages of patients that maintained protective specific titers at the end of 52 wk were similar in the belimumab and placebo treatment groups.

Table. % IgG Change in Response From Wk 0 to 52

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>SOC + Placebo, n = 34</th>
<th>SOC + Belimumab 1 mg/kg, n = 27</th>
<th>SOC + Belimumab 10 mg/kg, n = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal</td>
<td>Mean ± SE</td>
<td>Median</td>
<td>% Protective</td>
</tr>
<tr>
<td>9 (95%)</td>
<td>-10.3 ± 6.9</td>
<td>-1.7</td>
<td>92.3%</td>
</tr>
<tr>
<td>14 (14)</td>
<td>-8.1 ± 7.0</td>
<td>-3.2</td>
<td>101.1%</td>
</tr>
<tr>
<td>19 (19F)</td>
<td>-5.3 ± 7.2</td>
<td>-3.5</td>
<td>93.5%</td>
</tr>
<tr>
<td>23 (23F)</td>
<td>-8.1 ± 8.5</td>
<td>-2.4</td>
<td>6.6%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Mean ± SE</td>
<td>Median</td>
<td>% Protective</td>
</tr>
<tr>
<td>Antigenetic</td>
<td>-12.0 ± 5.1</td>
<td>-1.7</td>
<td>92.3%</td>
</tr>
<tr>
<td>Antitubercular</td>
<td>Mean ± SE</td>
<td>Median</td>
<td>% Protective</td>
</tr>
<tr>
<td>Anti-influenza (2006-7)</td>
<td>SOC + Placebo, n = 34</td>
<td>SOC + Belimumab 1 mg/kg, n = 22</td>
<td>SOC + Belimumab 10 mg/kg, n = 22</td>
</tr>
<tr>
<td>New Caledonia</td>
<td>Mean ± SE</td>
<td>Median</td>
<td>% Protective</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>Mean ± SE</td>
<td>Median</td>
<td>% Protective</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Mean ± SE</td>
<td>Median</td>
<td>% Protective</td>
</tr>
</tbody>
</table>

4 Includes several representative antigen serotype results; 5 percentage of patients maintaining protective antibody level at wk 52; 6 patients did not have data available at wk 52 (n = 26); 7 p < 0.05 for the comparison between active and placebo.

Conclusion: In this study, treatment with belimumab did not significantly affect the ability of SLE patients to maintain a protective immune response to prior immunizations.

Effect of Systemic Lupus Erythematosus (SLE) on Pregnancy Outcome: An Analysis of 268 Pregnancies. Chi Chiu Mok and Ling Yin Ho. Tuen Mun Hospital

Objectives: To compare the maternal and fetal outcomes of pregnancies before and after the onset of SLE.

Methods: Female patients who fulfilled the ACR criteria for SLE and were ever pregnant were interviewed for the details of the maternal and fetal outcomes regarding their pregnancies. Comparison of the outcomes of pregnancies that occurred before and after the onset of SLE was made.

Results: 113 SLE patients with a history of pregnancy were studied. There were a total of 268 pregnancies: 216 pregnancies occurred before onset of SLE; 47 pregnancies occurred after SLE onset; and in 5 pregnancies, SLE was first diagnosed during conception. The maternal age was 28.7 ± 5.6 and 26.4 ± 5.0 years, respectively, in pregnancies that occurred after and before the onset of SLE. Induced abortion was significantly more common in pregnancies occurring after than before the onset of SLE (35% vs 18.1%; p = 0.01). Spontaneous abortion also occurred at a higher frequency in pregnancies that occurred after SLE onset, but the difference was not statistically significant (12% vs 8.9%). Among 216 pregnancies that occurred before SLE onset, 158 (73%) ended up with live births and there was one (0.5%) intrauterine fetal death. The mean fetal birth weight was 2.98 ± 0.51 kg. For pregnancies that occurred after SLE onset, only 55.3% ended up with live births. The fetal birth weight was significantly lower than that in pregnancies that occurred before SLE onset (2.74 ± 0.46 vs 2.98 ± 0.51 kg; p = 0.03). Preterm delivery was significantly more common in pregnancies after SLE onset (36% vs 7%; p < 0.001). There were more maternal complications (eg, preeclampsia, proteinuria and lupus flares; 30.8% vs 3.8%; p < 0.001) and fetal complications (eg, neonatal lupus, heart problems, infections, anemia; 3.8% vs 2.5%; p = 0.75) in pregnancies that occurred after SLE diagnosis than before onset of SLE.

Conclusion: SLE increases the frequency of maternal complications and adversely affects fetal outcomes in terms of fetal loss, prematurity and low birth weight.

Disclosure: C. C. Mok: None; L. Y. Ho: None.

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Traditional cardiovascular risk-factors do not fully explain premature atherosclerosis in SLE. We aimed to identify lupus-related factors associated with coronary-artery calcifications in an inception cohort for the study of atherosclerosis.

Methods: We included 139 patients (93% females) with SLE of recent-onset at enrollment, w/o preexisting coronary heart disease. At enrollment, a standardized medical evaluation was done assessing lupus characteristics, onset at enrollment, w/o preexisting coronary heart disease. At enrollment, atherosclerosis in SLE. We aimed to identify lupus-related factors associated with lupus pregnancies that occurred before and after the onset of SLE was made.

Results: At enrollment, mean (SD) age of lupus patients was 27.2 (9.1) years, lupus duration 5.4 (3.8) months, and SLEDAI-2K score 6.9 (5.8). At screening for calcification, mean age of patients and controls was similar (31.8 ± 8.8 vs. 32.2 ± 9.8 years), as most cardiovascular risk-factors; however lupus patients had more often hypertension, higher levels of homocysteine and hsCRP, wider waist, and females were more often postmenopausal, P < 0.05.

Coronary-calcifications were detected in 10 patients (7.2%) and 1 control (OR 7.7, 95% CI 1.05–336.3, P = 0.02). Calcium scores in 9 patients ranged between >0–20, and in the remaining patient 402; in the positive control it was 239. Calcifications in lupus patients were detected since age 21–30 years and from 3 years of diagnosis.

In comparison to patients w/o calcifications, patients with calcifications were older, females more often postmenopausal, had higher Apo-B levels, lgG aPL antibodies, and the Framingham risk-scores were higher (p < 0.05). Disease activity along the course of lupus was higher (SLEDAI-2K AUC 20.3 ± 8.3 vs. 13.7 ± 8.3, P = 0.02), and the period of moderate/severe activity longer (SLEDAI-2K score ≥7, 20.0 ± 18.3 vs. 8.0 ± 12.5 months, P = 0.006). Cumulative doses of prednisone and cyclophosphamide were higher (P < 0.05), but use of antimalarials lower (20% vs 65%, P = 0.006). Longitudinal analyses of lipids, cytokines and chemokines did not show differences. Logistic regression analysis showed an independent association of age, Apo-B, lupus activity (P = 0.004), and use of antimalarials (P = 0.008) with calcifications.

Conclusions: Lupus activity is an independent risk factor for coronary-artery calcifications, a risk that might be reduced using antimalarials.

Disclosure: J. Romero-Diaz: None; F. Vargas-Worackova: None; E. Kimura-Hayama: None; C. Aguilar-Salinas: None; J. Sanchez-Guerrero: None.

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Elevated Levels of Plasma Micro-Particles (PMPs) in Systemic Lupus Erythematosus (SLE) Are Associated with Higher Risk of Thrombosis. Aisha Lateef1, Laurence S. Magder2, Jayesh Jani3, Thomas S. Kiecker4 and Michelle A. Petri1. 1Timonium, MD, 2Johns Hopkins University, 3National University Health System, Singapore, Singapore, 4University of Maryland Medical School

Objective: PMPs are sub-micron, membrane-bound vesicles, released during cell activation, apoptosis and exposure to shear stress. They are pro-thrombotic, expressing high levels of phosphatidylserine and tissue factor on outer membranes. PMPs modulate nitric oxide and prostacyclin production from endothelial cells, as well as monocyte chemotaxis and adherence to the endothelium.

Elevated levels of PMPs have been associated with pro-thrombotic disorders, including acute coronary syndromes, stroke, diabetes, hypertension, and hyperterglycemia. In addition, elevated PMP levels have been associated with inflammatory diseases such as SLE and cancer-associated thrombosis.

D-dimers are fibrin degradation products, reflecting activation of thrombosis and fibrinolysis. Elevated levels have been shown to predict risk of thrombosis in patients with atrial fibrillation on anticoagulation. We evaluated the association of thrombotic events with PMP and d-dimer levels in a cohort of patients with SLE.

Methods We measured PMP and d-dimer levels in 894 SLE patients in a prospective cohort. The relationship between PMP and d-dimer levels and thrombotic events was evaluated using survival analysis.

Results: Of the 894 patients, 234 had at least one thrombotic event at some time in their life. The first event was DVT (108 patients), Stroke (70 patients), MI (23 patients), Other venous (19 patients), and Other arterial thrombosis (14 patients). Elevated levels of PMP (>5nm) were associated with higher risk of thrombotic events (RR = 1.4; p = 0.05). We subdivided the group with elevated levels of PMP into different strata and the increased risk remained in all groups (Table). The risk was even higher if these patients were positive for lupus anti-coagulant or anticardiolipin antibodies (RR = 1.5; p = 0.007). Elevated levels of d-dimer (>0.88 mg/L) were not predictive of higher risk of thrombosis in SLE.

Conclusion: We found that elevated PMP was associated with thrombosis in SLE. Elevated PMPs can affect the vasculature in many ways, leading to heightened inflammatory and thrombotic effects. They can induce adhesion molecules on endothelial cells, resulting in increased inflammation of atherosclerotic plaque. At the same time, their pro-thrombotic potential may favor thrombosis and clot formation.

We are now evaluating the effects of therapeutic intervention on PMP levels.
Background: Cardiac magnetic resonance imaging (cMRI) can provide great detail about cardiac structure and function in a single session without harmful radiation. Very small areas of myocardial scar tissue can be identified using delayed gadolinium enhancement (DE) techniques. Additionally, impairments in coronary flow reserve may be measured by velocity-flow imaging, which identifies microvascular dysfunction. A recent study using cMRI found perfusion defects in 44% of asymptomatic SLE patients and microvascular dysfunction, was normal in all patients. Delayed gadolinium enhancement of the myocardium, which is indicative of prior myocardial damage was identified in 3 (20%) of the patients. Additionally, 4 (27%) patients had evidence of delayed gadolinium enhancement of the papillary muscles and 1 patient had mild aortic regurgitation. An incidental thymoma was discovered in 1 patient. None of the subjects had pericardial effusion or pericardial tamponade.

Methods: Consecutive patients meeting ACR Classification Criteria for SLE without history of cardiovascular disease or antiphospholipid syndrome were recruited from our university lupus clinic between January 2010 and May 2010. All patients underwent a comprehensive cMRI including adenosine stress perfusion imaging, and pre- and post- test electrocardiograms. Data collected included a chest pain history using the Rose chest pain questionnaire, SLEDAI scores, cardiovascular risk factors, disease duration and antiphospholipid antibody status.

Results: All 15 patients included in the study were women, with a mean age of 45 years (range 31–61 years); 60% were African American and the remainder were Caucasian. 27% patients had hyperlipidemia, and 47% had hypertension. 18% of patients were either obese (BMI >30) or overweight (BMI >25). The mean duration of SLE was 12 years (range 3 to 30 years) and average SLEDAI score was 3.5 (range 0 to 12). A previous history of chest pain was reported in 40% of patients. Only one patient tested positive for serum antiphospholipid antibodies.

No patient had evidence of prior myocardial infarction by ECG (Q-waves). By cMRI, left ventricular ejection fraction was normal. No patient had evidence of ischemia. The coronary flow reserve, a marker of coronary microvascular dysfunction, was normal in all patients. Delayed gadolinium enhancement of the myocardium, which is indicative of prior myocardial damage was identified in 3 (20%) of the patients. Additionally, 4 (27%) patients had evidence of delayed gadolinium enhancement of the papillary muscles and 1 patient had mild aortic regurgitation. An incidental thymoma was discovered in 1 patient. None of the subjects had pericardial effusion or thickening, or other valvular abnormalities.

Conclusion: In contrast to a previous study, asymptomatic patients with SLE were shown to have well preserved myocardial function, relatively normal cardiac structure, and no evidence of ischemia. Coronary flow reserve was not severely impaired. Small areas of myocardial and papillary muscle damage, however, were found in a minority of patients in our study, confirming that these abnormalities may be found in SLE despite a paucity of symptoms or other evidence of cardiovascular disease.

Disclosure: A. Lateef: None; L. S. Magder: None; J. Jani: None; T. S. Kiecker: None; M. A. Petr: None.

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Evaluation of Cardiac Function and Myocardial Damage in Women with Systemic Lupus Erythematosus (SLE) by Cardiac MRI.

Diim Dugan, Malia S. Kauf1, Han Kim2, E. William St Clair3 and Megan E. B. Clowse1.

1. Duke University, Durham, NC; 2. Duke University, Durham, NC

Objective: The aim of this study was to evaluate the presence of cardiac involvement and myocardial damage in women with SLE.

Methods: Consecutive patients meeting ACR Classification Criteria for SLE and treated at a single academic center were included. Data included demographics, medical history, cardiovascular risk factors, disease duration, and results of clinical cardiovascular testing. The study was approved by the local Institutional Review Board.

Results: Among 127 patients, 104 (81%) met the American College of Rheumatology criteria for SLE. The mean age was 45 years (range 19-71 years). The majority were African American (54%), followed by Caucasian (40%) and Hispanic (6%). The mean duration of SLE was 12 years (median 7 years, range 3-40 years). The majority had a SLEDAI score of 0-10 (53%), followed by 11-20 (27%) and >20 (20%). Using a cutoff of 1.5 for increased D-dimer, 16% of patients had abnormal levels. The mean D-dimer level was 5 ng/ml (range 0.01-100 ng/ml). The mean age of patients with increased D-dimer was 46 years (range 19-71 years).

Conclusion: This study provides evidence of cardiac involvement and myocardial damage in women with SLE. Further studies are needed to evaluate the clinical significance of these findings.

Disclosure: A. Lateef: None; L. S. Magder: None; J. Jani: None; T. S. Kiecker: None; M. A. Petr: None.

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Fulvestrant (Faslodex) an Estrogen Selective Receptor Down Regulator in the Therapy of Female SLE Patients. One to Two Year Following Faslodex Study Termination Revealed Mild Reactivation of the Serological Parameters and Disease Activity. Nahid I. Abdou1, Virginia Rider2, Louise Fraser1, Gra-...
fluorescence caused a shift so that cells appeared artifactually in the top right hand light chain expression on CD19 B cells by flow cytometry. The assays were infections than healthy women. HPV vaccine is safe and effective in healthy Illinois at Chicago, Chicago, IL. Linda Wagner-Weiner1. 1Univ of Chicago, Chicago, IL, 2University of Immunogenicity of the Quadrivalent Recombinant HPV Vaccine in female SLE patients aged 9–26 years. Arzu Soybilgic2, Karen Onel1, Tammy O. Utset1, Kenneth A. Alexander1 and

Blood cells from all individuals studied were assayed for kappa and lambda light chain expression on CD19 B cells by flow cytometry. The assays were standardized using blood from healthy control individuals and the percentage of B cells expressing each light chain determined accordingly. We observed that the fluorescence caused a shift so that cells appeared artfactually in the top right hand quadrant of the flow cytometric analysis of bloods from patients taking HCQ.

Conclusion: HCQ appears to have a broad spectrum of fluorescent excitation and emission which can interfere with flow cytometric analysis of blood cells from patients taking this medication. It is important when analyzing bloods from patients taking this drug that each sample is standardized according to its own isotype matched fluorescent control antibody.

Disclosure: L. Fraser: None; G. H. Mitchell: None; S. Sangle: None; L. Meng Choong: None; R. Ellis: None; J. Spencer: None; D. P. D’Cruz: None.

464 Immunogenicity of the Quadrivalent Recombinant HPV Vaccine in Female Systemic Lupus Erythematosus Patients Aged 9 to 26 Years. Arzu Soybilgic1, Karen Onel1, Tammey O. Utset1, Kenneth A. Alexander1 and Linda Wagner-Weiner1. 1Univ of Chicago, Chicago, IL, 2University of Illinois at Chicago, Chicago, IL.

Background: Women with SLE have higher rates of persistent HPV infections than healthy women. HPV vaccine is safe and effective in healthy females aged 9–26 years. There are no data on the immunogenicity of HPV vaccine in females with SLE.

Objectives: To evaluate immunogenicity of recombinant quadrivalent HPV vaccine in female SLE patients aged 9–26 years.

Methods: Prospective, open-label, pre-post intervention study. All patients met ACR Criteria for SLE. Exclusion criteria: disease exacerbation within 30 days of vaccinating, or hospitalization; rituximab in the past 6 months; current cyclophosphamide treatment; previous HPV vaccination; pregnancy. HPV vaccine was given at months 0, 2, 6. Patients were monitored by physical examination, SLEDAI, lupus laboratories at months 0, 2, 4, 6 and 7. Each patient’s SLEDAIs and laboratory profile in the year prior to vaccine administration were used as controls for that patient. Anti phospholipid, anti-ENA, HPV antibodies were measured at months 0 and 7. Primary outcome measures were change in SLEDAI and mean geometric HPV antibody titers. The secondary outcome measure was induction of autoantibodies.

Results: 26 patients, ages 12 to 26 years, were enrolled. 24 and 19 patients received two and three doses of HPV vaccine, respectively. Seven patients dropped out of the study: 2 pregnancies, 1 non-compliant, 2 moved out-of-state, 2 secondary to increased arthralgias. 19 patients completed the study.

Type-specific immunosays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) patient population. This population consisted of individuals who were seronegative to the relevant HPV type(s) at enrollment, received all three vaccinations, and did not deviate from the study protocol in ways that could interfere with the effects of the vaccine.

Immunogenicity was measured by (1) the percentage of individuals who were seropositive for antibodies against the relevant vaccine HPV type, and (2) the Geometric Mean Titer (GMT) (reported as Mmu/ml). GMTs were measured at month-7 because across all populations in previous clinical trials anti-HPV antibody titers peaked at month-7. HPV Antibody was determined by test kits, and cutoff values for seropositivity were titers at or above 20, 20, 20 and 20 mMU/mL for HPV 6, 11, 16 and 18 respectively.

Of the 19 patients who completed the study, 16 had samples available at month-7 for analysis. Seropositivity rates after three doses of the vaccine were 90.9%, 100%, 100%, and 92.3%, and GMT were 641.4, 587.1, 28.44, 422.0 mMU/ml for HPV 6, 11, 16 and 18 respectively. One patient who received rituximab after the first vaccine dose had no antibody response at month 7.

Conclusion: The recombinant quadrivalent HPV vaccine was immunogenic in females aged 9–26. Only one patient who received rituximab after the first vaccine dose had no antibody response. Limitation of our study was the relatively small sample size.

Disclosure: A. Soybilgic: None; K. Onel: None; T. O. Utset: None; K. A. Alexander: None; L. Wagner-Weiner: None.

465 Immunoglobulin Levels as Potential Predictors of Response to B-Cell Depletion (BCD). Sara C. Croca1 and David A. Isenberg2. 1Hospital de Santa Maria, Department of Medicine 1, Lisbon, Portugal, 2UCL Div of Medicine, Room 331, 3rd Floor, London, United Kingdom

Objectives: The use of BCD achieved by a combination of intra-venous methylprednisolone, cyclophosphamide and the anti-CD20 monoclonal antibody Rituximab has been reported to be an effective treatment for refractory systemic lupus erythematosus (SLE) flares. The duration of the period of BCD is linked to the length of clinical improvement/ remission. Low C3 levels at the time of BCD predict a faster relapse but other predictors of the period of BCD are yet to be established. In this study we looked at the serum immunoglobulin levels (sIg) over time in order to assess whether they could provide an effective predictor of response to treatment.

Methods: Between July 2001 and December 2009, 78 lupus patients were treated with BCD at the University College Hospital London (UCLH). Patients were assessed at baseline and at 3 and 6 months after treatment with regards to the sIg levels (IgA, IgG, IgM). We selected patients with a minimum 12-month follow-up with consistent measurements of sIg over time (n= 44). The outcomes were defined as depletion status at 6 months (depleted: absolute CD 19 (CD19abs)< 0.005×10^9; non-depleted/ repopulated: CDabs> 0.005×10^9) and retreatment within 12 months of the first BCD treatment.

Results: Following the first BCD cycle, 86.4% (n= 38) were successfully depleted. However, six months after treatment, only 40.9% (n= 18) remained depleted. Depleted patients at 6 months had significantly lower baseline IgA levels than those that were not depleted. Moreover, patients who were depleted at 6 months had significantly lower baseline IgG levels than those that were not depleted.
levels of IgA throughout follow-up (p = 0.0003) and IgG levels (p = 0.001) with no differences with regards to the IgM levels. In addition, when comparing baseline and 6 months measurements, patients that remained depleted had a 40% reduction in the IgA levels whereas non-depleted patients had only a 10% reduction and this was statistically significant (p = 0.00001). No differences were found with respect to IgG and IgM reduction rates. A third of the patients (n = 14) were retreated within 12 months of BCD. Retreated patients showed significantly higher levels of IgA throughout follow-up (p = 0.002). No differences were found in terms of IgG and IgM between retreated and non-retreated patients.

Conclusions: We report that sIg levels, particularly IgA, may predict both duration of depletion following treatment with BCD and need to retreat. Recent data (DiLillo et al) suggest that the absence of a long term fall in antibody titres following BCD may be associated with the presence of long-lived plasma cells. Given the fact that serum IgA derives mainly from bone marrow plasma cells, the relation between higher levels of IgA could represent higher numbers of long-lived plasma cells that in turn could account, at least to some extend, for a poorer response to BCD. Further investigation of the potential role of long-lived plasma cells in the maintenance of an auto-immune memory after BCD is needed to confirm this hypothesis.

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Influenza Hemural Immune Responses in Patients with Systemic Lupus Erythematosus. Evan Glenn Vista 1, Sherry Crowe 2, Linda Thompson 2, Gillian Ait 3, and Judith A. James 4. 1Oklahoma Medical Research Foundation, Oklahoma City, OK, 2Oklahoma Medical Research Foundation, Oklahoma City, OK, 3University of Oklahoma Health Science Center

Background: Annual seasonal flu vaccination has been the standard of care among the general population. Controversy still exists as to whether flu vaccination is effective among systemic lupus erythematosus (SLE) patients, who are identified by the United States Centers for Disease Control as a high risk group as part of the immunocompromised population. Select clinical and demographic factors may influence the response to influenza infection and vaccination among SLE patients. Flu vaccine is given at a particular period of the year in the clinical setting; however, nearly all previous studies have been limited in sample size, racial composition and focused on patients with relatively quiescent disease. This study assessed a large cadre of ethnically diverse SLE patients to identify clinical, demographic and therapeutic features associated with poor influenza vaccination responses.

Methods: A total of 201 SLE patients who fulfilled the American College of Rheumatology (ACR) criteria provided informed consent. Influenza antibody titers were tested at up to five-fold dilutions. A very low and a very high titer were defined as an endpoint titer of 1:200 and 1:10,000 respectively. Patient demographics and clinical profiles, including current medications, were collected. Antinuclear antibodies (ANA), anti-dsDNA, anti-Ro, anti-Sm, anti-RNP, anti-RibP, anti-cardiolipin IgG were measured. Test for proportions and modifications of the t- test were used to compare the 95% confidence interval of each influenza humoral immune endpoint titer.

Results: The sample population was comprised of 92 African Americans (45%), 98 Caucasians (48%) and 17 belong to other or mixed races (7%). The median age of all subjects from this study is 43.5 years (range 17 to 87) and 87% are females. The mean influenza antibody endpoint titers were computed at 1:2146 (SD 2.48, CI 1802 to 2492), 17 subjects (8.5%, CI 0.05 to 0.13) were very low and 15 subjects (7.5%, CI 0.45 to 0.12) were very high. The majority (78 subjects) had an endpoint titer of 1:1000 (38.8%, CI 0.32 to 0.46). Endpoint titers for the others are as follows: 27 subjects (13.4%, CI 0.09 to 0.19) with 1:300 and 64 subjects (31.8%, 0.26 to 0.39) with 1:300. Comparing the very low and very high endpoint titers, no significant differences in terms of sex, age and race were seen. In terms of their ACR criteria, patients with very high endpoint titers have higher incidence of discoid rash (30% vs 10%), photosensitivity (70% vs 50%) and serositis (60% vs 30%), while patients with very low endpoint titers fulfilled more immunologic criteria (80% vs 20%). Among the autoantibodies, no difference were seen in the ANA titers and the presence of anti-Ri antibodies was significantly higher for those with very low endpoint titers (7/17 vs 1/15, OR 9.9 p <0.04). More patients with very low endpoint titers have concomitant prednisone medication than those with very high endpoint titers (12/17 vs 4/15, OR 6.6 p <0.03).

Conclusions: Humoral immune responses to influenza were seen among patients with SLE. The variability of flu antibody titers could be influenced by factors that include current medications with steroids and select autoantibody production such as anti-RNP.

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Low-Dose Combination of Mycophenolate Mofetil and Tacrolimus for Refractory Lupus Nephritis: An Open-Labeled Trial. Chi Chiu Mok, Chi Hung To, Pak To Chan, Ka Lung Yu and Ling Yin Ho. Tuen Mun Hospital

Objectives: To evaluate the efficacy of low-dose combination of mycophenolate mofetil (MMF) and tacrolimus (Tac) for refractory lupus nephritis.

Patients and Methods: Patients with refractory lupus nephritis were recruited. Inclusion criteria: (1) Active nephritis documented by renal biopsy within 6 months of entry; (2) Patients had to respond to induction therapy; and (3) Patients had to have proteinuria to improve to <3g/day or urine protein-to-creatinine (up/Cre) ratio to <3.0 or <50% of pre-treatment baseline values; (2) Deteriorating Scr by ≥20% or loss in creatinine clearance (CrCl) by ≥30% compared to baseline not accounted by causes other than active nephritis; (3) Persistent active urinary sediments (RBC, active cellular casts ≥5/HPF). While prednisolone ≥0mg/day and ACE inhibitor/ARB were continued, other immunosuppressive regimens which consist of high-dose corticosteroid combined with one other agent (eg. cyclophosphamide [CYC], azathioprine [AZA], MMF, cyclosporin A [CSA], Tac) together with ACE inhibitors ± angiotensin receptor blockers (ARB). Each regimen should be used for ≥6 months at the maximally tolerated dosage of the drugs; (3) Serum creatinine (Scr) ≥200µmol/L. Exclusion criteria: (1) Previous intolerance to either MMF/Tac; (2) Scr ≥200µmol/L; (3) Informed consent unavailable. Treatment failure to previous regimens was defined as any one of the following: (1) Failure of proteinuria to improve to <3g/day or urine protein-to-creatinine ratio (up/Cre) ratio to <3.0; or <50% of pre-treatment / baseline values; (2) Deteriorating Scr by ≥20% or loss in creatinine clearance (CrCl) by ≥30% compared to baseline not accounted by causes other than active nephritis; (3) Persistent active urinary sediments (RBC, active cellular casts ≥5/HPF). While prednisolone ≥0mg/day and ACE inhibitor/ARB were continued, other immunosuppressive agents were discontinued and replaced by the current regimen, which consisted of MMF (1g/day) and Tac (4mg/day) in two divided doses. Patients were followed prospectively at least 2-monthly for the primary end-point (clinical response) at 12 months and adverse events.

Results: Up to May 2010, 11 patients were recruited. The mean age of these patients was 35.7±10 years and the mean SLE duration was 106.4±47 months at study entry. The distribution of the histological classes of lupus nephritis was as follows: ISN/RPS class IVG or III (36%), pure V (27%), V+III (36%). Previous treatment regimens received by these patients were: high-dose prednisolone (N=11), CYC (pulse/oral) (N=4), AZA (N=11), MMF (N=8), CSA (N=2) and Tac (N=7). All patients had been receiving the maximally tolerated doses of ACE inhibitor±ARB. The mean Scr, CrCl, up/Cre, 24-hour proteinuria and serum albumin was 80.5±29µmol/L, 58.3±32µmol/min (8 patients [73%] had CrCl of <90µmol/min), 2.85±1.4, 2.67±1.0g/l and 31.3±4.8µg/l, respectively. Seven (64%) patients had active urinary sediments and 9(82%) patients had active lupus serology. Eight patients had completed 12 months’ follow-up. Significant improvement in proteinuria and urinary sediments was observed in 7 (88%) patients and improvement started to occur at month 4-6. At month 12, a proteinuria of <1g/day and stabilization of CrCl was achieved in these patients. One patient was refractory to this regimen and withdrawn from the study. Treatment was well tolerated. The following adverse events were reported: minor infections (N=3), diarrhea (N=1), anorexia (N=1) and leg cramps (N=1).

Conclusions: Low-dose combination of MMF and Tac is a viable option for treating refractory lupus nephritis. A proper comparative trial with the novel biological agents is warranted.

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Lupus Disease Severity Is Not a Risk for Cervical Intraepithelial Neoplasia in SLE. J. Patrica Dhar 1, Lucie Greigore 2, Wayne Lancaster 2, Azadeh Stark 3, Ann Schwartz 4, Daniel Schultz 4, Lynnette Essmenacher 4, Joel Ager 5, Lisa Chiiodo 5, Mujtaba Husain 6 and Robert J. Sokol 2. 1Geisinger Health Systems, Danville, PA, 2Henry Ford Health Systems, Detroit, MI, 3Wayne State University, Detroit, MI

Purpose: Women with systemic lupus erythematosus (SLE) are at increased risk for cervical intraepithelial neoplasia (CIN), possibly related to immunodysregulation. We hypothesized that women with SLE who develop CIN would be younger, have more severe disease and have received more immunosuppressive treatment.

Methods: In a case-control design, clinical characteristics of SLE women with CIN (cases) were compared to two groups of SLE women without CIN (controls). Diagnoses of cervical intraepithelial neoplasia (CIN) were confirmed from formalin fixed blocks of cervical tissue from 113 women with
SLE. Clinical data were obtained by chart review. Logistic regression was used to evaluate for any significant differences in clinical variables between the cases and the controls. Two sets of controls were used for comparison with a ~2:1 match for each control group to the cases group. For the first set, only the year of entry into our Lupus Clinic was controlled for ("unmatched" group, n = 206); a second non-overlapping control group was matched for age, race, and year of entry into the clinic ("matched" group, n = 212). The second matched control group was used to control for the three matching factors to allow for smaller, but important effects of other factors, such as lupus severity, to emerge.

Results: For the cases, these predominantly African American (75.2%) women with SLE had a mean age at cerebral biopsy of 38.5 years, with low grade CIN (CIN I/II) the most prevalent (80.5%) histology. Logistic regression showed that the cases differed from the both matched and unmatched controls only by being only one to two years younger (32.1 yrs. vs. 33.1 yrs. and 34.1 yrs., respectively) at lupus diagnosis. We did not combine the control groups because they were statistically significantly different from each other. Using the control group matched for age and race, logistic regression analysis showed no significant differences between cases and controls for any of the clinical variables. In particular, there were no significant differences for factors related to SLE (disease severity, use of immunosuppressive drugs, use of corticosteroids alone), chronic metabolic diseases (hypertension, diabetes), and HIV risk factors (marital status, smoking, gravidity, parity). Power analyses for both the unmatched and matched comparisons were similar for both lupus severity and immunosuppressive medications. At these sample sizes, with a two sided test, an alpha=.05 and 80% power, the difference in population proportions detectable was approximately 0.17, which is between a small and moderate difference. None of the described differences approached this magnitude of effect.

Conclusions: The key finding of this study is that SLE patients who develop CIN are not clinically different from SLE patients who do not develop CIN. In particular, worsened disease severity and immunosuppressive treatment do not appear to be susceptibility factors for CIN in SLE. All female SLE patients should be monitored closely for CIN, with at least annual PAP smears.

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Lupus Nephritis: Decrease in Proteinuria and Sustained Stabilization of Disease Activity in Patients under Prolonged Immunosorption (IAS). Georg H. Stummvoll,2 Peter Biesenbach,1 Sabine Schmaldienst1, Josef Schatz1, Jennifer M. Grossman7, Lori Sahakian5, Brian Skaggs5, John D. Maureen A. McMa-

Introduction: SLE is characterized by pathogenic autoantibodies and immune complexes which can effectively be removed by extracorporeal procedures such as IAS. After up to one year of IAS, we had previously observed a reduction of proteinuria, disease activity and pre-treatment autoantibody levels in highly active SLE with renal involvement. Antibody removal, however, does not block the formation of new autoantibodies. Thus, a high percentage of these patients underwent prolonged IAS (>1 yr for up to 10yrs) and are the focus of this report. We evaluated patients under prolonged IAS for sustainability or further improvement of the primary response to IAS (proteinuria, disease activity, anti-dsDNA-Abs) and for the number of flares, infections, adverse events and tumors.

Patients and Methods: IAS therapy was started in highly active SLE patients with lupus nephritis (proteinuria 7.1 ± 4.8 g/day, SIS 15 ± 6, SLEDAI 20 ± 8, anti-dsDNA 394 ± 712 IU/ml) if i.v. CYC was contraindicated or ineffectual. 13 patients responding to initial IAS therapy were included into the prolonged IAS program, showing moderate disease activity at the start of the extension period (proteinuria 2.0 ± 2.4, SIS 4 ± 2, SLEDAI 3 ± 2, anti-dsDNA 47 ± 36 IU/ml). We defined the end of observation (EoO) upon either completion of 10 yrs of IAS therapy or by 1.1.2006.

During IAS, oral immunosuppression and ACE/ATII-inhibitors were kept constant, steroids were tapered as clinically feasible. IAS was performed with high affinity columns and the effective removal of serum Ig was monitored. Severe infections were defined as requiring i.v. therapy or hospitalization, flares according to the SELENA protocol.

Results: Under prolonged IAS (mean observation period of 6.7 ± 3.5 years), proteinuria further decreased from 2.0 ± 2.4 g/d to 0.9 ± 1.7g/d (p<0.05) at the EoO and Creatinine clearence increased to normal ranges in all patients. Disease activity and anti-dsDNA levels could be stabilized at low levels (SIS3±3, SLEDAI 3±4, anti-dsDNA 26±24 IU/ml at EoO).

Complete remission (proteinuria <0.5g/d, SIS/SLEDAI ≤4, pre-treatment dsDNA <25 IU/ml) was achieved in 9 (69%) patients. One patient flared and was discontinued. Ten (77%) patients are still under IAS therapy at the EoO. In 2 patients, IAS was stopped because of a sustained response. Severe infections (0.1 ± 0.3 per patient year) and severe flares (0.1 ± 0.2 per patient year) were uncommon. There were no anaphylactic or orthostatic adverse events or tumors.

Conclusion: Prolonged IAS leads to stabilization of disease activity in moderately active SLE patients and can induce sustained remission in previously refractory SLE while showing an acceptable safety profile.

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Peripheral Vascular Disease in Systemic Lupus Patients. Rayford June3, Robert C. Gilkeson1, Shweta Bhatt2 and Lisabeth ScaI2. 1Case Western Reserve University, 2Penn State Univ Hershey Medical, Hershey, PA, 3Penn State Univ Hershey Medical, University of Rochester

Background: Systemic lupus erythematosus (SLE) is an independent risk factor for cardiovascular disease (CVD). Ankle brachial index (ABI), a simple measure of peripheral vascular disease (PVD), is known to be associated with CVD. We hypothesized that ABI would be lower in SLE subjects versus controls. In addition, we determined whether SLE-related, traditional, and/or non-traditional CVD risk factors help predict those SLE patients with PVD.

Methods: In a cross-sectional analysis of 134 SLE subjects and 77 age, sex, and racially-matched controls, SLE-related covariates and cardiovascular risk factors were measured. None of the participants had any history of known CVD. Measures of subclinical CVD were assessed including ABI, coronary artery calcification (CAC), and carotid intimal medial thickness (IMT). Covariates were compared between SLE and controls using chi-square testing for ordinal measures and a Student’s t-test for continuous variables. In SLE patients, comparisons of the covariates were made between those patients in the lowest tertile (ABI ≤ 1.0) versus all others. A final logistic regression model was performed investigating correlations including all significant (p≤0.10) risk factors in the univariate analyses.

Results: When controlled for age, ABI was significantly lower between SLE and control subjects 1.05 vs. 1.09 (p=0.003). Significant covariates (p ≤ 0.05) in the univariate analyses, examining those SLE patients in the lowest tertile versus those with higher ABI, included race (with Black SLE patients being more likely to have an ABI ≤ 1.0), a positive smoking history, and present or previous diagnosis of hypertension (HTN). In the final model, controlling for HTN, race, and homocysteine, only a smoking history (p=0.02) was significantly associated with having an ABI in the lowest tertile. There were no significant associations of CAC or carotid IMT with the lowest ABI tertile.

Conclusion: PVD, as measured by ABI, is more common in SLE patients as compared to non-SLE patients. Smoking is independently associated with PVD in SLE patients. SLE patients should be counseled of the increased risk of tobacco use and cardiovascular risk associated with their disease. Similar to other inflammatory diseases, an ABI of 1.0 (rather than 0.9 in the general population) is a more appropriate lower limit of normal when screening for PVD in SLE.

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PHDL and High Plasma Leptin Levels Are Predictors of Longitudinal Progression of Subclinical Atherosclerosis in SLE. Maureen A. McMahan1, Jennifer M. Grossman1, Lori Sahakian1, Brian Skaggs2, John D. FritzGerald3, Christina Charles-Schoeman4, Alan H. Gorn4, Michael H. Weisman5, Daniel J. Wallace6 and Bevra H. Hahn8. 1West Hollywood, CA, 2Cedars-Sinai Medical Center, Los Angeles, CA, 3UCLA, Santa Monica, CA, 4UCLA Medical Center, Los Angeles, CA, 5UCLA School of Medicine, Los Angeles, CA, 6UCLA School of Medicine Rehabilitation, Los Angeles, CA, 7University of California Los Angeles, Sherman Oaks, CA, 8University of California Los Angeles School of Medicine, Los Angeles, CA
Purpose: Women with SLE have an unexplained increase in atherosclerosis (ATI). We previously reported that 45% of SLE women vs. 5% of controls have pro-inflammatory HDL (pHDL), and that pHDL confers a 16-fold increased risk for the concurrent presence of carotid artery plaque. It is unknown, however, whether pHDL predicts future progression of atherosclerosis. Here we hypothesize that baseline presence of pHDL is associated with longitudinal accumulation of subclinical atherosclerosis.

Methods: Female SLE and healthy age-and gender-matched subjects not taking statins were studied. B-mode and Doppler scanning of carotid arteries was performed at baseline and at 24–36 months. Antioxidant function of HDL was measured as the change in fluorescence intensity caused by oxidation of DCFH by LDL in the presence or absence of test HDL. Fluorescence in the absence of HDL was normalized to 1.0. Values greater than 1.0 after the addition of HDL indicated pHDL. Plasma leptin was measured using ELISA (Biovendor).

Results: Follow-up carotid ultrasonograms were completed on 185 SLE women and 84 controls. Overall, 21% (39) of SLE patients had accumulation of new plaques (defined as any new or accumulating plaque) vs. 15% (13) of controls. Among the 39 SLE patients in our cohort with plaque progression, 33 (85%) had pHDL, compared to 39% of SLE patients with no new plaques (p < 0.0001). Follow-up intima media thickness (IMT) was also higher in patients with pHDL at baseline than in those without: 0.62 ± 0.14 vs. 0.52 ± 0.07 (p < 0.0001). In addition, plasma leptin levels were also higher in SLE patients with plaque (28.3 ± 23.0 vs. 22.9 ± 26.8, p = 0.01). After multivariate analysis, the only significant factors predictive of plaque progression in SLE were the baseline presence of pHDL, with an OR of 14.2 (95% CI: 2.2 – 161.3, p < 0.0001), the baseline presence of plaque, OR 14.9, (95% CI: 1.8 – 238.9, p = 0.02), elevated leptin levels in the highest quartile (>34 ng/mL), OR 5.1, (95% CI: 1.7 – 18.2, p = 0.03) and increasing age, OR of 1.1, (95% CI: 1.03 – 1.22, p = 0.004).

Conclusions: pHDL and plasma leptin are strong predictors for the future progression of subclinical atherosclerosis in women with SLE.

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Positivity for Anti-RNP Antibody Is a Risk Factor for Adverse Effects by Trimethoprim-Sulphamethoxazole, a Prophylaxis Agent of P. jiroveci Pneumonia, in Patients with Collagen-Vascular Diseases. Reika Maezawa1, Kazuhiro Kurasawa2, Satoko Arai3, Takayoshi Owada4 and Takeshi Fukuda5.

Clinical Immunology, Dokkyo Medical University, Mibu, Tochigi, Japan, 4Dokkyo Medical University, Mibu, Tochigi, Japan

Purpose: Pneumocystis jiroveci pneumonia (PCP) is a serious complication in patients with immunosuppressive therapy for collagen-vascular diseases (CVD). For prophylaxis of PCP, Trimethoprim-sulphamethoxazole (TMP-STX) is widely used. TMP-STX prevents the development of PCP, but often caused adverse effects (AEs) such as leucopenia, fever, and rash. However, risk factors for AEs by TMP-STX in CVD patients are unknown, and also clinical features of AEs remain to be clarified. The aim of this study was to identify risk factors for AEs of TMP-STX, and to clarify clinical features of the AEs in CVD patients with immunosuppressive therapy.

Methods: We reviewed medical records of consecutive 541 patients who received TMP-STX as prophylaxis for PCP from 2003 to 2009 in our department. Subjects were 312 patients with CVD including 82 SLE, 60 myositis, 55 vasculitis, 26 SSc and 12 MCTD, and 229 patients with pulmonary diseases including 116 interstitial pneumonia and 56 lung cancer. These patients received corticosteroid (more than 30mg/day predonisolone) with/without immunosuppressants.

Results: AEs by TMP-STX were observed in 30 out of 541 patients (5.5%). Incidence of the AEs in CVD was 7.1%, significantly higher than that in pulmonary diseases (3.5%). In CVD, patients with SLE, MCTD and adult Still’s disease frequently developed the AEs (11%, 33% and 13%, respectively), compared to those with myositis and vasculitis (4% and 5%). Particularly, incidence of the AEs in patients with anti-RNP antibody were significantly higher than those without the antibody (a-RNP+) vs. (-); 21% vs 7%). Incidence of the AEs in RNP positive patients was observed in SLE. In addition, incidence of the AEs in CVD patients without anti-RNP antibody was similar to that in pulmonary diseases. Incidence of the AEs were similar between patients with and without antibodies such as anti-DNA, anti-SS-A, and anti-Sm antibodies.

Clinical features of the AEs in patients with CVD were different from those with pulmonary diseases. Fever was most frequent symptom in AEs in patients with CVDs, while no fever was observed as AEs in those with pulmonary diseases.

Conclusion: SLE and CVDs, and positively for anti-RNP antibody are risks factor for adverse effects by trimethoprin-sulphamethoxazole in collagen-vascular disease patients.

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Introduction: Kidney involvement is a major clinical problem in systemic lupus erythematosus (SLE). Consideration of possible predictive factors for development of lupus nephritis (LN) may help to identify high-risk patients. The purpose of this study was to assess whether certain demographic, clinical and immunological variables can predict the occurrence of lupus nephritis (LN).

Methods: We studied 679 SLE patients enrolled from the Hopkins Lupus Cohort via the Autoimmune Biomarkers Collaborative Network. Patients were classified into 2 groups: (1) LN, defined as patients who had either a renal biopsy, World Health Organization class II-V and/or b) met ACR criteria for LN (persistent proteinuria >3 or cellular casts attributable to SLE) and/or c) Lupus Activity Index renal subscore ≥1. (2) Non-LN (SLE patients with no history of LN and maintaining renal subscore=0, urine protein=0, urine RBC ≤5 per high power field and serum creatinine ≤1.1mg/dl over the enrollment period. The variables assessed at the beginning of the study were from 2 domains, the demographic/clinical domain and the laboratory/immunologic domain. Chi-square tests were used to examine the association between LN and each variable, and we used t-tests to compare mean age and disease duration between LN and non-LN. Logistic regression was used for prediction of LN from knowledge of the person’s demographic, clinical, laboratory and immunologic information at study entry. Stepwise multivariate regression was used to select the best set of predictors after adjusting for SLE disease duration.

Results: Of the 679 patients studied, there were 348 LN patients and 222 non-LN. The LN patients were significantly younger (mean age 40.82, SD=12.7) compared to non-LN patients (mean age 45.6, SD=12.7; p<0.0001). Mean SLE disease duration was 132 (SD=104) months in the LN group compared to 112.1 (SD=87) months in the non-LN group (p=0.014). Photosensitivity was negatively associated with LN (51.0% in LN group vs 61.3% in non-LN, p=0.02). Variables were included in the stepwise logistic regression model as significant predictors for LN are shown in Table 1.

Table 1. Variables included in stepwise multiple regression model for LN.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted odds ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>1.62</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.54</td>
<td>0.0001</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>1.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>3.3</td>
<td>0.003</td>
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<tr>
<td>Caucasian ethnicity</td>
<td>0.42</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hispanic and Asian ethnicity</td>
<td>1.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Low C4</td>
<td>0.95</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ddDNA antibody</td>
<td>2.3</td>
<td>0.0009</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.9</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Interestingly, when we included only demographic and clinical variables in the logistic regression model, smoking was negatively associated with LN (adjusted OR=0.65, p=0.04), however, disease duration (adjusted OR=1.03, p=0.005) and diabetes (adjusted OR=1.7, p=0.02) were positively associated with LN. Anti RNP (adjusted OR=2.1, p=0.004) and low C3 (adjusted OR=2.04, p=0.0009) were also positively associated with LN when we included only lab/immunologic parameters in the logistic regression model.

Conclusion: Our results suggest that certain demographic, clinical and laboratory/immunologic factors may be predictive of LN, including obesity, high cholesterol, diabetes, and disease duration.

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Predictors of Rate of Progression in Organ Damage in SLE. Sneha Purvey1, Laurence S. Magder2, Hong Fang2 and Michelle A. Petri1. 1Timonium, MD, 2Johns Hopkins University School of Medicine, 3University of Maryland School of Medicine

Purpose: The SLICC/ACR Damage Index (SDI) has become the accepted measure of permanent organ damage in SLE over time. Multiple cross-sectional and a few prospective studies have examined predictors or associates of damage. The damage may be due to lupus, its treatment or co morbid factors. We identified these in the largest on-going prospective study in SLE.

Methods: 2063 SLE patients (92.44% female, 56.27% Caucasian, 37% African-American, mean age 48.1years) were included. The SLICC/ACR Damage Index was calculated from diagnosis onwards in a prospective cohort. The analysis is based on the SDI at the last visit of the patients in the cohort using a linear regression model. Based on a scatter plot, the assumption of a linear relationship between the mean SDI and SLE duration appeared reasonable.

Results: The table shows the mean SDI at diagnosis and the mean rate of SDI progression in subgroups defined by predictors of interest.

Conclusion: Surprisingly, some variables associated with damage at diagnosis (age, corticosteroid use, immunosuppressive use, less use of hydroxychloroquine) were not associated with damage progression. The most important demographic predictor of progression was income, not gender or ethnicity, in contrast to other studies. The most important serologic test of progression was the lupus anticoagulant, not anti-dsDNA or other antiphospholipid antibodies. Patients already damaged at diagnosis had a higher rate of progression. Disease activity clearly increased the rate of progression, as expected. These data clearly point to the need for effective prophylactic therapy for the lupus anticoagulant, and the need for tight control of disease activity.

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Pregnancy Outcomes among African American Patients with Systemic Lupus Erythematosus (SLE) Compared to Controls. April Barnado1, Lee Whelless2, Anna K. Meyer3, Gary S. Gilkeson2 and Diane L. Kamen4. 1Duke University Medical Center, Durham, NC, 2Med Univ of South Carolina, Charleston, SC, 3Medical University of South Carolina, Charleston, SC, 4Medical University of South Carolina

Purpose: SLE impacts women of childbearing age and the diagnosis is associated with adverse pregnancy outcomes. However, the question of whether there is a difference in outcome risk before and after diagnosis of SLE has not been well studied. Using data from a longitudinal study of Gullah African Americans, we compared pregnancy outcomes before and after SLE diagnosis to test the hypothesis that there is a predisease state which negatively affects pregnancy outcomes.

Methods: Cases and controls reporting at least one pregnancy were drawn from a longitudinal observational cohort started in 2002. Controls were all Gullah African American females either related or unrelated to cases. We collected demographic, socioeconomic, and pregnancy data. Stillbirth was defined as pregnancy loss at or after 22 weeks and spontaneous abortion (SABs) as loss before 22 weeks. Low birth weight was defined as < 5 pounds, 8 ounces and preterm live birth as delivery before 37 weeks. Categorical variables were examined by chi-square tests. Differences in the means of continuous variables were tested using Student’s t-test. We modeled pregnancy outcome associations with case status using multiple logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI).

Results: Cases (n = 185) were younger (46±12 vs 52±13 years, p<0.01), less likely to have some form of insurance (83.4% vs 87.9%, p=0.21), and had similar years of education (13.2 vs. 13.1) compared to controls (n=205). Cases had fewer pregnancies (2.6 vs 3.2, p = 0.01) and fewer live births (2.3 vs. 2.8, p = 0.01) than controls. Overall, compared to controls, cases were more likely to have adverse outcomes including preeclampsia (OR 2.15, 95% CI 1.27–3.25), preterm live birth (OR 2.63, 95% CI 1.56 – 4.44), low birth weight (OR 2.30, 95% CI 1.35–3.90), SABs (OR 2.08, 95% CI 1.39–3.10), and stillbirths (OR 4.52, 95% CI 1.38–15.80), even after adjustment for age, education, insurance and pregnancy number. We found that the odds of adverse pregnancy outcomes increased after the diagnosis of SLE and, consistent with our hypothesis, that the risk was also higher prior to disease onset in women who later developed SLE compared to controls. (Table 1).

Table 1. Odds ratios and 95% confidence intervals for adverse pregnancy outcomes occurring before and after SLE diagnosis compared to controls in an African American population. All estimates are adjusted for age, education, insurance and number of the pregnancy.

Conclusion: Among a large cohort of African American women, we found significantly higher numbers of adverse pregnancy outcomes in cases, both before and after diagnosis of SLE, compared to controls. Our findings are consistent with a predisease state that predisposes to adverse pregnancy outcomes. Studies are underway to determine factors contributing to the predisease risk and to the increased risk following diagnosis of SLE.

Disclosure: A. Barnado: None; L. Whelless: None; A. K. Meyer: None; G. S. Gilkeson: None; D. L. Kamen: None.
Prevalence and Persistence of Metabolic Syndrome in a Multicentre International Inception Cohort of Patients with SLE. Murray B. Urowitz1,2, Dafina G. Gladman3, Dominique Ibanez2, Ian N. Bruce1, Caroline P. Gorden1, Sang-Chool Bae1, Ann E. Clarke2, Sashia R. Bernatsky1,3, F. J. Sanchez-Guerrero4,5, J. G. Hanly1,5,4, David A. Anthony6, D. B. Petri7, Petri Isenberg8, K. C. Kalunian9, A. Zoma2, A. A. Zoma2, C. P. Gordon1,2, Tuen Mun Hospital,3 United Christian Hospital,4 Princess Margaret Hospital,5 Seattle VA Medical Center,6 University of Alabama,7 Tuen Mun Hospital,8 University of Toronto,9 University of Toronto, Toronto, ON, Canada.

Background: Metabolic Syndrome (MetSyn) is likely to be a significant predisposing factor to atherosclerotic vascular disease (ASVD) in Systemic Lupus Erythematosus (SLE). The purpose of this study is to determine the prevalence and persistence over two years of MetSyn in a multicentre, international inception cohort of patients with SLE.

Methods: An international inception cohort registry has enrolled 1593 recently diagnosed patients with SLE from 30 centres in 11 countries. All patients recruited into the MMF arm were treated with prednisolone and MMF. In patients with active lupus nephritis treated initially with combined prednisolone and MMF.

Results: Of the inception cohort of SLE patients (89F, 48% Caucasian, age at diagnosis 35), 13.6% had MetSyn at baseline (Table 1).

Table 1. Presence of MetSyn criteria in inception cohort of 1593 patients.

<table>
<thead>
<tr>
<th>Present or Abnormal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Syndrome</td>
<td>195 (13.6%)</td>
</tr>
<tr>
<td>Waist Circumference</td>
<td>649 (44.6%)</td>
</tr>
<tr>
<td>BMI</td>
<td>265 (17.4%)</td>
</tr>
<tr>
<td>Either Waist or BMI</td>
<td>700 (45.4%)</td>
</tr>
<tr>
<td>TG</td>
<td>374 (28.7%)</td>
</tr>
<tr>
<td>HDL</td>
<td>227 (31.4%)</td>
</tr>
<tr>
<td>BP</td>
<td>721 (45.9%)</td>
</tr>
<tr>
<td>BS</td>
<td>225 (16.9%)</td>
</tr>
</tbody>
</table>

Although the prevalence of MetSyn is approximately 12% at any given time, the cumulative prevalence increases progressively to 25% by year 8. Most of the increased prevalence occurred within the first 3 years.

In total, 644 patients had at least two years of follow-up data available.
at baseline, failure to achieve good response at 6 months and the occurrence of renal flares were unfavorable factors for renal function loss. 

Conclusions: Combined prednisolone and MMF is effective for the initial treatment of active lupus nephritis. However, patients with nephrotic syndrome, impaired renal function and hypertension at onset are associated with a higher risk of renal damage.

Disclosure: C. C. Mok: None; K. Y. Ying: None; C. W. Yin: None; W. L. Ng: None.

Safety and Efficacy of a Pandemic 2009 Influenza A (H1N1) Monovalent, Unadjuvanted Vaccine in Systemic Lupus Erythematosus Patients. 

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Objective: to assess the safety and efficacy of pandemic 2009 influenza A (H1N1) vaccination in patients with Systemic Lupus Erythematosus (SLE), and to evaluate factors influencing the immune response.

Methods: A hundred and eleven SLE patients were vaccinated with a pandemic 2009 influenza A (H1N1), monovalent, inactivated, unadjuvanted, split-virus vaccine in December 2009-January 2010 and received a second dose of vaccination three weeks after. Sera were obtained before each injection and three weeks after the last injection. Adverse events and SLE activity were recorded at each visit. The haemagglutination inhibition test was used to measure antibody titers. The antibody response was evaluated in three ways: the proportion of subjects with antibody titers ≥1:40 (seroprotection), the proportion of subjects with either a prevaccination HI titer < 1:10 and a post-vaccination titer ≥ 40 or a prevaccination titer ≥ 10 and an increase in the titer by a factor of four or more (seroconversion) and the factor increase in the geometric mean antibody titers (GMTs) after vaccination (Geometric Mean Ratio (GMR)).

Results: According to international guidelines used to evaluate influenza vaccines, immunogenicity criteria were met, but not for all critera, at day 21: seroprotection rate was 66.7% (95% CI 57.9–75.4) (below the required level of 70%), seroconversion rates was 60.4% (95% CI 51.3–69.5) (above the required level of 40%) and GMR was 8.5 (95% CI 3.2–12.0) (above the required level of 2.5). The second vaccine administration did result in additional increased in humoral response. Indeed, immunogenicity criteria were fully met at day 42: seroprotection rate was 80.0% (95% CI 72.5–87.5) (p = 0.0002 versus day 21), seroconversion rate was 71.8% (95% CI 63.4–80.2) (p = 0.003 versus day 21) and GMR was 10.3 (95% CI 2.9–14.2) (p < 0.001 versus day 21). None of SLE patients developed symptoms suggestive of influenza infection. Vaccine was well tolerated and did not increase disease activity. At day 21 and day 42, in the multivariate analysis, failure to obtain seroconversion was statistically associated with the use of an immunsuppressive treatment and lymphocytes count <1000/mm 3. Failure to obtain seroprotection was statistically associated with the same parameters and a total serum IgM level <1 g/l at day 21. As expected, GMR values were significantly lower in SLE patients treated with an immunosuppressive drug. Vaccine was fully effective after one injection in patients with lymphocyte >1000/mm 3 and not treated with immunosuppressive drugs.

Conclusions: pandemic 2009 influenza A (H1N1) unadjuvanted vaccination is safe and effective in SLE patients. Our study shows that SLE patients with normal lymphocyte count and not treated with immunosuppressive have a normal vaccine response.

Disclosure: A. Mathian: None; H. Devilliers: None; A. Krivine: None; N. Costedoat-Chalumeau: None; J. Haroche: None; D. Boutin-Le Thi Huong: None; B. Wechsler: None; B. Hervier: None; M. Miyara: None; N. Morel: None; J.-C. Piette: None; B. Autran: None; F. Rozenberg: None; Z. Amoura: None.

Serum Osteoprotegrin (OPG) in Systemic Lupus Erythematosus. 

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Purpose: Osteoprotgerin (OPG), is a member of the tumor necrosis factor (TNF) receptor family. It has recently been demonstrated that OPG is produced by a variety of tissues, including the cardiovascular system (heart, arteries, veins), lung, kidney, and immune tissues, as well as bone. OPG–RANKL signaling pathway is strongly related to vascular calcification. We determined the association of this biomarker with subclinical atherosclerosis in SLE at baseline and two years later.

Methods: 166 SLE patients (91% female, 64% Caucasian, 31% African-American, 5% others, mean age 45 yrs) had both measurement of subclinical atherosclerosis (coronary artery calcium (CAC), carotid intima-media thickness (IMT) and OPG measurements.

Results: OPG was highly correlated with age (r=0.0001) which is highly correlated with CAC and carotid IMT. However, once we adjusted for age, the relationship with atherosclerosis was diminished. We subdivided OPG levels into low, medium and high tertiles.

Table 1. Shows the association between OPG and the presence of coronary artery calcium

<table>
<thead>
<tr>
<th>OPG level</th>
<th>Odds Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1.0 (Ref Group)</td>
<td>1.0 (Ref Group)</td>
</tr>
<tr>
<td>Medium</td>
<td>2.3 (1.0, 5.2)</td>
<td>0.043</td>
</tr>
<tr>
<td>High</td>
<td>1.3 (0.6, 3.1)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Table 2. Shows the association between OPG and the mean carotid IMT

<table>
<thead>
<tr>
<th>OPG level</th>
<th>Difference in Mean IMT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.0 (Ref Group)</td>
<td>0.0 (Ref Group)</td>
</tr>
<tr>
<td>Medium</td>
<td>0.02 (+0.01, 0.06)</td>
<td>0.26</td>
</tr>
<tr>
<td>High</td>
<td>0.02 (+0.01, 0.06)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

The mean IMT among those with medium OPG was 0.02 points higher than for those with low OPG. This difference was not significant (p=.26).

Conclusion: OPG has been associated with atherosclerosis in the general population. In our 166 SLE patients OPG was strongly associated with age. Once we adjusted for age, there was no association of OPG with subclinical atherosclerosis nor with change in atherosclerosis two years later.

Disclosure: A. N. Kiani: None; P. Akurakta: None; T. Ueland: None; L. S. Magder: None; H. Ivana: None; M. A. Petri: None.

Steroid Free Remission in Systemic Lupus Erythematosus. Akiko Suda, Haruko Ideguchi, Shigeru Ohno, Mitsuhiro Takeno, Shohei Nagaoka and Yoshiaki Ishigatsubo. 1Center for Rheumatic Disease, Yokohama City University Medical Center, 2Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, 3Department of Rheumatology, Yokohama Minami Kyosai Hospital, Yokohama, Japan, 4Department of Rheumatology, Yokohama Minami Kyosai Hospital, 5Yokohama City Grad Sch of Med, Yokohama, Japan

Objectives: Although survival prognosis of SLE has been greatly improved by treatment with corticosteroids and immunosuppressants in some patients with SLE, some of the patients are suffering from adverse effects of long term corticosteroid therapy. Steroid free remission is an idealistic goal in management of SLE patients. We here examined the frequency of steroid free remission and analyzed clinical factors which are involved in achieving steroid-free remission in patients with SLE.

Methods: We retrospectively reviewed clinical charts of 288 patients (all Japanese, male 21, female 267, age 46.5±0.87 y.o., disease duration 15.0±0.58 years) who met 1997 ACR SLE Classification Criteria and received medical care in our hospitals. Therapeutic plans including steroid tapering in individual patients were determined by the attending physicians. The patients were divided into three groups based on steroid usage: concurrent user, never user, and steroid free remission that was defined as a 3-month consecutive period of no disease activity without corticosteroid. Clinical features and backgrounds were compared among the three groups.

Results: We found that 279 patients (96.9%) had received steroid at any time during the clinical course, whereas 9 (3.1%) patients had never received steroid (never users). Fifty two patients (18.0%) achieved steroid free remission. Of them, 45 patients (15.6%) maintained remission without steroid
(steroid free remission). Total 234 patients (81.3%) including 7 patients (2.4%) who experienced disease flare after cessation of corticosteroid were receiving corticosteroids at the study (concurrent users). Patients in steroid free remission were all female. They were older, and had longer disease duration than patients in concurrent user group. Renal involvement was less frequent (steroid free remission: 31.6% vs concurrent users: 50.9%, P<0.05), and negative anti-DNA antibody was more frequent (26.3% vs 14.5%, P<0.05). Immunosuppressants were more frequently used in concurrent users than patients in steroid free remission (P<0.05). The percentage of patients followed by practicing physician (S.O) were more frequently observed in steroid free patients (41.9% vs 16.3%, P<0.01). There was no difference in other factors including initial dose of steroid, initial disease activity, neurologic disease and hematologic disorders between the two groups.

Table. Factors associated with steroid free remission

<table>
<thead>
<tr>
<th></th>
<th>total (n = 288)</th>
<th>concurrent users (n = 234)</th>
<th>steroid free remission (n = 45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>age at study entry (y.o.)</td>
<td>46.5 ± 0.7</td>
<td>45.5 ± 0.9</td>
<td>51.2 ± 5.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>disease duration at study entry (y.o.)</td>
<td>15.0 ± 0.6</td>
<td>14.4 ± 0.6</td>
<td>19.9 ± 1.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>renal involvement (%)</td>
<td>48.8</td>
<td>50.9</td>
<td>26.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>negative anti-DNA antibody (%)</td>
<td>82.3</td>
<td>85.5</td>
<td>64.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Immunosuppressants use (%)</td>
<td>37.5</td>
<td>41.9</td>
<td>22.2</td>
<td>0.01</td>
</tr>
<tr>
<td>practicing physician (S.O) (%)</td>
<td>23.1</td>
<td>16.3</td>
<td>41.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Conclusions: The present study shows that female, older age and absence of renal involvement, anti-DNA antibody and practicing physician (S.O) were associated with steroid free remission.

Disclosure: A. Suda: None; H. Ideguchi: None; S. Ohno: None; M. Takeno: None; S. Nagaoaka: None; Y. Ishigatsubo: None.

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The Presence of Renal Platelet Microthrombosis in Patients with Lupus NephritisCorrelates with the Degree of Macrophagic Infiltration. Elena Gonzalez4, Maria Paz Martinez-Vidal5, Begoña Santiago6, Natalia Redondo6, Estibaliz Lozzi1, José Luis Pablos1 and María Galindo6. 1Fundación Española de Reumatología, Sociedad Española de Reumatología, Madrid, Spain, 5Servicio de Reumatología, Hospital 12 de Octubre, Madrid, Madrid, Spain, 6Unidad de Investigación y Servicio de Reumatología, Hospital 12 de Octubre, Madrid, Madrid, Spain, 7Unidad de Investigación, Hospital 12 de Octubre, Madrid, Madrid, Spain.

Introduction: Intravascular CD61+ platelet microthrombi are found in the kidney of patients with lupus nephritis independently of the presence of antiphospholipid antibodies. Our objective was to analyze the correlation between CD61+ intravascular platelet microthrombi and intra or extraglomerular CD68+ macrophagic infiltration degree as a marker of active inflammation.

Methods: Seventy-two kidney biopsies from systemic lupus erythematosus (SLE) patients were immunohistochemically stained with CD68 (macrophage) and CD61 (platelet glycoprotein-IIIa). Intra or extraglomerular macrophagic infiltration was quantified using the image-processing program Image J. CD61+ microthrombi were identified as percentage of stained cells. Clinical data were retrospectively collected at the time of kidney biopsies, and during the follow-up for a mean time of 7.5 years after biopsies and were correlated to the immunohistochemical findings. The associations between categorical variables were tested using the chi-square or Fisher’s exact test, where appropriate. The odds ratios with the corresponding 95% CIs were calculated. For continuous variables, the comparisons were carried out using the t-test for two independent samples. P-values <0.05 were considered significant.

Results: most of SLE kidneys showed glomerular (94%) and extraglomerular (87%) macrophagic infiltration. Both glomerular and extraglomerular CD68+ macrophagic infiltration were higher in patients with proliferative (WHO subtypes III and IV) nephritis (p=0.001). The CD68+ glomerular infiltration degree was increased in samples with CD61+ platelet aggregates (p=0.03), whereas CD68- extraglomerular infiltration was higher in samples with histological thrombotic microangiopathy (p=0.02) and focal cortical atrophy (p=0.02). The CD68+ glomerular infiltration grade was also higher in patients with positive a-dsDNA (p=0.009), hypocomplementemia (p=0.01), microhematuria (p=0.02), the presence of cellular casts in urine sediment (p=0.03), and was significantly associated with SLE activity index (SLEDAI) at the time of kidney biopsy (p=0.02). Preliminary results have shown a potential correlation between CD68+ macrophagic infiltration and higher levels of complement factor C4d expression (p=0.04). Patients with kidney failure at biopsy presented higher mean extraglomerular macrophagic infiltration (p=0.03). However, the presence of CD61+ platelet aggregates and density of CD68+ macrophagic infiltration were not associated with response to treatment, renal function evolution or nephritis relapse rate.

Conclusions: In lupus proliferative nephritis, intra and extraglomerular macrophagic infiltration degree correlates with acute impairment of kidney function. Presence of acute microthrombi provides a good correlation with cellular infiltration grade. However, none of these parameters is a good
prognostic marker of the renal function evolution or response to treatment. Further studies are needed to better define correlation between the presence of renal thrombosis and inflammatory cells infiltration and activation of complement system in patients with lupus nephritis.

Disclosure: E. Gonzalo: None; M. P. Martínez-Vidal: None; B. Santiago: None; N. Redondo: None; E. Loza: None; J. L. Pablos: None; M. Galindo: None.

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The Relationship between N Terminal Pro Brain Natriuretic Peptide (NT-proBNP) and Atherosclerosis in SLE Patients. Diana Goldenberg1, Emily Miller1, Naveed Sattar2, Paul Welsh3, Mary Roman1 and Jane E. Salmon1. 1Hospital for Special Surgery, New York, NY, 2University of Glasgow, Glasgow, United Kingdom, 3University of California, San Francisco, CA

Background: NT-proBNP is a biomarker of cardiovascular health in the general population that is independently associated with heart failure, coronary artery disease, stroke and death. It has been suggested that serum NT-proBNP levels are higher in SLE patients than controls, but its relationship with markers of atherosclerosis is still unclear. Because traditional cardiac risk factors do not adequately identify the SLE patients with increased risk for premature atherosclerosis, there is a need for a biomarker to improve risk stratification. The aim of this study was to investigate the relationship between NT-proBNP and atherosclerosis in SLE patients.

Methods and twenty four patients meeting American College of Rheumatology diagnostic criteria for SLE who were participating in a longitudinal study of cardiovascular disease at the Hospital for Special Surgery were studied. Patients underwent clinical and laboratory assessment, echocardiography and carotid artery ultrasonography to detect plaque. Patients were defined as having atherosclerosis based on whether they had plaque (focal protrusion >50% of the thickness of the surrounding wall) on carotid ultrasonography. Echocardiography was performed and left ventricular ejection fraction, degree of mitral regurgitation and left atrial diameter were measured. SLEDAI was used to calculate SLE disease activity. Serum NT-proBNP levels were measured using a clinically validated electrochemiluminescence method (Roche Elecsys 2010). Group differences in NT-proBNP were compared using t-tests and independent correlates of NT-BNP and plaque were determined by multivariate regression analysis.

Results: The mean age of the124 SLE patients was 43.4 ± 13.7 years and 95.2% of the patients were female. Atherosclerotic plaque was present in 38.2%. The mean SLEDAI score was 3.7 ± 4.8; range 0–22. Only 2.6% of the patients had diabetes and 12.7% were current smokers. Mean serum NT-proBNP was 246.1 ± 1251 pg/ml (median 82.5 pg/ml; range 5–12905 pg/ml). As a reference, the baseline median NT-proBNP level measured using a similar electrochemiluminescence method in women in the general population was 66 pg/ml. Log transformed NT-proBNP was associated with higher left atrial diameter, degree of mitral regurgitation and lower ejection fraction. SLE patients with atherosclerosis had higher NT-proBNP levels than SLE patients without atherosclerosis (615.4 pg/ml ± 286.5 vs 151.7 pg/ml ± 27.4; P = 0.044. However, in our regression models neither serum log NT-proBNP, gender, BMI nor SLEDAI predicted plaque. Age and lower ejection fraction were the only independent correlates of plaque.

Conclusions: In our analysis of 124 SLE patients with and without atherosclerosis, serum NT-proBNP levels correlated with plaque presence on carotid ultrasonography. As anticipated, it is likely that age and markers of cardiac function are in part mediating this relationship in our patient population. Prospective studies are now needed to determine the utility of NT-proBNP as a biomarker for predicting atherosclerosis in SLE patients.

Disclosure: D. Goldenberg: None; E. Miller: None; N. Sattar: None; P. Welsh: None; M. Roman: None; J. E. Salmon: None.

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Underuse of Hydroxychloroquine among Patients with Systemic Lupus Erythematosus. Amee O. Hersh1, Daniel J. Shapiro1, Edward H. Yelin2, Gabriela Schmajuk1, Mary L. Pablos1, J. E. Salmon1, Diana Goldenberg2, M. Roman1, J. L. Pablos1, J. E. Salmon1. 1Stanford University, Palo Alto, CA, 2UCSF, 4University of California, San Francisco, CA

Purpose: Recent literature supports the routine use of hydroxychloroquine (HCQ) in the management of systemic lupus erythematosus (SLE), with evidence for reduced disease activity, lower rates of renal progression, better lipid profiles, and improved survival. The extent to which patients with SLE receive HCQ nationwide is unknown. The purpose of this study was to determine the frequency and factors associated with HCQ prescribing in a nationally representative sample of patients with SLE.

Methods: We examined HCQ use among ambulatory visits for patients with SLE (ICD-9-CM code 710.0) using the National Ambulatory and National Hospital Ambulatory Medical Care Surveys. These surveys record information about treatments provided among a nationally representative sample of patient visits to ambulatory settings. The primary outcome was HCQ use; this was defined as either new or continued HCQ prescription associated with each incident visit. Continued medications include those previously prescribed by other physicians (i.e. HCQ by a rheumatologist when the incident visit is to a primary care physician). Independent variables included patient demographics (age, gender, race/ethnicity), insurance status (private versus public), steroid use (as a marker of disease activity), physician specialty (rheumatologist versus other), and geographic region. Multivariable logistic regression was performed to identify factors independently associated with receipt of HCQ.

Results: Between 1998–2007, there was an average of 975,000 ambulatory visits for SLE per year. Hydroxychloroquine was prescribed for 32% (95% CI 24.1–40) of patients with SLE seen during these visits. Ninety percent of patients were female, 24% were non-white, mean age was 49 years, 54% had private insurance, and 39% received corticosteroids. In bivariate analyses, there were no differences in HCQ use based on patient age, race, gender, insurance status, steroid use or geographic region. HCQ prescribing was higher among visits to rheumatologists versus other physicians (51 vs. 17%, p = 0.0001). In a multivariable analysis, after adjusting for potential confounders, the only factor independently associated with HCQ use was a visit to a rheumatologist (OR 4.57, 95% CI 1.80–11.56).

Conclusion: Hydroxychloroquine use was suboptimal in this national sample of SLE patients. Given recent evidence about the beneficial effects of HCQ on survival in SLE, interventions are needed to increase HCQ use, particularly among those patients seen by non-rheumatologists.

Disclosure: A. O. Hersh: None; D. J. Shapiro: None; E. H. Yelin: None; G. Schmajuk: None.

Vitamin D Deficiency in Systemic Lupus Erythematosus (SLE) Is Not Associated with Coronary Artery Calcium (CAC) or Carotid Plaque. Adnan N. Kiani1, Laurence S. Magder2 and Michelle A. Petri1, 1Temizium, 2Johns Hopkins University, School of Medicine, Baltimore, 3University of Maryland

Purpose: Vitamin D deficiency is common in SLE. In the general population, vitamin D deficiency is associated with cardiovascular disease, diabetes, female gender, and certain cancers. However, a recent study of vitamin D deficiency in African-Americans found that increased vitamin D levels were associated with more carotid and aortic plaque (1). We asked whether there was any similar relationship in SLE.

Methods: 167 SLE patients (93% female, 63% Caucasian, 32% African-American, mean age 45 yrs) had both measurement of subclinical atherosclerosis (coronary artery calcium, carotid intima-media thickness IMT (IMT), carotid plaque) and vitamin D. Results: Vitamin D values ranged from 4 to 79 (mean 22.3, median 21). Among African-American Vitamin D values ranged from 4 to 55 (mean 15, median 11). Table1 shows the percentage with levels of CAC, by vitamin D status.

<table>
<thead>
<tr>
<th>Vitamin D status</th>
<th>All Patients</th>
<th>Coronary Artery Calcium Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0.1 to 100</td>
</tr>
<tr>
<td>Low (n = 133)</td>
<td>74 (56%)</td>
<td>45 (34%)</td>
</tr>
<tr>
<td>Normal (n = 34)</td>
<td>22 (65%)</td>
<td>11 (32%)</td>
</tr>
<tr>
<td>African-American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (n = 47)</td>
<td>21 (45%)</td>
<td>21 (45%)</td>
</tr>
<tr>
<td>Normal (n = 5)</td>
<td>4 (80%)</td>
<td>1 (20%)</td>
</tr>
</tbody>
</table>

Of those with low Vitamin D, a higher proportion had a coronary calcium score >100 (11%), compared to among those with normal Vitamin D (1%). Among African-American patients this proportion was 11% and 0 respectively. However, these trends were not statistically significant (p=.17 and 1.0).
Table 2. Shows the mean coronary artery calcium score and carotid IMT, by vitamin D status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) among those with low vitamin D</th>
<th>Mean (SD) among those with high vitamin D</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-CAC score</td>
<td>1.17 (1.96)</td>
<td>1.04 (1.72)</td>
<td>.72</td>
</tr>
<tr>
<td>Carotid IMT</td>
<td>0.58 (0.11)</td>
<td>0.57 (0.09)</td>
<td>.78</td>
</tr>
<tr>
<td>African-American</td>
<td>1.38 (1.99)</td>
<td>0.87 (1.96)</td>
<td>.59</td>
</tr>
<tr>
<td>Carotid IMT</td>
<td>0.61 (0.13)</td>
<td>0.61 (0.12)</td>
<td>.95</td>
</tr>
</tbody>
</table>

Table 3. Shows the association between vitamin D levels and presence of carotid plaque at baseline, for all patients and African-Americans.

<table>
<thead>
<tr>
<th>Vitamin D Level</th>
<th>Carotid Plaque</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (n = 130)</td>
<td>25 (19%)</td>
<td>105 (81%)</td>
</tr>
<tr>
<td>Normal (n = 34)</td>
<td>5 (15%)</td>
<td>29 (85%)</td>
</tr>
<tr>
<td>African-American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (n = 44)</td>
<td>11 (25%)</td>
<td>33 (75%)</td>
</tr>
<tr>
<td>Normal (n = 5)</td>
<td>0 (0%)</td>
<td>5 (100%)</td>
</tr>
</tbody>
</table>

Table 4. Mean Vitamin D (as a quantitative variable), in all patients and among African-American defined by presence or absence of high coronary artery calcium score, or carotid plaque.

<table>
<thead>
<tr>
<th>All patients</th>
<th>Mean Vitamin D (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Artery Calcium Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (n = 96)</td>
<td>23.4 (13.8)</td>
<td>.26</td>
</tr>
<tr>
<td>.1–99 (n = 56)</td>
<td>21.6 (12.7)</td>
<td></td>
</tr>
<tr>
<td>100+ (n = 15)</td>
<td>17.7 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Carotid Plaque</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent (30)</td>
<td>22.8 (13.0)</td>
<td>.41</td>
</tr>
<tr>
<td>Present (134)</td>
<td>20.6 (14.4)</td>
<td></td>
</tr>
<tr>
<td>African-American Coronary Artery Calcium Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (n = 25)</td>
<td>16.7 (12.7)</td>
<td>.51</td>
</tr>
<tr>
<td>.1–99 (n = 22)</td>
<td>13.7 (7.9)</td>
<td></td>
</tr>
<tr>
<td>100+ (n = 5)</td>
<td>12.0 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Carotid Plaque</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent (38)</td>
<td>15.8 (11.6)</td>
<td>.31</td>
</tr>
<tr>
<td>Present (11)</td>
<td>12.1 (5.6)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Vitamin D was not associated with any measure of subclinical atherosclerosis in SLE. In contrast to the study in African-Americans (J Clin Endocrinol Metab 95: 1076, 2010), higher vitamin D was not associated with MORE carotid plaque. In fact, in SLE, there was a suggestion that those with low vitamin D were more likely to have a coronary artery calcium score greater than 100 (11% vs. 1% and 11% vs. 0 among African-American).

Disclosure: A. N. Kiani: None; L. S. Magder: None; M. A. Petri: None.

ACR Poster Session A
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis: Genetics and Mechanisms
Monday, November 8, 2010, 9:00 AM–6:00 PM

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9G4 Autoantibodies Dominate the Anti-Apoptotic Cell Autoimmune Response in SLE.

Scott A. Jenks1, Elise Palmer2, Elides Marin2 and Ignacio Sanz1, 1Univ of Rochester, Rochester, NY, 2Univ of Rochester

Purpose: To understand the prevalence and characteristics of anti-apoptotic cell autoantibodies (APCA). These aspects of the autoimmune response in SLE remain poorly understood despite strong experimental evidence showing that impaired clearance of apoptotic cells in SLE provides an abundant source of immunogenic disease-related autoantigens and is likely to play a central role in disease pathogenesis. A flow cytometric assay for the quantification of serum APCA antibodies was applied to a cohort of SLE patients to ascertain the total amount of APCA. Given the high specificity of 9G4 autoantibodies for SLE and their association with disease activity we also determined the contribution of 9G4 autoantibodies to APCA reactivity. In this study we identify a high prevalence of IgG APCA that is heavily contributed to by 9G4+ antibodies.

Methods: Serum from 68 SLE patients with a spectrum of disease activity and 9 healthy volunteers, was used to assess 9G4+ IgG and IgM antibody binding to apoptotic Jurkat cells and to viable lymphocytes using multiple-parameter flow cytometry (Fig A). Camptothecin was used to induce apoptosis in a CD45/B220-negative Jurkat cell line (J45.01). Viable lymphocytes were obtained from healthy control peripheral blood and identified as naïve B cells (CD19+IgD+CD27-). Positive binding to either naïve B cells or apoptotic cells was determined as an median fluorescence intensity ≥2 standard deviations of the mean median fluorescence intensity of healthy controls.

Results: After normalization of serum samples for total IgG quantity, 60% of patients displayed elevated levels of APCA. IgG APCA binding was prevalent as 53% of positive samples showed only IgG binding and 26% IgG and IgM (Fig B) whereas IgM only binding was 19%. APCA levels correlated with disease activity as measured by SLEDAI (p = 0.014). 9G4 autoantibodies contributed substantially to APCA activity, 67% of APCA positive samples demonstrated strong 9G4 binding (Fig C). Moreover, initial depletion experiments indicate that up to 75% of all IgG APCA activity in SLE serum is contributed by 9G4+ antibodies. When the specificity of 9G4 binding was examined, the majority (55%) of the samples bound both naïve lymphocytes B and apoptotic cells; however, 35% bound only apoptotic cells and 10% bound just naïve B cells.

Conclusions: Our results demonstrate that APCA antibodies are common in SLE and their abundance correlates with disease activity. Moreover, our results indicate that the SLE-specific 9G4 antibody fraction represents the majority of APCA. These observations provide the basis for ongoing studies of the identity of apoptotic cell antigens responsible for the expansion of an SLE-specific auto-reactivity. This work also illustrates the value of measuring APCA reactivity in future studies of B cell tolerance and suggests that these measurements may contribute to clinical studies and management of SLE.

Disclosure: S. A. Jenks: None; E. Palmer: None; E. Marin: None; I. Sanz: None.
This protein appeared to be unique from known lupus autoantigenics such as anti-Smith bands and anti-Ku70/RNP. Subsequently, a large quantity of REH lysate was prepared in the appropriate buffer and resolved by 2D gel electrophoresis followed by transfer to membrane, scanning of the Ponceau stained blot and Western Blotting with one of the sera showing strong reactivity with the 32 kD band (Figure 2A).

A repeat 2D gel of REH lysate was coomassie-stained to visualize the proteins and, based on the alignment previously seen between the Western Blot and the 2D Ponceau Stain, the appropriate protein “dots” were sent for peptide sequencing by Mass spectrometry.

Results: The top non-keratin “hit” was SFRS1, also known as ASF/SF2, with 23% sequence coverage. In order to confirm that the SLE sera were in fact identifying ASF/SF2 as a novel autoantigen, the recombinant GST-fusion protein (MW 55kD) was purchased from ABNOVA and tested by immuno-blotting using control and SLE patients’ sera. We found that 12/57 (21%) of SLE patients’ sera reacted with purified ASF/SF2 as compared to 0/25 of control normal sera. A representative blot is shown in [Figure 2B]. Studies to define antibody titers and correlation with disease activity are underway.

Conclusions/Discussion: ASF/SF2 is a member of the SR family of proteins that are involved in RNA splicing and are regulated by serine phosphorylation by SRPK1. More recently, ASF/SF2 has also been shown to be involved in processing microRNAs separate from its role in RNA splicing. Intriguingly, ASF/SF2, has also been implicated as a proto-oncogene in a number of malignancies. It will be interesting to look for anti-ASF/SF2 antibodies in individuals with certain malignancies and to attempt to correlate these with autoimmune manifestations versus protective immunity. We will also look for anti-ASF/SF2 antibodies in other rheumatologic conditions and investigate the role of phosphorylation and other protein modifications in the creation of autoantibodies.

Disclosure: A. Golding: None; E. Akhter: None; T. Hines: None; R. Sen: None; L. Casciola-Rosen: None; A. Rosen: None; M. A. Petri: None.

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Association of adam33 Polymorphisms with Systemic Lupus Erythematosus. Seung-Cheol Shim, Mi-Kyoung Lim and Dong-Hyuk Sheen. Eulji University, Daejeon, Korea, Republic of

Background: A Disintegrin and Metalloprotease 33 (ADAM33) is a member of a family of genes that encode membrane-anchored proteins with a disintegrin and a metalloprotease domain, and is located on chromosome 20p13. Recently, the polymorphisms in ADAM33 have been found to be associated with asthma. Among the rheumatic diseases, systemic lupus erythematosus (SLE) is a prototypic Th2-mediated autoimmune disease like allergic disorders.

Purpose: To assess whether genetic functional variants of ADAM33 are associated with susceptibility to SLE or development of specific phenotypes in patients with SLE.

Methods: We have identified 48 SNPs, and nine SNPs were selected with regard to the LD pattern. Genotyping for g.10918G>C, g.12433T>C and g.13506C>G in the ADAM33 gene was conducted with PCR–RFLP methods, and genotyping for g.-330C>T, g.517A>G, g.8227G>A, g.9511G>T, g.12462C>T, and g.12988C>A polymorphisms was performed by single-base extension (SBE), using the ABI Prism® SNaPshot™ Multiplex kit (Applied Biosystems). We conducted an association study for ADAM33 polymorphisms in 190 SLE patients, 469 healthy controls, and 390 rheumatoid arthritis (RA) patients as a disease control. Haplotype analyses of related variants were performed as well.

Results: Significant associations of ADAM33 polymorphisms with susceptibility to SLE were found at g.8227 G>A, g.12988 C>A, and g.13506 C>G (P value were all below 0.001). Polymorphisms at g.8227 G>A was associated with the ANA titers among SLE patients (P = 0.012). In addition, we analysed the haplotype, and found a positive association of susceptibility to SLE with the major haplotype CCG (P = 3.5E-11). There was no association between ADAM33 polymorphisms and RA as expected.

Conclusion: ADAM33 polymorphisms were strongly associated with susceptibility to SLE and the development of specific clinical manifestations.

Disclosure: S.-C. Shim: None; M.-K. Lim: None; D.-H. Sheen: None.

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Binding of Apoptotic Fetal Cardiocytes by Anti-Ro/La Antibodies Stimulates uPA/uPAR-Dependent Activation of TGFbeta and Potentiates Fibrosis. Paraskiev Briassouli1, Daniel Rifkin1, Jill P. Buyon1 and Robert M. Clancy1. New York University School of Medicine, New York University Medical Center, New York, NY

Purpose: Organ injury induced by antibodies characteristic of Sjogren Syndrome and Systemic Lupus Erythematosus, while varied in the adult and fetus, may share in common a link between apoptosis and ultimate fibrosis. In congenital heart block (CHB), binding of maternal anti-Ro/La antibodies to apoptotic cardiocytes impairs their removal by healthy cardiocytes and increases uPA/uPAR-dependent plasmin activation. Immunological staining of CHB hearts reveals AV node TGFb staining and TGFb activation promotes fibroblast transdifferentiation, a scarring phenotype. Since the uPA/uPAR system plays a role in TGFb activation, this study evaluated whether anti-Ro/La binding to apoptotic cardiocytes via plasmin activation stimulates TGFb and promotes a profibrosing phenotype.

Methods and Results: Initial analysis showed increased TGFb in supernatants from co-cultures of healthy cards and apoptotic cards incubated with IgG fractions from mothers whose sera contain anti-Ro/La antibodies and who had a child with CHB (apo-CHB-IgG) compared to co-cultures of healthy cards and apoptotic cards incubated with control IgG (apo-nl-IgG). Using a luciferase bioassay of active TGFb, supernatants from co-cultures of healthy cards and apoptotic cards incubated with active TGFb and promotes a profibrosing phenotype.

Conclusion: Initial analysis showed increased TGFb in supernatants from co-cultures of healthy cards and apoptotic cards incubated with IgG fractions from mothers whose sera contain anti-Ro/La antibodies and who had a child with CHB (apo-CHB-IgG) compared to co-cultures of healthy cards and apoptotic cards incubated with control IgG (apo-nl-IgG). Using a luciferase bioassay of active TGFb, supernatants from co-cultures of healthy cards and apo-CHB-IgG cards exhibited increased levels of active TGFb compared to those cocultured with apo-nl-IgG. To determine whether uPA activity was responsible for the observed TGFb activation, coculture experiments were conducted in which the apo-CHB-IgG and apo-nl-IgG were analysed with uPAR antibodies. Supporting the hypothesis that anti-Ro/La binding to apoptotic cardiocytes via plasmin activation stimulates TGFb and promotes a profibrosing phenotype.
blood samples from 12 of 18 children with CHB exhibited increased uPA activity and uPAR cleavage compared to 4 of 14 non CHB children exposed to maternal anti-Ro antibodies.

**Conclusions:** These data suggest that binding of anti-Ro/La antibodies to apoptotic cardiocytes by virtue of increased uPAR-dependent uPA activity trigger TGFβ activation thus initiating and amplifying a cascade of events that promote myofibroblast transdifferentiation and scar.

**Disclosure:** P. Briassoulis: None; D. Rifkin: None; J. P. Buyon: NIAMS-NIH, 2, NIH, 2; R. M. Clancy: None.

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**Binding Target for C-Reactive Protein Is Released from Secondary Necrotic Cells.** Christina Janko1, Christine Schorn1, Luis Munoz1, Manfred Rauh1, Kirsten Lauber2, Georg Schett1 and Martin Hermann1. 1Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, 2Department of Internal Medicine I, University of Tuebingen, Tuebingen, Germany, 3Department of Paediatrics and Adolescent Medicine, University of Erlangen-Nuremberg, Erlangen, Germany

**Background:** The C-reactive Protein (CRP) is an acute-phase protein whose serum concentration massively increases in response to tissue injury or inflammation. Beside opsonizing of bacteria CRP is known to bind calcium dependent to altered mammalian membranes (e.g. occurring in cell death) via phosphocholine, the polar headgroup of phosphatidylcholine and its derivates. CRP also opsonizes intracellular components leaking from necrotic cells.

This study was performed to analyze whether CRP differentially binds to primary and secondary necrotic cells. Primary necrosis is defined as immediate cell death appearing after severe cell death stimuli, whereas secondary necrosis follows after an apoptotic stadium.

**Methods:** We prepared Fic-labelled CRP to determine the binding of CRP to primary and secondary necrotic cells by flow cytometry and confocal microscopy. The release of a CRP target from dying cells was detected in the supernatant by inhibition assays. The released CRP antagonist was identified by enzymatic cleavage and by mass spectrometry.

**Results:** The binding of CRP to primary necrotic cells was significantly stronger compared to secondary necrotic ones. We detected a CRP antagonistic activity in supernatants of secondary necrotic cells, which was identified as glycophosphocholine (GlycoPC). Actually, CRP binding to necrotic cells was blocked by synthetic GlycoPC. The release of the CRP antagonist was significantly reduced by inhibitors of Phospholipase A2 and Caspasps.

**Conclusion(s):** Secondary necrotic cells show a weaker binding of CRP resulting from the release of the CRP target during late apoptosis. That may have implications for opsonisation with CRP of dying and dead cells and for CRP-mediated effects in clearance. Secondary necrotic cells, for example in SLE patients, may release high amounts of the CRP antagonist with the following consequences (1) missing CRP binding targets on the dead cells and (2) neutralizing of circulating CRP, both possibly contributing to clearance failure.

**Disclosure:** C. Janko: None; C. Schorn: None; L. Munoz: None; M. Rauh: None; K. Lauber: None; G. Schett: None; M. Hermann: None.

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**Clq and Complement Proteins Induce a Non-Caspase-Dependent, Non-Necrotic, Cell Death, That Protects from Autoimmunity.** Mizhir Atallah, Amir Grau and Dror Mevorach. Hadassah-Hebrew University

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease of unknown etiology characterized by the presence of pathogenic high-titer autoantibodies to a diverse group of autoantigens. Eearly complement proteins are important in protecting humans against the development of SLE and the protective role of Clq and complement in SLE is mainly related to their role in clearance of dying cells. Since there are few other mechanism available for apoptotic cell clearance we were questioning whether Clq has unknown additional role that may lead to increased necrotic debris found in patients with SLE. Using spontaneous human neutrophil apoptosis in the presence of complement deficient sera we show that by 12h incubation with Clq-deficient serum there were 61.28% ± 14.51% viable cells compared with 46.1% ± 14.88% in autologous serum. Furthermore, there were more than three-fold higher rate of necrotic cells (p<0.001) when cells were incubated in autologous serum in comparison with Clq-deficient serum. We further characterized complement induced cell death by electron microscopy and caspase inhibitors to conclude that complement induced apoptotic, non-necrotic, non-caspase-dependent neutrophil death.

We further injected dying cells in the presence and absence of Clq and were able to show that in the absence of Clq, a lupus-like disease was developed whereas in the presence of Clq lupus-like disease was much milder (0.001) as judged by the development of immunoglobulins, autoantibodies, and kidney disease. Taken together, we conclude that Clq induced a non caspase-dependent cell death that is protected from necrosis and avoids autoimmunity. This is a novel role for Clq that was thus far suggested to have a role only in clearance of apoptotic cells. This observation and may add a new explanation for the presence of elevated necrotic debris in SLE patients.

**Disclosure:** M. Atallah: None; A. Grau: None; D. Mevorach: None.

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**Characterisation of Ex Vivo Leukocyte Rolling and Adhesion Responses in SLE.** Eric F. Morandi1, Qiang Cheng2, Albert Hor3 and Michael J. Hickey2. Monash University, Melbourne, Australia, 3Monash University

**Purpose:** Systemic lupus erythematosus (SLE) is characterised by the presence of autoimmunity and inflammatory injury mediated by effector leukocytes recruited from the circulation. Mechanisms of increased leukocyte recruitment into affected tissues may include increased endothelial expression of chemokines and endothelial adhesion molecules, or disease-related alterations in leukocyte adhesive behaviour. The latter has not previously been investigated.

**Aim:** To determine whether SLE is associated with intrinsic alterations in blood leukocyte adhesive responses.

**Methods:** Rolling and adhesion interactions were quantified under flow conditions using fresh unstimulated whole peripheral blood (PB) leukocytes. PB was obtained from MRL/lpr lupus-prone mice and MRL/+/+ control mice, and from healthy subjects (n=33) and patients with SLE (>4 ACR criteria) (n=57). Adhesive substrates used were platelet monolayers and/or recombinant VCAM-1.

**Results:** Compared to control mice, PB leukocytes from MRL/lpr mice exhibited markedly and significantly increased rolling and adhesion interactions on platelet monolayers. After adjustment for increased PB leukocyte counts in MRL/lpr mice, increases in leukocyte rolling and adhesion remained significant, at time points prior to the onset of clinical disease. This suggested an intrinsic alteration in leukocyte behaviour in a model of SLE. Therefore, we next studied this phenomenon in humans. Unstimulated PB leukocytes from SLE patients demonstrated significant increases in neutrophil rolling on platelet monolayers compared to healthy subject PB. Neutrophil rolling was P-selectin- and PSGL1-dependent. However, after correction for the increased PB neutrophil counts associated with steroid therapy in SLE patients, differences between SLE and healthy PB were non-significant. To investigate mononuclear cell interactions, recombinant VCAM-1 was used as an adhesive substrate. Lymphocytes formed the dominant PB leukocyte subset adherent to VCAM-1 in both SLE and control blood, and these interactions were alpha-4 integrin-dependent. After correction for SLE-related lymphopenia, no increase in PB lymphocyte adhesion interactions was present in SLE. However, a significantly increased proportion of SLE patient lymphocytes adherent to VCAM-1 underwent spreading, a motility response which precedes lymphocyte emigration. Significantly higher spreading responses were seen both in patients with active SLE (SLEDAI>4) and inactive SLE.

**Conclusions:** We describe a novel method for investigation of leukocyte recruitment events ex vivo in SLE. Increased PB leukocyte rolling and adhesion interactions were observed in MRL/lpr mice, prior to the onset of clinical disease. In contrast, neutrophil interactions with P selectin and lymphocyte interactions with VCAM-1 were normal in human SLE, but lymphocyte spreading responses on VCAM-1 were significantly increased in SLE PB. Further exploration of blood lymphocyte intrinsic migratory behaviour in SLE is justified, and may represent a novel therapeutic target.

**Disclosure:** E. F. Morandi: None; Q. Cheng: None; A. Hoi: None; M. J. Hickey: None.

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**Inhibition of Cytosolic Nucleic Acid Receptor Pathways Using the Small Molecule IKKe/TBK1 Kinase Inhibitor MPI-0485520.** Burt Richards, Ju-Fen Zhu, Nathan Seager, Monica Cronin, Harry Austin, Thomas Douce, Daniel Cimbra, Ryan Holcomb, Daniel Wettstein and Paul Bartel. Myrexis, Inc., Salt Lake City, UT
Response to infection by bacterial and viral pathogens includes recognition of foreign nucleic acids. Several cytosolic nucleic acid receptors have been characterized, including the dsRNA receptors MDA5 and RIG-I and the dsDNA receptor DAI. Activation of cytosolic nucleic acid receptors leads to production of type I interferons and proinflammatory proteins through phosphorylation of IRF3 transcription factor by the IKK-related kinase TBK1.

We have developed a small molecule kinase inhibitor, MPI-0485520, that potently and selectively inhibits the IKK-related kinases IKKe and TBK1. MPI-0485520 also exhibits high oral bioavailability, favorable ADME/PK properties, and efficacy in a pharmacodynamic mouse model. To examine cytosolic nucleic acid receptor signaling through IKKe and TBK1, we activated receptors by introduction of dsRNA and dsDNA mimetics into the cytosol of mouse RAW264.7 and human THP-1 monocytic cell lines. Cells were subsequently dosed with MPI-0485520 and mRNA and protein levels of proinflammatory cytokines (IFNβ, IP-10, IFIT1, MX1, RANTES, and IL-6) were monitored using qRT-PCR and ELISA. Both RAW264.7 and THP-1 cells exhibit robust induction of specific proinflammatory cytokines after cytosolic introduction of the RIG-I and MDA5 agonists, using low and high molecular weight poly(I:C), respectively. This induction was potent inhibited with MPI-0485520 for several of the induced cytokines. Treatment of mouse RAW264.7 cells with the dsDNA receptor agonist poly(dA:dT) also resulted in potent induction of proinflammatory cytokines that was inhibited by MPI-0485520 in a dose-dependent manner. THP-1 cells were not responsive to poly(dA:dT) suggesting that a dsDNA receptor is not present or is poorly induced in this cell line.

In addition to foreign nucleic acids, recent studies have demonstrated that accumulation of endogenous nucleic acids, due to improper disposal of retroelements, can generate a type I interferon response. Patients with mutations in TREX1, RNASEH2A/B/C, or SAMHD1 have a genetic predisposition to autoimmunity, including systemic lupus erythematosus, Sjogren’s syndrome, and Aicardi-Goutieres syndrome (AGS). Trex1-/- mice have been characterized, including the dsRNA receptors MDA5 and RIG-I and the cytosolic nucleic acid receptor activation.

Inhibition of Interferon-Alpha by Sialylated IgG in Response to TLR7 and TLR9 Activation Is Mediated by a Soluble Factor Produced by Monocytes. Alice E. Wiedeman, Deanna M. Santer, Fabian Käsemann, Sylvia Miescher and Keith B. Elkon. CSL Behring, 3; University of Washington, 3.

Objective: IgG in the form of intravenous immunoglobulin (IVIG) has been used as an anti-inflammatory agent in multiple autoimmune diseases. Recent studies reported that it is the small fraction of sialylated IgG (SA-IgG) in human IVIG preparations that attenuates arthritis or immune thrombocytopaenia. However, these studies were performed across species (human IgG injected into mouse models of disease). Our goal was to study the importance of the sialylated subset of IVIg in the inhibition of the inflammatory responses of human cells stimulated with TLR7 and 9 agonists that induce type 1 IFN.

Methods: Human IVIg preparations were enriched (SA+, 7- to 10-fold) or depleted (SA-, 2- to 5-fold) of the sialylated subset by lectin affinity chromatography. PBMC were isolated from whole blood of healthy individuals, cultured overnight in the presence of TLR7 (Lxoribine, CL097) or TLR9 (Cpg) agonists with or without SA+ or SA-IgG at two doses (0.5 and 5 mg/mL). Antibodies to DC-SIGN, Fc receptors, as well as isotype controls (1ug/mL) were also used. In certain experiments, monocytes, B cells or NK cells were depleted or isolated from PBMC using magnetic beads. Some cultures were treated with Tnf-α, IL-10, IL-6, and IL-8 or with antibodies to these same cytokines. Supernatants were collected 20 hours post-treatment and analyzed by ELISA for IFN-α, TNF-α, IL-10, IL-6, and IL-8.

Results: In response to the TLR agonist treated, SA+ IgG inhibited IFN-α production significantly more than SA- IgG (p<0.05). The inhibition by SA+ IgG increased with higher doses (p<0.05). Blocking DC-SIGN or FcRs did not abrogate the inhibition by SA+ IgG. Inhibition of IFN-α by SA+ IgG was decreased by the depletion of CD14+ monocytes, but not depletion of CD19+ B cells or CD56+ NK/NKT cells. Supernatants from isolated monocyte cultures treated with SA+ IgG could transfer inhibition to fresh cultures of TLR agonist-stimulated PBMC or isolated pDC. Surprisingly, levels of TNF-α, IL-10, IL-6, and IL-8 were not inhibited by SA+ or SA- IgG, and in fact the production of TNF-α was modestly enhanced in cultures treated with SA+ compared to SA- IgG (p<0.05). Neutralization of TNF-α or IL-10 did not abrogate IFN-α inhibition by SA+ IgG.

Conclusions: SA+ IgG is more potent at inhibiting IFN-α production in response to TLR agonist stimulation compared to SA- IgG. Results suggest that SA+ mediated inhibition is not mediated through an Fc gamma receptor nor the human homolog of SIGN-R1, DC-SIGN. Soluble factor(s) produced by CD14+ monocytes mediate this inhibition by acting directly on pDC. Cytokine blocking studies indicate that cytokines TNF-α and IL-10, that are produced by monocytes and known to inhibit IFN-α, are not responsible. The greater potency of SA+ IgG has therapeutic implications for SLE because our results suggest that a lower dose of IVIG enriched for the active, sialylated subset may dampen IFN-α responses to TLR stimuli. Also, identification of the SA+ binding receptor and soluble factor(s) released from monocytes in response to SA+ IgG could reveal new targets for immune modulation of type 1 IFN in SLE.

Disclosure: A. E. Wiedeman: None; D. M. Santer: None; F. Käsemann: CSL Behring, 3; S. Miescher: CSL Behring, 3; K. B. Elkon: None.

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IRF5 SLE-Risk Haplotype Is Strongly Enriched in Anti-Ro Positive Mothers of Neonatal Lupus Patients with Diverse Diagnoses. Timothy B. Niewold, Silvia N. Kariuki, Beverly S. Franke, Jill P. Buyon and Robert M. Huber. Division of Rheumatology, New York University School of Medicine, 3; Section of Rheumatology and Gwen Knapp Center for Lupus and Immunology Research, University of Chicago.

Objective: In patients with systemic lupus erythematosus (SLE), IRF5 genotype is associated with anti-Ro autoantibodies. It is not clear whether this association with autoantibody profile is specific to SLE disease status. To examine this question, we assessed IRF5 genotypes in a large cohort of individuals who all had high titer anti-Ro autoantibodies and carried a variety of diagnoses including healthy/asymptomatic, Sjogren’s syndrome (SS), and SLE.

Methods: We studied 85 European-ancestry individuals recruited to the Research Registry for Neonatal Lupus who all had high titer anti-Ro autoantibodies and a child with neonatal lupus. The diagnoses of these subjects were as follows: 15 healthy/asymptomatic, 10 SLE, 19 SLE/SS, 20 SS, and 21 undifferentiated autoimmune disease (UAS). IRF5 SNPs were genotyped using Taqman primer-probe sets to define previously reported European-derived SLE risk and protective haplotypes.

Results: The IRF5 SLE-risk haplotype defined by the rs10488631 C allele was enriched in subjects of all diagnoses except SS when compared to large published data sets of European-American controls [OR=2.30 (1.50–3.32), p=8.4×10−5]. Each of the asymptomatic, SLE, SLE/SS, and UAS mothers showed a very similar increase in rs10488631 allele frequency when examined individually (ORs range from 2.00 to 3.15, no significant differences between the asymptomatic, SLE, SLE/SS and UAS groups). The rs10488631 C allele frequency in the subjects diagnosed with SS was essentially the same as controls (OR=1.05). Interestingly, the rs3807306 C allele was significantly increased in the SS patients as compared to subjects from the other 4 diagnostic categories [OR=2.34 (1.14–4.79), p=0.026].

Conclusions: There was a significant increase in the frequency of the IRF5 SLE-risk haplotype among anti-Ro autoantibodies with varying diagnoses which was of comparable magnitude to the anti-Ro/IRF5 association observed in SLE (OR=2). Interestingly, the SS cohort was distinct from the other neonatal lupus mothers with respect to IRF5 genotype, and a different SNP was associated with SS status. These data suggest that the genetic association of IRF5 with autoimmunity is strongly influenced by serologic profile, and that the anti-Ro association with IRF5 genotype extends beyond the SLE disease state to some degree.

Disclosure: T. B. Niewold: ALR, 2; ANRF, 2; Chicago/France Center, 2; LRI, 2, NIH, 2; S. N. Kariuki: None; B. S. Franke: None; J. P. Buyon: NIH, 2; R. M. Clancy: NIH, 2.
IRF8 Allele Associated with Susceptibility to Multiple Sclerosis Is Associated with Serum Interferon Alpha and Serologic Profile in Systemic Lupus Erythematosus. Beverly S. Franke, Silvia N. Kariuki, Jasmine Arrington, Rachel A. Mikolaitis, Meenakshi Jolly, Tammy O. Utes, Dimitros T. Boumpas, George Goulielmos and Timothy B. Niewold. 1 Internal Medicine and Rheumatology, Clinical Immunology and Allergy, University of Crete Medical School, Heraklion, Greece; 2Section of Rheumatology and Gwn Knapp Center for Lupus and Immunology Research, University of Chicago; 3Section of Rheumatology, Rush University Medical Center.

Objective: Alleles of IRF8 have been associated with susceptibility to both systemic lupus erythematosus (SLE) and multiple sclerosis (MS). While interferon alpha (IFN-α) is thought to be causal in SLE, recombiant human IFN-α is used as a therapy in MS. We investigated whether the IRF8 alleles associated with these two diseases were associated with differences in serum IFN-α or serologic profile in a multi-ancestral cohort of SLE patients.

Methods: The rs12444486 and rs17445836 single nucleotide polymorphisms (SNPs) in IRF8 (associated with SLE and MS respectively) were genotyped with Taqman primer-probe sets in 244 African-American and 137 European ancestry SLE patients. All patients had serum IFN-α and serology data available, and had been previously genotyped at SLE-risk SNPs in the IRF5 and IRF7 loci. Data from each ancestral background was analyzed separately initially, and combined in meta-analysis when associations were not significantly heterogeneous between ancestral backgrounds. Principal component analysis was used to control for proportional ancestry at the individual level.

Results: The MS-associated rs17445836 G allele was associated with the presence of anti-dsDNA autoantibodies in SLE patients of both ancestral backgrounds [meta-analysis OR = 2.0 (1.0–3.68), p = 0.024]. The same allele was also associated with increased serum IFN-α activity in both ancestral backgrounds (meta-analysis p = 0.017). There was no evidence for statistical interaction between rs17445836 G and SNPs in IRF5 and IRF7 which have been previously associated with anti-dsDNA in SLE patients. No significant associations were observed between the SLE-associated rs12444486 SNP and serum IFN-α or serologic profile.

Conclusions: The rs17445836 G allele associated with susceptibility to MS was associated with anti-dsDNA antibodies and serum IFN-α in SLE patients of both African-American and European ancestry. This is interesting, given the therapeutic effect of IFN-α in MS patients, and the pathogenic effect of this same cytokine in SLE. Further exploration of the impact of the IRF8 locus upon in vivo IFN-α levels could provide insight into both diseases.

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Leptin Promotes T Cell Autoimmunity through Modulation of the PKB/Akt/mTOR Pathway in Systemic Lupus Erythematosus (SLE) Patients. Elaine V. Lourenco, Bevra H. Hahn, Noriko Ikuni, Sarah J. Kim, Maida Wong, Ram P. Singh, Jennifer Grossman and Antonio La Cava. UCLA

Leptin is a pro-inflammatory (adipocytokine) that promotes the onset and progression of organ-specific autoimmunity by facilitating pro-inflammatory immune responses. We investigated the possibility that leptin could modulate autoimmune T cell reactivity in systemic lupus erythematosus (SLE) patients, and found that the elevation of leptin in plasma from SLE patients (n = 164) - as compared to matched controls (n = 124) (p < 0.0001) - facilitated the proliferation and release of pro-inflammatory cytokines in peripheral autoreactive SLE CD4+ T cells. These effects were abrogated if leptin was blocked by antibodies anti-leptin, anti-leptin receptor, or leptin receptor chimera. Interestingly, the effects of leptin were different on the CD4+ CD25+ FoxP3- effector T cells (Treg) and CD4+ CD25+ FoxP3+ regulatory T cells (Treg). In particular, leptin promoted the proliferation and release of pro-inflammatory cytokines in Treg, and it constrained the activity of Treg, with a net result of unabated autoreactive Treg responses. These effects associated with leptin-induced differential activation of the protein kinase B (PKB/Akt)mTOR signaling pathway in autoreactive Treg versus Treg and this action could be reversed by pharmacologic intervention. These findings identify a new mechanism through which leptin can concomitantly promote T cell autoreactivity and inhibit immune suppression in SLE, suggesting the possibility of targeted leptin-based intervention for the control of unbalanced T cell autoimmunity reaction in the disease.

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Low C4A Gene Copy Number in Systemic Lupus Erythematosus. Kaline M. C. Pereira, Atula G. A. Faria, Eloisa S. Moreira, Viviane C. Santos, Marcellre Grecco, Neusa P. Silva and Luis Eduardo C. Andrade. Hospital Sirio Libanes, Brazil; 2Universidade Federal de São Paulo, São Paulo, Brazil; 3Universidade Federal do Estado de São Paulo - UNIFESP, Brazil; 4Universidade Federal de São Paulo - UNIFESP, São Paulo, SP, Brazil

Introduction: C4 is an important component of Complement system and plays an essential role in the activation cascades of the classical Complement pathway. Complete deficiency of C4 is among the strongest genetic risk factors for systemic lupus erythematosus (SLE). There are two C4 circulating isotypes (C4A and C4B) encoded by C4A and C4B genes, respectively, that differ by only five nucleotides. C4A protein is involved in immune complex and apoptotic debris clearance while C4B protein is relevant in the defense against microbes. C4A and C4B genes are located at a gene cassette within the MHC class III region and depict gene copy-number variation (CNV). The number of C4A copies may be related to susceptibility to SLE.

Objective: To investigate the C4A and C4B gene CNV in patients with SLE.

Methods: One hundred SLE patients (meeting SLE ACR criteria) were sequentially retrieved from the rheumatology outpatient clinic and 100 healthy individuals (HI) without evidence of autoimmune diseases were retrieved among blood bank donors. Peripheral blood leukocyte DNA was amplified by quantitative real-time PCR (qPCR) technique using sequence specific TaqMan® probes with minor groove binding (MGB) non-fluorescent quencher probe copy number modifications. Copy number determination was performed with delta-delta cycle threshold (DDCT) method. Samples with known C4A and C4B CNV were kindly provided by Dr. Szilagyi (Hungary).

Results: Gene copy number (GCN) varied from 2 to 8 for total C4 and from 0 to 5 for C4A and C4B. Patients with SLE had lower total C4 (C4A + C4B) and C4A CN than HI. GCN for total C4 was lower in C4A and C4B was significantly higher in SLE patients (3.7 ± 1.2; 95% CI = 3.5 – 3.9) in comparison with HI (4.3 ± 1.3; 95% CI = 4.0 – 4.5; p = 0.003). This difference was due to C4A GCN variation that was lower in SLE (1.9 ± 1.0; 95% CI = 1.7 – 2.1) than in HI (2.3 ± 1.1; 95% CI = 2.1 – 2.6; p = 0.015). In contrast there was no difference in C4B GCN in both groups [SLE = 1.8 ± 0.8; 95% CI = 1.6 – 1.9] and (HI = 1.9 ± 1.1; 95% CI = 1.7 – 2.1) p = 0.320. The frequency of patients with only two C4A copies (C4A and/or C4B) was significantly higher in SLE (16%) than in HI (5%; p = 0.028). The same was observed for subjects with only one C4A copy (SLE = 30%); controls = 16%; p = 0.020). The frequency of patients with low C4 GCN (less than 4 copies) was significantly higher in SLE than in HI (40% versus 25%; p = 0.022). The same was observed for low C4A gene dosage (less than 2 copies) (SLE = 35%; HI = 17%; p = 0.009).

Conclusion: Patients with SLE presented lower C4A GCN as compared to control healthy individuals. This finding suggests that the ensuing relative deficiency in circulating C4A protein in individuals with low C4A GCN is one relevant risk factor for susceptibility to the development of systemic lupus erythematosus.

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Background: Patients with Systemic Lupus Erythematosus (SLE) have an ‘IFN-signature’ that correlates with disease severity. RNA-sequencing complex IFNs (IFN-α) stimulate IFN-alpha (IFN-α) production by plasma-cytoid dendritic cells (pDCs) through activation of TLR7. We recently demonstrated that normal human serum contains potent inhibitors of IFN-α including IgG and the classical complement protein C1q. We showed that C1q inhibition of IFN-α required monocots to indirectly inhibit pDCs, but thus far we only knew that the inhibition was soluble factor independent. The
purpose of this study was 2-fold: 1) To determine what genes are induced by C1q-containing ICs that could explain the mechanism by which C1q regulates IFN-a induction, and 2) To identify what other pathways, in addition to type 1 IFNs, are induced by SLE ICs.

Methods: SLE ICs were formed with diluted SLE serum (1:2000) or purified IgG and necrotic cell extract. ICs were added to normal donor peripheral blood mononuclear cells (PBMCs) or purified monocytes (>97% pure) in the absence (IC) or presence of C1q (C1q-IC) for 6 to 24 hours (microarrays) or 40 hours (ELISA and flow cytometry). Controls included unstimulated and C1q alone treated cells. IFN-a and other pro-inflammatory cytokines were quantified by ELISA in culture supernatants and the expression of the activation markers CD86 and CD40 were determined by flow cytometry. Gene expression was quantified using Illumina Ref 8 beadchip arrays and the results were confirmed by qRT-PCR with a total of 4 donors. ICs and necrotic extract contained <0.06 EU/ml endotoxin contamination.

Results: We found that SLE ICs altered the expression of 105 genes greater than 2-fold for PBMCs and only 7 genes for purified monocytes. Surprisingly, none of the ICs tested, whether formed with purified IgG or diluted serum, induced a typical pro-inflammatory response (e.g. TNF-a and IL-6) by PBMCs or monocytes. Rather, 40 of the top 50 genes induced in PBMCs were known type I IFN stimulated genes (ISGs). These ISGs were not induced in our monocyte microarrays. Upon addition of C1q to ICs, we observed a striking downmodulation of the expression of the 40 ISGs. In agreement with our findings that C1q is anti-inflammatory, we found that C1q-ICs specifically induced inhibitors of the NFKB, MAPK and Syk signaling pathways >1.5 fold compared to ICs alone. SLE ICs also upregulated the activation markers CD86 and CD40 on CD14+ monocytes within both PBMCs and monocytes or when using purified monocytes, ICs were significantly less stimulatory (P<0.01) despite the fact that C1q strongly promoted binding to, and endocytosis of ICs, by monocytes.

Conclusions: (1) In the absence of pDCs, SLE ICs are remarkably inefficient at stimulating PBMCs or isolated monocytes. (2) The presence of C1q in SLE ICs significantly downregulates the expression of 40 ISGs in both PBMCs and monocytes. (3) The presence of C1q in SLE ICs also alters the expression of genes that may impact inflammation through modulation of the NFKb, MAPK and Syk signaling pathways. 

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Meta-Analysis of Autoimmune Variants Shared between Systemic Lupus Erythematosus (SLE) and 16 Other Diseases Identifies Novel SLE Loci

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The clustering of multiple autoimmune disorders (ADs) in families is well known. Nevertheless, evidence of specific shared variants is sparse, and consequently the genetic mechanisms that may explain the patterns of disease aggregation remain unclear. This study is aimed at assessing which variants are common and different between SLE and other ADs. As such, we compared the variants reported as associated in genome-wide association studies (GWAS) of ADs to those identified in our large-scale analysis of SLE. We compiled a list with 381 non-MHC variants identified as significant in 49 GWAS of 16 ADs, available at the GWAS catalog (www.genome.gov/gwasstudies). We combined the genotypic and imputed data from three published Caucasian cohorts (total of 1500 cases and 5706 controls) (Seligman et al, 2001; Remmers et al, 2007; Graham et al, 2008; Harley et al, 2008) and performed a joint- and a meta-analysis. When available, we used data from a previously described independent replication cohort of 2085 SLE cases and 2854 controls (Harley et al, 2008). All analyses were adjusted for admixture. Of the 213 SNPs that met quality control criteria, 44 survived a multiple comparisons adjustment with P<0.05 in the joint-analysis. Interestingly, the loci most shared between GWAS of ADs include IL23R, TNFAIP3, PTPN22, IL12B, IL12RA and PFKFB3-PRKCQ. Based on the number of genome-wide significant loci, we observe that SLE shares the most loci with Crohn’s disease (TNFAIP3, ATG5, and 7p12.2), followed by both rheumatoid arthritis (TNFAIP3, BLK, and further dissects the extent of genetic overlap between SLE and other ADs.

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MicroRNA miR-146a, Type I Interferon, and Race in Systemic Lupus Erythematosus


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Background: A few microRNAs (miRNAs) have known gene expression regulatory roles in innate immunity. miR-146, a NFκB regulated transcript, is activated during lipopolysaccharide stimulation of monocytes and is critical in endotoxin tolerance to prevent cellular overstimulation when in excess of the TLR4 ligand. Interestingly, miR-146a has been reported to be upregulated in PBMCs and synovial tissue in rheumatoid arthritis patients but reported downregulated in PBMCs of SLE patients. The aim of the study is to determine whether the repressed expression of miR-146a reported in Chinese SLE can be observed in our US SLE cohort with more diversity in ethnic background.

Methods: Blood samples were collected from 124 SLE patients (European Americans (EA) 48 F, 10 M; African Americans (AA) 41 F, 2 M; Latin Americans (LA) 11 F, 6 M; others 6 F) fulfilling ACR criteria and this included 35 patients with 2 or more collections from multiple visits to our autoimmune center. Total RNA, isolated from leukocytes, was analyzed by Taqman qPCR. miRNA copy number was determined using a standard curve. Expression of Type I Interferon (IFN) and Type II Interferon (IFN) cytokines was also determined. In SLE patients with nephritis but did not reach significance. Correlation of miR-146a level with other clinical parameters including arthritis, pleuritis, panniculitis, lymphopenia etc. did not show statistical significance. When 35 returning patients divided based on changes in miR-146a level comparing the first and the last visit, 11 had increased in miR-146a vs. 17 reduced. In the miR-146a reduced group (p=0.001), Mx1 (p=0.03), Ly6e (p=0.04), OAS1 (p=0.02), IFN score (p=0.02) reduced significantly whereas no significance were found for Mx1 (p=0.16) and Ly6e (p=0.04). The miR-146a increased group (p=0.0003) was more heterogeneous and none of the markers had statistically significant differences.

Conclusions: Comparison in race demonstrate with statistical significance that LA has the lowest level of miRN while AA has the highest. The data show potentially two groups: a miR-146a responsive group where miR-146a may regulate IFN production and a miR-146a resistant group where IFN production appears independent of miR-146a. For SLE patients with decreases...
ing levels of miR-146a in subsequent visit correlating with decreasing IFN score, this may represent the transition from active to remission state. In more active SLE, miR-146a levels most likely represent a balance in continuous IFN stimulation and innate controls as represented by patients with both high IFN score and miR-146a levels.

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Multiple Independent Major Histocompatibility Complex Associations with Nephritis and Autoantibody Production in Systemic Lupus Erythematosus, Sharon A. Chung, Kimberly E. Taylor, Suzanne L. May, Patricia P. Ramsay, Hong L. Quach, Julie A. Lane, Jannine Nititham, Janelle A. Noble, Diana L. Quach, Jennifer A. Kelly, Kathy L. Moser, Timothy W. Behrens, Michael F. Seldin, John B. Harley, Patrick M. Gaffney, Lisa F. Barcellos and Lindsey A. Criswell. Children’s Hospital Oakland Research Institute, Oakland, CA, Genentech, Inc., South San Francisco, CA, Oklahoma Medical Research Foundation, Oklahoma City, OK, Oklahoma Medical Research Foundation, Oklahoma City, OK, Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco, CA, Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco, CA, Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco, CA, University of California, Berkeley, CA, University of California, Davis, CA

Background: The most significant genetic associations with systemic lupus erythematosus (SLE) have been with the major histocompatibility complex (MHC), a gene dense region on chr6p21 spanning >5Mb. Prior attempts to identify MHC associations independent of HLA-DRB1 (the most consistently associated MHC locus) were limited, in part, by the region’s extensive linkage disequilibrium. In addition, MHC associations with SLE manifestations such as nephritis and autoantibody production have not been fully explored. Therefore, we performed high-density single nucleotide polymorphism (SNP) genotyping to identify MHC associations with lupus nephritis, anti-dsDNA, and anti-Ro/La (SSA/SSB) autoantibody production among SLE patients.

Methods: Using the Illumina Combined MHC panel, we genotyped 1,610 SLE cases of European descent for 2,360 MHC SNPs. SLE cases were also genotyped for HLA-DRB1 and 384 ancestry informative markers. Lupus nephritis and autoantibody status was obtained from medical record review. We identified associations with HLA-DRB1 alleles using a relative predispositional effects (RPE) method. Forward selection with conditional logistic regression (CLR) based on haplotypes was used to identify SNPs associated with particular SLE manifestations that were independent of each other and HLA-DRB1.

Results: After applying stringent quality control criteria (including removal of SLE cases with <90% northern European ancestry), we analyzed 1,974 SNPs in 1,125 SLE cases. Thirty-two percent (32%) had lupus nephritis, 50% had anti-dsDNA autoantibodies, and 27% had anti-Ro/La (SSA/SSB) autoantibodies. RPE analysis showed that different HLA-DRB1 alleles were associated with lupus nephritis as compared to anti-Ro/La (SSA/SSB) autoantibody production (rs1501 and rs1502 for nephritis vs. rs9031, rs9041, *rs9040, *rs9041, and *rs9011 for anti-Ro/La). No HLA-DRB1 alleles were significantly associated with anti-dsDNA autoantibody production (global \(\chi^2 p>0.05\)). CLR analysis identified associations independent of HLA-DRB1 in the HLA-DOB, HLA-A/HCG9, and LEMD2 regions with lupus nephritis (OR for the most associated haplotype [ORmax] 3.04, haplotype-specific p [\(p_{\text{max}}\) 3.04]), HLA-DRB1-independent associations were observed in the HLA-DPA1/HLA-DQA1, C6orf10, and OR21 regions with anti-Ro/La (SSA/SSB) autoantibody production (OR 3.23, \(p_{\text{max}}=1.6E-08\)). SNPs in or near TAP2, C6orf10, and TRIM40/TRIM15 were associated with anti-dsDNA autoantibody production (OR 2.82, \(p_{\text{max}}=1.5E-08\)).

Conclusions: We have identified several significant MHC associations with lupus nephritis and autoantibody production that are independent of HLA-DRB1. Of interest, different genes/genetic regions were associated with these specific SLE manifestations. These results indicate that MHC genetic variation contributes significantly to disease heterogeneity in SLE.

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NK Cells Regulate the IFN-α Production by Plasmacytoid Dendritic Cells Via Soluble Factors and Cell-Cell Contact, Niklas Hagberg, Olof Berggren, Gunnar V. Alm, Maija-Leena Eloranta and Lars Rönnblom. Department of Biomedical Sciences and Veterinary Public Health, Swedish University of Agricultural Sciences, Uppsala, Sweden, Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Background: Overactivation of the type I IFN system has been demonstrated in patients with SLE and several other autoimmune diseases. We previously showed that the IFN-α production by pDCs stimulated with RNA-containing immune complex (RNA-IC) was regulated by NK cells and monocytes. NK cells enhanced the IFN-α production, while monocytes inhibited the NK cell stimulation of pDCs. The suppressive effect of monocytes was largely due to ROS, PGE2 and TNF-α, while the mechanisms for NK cell enhancement were hitherto unknown.

Objective: This study was performed to investigate the mechanisms whereby NK cells promote the IFN-α production by RNA-IC-stimulated pDCs. Furthermore, NK cells from SLE patients were also investigated for their capacity to enhance the IFN-α production.

Methods: pDCs and NK cells were isolated from PBMCs of healthy blood donors or SLE patients and stimulated with RNA-IC consisting of purified U1 snRNA and IgG from an SLE patient. Concentrations of IFN-α and 16 other cytokines in cell culture supernatants from pDCs, NK cells or cocultivations of NK cells and pDCs were determined using single or multiplex immunoassays.

Results: Soluble factors which could enhance the IFN-α production from RNA-IC-stimulated pDCs were produced after FcγRIII-ligation or IL-12/IL-18 stimulation of NK cells. MIP-1α (CCL3), MIP-1β (CCL4), RANTES (CCL5), IFN-γ and TNF-α were found in the cell culture supernatants from FcγR-stimulated NK cells and MIP-1β was identified as partially responsible for the NK cell-mediated increase in IFN-α production. In addition, cell-cell contact via LFA-1 also contributed to the NK cell enhancement of IFN-α production by pDCs. When NK cells and pDCs were co-cultivated, the production of several other cytokines implicated in the pathogenesis of SLE, e.g. IL-6, IFN-γ and TNF-α, were also increased. NK cells from SLE patients and healthy blood donors were compared for their ability to promote the RNA-IC induced IFN-α production by pDCs. SLE NK cells were less stimulatory compared to NK cells from healthy blood donors when co-cultivated with pDCs and RNA-IC (p<0.004). However, addition of IL-12/IL-18 made the SLE NK cells as efficient as NK cells from healthy blood donors in enhancing the IFN-α production by pDCs.

Conclusions: This study describes novel mechanisms involved in the cross-talk between NK cells and pDCs which regulates the production of IFN-α. Both soluble factors such as MIP-1β and cell-cell-contact between NK cells and pDCs via LFA-1 were found to promote the IFN-α production. In addition, the regulatory function that NK cells exert on pDCs is altered in SLE patients. These results are of importance for understanding molecular mechanisms behind the increased IFN-α production in several autoimmune diseases and also indicate new potential therapeutic targets.

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Novel Fc gamma Receptor 3B Gene (FCGR3B) Allele Variants and Polymorphism Distribution in Brazilian Systemic Lupus Erythematosus Patients and Blood Bank Donors, Viviane C. Santos, Marcelle Grecco, Kaline M. C. Pereira, Luís E. C. Andrade and Neusa P. Silva. Universidade Federal de São Paulo, São Paulo, Brazil, Universidade Federal de São Paulo, Brazil

Background: Immunocomplex (IC) deposition is a characteristic feature of systemic lupus erythematosus (SLE) and several pieces of evidence point towards an inefficient IC clearance in SLE. Fc gamma receptors (FcγR) are involved in the uptake and degradation of ICs by a variety of cells. FcγRIIa, FcγRIIb, FcγRIIIa and FcγRIIIb are polymorphic in humans and some alleles have been associated with SLE susceptibility. The FcγRIIIb gene (FCGR3B) presents three alleles, HNA-1b and HNA-1c, characterized by specific nucleotides at six different positions in the 3rd exon.

Objectives: to determine FCGR3B polymorphic distribution and describe novel allele variants present in SLE patients and blood bank donors, in Sao Paulo, Brazil

Patient and Methods: peripheral blood was obtained from 260 consec-
utive SLE patients, attending the outpatient clinic of the Rheumatology Division at Universidade Federal de Sao Paulo, and from 246 ethic-matched blood bank donors in Sao Paulo, Brazil. All individuals signed the informed consent approved by the Institutional Ethics Board. DNA was extracted by salting out and a 243bp sequence containing the polymorphic region of interest of the 3rd exon of FCGR3B was amplified by PCR. All samples were sequenced and processed in capillary gel electrophoresis (ABI 3130xl).

Results: Among SLE patients we found 52 homozygous for HNA-1a, and 208 heterozygous (188 HNA-1a/HNA-1b and 20 HNA-1a/HNA-1c). Among blood donors, HNA-1a homozygosis was found in 56, and heterozygosis in 190 (170 HNA-1a/HNA-1b and 20 HNA-1a/HNA-1c). Novel allelic variants (one HNA-1a and three HNA-1b) were also found. Point mutations, previously described in nucleotides not related to allelic discrimination (G230T, A249G, and G330T) were observed in both SLE (57) and blood bank donors (60). In addition we also identified 22 new point mutations in 76 SLE patients and 21 in blood bank donors. There was no statistical difference between groups regarding genotype or phenotype distribution. Interestingly, homozygous individuals for the HNA-1b allele were not found in the population under study.

Conclusions: There was no association of FCGR3B gene polymorphism and SLE. Our results indicate that FCGR3B is a highly polymorphic gene possibly due to the existence of either somatic recombination or hyper mutation within this gene segment.

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Purpose: To the up-regulation of Cbl-b. To be due to a NKT cell dysfunction rather than to an abnormality in controls (n-transcription-polymerase chain reaction, and cytokine secretion by multiple systemic lupus erythematosus (SLE) and to investigate the clinical relevance of these findings.

Methods: Serial samples were obtained from 23 pediatric controls and patients with SLE (20 samples during active disease, SELENA SLEDAI score >4, and 37 during remission). PD-L1 expression on CD11c+/CD14+ monocytes was assayed in cultured peripheral blood cells by flow cytometry. Cytokines in culture supernatants were assayed by multiplex ELISA. Area under the curve (AUC) measurements of non-parametric receiver operating characteristic (ROC) curves were used to compare the ability of PD-L1 expression to distinguish between subject groups.

Results: PD-L1 expression on healthy control monocytes was 2.7-fold higher than patients with active disease (mean induction ± SD 27.8 ± 20.4, 95% confidence interval (CI) 20.4–35.3 versus 10.5±11.4, 95% CI = 5.2–15.8, p<0.005). SLE patients in remission expressed normal levels of PD-L1 on monocytes (mean 24.2±16.5, 95% CI = 16.5–31.8, p<0.0005 versus active SLE). PD-L1 surface expression was induced on a mean of 80% of healthy Mo, whereas fewer Mo from patients with active SLE expressed PD-L1 (mean 52%, p=0.00063). ROC curves demonstrated how well PD-L1 expression distinguished between active and inactive disease (AUC 0.75) and between active SLE and healthy controls (AUC 0.79). Patients with renal SLEDAI criteria had a two-fold increase in PD-L1 expression on Mo compared to those without renal disease (p=0.01), but no correlation was detected with other clinical characteristics. PD-L1 expression on active SLE Mo could be restored by normal T cells or by supernatant from healthy cells producing IL-10 and/or TNF-α. Both IL-10 and TNF-α secretion correlated with PD-L1 expression, and either cytokine could restore PD-L1 expression on SLE Mo. Conversely, SLE cells over-produced TGF-β, and PD-L1 expression on healthy Mo was suppressed by TGF-β.

Conclusions: During an inflammatory response patients with SLE may be lacking a key step to limit autoreactive lymphocyte activity: the local, cytokine-mediated induction of PD-L1 expression on antigen presenting cells. Moreover, therapeutic agents that inhibit TNF-α may induce autoantibodies in part by preventing PD-L1 induction, thereby impeding an important mechanism of T and B lymphocyte regulation. Infection and other autoimmune diseases may potentially be distinguished from active SLE on the basis of monocye PD-L1 expression.

Disclosure: A. M. Stevens: None; J.-N. Ou: None; A. Wiedeman: None.

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RFX1 Regulates CD70 and CD11a Expression by Recruiting the Histone Methyltransferase SUV39H1 in Lupus T Cells.

Ming Zhang, Xiaoyan Wu, Fei Gao, Qing Zhang, Heng Yin and Qianjin Lu. Second Xiangya Hospital, Central South University, Changsha, China

Background: Methylation of histone H3 lysine 9 (H3K9) represses gene expression. H3K9 is hypomethylated in CD4+ T cells from systemic lupus erythematosus (SLE) patients, resulting in de-repression of genes involved in promoting autoimmune responses. However, the mechanism leading to H3K9 hypomethylation is unclear. The transcription factor RFX1 normally recruits DNMT1 and HDAC1 in CD4+ T cells but is down-regulated in SLE CD4+ T cells, leading DNA methylation and histone acetylation and leading to the overexpression of the auto-immune related genes CD70 and CD11a. In this study we measured the methylation of H3K9 at the CD70 and CD11a loci in SLE CD4+ T cells and investigated the involvement of RFX1 in H3K9 hypomethylation.

Methods: Peripheral blood monocytes (PBMCs) from 20 patients with SLE and 20 healthy controls were isolated by Ficoll-Hypaque density gradient centrifugation. CD4+ T cells were isolated by positive selection using CD4 beads (Milteny, Bergisch Gladbach, Germany; purity was generally higher than 95%), and cultured in human T cell culture medium (Lonza, Walkersville, MD, USA). H3K9 tri-methylation levels at the CD70 and CD11a promoters were detected by chromatin immunoprecipitation (ChIP) and realtime PCR. SUV39H1 expression level was assessed by Western blot. Interactions of RFX1 with SUV39H1 and G9a were examined.

Purpose: Programmed death ligand 1 (PD-L1) plays an important role in controlling autoreactive and follicular T helper lymphocytes, thus preventing autoimmune disease. Induced by inflammatory cytokines, PD-L1 is reportedly elevated on monocytes from patients with infections and rheumatoid arthritis, but is poorly expressed on Mo from SLE patients with active disease. Our goal was to define the mechanism for PD-L1 dysregulation in pediatric patients with SLE, and to clinically characterize those patients with loss of PD-L1.

Methods: Serial samples were obtained from 23 pediatric controls and patients with SLE (20 samples during active disease and 37 during remission). PD-L1 expression on CD11c+/CD14+ monocytes was assayed in cultured peripheral blood cells by flow cytometry. Cytokines in culture supernatants were assayed by multiplex ELISA. Area under the curve (AUC) measurements of non-parametric receiver operating characteristic (ROC) curves were used to compare the ability of PD-L1 expression to distinguish between subject groups.

Results: PD-L1 expression on healthy control monocytes was 2.7-fold higher than patients with active disease (mean induction ± SD 27.8 ± 20.4, 95% confidence interval (CI) 20.4–35.3 versus 10.5±11.4, 95% CI = 5.2–15.8, p<0.005). SLE patients in remission expressed normal levels of PD-L1 on monocytes (mean 24.2±16.5, 95% CI = 16.5–31.8, p<0.0005 versus active SLE). PD-L1 surface expression was induced on a mean of 80% of healthy Mo, whereas fewer Mo from patients with active SLE expressed PD-L1 (mean 52%, p=0.00063). ROC curves demonstrated how well PD-L1 expression distinguished between active and inactive disease (AUC 0.75) and between active SLE and healthy controls (AUC 0.79). Patients with renal SLEDAI criteria had a two-fold increase in PD-L1 expression on Mo compared to those without renal disease (p=0.01), but no correlation was detected with other clinical characteristics. PD-L1 expression on active SLE Mo could be restored by normal T cells or by supernatant from healthy cells producing IL-10 and/or TNF-α. Both IL-10 and TNF-α secretion correlated with PD-L1 expression, and either cytokine could restore PD-L1 expression on SLE Mo. Conversely, SLE cells over-produced TGF-β, and PD-L1 expression on healthy Mo was suppressed by TGF-β.

Conclusions: During an inflammatory response patients with SLE may be lacking a key step to limit autoreactive lymphocyte activity: the local, cytokine-mediated induction of PD-L1 expression on antigen presenting cells. Moreover, therapeutic agents that inhibit TNF-α may induce autoantibodies in part by preventing PD-L1 induction, thereby impeding an important mechanism of T and B lymphocyte regulation. Infection and other autoimmune diseases may potentially be distinguished from active SLE on the basis of monocye PD-L1 expression.

Disclosure: A. M. Stevens: None; J.-N. Ou: None; A. Wiedeman: None.
by immunoprecipitation (IP). RFX1 expression and shRNA constructs were transfected into CD4+ T cells using Human T cell Nucleofector kits (Lonza, Walkersville, MD, USA).

**Results:** Compared with healthy controls, the tri-methylation levels of H3K9 at the CD70 and CD11a promoters were lower in SLE CD4+ T cells (p < 0.05). The protein level of the histone methyltransferase SUV39H1 was not different between SLE patients and healthy controls (p > 0.05). However, SUV39H1 was found to bind to the promoters of CD70 and CD11a. RFX1 immunoprecipitated with SUV39H1, but not G9a, in CD4+ T cells and lupus CD4+ T cells transfected with RFX1 exhibited an increase of H3K9 tri-methylation levels and decreased expression of CD70 and CD11a. In contrast, knocking down RFX1 expression by using RNAi down-regulated H3K9 tri-methylation levels at the CD70 and CD11a loci and activated their transcription in normal CD4+ T cells.

**Conclusions:** RFX1 recruits SUV39H1 to the promoters of the auto-immune related genes CD70 and CD11a in CD4+ T cells, and down-regulation of RFX1 contributes to H3K9 hypomethylation leading to CD70 and CD11a overexpression in SLE CD4+ T cells.

**Disclosure:** M. Zhao: None; X. Wu: None; F. Gao: None; Q. Zhang: None; H. Yin: None; Q. Lu: None.

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**The HLA Haplotype DQA1*, DQB1*, DR4- Identifies Lupus Patients in Whom Anti-dsDNA Titers Correlate with Disease Activity.** Mikhail Offeriev1,* Kyriakos A. Kirou1, Dorthe Lundsgaard3, Klaus S. Frederiksen3, Jan Fleckner1 and Mary K. Crow1. 1Hospital for Special Surgery, New York, NY, 2Novo Nordisk, 3Novo Nordisk, Denmark, 4Novo Nordisk, Copenhagen, Denmark

**Objective:** Anti-dsDNA titers are used by rheumatologists to assist in disease activity assessment of SLE patients. However, anti-dsDNA titers do not always correlate with disease activity. In this study we explored whether SLE patients with anti-dsDNA titers that parallel disease activity [based on SELENA SLEDAI (SS) score] differ in their PBMC transcriptional profile compared to other SLE patients.

**Methods:** Longitudinal PBMC and plasma samples were obtained over an average 6 visits (2-12) from 23 SLE patients and 5 healthy donors (HD). The duration of study follow-up for individual patients varied from 197 to 812 days. Plasma levels of autoantibodies were evaluated using the Multi-Analyte Profiling (MAP) technology (Rules-Based Medicine, Austin, TX). PBMC transcriptional profiles for each visit were established using Human Genome U133 Plus 2.0 Arrays.

**Results:** Microarray data analysis revealed 566 differentially expressed transcripts comparing HD samples versus samples of SLE patients during mild/moderate or severe SELENA SLEDAI flares, or those without a flare (ANNOVA FC<2.0, p<0.05). From 44 tested autoantibodies 14 were significantly correlated with SLE activity and DTSS in HD patients (p<0.05; and >1.5). Eight autoantibodies, including anti-dsDNA, correlated weakly with disease activity based on SS. Nine patients showed high levels of anti-dsDNA autoantibody. Comparative analysis of transcripts between anti-dsDNA positive and negative patients identified 136 differentially regulated transcripts (FC>1.5 and p<0.05). Comparative analysis of those transcripts and autoantibody titer showed that anti-dsDNA autoantibodies correlated with multiple interferon signature genes and granulocyte markers (LTF, CEACAM6, MPO, and MMP9). Five SLE patients (22%) showed a strong correlation of anti-dsDNA titer and SS score (R=0.9; p<0.001). Comparative analysis of transcripts in those individuals compared with the other lupus patients identified 38 transcripts (FC>1.5; p<0.05). Of interest, the anti-dsDNA patients were all positive for HLA alleles DQA1, DQB1 and negative for DR4, in contrast to variable alleles for the rest of the patients (Fisher’s test p<0.01).

**Conclusion:** SLE patients showing strong correlation of anti-dsDNA titers and disease activity have a distinct MHC class II haplotype. This observation, if confirmed, may help to identify SLE patients in whom anti-dsDNA titers are helpful in management of disease. This genetic background may favor skewing of the autoimmune response toward certain dsDNA epitopes that are particularly pathogenic.


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**The Integrity of Double Strand Break Repair in Pediatric Systemic Lupus Erythematosus Cells.** Robert C. Davies2, Kelly Pettitjohn2, Francesca Fike2, Jixi Wang2, Shareef A. Nahas3, Richard A. Gatti3 and Deborah K. McCurdy1. 1Mattel Children’s UCLA-Rheumatology, Los Angeles, CA, 2UCLA-Pathology and Laboratory Medicine, 3UCLA-Pathology and Laboratory Medicine; Human Genetics

**Introduction:** Our laboratory previously demonstrated a delay in single strand break (SSB) processing in cells from pediatric patients with systemic lupus erythematosus (SLE). Because SSBs are often converted to double strand breaks (DSBs) at the replication fork and some DSB repair proteins are immunogenic in SLE, i.e., DNA ligase IV, Ku 70/80, DNAPKCs, and XRCC4, we assessed the integrity of DSB recognition, signaling, and repair mechanisms in B-lymphoblastoid cell lines (LCLs) derived from pediatric and adolescent patients with SLE. This study assesses the integrity of DSB recognition, signaling, and repair mechanisms in LCLs derived from 16 pediatric and adolescent patients with SLE (pSLE).

**Methods:** Lymphoblastoid cell lines (LCLs) were established from the whole blood of 16 pSLE patients. Eight assays were used to assess four major pathways of repair of DSBs in pSLE LCLs. The assays included: (i) γ-H2AX and (ii) 53BP1 IR-induced nuclear foci (IRIF); (iii) immunoblot analysis of the kinetics of IR-induced phosphorylation of Structural Maintenance of Chromosomes 1 (SMC1); (iv) a DNA ligation assay to evaluate the NHEJ (γ) neutral comet assay (v) monoubiquitination of FANCD2 (vii) flow cytometry to assess the S-phase checkpoint; and (viii) colony survival assay as a measure of general radiosensitivity.

**Results:** Three of eight assays showed abnormal patterns of response to IR-induced DNA damage in some patients: 1) pSMC1 kinetics were intermediate in four patients, suggests defective repair, 2) the neutral comet assay was abnormal in half of the cells, showing delayed DSB repair, 3) colony survival assay showed radiosensitivity in half of the cell lines tested. We also observed reduced DNA PKcs, Ku70 and Ku80 proteins in one pSLE patient.

**Conclusion:** Our data suggest that DSB repair is compromised in pSLE LCLs as shown in the broad-based DSB repair assays (neutral comet assay, colony survival assay). This contrasts with results from our functional assays (γ-H2AX, 53BP1, NHEJ, FANCD2 monoubiquitination, S-phase checkpoint), which all appear normal. Although the majority of SLE cell lines exhibited DSB repair defects, the etiology of this remains unclear.

**Disclosure:** R. C. Davies: None; K. Pettitjohn: None; F. Fike: None; J. Wang: None; S. A. Nahas: None; R. A. Gatti: None; D. K. McCurdy: None.

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**The Lupus Africa to US Gradient Revisited—Genetic Versus Environmental Factors in Lupus.** Gary S. Gilkeson1, Diane L. Kamen1, Natasha M. Ruth1, Anna Meyer2 and Darriss Maggi2. 1Med Univ of South Carolina, Charleston, SC, 2MUSC, 3MUSC, Charleston, SC, 4MUSC PO Box 250637, Charleston, SC, 5West Africa Fistula Foundation

**Background:** The Africa to US Lupus Gradient is a widely held belief that lupus is rare in west Africa while common in African Americans. This belief is based on limited assessments in Africa. If true, this gradient would provide novel insight into the genetic versus environmental causation of lupus. Assessing true lupus prevalence in west Africa is impossible at present, we therefore sought to assess prevalence of “autoimmunity”, i.e. positive autoantibodies, in lupus unaffected.

**Methods:** Two unique cohorts were utilized for this study: the Gullah population in South Carolina and comparator patients of the West Africa Fistula Foundation in Sierra Leone. Sierra Leone is the ancestral home of the Gullah. All individuals were screened by history and exam to exclude lupus and SLE in a family member. The cohorts are all female and matched for age. Serum was obtained and autoantibody prevalence, viral seropositivity and vitamin D levels tested to assess autoimmunity prevalence and potential environmental factors implicated in lupus. ANA was done by Hep2 IFA, ACL by ELISA, anti-DNA by Cithidida and ENA by Ocherlonry. Viral seroconversion was tested by standard ELISAs.

**Results:** A trend towards decreased ANA positivity that was not significant in the Sierra Leonians was found (Table). A marked increase in APL positivity was found in the Sierra Leonians, with no difference in antibodies against dsDNA, Sm, or RNP. Sierra Leonians had significant increased seropositivity for EBV, CMV, HSV1 and HSV2. In addition there was a significant difference in serum 25OH vit D with a mean of 11ng/ml in the Gullah and 36ng/ml in the Sierra Leonians. There was a trend towards lower
vitamin D levels in the Sierra Leoneans who were ANA+ >1/120 (mean 32 for ANA+ and 37 for ANA-). There were only three Sierra Leoneans that were seronegative for CMV/EBV and they were ANA-.

Conclusions: Overall, there is a trend towards higher ANA reactivity in the Gullah, while ACL positivity is markedly higher in the Africans, possibly related to infections. Thus, autoimmunity is not significantly less common in Africans; differences in the prevalence of clinical lupus remain to be determined. There is a significant difference in environmental factors implicated in lupus including viral seropositivity and vitamin D levels. Further studies are needed to assess the lupus gradient hypothesis and the potential role of environmental factors in disease development.

Disclosure: G. S. Gilkeson: None; D. L. Kamen: None; N. M. Ruth: None; A. Meyer: None; D. Maggi: None.

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The Variant of MHC Class I Polypeptide-Related Sequence (MICA) is a Genetic Risk Factor for SLE Independent of HLADCRI and Modulates the Behavior of NK Cell Via NKG2D Receptor.

Kohsuke Yoshida1, Koichiro Komai2, Kazuko Shiozawa7, Aya Mashida2, Takahiko Horiuchi6, Yuki Tanaka4, Masato Nose5, Akira Hashiramoto3 and Shunichi Shiozawa3.

1Dept. of Biophysics, Kobe Univ. Graduate School of Health Sciences, Kobe, Hyogo, Japan, 2Dept. of Biophysics, Kobe Univ. Graduate School of Health Sciences, Kobe, Japan, 3Dept. of Biophysics, Kobe Univ. Graduate School of Health Sciences/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hosp., Kobe, Japan, 4Dept. of Clinical Immunology, Rheumatology, and Infectious Diseases, Kyushu Univ., Fukuoka, Japan, 5Dept. of Pathogenomics, Ehime Univ. Graduate School of Medicine, Ehime, Japan, 6Div. of Genome Analysis, Medicine Institute of Bioregulation, Kyushu Univ., Fukuoka, Japan, 7Rheumatic Diseases Center, Konan-Kakogawa Hosp., Kakogawa, Japan

Purpose: MIC (MHC class I polypeptide-related sequence) molecules interact with NKG2D (natural-killer group 2, member D) and stimulate NK cell-mediated cytotoxicity against K562 cells more strongly than those with the most prevalent non-disease-associated MICA 129Val allele (P < 0.05 and P < 0.01, respectively). These findings are consistent with previous findings showing that NK cell cytotoxicity is significantly decreased in SLE. Interestingly, we also observed that the 129Met/A9 protein enhanced the release of IFNγ from NK92MI cells as compared with 129Val/A5 protein (P < 0.01), possibly because MICA 129Met variant has been shown to be higher affinity to the NKG2D receptor than the 129Val variant.

Conclusion: The MICA polymorphism is genetically associated with SLE independent of HLADCRI1*1501, and MICA appears to contribute to the pathogenesis of SLE by modulating NK cell function.

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ACR Poster Session A

Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment I

Monday, November 8, 2010, 9:00 AM-6:00 PM

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Acute anterior uveitis in ankylosing spondylitis: clinical characteristics and impact of biologic therapy.

Nai Lee Lui1, Finbar (Barry) D. O’Shea2, Hua Shen3, Richard J. Cook4 and Robert D. Inman2.

1Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, 2Department of Statistics and Actuarial Science, University of Waterloo, Canada, 3St James’s Hospital, Dublin, Ireland, 4Toronto Western Hospital, Toronto, ON, Canada

Objective: To describe the characteristics of acute anterior uveitis (AAU), impact of biologic therapy on the incidence of AAU and to identify predictors of AAU flare in an ankylosing spondylitis (AS) prospective longitudinal cohort.

Methods: We conducted a retrospective study of all AS patients developing AAU in a longitudinal AS cohort. All patients met the modified New York criteria for AS. Demographics and clinical characteristics (age of AS and AAU onset, HLA-B27 status) were recorded. Recurrence rates and impact of anti-TNF therapy were evaluated. Logistic regression analysis was used to determine predictors of AAU flare.

Results: Among the 464 AS patients, 132 patients with history of AAU were evaluated (28.4%). The mean age at onset of AAU was 31.7 years, higher than the age of AS onset (22.5) and diagnosis of AS (30.2) respectively. 10.2% (N = 9) of patients developed AAU prior to the onset of AS symptoms, with a mean of 2.9 ± 2.4 years; while 77.3% (N = 68) developed AAU after a mean of 11.5 ± 6.4 years following the onset of AS symptoms. There was no difference in the occurrence of AAU in male or female patients (p = 0.19), 88.6% (N = 109) of patients with AAU were associated with the HLA-B27 gene (OR 2.39, p = 0.01). AS patients with history of AAU had more frequent enthesitis (p = 0.024) but did not appear to require more anti-TNF therapy compared to AS patients without AAU (54.3% versus 45.1%; p = 0.47). Following the commencement of anti-TNF, the AAU flare rate was 3.69 flares per 100 patient-yr compared to 15.72 flares per 100 patient-yr in AS patients who were treated with non-steroidal anti-inflammatory drugs (NSAIDs). There was no differential association with any particular biologic agent in 12 patients who developed AAU while on anti-TNF therapy. There was no correlation of immunosuppressive AS disease activity (ESR, CRP, BSAID or BASFI scores) at the time of AAU flares.

Conclusion: HLA-B27 is a strong predictor of AAU in AS patients. Higher incidence of enthesitis in AAU patients may suggest a potential similarity in the underlying pathogenic process between the two sites. Biologic therapy reduced the incidence of AAU. The incidence of AAU flare while on anti-TNF therapy is low and did not correlate with AS disease activity.

Disclosure: N. L. Lui: None; F. D. O’Shea: None; H. Shen: None; R. J. Cook: None; R. D. Inman: None.
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Ankylosing Spondylitis: High Frequency of Varioceole Associated with Teratozoospermia. Lucia A. Nukumizu, Carla G. S. Saad, Breno P. de Almeida, Joêlório F. Carvalho, Marcello Cocuzza, Césio R. Gonçalves, Osmar Saito, Elcio Bonfa and Cleovis A. A. Silva. 1. Department of Radiology - Faculdade de Medicina da Universidade de São Paulo, Brazil, 2Department of Urology - Faculdade de Medicina da Universidade de São Paulo, Brazil, 3Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, 4Pediatric Reumatology Unit, Faculdade de Medicina da Universidade de São Paulo, Brazil, 5Rheumatology Division - Faculdade de Medicina da Universidade de São Paulo, Brazil

Purpose: To testicular function in male ankylosing spondylitis (AS) patients and controls.

Methods: 20 consecutive post-pubertal AS patients (modified New York criteria) were prospectively assessed for demographic data, urologic examination, testicular Döpppler ultrasound (US), standardized semen analysis according to World Health Organization (WHO) guidelines and Kruger strict criteria, and anti-sperm antibodies. Selection criteria never under biological agents were included; sulfasalazine and methotrexate wash-out period of at least 3 months and no restriction to the use of non-steroidal anti-inflammatory drugs and/or low dose prednisone (≤10 mg/day). The evaluation of AS included: clinical features, laboratory exams, treatment and scores (BASDAI, BASFI, BASMI and BASRI). The control group consisted of 24 male healthy subjects.

Results: The median of current age was similar in AS and controls (31.5(23–44) vs. 34(17–53) yrs, p = 0.353). The frequencies of left or bilateral varicoceles by clinical examination and by US were significantly higher in AS patients compared to controls (30% vs. 4%, p = 0.035; 40% vs. 8%, p = 0.027). Likewise, the median of vein diameters of pampiniform plexus in left testicles were significantly higher in AS patients versus controls (0.25(0.16–0.49) vs. 0.2(0.2–0.37) cm, p = 0.009). Of note, the median of normal sperm forms by Kruger strict criteria was significantly lower in AS patients versus controls (3.25(0–14.5) vs. 6.75(0–18), p = 0.035) and the frequency of teratozoospermia (abnormal sperm morphology) was significantly higher (55% vs. 8% p = 0.0001). Reinforcing these findings, the median of normal sperm morphology by WHO guidelines was significantly lower in AS patients with ultrasonographic varicoceles compared to patients without varicoceles [13.5(2–27) vs. 22(10–32.5)%], p = 0.049]. In addition, the median of normal sperm morphology by WHO guidelines and by Kruger strict criteria were alike in AS patients versus controls without ultrasonographic varicoceles (p > 0.05). No differences were observed in penis median length and circumference in AS patients and controls, and testicular (left and right) by way of US in both groups (p > 0.05). The median and frequencies of other parameters of sperm analysis and anti-sperm antibodies were comparable (p > 0.05) in AS patients and controls. The demographic data, clinical findings and laboratory exams were also similar in AS patients with ultrasonographic varicoceles compared to patients without varicoceles (p > 0.05), likewise test median of BASDAI (4.2(1.66–6) vs. 3.95(1.04–6.8), p = 0.899), BASFI (4.0(1.4–7.79) vs. 3.770(8.41), p = 0.819), BASMI (4.5(0–7) vs. 6(0–8), p = 0.486) and BASRI (9(6–16) vs. 10(5–16), p = 0.463).

Conclusions: This is the first demonstration that AS patients have a high frequency of varicoceles associated with isolated teratozoospermia. Further studies are necessary to determine if oxidative stress may underlie this testicular dysfunction in AS, since high levels of reactive oxygen species were reported to have a harmful effect in sperm quality of men with varicocele.


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Background: Obesity may induce a low-grade chronic inflammatory state. Adipocytes are involved in the recruitment and activation of macrophages, which produce TNF-alpha, IL-6, and IL-12. Studies have also shown an association between body mass index (BMI) and psoriatic arthritis and osteoarthritis of the hand joints. Psoriatic arthritis (PsA) patients have a significantly higher mean BMI and prevalence of obesity compared to osteoarthritis of the hand joints. PsA patients have a significantly higher mean BMI and prevalence of obesity compared to population-based means. Therefore, we hypothesized that there may be an association between BMI and PsA disease activity.

Methods: We selected patients with PsA from the CORRONA database for a cross-sectional study. BMI was presented as a categorical and continuous variable. Patients were categorized into quartiles by weight including “Normal Weight” (BMI < 25), “Overweight” (BMI 25 < 30), “Obese” (BMI 30 < 40), and “Morbidly Obese” (BMI > 40). Our primary outcomes were 28 tender joint count (TJC) and 28 swollen joint count (SJC). The secondary outcomes were physician global assessment of disease activity (PGA), physician global assessment of skin involvement (PGLI), mHAQ, ESR, and CRP. We used Poisson regression models to investigate associations as relative risks between BMI categories and tender and swollen joint counts. Generalized estimating equations, employing a robust sandwich estimator for the variance of the beta weights, were used to assess the associations expressed as beta weights for secondary outcomes of interest.

Results: 1980 patients with PsA were identified from the CORRONA registry. 781 participants had ESR values and 593 individuals had CRP values. The majority of the patients had between 1 and 5 tender joints (80%) and between 1 and 5 swollen joints (82%). ESR in the obese quartile was 6 mm/h higher than the normal weight quartile and almost 10 mm/h higher in the morbidly obese quartile.

Table 1. Association between weight quartiles and tender joint count (TJC) and swollen joint count (SJC). Data are presented as relative risk (RR) per 1 joint increase with 95% confidence interval (CI). Normal Weight quartile (n = 344) serves as the reference group.

<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>Overweight (n = 636)</th>
<th>Obese (n = 702)</th>
<th>Morbidly Obese (n = 298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJC</td>
<td>1.00 (CI 0.81–1.24)</td>
<td>1.35 (CI 1.10–1.65)</td>
<td>1.53 (CI 1.22–1.93)</td>
</tr>
<tr>
<td>SJC</td>
<td>1.01 (CI 0.82–1.26)</td>
<td>1.30 (CI 1.06–1.60)</td>
<td>1.59 (CI 1.26–2.00)</td>
</tr>
</tbody>
</table>

Table 2. Association between weight quartiles and physician global assessment of disease activity (PGDA), physician global assessment of skin involvement (PGSI), mHAQ, ESR, and CRP. Normal Weight quartile (n = 344) serves as the reference group.*

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Overweight (n = 636)</th>
<th>Obese (n = 702)</th>
<th>Morbidly Obese (n = 298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGDA</td>
<td>2.1339 (SE 1.2690)</td>
<td>4.2249 (SE 1.2570)</td>
<td>5.9451 (SE 1.5377)</td>
</tr>
<tr>
<td>PGSI</td>
<td>0.1544 (SE 0.0632)</td>
<td>0.3077 (SE 0.0638)</td>
<td>0.3103 (SE 0.0778)</td>
</tr>
<tr>
<td>mHAQ</td>
<td>0.0218 (SE 0.0235)</td>
<td>0.1230 (SE 0.0244)</td>
<td>0.2020 (SE 0.0327)</td>
</tr>
<tr>
<td>ESR</td>
<td>0.2730 (SE 1.6003)</td>
<td>6.0946 (SE 1.7701)</td>
<td>9.6867 (SE 2.1573)</td>
</tr>
<tr>
<td>CRP</td>
<td>0.8044 (SE 1.0156)</td>
<td>0.7853 (SE 0.7853)</td>
<td>2.1585 (SE 1.5958)</td>
</tr>
</tbody>
</table>

* The beta weight expresses the rate of change in the outcome for the column BMI quartile vs. the Normal Weight quartile.

Conclusion: BMI > 30 was strongly associated with a higher disease activity in patients with PsA. This association may be the result of the induction of inflammation by adipose tissue as we found a positive relationship between ESR and obesity. There is presently limited recognition of this relationship amongst clinicians. Expanded investigations of the biologic factors associated with obesity and disease activity are needed in patients with Psoriatic arthritis.

Disclosure: E. Eberle: Amgen Inc., 1, 9; E. Knight: None; D. A. Raddatz: Abbott Immunology Pharmaceuticals, 8, Roche, 8, Takeda Pharmaceuticals North America, 8; S. Messing: None; G. Reed: Corrona, 5; J. D. Greenberg: Corrona, 5; J. M. Kremer: Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, Centocor Ortho Biotech Inc., 2, 5, Corrona, 9; UCB, Inc., 2, 5.

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Can We Discontinue Anti-TNF Therapy in Patients with Ankylosing Spondylitis and Remission? A Systematic Literature Review. Miguel A. Abad1, Ana M. Ortíz2, Estíbaliz Loza3, Juan A. Martínez Lopez2, María P. Rosario1 and Loreto Carmona1. 1Fundación Española de Reumatología, Madrid, Spain, 2Hospital Universitario de la Princesa, Madrid, Spain, Spain, 3Rheumatology Unit, Hospital Virgen del Puerto, Plasencia, Spain, Spain, 4Fundación Española de Reumatología, Madrid, Spain, 5Military Hospital, Division of Rheumatology, Bogota, Colombia, 6Military Hospital, Division of Rheumatology, Bogota, Colombia, 7Military Hospital, Division of Rheumatology, Bogota, Colombia.

Background: The introduction of anti-TNF agents has changed the management of patients with Ankylosing spondylitis (AS). At present there is no doubt about the efficacy of anti-TNF agents: Infliximab (IFX), etanercept (ETN) and Adalimumab (ADA) in controlling symptoms of AS. However, it is unclear which should be the attitude once patients have achieved remission. Objectives: To analyze the effect of discontinuing anti-TNF therapy in AS patients who achieved complete remission, and to assess whether the readministration would be effective and safe in case of relapse. Methods: We conducted a systematic literature search for studies published up to January 2009 on the efficacy of IFX, ETN and ADA in AS in Medline, Embase and the Cochrane Central databases. Selection criteria were: a)Type of study: clinical trials with any quality level (according to Jadad scale). b)Participants: patients with AS; c)Intervention: IFX, ETN or ADA d)Outcome: clinical relapse (according to ASAS criteria), time to relapse, effectiveness and safety after readministration of anti-TNFs. Two reviewers screened the titles and abstracts of the retrieved articles for selection criteria independently and collected the data by using ad hoc standard forms. One of them also graded the quality of the selected studies using a modification of the Oxford Centre for Evidence-based Medicine Levels of Evidence in its May 2001 update. A hand search was completed by reviewing the references of the included studies. Results: We identified a total of 406 titles, of which 390 were excluded after reading the title and abstract. The final number of selected studies for a detailed review was 16. Finally 9 were excluded and 6 included (1 was a randomized controlled trial, 1 an open trial and the other 4 were follow-up studies) 2 evaluated ETN, 4 IFX. We did not found studies regarding ADA. After the discontinuation of IFX in AS patients who achieved remission, almost 100% relapsed. The mean time to relapse was 17.5 weeks ± 7.9 weeks (range 7–45). Patients who were in partial remission and those with normal C-reactive protein levels at the time point of withdrawal had longer times to relapse. Retreatment with IFX was safe and the clinical improvement was similar to that before the treatment was stopped. All of AS patients on ETN relapsed after treatment cessation. The median time to recurrence after discontinuation was 6.2 weeks ± 3 weeks, with relapse at 3 months 75% and 100% 9 months. Retreatment with ETN was efficacious and safe after readministration over 1 year in patients with active AS.

Conclusion: The discontinuation of IFX leads to a relapse in almost all of AS patients who achieved remission within weeks or few months (level of evidence 1b, grade of recommendation A). The reintroduction of ETN is safe and the clinical improvement is comparable to the observed before the discontinuation (level of evidence 4, grade of recommendation C). The discontinuation of ETN leads to a relapse in almost all of AS patients who achieved remission within weeks or few months (level of evidence 1b, grade of recommendation A). The reintroduction of ETN achieved similar clinical response to that observed previously (level evidence 4, recommendation grade C).


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Clinical and Demographic Characterization of a Colombian Cohort of Patients with Diagnosis of Spondyloarthritides. Wilson A. Bautista1, John Londos2, Martlon Forras3 and Rafael R. Valle.1 1Military Hospital, Division of Rheumatology, Bogota, Colombia, 2Military Hospital, Division of Rheumatology, Bogota, Colombia, 3Military Hospital, Division of Rheumatology, Bogota, Colombia.

Purpose: The Spondyloarthritides are a heterogeneous group of diseases characterized by axial as well as peripheral enthesitis and arthritis. Their presentation and clinical course is influenced by ethnicity, age at onset and sex; and share certain clinical features and laboratory findings, according to the population group. Given genetic susceptibility, environmental and socio cultural characteristics in our region, the clinical manifestations are different. Our objective is to describe clinical and demographic characteristics of a cohort of patients with spondylarthropathies in our country.

Method: Data was collected from a database of Rheumatology Service; which includes the clinical and paraclinical information related to the disease. The patients were evaluated following the ASAS recommendations. Patient demographics, disease duration, family and personal history, clinical pattern (axial, peripheral) and HLA status were recorded. Questionnaires were administered for functional status (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI)). All analyses were performed using SPSS software.

Results: 282 patients with spondylarthropathies were identified. 69.6% were men with a mean age of 35.9 years. The main characteristics are as follows: 99 (35.1%) with Ankylosing Spondylitis, 111 (39.4%) with Undifferentiated Spondylarthritides, 51 (18.1%) with Reactive Arthritis, 10 (3.5%) with Psoriatic Arthritis and 1 (0.4%) with Inflammatory Bowel Disease associated to Spondylarthiritides. 9 patients (3.2%) did not have a specific diagnostic. In 244 (86.5%) patients who had HLA report, 146 (51.8%) were negative and 98 (34.8%) positive. 77 patients were B15 positive.

According to the form of disease onset, 92 patients (32%) had axial involvement, 98 (34.8%) had peripheral and 79 (28%) mixed onset. When we analyzed the data according to initial symptoms, we found that arthritis was the initial manifestation in 80 (28.4%) patients, enthesopathy in 17 (6%) back pain in 98 (34.8%), uveitis in 4 (1.4%) and buttock pain in 2 (0.7%) patients. In 70 patients (24.8%) several initial symptoms were presented to the onset of the disease. Inflammatory back pain was present in 215 (76.2%) patients. The average age of onset of symptoms was 28 with a minimum of 11 and maximum of 71. In addition, we found a history of infection in 30.1% of patients mainly acute diarrheal disease. Only 6.1% of the patients had a known family history of spondloarthritides. Also we evaluate the functional status and level of activity of the disease, using the BASFI and BASDAI questionnaires at the time of examination. The main BASDAI score was 5.53 and main BASFI score was 5.26.

Conclusion: The clinical and demographic presentation of Spondyloarthri-
Comparison of ASAS Partial Remission and Low ASDAS as Indicators of Remission-Like States in Ankylosing Spondylitis. Desree van der Heijde,1 Joachim Sieper,2 Steve Brown3, Frederic Lavie4 and Aileen Pan- gan5. 1Abbott Laboratories, Rungis, France, 2Abbott Laboratories, Abbott Park, IL, 3Charité Universitätsmedizin Berlin, Berlin, Germany, 4Leiden University Medical Center, Leiden, The Netherlands

Introduction: Definition of remission in patients with Ankylosing Spondylitis (AS) has previously been based on the ASAS partial remission (ASAS PR) criteria. More recently, the AS Disease Activity Score (ASDAS) was developed and cut-offs validated, including low ASDAS (<1.3) as indicator of a remission-like state.

Objective: To compare the performance of ASAS PR and low ASDAS in identifying patients in remission in the 5-year ATLAS (Adalimumab Trial Evaluating Long-Term Efficacy and Safety for AS) clinical trial and to determine potential causes of observed differences in response rates.

Methods: Patients were randomized to receive adalimumab (ADA) 40 mg every other week (wk) or placebo (PBO) during a 24-wk double-blind period, followed by an open-label extension of up to 236 wks (total of 5 years). Efficacy and safety were assessed throughout the study. We evaluated the proportion of patients achieving ASAS PR, low ASDAS, ASDAS clinically important improvement (CI, decrease of at least 0.50 from baseline) at weeks 12 and 24 using a non-responder imputation analysis; and at weeks 52, 104 and 260 using observed analysis. Because ASDAS is calculated using the same components as the ASAS PR except for BASFI, plus the addition of CRP and peripheral pain/swelling (BASDAI Question 3), we also determined if baseline BASFI and mSASSS scores contributed to the observed differences in ASAS PR and low ASDAS response rates.

Results: ATLAS enrolled 315 patients (208 ADA, 107 PBO). Only patients in the ADA arm could have received 5 years of ADA therapy. At week 12 there were more patients in the ADA arm compared with PBO who achieved ASAS PR (20.7% vs. 3.7%, p<0.001), low ASDAS (36.5% vs. 2.8%, P<0.001), CI (61.5% vs. 17.8%, P<0.0001) and MI (39.9% vs. 3.7%, P<0.0001). At 1, 2, and 5 years of ADA exposure, the response rates (%) were higher for the 3 ASDAS-based response criteria compared with ASAS PR: (N, low ASDAS, CI, MI, ASAS PR) – 1 year (N=282, 42%, 69%, 47%, 33%); 2 years (N=261, 53%, 77%, 53%, 38%); 5 years (N=124, 61%, 87%, 65%, 51%). Higher baseline BASFI and mSASSS were noted for subjects who achieved low ASDAS but not ASAS PR, compared with those who achieved ASAS PR (Table 1). Even higher baseline BASFI and mSASSS were noted for those who did not fulfill either criteria. BASFI was the most frequently observed ASAS component to have not met the required value of <20 in the sub-group “low ASDAS + ASAS PR -.”

Conclusion: Low ASDAS detects more subjects in a remission-like state and allows for better differentiation between active treatment (ADA) and placebo than ASAS PR. This is likely due to the inclusion of BASFI in ASAS PR criteria, which may not reflect response to effective therapies if irreversible damage and functional disability are present.

Disclosure: D. van der Heijde: Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, Chugai, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 5, Pfizer Inc. 5, Roche, 5, sanofi-aventis, 5, Schering-Plough, J. Sieper: Abbott Laboratories, 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Centocor, Inc., 2, 5, 8, Merck Pharmaceuticals, 5, 8, Novartis Pharmaceuticals Corporation, 5, 8, Pfizer Inc. 2, 5, 8, Roche, 5, 8, sanofi-aventis, 5, 8, Schering-Pl. S. Brown: Abbott Laboratories, 1, 3; F. Lavie: Abbott Laboratories, 1, 3; A. Pangan: Abbott Laboratories, 1, 3.

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Complex Assessment of Subclinical Vascular Disease Associated with Ankylosing Spondylitis. Nora Bodnar,1 György Kerekes,2 Zoltan Szekanezz,3 Ilidio Seres2,4 György Paragh,2 Pál Soltész,5 Gabriella Szűcs2 and Sándor Szántó5. 1University of Debrecen Med Ctr, Debrecen, Hungary, 2University of Debrecen Medical and Health Sciences Center, Department of Medicine, 3University of Debrecen Medical and Health Sciences Center, Department of Rheumatology, 4University of Debrecen Medical and Health Sciences Center, First Department of Medicine

Background: There have been recent studies indicating that ankylosing spondylitis (AS), as well as rheumatoid arthritis, may be associated with accelerated atherosclerosis and vascular disease.

Objectives: Here we assessed endothelial dysfunction, carotid atherosclerosis and aortic stiffness in AS in context with several clinical and laboratory parameters.

Methods: Forty-three AS patients and 40 matched healthy controls were studied. We assessed common carotid intima-media thickness (ccIMT), flow-mediated vasodilation (FMD) and pulse-wave velocity (PWV) in association with age, disease duration, smoking habits, body mass index, patient’s assessment of pain and disease activity, BASDAI, BASFI, metric parameters, ESR, CRP and HLA-B27 status.

Results: We found impaired FMD (6.85±2.98 versus 8.30±3.96 %, p=0.005), increased ccIMT (0.65±0.15 versus 0.54±0.15 mm; p=0.01) and higher PWV (6.84±2.44 versus 8.00±2.16 m/s; p=0.03) in AS patients compared to controls. ccIMT negatively correlated with FMD (r=-0.562; p=0.0001) and positively correlated with PWV (r=0.374; p=0.018). In addition, both ccIMT and PWV correlated with disease duration (r=0.559; p=0.013 and r=0.520; p=0.022, respectively), BASFI (r=0.691; p=0.003 and r=0.654; p=0.006, respectively), decreased lumbar spine mobility (r=-0.656; p=0.006 and r=-0.604; p=0.013, respectively) and chest expansion (r=-0.502; p=0.047 and r=-0.613; p=0.012, respectively) and increased wall-occiput distance (r=0.509; p=0.044 and r=0.614; p=0.011, respectively).

Conclusion: In this well-characterized AS population, impaired FMD, increased ccIMT and PWV indicate abnormal endothelial function, increased atherosclerosis and aortic stiffness, respectively. The early determination of FMD, ccIMT and PWV may be useful to assess and treat AS patients with high cardiovascular risk.

Disclosure: N. Bodnár: None; G. Kerekes: None; Z. Szekanezz: None; I. Seres: None; G. Paragh: None; P. Soltész: None; G. Szűcs: None; S. Szántó: None.

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Correlates of Physical Function in Axial Spondylarthropathy; Fear of Movement as an Independent Contributor. Thijs Swinnen,1 Johan Vlaeyen,2 Wim Dankert3, Rene Westhovens and Kurt de Vlam3. 1Department of Rehabilitation Sciences, Catholic University of Leuven, Leuven, Belgium, 2Department of Rheumatology, University Hospitals Leuven, Sint Martens Leeuw, Belgium, 3Department of Rheumatology, University Hospitals Leuven, Department of Rehabilitation Sciences, Catholic University of Leuven, Leuven, Belgium, 4Research Group on Health Psychology, Catholic University of Leuven, Department of Clinical Psychological Science, Maastricht University, Leuven, Belgium, 5University Hospitals Leuven, Department of Rehabilitation Sciences, Catholic University of Leuven, Leuven, Belgium

Purpose: To establish the independent contribution of the psychological attribute “fear of movement and (re)injury” in explaining physical function in a large cohort of patients with axial Spondylarthropathy (aSpA).

Methods: We collected measures of anthropometrics (Body Mass Index), gender, disease duration, the use of medication (Biologics and NSAIDs), physical function (Bath Ankylosing Spondylitis Functional Index), stiffness
Purpose: 20% of psoriasis (Ps) patients (pts) develop psoriatic arthritis (PsA) within 10 years of Ps onset. Identification of an arthritis biomarker in Ps pts would facilitate early intervention and possibly delay or prevent onset of PsA. Previously, we reported an increased frequency of circulating osteoclast precursors (OCP) in one third of Ps pts without arthritis. We hypothesized that DC-STAMP (Dendritic Cell-Specific Transmembrane protein), a transmembrane protein that is required for the fusion of monocytes with osteoclasts, may serve as an arthritis susceptibility biomarker.

Methods: We previously identified 4 major DC-STAMP expression patterns in human PBMC with an anti-DC-STAMP antibody by flow cytometry. Most healthy controls have low OCP and show DC-STAMP pattern I, whereas PsA pts demonstrate elevated OCP and are more likely to manifest DC-STAMP pattern IV. We analyzed DC-STAMP expression patterns by flow cytometry and OCP frequency in cultured monocytes in a longitudinal cohort of 24 Ps pts. They were assessed by rheumatologists based on standard criteria and did not have PsA. They have been followed for 3 years on their standard of care.

Results: Table 1 summarizes the baseline clinical features, DC-STAMP patterns and frequency of OCP in 24 pts. Two, 6, 10, 6 Ps pts manifested DC-STAMP pattern I, II, III, and IV, respectively (column (a) & (b)). The OCP frequency (mean ± standard deviation) is shown in column (c). Within 3 years, 2 pts developed PsA by the CASPAR criteria (column (f)). Their demographics and clinical variables are depicted in Table 2.

Table 1.

<table>
<thead>
<tr>
<th>(a) DC-STAMP Pattern</th>
<th>(b) # of subjects</th>
<th>(c) OCP frequency (per 10⁶ monocytes)</th>
<th>(d) Average age</th>
<th>(e) PASI score</th>
<th>(f) # of pts develop PsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2</td>
<td>47 ± 25</td>
<td>62</td>
<td>4.6</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>279 ± 365</td>
<td>57</td>
<td>2.9</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>10</td>
<td>380 ± 398</td>
<td>49</td>
<td>8.2</td>
<td>1</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>1063 ± 954</td>
<td>36</td>
<td>4.1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2.

<table>
<thead>
<tr>
<th>(b) DC-STAMP Pattern</th>
<th>(c) OC frequency (per 10⁶ monocytes)</th>
<th>(d) PASI score after arthritis onset</th>
<th>(e) Years from Ps to PsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3.5</td>
<td>57</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>3.1</td>
<td>57</td>
<td>2.7</td>
</tr>
<tr>
<td>III</td>
<td>5.7</td>
<td>57</td>
<td>2.9</td>
</tr>
<tr>
<td>IV</td>
<td>5.4</td>
<td>57</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Conclusions: Data from this longitudinal cohort registry suggest that DC-STAMP is a potential marker to predict development of PsA in Ps pts. Two pts who developed PsA have DC-STAMP pattern III and pattern IV, the most common patterns seen in PsA pts. Additional studies are required further to explore the potential of DC-STAMP as an arthritis susceptibility biomarker.

Disclosure: None.

522 Development and Validation of a Questionnaire for Evaluation of Spondyloarthritides Related Manifestations in the First Degree Relatives of Patients with Ankylosing Spondylitis

Background: Previous studies have shown increased frequency of spondyloarthritides (SpA) related phenotypes in the first-degree relatives (FDR) of patients with Ankylosing Spondylitis (AS). However, large scale familial aggregation studies have been hampered by difficulties in screening and diagnosis confirmation. Our goal was to develop and validate a self-administered tool to evaluate the prevalence of SpA manifestations in the FDRs of AS patients.

Methods: A multidisciplinary team of rheumatologists, ophthalmologists, epidemiologists, and patient focus groups were involved in the design of the questionnaire. The low back pain questions were developed in close collaboration with the CDC/NHANES 2009 group and modified for utilization as a self-administered instrument. In the validation step, family members of AS patients completed the questionnaire and were subsequently examined by a rheumatologist at the study sites. A pelvic X-ray was obtained if inflammatory back pain (IBP) symptoms were present. We compared the questionnaire (method 1) to the physician evaluation (method 2) for each SpA manifestation and for the IBP criteria by Rudwaleit. IBP was defined as presence of at least 2/4 IBP criteria in conjunction with chronic lower back pain (> 3 months) and age at symptom onset ≤ 50 years. The agreement and equivalency between the questionnaire and study site assessments were examined by Kappa statistics and Nam’s equivalence test.

Results: Ninety one FDRs of AS patients with mean age of 50.7 (±16.6) years were enrolled, consisting of 36 parents, 28 siblings, and 27 children. Overall, 56% of study subjects were female and 87% were Caucasians. We confirmed IBP in 27, AS in 10, Achilles’ tendinitis in 25, peripheral arthropathies due to SpA in 7, uveitis in 6, psoriasis in 4, reactive arthritis (ReA) in 2 study subjects. No case of inflammatory bowel disease was reported. As shown in Table, the agreement rates ranged from 76.9% to 98.9% between two modes of acquisition. The assessment for inflammatory back pain, Achilles’ tendinitis, uveitis, psoriasis and reactive arthritis showed good to very good agreement between the questionnaire and site visit results. Furthermore, the questionnaire had adequate sensitivity and specificity for all SpA manifestations except for peripheral arthritis secondary to SpA. Particularly, the sensitivity and specificity of the instrument for capturing IBP according to Rudwaleit criteria was 81.8% and 88.4%, respectively.

523 Spondyloarthritis in First Degree Relatives of Patients with Ankylosing Spondylitis

Purpose: We previously identified 4 major DC-STAMP expression patterns in patients with spondylitis. The Baltimore Washington Study (BONE) is a longitudinal cohort of 337 patients with spondylitis followed for up to 20 years. We aimed to further define the DC-STAMP patterns and association with disease severity.

Methods: We analyzed DC-STAMP expression by flow cytometry in 337 pts with spondylitis. We assessed pts with AS, PsA, reactive arthritis and enthesitis-related arthritis in the BONE cohort.

Results: We identified 4 DC-STAMP expression patterns in pts with spondylitis. Pattern I was associated with active disease, while patterns II, III and IV were associated with remission.

Conclusions: DC-STAMP is a potential marker to predict development of PsA in Ps pts. Two pts who developed PsA have DC-STAMP pattern III and pattern IV, the most common patterns seen in PsA pts. Additional studies are required further to explore the potential of DC-STAMP as an arthritis susceptibility biomarker.

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Disclosure: None.
importantly, IBP per questionnaire had a sensitivity of 80% and specificity of 77% for AS as confirmed at the site visit.

**Conclusion:** These findings suggest that the developed questionnaire captures the SpA manifestations including AS with adequate diagnostic accuracy. This raises the possibility of utilization of this instrument for screening the FDR’s of AS patients for SpA manifestations.

### Demographics and Body Mass Index (BMI) of the Study Population

Vidula M. Bhole1, Hyon K. Choi5, Lindsay C. Burns1, Cristian Vera Kellet2, D. D. Gladman3, M. H. Weisman4, J. P. Dutz4

1. Arthritis Research Centre of Canada, Vancouver, BC, Canada, 2. Department of Dermatology, Pontificia Universidad Catolica de Chile, Santiago, 3. Toronto Western Hospital, Toronto, ON, Canada, 4. Univ of British Columbia, Vancouver, BC, Canada, 5. Universit of Leeds, UK

**Purpose:** To compare the adiposity among individuals with psoriatic arthritis (PsA), psoriasis (Ps), rheumatoid arthritis (RA), and general population (N), as well as identify correlates of adiposity among individuals Ps or PsA.

**Method:** We included: 1) 448 dermatologist-diagnosed Ps patients and 2) 644 rheumatologist-diagnosed PsA patients from the International Psoriasis and Arthritis Research Team (IPART) database; 3) 350 RA patients who participated in a longitudinal study of RA care; and 4) the general population from Canadian Community Health Survey 3.1. All PsA cases met the Classification of Psoriatic Arthritis (CASPAR) criteria. We compared the body mass index (BMI) among the four groups (PsA, Ps, RA, N) using analysis of variance (ANOVA) and performed all pairwise comparisons using Tukey’s test. We performed age-and-sex adjusted linear regression analyses using BMI as a continuous outcome, as well as logistic regression analyses using obesity (≥30 kg/m²) as a dichotomous outcome. We conducted multivariate analyses limited to Ps and PsA groups to determine the independent correlates of adiposity in these patients.

**Results:** 

The differences in BMI were significant for all the categories (ANOVA p < 0.0001, Tukey test p<0.05) except those between Ps and RA. Adjustments for age and sex using linear and logistic regressions did not change the results materially (all p values <0.0001). In the multivariate linear regression analysis limited to Ps and PsA groups, after adjustments for age, sex, smoking, Ps duration, Psoriasis Area Severity Index (PASI) score, DMARDs, glucocorticoids and biologics; BMI of PsA remained higher than that of Ps by 1.54 kg/m² (95% CI: 0.63–2.56). In similar multivariate logistic regression analyses, the odds ratio of obesity increased by 50% in those with PsA compared to those with Ps (95% CI: 1.09 – 2.05). Age, smoking, PASI score, glucocorticoid use, and female gender were significantly associated with a higher BMI or increased odds of obesity in patients with Ps or PsA.

**Conclusion:** BMI is higher in PsA (skin and joint disease) than that in Ps (skin disease), RA (joint disease) or the normal population. Furthermore, our results suggest that the BMI difference between PsA and Ps is independent of other risk factors of obesity. Other significant correlates of increased BMI or obesity among individuals Ps or PsA were age, smoking, PASI score, glucocorticoid use, and female gender.

**Disclosure:**

V. M. Bhole: None; H. K. Choi: None; L. C. Burns: None; C. V. Kellet: None; D. V. Lacaille: None; D. D. Gladman: None; J. P. Dutz: None.

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Disease Activity Assessment by ASDAS Doesn’t Predict Sacroiliac Inflammation with MRI in Axial SpA

Sibel Z. Aydin1, Alex Bennett1, Paul Emery2, Dennis McGonagle2 and Helena Marzo-Ortega2

1. Defence Medical Rehabilitation Centre, Headley Court, Epsom, Surrey, 2. University of Leeds, UK

**Objective:** The ASDAS (Ankylosing spondylitis disease activity score) is a newly developed composite index to measure disease activity in AS. It incorporates items of back pain, morning stiffness, patient global assessment of disease activity, pain/swelling of the peripheral joints and the CRP using a weighted formula. In the present study we aimed to test the construct validity of ASDAS comparing it with active inflammation of the sacroiliac joints (SIJs) as shown by MRI.

**Methods:** Twenty-three patients (n=23) with axial SpA according to the ASAS criteria were included. All patients were questioned for the parameters included in ASDAS and had an MRI scan of the SIJs. ASDAS values were categorized according to the different cut-off levels recently presented at OMERACT 10 and compared to the MRI findings according to the guidance of ASAS proposals. Further scoring to identify patients with severe MRI sacroilitis (grade 3 according to the Leeds MRI SIJ Scoring System) and total MRI scores (sum of scores at all quadrants with a maximum score of 24) were also available.

**Results:** All patients had active disease according to ASDAS (scores >1.3).

**Table 1. Distribution of ASDAS according MRI findings**

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<thead>
<tr>
<th>Disease activity according to ASDAS</th>
<th>ASDAS cut off levels</th>
<th>Positive MRI (n)</th>
<th>Severe sacrolitis by MRI (n)</th>
<th>MRI scores median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ n = 18</td>
<td>– n = 5</td>
<td>+ n = 4</td>
<td>– n = 19</td>
</tr>
<tr>
<td>inactive disease</td>
<td>≤ 1.3</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>moderate activity</td>
<td>1.3–2.1</td>
<td>1</td>
<td>1</td>
<td>5 (0–16)</td>
</tr>
<tr>
<td>high activity</td>
<td>2.1–3.5</td>
<td>7</td>
<td>2</td>
<td>8 (1–18)</td>
</tr>
<tr>
<td>very high activity</td>
<td>&gt;3.5</td>
<td>9</td>
<td>2</td>
<td>2 (0–12)</td>
</tr>
</tbody>
</table>

Moderate disease was found in 13%, 39% had active and 48% had very active disease. No relationship was found between the different states of disease activity according to ASDAS and MRI findings, including severity of the MRI. Similarly, ASDAS levels were found comparable in groups with/without sacroilitis by MRI (3.5 ±1.1 vs 3.1±0.9, p=0.5, respectively) and severe sacroilitis by MRI (3.5 ±1.8 vs 3.4±0.9, p=0.8, respectively). MRI scores were also independent from ASDAS categories.

**Conclusion:** Besides the clinical benefits of ASDAS, there does not appear to be a relationship between ASDAS and the presence of bone marrow oedema on MRI at the SIJ of axial SpA patients.

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Estimation of Optimal Cut-Off Point of Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Mini-BASDAI, Ruxandra Schiotis1, Eliza Muñoz Gomariz2, Juan Muñoz5, Xavier Juanola4, Janitza Vazquez-Mellado2, Per-cival D. Sanchez-Ibañez1 and Edwundo Caras6, 1Department of Rheumatology, General Hospital of Mexico, Mexico City, 2Division of Rheumatology, University of São Paulo, 3Instituto Maimonides de Investigación Biomédica/Hospital Universitario Reina Sofia, Córdoba, Spain, 4Rheumatology Department, Hospital Puerta de Hierro Majadahonda, Madrid, Spain, 5Rheumatology Department, Hospital Reina Sofia, Córdoba, Spain, 6University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania

Objective: To estimate the best optimal cut-off point of Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and modified BASDAI (mini-BASDAI) in a large population of patients with ankylosing spondylitis (AS)

Methods: The analysis was performed in two large cohorts of patients from two registries of spondylarthropathies patients: REGISPONSER (Spain) and RESPONDIA (Latin-America). For performing further analyzes patients were divided in two subgroups with and without peripheral arthritis: (1) AS peripheral and (2) AS axial. The optimal cut-off point of the three scored disease indexes was estimated with the ROC curves. The discrimination between active and inactive disease was performed with the area under the curve ROC. The “gold standard” used in our analysis was the physician global assessment obtained on a numerical rating scale (NRS).

Results: The optimal cut-off point for ASDAS, BASDAI and mini-BASDAI were as follows: 2.68; 4.24 and 5.14 respectively. ASDAS cut-off point statistical significantly discriminated active disease compared to BASDAI (P < 0.015) and mini-BASDAI (P = 0.002). The same tendency of ASDAS cut-off in discriminating active disease was found in both “AS peripheral” and “AS axial” although, significant statistical difference was encountered only in the “AS axial group” (ASDAS vs BASDAI, P = 0.027 and ASDAS vs mini-BASDAI, P = 0.040). Higher activity scores were found in “AS peripheral group” for all three studied indexes.

Conclusion: ASDAS is a validated instrument that offers a high discriminatory capacity of active disease when compared with BASDAI and mini-BASDAI, for all presenting AS forms. ASAS should be the preferred score in assessing AS patients in daily practice.

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Evaluation of the New ASAS Instrument To Assess Disease Activity, the ASDAS, in Patients with Ankylosing Spondylitis Treated with TNF Blockers over 8 Years, Xenofon Baraliakos1, Claudia Fritz3, Joachim Listing5, Joachim Sieper1 and Juergen Braun4, 1Charité Campus Benjamin Franklin, Berlin, Germany, 2German Rheumatism Research Center, 3Rheumazentrum Ruhrgebiet, Herne, Germany, 4Rheumazentrum Ruhrgebiet Herne

Background: Currently used clinical parameters for assessment of disease activity (BASDAI) or response to therapy (BASDAI50%, ASAS20% and 40%) in patients with AS mainly rely on patient’s opinion. The Spondyloarthropathies International Society (ASAS) has recently developed a new disease activity score, the ASDAS, which includes clinical measures and CRP and has a high discriminatory capacity for assessing disease activity in AS.

Objective: To compare the performance of established tools with the new instrument, the ASDAS, in a long-term clinical of continuous anti-TNF therapy with infliximab in patients with active AS (n = 33) after 3, 5 and 8 years.

Methods: According to recent data, an ASDAS < 1.3 was considered as ‘inactive’, 1.3–2.1 as ‘moderate’, 2.1–3.5 as ‘high’ and > 3.5 as very high disease activity. An ASDAS change > 1.1 was defined as ‘minimally important improvement’ and ≥ 2 as ‘major improvement’, as recently proposed.

Results: The mean BASDAI decreased from 6.4 ± 1.9 at baseline to 2.3 ± 2.0 at 3y (64% decrease), to 2.4 ± 2.0 at 5y (63% decrease), and to 2.6 ± 1.9 (59% decrease) at 8y (all p < 0.05). In comparison, the ASDAS decreased from 4.3 ± 0.8 at BL to 1.5 ± 1.0 (65% improved) at 3y, to 1.6 ± 1.0 at 5y and to 1.6 ± 0.9 at 8y (63% decrease).

Overall, a BASDAI < 3 was achieved by 22/33 patients (66.7%) at 3y and by 21/33 patients (63.6%) at 5y and 8y years. In comparison, at 3y, 5y and 8y, an ASDAS <1.3 was found in 15 (46%), in 13 (39%), and in 17 (52%) patients, respectively. An ASDAS between 1.3–2.1 was seen in 11 (33%), in 13 (39%) and 6 (19%) patients after 3y, 5y and 8y, respectively. An ASDAS > 2.1–3.5 was found in 6 (18%), in 9 (27%) and in 9 (27%) after 3y, 5y and 8y, respectively and an ASDAS > 3.5 was seen in only 1 (3%) patient at all time points. The comparison of different outcome parameters for change is shown in Table 1.

Conclusions: The ASDAS, a new composite disease activity score for AS proposed by the ASAS, was more sensitive than the conventional scores for disease activity and change, confirming recent data on short-term outcomes. More studies are needed to establish the ASDAS as a standard tool for assessment of disease activity in patients with AS in clinical practice.

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Evolution of Familiar Spondylarthropathy (SPA) without Radiographic Sacroiliitis over Time: Results of a Prospective Follow Up Study, Nadine Zehouglou-Klorza1, Roula Said-Nahal1, Maria-Antonietta D’Agostino3 and Maxime Breba3, 1Hôpital Ambroise Paré, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt, France, 2Hôpital Ambroise Paré, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt, France; INSERM Unité 1016; Université Versailles Saint Quentin en Yvelines, F-78000, Versailles, France, 3Hôpital Ambroise Paré, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt, France; Université Versailles Saint Quentin en Yvelines, F-78000, Versailles, France

Background: Transversal study of familial SPA shows that all subtypes of SPA, (i.e. ankylosing spondylitis (AS), SPA associated with psoriasis or inflammatory bowel disease (IBD), with or without radiographic sacroilitis, and undifferentiated SPA (uSPA)) coexist in families, and that longer disease duration correlates with higher frequency of radiographic sacroilitis (Arthritis Rheum. 2000;3:1356). It was previously suggested that the various subtypes of familial SPA may correspond to different stages of the same disease but this remains as yet unresolved. Only longitudinal study could properly address this question.

Material and Methods: The study population consisted of an adult (≥ 16 years) cohort of familiar SPA fulfilling Amor’s criteria and/or European Spondylarthropathy Study Group criteria, without definite radiographic sacroilitis at inclusion (i.e. ≥ grade 2 bilateral or ≥ grade 3 unilateral, according to the New York modified criteria). Patients underwent thorough clinical evaluation, and a pelvic radiograph at the inclusion and at the end of follow up, which lasted 5 to 15 years. Blinded films were read by 2 expert examinators. Univariate and multivariate logistic regression were performed to identify factors present at inclusion which could predict the evolution of SPA without definite sacroilitis and evolution of uSPA to a differentiated form, and notably to AS.

Results: Of the initial cohort consisting of 150 non-radiographic SPA followed more than 5 years, analysis were performed on 83 patients (68.7% of females; 93.7% HLA-B27+, 71.1% of uSPA, 25.3% with psoriasis, 3.6% with IBD) with available pelvic radiograph at the end of follow up. At inclusion, age (mean ± SD) was 43 ± 13.5 years and disease duration was 14.8 ± 12.1 years. The mean duration of follow up was 8.3 ± 2.2 yrs. At the end of follow-up, definite radiographic sacroilitis (i.e. AS) was detected in 21.7% of the patients (7.2% with psoriasis). Of the remaining patients, 21.7% had psoriasis, 9.6% IBD and 47.0% had uSPA. Of 59 initial uSPA, 20 (33.4%) developed a differentiated form of SPA: 13 (65.0%) AS (1 with psoriasis), 4 (20.0%) non-radiographic SPA with psoriasis, 3 (15.0%) non-radiographic SPA with IBD. The only factor at inclusion that was moderately but significantly associated with a higher risk to develop radiographic sacroilitis was a disease duration < 10 years: Odds Ratio = 0.26 (95% Confidence Interval 0.09–0.77).

Conclusion: This prospective study conducted on familial SPA without definitive sacroilitis at inclusion shows for the first time that a
substantial proportion of them develop AS and that uSPA tends to evolve to differentiated form over time. This validates the hypothesis that distinct subtypes of familial PsA correspond to different stages of the same disorder.

Disclosure: N. Zeboulou-Kiorza: None; R. Said-Nahal: None; M.-A. D’Agostino: None; M. Breban: None.

Methods: Study design: retrospective single center observational study in 2010 (COSPArA). Patients: definite SpA (Amor’s criteria). Each patient underwent direct interview by a physician. Data collection: prevalence of hip involvement, and if present, the date of appearance, the localization and nature of the pain, treatments performed (intra-articular injections, surgery) and outcomes of total joint replacement (TJR). Analysis: descriptive analysis.

Results: To date, 148 consecutive SpA patients were assessed: 26 (18%) patients suffered from SpA-associated hip involvement; median age 44.2 (range 25.9–69.4) years, median symptom duration 23.5 (5–51) years, 99% were men, 22/24 (92%) were B27 positive. 22/26 (85%) of patients with hip involvement had been treated by anti TNF at data collection versus 65/120 (54%) of other patients. Hip involvement appeared during the first 5 years of disease duration in 68% and during the first 10 years in 81%. Prevalence varied according to SpA predominant manifestation: more frequent in axial patients (20%, 22/110), than in peripheral disease (14%, 4/29). Hip involvement was bilateral in 46% (12/26) and unilateral in 54% (14/26); 11 patients (46%) received intra articular corticoid injections (of which, 23% were triamcinolone hexacetonide). In all, 9 patients (6% of the whole group and 36% of patients with hip involvement) had a TJR; the median delay between first hip symptoms and TJR was 36 months (range 0–27 years). After a median follow-up of TJR of 101 months (range 2–27 years), TJR was considered as having a good function in 100% and only 22% (2/9) patients had TJR complications with a second TJR of the hip for both of them.

Conclusion: Hip involvement occurs in 18% of our SpA patients; hip involvement seems to start usually in the first 10 years of the disease (81% of our patients) with almost equal bilateral or unilateral involvement. TJR is still the best treatment at the moment for serious destruction, with good results even if corticoid intra articular injections are used to retard it.

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HLA-Cw*06 Allele Increases the Duration of Time between the Onset of Psoriasis and Psoriatic Arthritis. Lihu Edzer1, Vinod Chandran2, Fawwada Pellet3, Sutha Shannumgarajah2, Hua Shen3, Richard Cook4 and Dafina D. Gladman1. 1Toronto Western Hospital, Toronto, ON, Canada. 2University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital, 3University of Waterloo

Aim: Most of the patients with psoriatic arthritis (PsA) develop arthritis following the onset of the skin disease, with a mean duration of approximately 7 years. It was suggested recently that the risk of developing PsA remains constant after the diagnosis of psoriasis. We aimed to investigate whether the rate of PsA after the onset on psoriasis is constant and whether it is affected by clinical and genetic factors.

Methods: We performed a retrospective cohort analysis of patients with PsA and psoriasis without arthritis. The PsA patients were part of a large single centre longitudinal cohort. The psoriasis patients were recruited from a recently established prospective cohort of psoriasis without arthritis. They were recruited annually by a dermatologist (I.G.) and a rheumatologist (D.G.) who had studied the development of arthritis after the onset of psoriasis were included. We analyzed the rate of PsA cases per year from the onset of psoriasis. Patients with psoriasis alone were censored at their last visit to the clinic. Parametric survival analysis was used to determine the probability model that predicts the risk of developing PsA after the onset of psoriasis. The following variables were tested for their effect on the interval of time from psoriasis to PsA: HLA-Cw*06, HLA-B*27, gender, type I vs. II psoriasis.

Results: 438 patients with psoriasis and 769 patients with PsA were included in the study. The mean age at onset of psoriasis and PsA were 26.8±14.7 and 37.3±13.3 years. The sex ratio was 1.3:1 (male: female). The proportion of type I psoriasis was 82.8%, 36% of the participants were carriers of HLA-Cw*06 allele and 11% of the participants were carriers of HLA-B*27 allele. The mean time from the onset of psoriasis to development of PsA was 12.2±10.7 years. The estimated annual probability of PsA was fit with an exponential probability model, suggesting that the risk of developing PsA over time was constant. Tests for trend did not suggest any evidence of departure from a constant hazard. HLA-Cw*06 carriers were associated with longer intervals of time between psoriasis and development of PsA (Relative Risk 0.54, 95% Confidence Interval 0.37–0.78, p=0.001). HLA-B*27, type of psoriasis and gender were not found to affect the time interval between psoriasis and PsA.
Conclusions: The risk of developing PsA over time among psoriasis patients is constant. HLA-Cw*06 allele doubles the duration of time between the onset of psoriasis and PsA.

Disclosure: L. Eder; None; V. Chandran; None; F. Pellett; None; S. Shanmugarakajh; None; H. Shen; None; R. Cook; None; D. D. Gladman; None.

Hypertension and Diabetes Significantly Enhance the Risk for Cardiovascular Disease in Patients with Psoriatic Arthritis (PsA).

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Maria Helena Sampai o Favarato1, Carla Goncalves Saad2, Celio Roberto Goncalves2, Percival Degrava Sampai o-Barnos2 and Claudia Goldenstein-Schaimberg2, 1 Rheumatology, HC-FMUSP, Sao Paulo, Brazil, 2 Rheumatology, HC-FMUSP.

New evidence has lightened the linkage between psoriatic arthropitits (PsA) and the development of atherosclerosis and cardiovascular disease (CVD) events.

Objective: To describe the prevalence of cardiovascular events and associated risk factors among patients with PsA from a tertiary hospital.

Methods: Retrospective evaluation of medical records from all current patients who fulfilled the CASPAR criteria for PsA attending a specialized spondyloarthrits clinic at a university tertiary hospital.

Results: 158 PsA patients, 48.73% females and 51.27% males, aged 53.67 ± 13.89 yrs (52.61 ± 14.96yrs for women and 54.69 ± 12.80yrs for men, p = 0.34).

Mean joint disease duration was 13.7 ± 8.92yrs. Cutaneous psoriasis preceded articular involvement in 53%, was concomitant in 38% and followed joint disease in 9%. Polyarticular subtype was the most common presentation accounting for 42% of PsA patients, while peripheral oligoarticular involvement occurred in 20%, axial + peripheral polyarticular in 18%, pure axial disease in 12% and axial + peripheral oligoarticular in 8% of cases. According to drug therapy, 32 (20%) were under the action of TNF-α inhibitors, 94 (60%) were taking metothrexate, 18 (11%) leflunomide, 13 (8%) sulfasalazine, 5 (3%) other immunosuppressors and 4 (2.5%) chloroquine; 85 (54%) were using NSAIDs and 21 (13%) were under the action of anti-TNFα agents, 94 (60%) were taking methotrexate.

Feature OR 95% IC p
Female gender 0.88 0.32–3.40 0.853
FQ 1.01 0.98–1.03 0.624
VAS pain 1.00 0.97–1.02 0.798
FM symptoms ≥ 6 20.05 7.15–56.23 0.000
Enthesitis score ≥ 3 0.53 0.20–1.44 0.212
Tender points ≥ 8 16.49 4.62–58.86 0.000
No response to NSAIDs 6.37 1.52–26.71 0.011

Conclusions: Number of FM-associated symptoms, number of tender points, and response to NSAIDs were significantly predictive of FM.

Disclosure: C. Goldenstein-Schainberg; None. E. Lubrano; None. C. G. Saad; None. C. Goldenstein-Schainberg; None.

Impact of Environmental Factors on Disease Activity in Spondyloarthritis (SPA): Results of the Prospective Co-Ev Cohort. Nadine Zebozulon-Korza1, Pierre-Yves Boile1, Roula Saad-Nahoul1, Maria Antonietta D’Agostino1, Jean-Francois Viber1, Emmanuelle Durand1, Homa Madrakian1, Odile Launay1, Alfred Mahr2, Antoine Flahaut3, Thomas Hanslik4 and Maxime Breban2.

Table 1. Multivariate logistic regression of the main features associated with FM

Feature OR 95% IC p
Female gender 0.88 0.32–3.40 0.853
FQ 1.01 0.98–1.03 0.624
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No response to NSAIDs 6.37 1.52–26.71 0.011

Conclusions: Number of FM-associated symptoms, number of tender points, and response to NSAIDs can help distinguish between polyenthesitic PsA and FM.

Disclosure: A. Marchesoni; None. V. Varisico; None. F. Atzeni; None. A. Spadaro; None. E. Lubrano; None. S. D’Angelo; None. A. Cauli; None. C. Salvarano; None. G. Provenzano; None. R. Scarpa; None. D. Melchiorre; None. P. Sarzi Puttini; None. I. Olivieri; None. M. Atzeni; None. M. Montepane; None. G. De Marco; None. L. Rotunno; None. M. Manara; None.

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Identification of the Clinical Features That Can Distinguish between Psoriatic Polyenthesitis and Fibromyalgia.

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AOUC University of Florence, Italy, 2CTO Hospital, Palermo, Italy, 3Department of Clinical and Medical Therapy, Sapienza-University of Rome, Italy, 4Department of Medical Sciences, University of Cagliari, Italy, 5Fondazione Maugeri IRCs, Telese Terme, Italy, 6G.P. Orthopedic Institute, Milan, Italy, 7L. Sacco University Hospital, Milan, Italy, 8Reggio Emilia Hospital, Italy, 9Rheumatology Research Unit, University Federico II Naples, Italy, 10San Carlo Hospital of Potenza, Italy.

Background and Purpose: As polyenthesitic psoriatic arthritis (PsA) is sometimes hard to distinguish from fibromyalgia (FM), secondary FM in PsA patients and PsA in FM patients can be misdiagnosed. The purpose of this study was to identify which clinical features can help distinguish between polyenthesitic PsA and FM.

Materials and Methods: This was a multicentre cross-sectional study carried out by 10 Italian tertiary Rheumatologic (8 recruiting PsA patients and 2 FM patients) centres from January 2009 to September 2009. All of the consecutive patients with PsA (CASPAR criteria) and FM (ACR criteria) who accepted to participate to the study were enrolled in it. For each patient all of the standard clinical and laboratory data, including the questionnaires for PsA and FM, were collected. For the statistical analysis, Student’s t test, x² test, Fisher’s exact test, univariate and multivariate logistic regression and Receiving Operating Characteristic (ROC) curves, were used as appropriate.

Results: Two-hundred-sixty-two PsA patients (122 females and 140 males, mean age 51.9 ± 12.8, mean disease duration 10.1 ± 9.2 years) and 96 FM patients (89 females and 7 males, mean age 50.6 ± 1.8, mean disease duration 5.4 ± 4.1 years) were enrolled in this study. Eighteen (6.9%) PsA patients met the classification criteria for FM. Tender and swollen joint counts, dactylitis count, ESR and CRP, and response to NSAIDs were significantly higher in the PsA group. Inflammatory back pain, HAQ values, and PGaA scores were comparable in the two groups. Enthesitis score, tender joint count, morning stiffness, VAS pain by patient, and all of the typical symptoms of FM (headache, irritable bowel syndrome, sleep disturbances, paresthesia, anxiety, depression, Raynaud’s phenomenon) were significantly associated with FM. However, using the univariate logistic regression, the ORs of morning stiffness, anxiety, and depression were not statistically different between the two groups. The ROC curves showed that 6 or more FM-associated symptoms (sens. 93%, spec. 86%) and 8 or more tender points (sens. 93%, spec. 82%) had the best performance in identifying FM patients. The multivariate logistic regression (table 1) showed that 6 or more FM-associated symptoms, 8 or more tender points, and no response to NSAIDs were significantly predictive of FM.
disease evolution has not yet been elucidated. The objective of this study was to prospectively investigate the impact of several environmental factors on disease activity.

**Methods:** The study population consisted of a dedicated cohort of adult (age ≥ 18 years) SPA patients fulfilling Amor’s criteria. The follow up period extended over 3 years (December 2005 to October 2008). Patients were asked to log on a secured website every 3 months and to complete a standardized auto-questionnaire. They notified if they were exposed since the previous connexion to environmental factors suspected of being non-specific stimulants of inflammatory response, such as infections (respiratory tract infection, gastroenteritis, urinary tract infection), stressful or traumatic life events and vaccinations. Outcome variables included the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the patient global assessment (PGA), and the Bath Ankylosing Functional Index (BASFI) (rated each from 0 to 10). Univariate and multivariate analysis were performed using a standard generalizied estimating equation approach for repeated measures adjusting on the connexion to environmental factors.

**Results:** Two hundred and sixty two patients (57% of females) were included in the analysis (2078 patient-connexions). Mean Age (± SD) was 43.6 ± 10.5 years and disease duration was 16.8 ± 11.3 years. The mean total number of connexions per patient was 8.0 ± 2.0. The mean time between two connexions was 4.1 ± 2.4 months. Occurrence of life events were followed by an average increase of 0.4 points (95% confidence interval [CI] 0.3–0.6) on the BASDAI score (p<0.0001) (consecutive to an increase of the score of each question), of 0.6 points (95% CI 0.4–0.8) of the PGA (p<0.0001) and of 0.4 points (95% CI 0.2–0.6) on the BASFI score (p<0.0001). A moderately significant link between vaccination and disease activity was found with the BASDAI rising by 0.3 points (95% CI 0.0–0.6) (p=0.028). There was no relationship with disease activity for any of the other investigated events.

**Conclusion:** This prospective study conducted in a large cohort of SPA patients shows for the first time a link between stressful events and disease activity. This may offer insights into pathogenesis and approaches to disease management.

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**Increased Risk of Cardiovascular Disease in Patients with Active Ankylosing Spondylitis.** Inger J. Berg, Anne G. Semb, Hanne Dagfinrud, Camilla Fongen, Sella A. Provan and Tore K. Kvien. Dep of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

**Background:** Several inflammatory rheumatic diseases are associated with an increased risk of cardiovascular disease (CVD). There are also some studies suggesting a higher risk of CVD in patients with ankylosing spondylitis (AS).

The aim of this study was to compare prevalence of CVD and levels of Augmentation index (Aix), a surrogate markers for CVD risk, between a cohort of AS patients and a population control group. Comparisons were made between patients with high and low disease activity.

**Methods:** 161 patients with AS and 134 controls were examined in 2008–2010. The AS patients derived from the 5-year longitudinal follow-up of a cohort of hospital-recruited patients diagnosed according to the New York Classification criteria. The control population was randomly selected by Statistics Norway. Aix estimation was performed using the Sphygmocor apparatus. BASDAI score was calculated from the standard questionnaire. Statistical analyses were performed in SPSS ver 14.0 using bivariate tests as appropriate. The risk of CVD and levels of CVD risk markers were explored across levels of BASDAI (dichotomized at the median) and compared to controls in logistical and linear regression models adjusted for age, sex and smoking habit.

**Results:** The groups were comparable regarding demographic data (AS vs controls): age (51.2 vs 53.1 p=0.18), gender/male (62.7% vs 57.9% p=0.41) and smoking (56.4% vs 60.2% p=0.52), but as expected there were significant differences regarding ESR (17 vs 8 p≤0.001). Total cholesterol was significant lower in the AS group (5.43 vs 5.75 p=0.01). The subgroup analyses are presented in Figure 1.

**Conclusion:** We found significantly higher OR for established CVD among patients with active AS compared to controls. The increased risk of CVD was further confirmed by a significantly increased Aix in patients with high BASDAI. The results indicate that there might be a higher risk of CVD in the AS patient with the most active disease. These findings will be investigated in further analysis.

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**Increased Risk of Gastrointestinal Complications among Persons with Ankylosing Spondylitis: A Population-Based Study from Quebec, Canada.** Adrian R. Levy1, Shelagh M. Szabo2, Walter P. Maksymowych1, Sumati Rao1, Diane V. Lacaille1 and Mary Cifaldi3. 1Abbott, 2Arthritis Research Ctr Canada, Vancouver, BC, Canada, 3Oxford Outcomes, 4University of Alberta, Edmonton, AB, Canada

**Purpose:** Individuals with ankylosing spondylitis (AS) may be at increased risk of developing gastrointestinal (GI) complications as a result of at least two pathways. First, both subclinical and manifest GI inflammation is frequently observed in persons with AS. Second, the symptoms of AS are often treated with non-steroidal anti-inflammatory drugs; an unintended consequence of these medications is increased risk of GI ulcers. However, the magnitude of increased risk of GI complications in AS and the demographics of patients at more pronounced risk is not well-characterized. Published studies of the excess risks of GI disorders among persons with AS have been clinic- and not population-. Based. The objective was to estimate the age- and sex-specific risk of GI disorders in a population-based cohort of persons with AS compared to a cohort of persons without AS.

**Methods:** A retrospective cohort study was conducted using the population-based administrative physician-billing database maintained by the Régie de l'Assurance Maladie du Québec. The cohort included individuals with at least one International Classification of Diseases 9th Revision, (ICD-9) billing code for AS between 1996 and 2006. The comparison cohort was a 1% random sample of individuals without AS. GI complications were defined according to ICD code, and included: ulcer-related GI complications (hemorrhage, ulcer, esophagitis, gastritis, or duodenitis); inflammatory GI diseases (Crohn’s or colitis); and other GI complications (irritable bowel or diverticulitis). We calculated incidence rates per person-year and age- and sex-adjusted incidence rate ratios (IRRs) with 95% confidence intervals (CIs) compared to the comparison cohort.

**Results:** Among 8,616 persons with AS, 55% were male and median age at diagnosis was 42.5 years. Age-specific incidence of GI complications increased with age from 43 to 59 per 1000 person-years among males aged 20–49, and >60 years, respectively; and from 52 to 58 per 1000 person-years among females aged 20–39, and >60 years, respectively. There seemed to be a trend of decreasing IRRs (95% CI) with increasing age; among men, from 1.7 (1.6–1.8) for those 20–39 years, to 1.5 (1.4–1.6) for those >60 years; and, among women, from 1.7 (1.6–1.8) for those 20–39 years to 1.3 (1.2–1.4) for those >60 years. Ulcer-related GI events were the most frequent complication (incidence rate, 32 per 1000 person-years) followed by other GI events (27 per 1000 person-years), and inflammatory GI diagnoses (25 per 1000 person-years). Age- and sex-adjusted IRRs were: hemorrhage: 1.9 (1.7–2.2); ulcer: 2.0 (1.9–2.2); esophagitis: 1.7 (1.6–1.8); gastritis: 1.8 (1.7–1.9); Crohn’s: 4.6(4.1–5.0); Colitis: 1.8 (1.7–1.9); irritable bowel: 2.3 (2.1–2.5); and diverticulitis: 1.6 (1.5–1.8).

**Conclusions:** Individuals with AS are at increased risk for many types of GI complications. The excess risk may be more pronounced among younger...
individuals. Ulcer-related GI complications were the most common and the increased risk among persons with AS was highest for inflammatory GI diseases. These data support a policy of routine assessment of GI disorder among patients with AS.


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Inflammation in an Individual Joint Predicts Damage to That Joint in Psoriatic Arthritis. Vinod Chandran1, Lynne Creswell1, Vernon T. Farewell1 and Dafna D. Gladman2. 1MRC Biostatistics Unit, Cambridge, UK, 2Toronto Western Hospital, Toronto, ON, Canada, 3University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital

Background: Psoriatic arthritis (PsA) leads to progressive joint damage and disability. Predictors for joint damage progression have been identified. However, these analyses were based on total joint counts in the individual patient and not on the presence of swelling, tenderness or damage at the individual joint level. We aimed to identify predictors of damage to individual joints in the hands and feet of patients with PsA, in particular those that capture previous activity.

Methods: Data from 705 patients followed prospectively at a large PsA clinic between 1978 and 2006 were available for analysis. Data from 511 patients who had no clinical damage in their hands or feet [wrists, MCP, PIP and DIP (total 30)] at clinic entry were included in the analysis of the hand joints; data from 552 patients who had no clinical damage observed in the joints of the feet [ankles, MTP, IP (total 22)] at clinic entry contributed data to the analysis of the foot joints. An active joint was defined as a joint with either tenderness or swelling. Clinical damage was determined by the presence of a limitation of range of movement of >20% of the range not related to the presence of joint effusion, the presence of joint deformities, subluxation, flail joints or ankylosis. Logistic regression was used to relate the probability of a joint developing damage, within a specified time interval after the most recent clinic visit, to potential predictor variables. The predictor variables considered encompassed the history of disease activity of the joint and elsewhere, previous damage and the timing of clinical assessments.

Results: 511 patients (286 males, median age 41 years, PsA duration 3 years, active joint count in hands 2) with no hand damage at clinic entry and 552 patients (310 males, median age 41 years, PsA duration 3 years, active joint count in feet 2) with no foot damage at clinic entry were included in the analysis of the hand and foot joints, respectively. The results of the multivariate analyses are given in tables 1 and 2.

Table 1. Results for the Final Multivariate Model for Damage to Hand Joints

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint specific activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EWMA</td>
<td>1.40 (1.25, 1.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PROP</td>
<td>1.33 (1.20, 1.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swelling at any visit</td>
<td>1.63 (1.35, 1.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global activity variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling in the same hand at any of most recent 3 visits</td>
<td>1.55 (1.30, 1.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Damage variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Damage in the symmetric joint</td>
<td>2.24 (1.79, 2.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Damage in an adjacent joint</td>
<td>1.53 (1.22, 1.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EWMA = Exponentially Weighted Moving Average; PROP = proportion of visits with activity observed in the joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symmetric joint = equivalent joint on the opposite hand/foot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjacent joint = a joint of the same type (MCP,PIP or DIP) of an adjacent finger</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The odds ratio for the EWMA and PROP are presented in a form that describes the multiplicative effect on the odds of damage developing caused by an increase of 0.25</td>
<td></td>
<td></td>
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</tbody>
</table>

Table 2. Results for the Final Multivariate Model for Damage to Foot Joints

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint specific activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity at any visit</td>
<td>1.48 (1.27, 1.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swelling at any visit</td>
<td>1.44 (1.17, 1.78)</td>
<td>0.001</td>
</tr>
<tr>
<td>Global activity variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity in the feet at any of the three most recent visits</td>
<td>1.56 (1.32, 1.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Activity in the other toe joint at any visit</td>
<td>2.14 (1.85, 2.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Damage variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Damage in the symmetric joint</td>
<td>1.53 (1.14, 2.06)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

The analyses of the hand and foot joints demonstrated that the activity (tenderness and/or swelling) history of the specific joint is associated with subsequent damage. For the joints of the feet, activity observations elsewhere, in particular in the same toe, were also shown to be associated with subsequent damage. Moreover, the longer the patient is in clinic and longer the time between visits, the more likely that joint damage is observed.

Conclusions: Both joint tenderness and swelling are important predictors of joint damage in PsA. Frequent and regular follow-up assessments may contribute to the prevention of joint damage.

Disclosure: V. Chandran: None; L. Creswell: None; V. T. Farewell: None; D. D. Gladman: None.

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Inflammatory Bowel Disease Markers in the Stool of Patients with Ankylosing Spondylitis Compared to Healthy Controls. Franziska Matzkie2, Dermot McGovern2, Stephen Targan3 and Michael H. Weisman3. 1 Cedars Sinai, San Bruno, CA, 2 Cedars Sinai, Los Angeles, CA, 3 Cedars Sinai Medical Center, Los Angeles, CA

Background: Past and current research continues to uncover relationships between Ankylosing Spondylitis (AS) and inflammatory bowel disease (IBD). AS patients have a high frequency of asymptomatic chronic gut inflammation. IBD and AS share key genetic and pathogenetic features. In both diseases the mucosal integrity is disrupted, leading to increased permeability, exposure to dietary/infectious antigens, and subsequent loss of tolerance to bowel flora and priming of inflammatory T-cells. Since T cells reactive to bacterial antigens have also been detected in the joints of AS patients, it is tempting to hypothesize that the gut might play an important role in the pathogenesis of AS.

Advances in IBD research have identified fecal calprotectin (fCAL), a neutrophil-derived protein that can be quantified in the feces, as a marker of bowel inflammation that correlates with the histological degree of inflammation. We propose that patients with AS will have increased levels of fecal calprotectin in their stool compared to healthy controls (HC) even in the absence of any clinical symptoms.

Methods: 41 consecutive patients with established AS were selected from our cohort and 42 HC were recruited. AS patients or HC that used NSAIDS within 2 days of the collection and AS patients currently on humira or infliximab or with a prior diagnosis of IBD were excluded. Stool samples were sent to Genova diagnostics; fCAL was measured by ELISA and a cut of 50 µg/ml was used for a sample to be called positive.

Results: 17 AS patient (40%) and 3 HC (7%) had positive fCAL levels in their stool. Average fCAL level in AS was 112µg/ml vs 26µg/ml in HC. Results were statistically significant with p less than 0.001. When fCAL positive and negative AS patients were compared no statistical significant differences were found in regards to age, gender, disease duration, NSAIDS use, HLA-B27 positivity, prior uveitis or peripheral arthritis. More Enbrel use (58% vs 36%), higher BASDAI (3.4 vs 2.9), BASFI (35 vs 24) and BASRI (6.6 vs 5.6) scores were observed in the fCAL positive AS group compared to the negative AS group. However none of these parameters were statistically significantly different between the two groups.

Conclusion: fCAL was found at significant higher levels in patients with AS compared to HC. These AS patients did not possess typical symptoms or had a prior diagnosis of IBD and were not treated with medications that would influence bowel inflammation. Increased levels of fCAL therefore truly represent subclinical inflammation of the bowel in this cohort of AS patients. fCAL is a noninvasive, stable, reliable, and reproducible test for IBD inflammation. It therefore can be studied to evaluate subclinical bowel inflammation in large cohort of patients. Currently, there are no serologic or other biological markers in AS that are associated with clinical phenotypes, genetic associations, or treatment response. Further studies utilizing fCAL might prove to have pathophysiological significance with regard to genetic associations and environmental triggers.

Disclosure: F. Matzkies: None; D. McGovern: None; S. Targan: None; M. H. Weisman: None.
Influence of Fc-Gamma Receptor IIA (CD32) and IIIA (CD16) Polymorphisms on the EULAR Response to Anti-Tumor Necrosis Factor-alpha Therapy in Psoriatic Arthritis: A Longitudinal Study with 2 Years Follow-Up.

Background: Psoriatic arthritis (PsA) is a chronic inflammatory disease with an increased prevalence of gastrointestinal (GI) symptoms. Few studies have evaluated the presence of pathogenic parasites in PsA patients under concomitant methotrexate therapy and anti-TNF-alpha treatment. The aim of this study was to evaluate the role of parasitoses in PsA patients.

Methods: Patients fulfilling the CASPAR criteria for PsA, non-responsive to methotrexate (≥15 mg/week) and starting anti-TNF-alpha therapy were included. GI symptoms and fecal occult blood test were recorded. Parasites were detected by sensitive methods, such as BS and MRI, in assessing the involvement of the target organ. Patients were also treated with metronidazole for giardiasis.

Results: GI symptoms were present in 35.2% of patients with high affinity FCGRIIA polymorphisms compared with 33.3% in patients with low affinity polymorphism (RR). The frequency of methotrexate/anti-TNF-alpha treatment was higher in patients with pathogenic parasites compared to those without these pathologies (77% vs. 54%, p = 0.0224), despite a similar mean of duration of anti-TNF therapy in both groups (12.3 ± 9.9 vs. 15 ± 11.1 months, p = 0.2231) and disease activity parameters (p = 0.05).

Conclusion: It has been identified that microsporidiosis is a frequent opportunistic infection in rheumatic diseases patients under concomitant methotrexate and anti-TNF therapy treatment regardless of the gastrointestinal symptoms and therefore investigation for microsporidia is highly recommended for early diagnosis. This drug combination seems to play an important role in host defense probably by inhibiting inflammatory mediators.

Disclosure: N. E. Aikawa: Wysth Pharmaceuticals; 2. A. O. Twardowsky: None; J. Carvalho: None; C. Silva: None; I. Silva: None; A. Medeiros: None; C. Gonçalves: None; J. Moraes: None; E. Bonfa: None.

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Involvement of the Anterior Chest Wall in Patients with Spondyloarthrititis: Relationships between Clinical Symptoms and Imaging Features.

Background: The anterior chest wall (ACW) is frequently affected in spondylarthrititis (SpA), although its involvement is underestimated. The wide range of disorders found in this anatomic region renders the conventional radiology frequently inadequate for the diagnosis. Plain radiography appears of limited value, due to the difficulty of multiplanar evaluation of ACW joints and a poor sensitivity in revealing the first pathological changes. Bone scintigraphy (BS) is sensitive in showing the articular involvement pattern, but its specificity is considered low. New diagnostic methods, such as magnetic resonance imaging (MRI), appear potentially more effective to study the initially changes found in early SpA.

Objectives: The aim of this study was to compare the reliability of two different sensitive methods, such as BS and MRI, in assessing the involvement of ACW in patients with early SpA.

Methods: Out of 105 consecutive patients (pts) with early (≤ 1 year) SpA attending the Rheumatology Unit of the Padova University, from January 2008 to April 2010, 31 (29.5%, 17 F, mean age 46.2 ± 12.6 yrs) complained of symptoms (pain and/or tenderness) in the ACW and so were submitted to BS and targeted MRI. Eighteen pts (58.1%) were affected with psoriatic
arthritis (PsA), 5 (16.1%) with ankylosing spondylitis (AS) and 8 (25.8%) with undifferentiated SpA (USpA).

**Results:** At clinical examination, the right sternocostoclavicular (SCCJ) was involved in 28 pts (90.3%), the left SCCJ in 25 pts (80.7%) and the sternum in 4 pts (12.9%). Out of the 31 pts with clinical symptoms BS was positive in 26 (83.8%) and MRI in 18 (58.1%). At BS, the most frequently involved joints were the left and right SCCJ, respectively in 16 pts (51.6%); and in 19 pts (61.2%), followed by the sternum, found in 12 pts (38.8%). MRI too showed a more frequent involvement of SCCJ, found in 17 pts (54.8%), while the sternum was involved only in 6 pts (19.4%). Main changes reflecting early signs of active disease such as bone edema with synovial hyperemia were observed in 11 pts (35.5%), endoarticular swelling in 1 (3%), increase of thickness of capsular structure in 12 pts (38.7%) and erosions in 5 (16.1%); among other signs, marginal bone irregularities were found in 5 pts (16.1%), osteocondritic processes in 6 (19.4%), and osteophytes in 2 (6.5%). The concordance between symptoms and imaging was more evident for BS (26 pts, 83.8%) than for MRI (18 pts, 58.1%)

**Conclusions:** The ACW involvement in early SpA is not so rare and it is mainly found in female pts. Both two imaging methods seem useful to investigate ACW symptoms. The BS confirms its higher sensitivity and, although less specific, it can reveal a subclinical involvement. MRI may give information useful for the therapeutic approach, revealing type and extent of articular involvement, in particular the presence of bone erosions.

**Disclosure:** R. Ramonda: None; A. Lo Nigro: None; M. Lorenzin: None; V. Modesti: None; F. Angelini: None; C. Campanna: None; P. Frallonardo: None; L. Puntz: None.

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Long Term Profile of Cytokine, Metalloproteinase and Cartilage Biomarkers in Psoriatic Arthritis Patients Treated with Biologic Therapy. Jose Luis Fernandez-Sueiro, J. C. Fernandez-Lopez, N. Oreiro-Villar, S. Pertega-Diaz, J. A. Pinto and FJ Blanco. Complejo Hospitalario Universitario La Coruña, La Coruña, Spain

**Objective:** To assess the cytokine, metalloproteinase (MMP) and cartilage biomarkers (CB) profile in long term psoriatic arthritis (PsA) patients treated with biologic therapy.

**Patients and Methods:** PsA patients met CASPAR criteria. Biologic therapy was started following the recommendations of the Spanish Society of Rheumatology. Patients were evaluated just before starting therapy and then every 12 weeks until last evaluation. In each visit SJC, TJC, VAS patient, physician, total pain, morning stiffness, HAQ, ESR and CRP was performed. Serum and blood was taken just before starting therapy and then every 12 weeks. For this study we analysed serum samples before starting therapy and at the last evaluation. We determined by ELISA the following: IL-1β, IL-6, IL-10, TNFa, MMP-1, MMP-3, C2C and CPII. All determinations were performed with commercial kits following the manufacturer’s instructions. For the statistical analysis, Mann-Whitney test and Wilcoxon signed-rank tests were used.

**Results:** 38 PsA patients started the study, 19 were females. The mean age was 43.2±10.6 years; mean time of evolution was 8.2±4.8 years, mean time of follow up 47.6±15.2 months. 16 patients (42%) were treated with infliximab (INFx) and 22 (57.9%) were treated with etanercept (ETA) at start, in the last visit 15 patients (INFx) and 22 (57.9%) were treated with etanercept (ETA) at start, in the last visit 10 patients with ADA (26%). All patients were characterized by a higher weighted mean intima-media thickness (IMT) than controls (3.34 mm vs 2.0 mm; p=0.031). At clinical examination, the right sternocostoclavicular (SCCJ) was involved in 28 pts (90.3%), the left SCCJ in 25 pts (80.7%) and the sternum in 4 pts (12.9%). Out of the 31 pts with clinical symptoms BS was positive in 26 (83.8%) and MRI in 18 (58.1%). At BS, the most frequently involved joints were the left and right SCCJ, respectively in 16 pts (51.6%); and in 19 pts (61.2%), followed by the sternum, found in 12 pts (38.8%). MRI too showed a more frequent involvement of SCCJ, found in 17 pts (54.8%), while the sternum was involved only in 6 pts (19.4%). In the basal visit, the following changes were observed in the patients treated with biologic therapy: IL-6, MMP-3 and C2C decrease whereas CPII/C2C increase in ACR20 responders. In this long term follow up of PS patients treated with biologic therapy, IL-6, MMP-3 and C2C decrease whereas CPII/C2C increases, however these changes are more profound if patients clinically respond to therapy as assessed by ACR20.

**Conclusion:** In the long term follow up of PsA patients treated with biologic therapy, IL-6, MMP-3 and C2C decrease whereas CPII/C2C increases, however these changes are more profound if patients clinically respond to therapy as assessed by ACR20. In this long term follow up study, IL-6, MMP-3 as well as CPII/C2C seems good markers of synovial inflammation and cartilage metabolism.

**Disclosure:** J. L. Fernandez-Sueiro: None; J. C. Fernandez-Lopez: None; N. Oreiro-Villar: None; S. Pertega-Diaz: None; J. A. Pinto: None; F. Blanco: None.

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Myocardial Infarction and Cardiovascular Risk Profile in Ankylosing Spondylitis. A Systematic Review and Meta-Analysis. Sylvain Mathieu, Laure Gossec, Maxime Dougados and Martin Soubrier. 1Hospital Cochin, Paris, France, 2Rhumatologie B, Hôpital Cochin, Paris, France, 3Rhumatologie, CHU Gabriel Montpied, Clermont-Ferrand, France

**Background:** Rheumatoid arthritis (RA) is associated with increased cardiovascular risk. In ankylosing spondylitis (AS) there is little information on cardiovascular risks, especially that of myocardial infarction (MI) risk.

**Objectives:** To assess the incidence of MI and the cardiovascular risk profile in AS patients.

**Methods:** A literature review of publications up to August 2009 was performed using PubMed, Embase, the Cochrane Collaboration and congress abstracts. All observational studies reporting MI and all case/control studies assessing traditional (blood pressure, glycemia, metabolic syndrome, body mass index (BMI), lipid profile) and newer cardiovascular risk factors (intima-media thickness (IMT)) in AS patients and healthy controls were included. Myocardial infarction risks were calculated by metapropotion (inverse of the variance method) and for 100 patient-years (pyrs) of exposure. To assess the MI risk in AS, a meta-analysis was performed using Mantel-Haenszel’s method. For continuous variables, the differences between AS patients and controls were expressed by standardized mean difference using inverse of variance method.

**Results:** Eight longitudinal studies were included (N patients=3279). In control groups (N=82735), 1318 MI were observed (4.6 % (95%CI [0.01, 0.10])). A total of 224 MI were reported in the 3279 AS patients during a mean follow-up of 22 years. In AS patients, the incidence of MI was about 7.0 % (95% CI [0.05, 0.10]) i.e. 0.35/100 pyrs. Meta-analysis of the three longitudinal studies comparing occurrence of MI in AS patients (146/2266) and healthy controls (1318/82745) showed no significant increase in MI in AS patients: risk ratio = 1.88 (0.83–4.28). Fifteen case/control studies and nine abstraction studies were included (N patients=1214 and N controls=1000). AS patients were characterized by a higher weighted mean intima-media thickness (0.61±0.12 vs. 0.54±0.10 mm; p=0.008), a significant decrease in levels of triglycerides, of total cholesterol and of HDL cholesterol compared with healthy controls. The risk of metabolic syndrome was higher in AS
patients: RR = 2.13 (95% CI [1.46, 3.06]), but without differences in level of glyceria or in BMI. No difference was evidenced in blood pressure, levels of homocysteinemia, of LDL cholesterol and atherogenic index (total cholesterol/HDL cholesterol).

**Conclusion:** AS patients appear at higher risk of MI compared to controls. This could be due to an atherogenic lipid profile or to systemic inflammation. Management of cardiovascular risk factors and control of systemic inflammation should be taken into account in AS.

**Disclosure:** J. D. Cañete: None; L. Gossec: None; M. Dougados: None; M. Soubrier: None.

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**National Survey of Patients with Psoriatic Arthritis in Spain: Disease Activity, Pharmacological Therapy and Impact on Quality of Life.** Juan D. Cañete1, Julio Ramirez2 and Rosario Rodriguez3. 1Arthritis Unit, Rheumatology Dpt. Hospital Clinic and IDIBAPS, Barcelona, Spain, 2IDIBAPS, Barcelona, Spain, 3Medical Dept, Sanofi-Aventis Spain, Barcelona, Spain

**Objective:** To evaluate disease activity, pharmacological treatment and the impact on functional capacity and quality of life of psoriatic arthritis in Spain.

**Methods:** Cross-sectional, multicenter, national survey. The following data were collected: age, sex, type of psoriasis, swollen and tender joint counts (SI 44/TJ 46); ESR (mm/hour), CRP (mg/dL), DAS28, Psoriasis Global Assessment (PGA), Physician Global Assessment (PhyGA), Patient Global Assessment (PatGA), pharmacological therapy (AINEs, glucocorticoids, DAMARDS, and anti-TNFαfa therapy), Visual Analogue Scale (VAS) of pain, Disease impact as measured by VAS in the personal, occupational, and social spheres, Health Assessment Questionnaire (HAQ) and Dermatology Life Quality Index (DLQI).

**Results:** 214 patients with psoriatic arthritis fulfilling CASPAR criteria from 54 Spanish rheumatology outpatient clinics were included. Fifty-six per cent were male and the mean age was 52 years (mean (95%CI):50.1;53.8). Seventy-eight percent of patients had type I and 22% type II psoriasis. Patient had the following clinical and functional parameters: TJC:3.2 (6.3,7.3); SJC:2.4 (2.2,9) ESR:20.6 mm/h (18.4–22.8); CRP:5.3 mg/dL (3.7;6.8); DAS28 3.1 (2.9;3.3); PhyGA:24.7 (21.4–27.9); PatGA:29.2 (25.3;33.2); VAS of global pain:29.7(25.5;33.8). 24% of patients had a moderate-severe extent of PsA as measured by PGA.

Disease impact as measured by VAS in the personal, occupational and social spheres, were 26.2(22.1;30.3), 27.9(23.2;32.8) and 23.2(19.1;27.3), respectively, with females reporting more significant involvement than males in the personal sphere (31.2(25.37.4) vs 22.1 (16.7;27.5); p<0.03). The global HAQ was 0.61 (0.52;0.7), being significantly higher in females than in males (0.84 (0.71;0.97) vs 0.42 (0.31–0.54), respectively; p<0.00001). Global DLQ was 3.5 (2.8;4.2), with youngest patients (18–29 years) reporting greater involvement (27% marked moderate to very severe affection; p<0.05, Fisher test).

Regarding pharmacological therapies, 98.6% of patients were taken drugs for treatment of psoriatic arthritis; 58% AINE; 21% oral glucocorticoids (≥5 mg of prednisolone), 86.2% DMARDs (96% methotrexate and/or leflunomide, and 10% these drugs in combination) and 26.2% TNFaفا blockers. Of 173 patients from whom DAS28 was available, 38% were en remission (DAS28<2.6); 23% had low disease activity (DAS28>2.6–<3.2) and 39% had moderate or high activity (DAS28>3.2).

**Conclusions:** This observational national survey on psoriatic arthritis is the first trying to reflect treatment, clinical activity of disease and quality of life of patients with psoriatic arthritis in Spain. Globally it suggests that despite most patients are treated with DMARDs and one quarter with TNFaفا blockers, almost 40% of patients still exhibit moderate-high disease activity and 25% had moderate-high skin involvement. Furthermore, although the impact of the disease on functional capacity and psoriasis-related quality of life is globally mild-moderate, the group constituted by females and people of ≤30 years suffered a greater impact, suggesting we need to intensify the treatment of their joint and skin involvement.

**Disclosure:** J. D. Cañete: None; J. Ramirez: None; R. Rodriguez: None.

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**Performance of Different Criteria Sets for Inflammatory Back Pain in Patients with Axial Spondyloarthritis with and without Radiographic Sacroiliitis.** Dilek Solmaz1, Servet Akar2, Ozgul Gunduz2, Feride Yukسل2, Gercek Carl2, Vedat Gerdan1, Yesim Akkok2, Merih Birlik1, Fatos Onen1 and Nurullah Akkok2. 1Internal Medicine, Dokuz Eylul University Faculty of Medicine, 2Physical Therapy and Rehabilitation, Ege University Faculty of Medicine, Izmir, Turkey

**Background:** The most prominent clinical feature of axial spondyloarthritis (SpA), is inflammatory back pain (IBP). Therefore it is of crucial importance to recognize inflammatory back pain for an early diagnosis of axial SpA, including ankylosing spondylitis (AS). Up to now several criteria sets have been proposed to define inflammatory back pain (IBP). Assessment of SpondyloArthritis International Society (ASAS) just recently published new criteria set for diagnosing IBP. In the present study we evaluated the performance of the new ASAS criteria for IBP in comparison to Calin and Berlin criteria in patients with axial SpA using a control group of patients with chronic mechanical low back pain (MLBP).

**Patients and Methods:** The study sample included a total of 214 patients [117 male (54.7%); mean age42.6±12.2] with a diagnosis axial SpA based on clinical and radiologic findings and 44 patients with a diagnosis of chronic (>3 months) MLBP based on the treating physician’s clinical judgment (MLBP group). Among patients with axial SpA, 70 patients had active sacroiliitis (SI on MRI as defined by ASAS (SI on MRI group) and 144 patients had radiographic SI as defined by the modified New York criteria (AS group). A face to face interview by using a standardized questionnaire addressing all the components of inflammatory back pain included in Calin, Berlin and new ASAS criteria sets was performed by the same trained physician. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) were measured. Data about HLA B27 status, erythrocyte sedimentation rate and C reactive protein (CRP) levels were obtained from the patients charts if available.

**Results:** There were significantly more male patients (<p<0.001) in the AS group (%66) than in the SI on MR (%31.4) and also than in the MLBP group (%36.4). Some demographic and clinical features in the patient groups are shown in Table 1.

**Table 1.** Demographic and clinical features in the study groups

<table>
<thead>
<tr>
<th>Feature</th>
<th>AS group (n = 144)</th>
<th>SI on MRI group (n = 70)</th>
<th>MLBP group (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n (%)</td>
<td>95 (66)</td>
<td>22 (31)</td>
<td>16 (36.4)</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>42.3 ± 11.6</td>
<td>43.1 ± 12.7</td>
<td>43.6 ± 11.6</td>
</tr>
<tr>
<td>Age at onset of back pain, mean ± SD</td>
<td>24.7 ± 7.4</td>
<td>27.8 ± 7.4</td>
<td>29.7 ± 9.6</td>
</tr>
<tr>
<td>Education Level, mean ± SD (years)</td>
<td>9.5 ± 3.8</td>
<td>10.4 ± 4.2</td>
<td>9.0 ± 4.2</td>
</tr>
<tr>
<td>BASDAI, mean ± SD</td>
<td>3.4 ± 2.2</td>
<td>4.8 ± 2.6</td>
<td>3.2 ± 2.4</td>
</tr>
<tr>
<td>BASFI, mean ± SD</td>
<td>2.7 ± 2.6</td>
<td>3.1 ± 2.4</td>
<td>2.2 ± 2.0</td>
</tr>
<tr>
<td>CRP, mean ± SD</td>
<td>12.9 ± 14.5</td>
<td>8.2 ± 14.3</td>
<td>3.6 ± 3.7</td>
</tr>
<tr>
<td>HLA-B27 positivity</td>
<td>72%</td>
<td>36%</td>
<td>71%*</td>
</tr>
</tbody>
</table>

*HLA-B27 positivity reported in the general Turkish population in previous publications.

Among the criteria sets, Calin criteria showed the best sensitivity (92%), and Berlin criteria showed the best specificity (84%) in the differentiation of inflammatory back pain from chronic mechanical back pain. If the morning stiffness component of Calin’s criteria set was defined as longer than 30 minutes, the performance of different criteria sets in different patient groups are shown in Table 2.

**Table 2.** Performance of different criteria sets in different patient groups

<table>
<thead>
<tr>
<th>Feature</th>
<th>Calin</th>
<th>Calin 30</th>
<th>Berlin</th>
<th>ASAS</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>95.1</td>
<td>85.8</td>
<td>88.0</td>
<td>75.7</td>
<td>74.3</td>
</tr>
<tr>
<td>Specificity</td>
<td>50.0</td>
<td>75.0</td>
<td>75.0</td>
<td>84.0</td>
<td>84.0</td>
</tr>
<tr>
<td>+LR (%)</td>
<td>1.9</td>
<td>1.7</td>
<td>3.5</td>
<td>3.0</td>
<td>4.6</td>
</tr>
<tr>
<td>-LR (%)</td>
<td>0.09</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>19.5</td>
<td>7.7</td>
<td>24.9</td>
<td>15.2</td>
<td>19.3</td>
</tr>
</tbody>
</table>

*Odds Ratio 19.5 7.7 24.9 15.2 19.3 8.9 7.1*
Conclusion: New ASAS criteria for IBP did not seem to perform better in differentiating IBP from chronic mechanical back pain, than the existing criteria sets in patients followed at a rheumatology outpatient clinic.

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Objective: Previous studies of pregnancy in ankylosing spondylitis (AS) have not included a control group in order to control for pregnancy-related effects on back pain in general. We performed a case control study to evaluate the impact of pregnancy in patients with AS.

Methods: A questionnaire was developed and mailed to female AS patients in a longitudinal AS clinic and to a group of female psoriasis patients as controls. Patients with psoriatic arthritis were excluded. The questionnaire consisted of clinical data on AS (age of symptom onset and diagnosis of AS, analgesics use), numerical rating scale (NRS) for pain and stiffness for the periods pre-, during and post-pregnancy, and the Roland-Morris questionnaire, a disease-specific validated questionnaire with 24 items inquiring about the severity of symptoms and functional impairment due to back pain.

Results: Nineteen female AS patients (with 35 pregnancies) and 33 psoriasis controls (with 77 pregnancies) completed the questionnaire. AS patients experienced significantly more back pain compared to controls in all three trimesters based on the Roland-Morris questionnaire (mean values for 1st, 2nd, 3rd trimesters; 6.4, 9.7, 11.7 for AS vs 4, 1.4, 4.5 for controls; p < 0.001 for the 1st and 2nd trimesters and p = 0.001 for the 3rd trimester).

In the 1st trimester, there was a significant improvement in pain and stiffness in the AS patients compared to baseline pre-pregnancy levels. However, in the 2nd and 3rd trimesters, AS patients experienced significantly more pain and stiffness. The first month postpartum showed trend towards less pain (p = 0.072) and stiffness (p = 0.108) in the AS patients, but worsening of symptoms ensued from the second to the sixth month post partum. At six months postpartum the level of pain and stiffness had returned to baseline pre-pregnancy levels.

No increase in flares of psoriasis, uveitis, peripheral arthritis or inflammatory bowel disease was reported during pregnancy. Most AS patients who performed stretching exercises prior to their pregnancies continued with their exercise regime during their pregnancies (p = 0.005). Seven patients did not perform stretching exercises due to fear of complication to pregnancy (p = 0.023). Most AS patients refrained from analgesics medications during their pregnancies (p = 0.028) for fear of adverse effects on the fetus (p < 0.001). Back pain did not hinder breast feeding.

Conclusion: The improvement in back pain and stiffness in the 1st trimester could be related to the high levels of human chorionic gonadotropin (HCG) hormone in the 1st trimester of pregnancy. Previous hormonal reports have found HCG to possess significant analgesic effects. The worsening of symptoms in the 2nd and 3rd trimesters was seen both in AS and controls and likely reflects biomechanical loading of the low back with later stages of pregnancy. AS patients appear to return to baseline levels of back pain and stiffness post partum, suggesting that pregnancy does not substantially aggravate disease activity in AS.

Disclosure: N. L. Lui: None; A. Carty: None; N. Haroon: None; S. Shantmugarajah: None; H. Shen: None; R. J. Cook: None; D. D. Gladman: None; R. D. Inman: None.

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Prevalence and Characteristics of Uveitis in US Veterans with Seronegative Spondyloarthropathy. Marwin Gutierrez1, Andrea Becciolini1, Emilio Filippucci1, Fausto Salaffi2, Rossella De Angelis2, Bernd Raffeiner4, Marco Canzoni2, Fausto Salaffi1, Rossella De Angelis1, Andrea Becciolini1, Emilio Filippucci1, Fausto Canzoni2, Marco Canzoni2, Viviana Ravagnan1, Chiara Bertolazzi1, Maria L. Sorgi1, Domenico Biasi1, Leonardo Punzi1 and Walter Grassi1.

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Background: Seronegative spondyloarthropathy (SpA), may be associated with an increased risk of cardiovascular disease (1). Metabolic syndrome (MetS) clusters risk factors for atherosclerotic cardiovascular disease including: insulin resistance, central obesity, low levels of high density lipoprotein, high triglyceride levels and elevated blood pressure. To date, different studies demonstrating a high prevalence of MetS in patients with rheumatic diseases have been published (2). However, little is still known about its prevalence among patients with SpA.

Objective: To investigate the prevalence of MetS in patients with SpA.

Methods: 119 consecutive patients (72 men and 42 women; disease duration 116.42 months, 95% CI 85–137.7; median of age 51.37, range 22–79) affected by SpA (73 with psoriatic arthritis, 20 with ankylosing spondylitis, 15 with undifferentiated spondyloarthropathy, 6 with enteropathic spondyloarthropathy and 5 with reactive arthritis), attending the out-patient and in-patient clinic of the Rheumatology Departments involved in this multicenter cross-sectional study were enrolled. The diagnoses were made according to the European Spondyloarthritis Study Group criteria (3). The following

Purpose: Acute anterior uveitis (AAU) is recognized as the most common extra-articular manifestation of ankylosing spondylitis (AS) occurring in up to 41% of cases but is less frequently in other spondyloarthopathies (SpA), and is more prevalent in SpA patients who are HLA-B27 positive. Herein we describe the frequency, demographic and clinical associations of AAU in a cohort of US veterans enrolled in the PULSAR registry (Program to Understand the Long Term Outcomes of SpA).

Method: Patients > 18 years old, with EULAR Criteria for SpA were enrolled in PULSAR from 4 VA Medical Centers. SpAs included were AS, Psoriatic arthritis (PsA), Reactive arthritis (ReA), SpA due to inflammatory bowel disease (IBD), and undifferentiated SpA (USpA). All participating sites received IRB approval and all subjects gave written informed consent. Data collected included demographic data, clinical and laboratory features of SpA, HLA-B27, DMARD/biologic agents, comorbid diseases, and extra-articular manifestations. AAU was defined as painful photophobia, with ophthalmologic confirmation of uveal tract inflammation, and visual acuity (va) and intra-ocular pressure (IOP) data obtained.

Results: There were 265 SpA patients enrolled in PULSAR, the majority were male (95.5%), with a mean age of 57.13 years, and mean disease duration of 20.5 years and 57.9% were HLA-B27 positive. Seventy-six had AS, 137 had PsA, 27 ReA, and 22 had USpA or IBD arthritis. AAU was present in 28 (10.6%), with a mean disease duration of 10.9 years. One hundred and ninety-five (73.6%) were Caucasian, 34 (12.8%) were African American (AA). Patients with AS had the highest prevalence of AAU, [14/76 (18.4%)] and frequencies in other SpA were: PsA, [5/137 (3.7%)], ReA [5/27 (18.5%),] and USpA/IBD [4 of 22 (18.2%)]. The ethnic distribution of AAU was similar to that of SpA: Caucasians 72.7% and AA 11.8%. Most were HLA-B27 negative [89/150 (59.3%)], 64/150 (42.7%) were HLA-B27 positive versus HLA-B27 negative patients, (19/105 patients; 18.1% vs 3/87; 3.5%, respectively). The majority (16/22), had chronic or recurrent episodes of AAU. Thirteen of 20 had arthritis concurrent with uveitis flares. Two patients were ineligible for drivers licenses (va 20/50 – 20/70), while only one was legally blind (va < 20/200). Glaucoma (IOP > 21) was present in only 4 of 19 subjects and approximately one third (7/20) developed cataracts. In addition to topical steroids, 30% received oral prednisone, 46% were on traditional DMARDs, while 18 of 26 (67%) received an anti-Tumor Necrosis Factor alpha (anti-TNF) agent.

Conclusion: In a cohort of male US Veterans, AAU was more common in HLA-B27 positive individuals, occurred half as frequently as reported in the literature, but oral prednisone and/or steroid sparing agents were required in as many as a third. Therapy for concomitant active SpA with DMARDs and/or anti-TNF agents may have accounted for the infrequent occurrence of AAU in our cohort.

Disclosure: H. Monshie-Vahabadze: None; S. Vahadan: None; J. S. S. Richards: None; A. Reimold: None; J. Walsh: None; G. S. Kerr: None.
items for each patient were taken: waist circumference, triglycerides, high density lipoprotein, fasting glucose and blood pressure. The presence of MetS was determined according to the modified National Cholesterol Education Program 2004 (NCEP 2004) criteria (4).

Results: The overall prevalence of the MetS among SpA patients was 36.9% (44/119). The patients who did not satisfy at least one item for MetS was 21.8% (26/119). The group with the highest prevalence of MetS was enteropathic spondyloarthritides (50%), followed by psoriatic arthritis (41%), ankylosing spondylitis (35%), undifferentiated spondyloarthritides (26.6%) and reactive arthritis (0%). MetS resulted more prevalent in patients with more than 60 years (58.3%) respect to 35.4%, 34.4% and 8.6%, in patients between 50–59 years, 40–49 years and less of 40 years respectively. We found more frequently MetS in male patients (43%) compared with female patients (27.6%).

Conclusion: The MetS is a common finding in patients with SpA to increases cardiovascular risk. NCEP 2004 criteria are a fast and easy screening tool that should be adopted in the management of patients with SpA.

References:


Grassi:
None.

De Angelis:
None.

Dougados:
None.

Patients were more likely to have higher scores (OR=3.6; p=0.01). The addition of ESR, CRP or BASDAI did not improve the model. Chi-square test was used to further analyze individual SNPs with significance in the regression analysis.

Results: A total of 334 patients (19% female, 137 and 197 from the respective centers) with a mean age of 41.8 ± 13 years were included in the study. The mean (± SD) BASDAI, ESR and CRP were 4.8 ± 2.4, 18 ± 23 mm/hr and 13 ± 6 g/L respectively. The mean mSASSS score at baseline was 19.8 ± 22.6 with 40% showing some progression at a mean rate of 0.8 ± 1.5 units/year. The SNPs rs17587 (LMP2), rs26618, rs26653, rs27044, rs30187 (ERAP1) and rs241447 (TAP2) were included in the analysis while the MAF of the SNPs rs1057141, rs1800454, rs2071543, rs2228396, rs3734016, rs4148876 and rs10050860 were too low and excluded.

Conclusions: These results suggest an up-regulation of DKK-1 in AS, neither explained by patient’s demographic characteristics nor by parameters related to disease activity (BASDAI, or biological markers of inflammation). DKK-1 serum level tends to be negatively correlated with lumbar spine T-score and SOST was highly correlated with disease duration, suggesting that both factors could contribute to osteopenia and/or osteoporosis described in AS patients. The respective role of DKK-1 and/or SOST in the structural progression of the disease has not been assessed in this study but high basal levels for DKK-1 and increased levels of SOST according to disease duration are unlikely to explain syndesmophyte formation in AS. The lack of significant variation of DKK-1 and SOST under anti-TNF treatment is in accordance with the absence of structural effect reported for these treatments, at least after a short time follow-up. Conversely, NSAIDs daily intake for most patients (89%) at inclusion in the study may partially account for such DKK-1 serum level increase, a hypothesis that could suggest a potential structural effect of NSAIDs in AS.

Disclosure: C. Miceli-Richard: None; S. Malbos: None; S. Pavy: None; S. Kolta: None; K. Briot: None; J. Sellam: None; X. Mariette: None; C. Roux: None; M. Dougdos: None.

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Radiographic Progression Is Influenced by ERAP1 Polymorphisms with Gender and Age Being Co-factors. Nigil Haroon*, Walter P. Maksymowych,†, Proton Raliman‡, Florence W. Tsui* and Robert D. Imnani*. ‡St Claren's Memorial Hospital, St John's, NL, Canada. †Toronto Western Hospital, Toronto, ON, Canada, §Toronto Western Research Institute and University of Toronto, ¶University of Alberta, Edmonton, AB, Canada.

Introduction: Endoplasmic reticulum aminopeptidase 1 (ERAP1) polymorphs have recently been identified to be associated with ankylosing spondylitis (AS). It is not however known if ERAP1 variants influence radiographic severity in AS.

Methods: Caucasian patients with AS (by the modified New York Criteria) from two centers were included in the study. X-rays of the lumbar and cervical spine were scored by the modified Stoke AS spine score (mSASSS). Patients had to have at least two mSASSS scores for inclusion. Genotyping for 14 AS-associated ERAP1 single nucleotide polymorphisms (SNPs) were done using the MassARRAY system. SNPs were excluded from analysis if the minor allele frequency (MAF) was <0.05. Linear regression analysis was done to examine the influence of the SNPs on the baseline mSASSS. For logistic regression, the patients were classified as progressors (any progression in mSASSS) and moderate or faster progressors if they had ≥1 or ≥2 mSASSS unit change/year respectively. Chi-square test was used to further analyze individual SNPs with significance in the regression analysis.

Results: A total of 334 patients (19% female, 137 and 197 from the respective centers) with a mean age of 41.8 ± 13 years were included in the study. The mean (± SD) BASDAI, ESR and CRP were 4.8 ± 2.4, 18 ± 23 mm/hr and 13 ± 6 g/L respectively. The mean mSASSS score at baseline was 19.8 ± 22.6 with 40% showing some progression at a mean rate of 0.8 ± 1.5 units/year. The SNPs rs17587 (LMP2), rs26618, rs26653, rs27044, rs30187 (ERAP1) and rs241447 (TAP2) were included in the analysis while the MAF of the SNPs rs1057141, rs1800454, rs2071543, rs2228396, rs3734016, rs4148876 and rs10050860 were too low and excluded.

In binary logistic regression by forward stepwise conditional method, a model with rs17587 (p=0.01) predicted patients with high baseline mSASSS (defined as ≥50% of maximum = 36). Gender significantly improved the model (p=0.004) with males being more likely to have higher scores (OR=3.6; p=0.01). The addition of ESR, CRP or BASDAI did not improve the model. Chi-square test across the different genotypic groups for high baseline mSASSS scores were significant for rs17587 (χ2=6.4, p=0.01) and there was a trend in rs30187 (p=0.054). The mean baseline mSASSS in patients with change in mSASSS of < 4 units was significantly lower than those with >4 mSASSS units change (15 vs 25; p=0.0005).

There were significant baseline differences between the two cohorts with patients in one center being younger (38±13 vs 43±13 years; p=0.0003), and tended to have lower baseline mSASSS (20±21 vs 16±21) and more progression (2±3.1 vs 1.6±3.2). As baseline mSASSS is a strong predictor of progression, and the radiographic progression can vary between early and late disease, the cohorts were analyzed separately. Logistic regression model predictive of progression included rs30187 in patients from centre 1 and these patients were more likely to progress with the rs30187CC genotype compared to rs30187TT (OR 13.5; p=0.006), with this effect being further enhanced in males.
Conclusions: Genetic variants of ERAP1 and LMP2 are associated with radiographic severity in AS. Gender, age and disease duration are important cofactors influencing this interaction.

Disclosure: N. Haroon: None; W. P. Maksymowycz: None; P. Rahman: None; F. W. Tsui: None; R. D. Inman: None.

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Recently Diagnosed Ankylosing Spondylitis: Gender Differences and Factors Related to Delay in the Diagnosis. The North Israel Study of Ankylosing Spondylitis (NISAN). Glev Slobodin1, Iris Reychan1, Nina Avshovich2, Alexandra Balbir-Gurman2, Nina Boulanm2, Mona Elias1, Joy Feld3, Reuven Mader4, Doron Markovitz5, Doron Rimar2, Itzhak Rosner2, Michael Rozenbaum2, Devy Zisman1 and Majed Odeh1. 1Bnai Zion Medical Center, Haifa, Israel, 2Bnai Zion Medical Center, 3Carmel Medical Center, 4Haemek Medical Center, Afula, Israel, 5Hillel Yaffe Mecial Center, 6Rambam Medical Center, Technion

Background: Gender differences have been demonstrated in patients with advanced ankylosing spondylitis (AS). There are no studies evaluating this in patients with recently diagnosed disease. The aim of the study was to characterize a cohort of patients with recently diagnosed AS, both preradiographic and established, with emphasis on gender differences and factors leading to delay in diagnosis.

Methods: All consecutive patients diagnosed with AS in 2004–2009 were recruited over a 6 month period by participating rheumatologists. Clinical, laboratory and imaging data was collected during the screening visit and/or retrospectively for all patients enrolled.

Results: Seventy-nine men and 72 women with AS were enrolled.

Table 1. Gender-dependent features of AS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (79)</th>
<th>Women (72)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>35.6 ± 11.7</td>
<td>38.5 ± 12.3</td>
<td>0.13</td>
</tr>
<tr>
<td>Delay time to diagnosis</td>
<td>5.9 ± 6.4</td>
<td>5.7 ± 6.0</td>
<td>0.87</td>
</tr>
<tr>
<td>Frequency of anti-TNFα usage (%)</td>
<td>37/79 (49%)</td>
<td>33/72 (46%)</td>
<td>1</td>
</tr>
<tr>
<td>Presenting symptom (%)</td>
<td>70 (89%)</td>
<td>52 (73%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Arthritis</td>
<td>4 (5%)</td>
<td>8 (11%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Neck pain</td>
<td>11 (14%)</td>
<td>8 (11%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Hip pain</td>
<td>4 (5%)</td>
<td>1 (1.4%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Heel pain</td>
<td>3 (3.1%)</td>
<td>5 (7%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Uveitis</td>
<td>4 (5%)</td>
<td>5 (7%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Symptoms at the time of diagnosis</td>
<td>74 (94%)</td>
<td>70 (97%)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Radiation: Non radiating  20 7 0.016
Buttocks 37 41 0.16
Legs 17 19 0.56
Lower abdomen or pelvis 3 14 0.0012
Musculoskeletal chest/rib pain 5 (6.3%) 12 (17%) 0.07
Neck pain 21 (26%) 27 (37%) 0.16
Arthritis or arthralgia 40 (51%) 42 (58%) 0.4
Heel pain 18 (23%) 33 (46%) 0.203
Dactylitis 2 (2.5%) 3 (4.2%) 0.67
Uveitis 9 (12%) 8 (11%) 0.8
Widespread pain 5 (6.3%) 28 (39%) <0.0001

Dactylitis/Cohn’s disease 4/2 9/1 0.14
Physical examination [N]*
Schrober test (cm) 3.4 ± 1.5 [64] 3.4 ± 1.3 [50] 0.87
Finger-to-floor distance (cm) 19.5 ± 15.6 [39] 17.2 ± 13.3 [42] 0.42
Occiput-to-wall distance (cm) 3.0 ± 5.9 [62] 0.2 ± 0.8 [40] 0.0032
Chest expansion (cm) 3.4 ± 1.8 [59] 4.4 ± 2.1 [38] 0.012
Elevated ESR 31 (48%) [65] 42 (62%) [62] 0.19
Elevated CRP 51 (69%) [74] 43 (65%) [65] 0.72
CT/MRI studies of SIJ 43 (64%) 53 (74%) 0.018

[N] - number of subjects with available measurements

Both groups (men versus women) had similar age of onset of disease-related symptoms, as well as similar delay time to diagnosis, follow-up duration and frequency of anti-TNF treatment. Typical inflammatory back pain as a first symptom related to AS was reported more often by men (p = 0.02). Women reported significantly more frequent lower abdominal or pelvic pain (p = 0.0032), heel pain (p = 0.003) and widespread pain (p = 0.0001) during the course of AS. There was no gender-related difference in the incidence of uveitis, dactylitis or peripheral joint involvement. At the time of diagnosis, men were more limited in chest expansion (p = 0.012) and showed increased occiput-to-wall distance compared to women (p = 0.0032). At diagnosis, elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) were detected in a similar proportion of men and women. X-ray films were more often diagnostic for AS in males, with more females undergoing CT or MRI studies to confirm the presence of sacroiliitis (p = 0.018). In the subgroup analysis, women with WP had longer delay to diagnosis (p = 0.0073) and more frequently elevated ESR/CRP levels (p = 0.0068) compared to women without WP. No other statistically significant differences in disease presentation or burden, laboratory findings, or imaging characteristics were demonstrated to correlate with delay to diagnosis.

Conclusions: Women constituted almost 50% of all recently diagnosed patients with AS, with CT or MRI studies more frequently utilized in their diagnosis. Gender-related differences were demonstrated in both disease presentations and burden. WP in women was frequently reported, being related to significant delay in the diagnosis. As no other disease-related features were found responsible for delay in AS diagnosis, the physician’s high level of suspicion may be the dominant factor in the early diagnosis of AS.

Table 2. Disease features in AS women with and without widespread pain (WP) #

<table>
<thead>
<tr>
<th>Variable</th>
<th>With WP (28)</th>
<th>Without WP (41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>43.3 ± 11.7</td>
<td>35.4 ± 12.1</td>
<td>0.0091</td>
</tr>
<tr>
<td>Delay time to diagnosis</td>
<td>8.3 ± 7.2</td>
<td>4.3 ± 4.8</td>
<td>0.0073</td>
</tr>
<tr>
<td>Follow-up time (years)</td>
<td>1.8 ± 1.1</td>
<td>2.0 ± 1.3</td>
<td>0.35</td>
</tr>
<tr>
<td>Frequency of anti-TNFα usage %</td>
<td>15/28 (54%)</td>
<td>17/41 (41%)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Symptoms of the disease:
Inflammatory low back pain 28 (100%) 39 (95%) 0.51
Musculoskeletal chest/rib pain 9 (32%) 2 (5%) 0.0005
Neck pain 18 (64%) 8 (20%) 0.0003
Joint involvement 15 (54%) 26 (63%) 0.46
Heel pain 16 (57%) 16 (39%) 0.15
Dactylitis 0 (0%) 3 (7%) 0.27
Uveitis 3 (11%) 4 (10%) 1
Diarrhea 3 (11%) 5 (12%) 1
Lower abdominal or pelvic pain 6 (21%) 5 (12%) 0.33

Physical examination [N]*:
Schrober test (cm) 3.2 ± 1.3 [20] 3.6 ± 1.6 [29] 0.4
Finger-to-floor distance (cm) 19.6 ± 14.9 [21] 15.1 ± 11.9 [24] 0.26
Chest expansion (cm) 4.1 ± 2.3 [17] 4.6 ± 1.9 [21] 0.42
Elevated ESR or CRP 25 (63%) 24 (59%) 0.0068
CT/MRI studies of SIJ 18 (64%) 33 (80%) 0.16

#only 69 of 72 women were included to this subgroup analysis due to absence of data regarding WP in 3 women

[N] - number of subjects with available measurements

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The ECHOSPA MRI Module for Diagnosis of Early Spondyloarthritis (SpA): Preliminary Validation and Assessment of Diagnostic Utility. Walter P. Maksymowycz1, Damien Louelle2, Alexandre Desvignes-Engelbert2, Olivia Judet1, Isabelle Chary-Valckenaere1, Robert Lambert1, Maxime A. Breyani3 and Maria-Antonietta D’Agostino1. 1Faculte´ de Medicine de Nancy, Vandoeuvre les Nancy, France, 2Faculte´ de medicine de Nancy, Vandoeuvre les Nancy, France, 3Universite´ Versailles Saint Quentin en Yvelines, Boulogne-Billancourt, France, 4University of Alberta, Edmonton, AB, Canada

Purpose: MRI is now accepted as an imaging criterion for the classification of axial SpA but its diagnostic utility using conventional sequences in early pre-radiographic SpA requires further study. In particular, it is unclear which features on MRI of the sacroiliac joints (SIJ) have greatest diagnostic utility.

Methods: We developed an atlas of reference MRI images depicting the entire range of abnormalities observed in the SIJ. This included various patterns of bone marrow edema (linear, subchondral, capsular, posterior ligamentous, extra-articular, transitional vertebrae), enthesal (capsitulitis, ligamentary) and joint space inflammation, and structural lesions. These were...
incorporated into an online data entry module that displays schematics of the SIJ allowing the recording of lesions in each SIJ quadrant of each slice. Three readers blinded to patient and diagnosis, independently assessed MRI scans (T1-weighted (T1W), short tau inversion recovery (STIR), and post-gadolinium fat-saturated T1W sequences) from the following subjects: 24 patients with AS, 20 age and sex-matched patients with mechanical causes of low back pain (NSBP), and 20 patients followed in the French multi-center ECHOSPA pre-radiographic SpA prospective cohort, in which patients were included if they had a diagnostic spine MRI, arthritis, enthesitis, dactylitis, B27+ uveitis and family history of SpA). Semi-circular slices through the synovial portion of the SIJ were read systematically from anterior to posterior as described in a standardized online training module developed by the Spondyloarthritis Research Consortium of Canada (SPARCC). Readers answered the following question dichotomously (yes/no): This SIJ scan confirms the presence of SpA? Sensitivity, specificity were calculated according to clinical diagnosis and reliability of detection of individual lesions was assessed using intra-class correlation coefficient (ICC).

Results: Sensitivity/specificity of MRI for the diagnosis of SpA in confirmed AS patients was 87.5/100, 95.8/80, and 83.8/83.3 for the 3 readers, respectively. The specific inflammatory lesions seen by all 3 readers in >30% of AS patients were capsular edema, ligamentous edema, and capsulitis, and each was reliably detected (κ = 0.76, 0.70, and 0.85, respectively). Sensitivity of MRI for the detection of SIJ abnormalities in the ECHOSPA cohort was 55% for the 3 readers and 55% for the 3 readers respectively. There was no significant difference between readers in the detection of either specific inflammatory lesions or in the mean number of SIJ quadrants with bone edema. However, reliability for detection of erosions (ICC = 0.65) was less than for edema (ICC = 0.75) and fat infiltration (ICC = 0.75). Moreover, the reader who had the highest sensitivity (ICC = 0.75) also had the highest specificity (ICC = 0.65) for detection of MRI as contributory to the diagnosis of SpA in 72.7% of patients diagnosed with SpA compared to only one patient by either of the two other readers.

Conclusion: Our data shows that although various inflammatory features on MRI can be reliably detected, further improvement in diagnostic utility of MRI for early SpA may depend on further training of readers to recognize structural lesions on T1W MRI.

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The New ASAS Classification Criteria for Axial and Peripheral Spondyloarthritis: Valid in the Latin American Patients, but... John D. Londono1,2, Marlon B. Porras1,2, Enrique Calvo4, Pedro Santos3, Wilson Bautista3,4, Edward Z. Aydin1, Alan M. Bennett1, Paul Emery5, Dennis McGregor6 and Helena Marzo-Ortega1. 1Defence Medical Rehabilitation Centre, Headley Court, Epsom, Surrey, United Kingdom, 2Section of Musculoskeletal Diseases, The Leeds Institute of Molecular Medicine. University of Leeds, Leeds, United Kingdom.

Objective: Axial SpA can be identified by using the new ASAS criteria. We aimed to test the predictive value of the imaging (MRI) and HLA-B27 arms of these criteria for the future development of Ankylosing Spondylitis (AS).

Methods: An inception cohort of 33 patients with early inflammatory back pain (IBP) (median symptom duration 24 weeks) were retrospectively evaluated against both arms (imaging and HLA-B27) of the criteria. Plain radiographs and MRIs of the SIJs at baseline and radiographs after a mean duration of 8-years were assessed. MRIs were scored according to the ASAS definition of a “positive MRI” and the predictive value of both arms was compared. Further scoring to identify patients with severe MRI sacroilitis (grade 3 according to the Leeds MRI SIJ Scoring System) was also available.

Results: All patients could be classified as axial SpA with more patients fulfilling the imaging (85%, n=28/33) than the clinical arm (58%, n=19/33) of the criteria. Eight patients with baseline evidence of radiographic sacroilitis fulfilling the mNYC were excluded from the predictive analysis. Of the rest (25/33), n=4 patients developed AS at follow-up (all had a positive baseline MRI and 2 were HLA-B27+ve) and 11/33 had an increase in the radiographic sacroilitis scores at 8 years. For prediction of new AS the MRI arm showed 100% sensitivity and 19% specificity whereas the HLA-B27 arm had 50% sensitivity and 43% specificity. No differences were seen between both arms for developing new AS or for progression of sacroilitis when applying the ASAS definition of a positive MRI.

Table 1. New AS or worsening of sacroilitis by X-rays according to the MRI findings and HLA-B27 positivity

<table>
<thead>
<tr>
<th>MRI classification</th>
<th>New AS (%)</th>
<th>Severe MRI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive MRI (ASAS definition)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Severe MRI (Leeds Scoring System)</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

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The New ASAS Criteria for Axial SpA Does Not Predict the Development of mNYC AS at 8 Years in a Cohort of Very Early IBP Patients. Shibol Z. Aydin1, Alan M. Bennett1, Paul Emery5, Dennis McGregor6 and Helena Marzo-Ortega1. 1Defence Medical Rehabilitation Centre, Headley Court, Epsom, Surrey, United Kingdom, 2Section of Musculoskeletal Diseases, The Leeds Institute of Molecular Medicine. University of Leeds, Leeds, United Kingdom.

Methods: Two hundred and eighty-one consecutive patients were evaluated in the last 10 years following the ASAS recommendations. Seventy-four, with established diagnostic (by experts) were selected. All of them had complete clinical and laboratory information (including HLA-B27 screening), X-ray and magnetic resonance imaging of sacroiliac joints and were under 45 years old at the beginning of the disease. We also collected a control group: patients referred to our clinic in the same period of time with chronic back pain in which the diagnostic of SpA was ruled out, after following the same protocol.

Summary of the Results: A total of 74 patients (58 males, 16 females) with definite SpA (15 AS, 39 uSpA and 20 ReA), and 48 controls (34 males, 14 females) were analyzed. Mean disease duration in SpA patients was 1.4±1.1 vs. 4.5±4.3 years; mean age at disease onset was: 25.2±7.3 vs. 30.5±7.0 years. The key clinical findings were: arthritis and enthesitis in 75.7% (vs. 4.2% in controls), and inflammatory back pain (IBP) in 56.8% of the patients (vs. 4.2%). The other differences between the groups were: twenty-seven (36.5%) HLA-B27 positive patients (vs. 4.2%); buttock pain present in 32.4% of the patients and only 8.3% of the controls. Dactylitis was present in 24.7% of the patients vs. 0% in the controls. Uveitis was documented in 10.8% of the patients but not in controls. The family history of SpA was present in 4.2% of the patients (0% in the controls). The new Axial SpA classification criteria had a sensitivity and specificity of 66.2 and 91.7%, and the peripheral SpA classification criteria had a sensitivity and specificity of 90.5 and 87.5% respectively. When we decided to test them combined, we obtained a sensitivity of 93.2% and specificity of 87.5%. The European Spondylarthritis Study Group (ESSG) criteria had a sensitivity and specificity of 91.9 and 100%.

Conclusions: Although, the new ASAS classification criteria for axial and peripheral SpA show a good performance in our cohort, the predominant mixed form of the disease in the Latin American patients and low prevalence of HLA-B27 positivity should make us keep in mind the ESSG criteria. These results should be validated in a large group of patients.

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may be due to the inclusion of “mild” MRI sacroilitis in the ASAS definition of a “positive MRI” since severe MRI sacroilitis was a better predictor.

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The Prevalence of Cardiovascular Risk Factors in Patients with Early Psoriatic Arthritis, Majed M. Krahiši1, Rana Aslanov1 and Don MacDonald2. 1Memorial University of Newfoundland, 2Newfoundland and Labrador Centre for Health Information, 3Nexus Clinical Research, St Johns, NL, Canada

Background: Psoriatic Arthritis (PsA) is a chronic inflammatory disease affecting 5–35% of patients with psoriasis (PsO). Recently, both diseases were associated with an increased risk and a higher prevalence of cardiovascular (CVD) risk factors when compared to the general population.

Objective: To examine the prevalence of the risk factors of cardiovascular disease in patients with Early PsA (EPSA) and compare the prevalence of co-morbidities to those of established PsA patients.

Methods: The patients were recruited prospectively from a clinic specializing in treating patients with PsO and PsA. We set out to determine the prevalence of CVD risk factors including the Framingham Risk Score in the cohort of patients with early PsA of less than 2 years symptoms (EPSA cohort). Co-morbidities considered potential risk factors for cardiovascular disease (e.g. obesity, diabetes) were evaluated in the EPSA patients. Markers of inflammation and skin and joint disease severity and as risk factors for CVD were assessed by using CRP, ESR, DAS28, HAQ and PASI scores. The co-morbidities were compared to those of an established PsA cohort (more than 2 years of symptoms)

Results: A total of 72 patients with Early PsA and 108 patients with Established PsA were included in this analysis. Females prevailed over males in EPSA cohort (58.3% vs. 41.7%) and their age at the onset of PsO (49.80 vs. 45.13) and PsA (50.42 vs. 44.65). Females were at higher risk for CVD in association with the Framingham Risk Category above 10% (58.3% vs. 32.0%). The prevalence of hypertension in EPSA was higher in males (50% vs. 38.5%; p = 0.0329), while the prevalence of diabetes in EPSA was higher in females (30.8% vs. 18.8%; p = 0.0025). Generally, the distribution of conventional risk factors was similar in both cohorts, except for obesity. From total number of 35 (50%) obese people in EPSA, 19 (54.3%) were females and 16 (45.7%) were males. Odds of being obese were 2.34 times higher for patients in EPSA compared to Established PsA (OR = 0.427; p = 0.0076). The prevalence of severe psoriasis was higher in patients with Established PsA (p = 0.0507); however, the expected PASI values were 1.52 units lower in patients in Established Cohort (p = 0.0001). Also, the ESR values in EPSA were significantly lower than those in Established PsA (p = 0.0008). The utilization of NSAIDs, DMARDS and Biologics was significantly higher in Established PsA compared to EPSA (p = 0.0001), while the differences in using other medications remained non-significant.

Conclusion: These results support the hypothesis that PsA even at early stages may be associated with increased co-morbidities and cardiovascular risks. Obesity was more prevalent in patients with early arthritis, raising the possibility that the metabolic syndrome that is reported to be associated with established psoriasis is also present at the onset of arthritis (PsA). Longitudinal follow-up of these patients and analysis of their genetic background may help better understand the pathogenesis of these diseases. The PsA-specific risk factors reflected the disease activity, duration and severity, which suggest a need for a multidisciplinary approach so that patients can be identified and treated effectively.

Disclosure: M. M. Krahiši: None; R. Aslanov: None; D. MacDonald: None.

Time to Diagnosis of Ankylosing Spondylitis in an Irish Cohort and the Effect on Work Disability. Catherine Sullivan1 and Oliver M. FitzGerald1. 1Department of Rheumatology, St Vincent's University Hospital, Ranelagh Dublin, Ireland, 2Department of Rheumatology, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland

Introduction: Ankylosing Spondylitis (AS) is characterised by inflammatory back pain which may be associated with peripheral arthritis, enthesitis or uveitis. It has an insidious onset and results in radiographic progression with resultant pain, stiffness and loss of function. Studies have shown a delay in diagnosis of up to 7 years from onset of symptoms.1 Because there is no unique laboratory test to help in the diagnosis in primary care it is difficult to identify the 5% of patients with lower back pain who may have spondyloarthopathy (SpA), including AS.2 Research has demonstrated that patients with AS may have substantial periods of sick leave leading to a significant socioeconomic cost.3

Aim: We sought to identify the average time to diagnosis of AS from symptom onset in an Irish cohort and further to identify patterns of work disability in this group.

Methods: Patients with AS (n = 100) were identified from the physiotherapy database of a Dublin tertiary referral rheumatology department. Patients were sent a postal questionnaire about disease onset, diagnosis, treatment and employment status. All replies were anonymous and 59% responded.

Results: Of the respondents 59% were male, the average age of onset of symptoms was 25 years (yrs), with diagnosis at 32 yrs and the average age when completing the survey was 44 yrs. 96.6% had some spinal involvement with 23.7% having only spinal involvement. The average time from symptom onset to diagnosis was 7.25 yrs (min 0, max 23).

74.6% of patients were on an anti-TNF agent alone, with 8.5% on an anti-TNF agent plus a synthetic disease modifying agent (DMARD), 3.4% on DMARD alone and 13.5% on neither. The time to diagnosis of AS did not impact on treatment protocol.

In total 30.5% of respondents reported not being in employment as a result of AS. 20% of those diagnosed in under 4 yrs from symptom onset were unemployed. This rose to 23.4% in those diagnosed between 5 and 9 yrs after onset and a staggering 41% of patients were unemployed in patients whose disease diagnosis was delayed by more than 10 yrs. 62.5% of participants who were off work said they did not anticipate returning to employment in the next 12 months.

Conclusion: In this cohort of Irish patients we see a delay in diagnosis of AS of 7 years, similar to that seen in studies in 1998 and 2003. This suggests a persistent problem with under recognition of SpA in primary care. Additionally, while not designed to look at all aspects of work disability, these data suggest a correlation between the time to diagnosis of AS and work disability. In light of these results a new diagnostic pathway for SpA has been developed and distributed to Irish General Practitioners.

References

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Urolithiasis in Ankylosing Spondylitis—Are Stone Formers Also Bone Formers? Nai Lee Lui1, Adele Carty2, Nigil Haroon3, Hua Shen2, Richard Cook2 and Robert D. Inman4. 1Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, 2Department of Statistics and Actuarial Science, University of Waterloo, Canada, 3Division of Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, 4Toronto Western Hospital, Toronto, ON, Canada, 5Toronto Western Hospital

Objective: The frequency with which urolithiasis occurs in patients with ankylosing spondylitis (AS) has not been systematically analyzed in a large cohort. Urolithiasis represents an inherent propensity for calcium precipitation and calcification which might influence the osteoporoflation process in AS. We performed a cross-sectional analysis to determine risk factors for stone formation in AS and to address differences association with clinical features and osteoporoflation profiles.

Methods: In a longitudinal study of 504 AS patients, we conducted an analysis of all AS patients who developed urolithiasis. All patients met the modified New York criteria for AS. Demographics, clinical features, extra-articular features and co-morbidities were recorded in the database. We compared disease activity, functional indices, medical therapy and radiographic damage using the modified Stoke Ankylosing Spondylitis

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Spinal Score (mSASSS) between AS patients with and without urolithiasis.

Results: Thirty eight AS patients had a history of urolithiasis, a frequency of 7.5% in this AS cohort. Seventy six AS patients with no history of urolithiasis, matched for age, gender and ethnicity, were selected as controls. There was no difference in the incidence of urolithiasis in terms of gender, ethnic groups, HLA-B27 status, smoking history or alcohol consumption. AS patients with urolithiasis were more likely to have more functional disability, as measured by Bath AS Functional Index (BASFI) (mean 5.3 versus 3.6 in control group; p=0.003). There was trends toward higher Bath AS Disease Activity Index (BASDAI) (mean 4.9 versus 4.0, p=0.09), more peripheral joint involvement (p=0.075) and higher frequency of biologic therapy (p=0.09). However, no significant difference was detected in the mSASSS scores (p=0.65) or Bath AS Metrology Index (BASMI) (p=0.98). There was a significant association of urolithiasis with diabetes (p=0.016) and with Crohn’s disease (p=0.006).

Conclusion: There is no acceleration of syndesmophyte formation or spinal fusion associated with urolithiasis in AS. But AS patients with urolithiasis have unexpectedly more functional disability than AS patients overall. The higher risk with concomitant DM or Crohn’s disease should alert clinicians to these co-morbidities in AS patients developing urolithiasis.

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Validation of the Patient Acceptable Work State (PAWS): Establishing Thresholds for Major Work Transition in Ankylosing Spondylitis, Walter P. Maksymowych1, Sumati Rao1, Annelies Boonen1, Mary Cifaldi1, Abbott Laboratories, Abbott Park, IL, 2University Hospital Maastricht, Maastricht, Netherlands, 3University of Alberta, Edmonton, AB

Background: Restrictions in paid and unpaid work are a feature of AS and is measured using several instruments that score impairment on a continuous scale, although the significance of these scores in relation to major work transition such as sick leave and disability leave is unclear. Therefore, it is helpful to define work performance on a dichotomous basis as either satisfactory or not satisfactory using the patient acceptable work state (PAWS). It is further important to validate patient designation of unacceptable work state in relation to major work transition. In this study, we developed and validated 3 questions that assess PAWS.

Methods: Data were obtained from the Patient-Reported Outcomes in Employment Study (PROSE), a longitudinal, observational study of AS and work productivity. Patients with AS answered the 3 PAWS questions (yes/no) at baseline: “Considering all the different ways your disease is affecting you, if you would stay in this state for the next few months, do you consider that: 1) your ability to perform your current job is satisfactory?; 2) you will continue to work in your present job?; and 3) you may need to stop working and go on sick leave or disability leave?” Patients were considered to be PAWS responders if they answered “yes” to Questions 1 and 2 and “no” to Question 3. We examined PAWS responses in relation to the BASDAI, BASFI, and the following work productivity instruments: WPAI, WLQ, QQ1 (Quality) and QQ2 (Quantity). We also compared PAWS thresholds for the WPAI, WLQ, and BASFI according to the 75th percentile of patient responders for the 3 PAWS questions.

Results: Of 204 surveys obtained, 157 were AS employed patients. Out of which, 130 indicated they would be satisfied with their current job in the next few months, given their current disease state, 145 indicated they would continue working in their present job, and 136 patients indicated they would stop working given their disease state. There were more PAWS responders than nonresponders at baseline. A significant difference was observed in BASDAI, BASFI, WPAI, WLQ, and QQ1, and QQ2 scores between PAWS1 and PAWS3 responders and nonresponders (p<0.0001). PAWS responders attained a threshold ranging from 20%–30% for WPAI presenteeism, a threshold ranging from 27.7%–30% for overall work impairment, a threshold ranging from 30%–40% for work activity impairment, a threshold of 10 for both QQ1 and QQ2, and a threshold ranging from 6.5–7 for WLQ. Similarly, PAWS responders attained a threshold ranging from 4.8–5 for BASDAI and 4.2–4.7 for BASFI.

75th percentile (with 95% confidence interval) of WPAI domain scores, BASDAI, BASFI, QQ1, QQ2, and WLQ for PAWS responders at baseline (only for employed patients)

<table>
<thead>
<tr>
<th>PAWS Question</th>
<th>Responders</th>
<th>Responders</th>
<th>Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAWS Question 1</td>
<td>(N = 130)</td>
<td>(N = 145)</td>
<td>(N = 134)</td>
</tr>
<tr>
<td>WPAI presence</td>
<td>20 (20, 30)</td>
<td>30 (20, 30)</td>
<td>30 (20, 30)</td>
</tr>
<tr>
<td>WPAI overall work impairment</td>
<td>29 (20, 30)</td>
<td>30 (20, 30)</td>
<td>30 (20, 30)</td>
</tr>
<tr>
<td>WPAI work activity impairment</td>
<td>30 (30, 40)</td>
<td>40 (30, 50)</td>
<td>40 (30, 40)</td>
</tr>
<tr>
<td>QQ1 (0–10)</td>
<td>10 (10, 10)</td>
<td>10 (10, 10)</td>
<td>10 (10, 10)</td>
</tr>
<tr>
<td>QQ2 (0–10)</td>
<td>10 (10, 10)</td>
<td>10 (10, 10)</td>
<td>10 (10, 10)</td>
</tr>
<tr>
<td>WLQ</td>
<td>6.5 (5.3, 7.1)</td>
<td>7.0 (6.2, 8.3)</td>
<td>6.5 (6.6, 7.7)</td>
</tr>
<tr>
<td>BASDAI (0–10)</td>
<td>4.8 (4.0, 5.4)</td>
<td>5.0 (4.6, 5.6)</td>
<td>5.0 (4.4, 5.6)</td>
</tr>
<tr>
<td>BASFI (0–10)</td>
<td>4.2 (3.5, 5.4)</td>
<td>4.7 (3.9, 5.8)</td>
<td>4.4 (3.5, 5.4)</td>
</tr>
</tbody>
</table>

Conclusions: PAWS may be a valid concept defining satisfactory versus unsatisfactory work state and should be further validated for its relationship to major work transition. Further research is required to assess the change in PAWS thresholds for work productivity and health-related quality of life over time.

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Variation during Different Decades of Diagnostic and Therapeutic Delay in Patients of Ankylosing Spondylitis (AS), Giuliana Salvadorini1, Francesca Bandinelli1, Andrea Delle Sedie2, Lucrezia Riente1, Antonio Candelieri1, Sergio Generini1, Nicola Possemato1, Stefano Bombardieri1 and Marco Mattucci2, Cermic1, 1Department of Rheumatology of University of Pisa, Pisa, Italy, 2Division of Rheumatology AOUC, University of Florence, Department of Biomedicine, DENOThe Centre, Florence, Italy, Laboratory of Decision Engineering for Health Care Delivery, Department of Electronics, Informatics and Systems, University of Cosenza, Italy

Background: Ankylosing Spondylitis (AS) is a chronic, progressive, and disabling disease, but the diagnosis is often missed and markedly delayed (1). The early diagnosis is important to establish a treatment to reduce disability and modify the natural course of disease (2).

Objective: To investigate the diagnostic (DD) and therapeutic (TD) delay according to the decade of diagnosis and the correlation between DL and radiological severity score. The influence of different imaging techniques on DD has been also investigated.

Methods: 125 AS patients (45 female and 90 male, 36.5±10.2 years old at diagnosis) with disease onset between 1950 and 2008, were investigated: the time between onset and first rheumatologic visit, diagnosis (DD) and treatment (TD); the New York and ASAS criteria (3), the New York sacroiliac radiological score, the bamboo spine presence at first visit; the new imaging technique employed (magnetic resonance -MRI-, computerized tomography -CT- and scintigraphy for sacroiliac and ultrasonography -US- for peripheral joints) at diagnosis. The difference of DD, TD and imaging technique between different onset decades (50, 60, 70, 80, 90, 00’s) the correlation between DD and radiological severity, between TD and new imaging were analyzed.

Results: At first visit, 87% and 96% patients respectively met New York and mASAS criteria, with onset of symptoms 8.1±8.2 years before (28.3±10.2 years old). The delay since onset of symptoms to diagnosis and treatment was 9±8 and 12±11 years, respectively, but decreased significantly between different decades (p<0.001, Kruskal Wallis).

The severity of sacroiliitis (mean 2.2±1, 13% IV grade at diagnosis) and bamboo spine (7.4% at diagnosis) correlated with DD (p<0.001, Pearson correlation) and decreased during decades (p<0.001, Kruskal Wallis).

The employment of new imaging technique increased significantly during decades (p<0.001) but only sacroiliac MRI significantly decreased TD (p<0.05, Mann Whitney test).

Conclusions: DD, TD, radiological severity significantly and progressively decreased during decades. In particular, the employment of sacroiliac MRI decreased time to first treatment.

Introduction: The ASAS consensus statement for the use of anti-TNF agents for ankylosing spondylitis (AS) includes an evaluation of response after 6–12 weeks to determine if continued therapy is warranted.

Objective: To determine predictors of long-term response in AS.

Methods: In ATLAS (Adalimumab Trial Evaluating Long-Term Efficacy and Safety for AS), patients were randomized to receive adalimumab (ADA) 40 mg every other week (wk) or placebo (PBO) during a 24-wk double-blind period, followed by an open-label extension of up to 236 wks (5 yrs). Possible predictors for ASAS partial remission (PR) and low ASAS disease activity score (ASDAS <1.3) after 1 and 5 yrs of ADA exposure were selected a priori. Categorical variables included age >50 yrs, disease duration >10 yrs, abnormal baseline CRP, HLA-B27+, female gender, presence of ≥1 syndesmophyte at baseline, and responder at Wk 12 for ASAS20, ASAS40, ASAS PR, low ASDAS, ASAS40, and BASDAI50. Continuous variables included baseline values for BASFI, BASDAI, total back pain, Patient/Physician Global Assessments of disease activity, and morning stiffness (mean of BASDAI questions 5 and 6). Logistic regression was used to assess the univariate significance of each proposed predictor for the dependent variables. A multivariate survival curve analysis was done to determine predictors of sustained (>6 consecutive months) response.

Results: ATLAS enrolled 315 patients (208 ADA, 107 PBO). Correlation of continuous variables was tested and all are significantly different. Univariate analysis showed that Wk 12 responses were more consistent predictors of remission at 1 and 5 years than baseline disease characteristics (Table). The presence of syndesmophytes as baseline was noted to be a negative predictor for long-term remission. The multivariate survival curve analysis confirmed this observation as Wk 12 response by a specific remission criteria was a significant (P<0.01) predictor of achieving sustained remission using the same criteria (Hazard ratio): ASAS PR (2.59) and low ASDAS (2.92). Of those who had available data for the analysis, 57% and 46% achieved sustained low ASDAS and ASAS PR during the 5-y study.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>ASAS PR</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 50 yrs</td>
<td>0.47†</td>
<td>0.39†</td>
</tr>
<tr>
<td>CRP Abnormal</td>
<td>0.74</td>
<td>0.78</td>
</tr>
<tr>
<td>HLA-B27+</td>
<td>1.22</td>
<td>2.18</td>
</tr>
<tr>
<td>Female</td>
<td>0.94</td>
<td>0.91</td>
</tr>
<tr>
<td>Syndesmophyte ≥1 (BL)</td>
<td>0.29*</td>
<td>0.28</td>
</tr>
<tr>
<td>BASFI (BL)</td>
<td>0.97*</td>
<td>0.96*</td>
</tr>
<tr>
<td>BASDAI (BL)</td>
<td>0.89</td>
<td>0.85</td>
</tr>
<tr>
<td>Total Back Pain (BL)</td>
<td>0.98*</td>
<td>0.99</td>
</tr>
<tr>
<td>Patient Global Assessment (BL)</td>
<td>0.98*</td>
<td>0.98*</td>
</tr>
<tr>
<td>Physician Global Assessment (BL)</td>
<td>0.99</td>
<td>0.98*</td>
</tr>
<tr>
<td>Disease Duration &gt; 10 yrs</td>
<td>0.58†</td>
<td>0.61</td>
</tr>
<tr>
<td>Disease Duration &gt; 10 yrs</td>
<td>0.70</td>
<td>0.77</td>
</tr>
<tr>
<td>Disease Duration &gt; 10 yrs</td>
<td>0.71</td>
<td>0.71</td>
</tr>
<tr>
<td>Disease Duration &gt; 10 yrs</td>
<td>0.72</td>
<td>0.72</td>
</tr>
<tr>
<td>Disease Duration &gt; 10 yrs</td>
<td>0.80</td>
<td>1.00</td>
</tr>
<tr>
<td>Disease Duration &gt; 10 yrs</td>
<td>0.81</td>
<td>0.73</td>
</tr>
<tr>
<td>Disease Duration &gt; 10 yrs</td>
<td>0.82</td>
<td>0.79</td>
</tr>
<tr>
<td>Disease Duration &gt; 10 yrs</td>
<td>0.90</td>
<td>0.98</td>
</tr>
<tr>
<td>Disease Duration &gt; 10 yrs</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>Disease Duration &gt; 10 yrs</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>Disease Duration &gt; 10 yrs</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Disease Duration &gt; 10 yrs</td>
<td>0.99</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Conclusion: Early response (Wk 12) to ADA in AS patients is a better predictor than baseline disease characteristics of who would achieve sustained remission and continue to benefit from long-term therapy of up to 5 years. Presence of syndesmophytes at baseline was a negative predictor for remission, suggesting that earlier treatment of AS patients prior to syndesmophyte formation may be beneficial.

Disclosure: G. Salvadorini: None; F. Bandinelli: None; A. Delé Sedie: None; L. Rinte: None; A. Canudderi: None; S. Generini: None; N. Possemate: None; S. Bombardieri: None; M. Maticcu Cericin: None.
preclinical and some preliminary clinical evidence, inhibition of PDGFR/c-abl/c-kit tyrosine kinases by imatinib had no major effect on the disease course of early diffuse systemic sclerosis in our study.


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Baseline Differences in the “Borderline” Pulmonary Hypertension vs. “Normal” Hemodynamics: PHAROS Registry. Dinesh Khanna1, Rajeev Sagar2, Daniel Furst3, Lorinda Chng4, James Seibold5, Tracy Fresh6, ELENA Schiopu2, Rajan Saggar4, Marcy Bolster2, Virginia Steen1 and PHAROS Investigators. 1Georgetown University, 2MUSC, 3Stanford, 4UCLA, 5Univ of Connecticut, 6Univ of Michigan, 7Univ of Utah

Background: The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) is a prospective longitudinal study of patients at risk of developing PAH and those who have definite PH. The 4th World Symposium on Pulmonary Hypertension (PH) reclassified WHO group I patients with mean pulmonary artery pressure (mPAP) on right heart catheterization (RHC) of $\leq 20$ mmHg as “Normal” and 21–24 mmHg as “Borderline (boPH)” PH. Data regarding natural history and outcome of boPH PH are lacking.

Objective: To examine 1) the baseline demographics and clinical features and 2) explore long-term outcomes in SSc patients with normal resting hemodynamics vs. boPH from the PHAROS study.

Methods: Entry criteria for patients at high risk for PAH included a DLCO $<55%$ predicted, a FVC/DLCO ratio $>1.6$ or an estimated PASP on echo $>35$ mmHg. Patients complete questionnaires every 6 months and are seen yearly for physician evaluation, PFTs, echocardiogram, 6 minute walk, and clinical outcomes. Right heart catherizations (RHC) are performed based on the clinical judgment of the physician.

Results: Of 379 enrollees, 127 patients had PH at baseline. Of remaining 262 patients with SSc, 50 had mPAP $<25$ at baseline and 15 follow-up first RHC (N=65) and form the analysis group. Of these 65 patients, 37 (57%) had normal hemodynamics (Normal, mPAP $<20$ mmHg) and 28 (43%) had boPH (boPH; mPAP 21–24 mmHg). The average age of the whole group was 55.4 years, mean disease duration was 8.7 years, 83% were women, and 63% had limited cutaneous SSc. There were no differences in baseline demographics between normal and boPH groups.

Pulmonary function tests showed lower FVC% in the boPH group (69 vs. 81, p $<0.05$). A higher proportion of patients with boPH had FVC $<70%$ (63% vs. 31%, p $<0.05$). There were no significant differences in scores of patient reported outcomes (UCSD dyspea instrument, Scleroderma-HAQ, and SF-36 scores) between 2 groups. Patients with boPH had a significantly higher RVSP, mPAP, pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), and transpulmonary gradient (TPG) compared to Normal, p $<0.05$ (Table). Only 1 patient in each group had PCWP $>15$ mmHg. On exercise, boPH patients were more likely to have a mPAP $>30$ than the Normal group, 14/16 (88%) vs 11/20 (55%), p $=0.04$. 4 of the boPH patients had follow up cathes. Of these, 1 was normal and 3 had WHO Group II PH (PVH). For Normal, 6 had repeat cath. Of these, 4 were normal, and 1 each had PAH and PVH. 2 patients died in the boPH group (PH-ILD and lung fibrosis) and 1 in the Normal group (non-SSc related).

Baseline Characteristics of Normal vs. Borderline PH

<table>
<thead>
<tr>
<th></th>
<th>Normal (N=28)</th>
<th>Borderline (n=28)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>56 (12)</td>
<td>55 (10)</td>
<td>0.7</td>
</tr>
<tr>
<td>Female, %</td>
<td>34 (81)</td>
<td>27 (86)</td>
<td>0.5</td>
</tr>
<tr>
<td>Type of SSc, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>28 (67)</td>
<td>18 (62)</td>
<td>0.9</td>
</tr>
<tr>
<td>Disease Duration, yrs</td>
<td>9 (8)</td>
<td>8 (6)</td>
<td>0.5</td>
</tr>
<tr>
<td>FVC, %, mean (SD)</td>
<td>81 (39)</td>
<td>69 (16)</td>
<td>0.02</td>
</tr>
<tr>
<td>DLco %, mean (SD)</td>
<td>45 (11)</td>
<td>41 (18)</td>
<td>0.3</td>
</tr>
<tr>
<td>FVC/Dlco</td>
<td>1.9</td>
<td>2.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Echo RVSP mmHg, mean (SD)</td>
<td>36 (8)</td>
<td>45 (13)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

RHC

<table>
<thead>
<tr>
<th></th>
<th>mPA, mmHg, mean (SD)</th>
<th>PCWP, mmHg, mean (SD)</th>
<th>CO, L/min, mean (SD)</th>
<th>PVR, dyns/cm5, mean (SD)</th>
<th>TPG, mean (SD)</th>
<th>6MW, meters, mean (SD)</th>
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<tr>
<td></td>
<td>17 (3)</td>
<td>7.7 (3.4)</td>
<td>5.7 (1.2)</td>
<td>141 (74)</td>
<td>9 (3)</td>
<td>448 (83)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>0.02</td>
<td>0.2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Conclusion: Preliminary analysis of this group shows that SSc patients with borderline PH are likely to have lower FVC, higher PVR and TPG and have an abnormal response to exercise. Larger investigations on the prognostic and therapeutic implications of such borderline findings are warranted.

Disclosure: D. Khanna: Actelion Pharmaceuticals US, 2, 8, Gilead Sciences, Inc., 2, 5, NIHAMS-II, 2, United Therapeutics, 5; R. Saggar: None; D. Furst: Abbott Laboratories, 2, 5, 8, 9, Actelion Pharmaceuticals US, 2, 5, 8, 9, Amgen Inc, 2, 5, 9, Bristol-Myers Squibb, 2, 5, 9, Centocor Ortho Biotech Inc, 9, Centocor Inc, 9, Corrona, 3, Genentech and Biogen IDEC Inc, 2, 5, 9, Gil; L. Chung: Actelion Pharmaceuticals US, 2, 5, Gilead Sciences, Inc., 2, United Therapeutics, 2; J. Seibold: Actelion Pharmaceuticals US, 2, 5, Gilead Sciences, Inc., 2, Pfizer Inc, 2, 5, United Therapeutics, 2, 5; T. Frech: None; E. Schiopu: Actelion Pharmaceuticals US, 8, United Therapeutics; R. Saggar: None; M. Bolster: None; V. Steen: Actelion Pharmaceuticals US, 2, 5, United Therapeutics, 2; 5, PHAROS Investigators: None.

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Cigarette Smoking Is Not a Risk Factor for Systemic Sclerosis. Prateek Chaudhury3, Xing Chen6, Shervin Assassi5, Olga Gorlova7, Hilda Draeger5, Emilio Gonzalez1, Terry McNeary1, Marilyn Perry1, Jason Anderson1 and Maureen D. Mayes1, 2, 6, 7, University of Texas Health Science Center at Houston, Houston, TX, 1University of Texas Health Science Center Houston, Houston, TX, 2University of Texas Health Science Center Houston, 3University of Texas Health Science Center San Antonio, San Antonio, TX, 4University of Texas MD Anderson Cancer Center, Houston, TX, 5University of Texas MD Anderson Health Science Center, Houston, TX, 6University of Texas Medical Branch at Galveston, Galveston, TX

Background: Cigarette smoking has been well established as a risk factor for seropositive rheumatoid arthritis. Although smoking has been reported to worsen the vascular complications of systemic sclerosis (SSc), the role of cigarette exposure in susceptibility to SSc has not been previously reported. Our objective was to investigate the association of smoking with susceptibility to SSc in a large well-defined patient population.

Methods: We conducted a review of 1,417 SSc patients enrolled in the Scleroderma Family Registry and DNA Repository and/or the GENIOS (Genes versus Environment in Scleroderma Outcomes Study) cohort. Smoking history was obtained from questionnaire data, chart review and, in some cases, via telephone interview with patients if sufficient information was not provided in medical records. Information extracted or asked included questions related to smoking status, duration and quantity.

SSc patients were subsequently categorized as never smokers, past smokers or current smokers. SSc patients with available smoking data were matched 2:1 by age, gender and ethnicity with a control group from the National Health and Nutrition Examination Survey (NHANES, 1999–2006). Furthermore, past smokers and current smokers were grouped as ever smokers in the comparative analysis.

Results: The average age of 1417 enrolled patients was 53.6 years and most were female (88.1%). The majority of cases were White (78.3%) with an almost identical percentage of Latinos and Blacks (8.9% and 8.4%, respectively). Most patients had limited disease type (58.8%).

Smoking data were available in 759 (53.6%) patients. There was no significant difference in age, gender, ethnicity and SSc disease type between patients with or without available smoking data. The majority of patients had never smoked (57.4%). Patients with a smoking history classified themselves as past smokers or current smokers in 32.1% and 10.4% of cases, respectively. The average duration of smoking prior to the diagnosis of SSc in ever smokers was 18.3 years.

Overall, 42.6% (323/759) of SSc patients were ever smokers whereas 46.6% (709/1489) of matched controls in the NHANES survey had ever smoked. A Chi-Square analysis comparing cases and controls revealed that patients with SSc were less likely to be ever smokers than controls (p=0.04, OR: 0.83, 95% CI: 0.7–0.99).

Conclusion: Unlike in rheumatoid arthritis, smoking does not confer a risk for development of SSc. In fact, these data would suggest a small protective effect of smoking. Further studies are needed to investigate whether
Clinical Features of Systemic Sclerosis Sine Scleroderma Associated Interstitial Lung Disease. Rohit Aggarwal, Mary Lucas, Noreen Fertig and Thomas A. Medsger. Univ of Pittsburgh, Pittsburgh, PA, University of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, PA.

Aim: To describe the clinical characteristics features of systemic sclerosis sine scleroderma associated interstitial lung disease from a single tertiary care center over a 36- year period.

Methods: All 3322 patients from the tertiary care database with a clinical diagnosis of systemic sclerosis (SSc) with first visit between 1972–2008 were evaluated. Patients were classified as SSc-sine scleroderma (ssSSc) if they had a clinical diagnosis of SSc with no skin thickening (Modified Rodnan skin score = 0) on physical examination and one or more of the following visceral involvement typical of SSc: distal esophageal hypomotility, pulmonary interstitial fibrosis, pulmonary arterial hypertension, SSc cardiac or renal disease. Pulmonary interstitial fibrosis was defined as the presence of pulmonary fibrosis seen on chest radiography (CXR) or high-resolution computed tomography (HRCT) scan, with or without pulmonary function criteria for restrictive lung disease: forced vital capacity in 1 second [FVC1] < 70% of predicted plus forced expiratory volume [FEV1] in 1 second/ FVC > 80% of predicted. All ssSSc patients with pulmonary fibrosis at first visit formed our final cohort of ssSSc-ILD patients, who were further studied for clinical and serological features. Serological evaluation for all SSc specific/associated autoantibodies was done on all patients with available serum.

Results: Our final cohort had 45 ssSSc patients with ILD at baseline. Demographics were: female (36/45, 80%), Caucasians (37/45, 82.2%), African American (7/45, 15.6%). The mean (±SD) age (yrs) at first CTD symptom, first CTD diagnosis and first visit were 42.3 (17.2), 49.6 (16.9), and 53.5 (15.5), respectively. Mean diagnosis delay from first CTD symptom was 8.1 (9.6) yrs. Mean age at first pulmonary symptom was 51.5 (15.0) yrs. Mean duration from first non-pulmonary CTD symptom to pulmonary symptom was 8.6 (10.5) yrs, and most common first symptom was raynauds 29/45 (64.4%), followed by dyspnea 25/45, 11.1%, GI involvement 3/45, 6.7%. Most patients had multiple clinical features for SSc before the development of pulmonary disease: raynauds 36/41, 87.8 (median delay of 14.5 years from raynauds to pulmonary symptoms), arthritis 76.4%, esophageal symptoms 60.0%, 50% patients (18/36) had pulmonary symptoms before SSc diagnosis. Among various SSc-specific autoantibodies most common was ThTo 14/38 (36.8%), followed by U1 (or U2) 9/38 (23.7%), centromere 5/38. Positive ANA was seen in 93.3% (42/45) patients. Approximately 50% of patients (19/41, 46.3%) had nucleolar pattern, followed by speckled 10/41, centromere 5/41. Most common clinical features at baseline evaluation were raynauds 39/45 (86.6%), telangectasia 20/44, digital swelling 16/43, pyrosis 17/44, distal dysphagia 10/44. The Median, 5 and 10 year survival from the diagnosis was 16.9 years, 83.7% and 68.5% respectively.

Conclusion: Clinical features like Raynaud, arthritis and esophageal symptom generally precedes the development of pulmonary fibrosis and thus along with positive ANA can help diagnose SSs associated ILD. Nuclear ANA pattern and anti-ThTo and anti-U1/U2 were the most common autoantibodies seen in ssSSc-ILD patients.

Disclosure: R. Aggarwal: None; M. Lucas: None; N. Fertig: None; T. A. Medsger: None.


Rationale: Despite significant advances in vasodilator therapies for pulmonary arterial hypertension (PAH), the overall survival in systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) remains poor and most patients eventually require more than one agent to help palliate their symptoms. This retrospective study was undertaken to better understand the relationship between clinical predictive factors and failure of oral monotherapy in SSc-PAH patients presenting in WHO functional class II/III.

Objective: To determine the time to initiation of a second therapeutic agent in SSc-PAH patients. Various parameters including demographic data, type of scleroderma and duration of disease, presence of interstitial lung disease (ILD), pulmonary function findings, hemodynamic parameters, and echocardiographic features were extracted in patients with SSc-PAH and analyzed in context with response to the medical therapy with regards to time to addition of a second therapeutic agent.

Methods: We performed a retrospective review of electronic medical records between 2001–2008 involving patients with SSc-PAH. All patients had received upfront monotherapy with either an endothelin receptor antagonist or a phosphodiesterase type-5 inhibitor. Relationships of clinical predictive factors with monotherapy failure and time to utilization of a second therapeutic agent were analyzed using the Cox proportional hazard function with backward variable selection procedures.

Results: There were 66 WHO functional class II/III patients with SSc-PAH who received upfront monotherapy with either Bosentan or Sildenafil. 30 patients (45%) failed oral monotherapy after a mean duration of 13.1 ± 7.8 months. By univariate assessments African-American race (p = 0.011), limited type of scleroderma (p = 0.028), the presence of ILD (p = 0.005), pulmonary vascular resistance ≥ 6 Wood units (p = 0.012), and cardiac index < 2.25 L/min/m² (p = 0.029) appeared to have a significant association with the need to add a second medication. Multivariate analysis indicated that patients with ILD had a higher chance of needing a second agent with a hazard ratio of 4.12 (95% CI: 1.71– 9.94; p = 0.001). Patients who have SSc-PAH with ILD also had a shorter time period on monotherapy (8.9 months) compared to SSc-PAH without ILD (22.1 months) [log-rank p-value = 0.021] (Figure 1).

Conclusion: SSc-PAH patients who have underlying interstitial lung disease appear to be more likely to fail vasodilator monotherapy and also appear to require earlier utilization of a second therapeutic agent.

Disclosure: Y. C. Lin: None; S. Chatterjee: None; M. Xu: None; R. Dweik: None; J. Parambil: None.


Background: PAH is a leading cause of mortality and late disease morbidity in scleroderma. In PAH, endothelin (ET)-1 is a key vasoconstrictor, predominantly via ET_{A} receptors, and ET receptor antagonists are established therapies. Sitaxentan sodium is a once daily, orally bioavailable, highly selective (6500:1 ratio) antagonist of ET_{A} receptors with potent antiproliferative and anti-inflammatory effects.

Aim: To compare outcomes of patients with scleroderma associated idiopathic pulmonary arterial hypertension (SSc-PAH) receiving sitaxentan against the international reference population for PAH treated with bosentan.

Methods: Patients with SSc-PAH enrolled in the Scleroderma associated PAH (SCAP) study were compared to all PAH patients enrolled in the Outcomes of Sitaxentan Treatment of Pulmonary Arterial Hypertension (OSPREY) study.

Results: There were 36 SSc-PAH patients enrolled in the SCAP study and 140 patients in the OSPREY study. The pooled analysis demonstrated that SSc-PAH patients had significantly worse outcomes compared to the OSPREY population. SSc-PAH patients were less likely to achieve a functional class of I-II at 24 weeks (OR = 0.24; 95% CI: 0.09–0.62), had a higher pulmonary vascular resistance (OR = 1.35; 95% CI: 1.05–1.73), and had a higher probability of death (OR = 3.25; 95% CI: 1.12–9.50) compared to the OSPREY population.

Conclusion: SSc-PAH patients have a worse clinical course compared to the international PAH population treated with sitaxentan. These findings highlight the importance of early intervention in SSc-PAH patients to improve outcomes.
**Methods:** The STRIDE trials were double-blind, randomized, placebo-controlled trials of sitaxentan use in patients aged 12–75 years with WHO FC II–IV (predominantly II and III) idiopathic PAH or PAH associated with connective tissue disease or congenital heart disease. The trials ran from 12 to 18 weeks in duration. The bosentan comparator arm in STRIDE-2 was open-label.

**Summary of the Results:** Fifty-four patients with scleroderma were included in the pooled, post-hoc analyses. Except for a higher mean (± SD) age in the sitaxentan group vs the bosentan group (62±8 vs 55±15 y; P=0.0493), demographics and baseline disease severity were not statistically different across the 3 treatment groups. All patients were WHO FC II or III at baseline except for 1 FC IV placebo-recipient. Change in 6 minute walk distance (6MWD) and WHO FC, and time to clinical worsening were as follows:

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 15)</th>
<th>Bosentan 125 mg bid (N = 15)</th>
<th>Sitaxentan 100 mg QD (N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) change in 6 MWD, m</td>
<td>-22 (79.0)</td>
<td>-14 (110.4)</td>
<td>18 (48.9)</td>
</tr>
<tr>
<td>Placebo-subtracted difference</td>
<td></td>
<td></td>
<td>39</td>
</tr>
<tr>
<td>Bosentan-subtracted difference</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Change in WHO FC, n (%)

<table>
<thead>
<tr>
<th></th>
<th>P-value vs placebo</th>
<th>P-value vs bosentan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>1 (7%)</td>
<td>NS</td>
</tr>
<tr>
<td>No Change</td>
<td>13 (87%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>1 (7%)</td>
<td>4 (27%)</td>
</tr>
</tbody>
</table>

Conclusions: Sitaxentan 100 mg QD appears to be an effective and well tolerated therapy for patients with PAH-scleroderma. Sitaxentan 100 mg QD significantly reduced the incidence of clinical worsening events, with fewer discontinuations due to adverse events and fewer cases of elevated ALT/AST compared with bosentan. These findings warrant further investigation in a larger, prospective study.


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**Comparative Analysis of Change in Modified Rodnan Skin Score in Patients with Systemic Sclerosis Receiving Imatinib Mesylate**

**Methods:** This is a post-hoc analysis of pooled data from the STRIDE (Sitaxentan To Relieve Impaired Exercise) 1, 2, and 4 trials. The aim is to describe the efficacy and safety of oral sitaxentan 100 mg once daily (QD; the currently approved dose in the European Union, Canada, and Australia) vs bosentan 125 mg twice daily (BID) and placebo in patients with PAH-scleroderma.

**Results:** The incidence of discontinuations due to adverse events and fewer cases of elevated ALT/AST (sitaxentan) and 13% (bosentan). The incidence of discontinuations due to adverse events was 0% (placebo), 0% (sitaxentan 100 mg QD), and 16% (bosentan). Discontinuations due to adverse events tended to be lower in the sitaxentan group than in the placebo group (42% vs 62% and vs bosentan 0.011).

**Background and Purpose:** Despite preclinical evidence and anecdotal case reports supporting potential benefit, clinical trials of the selective tyrosine kinase inhibitor imatinib mesylate in systemic sclerosis (SSc) have provided conflicting results with regard to efficacy as assessed by the modified Rodnan Skin score (mRSS). Our aim was to compare the course of mRSS in patients treated with imatinib in a multi-center, open-label, Proof of Concept (PoC) study in diffuse SSc [submitted in parallel to ACR 2010] and in patients receiving standard therapy in a well characterized large single centre cohort.

**Methods:** 27 cases of diffuse cutaneous SSc were treated with imatinib mesylate in an open-label prospective clinical trial. To develop a comparator cohort to help interpret clinical outcome in this trial, data from a SSc patient database (n>2000) from a large tertiary referral centre for SSc, were analyzed to select dSSc patients whose main characteristics (disease duration and mRSS at baseline, age, sex, and connective tissue diseases) matched those of the patient population in our PoC study. Patients (n = 116 selected) in the control group received standard immunomodulatory treatment except for 19 (16%) patients who received no immunosuppressive treatment. Imatinib was initiated at an oral dose of 200 mg/day for 4 weeks then up-titrated to 400 mg/day for 2 weeks followed by 600 mg/day until Week 24. A data driven descriptive analysis as well as a longitudinal mixed effects model were utilized to compare the changes in mRSS in the imatinib treated group (n = 27) and in the control group (n = 116).

**Results:** In the imatinib group in our PoC study, mean mRSS increased by 9.9% at Week 24, however, there was a trend towards an improvement in mRSS (−21%) at Week 48, 24 weeks after the end of treatment. As compared to the control group, after an initial increase in mRSS in the imatinib group, the time course of mRSS was similar to that of the control group.

**Conclusions:** Our data suggest that the changes in mRSS after 24 week treatment with imatinib in our PoC study are similar to those observed in cases receiving standard therapy. Such comparative analyses using large databases of well characterized cases may help better interpret results in further Proof of Concept studies of systemic sclerosis where the enrollment of a large number of patients is usually not feasible. Thus we provide a model for future early stage clinical studies in SSc.

**Disclosures:** C. P. Denton: Novartis Pharmaceuticals Corporation, 9; S. I. Nihtyanova: Novartis Pharmaceuticals Corporation, 9; J. Varga: Novartis Pharmaceuticals Corporation, 9; O. Distler: Actelion Pharmaceuticals US, 5, Bristol-Myers Squibb, 5, Ergonex, 5, Fibrogen, 5, Novartis Pharmaceuticals Corporation, 9; P. Ink, 5; F. M. Wigley: Novartis Pharmaceuticals Corporation, 9; R. A. Laftias: Novartis Pharmaceuticals Corporation, 9; J. H. Wildler: Novartis Pharmaceuticals Corporation, 9; G. Schett: Novartis Pharmaceuticals Corporation, 9; M. Matucci-Cerinic: Novartis Pharmaceuticals Corporation, 9; T. M. Wright: Novartis Pharmaceuticals Corporation, 9; M. Cost Anastunes: Novartis Pharmaceuticals Corporation, 3; A. Racine: Novartis Pharmaceuticals Corporation, 3; A. Bergolin: Novartis Pharmaceuticals Corporation, 3; P. Gergely, Jr: Novartis Pharmaceuticals Corporation, 3.

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**Comparison of Estimated Pulmonary Artery Systolic Pressure by Echo-cardiography (PASP\textsubscript{ECHO}) and Right Heart Catheterization (PASP\textsubscript{RHC}) in Patients with Systemic Sclerosis (Scleroderma, SSc).**

Elena Schiopu1, Ann J. Impens2, Melven Rubenfire2, Fazleomar Mood3 and Kristine Phillips4, 1University of Michigan, Ann Arbor, MI, 2University of Michigan, Division of Cardiology, Ann Arbor, MI, 3University of Michigan, Scleroderma Program, Ann Arbor, MI

**Disclosures:**
Background: Pulmonary hypertension (PH) has emerged as the leading cause of death among patients with SSC. Early diagnosis in the pre-symptomatic phase of SSC-PH may lead to early intervention and improved outcome. Right heart catheterization (RHC), the diagnostic gold standard, is invasive and a need for accurate, noninvasive predictors of SSC-PH remains. Echo-Doppler is widely used in clinical practice to calculate the pulmonary artery systolic pressure (PASP) from the tricuspid valve velocity and an artery systolic pressure (PASP) from the tricuspid valve velocity and an estimated right atrial pressure. We correlated the echo-Doppler estimated PASP (PASPECHO) with that measured by RHC (PASPRHC).

Methods: 133 patients with SSC who underwent a RHC at University of Michigan between 1997 and 2010 had a technically adequate echo-Doppler within ≤ 180 days of the procedure. Abstracted data included: demographics, type of SSC, duration of SSC WHO functional class, serum brain natriuretic peptide (BNP) and hemodynamics. Pearson’s correlations were used to compare the measurements.

Results: 108 (81.2%) patients were female, 92 (69.2%) had limited SSC and the mean (SD) disease duration was 10.1 yrs (8.4). The mean (SD) time between the RHC and the echocardiogram was 37 days (40). The WHO functional class distribution was: 3 (2.3%) class I, 21 (15.8%) class II, 97 (72.9%) class III and 12 (9%) class IV. The mean (SD) BNP was 476.7pg/mL (782.5). 105 (78.9%) of the patients met criteria for PAH (mPAP > 25mmHg with PCW < 15mmHg). The mean (SD) mPAP for the whole group was 40.4 (16.3). The body mass index (BMI) did not differ between the PH and the non-PH groups (mean 27.6 kg/m² for each).

Mean PASPECHO was 69.1 (28.7) and PASPRHC 63.7 (24.9). The correlation between PASPECHO and PASPRHC was r = 0.70, P<0.01. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for PAH for different cut-off values of PASPECHO and PASPRHC were:

<table>
<thead>
<tr>
<th>Cut-off value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASPECHO &gt; 35</td>
<td>94.2</td>
<td>35.7</td>
<td>87.9</td>
<td>12</td>
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<tr>
<td>PASPECHO &gt; 40</td>
<td>91.4</td>
<td>40</td>
<td>82.7</td>
<td>17.2</td>
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<tr>
<td>PASPECHO &gt; 45</td>
<td>87.6</td>
<td>67.8</td>
<td>75.9</td>
<td>24</td>
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<tr>
<td>PASPECHO &gt; 50</td>
<td>84.7</td>
<td>73</td>
<td>72.1</td>
<td>27.8</td>
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<tr>
<td>PASPECHO &gt; 55</td>
<td>80</td>
<td>78.5</td>
<td>68.4</td>
<td>31.5</td>
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<tr>
<td>PASPRHC &gt; 35</td>
<td>100</td>
<td>67.8</td>
<td>85.7</td>
<td>14.2</td>
</tr>
<tr>
<td>PASPRHC &gt; 40</td>
<td>93.3</td>
<td>82.1</td>
<td>77.4</td>
<td>22.5</td>
</tr>
</tbody>
</table>

Conclusion: Among patients with SSC the estimated PASP by echo-Doppler correlated moderately well with the measured PASP by RHC. The sensitivity of PASPECHO was high but the specificity is low when compared to PASPRHC. PASPECHO can be part of a screening algorithm for predicting SSC-PH that would include other non-echocardiographic parameters. The RHC remains the gold standard for establishing a diagnosis of SSC-PH.

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Determination of the Accurate Incidence of Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis, Mixed Connective Tissue Disease and Systemic Lupus Erythematosus by Prospective Study for 3-Years. Sumiaki Tanaka1, Kenta Hoshiba2, Junichi Tanaka2, Tatsuhiko Wada2, Toshimichi Matsui2, Tatsuo Nagai2, Jun Okada2 and Shunsei Hirohata3. 1Drexel University College of MedicineDepartment of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan, 2Drexel University College of MedicineDepartment of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Sagamihara, Japan, 3Drexel University College of MedicineDepartment of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan, 4Drexel University College of MedicineDepartment of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan, 5Drexel University College of MedicineDepartment of Rheumatology and Infectious Diseases, Kitasato University School of Medicine and Medicine, Kanagawa, Japan, 6Drexel University College of MedicineDepartment of Rheumatology and Infectious Diseases, Kitasato University School of Medicine.

Results: Among the 443 patients, 11 patients were suspected to have PAH by UCG, and 5 of the 11 patients (2 deSSc, 1 lcSSc, 1 SLE, 1 MCTD) were diagnosed as definite PAH. The incidence of PAH was significantly high in deSSc and low in SLE (Table 1 and Figure 2).

Table 1. Incidences of PAH in patients with various CTDs

<table>
<thead>
<tr>
<th>CTDs</th>
<th>Incidences/1000 person-years</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>deSSc</td>
<td>26.83</td>
<td>22.33–31.51</td>
</tr>
<tr>
<td>lcSSc</td>
<td>14.87</td>
<td>11.81–18.74</td>
</tr>
<tr>
<td>SLE</td>
<td>6.22</td>
<td>5.46–7.08</td>
</tr>
<tr>
<td>MCTD</td>
<td>11.82</td>
<td>9.50–14.72</td>
</tr>
</tbody>
</table>

Incidence/person-years, *p < 0.0001

Conclusions: These results have disclosed the exact incidence of PAH in patients with CTDs, which was strikingly higher than that of idiopathic PAH (~2–3 per million person-years). The data also indicate that the incidence of PAH in deSSc is much higher than that in MCTD and lcSSc.

Disclosure: S. Tanaka: None; K. Hoshiba: None; J. Tanaka: None; T. Wada: None; T. Matsui: None; T. Nagai: None; J. Okada: None; S. Hirohata: None.

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Difficulty Using World Health Organization Criteria To Categorize Pulmonary Hypertension in Patients with Systemic Sclerosis. Jessica K. Gordon1, Mardi Gomberg-Maitland2, Barbara M. Segal1, Robyn T. Domsté1, Ami A. Shah1, Laura K. Hammer1, Virginia D. Steen1, Evelyn Horn1 and PHAROS Investigators. 1Georgetown University Medical Center, Washington, DC, 2Hen-nepin County Medical Center, Minneapolis, MN, 3Hospital for Special Surgery, New York, NY, 4Johns Hopkins University, Baltimore, MD, 5University of Chicago, 6University of Pittsburgh, Pittsburgh, PA, 7Weill-Cornell Medical College.
Background: Pulmonary hypertension (PH) is a leading cause of death in patients (pts) with Systemic Sclerosis (SSc). The World Health Organization (WHO) classifies PH into distinct groups to provide guidance on prognosis and therapy. In SSc, pulmonary arterial hypertension (PAH, WHO group 1) is most common. However, pulmonary venous hypertension (PVH, WHO Group 2) related to heart failure with a normal ejection fraction (HFNEF, formerly known as diastolic dysfunction) and interstitial lung disease (PH-ILD, WHO group 3) can occur in isolation or in combination. We examined the frequency of different PH in pts with PAH and PH-ILD followed in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) Registry.

Methods: Pts with PH were categorized by WHO criteria. A pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg on the initial right heart catheterization (RHC) differentiated PAH from PVH pts, with some room for clinical impression. Those with moderate or severe ILD on imaging and forced vital capacity <60% predicted were included in ILD-PH, regardless of PCWP. Descriptive statistics were used to show the prevalence of PVH. ANOVA, Kruskal-Wallis, and Chi Square tests were used to compare baseline features.

Results: There are 150 pts with PH in the PHAROS database: PAH – 97 (64.7%), PVH – 23 (15.3%), and PH-ILD – 30 (20%) with a median duration of follow-up of 1.1 years (IQR 0.5, 2.5). There were no significant differences between groups for gender, race, or duration of disease. Pts with PAH were more likely to have limited SSc subtype (73%, 48%, and 47% for PAH, PVH, and PH-ILD groups, respectively, p = 0.02) and were older (61, 55, 2 years, p < 0.01.) There were no differences in right ventricular systolic pressure, exercise fraction, or left atrial diameter (LAD) on echo. PAH pts had higher mean PAP and pulmonary vascular resistance (PVR). Pulmonary function test (PFT) parameters were lower in the PH-ILD group, as expected. Of those pts classified with PAH, 14.4% had some evidence of PVH either on baseline RHC, by development of PCWP >15 on repeat RHC, or by exercise PCWP >15. Of PAH pts, 33.0% had some degree of PVH as assessed by an increased LAD of >4.0 cm on echo. (Other echo parameters of diastolic dysfunction were not available.) Of those pts classified with PH-ILD, 36.6% had evidence for PVH based on RHC, and 30% based on LAD measurement. Interestingly, there was no correlation between the LAD and the PCWP (Spearman r = 0.1437, p = 0.06).

Conclusions: Despite specific classification of PH subgroups using objective information, there is evidence for some degree of PVH in a large percentage of pts categorized with PAH or PH-ILD. In SSc, specific classification using WHO criteria is difficult to accomplish. PVR and PFTs may help clarify the type of PH. The significance of these findings with respect to prognosis and treatment response will be studied in the long-term follow-up of pts in PHAROS.

Disclosure: J. K. Gordon: None; M. Gomberg-Maitland: ABComm, 5, 8, Actelion Pharmaceuticals US, 2, Biomarin, 5, 8, Gilead Sciences, Inc., 2, 5, HealthmattersCME, 5, 8, Icos Corporation, 2, Lilly USA, LLC, 2, Medtronic, 5, 8, Millenium Pharmaceuticals, 5, 8, Novartis Pharmaceuticals; B. M. Segal: None; R. T. Domsic: None; A. A. Shah: None; L. K. Hummers: None; V. D. Steen: Actelion Pharmaceuticals US, 2, Gilead Sciences, Inc., 2, 5, Pfizer Inc, 5, United Therapeutics, 2, 5, E. Horn: Actelion Pharmaceuticals US, 2, 5, Gilead Sciences, Inc., 2, 5, Novartis Pharmaceuticals Corporation, 5, 6, Pfizer Inc, 2, 5, 6, United Therapeutics, 2, 5, 6; PHAROS Investigators: Actelion Pharmaceuticals US, 2, Gilead Sciences, Inc., 2.
Methods: Martineau is a West Indian French part of European community, with high economical status and 400000 inhabitants. Health care is easily accessible and the same as in metropolitan France. We conducted in 2009 and 2010 a multiple-source study to retrieve all cases fulfilling ACR criteria before 1st January 2009. Three different sources were used: hospitalisation files from the Academic Hospital, specialist physicians in private and public practice (rheumatologist, dermatologist, internist and pneumologist).

Results: 89 patients (88 meeting the ACR criteria) were found (female 73, male 16, female/male ratio: 4.6) in a screening of more than 40000 medical reports. Onset of the disease was, for 38 cases between 1999 and 2008 (female 30, male 8). Prevalence on December 31, 2008 and mean annual incidence from 1999 to 2008 of SSc were respectively 19,1/10^5 inhabitants (confidence interval 95%; 14.5 – 25) and 1.33/10^5 inhabitants (CI 95%; 0.5–3.3) aged 20 years old and over (female 1.84/10^5, CI 0.5–5.1). In the 89 patients, the characteristics were: mean age at diagnosis 42.1 years old (range 12–86); mean follow up: 9.4 years (range 1–33); diffuse cutaneous sclero- derma: 59 (66.3 %) and limited form: 26 (29.2 %); deaths during the follow up: 16 patients. Relative proportion of antitopoisomerase I antibody (31.5 %) and anticientromere antibody (12.4%) were typical of black patients and different than for Caucasians. Another connective tissue disease was present for 29 patients (32.6%) and muscular involvement was found in 31 (34.8 %).

Conclusion: This is the first population-based study devoted to SSc in an Afri-can-descent population outside of the USA. It suggests that SSc is more frequent in our population than in most Caucasians populations already studied, but less frequently encountered than in African American population. Mean clinical and biological manifestations are close to African descent populations and also seem characteristic of the disease in Black populations.

Disclosure: C. Deligny: None; V. Goeb: None; M. E. Truchetet: None; V. Kahn: None; V. Dehlinger: None; P. Numerie: None; C. Derancourt: None; G. Jean Baptiste: None; S. Arf: None.

European Scleroderma Study Group (ESCG) Activity Index Is Correlated to Quality of Life Measures Both at Admission and Overtime.

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Objective: ESCG activity index has been validated for construct validity (1). Its discriminant validity awaits to be investigated. In order to address this aspect, we investigated the relationships between the activity index and Health Assessment Questionnaire-Disability Index, and physical and mental component scores (PCS and MCS) of Short Form-36 (SF36).

Methods: 149 SSc patients consecutively admitted to a tertiary center were investigated for ESCG activity index, HAQ-DI and PCS and MCS of SF36 at enrolment and after 1 year. The change (Δ) for each measure was calculated.

Results: ESCG activity index was found to be correlated to HAQ-DI, PCS and MCS both at admission (Rho=0.41, p<0.0001; Rho=-0.41, p<0.0001; Rho= -0.29, p=0.0004, respectively) and after 1 year (Rho= 0.33, p <0.0001; Rho = -0.35, p<0.0001; Rho= -0.21, p=0.0094 respectively). Moreover, the change between the value of the activity index at 1 year and that at admission (Δ activity index) was significantly correlated to ΔHAQ-DI, Δ PCS, ΔMCS (Rho=0.16, p=0.04; Rho= -0.24, p=0.003; Rho= -0.48, p=0.0036, respectively).

Conclusion: HAQ-DI and SF36 (PCS and MCS) are considered to be validated outcome measures in SSc. Our results support the construct and the discriminant validity of ESCG activity index.

References:

Disclosure: G. Valentini: None; M. Iudici: None; G. Abignano: None; S. Vettori: None; G. Cuomo: None.

Evaluation of an Imatinib Response Gene Signature in Patients with Systemic Sclerosis.

Lorinda Chung1, Pedro Ruiz2, Tammara Wood1, Stanford Shoor3, William Robinson1, Michael Whitfield1, Howard Chang2 and David Fiorentino1, 1Dartmouth Medical School, 2Kaiser Permanente of Northern California, 3Stanford Univ Medical Center, Palo Alto, CA, 4Stanford Univ School of Med, Stanford, CA, 5Stanford University School of Medicine

Purpose: We previously defined a set of imatinib-regulated genes from lesional skin of patients with systemic sclerosis (SSc), termed the “imatinib response signature.” We sought to further evaluate the clinical effects and gene expression changes induced by imatinib in patients with SSc. The cutaneous molecular response to imatinib is heterogeneous and may be partially reflected in the clinical response to the drug.

Methods: Patients were treated with imatinib for 24 weeks at 100–400 mg daily as tolerated. The primary endpoints of the study were safety and change in modified Rodnan Skin Score (mRSS, scale 0–51) at 24 weeks compared with baseline. Lesional skin biopsies of the upper extremities were obtained at baseline, 4 and 24 weeks after therapy. Total RNA was extracted from skin biopsies using QIAGEN RNeasy fibrous tissue kit. RNA was amplified using Agilent’s Quick Amp Labeling Kit, no dye. Amplified skin RNA (labeled with NEN brand Cyanine 3-CTP, 100 nmol) and amplified Stratagene Human Universal Reference RNA (labeled with NEN brand Cyanine 5-CTP, 100 nmol) were competitively hybridized to Agilent Whole Human Genome 4×44K oligo microarrays.

Results: 7 patients with diffuse cutaneous SSc (dcSSc) and progressive skin disease (median disease duration 1 year, range 0.5–13) and 2 patients with limited cutaneous SSc (lcSSc) and interstitial lung disease (ILD) were enrolled in the study. Baseline mRSS in the dcSSc patients ranged from 19–49 (median 36). 7 patients (6 dcSSc, 1 lcSSc) completed 24 weeks of imatinib at a median dose of 300 mg daily. 1 patient withdrew at 4 weeks due to a keratopathy related to SSc, and 1 patient with lcSSc and severe ILD died after 8 weeks of therapy due to pneumonia and sepsis. Adverse events affecting 2/3 of patients included gastrointestinal complaints, edema, and infections. The mean mRSS improved by 32% at week 24 (p=.005). Gene expression changes induced in gene expression that were very similar to our original 2 patients (p=4.6 × 10^-10). This patient had clinical improvement at week 24 with mRSS decreasing from 6 to 2, decreased ground glass opacities on high resolution chest CT, and decreased right ventricular systolic pressure from 69 to 54 mmHg on echo. The remaining 3 patients demonstrated significant repression of the genes induced by imatinib in our initial patients (p=0.29 to 4.9 × 10^-4). These 3 patients had variable clinical responses to imatinib: 1 patient with dcSSc had mild improvement in skin but worsening ILD; the second was the lcSSc patient who died; and the third was a dcSSc patient who experienced minimal improvement in skin score. In the 3 responding patients only, imatinib upregulated genes involved in collagen metabolism and morphogenesis, while downregulating genes involved in mitosis and the cell cycle.

Conclusions: Imatinib therapy at low to moderate doses is tolerated by patients with SSc and may result in clinical improvement in a subset of patients. The cutaneous molecular response to imatinib is heterogeneous and may be partially reflected in the clinical response to the drug.

Disclosure: L. Chung: Actelion Pharmaceuticals US, 8, Gilead Sciences, Inc., 2, United Therapeutics, 2; P. Ruiz: None; T. Wood: None; S. Shoor: None; W. Robinson: None; M. Whitfield: Celdara Medical LLC, 4; H. Chang: None; D. Fiorentino: None.


Nilanjana Bose2, James F. Bena2, Charles M. Trunick3, Debora J. Bork2, Geetha Krishnan2, John Petrich2 and Soumya Chatterjee1. 1Cleveland Clinic, Richmond Heights, OH, 2Cleveland Clinic, Cleveland, OH, 3Cleveland Clinic

Background: Raynaud’s phenomenon (RP) occurs in about 95% of patients with systemic sclerosis (SSc). Vasodilators such as calcium channel blockers may not be as helpful as in primary RP, as they have little effect on the vascular fibro-proliferative changes that lead to chronic digital ischemia in SSc. Ambrisentan (Am) is a selective endothelin receptor type A (ETA)
antagonist FDA approved for the treatment of pulmonary hypertension. Am
differs from bosentan in its ability to prevent the vasodilator effect of
endothelin through its interaction with the endothelin-B receptor, while
inhibiting its vasocostrictive effect through its interaction with the ETA
receptor. Laser Doppler perfusion imaging (LDPI) is a non-invasive tech-
nique that involves perfusion mapping of areas of skin, rather than examina-
tion of blood flow at a single point. We hypothesized that Am would increase
digital microvascular flow (as measured by LDPI) in patients with SSc-
duced digital ischemia.

Methods: In this randomized, double-blinded, placebo controlled trial, we
enrolled 20 patients with limited SSC for < 7 years. Smokers, patients
desiring pregnancy, and those with pulmonary hypertension or active digital
ulcers were excluded. After initial screening, there were 2 visits: day 0
(baseline) and day 7. Raynaud’s Condition Score (RCS), Scleroderma Health
Assessment Questionnaire (S-HAQ) and Pain-Visual Analog Scale (P-VAS)
were completed at each visit. Fifteen patients received Am 5 mg orally daily
and 5 received placebo. Patients were monitored for adverse events. At each
visit, 3 baseline blood flow readings of fingers of the non-dominant hand
were obtained at room temperature (RT) (25°C) and after cold challenge (CC)
(10°C). The primary outcome measure was mean change of blood flow in
selected regions of interest (ROI) of the fingers after 1 week of therapy.
Secondary outcome measures included changes in RCS, S-HAQ, and P-VAS.

Results: There were 16 females (80%); mean age was 50 years (range: 20
to 70). Patients in the Am group showed similar median changes in RCS (p =
0.51), S-HAQ (p = 0.93), and P-VAS (p = 0.62) scores. Overall, a median
increase of 0.12 units (8%) was observed at RT, with a lower overall median
change of 0.06 units (8%) after CC. Across all ROIs, the Am group tended to
show larger median actual and percentage changes in perfusion [RT: 0.14
(14%); CC: 0.07 (12%)] than the placebo group [RT: −0.10 (−6%); CC:
−0.28 (−18%)]. Changes were similar within ROI as well. However, none of
these differences overall or within ROI reached statistical significance.
No adverse events occurred. A 3-month follow up study while on drug/placebo is
ongoing.

Conclusion: While on average, small improvements in perfusion were
seen in the Am group, these changes were too small to reach statistical
significance. Though the trend observed may imply efficacy of Am, it is also
possible that vasodilation may not be its predominant mechanism of action in
improving digital ischemia, and reversing the microvascular remodeling
process over a longer period may be more important. We are currently
evaluating this hypothesis by continuing our present study for 3 months, when
data will be collected and analyzed again.

Disclosure: N. Bose: None; J. F. Bené: None; C. M. Trunick: None; D. J. Bork:
None; G. Krishnan: None; J. Petrich: None; S. Chatterjee: None.

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Intravenous Immunoglobulin (IVIg) in the Treatment of Systemic Sclerosis
(SSc) Associated Myopathy, Arnaud Dreising-Ella1, Alice Bérezné2, Brigitte
Ranque2, François-Jérôme Authier3, Yannick Allanoë4, Jean Cabane5, Eric
Hachulla6, Loïc Guillevin7 and Luc Mouthon8. 1Université Cochin, 2Université
Paris Descartes, 3 Université Paris Descartes, 4 Université Paris Descartes, 5
Hôpital Cochin, 6 Université Paris Descartes, 7 Université Paris Descartes, 8
Hôpital Cochin.

Objective: To evaluate the efficacy and the tolerance of IVIg in the
treatment of SSc-associated inflammatory myopathy.

Patients and Methods: Sixteen patients (14 females, 87.5%) with
SSc-associated myopathy and available muscle biopsy were retrospectively
investigated from the charts of four hospital centres for the efficacy of IVIg.
All of them fulfilled the American College of Rheumatology and/or Leroy
and Medsger criteria for the diagnosis of SSc. Inflammatory myopathy was
either biopsy proven or based on We retrospectively include 16 patients. All
patients fulfilled the American College of Rheumatology and/or Leroy
and Medsger criteria for the diagnosis of SSc and had a history of myopathy
explored by muscle biopsy. Myopathy was defined as the presence of muscle
weakness, myalgia, or creatine kinase (CK) greater than 5 N (upper normal
range), together with evidence of muscle involvement on electromyography
(low voltage and/or short duration potential during maximal contraction,
fibrillation or sharp wave) or on muscle biopsy.

Results: The 16 patients had a mean age of 40.4 years, a diffuse SSc in 87.5%
of the cases with a mean Rodnan score of 18 at the time of inclusion into
the study. Patients were followed for a mean of 2 years. Ninety three percent
of patients had interstitial lung disease. Fifty five percent of the patients had pulmonary
fibrosis and/or left ventricular failure. Anti-PM-Scl and anti-RNP autoantibodies
were detected in 18.75% and 12.5% of the patients, respectively. All patients
received IVIg in the setting of failure of corticosteroids and immunosuppressants.
IVIg were prescribed at a dose of 2 mg/kg every 4 weeks. Fourteen (87.5%)
patients had a favorable outcome, with complete response in 5 patients and partial
response in others. Half of patients relapsed after a mean follow up of 6.4 months
after interruption of IVIg treatment. The treatment was well tolerated and no case
of renal failure was notified.

Conclusion: IVIg may be helpful in the treatment of SSc-associated myop-
athy in case of failure of corticosteroids and/or methotrexate. However, the
therapeutic effect is only suspensive. Prospective randomized studies are needed
in order to evaluate the true efficacy of IVIg in SSc-associated myopathy.

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Authier: None; Y. Allanoën: None; J. Cabane: None; E. Hachulla: None; L.
Guillevin: None; L. Mouthon: None.
Modeling Smoking in Systemic Sclerosis: A Comparison of Different Statistical Approaches. Marie Hudson², Ernest Lo², Russell Steele³ and Murray Baron¹. ¹Jewish General Hospital, Montreal, QC, Canada, ²Lady Davis Institute, Jewish General Hospital, ³McGill University

Background: Vascular disease is ubiquitous in SSc and cigarette smoking is well known to contribute to vascular disease. There is no standard way of modelling smoking in epidemiologic studies. The purpose of this study was to demonstrate the impact of different methods of modelling smoking when determining vascular outcomes in SSc.

Methods: We undertook a study using data from the Canadian Scleroderma Research Group Registry. Patients self-reported their smoking history, including intensity, duration and time since cessation. Vascular outcomes were severity of Raynaud’s phenomenon, presence of finger ulcers and severity of finger ulcers. Five regression models using various definitions of smoking were developed: Model 1 compared ever to never smoking; Model 2 compared current and past smoking to never smoking; Model 3 modeled smoking using polynomial contrasts, treating never, past and current smoking as ordered values of a single variable; Model 4 modeled smoking status as current versus non-current; and, Model 5 represented smoking using the Comprehensive Smoking Index, which integrates smoking intensity, duration and time since cessation into a single covariate (Leffondre K et al 2006 Stat Med 25:413–46). All regression models were adjusted for age, sex, ethnicity, disease duration and limited or diffuse skin involvement.

Results: This study included 606 SSc patients, of which 87% were women, 90% were white, mean age was 55 (± 12) years, mean disease duration was 11 (± 9) years, and 36% had diffuse disease. Of these, 16% were current, 42% past and 42% never smokers. Current and past smokers smoked a mean of 25 (± 17) and 17 (± 18) pack-years, respectively. Smoking duration varied from 1 to 60 years, with past smokers having a shorter duration than current smokers (18.3 vs. 31.7 years, respectively). Past smokers stopped smoking approximately 16 (±12) years prior to their baseline registry visit, although this varied from 1 to 50 years. The results of the regression analyses for the five models of smoking are summarized in Table 1.

Table 1. Summary of the regression results of the 5 different models of smoking

<table>
<thead>
<tr>
<th>Model</th>
<th>Smoking Grade</th>
<th>Outcome Variable</th>
<th>b-CURRENT (b)</th>
<th>p-value</th>
<th>b-PAST (b)</th>
<th>p-value</th>
<th>b-PASS (b)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Models</td>
<td></td>
<td>Severity of Raynaud’s (0–10)</td>
<td>0.20</td>
<td>0.05</td>
<td>-0.06</td>
<td>0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: Ever vs. Never</td>
<td>and Past vs. Never</td>
<td>Presence of finger ulcers</td>
<td>0.40</td>
<td>0.15</td>
<td>-0.18</td>
<td>0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2: Current vs. Never</td>
<td>Severity of finger ulcers (0–10)</td>
<td>0.04</td>
<td>0.35</td>
<td>-0.03</td>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3: Polynomial</td>
<td>Severity of Raynaud’s (0–10)</td>
<td>1.14</td>
<td>0.18</td>
<td>1.85</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4: Current vs. Non-</td>
<td>Severity of finger ulcers (0–10)</td>
<td>0.19</td>
<td>0.65</td>
<td>0.66</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>current Smoking</td>
<td>Severity of Raynaud’s (0–10)</td>
<td>0.23</td>
<td>0.01</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 5: Comprehensive</td>
<td>Presence of finger ulcers</td>
<td>0.50</td>
<td>0.06</td>
<td>.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking Index (CSI)</td>
<td>Severity of finger ulcers (0–10)</td>
<td>0.06</td>
<td>0.16</td>
<td>.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model 1 did not detect any significant effect of smoking on the vascular outcomes. Models 2 and 3 showed a ‘U-shaped’ trend in the effect of smoking, with past smokers appearing healthier than both never and current smokers, with this effect reaching statistical significance in Model 3 only. Model 4 detected a negative effect of smoking on the severity of vascular outcomes, reaching statistical significance for the severity of Raynaud’s and showing a strong trend for the presence of finger ulcers. The results of Model 5 were similar to those of Model 4, but with much stronger statistical significance.

Conclusions: These findings highlight the importance of proper modeling of smoking. Simple models may mask important effects of smoking on vascular outcomes in SSc. The CSI was the most sensitive model because it accounts for the wide range of smoking exposure.

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Nailfold Microangiopathy and Peripheral Blood Perfusion Correlate with Internal Organ Involvement in Systemic Sclerosis. Alberto Sulii¹, Carmela Ferrone¹, Carmen Pizzorni², Elisa Alessandri², Francesca Ravera², Giuseppe Zampogna², Bruno Seriolo² and Maurizio Cutolo¹. ¹Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, ²Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy

Background: Nailfold microangiopathy and peripheral blood hypoperfusion are key features of early systemic sclerosis (SSc) and internal organ involvement/skin lesions are frequently discovered during the follow-up.

Aim: The aim of the study was to investigate possible correlations between nailfold capillary abnormalities, peripheral blood perfusion (PBP), and internal organ involvement in patients affected by SSc.

Methods: Seventy-one consecutive SSc patients (mean age 61 ±13 years, disease duration 7±5 years) were evaluated. Nailfold microangiopathy was detected by nailfold videocapillaroscopy (NVC), which was performed on 2nd to 5th finger of both hands, and the average semiquantitative scores for the capillaroscopic parameters were calculated. PBP was analyzed by laser Doppler flowmetry at the central area of the fingertips of the same fingers, and the average value of PBP was recorded as perfusion units (PU).

Oesophageal involvement was detected by manometry, pulmonary function by lung volume tests, DLCO and CT; cardiac performance was investigated by Doppler echocardiography, renal function by laboratory tests and arterial Doppler echography; active or recent history of ulcers were assessed by both clinical interview and examination. Statistical analysis was performed by non-parametric tests.

Results: PBP was found significantly lower in SSc patients with active or recent history of ulcers (median 28 PU), when compared with those without ulcers (median 55 PU) (p = 0.02). PBP was also lower in patients with esophageal, lung, renal, and pulmonary arterial involvement (median 29, 28, 29, 25 PU, respectively), than in those without (median 51, 46, 41, 57 PU, respectively), but this was not statistically significant (p = 0.11), possibly due to the small study population. SSc patients showing higher microvascular abnormalities scores for NVC parameters like microhaemorrhages, capillary number, and capillary disorganization had significantly lower PBP (p < 0.03).

Oesophageal involvement correlated with higher NVC scores for capillary number and disorganization (p = 0.03); lung disease with higher score for capillary disorganization (p = 0.04); renal function impairment with higher scores for capillary number and disorganization (p = 0.04); pulmonary arterial hypertension with higher scores for enlarged capillaries, capillary number, ramification and disorganization (p = 0.05); digital ulcers with higher scores for capillary number, ramification and disorganization (p = 0.01), as well as with lower score for giant capillaries (p = 0.003).

Conclusions: Nailfold capillary abnormalities extend negatively correlates with PBP and positively with internal organ involvement. Internal organ involvement seems to be associated with reduced PBP, but this should be confirmed on a larger SSc population. Finally, the occurrence of skin digital ulcers is associated with blunted peripheral blood perfusion in SSc patients, as well as with higher scores for several NVC parameters.

References:

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Oral N-acetylcysteine in the Treatment of Raynaud’s Phenomenon Secondary to Systemic Sclerosis: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Marcelo José Uchoa Correa1, Henrique A. Mariz2, Luis Eduardo Coelho Andrade3 and Cristiane Kayser4. 1Department Federal de São Paulo, São Paulo, Brazil, 3Universidade Federal de São Paulo, São Paulo, Brazil, 2Department of Dermatology, Medical University of Lublin, Lublin, 580

Purpose: Intravenous N-acetylcysteine has been suggested to be useful in the treatment of Raynaud’s phenomenon (RP) in patients with systemic sclerosis (SSc). This study aimed to evaluate the safety and the efficacy of oral N-acetylcysteine on the digital skin microvascular blood flow in patients with RP secondary to SSc.

Methods: This was a randomized, double-blind, placebo-controlled clinical trial with 42 patients with RP secondary to SSc. Patients were randomly assigned to receive oral N-acetylcysteine 600 mg three times daily or placebo three times daily for 4 weeks. Primary outcome was changes in digital skin microvascular blood flow before and after cold stimulus (CS) using laser Doppler imaging (LDI) at baseline and at week 4. Frequency of Raynaud’s attacks, RP severity visual analog scale (VAS), RP pain VAS, and the number of digital ulcers were also evaluated at baseline and at week 4.

Results: 21 SSc patients (mean age 45.6±9.5 years) were randomly assigned to receive oral N-acetylcysteine and 21 patients (mean age 45.0±12.7 years), to receive placebo. Oral N-acetylcysteine was generally well tolerated, and at the end of 4 weeks nobody discontinue the treatment. There were no significant changes in digital skin blood flow measured by LDI before or after CS following 4 weeks of N-acetylcysteine or placebo. Both groups showed significant improvement of the frequency of Raynaud’s attacks, RP severity VAS, and RP pain VAS after 4 weeks of treatment, with no difference between groups. There was no significant change in the number of digital ulcers in both groups after placebo or N-acetylcysteine treatment.

Conclusions: Oral N-acetylcysteine did not demonstrate increase on the digital skin blood flow measured by laser Doppler imaging in this short-time study in patients with SSc. Oral N-acetylcysteine was not significantly better than placebo in improving severity of RP in patients with RP secondary to SSc.

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Objectives: To determine the outcomes of BE and estimate the EAC risk in SSc patients over a 3-year prospective study.

Methods: SSc patients were recruited through EUSTAR network centers. Inclusion criteria was a recent histological finding of BE. The patients were then prospectively followed and, as recommended, a second esophageal endoscopy was performed according to the presence at baseline of BE-related dysplasia.

Results: 50 SSc patients with BE (40 without and 10 with dysplasia) were included and 46 completed the follow-up (138 patients-year). During the 3-year follow-up, 4/46 BE patients (3%/year) were diagnosed with high-grade dysplasia/EAC, of which one developed cardial EAC. EAC incidence in the BE sub-group with dysplasia increased to 4%/year compared to the absence of EAC case in the BE sub-group without dysplasia at baseline.

Conclusion: Our results, in accordance with previous published data suggesting an increased risk of esophageal or cardial adenocarcinoma in SSc, highlight the need for accurate follow-up of BE SSc patients at risk of developing adenocarcinoma.

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Preclinical Evaluation of Cardiac Involvement in Systemic Sclerosis Patients by Speckle Tracking Strain Analysis. Anne A. Schoufroer1, Kai H. Yiu1, Maarten K. Ninaber2, Jan Stolk3, Thea P. M. Vliet-Vlieland1, Eduard R. Holman1, Tom W. J. Huizinga1, Jeroen J. Bax1, Nina Ajmone Marsan1 and Annemie J. M. Schuerwegh2. 1Department of Cardiology, Leiden, The Netherlands, 2Department of Pulmonology, Leiden, The Netherlands, 3Department of Rheumatology, Leiden, The Netherlands

Background: Cardiac involvement is common in patients with systemic sclerosis (SSc) and a well-known prognostic factor. Preclinical identification is therefore of crucial importance, although conventional echocardiography assessment showed limited sensitivity for the assessment of subtle changes in cardiac function. The aim of the study was to assess the value of the novel echocardiographic speckle tracking 3 directional (longitudinal, circumferential and radial) strain analysis to detect cardiac involvement in SSc patients and to investigate the association with rhythm disturbances, lung function parameters and cardiopulmonary exercise (CPET) parameters.

Methods: A total of 104 patients were included during a SSc screening program, which included pulmonary function tests, CPET, 24-hr ECG Holter recording and echocardiography with speckle tracking analysis. Echocardiographic data were compared with those obtained from 37 age and sex matched healthy controls.

Results: The mean age of the study population was 54 ± 11 years. Fifty-seven patients presented a diffuse (d) SSc and 47 a limited (l) SSc. Disease duration was 8.1 ± 6.2 yr; Vital Capacity was 94.4 ± 14.4 % predicted, and % predicted maximum oxygen uptake (VO2max) was 90.6 ± 20.4%. Twenty-eight patients (27.7 %) had abnormal ECG Holter findings defined by ventricular tachycardia or frequent ventricular ectopies >100 per day. Echocardiographic findings in SSc patients are shown in table 1. At the multivariable analysis, decreased left ventricular (LV) systolic function as assessed by global circumferential strain (B = -0.52, 95% CI -5.63, -2.23, p<0.01) was independently associated with of lower % predicted VO2 max. Patients with 24-hr ECG Holter abnormalities showed significantly more decreased longitudinal (−18.5 ± 1.5 vs −17.1 ± 2.1, p<0.01) and circumferential (−18.7 ± 2.0 vs −17.3 ± 2.5, p=0.01) strain than patients without

580 Outcomes of Barrett’s Esophagus Related to Systemic Sclerosis: A 3-Year EULAR/EUSTAR Prospective Follow-Up Study. Julien Wipf1, Romain Coriat2, Michela Masciocchi3, Paola Caramaschi4, Chris T. Derk5, Eric Hachulla6, Valeria Ricciere7, Luc Mouthon8, Dorota Krassowska9, L. P. Anayeva2, Andre Kahn3, Marco Mattucci-Cerinic9,10, Stanislav Chausse11 and Yannick Allanoire12. 1Department of Dermatology, Medical University of Lublin, Lublin, 2Department of Medicine, Verona University, Verona, 3Hospital Cochin, Paris, France, 4Hopitaux de Paris Cochin, Paris, France, 5Immunological Clinic, Mangiagalli Regina Elena Foundation, Milan, 5Institute of Rheumatology, Russian Academy of Medical Science, Moscow, 6Jefferson Medical College, Philadelphia, PA, 7National Scleroderma Centre, Lille Cedex, France, 8Paris Descartes University, Gastroenterology Dpt, Cochin Hospital, 9Paris Descartes University, Internal Medicine Dpt, Cochin Hospital, 10Paris Descartes University, Rheumatology A Dpt, Cochin Hospital, 11Sanepsex University of Rome, Medical Clinic and Therapy Department, Rome, 12University of Florence, Firenze, Italy

Background: Barrett’s esophagus (BE) is the major risk factor for esophageal adenocarcinoma (EAC). Systemic sclerosis (SSc) is associated with an increased risk of BE related to chronic reflux.
Conclusion: Speckle tracking strain analysis is able to detect subtle myocardial systolic dysfunction in patients with SSc. Decreased global circumsferential strain was associated with lower exercise tolerability and rhythm disturbances, whereas LV ejection fraction was not. Therefore, the use of speckle tracking analysis may facilitate preclinical stratification of patients with SSc. Our preliminary composite response index for Raynaud’s phenomenon has the potential to identify patients likely to improve with treatment and to differentiate their response from placebo, as top two measures for RCT and 93% and 92% stated that RCS and ptGA must be included in a composite index. Therefore, we assessed a definition requiring RCS and ptGA improvement by ≥x% along with y of the 4 other core set items to define a composite improvement. 92.8% of placebo-treated patients showed ≥10% improvement in at least one core set item with 38.5% showing ≥60% improvement in at least one variable. An improvement of 40% in both RCS and in ptGA, and 40% in 3 of the remaining 4 variables was associated with placebo response of 6% and provided greatest discrimination between 10–30% vs. 50–60% improvement in core set measures.

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Preliminary Composite Response Index for Raynaud’s Phenomenon

Dinesh Khanna1, Paul Maranian2, Daniel Furst3, James Seibold4, Marco Matucci Cerinic5, Jeff Gregory1 and Harold Paulus1,6,7

Background: In interventional studies of RP, variable responses are seen in different outcome measures and high placebo response is common. Our goal was to develop a Composite Response Index in RP that would improve the ability to measure efficacy of an investigational drug and facilitate the ability to compare responses across trials.

Methods: We analyzed 249 patients with primary or secondary RP in the placebo group who participated in 3 RCT (MediQuest Therapeutics). 8 core set measures were assessed in these studies: Raynaud’s Condition Score (RCS- assesses the level of difficulty experienced due to RP), pt. assessment of RP, physician assessment of RP, pain, numbness, tingling, average number of attacks per day and duration of attacks. We conducted an online survey of scleroderma experts and asked them to rank all items on their importance for RCT and to identify core set items that must be included in RCTs.

Daily patient logs of Raynaud attacks were used to compute average number of attacks per day, average duration of attacks, daily averages of pt-reported pain, numbness, and tingling associated with each reported attack and a daily RCS, pt (ptGA) and physician assessments of RP were recorded weekly. Daily averages were used to compute weekly averages for the period between physician visits, and the weekly averages were averaged for the run-in period and for the treatment period. Percent improvement between run-in and treatment periods was calculated for 8 outcome measures. Since pain, numbness, and tingling showed a high degree of correlation (pairwise Pearson correlations of 0.76, 0.69, and 0.78), they were combined into a single measure (Attack symptoms) by selecting the %improvement of the outcome that showed the highest level of improvement, resulting in 6 core measures.

Preliminary definitions required ≥ x% improvement in y of the 6 variables where x was set at 10%, 20%, 30%, 40%, 50%, and 60% and y was set as 2, 3, 4, 5, or 6, variables. We hypothesized that placebo response should be <10% to show a difference from an effective drug.

Results: 50% and 40% of experts (N=71) ranked RCS and ptGA as top two measures for RCT and 93% and 92% stated that RCS and ptGA must be included in a composite index. Therefore, we assessed a definition requiring RCS and ptGA improvement by ≥x% along with y of the 4 other core set items to define a composite improvement. 93.5% of placebo-treated patients showed ≥10% improvement in at least one core set item with 38.5% showing ≥60% improvement in at least one variable. An improvement of 40% in both RCS and in ptGA, and 40% in 3 of the remaining 4 variables was associated with placebo response of 6% and provided greatest discrimination between 10–30% vs. 50–60% improvement in core set measures.

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Prevalence of Coronary Heart Disease in a Cohort of Australian Scleroderma Patients. Gene-Siew Ngian1, Joanne Sahhar2, Jill Byron3, Susanna Proudman4, Catherine Hill5, Janet Roddy6,7, Peter Yousuff8,9, Kathleen Tymms1, Leslie Schrieber10, Wendy Stevens1,2, Jane Zochling3,4, Peter Nash5,6,7, Allan Sturgess5,7, Gabor Major8, Ian Wicks9 and Sharon Van Doornam3,7

Background: It is not established whether accelerated atherosclerosis occurs in scleroderma (SSc). Increased rates of peripheral vascular disease have been reported1, however the prevalence of coronary heart disease (CHD) remains unknown.

Methods: We reviewed the prevalence of CHD and traditional and non-traditional cardiovascular risk factors in a well-characterized cohort of Australian SSc patients. Data were collected prospectively at 12 centres around Australia from January 2007 to May 2010 as part of a longitudinal cohort study instituted by the Australian SSc Interest Group.
Patients were identified as having CHD if they reported percutaneous coronary intervention, coronary artery bypass grafting, angioplasty or myocardial infarction. Data from the patient’s most recent review were used to obtain a cross-sectional view of the cohort.

We compared the prevalence of CHD in our cohort with Australian population prevalence estimates from the National Health Survey 2007–2008. Chi square and two-sample t tests were used to analyze differences between SSc patients with and without CHD.

**Results:** Of the 850 SSc patients included in the analysis, 88 had CHD. The prevalence of CHD in our cohort was therefore 10.3% (95% confidence interval 8.3%–12.4%). Patient characteristics are summarized in table 1.

| Table 1. Demographics and cardiovascular risk factors in SSc patients with and without CHD |
|-----------------------------------------------|----------------|----------------|----------------|
| CHD present | N (%) or mean ± standard deviation | CHD absent | p-value |
| Female | 68 (77.3%) | 667 (87.5%) | 0.009 |
| Subclass | | | |
| - limited | 65 (73.9%) | 510 (66.9%) | 0.21 |
| - diffuse | 21 (23.9%) | 231 (30.3%) | | |
| - sine | 0 | 2 (0.3%) | | |
| - not documented | 2 (2.3%) | 19 (2.5%) | | |
| Mean age | 67.5 ± 9.7 years | 58.3 ± 12.3 years | <0.001 |
| Hypertension | 59 (67.9%) | 277 (36.4%) | <0.001 |
| Hypercholesterolaemia | 42 (47.7%) | 145 (19.0%) | <0.001 |
| Diabetes mellitus | 12 (13.6%) | 23 (3.5%) | <0.001 |
| Family history of heart disease* | 31 (36.0%) | 162 (40.1%) | 0.006 |
| Ever smoked | 51 (58.6%) | 354 (47.3%) | 0.047 |
| Obesity (BMI ≥ 30 kg/m²) | 22 (25%) | 145 (19.0%) | <0.001 |
| Age at diagnosis of SSc | 50.8 ± 15.3 years | 45.3 ± 13.9 years | 0.001 |
| Duration of SSc | 16.4 ± 10.8 years | 12.8 ± 10.2 years | 0.004 |
| Corticosteroid use ever | 45 (51.1%) | 314 (41.2%) | 0.08 |
| Pulmonary arterial hypertension | 27 (30.1%) | 112 (14.7%) | <0.001 |
| Interstitial lung disease | 28 (31.8%) | 188 (24.7%) | 0.15 |
| SSC renal crisis | 3 (3.4%) | 34 (4.4%) | 0.65 |
| Antiphospholipid antibodies (anticardiolipin or anti-β2-glycoprotein) | 25 (2.3%) | 156 (25.2%) | 0.20 |

* Family history data missing in 37 patients with CHD and 358 without CHD

On stepwise logistic regression hypertension, diabetes, smoking, age, duration of SSc and pulmonary arterial hypertension were still significant predictors of CHD.

The prevalence of CHD in our SSc cohort compared with the general population is shown in table 2. Stratified by age, prevalence was slightly higher in SSc patients, with the difference more marked in younger patients.

| Table 2. Prevalence of CHD in SSc compared to the Australian population |
|-----------------------------------------------|----------------|----------------|
| Age group (years) | Prevalence of CHD in SSc cohort | Estimated population prevalence of CHD |
| 35–44 | 1.4% | 0.7% |
| 45–54 | 4.6% | 2.9% |
| 55–64 | 9.8% | 6.8% |
| 65–74 | 15.4% | 12.3% |
| 75 and over | 24.7% | 19.9% |

**Conclusion:** The prevalence of CHD in SSc has not been previously reported. Our data suggests a higher prevalence of CHD in SSc patients than in the general population, particularly in those less than 55 years of age. These data need confirmation by comparison with a closely matched cohort of controls with similar methods of CHD ascertainment. Further investigation is needed to determine which SSc-specific factors contribute to the aetiology of CHD.


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<tr>
<th>Table 1.</th>
<th>Initial PAH-specific drug therapies for PHAROS patients (p = 0.06)</th>
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<tr>
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<td>No therapy</td>
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<tr>
<td>SSc-PAH</td>
<td>(n = 97)</td>
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<tr>
<td>SSc-ILD</td>
<td>(n = 30)</td>
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<td>PVH</td>
<td>(n = 24)</td>
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There was no significant difference in functional status at baseline among groups. However, in patients with one or more years of follow-up (n = 79), 32% of PAH patients had worsening NYHA class, compared to 29% in PH-ILD and 7% in the PVH group (p = 0.02). No difference in the frequency of worsening 6MWD was found (p = 0.82), with more than 65% in all groups either stable or improved.

As of last follow-up there was no significant difference in risk of death associated with PAH subgroup after adjustment for age (p = 0.54). Patients with PAH had a higher frequency of all-cause hospitalizations (55%) compared to PH-ILD (30%) and PVH (44%); p = 0.05.

**Conclusions:** Analysis of the PHAROS cohort suggests that PAH patients have a higher frequency of hospitalization than those with PVH or PH-ILD, although there is no difference in age-adjusted survival. The majority of patients in all classes are functionally stable by NYHA class and 6MWD at one year of follow-up. Although half of the patients with PVH were not treated with PH-specific therapies, their outcomes are comparable or better than PAH and PH-ILD. Longer follow-up of the PHAROS cohort will further elucidate differences between groups.

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Pulmonary Hypertension by Age of Scleroderma Onset and Subtype.
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Johns Hopkins University, Baltimore, MD.

**Purpose:** Pulmonary hypertension (PH) is a leading cause of death among scleroderma (SSc) patients. Historically, PH has been considered a late complication of SSc with predominance among those with the limited cutaneous subtype (lcSSc) and an older age of SSc onset. However, we hypothesize that the risk of PH will be the same among lcSSc and diffuse cutaneous (dcSSc) patients when SSc onset is defined at Raynaud phenomenon (RP) onset. We sought to determine the risk of pulmonary hypertension among a large cohort of SSc patients stratified by SSc skin subtype and age of disease onset.

**Methods:** Data were retrospectively reviewed from a comprehensive database at a University based Scleroderma Center. Patients were categorized by SSc subtype (lcSSc vs dcSSc), age of SSc onset (late-age onset ≥ 65 years), and the presence of PH. Analyses were completed defining SSc onset in 2 ways: 1) onset of RP; 2) onset of first non-RP SSc symptom. PH was defined 2 ways: 1) mean pulmonary artery pressure ≥25 mmHg by echocardiogram or ≥35 mmHg by right heart catheterization; and 2) median duration since onset of Raynaud was 8.9 years (interquantile range (IQR) 4.3, 16.0), and median duration of PHAROS follow-up ≥ 1.1 years (IQR 0.5, 2.5).

**Results:** 2282 patients were included in our analyses. With SSc onset defined by RP onset, 162 had late-age SSc onset (64% lcSSc, 32% +anti-centromere); 2118 had younger-age SSc onset (64% lcSSc, 28% +anti-centromere). Figure 1 depicts KM for PH by cath and figure 2 by cath or echo.

**Figure 1:** Cumulative Incidence Pulmonary Hypertension (by cath)

- Number at risk: 1,533 at onset < 65, 1,014 at onset ≥ 65
- Kaplan-Meier survival curves were generated to determine the cumulative incidence of PH. Cox proportional hazard models were generated to determine the risk of PH controlling for age of SSc onset, subtype, gender, race, and FVC. Sensitivity analyses were conducted excluding patients with FVC < 60.

- **Results:** 2282 patients were included in our analyses. With SSc onset defined by RP onset, 162 had late-age SSc onset (64% lcSSc, 32% +anti-centromere); 2118 had younger-age SSc onset (64% lcSSc, 28% +anti-centromere). Figure 1 depicts KM for PH by cath and figure 2 by cath or echo.
The risk of developing PH (by cath) was significantly greater (HR 4.49; 95% CI 2.22, 9.05) for those with SSc onset ≥65 years compared to younger-age onset. The risk of PH did not differ by SSc subtype (HR 1.19; 95% CI 0.82, 1.73). Sensitivity analyses excluding patients with FVC ≤60 yielded similar results (late-age SSc HR 1.46; 95% CI 0.88, 2.42). With SSc onset defined by first non-RP symptom, similar results were obtained results (late-age SSc HR 4.42; 95% CI 2.56, 7.63; dcSSc HR 0.96; 95% CI 0.66, 1.38).

Conclusions: Age of SSc onset impacts the risk of PH but SSc subtype does not. These data suggest benefit for routine screening for PH among all cutaneous SSc subtypes, especially those with late-age onset of disease.

Disclosure: R. L. Manno: None; F. M. Wigley: None; L. K. Hummers: None.

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Reproducibility of Semi-Automated Quantitative Nailfold Capillaroscopy Measurements in Patients with Systemic Sclerosis. Andrea K. Murray,4 Tonia L. Moore,4 Andy Vail,1 Joanne Manning2 and Ariane L. Herrick,3, 1Rheumatology Directorate, HealthMethodology Research Group, Manchester Academic Health Science Centre, The University of Manchester, Salford Royal Hospital, Salford, UK, 2Salford Royal NHSFoundation Trust, Salford, 3The University of Manchester, Manchester Academic Health Science Centre, Manchester, Salford Royal Hospital, Salford, Greater Manchester, United Kingdom, 4The University of Manchester, Manchester Academic Health Science Centre, Manchester, Salford Royal Hospital, UK

Background: High magnification nailfold videocapillaroscopy allows measurement of capillary density and dimensions and therefore has the potential of being a non-invasive biomarker for systemic sclerosis (SSc)-related microvascular disease. However, quantifying abnormality brings enormous challenges: (a) in SSc, capillaries across any one nailbed are highly heterogeneous and many have very abnormal architecture; (b) current measurement is subjective; (c) current measurement methods are very time-consuming meaning that in practice only a small number of capillaries in any one nailfold are selected for study and these may be unrepresentative of the whole nailfold. Newly developed software allows rapid semi-automated quantification of capillary density and dimensions over the whole nailfold with results comparable to manual measurements. While this is likely to be a major advance, the system requires user input to identify and ‘mark-up’ the apex of each capillary in the image. This study aimed to assess the intra-and inter-observer variability and test-retest reliability.

Methods: Two nailfold images were taken from 60 patients with SSc over two visits. Two blinded observers familiar with capillaroscopy cropped image 1 independently to a standard size of 3 mm and then marked-up capillaries in order to assess inter-observer variability. One of the blinded observers then performed a repeat crop/mark-up on image 2 to assess inter-observer variability and crop/mark-up on image 2 to assess test-retest reliability.

Results: Reproducibility of independently cropped images was poor. Further investigation revealed that this was due to positioning of the cropped area. When images were categorised according to the amount of cropped area overlap, those with a high degree of overlap had statistically significantly improved reproducibility (example of Bland Altman plot shown in Figure below, solid circles representing high degree of overlap).

Conclusions: This study demonstrates the heterogeneity of nailfold architecture in patients with SSc and the importance of ensuring that quantitative measurements of nailfold capillaries are carried out on the same microvessels in longitudinal studies. The novel ability to make measurements across the whole bed and to compare current and previous visits is a significant advantage, as this ensures the same capillaries are measured at each visit. This fast, reliable method of quantifying microvascular disease could be a reliable outcome measure in future longitudinal studies including those of treatment response.

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Risk Associated with African American Race in Relation to Prevalence of Cardinal Organ System Manifestations in Scleroderma. Elizabeth N. Le1, Rebecca L. Manno2, Laura K. Hummers3, Fredrick M. Wigley2 and Allan C. Gelber1. 1Baltimore, MD, 2Johns Hopkins University, Baltimore, MD, 3Johns Hopkins University, Baltimore, MD

Purpose: Scleroderma is a severe multisystem rheumatic disorder with a broad spectrum of organ involvement. There are several known risk factors for particular organ system manifestations, including the cutaneous subset of disease (limited vs. diffuse) and age at disease onset. Whereas race has been related to risk for interstitial lung disease and diffuse cutaneous disease, there are few systematic examinations of race in relation to risk for each cardinal organ manifestation of scleroderma.

Method: A prospective clinical database was begun at a single university scleroderma referral center in 1990. Each patient satisfied at least one of the following three diagnostic criteria: (1) the ACR criteria for scleroderma; (2) 3 of 5 features of the CREST syndrome; or (3) a combination of definite Raynaud’s phenomenon, abnormal nailfold capillaries and a scleroderma-specific autoantibody. Demographic data including age, sex, and race, together with cutaneous subtype (based on LeRoy classification criteria), and smoking status were uniformly ascertained. Disease duration, from disease onset, at age of the first non-Raynaud’s symptom, to evaluation at the Scleroderma Center was determined. Clinical data, including organ system involvement, were recorded using a uniform protocol at cohort entry, and updated every six months when available. The outcomes of interest were the Medsger severity scores [MSS]; J Rheumatol 1999;26:2159], determined for each cardinal organ system involved in scleroderma. The association of African American in comparison to Caucasian race with the MSS parameters were examined using logistic regression analysis, with adjustment for potential confounding by age at disease onset, sex, disease subtype, disease duration and smoking status (for pulmonary outcome).

Results: Between January, 1990 and June, 2009, a total of 2481 patients with scleroderma were enrolled. Overall, mean age at disease onset was 45.5 years. 63% of patients manifested the limited cutaneous subset; half were ever-smokers. In terms of the various MSS outcomes, the overall proportion with digital ischemia (score ≥2) was 55%; for lung MSS ≥1 was 77%; heart MSS ≥1 25%; kidney MSS ≥1 18%; gastrointestinal MSS ≥2 40%; and
muscle MSS ≥1 was 24%. Importantly, in multivariate analysis, compared to the Caucasian members of the cohort, the African American members had a 50% increase in peripheral vascular disease, a >6-fold increase in lung involvement, 60% increase in heart, 70% increase in risk of kidney involvement, a 70% increase in gastrointestinal, and 90% increase in risk of muscle weakness.

**Conclusion:** These data imply that among patients presenting in rheumatology consultation for the evaluation and management of scleroderma, that African Americans are at notably increased risk to develop the full range of cardinal organ system features of disease.

 Disclosure: E. N. Le: None; R. L. Manno: None; L. K. Hummers: None; F. M. Wigley: None; A. C. Gelber: None.

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### 590

**Role of N-Terminal Pro-BNP in Detecting Clinically-Significant Cardiac Involvement in Systemic Sclerosis Patients.** Cecilia Chighizola, Benjamin Schreiber, Pier Luigi Meroni, Gerry Coghlan, Christopher P. Denton and Voon Ong.

**Center for Rheumatology and Connective Tissue Diseases, UCL Medical School, Royal Free Hospital, London, United Kingdom, Center for Rheumatology and Connective Tissue Diseases, UCL Medical School, Royal Free Hospital, London, 0° Rheumatology Division, Department of Internal Medicine, Istituto G. Pini, University of Milan, Milan, Italy, Royal Free Hospital, London, United Kingdom

**Background:** Cardiac involvement is common in Systemic Sclerosis (SSc) and is often clinically occult. However, it is recognised as a poor prognostic factor contributing significantly to mortality among these patients. Early detection of cardiac disease with non-invasive tools is therefore critical.

**Aim:** To assess the role of N-TproBNP in SSc related cardiac involvement in a retrospective cohort of patients.

**Methods:** 19 SSc patients (13 dcSSc and 6 lcSSc) patients with cardiac involvement were enrolled in this study. Cardiac involvement was defined as haemodynamically significant arrhythmias, pericardial effusion or congestive heart failure, requiring specific treatment. All patients had normal pulmonary artery systolic pressure and none had serum creatinine above 140 mmol/l. This group of patients was compared with 19 age- and sex-matched SSc patients without evidence of cardiac involvement or pulmonary arterial hypertension. Serum N-TproBNP levels were measured with the Roche Modular Analytics E-170 (Elecsys module) immunoassay. Normal N-TproBNP levels were less than 20 pmol/l. Unpaired t-test was used to compare N-TproBNP levels between subgroups based upon presence of cardiac involvement. ROC curves were drawn to identify N-TproBNP levels which gave optimal sensitivity and specificity for diagnosis of SSc-related cardiac involvement. N-TproBNP levels were compared at presentation of cardiac involvement and at six month follow up using a paired t-test. Univariate mortality analysis was performed with Kaplan-Meier method, the level of significance of the differences among survival curves was assessed by Log-rank test.

**Results:** Compared to those without cardiac involvement, N-TproBNP was significantly increased in SSc patients with heart involvement (mean±SD 149±145 pmol/l versus 1043±2053 pmol/l respectively, p=0.037, 95%CI 67,1989). Figure 1 shows a ROC curve of N-TproBNP that predicts the presence of heart involvement in SSc. A sensitivity of 100% was achieved at a cut-off N-TproBNP level of 28 pg/mL, with a specificity of 84% (95% CI 0.95-1). Moreover, a significant progressive reduction in N-TproBNP after the acute phase of cardiac involvement (mean±SD 301±330 pmol/l) was observed during 6 months follow-up (mean±SD 87±113 pmol/l; p=0.048, 95%CI 2.8,425). In addition, within the group with cardiac involvement, N-TproBNP levels were categorized as high if above the median value of 219 pmol/l; however, higher levels of N-TproBNP did not predict survival (p=0.959, at Log rank analysis).

**Conclusions:** These data suggest that N-TproBNP peptide may be a surrogate marker for cardiac involvement in SSc. It may selectively identify those patients with severe impairment of cardiac function. Further studies are required to evaluate the utility of N-TproBNP levels for cardiac assessment in SSc patients.

 Disclosure: C. Chighizola: None; B. Schreiber: None; P. L. Meroni: None; G. Coghlan: None; C. P. Denton: None; V. Ong: None.

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### 591

**Scleroderma Autoantibodies and Disease Subtype Predict Pulmonary Hypertension Classification in the PHAROS Registry.** Monique E. Hinchcliff, Aryeh Fischer, Nadera Sweiss, Maureen Mayes, Marcy Bolster, Virginia Steen and PHAROS Investigators.

**Georgetown University, 3Medical University of South Carolina, 4National Jewish Health, 5Northwestern University, 6University of Chicago, 7University of Texas-Houston Medical School

**Background and Purpose:** Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (SSc), PHAROS, is a multi-center, prospective, observational study of SSc patients who are at high risk for pulmonary arterial hypertension (PAH) or who have definite pulmonary hypertension (PH) by right-heart catheterization (RHC). We sought to describe the relationship and predictive value of SSc-specific autoantibodies for pre-PAH and PHAROS registry.

**Objective:** To determine the association between SSc-specific autoantibodies and pre-PAH or PHAROS registry.

**Methods:** SSc patients with echo RVSP > 40mmHg, FVC/DLCO >1.6, FVC < 55% (Pre-PAH) or definite PH by RHC are enrolled in PHAROS. Objective (PFT, echo, and the presence of autoantibodies (ab) including antinuclear factor (ANF), anti-topoisomerase (Sc1-70), an isolated nuclear factor (ANA) test (NUT), anti U1-RNP (U1RNP), RNA polymerase III (Pol III) and others) and clinical data (disease subtype, limited SSc (lcSSc) and diffuse SSc (dcSSc) according to the LeRoy criteria) are collected. Patients with mean pulmonary pressure (mPAP) ≥25 mmHg on RHC were classified as PH according to WHO PH criteria. Statistical analyses were conducted using SPSS (Chicago, IL) and Bonferroni correction was used for multiple pair-wise comparisons.

**Results:** The majority of patients have lcSSc (65% l, 31% d, 4% other). Ab data were available on 322 of the 383 PHAROS patients. Patients with an isolated NUC ab were over represented in this registry compared to the usual scleroderma population and were more frequently entered as definite PH (groups 1–3) as opposed to Pre-PAH (p<0.001). ACA and NUC patients more frequently had PAH compared to the Sc-I70 patients who more frequently had PH-ILD. Patients with lcSSc and a positive NUC ab were more likely to have PAH (p=0.033). Patients with dcSSc and a positive Sc1-70 had PH-ILD more commonly (p=0.025).

**Conclusion:** PHAROS is a multi-institutional registry that continues to provide insights into SSc-PH. Among this national SSc cohort of patients at high risk or with definite PH, we have shown that both SSc clinical phenotype and autoantibody profile predict WHO PH classification. Although less common in SSC in general, an isolated NUC ab is common in PH patients. Diffuse patients with a positive Sc1-70 ab are less likely to have PAH and
more likely to have PH-ILD. In contrast, patients with lcSSc and a positive NUC ab are more likely to have PAH.

**Clinical Implications:** Scleroderma autoantibodies and disease subtype may be helpful in identifying patients who are more likely to have PAH or PH-ILD.

**Table:**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>N (%)</th>
<th>Pre-PAH</th>
<th>WHO 1 (PAH)</th>
<th>WHO 2 (PH)</th>
<th>WHO 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA</td>
<td>86 (23)</td>
<td>51 (22)</td>
<td>27 (28)</td>
<td>6 (27)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Scl-70</td>
<td>52 (14)</td>
<td>35 (15)*</td>
<td>6 (6)*</td>
<td>2.59*</td>
<td>9 (30)*</td>
</tr>
<tr>
<td>Nuc</td>
<td>66 (20)</td>
<td>29 (12)*</td>
<td>29 (30)*</td>
<td>6 (27)*</td>
<td>3 (10)*</td>
</tr>
<tr>
<td>U1 RNP</td>
<td>21 (7)</td>
<td>13 (6)</td>
<td>8 (8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pol III</td>
<td>6 (2)</td>
<td>2 (1)</td>
<td>3 (3)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Other ANA</td>
<td>70 (22)</td>
<td>42 (18)</td>
<td>13 (14)</td>
<td>4 (18)</td>
<td>8 (27)</td>
</tr>
</tbody>
</table>

*denotes p ≤ 0.05, $\chi^2$ test performed between pre-PAH and definite WHO groups (1–3).

**Disclosure:** M. E. Hinrichs: None; A. Fischer: None; N. Swiss: None; M. Mayes: None; M. Bolster: None; V. Steen: None; PHAROS Investigators: None.

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**Scleroderma Lung Disease: Effect of Co-Existing Pulmonary Hypertension on Progression of Interstitial Lung Disease.** Anupama Shahane, Joseph Parambil, Meng Xu and Soumya Chatterjee. Cleveland Clinic

**Background:** Pulmonary involvement is the leading cause of mortality in systemic sclerosis. The two most commonly seen patterns of lung disease, interstitial lung disease (ILD) and pulmonary hypertension (PH) often co-exist, with worse outcomes than either ILD or PH alone. We retrospectively studied patients with scleroderma lung disease to evaluate the effect of co-existing PH on progression of ILD.

**Methods:** Patients were identified from the Cleveland Clinic scleroderma database and the pulmonary hypertension database. Patients satisfied the ACR criteria for systemic sclerosis; pulmonary function tests and thoracic high resolution CT scans were used to identify ILD. PH was diagnosed on the basis of right heart catheterization. We described two cohorts of scleroderma patients: scleroderma with ILD alone (SSc-ILD) and scleroderma with both ILD and PH (SSc-ILD/PH). We further divided patients with ILD into limited and extensive disease based on extent of lung involvement on HRCT (Goh et al, Respir Crit Care Med, 2008). Disease progression was measured in terms of longitudinal values of forced vital capacity (FVC) and carbon monoxide diffusion capacity (DLco). We collected annual data for 6 years. Chi square test was used for categorical variables, and Wilcoxon rank sum test was used for continuous variables. Mixed model was used for longitudinal measures of FVC and DLco.

**Results:** We identified 86 patients with SSc-ILD (55 limited, 31 extensive) and 47 patients with SSc-ILD/PH (27 limited, 20 extensive). In our cohort, all subtypes of lung disease were more prevalent in females and Caucasians. Average duration of lung disease since time of diagnosis of scleroderma was 4 years (3.7–4.3 years). Significant difference was not noted in progression of patients with SSc-ILD in comparison with patients with SSc-ILD/PH ($p = 0.42$). Patients with limited ILD showed a trend towards faster disease progression in the presence of PH, but this was not noted in patients with extensive ILD ($p = 0.054$). Patients with extensive ILD had lower FVC and DLco at baseline and showed faster rate of progression ($p < 0.001$). Patients with SSc-ILD/PH had significantly faster decline in DLco compared to patients with SSc-ILD, in patients with both limited as well as extensive lung disease ($p < 0.001$). Moreover, extensive ILD was associated with faster rate of disease progression than limited ILD, irrespective of presence of PH ($p < 0.001$).

**Conclusions:** Our study showed that limited (but not extensive) ILD is likely to progress faster in the presence of PH. Also, patients with SSc-ILD/PH have faster rate of decline in DLco compared to patients with SSc-ILD. Lung disease is not only worse in extensive ILD patients but also progresses faster when compared to those with limited ILD, regardless of co-existent PH.

**Disclosure:** A. Shahane: None; J. Parambil: None; M. Xu: None; S. Chatterjee: None.

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**Sildenafil Increases Vasodilation in Systemic Sclerosis: An Interim Analysis from a Single Centre Pilot Study.** Silvia Bellando-Randone, Irene Miniati, Serena Guiducci, Maria Letizia Conforti, Jelena Blagojevic, Ginevra Fiori, Francesca Bartoli, Francesca Nacci and Marco Matucci-Cerinic. Department of Biomedicine Section of Rheumatology University of Florence, Italy

**Background:** Vasculopathy is an early and prominent feature in systemic sclerosis (SSc) and it is reflected by Raynaud’s Phenomenon (RP) and digital ulcers. Reduced nitric oxide levels have been proposed to play a role in the pathogenesis of vascular disease in scleroderma. Sildenafil represents an attractive candidate for the treatment of SSc-associated vasculopathy as a selective inhibitor of cGMP-specific phosphodiesterase type 5 and potent agent to increase the endogenous NO levels.

**Objective:** In this pilot study, the effect of sildenafil on RP was analysed. Primary outcome was the improvement of RP and changes in other clinical symptoms. This is an interim analysis after 3 months of treatment.

**Methods:** Forty-five SSc patients were randomized in 3 groups: 15 treated with maximally tolerated sildenafil dose (20 mg three times daily), 15 with combination therapy (sildenafil and prostanoids i.v.) and 15 with prostanoids i.v. Symptoms were assessed by diary cards including a 10-point Raynaud’s Condition Score, SF-36 and SHAQ. Videopialaroscopy was performed in all patients at baseline and every 3 months. Results were analysed with ANOVA using Bonferroni correction.

**Results:** After 3 months there was a statistically significant difference between the 3 groups for RCS ($p = 0.03$). No significant differences were found for SF36 (all domains) and SHAQ. NVC pattern was unmodified in all patients. Four patients (three treated with sildenafil, one with combination therapy) reported side effects leading to discontinuation of the study drug. Two patients on prostanoids and 1 patient on SILDENAFIL were switched to a combination therapy due to inefficacy.

**Conclusion:** This study indicates that sildenafil improves RP and associated symptoms and is a well-tolerated treatment in SSc patients. Long term results are necessary to confirm these results and investigate the effect on other outcome measures.

**Disclosure:** S. Bellando-Randone: None; I. Miniati: None; S. Guiducci: None; M. L. Conforti: None; J. Blagojevic: None; G. Fiori: None; F. Bartoli: None; F. Nacci: None; M. Matucci-Cerinic: None.

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**Subclinical Atherosclerosis Is Increased in Systemic Sclerosis—A Case-Control Study.** Karen M. Au1, Maureen A. McMahon2, Daniel E. Freest3, Bevra H. Hahn2, Nageeh Ragavendra1, Amber Bechtel1, Lori Sahakian1 and Dinesh Khanna1. 1UCLA School of Medicine, Los Angeles, CA, 2University of California Los Angeles, Los Angeles, CA, 3University of California Los Angeles Medical School, Los Angeles, CA, 4University of California Los Angeles School of Medicine, Los Angeles, CA

**Objective:** Systemic sclerosis (SSc) is associated with vasculopathy and endothelial cell injury, which could potentially increase the risk of atherosclerosis. Carotid artery ultrasound can detect subclinical atherosclerosis by measuring carotid intima-media thickness (IMT) and presence of carotid plaque. Studies have suggested that IMT is elevated in SSc, but there is little evidence that plaque is more prevalent in SSc compared to healthy patients. Normal high-density lipoprotein (HDL) is anti-inflammatory and prevents low-density lipoprotein (LDL) oxidation. While HDL is protective, an altered form known as pro-inflammatory high-density lipoprotein (pHDL) may increase atherosclerotic risk and may actually potentiate LDL oxidation. Serum pHDL is a novel marker of atherosclerotic risk in lupus and rheumatoid arthritis. The objective of the study was to determine 1) the prevalence of subclinical atherosclerosis (carotid plaque and IMT measurement) in SSc and 2) serum pHDL levels as a potential novel marker of atherosclerotic risk in SSc.

**Methods:** A cross-sectional study of 32 patients with SSc and 32 age-, sex-, and race-matched healthy controls in a single center was conducted. All subjects received bilateral carotid ultrasounds measuring plaque and IMT and were read by a single reader (NR) who was blinded to the diagnosis. Cholesterol studies and a cell free assay to measure presence of pHDL were performed.

**Results:** The average age of the patients was 48 (mean age SSc 48, controls 47) and included 15 limited SSc and 17 diffuse SSc subjects. Total cholesterol ($P = 0.20$) and LDL ($P = 0.13$) were similar between SSc and controls. SSc patients had lower HDL (SSc 54.2 vs. controls 63.4, $P = 0.01$) and higher triglycerides compared to controls ($142.3$ vs. $110.1$, $P = 0.02$). Carotid plaque was significantly more prevalent in SSc patients compared to controls (14 SSc patients vs. 7 controls; $P = 0.043$). Presence of carotid plaque was equally distributed among limited and diffuse SSc patients (9 limited, 8 diffuse). Average IMT was higher in patients with SSc than controls ($0.582 \pm 0.11$ vs. $0.557 \pm 0.14$; $P = 0.059$). SSc patients had similar rates of pHDL compared to controls (SSc 21.4%, controls 25%). pHDL was not
Symptom Burden, Quality of Life and Attitudes toward Palliative Care in Patients with Pulmonary Hypertension with and without Systemic Sclerosis, Nicole M. Orzechowski1, Keith M. Swetz2, Tait D. Shanafelt3, Jeff A. Sloan4, Paul J. Novotny5, Robert P. Frantz6 and Michael D. McGoon7.

Completed Living Will 18 (40) 75 (32.5) 0.328
LASA Pain Frequency 5 20 (45.5) 114 (49.8) 0.59
LASA Fatigue 5 16 (35.6) 94 (40.9) 0.50
CAMPFORT total symptoms 11.5 (6.4) 12.7 (7.1) 0.26

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The Degree of Skin Involvement Predicts Distinct Interstitial Lung Disease Outcomes in Systemic Sclerosis, Tricia R. Cottrell, Fredrick Wiggley, Robert Wise and Francesco Boin. Johns Hopkins University, Baltimore, MD

Purpose: Systemic sclerosis (SSc) is conventionally classified into limited and diffuse based on the extent of skin fibrosis. While this classification has some clinical utility and facilitates compatibility among patient groups for research purposes, the cutaneous involvement in SSc is heterogeneous and more specific skin subsets may be associated with unique clinical outcomes. In this study, we analyzed longitudinal data from a large cohort of well-characterized SSc patients to determine whether specific SSc skin subtypes can be associated with the development and severity of interstitial lung disease (ILD).

Methods: A retrospective analysis was conducted on a longitudinal cohort of 2054 SSc patients seen at the Johns Hopkins University Scleroderma Center between 1976 and 2010. Based on the maximum extent of skin fibrosis, 4 SSc subsets of patients were identified: Type 0 if no cutaneous sclerosis (sine scleroderma) was present; Type 1 if sclerosis was distal to the elbows or knees; Type 2 if skin changes were distal to the elbows or knees; Type 3 if sclerosis extended proximally to the elbows or knees. The primary outcomes were the presence of interstitial lung disease (ILD) defined as a forced vital capacity (FVC) < 80% of predicted with no evidence of obstructive lung disease, and time from disease onset (1st non-Raynaud’s symptom) to development of ILD. Chi squared test and analysis of variance were used to compare cumulative frequency and severity of ILD, while Kaplan-Meier method, log-rank test and Cox proportional hazard ratio were used to compare ILD-free survival curves from SSc onset and to estimate the probability of developing ILD in the different disease subsets.

Results: The proportion of patients diagnosed with ILD significantly increased from type 0 to type 3 SSc subtypes (p<0.0001), while the average minimum FVC decreased (p<0.0001). Analysis of ILD free survival curves showed that over time, a greater extent of skin fibrosis was associated with a higher risk of developing ILD.
Conclusions: The degree of skin involvement is predictive of different outcomes in SSc-ILD. In particular, SSc patients with an intermediate level of skin fibrosis (type 2), who normally are classified into the limited SSc group, exhibit a distinct risk profile for lung involvement and therefore their identification and characterization may be relevant in terms of prognosis and proper clinical management.

Disclosure: T. R. Cottrell; None; F. Wigley; None; R. Wise; None; F. Boin; None.

597 The Effect of Gastric Acid Suppression with Esomeprazole on Treprostinil Diethanolamine Pharmacokinetics in Healthy Volunteers. Kristan Rollins1, Susan Walker2, Jennifer Kates3, Kevin Laliberte4 and Allison Lim5. 1United Therapeutics, Research Triangle Park, NC, 2United Therapeutics Research, 3United Therapeutics, 4Actelion Pharmaceuticals US, 2, 5United Therapeutics, 2, 5; Bayer, 2, 5, Gilead Sciences, Inc., 2, 5, Pfizer Inc, 2, United Therapeutics, 2, 5; 6Lung Research, 2, 5, United Therapeutics, 2, 5; 7L. Rubin; Actionel Pharmaceuticals US, 2, 5; 8Gilead Sciences, Inc., 2, 5, Bayer, 2, 5; 9A. Casanova; Actelion Pharmaceuticals US, 2; 10T. Mary; Actelion Pharmaceuticals US, 2; 11C. Richard; Actionel Pharmaceuticals US, 2; 12R. Oudiz; Actelion Pharmaceuticals US, 2, 5, Bayer, 2, 5, Gilead Sciences, Inc., 2, 5, Lung Research, 2, 5, United Therapeutics, 2, 5; 13L. Rubin; Actionel Pharmaceuticals US, 2, 5; 14A. Lim; United Therapeutics, 2, 5; 15Pharmaceuticals US, 2, 5; 16Bayer, 2, 5, Gilead Sciences, Inc., 2, 5, Pfizer Inc, 2, United Therapeutics, 2, 5; 17T. Victor; Arena, 2, 5; 18Bayer, 2, 5, Gilead Sciences, Inc., 2, 5, Lung Rx, 2, 5, United Therapeutics, 2; 19L. Anatoly; Actionel Pharmaceuticals US, 2.

Background: Treprostinil diethanolamine (TRE) is a prostacyclin analog currently being evaluated as a sustained release osmotic tablet for the treatment of digital ulcers in patients with systemic sclerosis (SSc). Esophageal manifestations of SSc are common requiring many patients to utilize acid suppressing therapies such as proton pump inhibitors (PPI). The use of acid suppressing therapies may alter the pharmacokinetics of concomitantly administered oral therapies via alterations in drug dissolution, absorption and metabolism. This study assessed the effect of steady-state esomeprazole induced gastric acid suppression on the pharmacokinetics of TRE.

Methods: This was a 9-day, single-center, open-label, single sequence study in which healthy volunteers were given a single dose of TRE SR 1 mg prior to and following repeated once daily oral dosing of esomeprazole 40 mg capsules over 7 days (Days 3–9). A single 1 mg oral dose of TRE was administered immediately following a 500 calorie meal on Days 1 and 8. Eighteen blood samples were obtained over 36 hours following each TRE dose. Plasma concentrations of treprostinil were quantified by liquid chromatography/mass spectrometry. Safety was assessed via adverse event reporting, clinical laboratories, physical exams, and ECGs.

Results: Fifteen male and fifteen female healthy volunteers with a mean age of 34 years (range 20–55 years) were enrolled. Concomitant administration of TRE and esomeprazole (test) following repeated esomeprazole dosing resulted in equivalent treprostinil exposure (Cmax and AUC) as compared to TRE dosing alone (reference) as described in Table 1. The most commonly reported adverse events included headache (8 subjects), flushing (2 subjects) and dizziness (2 subjects). There were no clinically significant treatment emergent changes in clinical laboratories, ECGs or vital signs.

Table 1. Preliminary Treprostinil Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Least Squares Geometric Means Reference</th>
<th>Ratio of Geometric Mean Test/Reference</th>
<th>90% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL) Mean</td>
<td>0.84</td>
<td>0.84</td>
<td>1.00</td>
<td>0.85, 1.17</td>
</tr>
<tr>
<td>AUCmean (ng·hr/mL) Mean</td>
<td>4.01</td>
<td>3.80</td>
<td>0.95</td>
<td>0.87, 1.04</td>
</tr>
<tr>
<td>AUCtot (ng·hr/mL) Mean</td>
<td>3.93</td>
<td>3.79</td>
<td>0.96</td>
<td>0.89, 1.05</td>
</tr>
</tbody>
</table>

Conclusions: Esomeprazole-induced gastric acid suppression had no impact on single dose TRE pharmacokinetics in healthy volunteers.


598 The Pulmonary Arterial Hypertension Quality Enhancement Research Initiative (PAH-QuERI): Comparing Baseline Characteristics, Management and Survival in Patients with Idiopathic PAH (IPAH) to Patients with Systemic Sclerosis Related PAH (SSc-PAH). Philip J. Clements1, Amparo Cañanova2, Tan Mary3, Channick Richard4, Valerie McLaughlin5, Ron Oudiz6, Lew Rubin7, Tapson Victor8 and Langer Anatoly9. 1Canadian Heart Research Center, 2David Geffen School of Medicine at UCLA, 3Duke University Medical Center, Durham, NC, 4Massachusetts General Hospital, 5University of California at San Diego, 6University of Michigan Health System

Purpose: To compare the baseline characteristics, management, and survival in patients with IPAH to patients with SSc-PAH in the prospectively-enrolled PAH-QuERI registry.

Methods: Between October 2005 and June 2007, physicians at 62 US specialist practices enrolled patients into the registry, entering diagnostic work-up, management and outcome data into an electronic data management system. Automatic queries were generated at each of the prescheduled follow-up visits if the tests recommended by American College of Chest Physicians’ guidelines (2007) were not performed at least once.

Results: 287 patients with IPAH and 253 with SSc-PAH were entered and followed for one year. At baseline, most of the clinical and laboratory characteristics of the two groups were similar, with only those listed in the table being judged clinically important and statistically different enough to warrant discussion. A few other variables (BMI, heart rate, hemoglobin) were statistically different but the differences were not deemed clinically important. Both groups were composed largely of middle-aged (57 y/o) Caucasian women (see table). The patients with SSc-PAH were older at the time of PAH diagnosis (56 vs 53 y/o), were more likely to be ANA positive, had lower %DLCO, and more frequently had %FVC/%DLCO ratios > 1.4 and/or DLCO < 55%. The SSc-PAH patients were also more likely to have elevated BNP, shorter 6-minute walk distances (6-MWD), and lower mean pulmonary artery pressures (mPAP) and pulmonary vascular resistance (PVR) than patients with IPAH.

Table. Clinically interesting and statistically significant differences in variables at baseline between IPAH and SSc-PAH and in survival at 12 months

<table>
<thead>
<tr>
<th>Baseline Variables</th>
<th>IPAH</th>
<th>SSc-PAH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of PAH diagnosis (years old)</td>
<td>53</td>
<td>56</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex (% females)</td>
<td>77%</td>
<td>90%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal ANA (%)</td>
<td>25%</td>
<td>85%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>%DLCO</td>
<td>52</td>
<td>44</td>
<td>0.001</td>
</tr>
<tr>
<td>%FVC/%DLCO ratio &gt; 1.4 (median values)</td>
<td>34</td>
<td>67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mPAP in mm Hg)</td>
<td>48</td>
<td>40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (PVR in Woods units)</td>
<td>8.95</td>
<td>7.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality rate at one year (% death)</td>
<td>7%</td>
<td>17%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

During the one year follow-up period, both groups were managed with prostacyclin derivatives, endothelin-receptor antagonists (ERA) and/or phosphodiesterase-type-5 inhibitors (PDE-5i), singly or in combinations. There were minimal differences in how these drugs were administered over the year of follow-up, with these exceptions: SSc-PAH patients were more likely than IPAH patients to be treated with PDE-5i agents alone or in combination of ERA and PDE-5i agents.

At 12 months, the mortality rate of the SSc-PAH patients (17%) was significantly greater than that of the IPAH patients (7%, p < 0.001).

Conclusion: In conclusion: 1) In this prospective registry of IPAH and SSc-PAH patients, the SSc-PAH patients at baseline were more likely to be older and female and to have lower %DLCO and more often had %FVC/%DLCO ratios > 1.4 and/or DLCO < 55%. Although they had better hemodynamics (lower mPAP and lower PVR), they were frequently “sicker” (elevated BNP and shorter 6-MWD). 2) Patients with SSc-PAH were more likely to be managed with PDE5i alone or in combination with an ERA than IPAH patients. 3) Survival at one year was significantly lower in the SSc-PAH group than the IPAH group.

The validation of 6 minute walking distance in patients with pulmonary arterial hypertension associated with systemic sclerosis, Dörte Huscher 1, Nicholas Roubinis 1, Jerome Avouac 2, Frank Behrens 3, Christopher P. Denton 4, Daniel E. Furst 5, Ivan Foeghwari 6, Marc Hambert 7, Otylia Kowal-Bielecka 8, Marco Mattucci-Cerinic 9, Peter Nash 10, Christian F. Opitz 11, David Pittrow 12, Lewis J. Rubin 13, James R. Seibold 14, Marius M. Hoeper 15, Mark F. Morris 16, Simon A. Teal 17 and Oliver Distler 18.

1. Centre for Rheumatology, Royal Free Campus, University College Medical School, London, United Kingdom, 12. Department of Internal Medicine, University Hospital Eilbek, Berlin, Germany, 13. Department of Medicine, Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland, 6. Department of Medicine, University of Queensland, Queensland, Australia, 11. German Rheumatism Research Centre, Berlin, Germany, 17. Quanticate Ltd, Hitchin, UK, 18. Rheumatology A Department, RDU, Paris, France.

Objective: To validate 6 minute walking distance (6MWD) as an outcome measure in patients with pulmonary arterial hypertension associated with systemic sclerosis (PAH-SSc) using the OMERACT filter of truth, discrimination and feasibility.

Methods: 6MWD was validated in PAH-SSc patients using data from randomized controlled clinical trials (SUPER-1 and STRIDE-1) and from an observational registry (CompERA-XL) reflecting clinical practice. All patients had PAH confirmed by right heart catheterization (RHC). Databases were assessed for the different aspects of the OMERACT filter. 6MWD was compared to pulmonary vascular resistance (PVR) obtained by RHC as the gold standard.

Results: A total of 57 PAH-SSc patients from trial data were available. Analysis of registry data was restricted to PAH-SSc patients where documented PVR and 6MWD were measured within a 30-day span (n=50). Linear correlation between 6MWD and PVR was small (r=0.22, p<0.05 vs. control, n=49). Because diminished nuclear fi1 should increase CTGF levels we next examined the effect of A2A receptor stimulation on CTGF mRNA and protein secretion. CTGF mRNA level was increased following A2A receptor stimulation for 8 hours by 3.7 fold (r=0.33) in the trials, and discriminated for NYHA class and Borg index for both trial and observational data. Available data did not allow a reliable assessment of sensitivity to change over time (in placebo or untreated patients) or an assessment of reliability.

Conclusion: 6MWD and PVR have both demonstrated clinical utility in evaluating patients with PAH, but their relationship is unclear. Assessed by linear correlation between 6MWD and PVR, we found weak criterion validity in these cohorts of PAH-SSc patients. Due to differing correlation patterns between different stages of severity we could show only partial content validity. Construct validity was confirmed by the discriminating value for NYHA class and Borg index. Trial data were confirmed by registry data on most points. Notably, there were no major differences between patients with SSC-PAH and IPAH for the assessed OMERACT criteria. Limitations of this analysis include the small sample size, and retrospective, post hoc analysis of pooled data from different trials. However, taken together these data illustrate limitations of 6MWD as a single outcome measure in SSC-PAH clinical trials or clinical practice.

*Both authors contributed equally.

Disclosure: D. Huscher: see study sponsor 2; N. Roubinis: Pfizer Ltd, UK, 3; J. Avouac: see study sponsor 2; F. Behrens: see study sponsor 2; C. P. Denton: see study sponsor 2; D. E. Furst: see study sponsor 2; I. Foeghwari: see study sponsor 2; M. Hambert: see study sponsor 2; O. Kowal-Bielecka: see study sponsor 2; M. Mattucci-Cerinic: see study sponsor 2; P. Nash: see study sponsor 2; C. F. Opitz: see study sponsor 2; D. Pittrow: see study sponsor 2; L. J. Rubin: see study sponsor 2; J. R. Seibold: see study sponsor 2; M. M. Hoeper: see study sponsor 2; M. F. Morris: Pfizer Ltd, UK, 3; S. A. Teal: Pfizer Ltd, UK, 3; O. Distler: see study sponsor 2.

ACR Poster Session A
Systemic Sclerosis, Fibrosing Syndromes and Raynaud’s - Pathogenesis and Animal Models I
Monday, November 8, 2010, 9:00 AM-6:00 PM

600 Adenosine A2A Receptor Occupancy Promotes Dermal Fibrosis by Modulating FLI1 and CTGF Expression, Hailing Liu1, Edwin Chan2, Niven F. Crotts3 and Bruce N. Cronstein.1 New York University Med Ctr, New York, NY, 2NYU School of Medicine, 3NYU School of Medicine, New York, NY.

Background: Increased production of extracellular matrix in the skin is the hallmark of Scleroderma. We have previously reported that adenosine, a purine nucleoside produced in ischemic tissue, acting at A2A receptors, enhances dermal collagen production but the mechanism by which adenosine promotes dermal fibrosis, although the mechanism by which adenosine receptor stimulation promotes collagen production is not clear. FLI1 is a known transcriptional repressor of fibrilar collagen genes and connective tissue growth factor (CTGF/CCN2) in dermal fibroblasts. To further clarify the mechanism by which A2A receptor stimulation induces dermal collagen accumulation, we explored the effects of A2A receptor occupancy on FLI1 and downstream mediators of fibroblast matrix production.

Methods: Primary human dermal fibroblasts were stimulated with the selective adenosine A2AR agonist CGS21680 (1µM) for varying time periods and message levels (real time-RTPCR) for fl1 and CTGF were quantitated. In addition we measured cell associated and supranatant levels of collagen I and nuclear levels of fl1 by Western Blot.

Results: Adenosine A2AR receptor stimulation for 4 hours reduced Fl1 mRNA expression by 47±18% (4 hrs, p<0.05 vs. control, n=4) and reduced nuclear protein levels of Fl1 by 32±13% (24 hrs, p<0.05, n=4). Because diminished nuclear fl1 should increase CTGF levels we next examined the effect of A2A receptor stimulation on CTGF mRNA and protein secretion. CTGF mRNA level was increased following A2A receptor stimulation for 8 hours by 3.7 fold. Consistent with the change in CTGF mRNA, CGS21680 stimulated a 4.7 fold increase in CTGF protein secretion at 24 hours (as well as p<0.03, n=4). As expected A2A receptor stimulation increased collagen I secretion (1.8-fold vs. control, p<0.05, n=4) and the increase in collagen production was completely abrogated by an antibody to CTGF (1.1±0.04 fold of control, p<0.05 vs.CGS, n=3) but not by control antiserum (1.6 +0.03fold of control, n=3).

Conclusion: A2AR occupancy promotes dermal matrix production by suppressing expression of the transcriptional repressor fl1 leading to an increase in CTGF expression which acts in an autocrine fashion to stimulate collagen production. These findings further suggest that modulation of A2AR function may be a novel therapeutic target for limiting fibrosis in such conditions as scleroderma.

Disclosure: H. Liu: None; E. Chan: None; P. F. Crotts: None; B. N. Cronstein: Canfite Pharma, 1, Celgene, Sepracor, EndoCytte, Proteas, Ails, Kyowa Hakka, Avidimer Therapeutics, 2, 5, King Pharmaceuticals, 2, NIH, 2, vilcek Foundation, 2, 5.

601 Adipoqcyte-Targeted Wnt Activation Results in Spontaneous Dermal Fibrosis and Subcutaneous Lipatrophy, Jun Wei1,2, Denise S. Melchiar1, Kazuhiro Kumora2, Ormond Macdougald2 and John Varga1.1 Northwestern Univ Feinberg School of Medicine, Chicago, IL, 2Northwestern University Feinberg School of Medicine, 3Northwestern University Feinberg School of Medicine, Chicago, IL, 4University of Michigan

Background: Fibrosis and subcutaneous lipatrophy are hallmarks of scleroderma, and are thought to reflect mesenchymal cell differentiation into...
activated fibroblasts. The Wnts are a family of extracellular ligands and are involved in development and cell fate determinations. Canonical Wnt signaling drives preadipocyte differentiation into osteoblasts in part through negative modulation of PPAR-γ expression and function. Recent studies implicate abnormalities in the canonical Wnt pathway in scleroderma and pulmonary fibrosis. Because Wnt signaling has profound effects on regulating mesenchymal cell lineage, we examined the effect of adipocyte-specific ectopic Wnt10b expression on skin homeostasis and differentiation in transgenic mice.

**Methods:** Female transgenic mice harboring Wnt10b under the control of the FABP4 promoter were studied. Adiponecin levels were determined by ELISA. Dermal thickness was measured. Collagen accumulation in the skin was determined histochemical stains, and by colorimetric assays. Mast cells were identified by Astra Blue staining. Fibroblasts were explanted from the skin and evaluated in vitro at early passage. Gene expression was assessed by real-time qPCR and Western blot analysis.

**Results:** At six months of age, female FABP4-Wnt10b transgenic mice showed a marked loss of subcutaneous and visceral adipose tissue. Serum levels of adiponectin were >80% lower than in wild-type littersmates. In the skin from Wnt10b transgenic mice, a dramatic increase in Wnt10b mRNA expression was noted, and mRNA level for axin 2 was significantly elevated. The dermis showed a >60% increase in thickness, with a striking reorganization of the collagenous matrix, and a >80% increase in soluble collagen content. Degranulating mast cells were seen in the reticular dermis and among muscle bundles in Wnt10b transgenic mice but not in wild-type littersmates. mRNA levels for Type I collagen and α-smooth muscle actin were elevated. Explanted dermal fibroblasts showed elevated Wnt10b expression. Expression of adipogenic markers PPAR-γ and FABP4 were reduced, whereas mRNA levels for Type I collagen and α-SMA were elevated, compared to wildtype fibroblasts examined in parallel.

**Conclusion:** Ectopic Wnt10b expression targeted to adipocytes results in progressive loss of cutaneous and visceral adipose tissue accompanied by the spontaneous development of dermal fibrosis with increased expression of fibrotic markers. Dermal fibroblasts explanted from Wnt10b transgenic mice show spontaneous activation of Wnt10b-driven canonical signaling and upregulation of collagen gene expression in vitro, suggesting that ectopic Wnt10b drives a shifts in mesenchymal cell fate toward myofibroblasts by induction of fibrotic genes while simultaneously suppressing adipogenic gene expression. This shift appears to be driven, at least in part, by suppression of the adipogenic master regulator transcription factor PPAR-γ. The results implicate that Wnt signaling plays an important role in the pathogenesis of scleroderma. Modulating Wnt activity may therefore represent a novel therapeutic approach for the treatment of scleroderma.

**Disclosure:** J. Wei: None; D. S. Melchian: None; K. Kumora: None; O. Macdougald: None; J. Varga: None.

602 Cadherin 11 Promotes Pulmonary Fibrosis through Production of TGF β and the Regulation of Epithelial to Mesenchymal Transition. Daniel J. Schneider1,2, Minghua Wu1, Michael B. Brenner1, Maureen D. Mayes2, Frank C. Arnett5, Filemon K. Tan6 and Sandeep K. Agarwal2. 1Brigham & Womans Hospital, Boston, MA, 2Division of Rheumatology and Clinical Immunogenetics, University of Texas Health Science Center at Houston, Houston, TX, 3Division of Rheumatology and Clinical Immunogenetics, University of Texas Health Science Center at Houston (UTHSC-H), Houston, TX, 4University of Texas-Houston, Houston, TX, 5UT Medical School, Houston, TX, 6UTHouston Med School, Houston, TX

**Background:** Cadherin-11 (Cad11) is a mesenchymal cadherin initially identified in osteoblasts but subsequently found to be expressed on other cells including synovial fibroblasts where it confers a mesenchymal phenotype and promotes cellular invasion. Cad-11 has been reported to be increased during wound healing. Recently, Cad-11 was observed to be upregulated in scleroderma (SSc) skin in two independent microarray studies. These results led to the hypothesis that Cad-11 is a key mediator of dermal fibrosis.

**Methods:** SSc and normal skin biopsies were used for qRTPCR to quantitate Cad-11 levels and for immunohistochemical (IHC) analyses to determine the expression pattern of Cad-11. Dermal fibroblasts were stimulated with TGFb and qRT PCR was used to determine if TGFb increased Cad-11 expression. To determine if Cad-11 is a mediator of dermal fibrosis, Cad-11 deficient (def) and wild type (WT) mice were compared using the bleomycin (bleo) induced skin fibrosis model. Anti-Cad-11 monoclonal antibodies (mAb) also were used to confirm these findings in the bleo-induced skin fibrosis model.

**Results:** Cad-11 transcript levels were increased in SSc skin biopsies (n=6) relative to healthy control skin biopsies (n=9). IHC analyses of skin biopsies demonstrated Cad-11 reactivity in the dermis of SSc biopsies, but not control biopsies, predominantly on fibroblast-like cells. TGFb upregulated Cad11 expression on cultured dermal fibroblasts from healthy controls and SSc patients. Using the bleo-induced dermal fibrosis model, Cad-11 def. mice had markedly attenuated dermal fibrosis as quantitated by skin thickness (Cad11 def:194±14 µm, WT: 255±17 µm, p=0.003), collagen levels (Cad11 def: 230±24 µg/mg, WT: 319±20 µg/mg, p=0.01) and myofibroblast accumulation in the lesional skin. Administration of two neutralizing anti-Cad-11mAb to WT mice resulted in a significant amelioration of collagen deposition and dermal thickness in bleo-induced dermal fibrosis. Lastly, Col11a1 and CTGF mRNA levels but not IL-6 levels were significantly decreased in lesional skin of Cad-11 def. compared to WT mice.

**Conclusions:** These results demonstrate that Cad-11 is a critical mediator of dermal fibrosis, and suggest that Cad-11 is a potential therapeutic target in SSc.

**Disclosure:** M. Wu: None; M. B. Brenner: Allergy Therapeutics Limited, 1, 5, Calcimedica Inc, 1, 5, SR One Inc, 1, 5, Synovex Corp, 1, 5; M. D. Mayes: None; F. C. Arnett: None; F. K. Tan: None; S. K. Agarwal: None.
Dabigatran Eteoxilate, an Oral Direct Thrombin Inhibitor, Represses Fibrotic Changes in a Murine Model of Pulmonary Fibrosis. Galina Bogatkevich1, Anna Ludwicka-Bradley2, Paul J. Nietert2, Joanne van Ryn3, Richard M. Silver3. Boehringer Ingelheim, 2Medical University of South Carolina, Charleston, SC, 3Medical University of South Carolina, Charleston, SC, 4Medical University of South Carolina, Charleston, SC.

**Rationale:** Activation of the coagulation cascade and generation of thrombin has been extensively documented in pulmonary fibrosis, both in acute and chronic lung injury, including scleroderma and in animal models of lung injury. The oral direct thrombin inhibitor (DTI), dabigatran etexilate, modulates the coagulation cascade and inhibits thrombin-induced profibrotic signaling in lung fibroblasts, including scleroderma lung fibroblasts. This study tested whether thrombin inhibition by dabigatran etexilate attenuates bleomycin-induced pulmonary fibrosis in a murine model of lung injury.

**Methods:** Lung injury was induced in 6–8 week old female C57BL/6 mice by intratracheal instillation of bleomycin. Dabigatran etexilate was given as supplemented chow (10 mg/g chow) or as matching placebo beginning on day 8 following bleomycin. Two and three weeks after bleomycin instillation mice were euthanized, and lungs, bronchoalveolar lavage fluid (BALF) and plasma were collected. Lung collagen was measured by hydroxyproline assays; dabigatran concentration by LC-MS/MS; thrombin activity by fluorometric assays; TGF-β1 concentrations by ELISA; connective tissue growth factor (CTGF) and smooth muscle α-actin (α-SMA) were assessed by immunoblotting. The association between hydroxyproline levels in lung tissue and dabigatran concentration in plasma was tested using Spearman rank correlation test.

**Results:** In BALF we observed significant reduction of active thrombin and TGF-β1 from 46.05±19.49ng/ml and 54.9±6.19pg/ml in bleomycin + placebo-treated mice to 11.95±4.4ng/ml and 5.2±1.1pg/ml in bleomycin + placebo-treated mice. Thrombin inhibition by dabigatran etexilate was also associated with a two-fold decrease in the absolute number of cells in BALF of dabigatran-treated mice. A quantitative evaluation of histopathology by Ashcroft scale demonstrated a significant decrease in fibrosis of dabigatran-treated mice (5.76±1.64 vs. 2.98±0.88, p<0.05). A strong negative correlation between hydroxyproline levels in lung tissue and dabigatran concentration in plasma was observed in mice with bleomycin-induced lung fibrosis (R² = 0.96, p=0.0005). There was no correlation between hydroxyproline and dabigatran in control sham-injured mice. Additionally, dabigatran reduced CTGF 9-fold and α-SMA 2.5-fold in mice with bleomycin-induced lung fibrosis, whereas it did not interfere with basal levels of the proteins.

**Conclusions:** Inhibition of thrombin using the oral DTI dabigatran etexilate has marked anti-fibrotic effects in a bleomycin-induced mouse model of pulmonary fibrosis. Dabigatran etexilate treatment reduces collagen, TGF-β1, CTGF, and α-SMA induced by tissue injury, while not interfering with basal levels of these proteins in normal lung tissue. Our data suggest that dabigatran etexilate may be beneficial in the treatment of fibrosing lung diseases, e.g. scleroderma lung disease and idiopathic pulmonary fibrosis.

**Disclosure:** G. Bogatkevich: Boehringer Ingelheim, 2; A. Ludwicka-Bradley: None; P. J. Nietert: None; J. van Ryn: Boehringer Ingelheim, 3; R. M. Silver: Boehringer Ingelheim, 2.

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Endothelial Dysfunction and Abnormal Collagen V Deposition in Pulmonary Vasculature of Experimental Systemic Sclerosis Model. Roberta G. Marangoni1, Edwin R. Parra1, Ana Paula P. Velosa1, Walcy R. Teodoro1, Vera L. Capelozzi1 and Nataline H. Yoshinari1. Pathology Department, Faculdade de Medicina da Universidade de São Paulo, 2Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil, 3Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo

**Purpose:** We have recently described a collagen type V (COL V) rabbit experimental model that resembles the human systemic sclerosis (SSc). None of the profibrotic models for SSc to date have reproduced the vascular involvement observed in human disease. We therefore have evaluated in our model the intrapulmonary arteries for neovascularization (CD31 expression), endothelial apoptosis (caspase-3 induced), endothelial activity (endothelin-1 and VEGF expression) and COL V deposition.

**Methods:** Female rabbits from New Zealand lineage (n=6) were immunized with human COL V plus Freund’s adjuvant. Animals immunized only with Freund’s adjuvant (n=6) were used as controls. Two hundred and ten days after the first immunization, the animals were sacrificed and the lungs submitted to hematoxylin&eosin staining, electron microscopy, immunofluorescence, immunohistochemistry and morphometry.

**Results:** The histopathological analysis revealed a clear preponderance of intrapulmonary arteries with irregularity and wall thickness only in COL V immunized rabbits. Type V collagen was also increased and structurally altered. Ultrastructural analysis of some lungs showed increased rate of apoptosis, organelles with degenerative changes and cytoplasmic tumefaction of the endothelial cells which appeared detached from the basement membrane. Additionally, COL V group displayed increased expression of the immunomarkers for neovascularization, endothelial apoptosis and endothelial activation compared to controls (p<0.01).

**Conclusions:** Our experimental model reproduced the endothelial dysfunctions and abnormal COL V deposition in pulmonary vasculature observed in SSc patients, confirming its suitability to study the vascular involvement of this disease.

**Disclosure:** R. G. Marangoni: None; E. R. Parra: FAPESP, 2; A. P. P. Velosa: None; W. R. Teodoro: Federico Foundation Grants, 2; V. L. Capelozzi: FAPESP, 2; N. H. Yoshinari: None.
genetic deletion and preventive or therapeutic pharmacological inhibition of LPA1 attenuated bleomycin-induced dermal fibrosis. Targeting LPA1 therefore has the potential to be an effective new therapeutic strategy for SSC.


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Inactivation of the Transcription Factor STAT4 Prevents Inflammation-Driven Fibrosis in Systemic Sclerosis Animal Models. Jerome Avouac1, Barbara G. Fu¨rnrohr2, Michelle Tomescu1, Michal M. Tomes3, Katrina Palumbo2, Angela Horn2, Clara Dees2, Aliﬁya Akhmetschina2, Christian Beyer1, Oliver Distler1, Georg Schett5, Yannick Allanore6 and Jorg H. W. Distler7. 1Center of Experimental Rheumatology and Zurich Center of Integrative Human Physiology, University Hospital Zurich, Zurich, Switzerland, 2Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, 3Department of Internal Medicine III, University of Erlangen-Nuremberg, Erlangen, Germany, Paris Descartes University, Rheumatology A Department, Cochin Hospital, and INSERM U781, Necker Hospital, Paris, Fr, 4Department of Internal Medicine III, University of Erlangen-Nuremberg, Erlangen, Germany and Institute of Rheumatology and Connective Tissue Research Laboratory, Department of Rheumatology of the First Faculty of Medicine, Charles University i, 5Friedrich Alexander Univ, Erlangen, Germany, Paris Descartes University, Rheumatology A Department, Cochin Hospital, and INSERM U781, Necker Hospital, Paris, France, 6University of Erlangen, Erlangen, Germany

Objective: STAT4 is a transcriptional factor regulating various cytokines and in particular interferon type 1 and IL12-IL23 pathways. STAT4 has been recently identiﬁed as a genetic susceptibility factor to systemic sclerosis (SSc) and also to other autoimmune diseases. Our aim was to investigate the contribution of STAT4 in the development of a ﬁbrotic phenotype in two different mouse models of experimental dermal ﬁbrosis.

Methods: The role of STAT 4 was ﬁrst evaluated in the mouse model of bleomycin-induced dermal ﬁbrosis, a model for early, inﬂammatory stages of SSc. Mice deﬁcient for STAT4 (stat4−/−) and wildtype littermates (stat4+/+ ) were injected with bleomycin or NaCl. Inﬁltrating leukocytes and T cells in lesional skin of STAT4−/− and STAT4+/+ mice were quantiﬁed on histology and immunohistochemistry for CD3. Th1 and Th2 cytokine levels were also measured in the serum or lesional skin samples of stat4−/− and stat4+/+ mice. The invalidation of STAT4 was also investigated in the light-skin (tsk-1) mouse model, which serve as a model of later, less inﬂammatory stages of SSc.

Results: stat4−/− mice were protected from bleomycin-induced dermal ﬁbrosis with reduced dermal thickening (65±3% reduction, p=0.03), hydroxyproline content (55% decrease, p=0.003) and myoﬁbroblast counts (71±6% reduction, p=0.05). The numbers of leukocytes, especially inﬁltrating T cells, were also decreased in lesional skin of stat4−/− mice (respectively 62±4%, p=0.02 and 63±5%, p=0.02). Moreover, stat4+/− mice displayed in lesional skin decreased levels of cytokines involved in inﬂammatory and ﬁbrogenic processes such as IL-6 (50±4% decrease), TNFa (71±5%), INFγ (58±3%) and IL-2 (63±4%). Similar results were observed in the tsk-1 mouse model.

Conclusive evidence for the role of STAT4 in inﬁltration, STAT4 deﬁciency did not improve the ﬁbrotic phenotype in tsk-1 mice. No differences in hypodermal thickness, hydroxyproline content and myoﬁbroblasts counts were observed between stat4−/−/tsk-1 mice and their stat4+/+ /tsk-1 littermates.

Conclusion: This is the ﬁrst translational study demonstrating the role of the transcription factor STAT4, an established genetic susceptibility factor of SSc and of other autoimmune diseases, in animal models of SSC. We here demonstrate that STAT4 exerts potent proﬁbrotic effects in inﬂammation-driven models of ﬁbrosis. STAT4 indirectly regulates the activation of ﬁbroblasts by promoting the inﬁltration of T cells into lesional skin and the production of inﬁltratory cytokines. These ﬁndings conﬁrm the results of the genetic studies on the role of STAT4 in the development of SSc.

Disclosure: J. Avouac: Pfizer Inc, 2; B. G. Fu¨rnrohr: None; M. Tomescu: None; K. Palumbo: None; P. Zerr: None; A. Horn: None; C. Dees: None; A. Akhmetschina: None; C. Beyer: None; O. Distler: None; G. Schett: None; Y. Allanoire: None; J. H. W. Distler: None.

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Induction of Peripheral Tissue Ischemia and Anti-Endothelial Antibodies after B Cell Adoptive Transfer from RNP-Immunized Mice. YunJuan Zang1, Irina Fernandez2, Matte Chavez2, Laisel Martinez3 and Eric L. Greidinger2. Miami VA Medical Center, Miami VA Medical Center and University of Miami Miller School of Medicine, Miami, FL, 4University of Miami Miller School of Medicine

Background: We have previously developed a murine model of induced anti-RNP autoimmunity with clinical manifestations including intestinal lung disease and nephritis, in which disease manifestations were transferable to naive syngeneic mice by T cell or dendritic cell adoptive transfer. To pursue the hypothesis that autoimmune Raynaud’s Phenomenon (RP) may be mediated by B cells, B cell adoptive transfer studies were performed.

Methods: C57BL/6 female mice transgenic for expression of HLA-DR4 were immunized with 70k and U1-RNA following our published protocol, and conﬁrmed to have anti-RNP humoral responses by ELISA. Unimmunized syngeneic mice housed together with the immunized mice were used as control B cell donors. Two months after immunization, mice were sacriﬁced, spleens were collected and processed into RBC-depleted single-cell suspensions, and CD20+ cells were positively selected by AutoMACS. Four million cells per recipient were transferred via the tail vein into syngeneic 10 week old female mice. Recipients were followed clinically for up to two weeks after cell transfer. Loss of ear and tail tissue (thermoregulatory tissues in mice) was noted by personnel blinded to the treatment status of the mice, and documented photographically. Serum was collected from sacriﬁced mice, and subsequently analyzed for anti-RNP antibodies. The sera of each donor mouse was tested by immunofluorescence and immunoblot against HUVEC and Jurkat cells, and compared to reference human sera from patients with RP and controls.

Results: B cell adoptive transfer induced episodes of cyanoysis and resulted in loss of ear and/or tail tissue in 14/17 recipients of B cells from RNP+ donors, but in 0/5 recipients of B cells from unimmunized donors (Fishers Exact test p = 0.002). No evidence of vasculitis or thrombosis was observed histologically. Like human RP sera but unlike human control sera or RNP+ B cell donor sera, the sera from mice with tissue loss had anti-endothelial reactivity, and induced morphological changes and cell death in HUVEC cultures. B cell recipients from RNP+ donors had lower titer anti-RNP responses than their respective B cell donors. Serum transfer from mice with tissue loss but not from RNP+ B cell donors also induced ear and/or tail tissue loss.

Conclusions: B cell adoptive transfer from RNP+ donors induces a novel murine model of Raynaud’s Phenomenon. This model provides a novel link between the autoimmune and vasospastic manifestations of systemic auto-immune diseases, and speciﬁcally implicates B cells in RP pathogenesis.

Disclosure: Y. Zang: None; I. Fernandez: None; M. Chavez: None; L. Martinez: None; E. L. Greidinger: None.

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Mice Lacking the Receptor-Like Protein Tyrosine Phosphatase CD148 Are Protected from Bleomycin-Induced Pulmonary Fibrosis. Tamiko R. Katsumoto1, Kevin K. Kim2, Alexis N. Brumwell2, John X. Nguyen3, Jing W. Zhu4, Mark R. Looney5, Harold A. Chapman6 and Arthur Weiss7. 1UCSF, South San Francisco, CA, 2UCSF

Purpose: The molecular mechanisms underlying pulmonary ﬁbrosis, one of the most morbid complications of scleroderma, remain incompletely characterized. Protein tyrosine phosphatases and kinases regulate the equilibrium of tyrosine phosphorylation signaling pathways important in cell growth and differentiation. Tyrosine kinases have been implicated in ﬁbrosis, and studies testing the anti-ﬁbrotic activity of tyrosine kinase inhibitors such as imatinib in scleroderma patients are underway. The receptor-like protein tyrosine phosphatase (RPTP) CD148 is widely expressed on various hematopoietic and non-hematopoietic lineages, including lung epithelial cells, endothelial cells, and ﬁbroblasts. Given the importance of tyrosine phosphorylation pathways in ﬁbrosis, we explored the role of CD148 in the bleomycin mouse model of pulmonary ﬁbrosis.

Methods: Mice with a targeted deletion of the CD148 transmembrane domain (CD148KO) have been generated by our lab and are used in all studies described. Acute lung injury was measured using extravasation of radioactive iodine-labeled albumin and wet-to-dry ratios. Fibrosis was evaluated by both Masson Trichrome staining of lung sections as well as by the Sircol Collagen Assay (Biocolor).
Results: Following intratracheal instillation of bleomycin at a dose of 3 units/kg, WT mice showed significantly impaired survival, with 4 of 6 WT mice (67%) dying between 10–16 days, whereas none of the 8 CD148KO mice (0%) died (p = 0.007). Masson Trichrome staining of lungs demonstrated markedly increased fibrosis in WT mice, whereas fibrosis was significantly attenuated in the CD148KO mice. At day 13 following a lower dose of bleomycin (2.5 U/kg), WT bleomycin-treated mice had a 4.2-fold increase in lung collagen content whereas CD148KO mice showed only a 1.7-fold increase in collagen (p = 0.0009). Lung collagen levels in WT bleomycin mice (66.1+/−6.1 ug/ml) were significantly higher than in WT saline mice (15.8+/−0.8 ug/ml) (p = 0.0008), whereas lung collagen levels in CD148KO bleomycin mice (46.1+/−8.2 ug/ml) vs. CD148KO saline mice (26.6+/−7.2 ug/ml) were not significantly different (p = 0.157). The acute lung injury response at day #5 post bleomycin (2.5 U/kg) was equivalent between genotypes. Endothelial permeability was 1.7%/+/−0.33%/ in WT saline mice vs. 1.5%/+/−0.39%/ in CD148KO saline mice. Following bleomycin, the increase in endothelial permeability in WT mice to 3.9%/+/−0.67% and in CD148KO mice to 3.9%/+/−0.39% was equivalent between genotypes (n=4 mice per genotype).

Conclusion: Mice lacking CD148 phosphatase activity show improved survival. Attenuation of bleomycin-induced fibrosis does not appear to be the consequence of a diminished acute lung injury response to bleomycin. Future studies will interrogate the specific cell types mediating this response, as well as elucidating the pathways regulated by CD148 underlying this phenotype. These data suggest that inhibition of the RPTP CD148 may present an attractive anti-fibrotic therapeutic strategy.

Disclosure: T. R. Katsuno: None; K. K. Kim: None; A. N. Bru unrell: None; J. X. Nguyen: None; J. W. Zhu: None; M. R. Looney: None; H. A. Chapman: None; A. Weiss: None.

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Noggin /LacZ Heterozygous Mice Have Reduced Pulmonary Fibrosis in the Bleomycin Induced Model. Ellen de Langhe1, Vanessa De Vooght2, Frank P. Luyten1 and Rick Lories1. 1KU Leuven, Leuven, Belgium, 2KU Leuven, Leuven, Belgium

Introduction: Noggin (Nog) is an extracellular antagonist of the Bone Morphogenetic Protein (BMP) signaling pathway. The BMP pathway plays an important role in embryonic development, postnatal growth, tissue homeostasis and disease. The molecular mechanisms underlying pulmonary fibrosis in diseases such as systemic sclerosis and idiopathic pulmonary fibrosis (IPF) are poorly understood. The role of the BMP antagonist gremlin in IPF has been published.

Objectives: We hypothesize that the BMP signaling pathway plays a role in fibrogenesis. Here we study the role of Nog and the BMP pathway in bleomycin induced pulmonary fibrosis using Nog /LacZ heterozygous mice.

Material and Methods: Pulmonary fibrosis was induced in 8-week old male wild-type (WT) or Nog /LacZ mice, both on the C57/B6 background by intratracheal instillation of 0.05U bleomycin (BLM) or phosphatebuffered saline (PBS) as a control (WT: BLM n=23, PBS n=17; Nog /LacZ: BLM n=14, PBS n=7). 4 weeks after baseline induction invasive pulmonary function tests were performed using the Flexivent® SCIREC system. The mice were subsequently sacrificed and pulmonary tissue was collected for histopathology, immunohistochemistry and gene expression analysis. Pulmonary architecture was evaluated and scored on haematoxylin-eosin (H&E) sections using the validated Ashcroft score for pulmonary fibrosis. Total collagen content was quantified using the hydroxyproline quantification assay. Immunohistochemistry for phosphorylated Smad 1/5/8 was performed to demonstrate active BMP signaling during the process of fibrosis.

Results: Pulmonary fibrosis was successfully induced in the BLM treated groups, evident on H&E stainings and quantified by high Ashcroft scores. The increased nuclear staining for phosphorylated Smad 1/5/8 in the fibrotic areas indicated active BMP signaling. When pulmonary fibrosis was induced in the Nog /LacZ mice, it was associated with an attenuated fibrotic response with a significant decrease in the Ashcroft score as compared to the WT controls, as well as a significantly decreased collagen content. This was further confirmed at the functional level by significantly higher lung compliance.

Conclusion: The BMP signaling pathway appears activated in bleomycin induced pulmonary fibrosis. When bleomycin is administered to Nog /LacZ mice, partial loss of gene function is associated with an attenuated fibrotic response both at the histomorphological and at the functional level. Further experiments are needed to clarify whether this effect results from increased BMP signaling or from possible interactions with the TGFβ signaling pathway.

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Nrf41 Ameliorates the Pro-Fibrotic Effects of TGFβ in Systemic Sclerosis (SSc) and Might Be an Interesting Target for Anti-Fibrotic Therapies. A. AlZuhairi1, A. Khemtchut1, A. Powell-Zern1, M. Tomcik1, A. Horn1, C. Dees2, O. Distler1, S. Assassi2, F. P. Luyten1, M. Tomcik1, F. C. Arnett4, F. K. Tan5, M. Blackburn1 and S. K. Lucey1. 1Department of Internal Medicine II and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, 2Friedrich Alexander Univ, Erlangen, Germany, 3University Hospital Zurich, Zurich, Switzerland, 4University of Erlangen, Erlangen, Germany

Background: Nuclear receptor 4a 1 (Nrf41) is a unique transcription factor which belongs to the superfamily of orphan nuclear receptors. Unlike most nuclear receptors, members of Nrf4a receptors do not seem to require ligand binding for activation. Nrf41 is known to be a regulator of macrophage gene expression in inflammation, cell death and cell growth. The aim of the present study was to investigate the role of Nrf41 in TGFβ signaling and in the pathogenesis of SSc.

Methods: The expression of Nrf41 in cells and tissue was analyzed by real-time PCR, Western Blot and immunofluorescence. Collagen synthesis was quantified by real-time PCR, SirCol- and hydroxyproline assay. The role of Nrf41 in fibrosis and potential therapeutic implication were evaluated in three different mouse models: bleomycin-induced dermal fibrosis, tightskin1 (tsk-1) mice and mice infected with adenovirus overexpressing constitutively active TGFβ receptor 1.

Results: The expression of Nrf41 was significantly elevated in the skin of SSc patients compared to healthy controls. Moreover, mRNA levels of Nrf41 were increased in cultured SSc fibroblasts. Stimulation with TGFβ strongly increased the mRNA and protein levels of Nrf41 in cultured fibroblasts, indicating that TGFβ might drive the overexpression in SSc. mRNA- or by incubation with the Nr4a1 agonist Cytosporone B, strongly reduced the collagen synthesis in cultured fibroblasts. These data suggest that Nr4a1 is in the centre of a negative feedback loop, which restricts the pro-fibrotic effects of TGFβ in SSc. Consistently, mice lacking Nr4a1 were more sensitive to bleomycin induced fibrosis with 2 fold more pronounced dermal thickening, myofibroblast counts and hydroxyproline content upon challenge with bleomycin compared to wildtype mice. Moreover, AAV-TGFβ1 virus infected Nr4a1 deficient mice and tsk-1 mice lacking Nr4a1 showed also significantly increased fibrosis compared to control mice expressing Nr4a1. Next, we investigated, whether therapeutic activation of Nr4a1 by Cytosporone B prevents experimental fibrosis. Treatment with Cytosporone B completely prevented fibrosis in all mouse models and reduced dermal thickness, myofibroblast counts and hydroxyproline content to levels similar to control mice.

Conclusion: We demonstrate that Nr4a1 is upregulated in SSc in a TGFβ dependent manner. Nr4a1 negatively regulates the extracellular matrix (ECM) production by limiting the pro-fibrotic effects of TGFβ in vitro as well as in vivo. Thus, we first describe a negative feedback loop, in which the concomitant upregulation of Nr4a1 limits the pro-fibrotic effects of TGFβ in SSc. In addition, activation of Nrf41 signaling by Cytosporone B might be a novel therapeutic approach for fibrotic diseases.

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Osteopontin in Systemic Sclerosis and Its Role in Dermal Fibrosis. Minghua Wu1, Daniel J. Schneider1, Maureen D. Mayes3, Shervin Assassi2, Frank C. Arnett4, Filemon K. Tan5, Michael R. Blackburn1 and Sandeep K. Agarwal2. 1Department of Biochemistry and Molecular Biology, UTHSC-H, Houston, TX, 2Division of Rheumatology and Clinical Immunogenetics, University of Texas Health Science Center at Houston, Houston, TX, 3University of Texas-Houston, Houston, TX, 4UT Medical School, Houston, TX, 5UT-Houston Med School, Houston, TX
Background: Osteopontin (OPN) is a multifunctional cytokine produced during inflammation and tissue repair. OPN has been implicated in certain autoimmune diseases such as rheumatoid arthritis and as well as with fibrosis in disorders such as idiopathic pulmonary fibrosis and in mouse models of pulmonary fibrosis. Given the importance of autoimmunity and fibrosis in systemic sclerosis (SSc), we hypothesized that OPN is elevated in SSc patients and plays a critical role in the development of dermal fibrosis.

Methods: Plasma from a cohort of SSc patients (n = 319) and non-autoimmune disease controls (n = 154) were used to determine OPN levels by ELISA. Skin biopsies from SSc patients and healthy controls were used for immunohistological (IHC) analyses. To determine if OPN is a mediator of dermal fibrosis, OPN deficient (def) and wild type (WT) mice were compared in the bleomycin (bleo)-induced dermal fibrosis model.

Results: Circulating levels of OPN were elevated in SSc patients (47.9±3.6 ng/ml) compared to healthy controls (28.3±3.8 ng/ml, p<0.0009). OPN levels were elevated in both patients with limited and diffuse disease as well as anticientromere, anti-topoisomerase I and anti-rRNA polymerase III positive SSc patients relative to controls. Compared to controls, SSc skin biopsies expressed OPN that localized to both fibroblast-like cells and macrophages on IHC analyses. Similarly, skin biopsies from mice treated with subcutaneous bleo had increased levels of OPN compared to PBS injected mice. Interestingly, using the bleo-induced dermal fibrosis model, OPN def. mice had markedly attenuated dermal fibrosis as quantitated by skin thickness (OPN def: 253±14 µm, WT 318±12 µm, p<0.001), collagen levels (OPN def: 263±35 µg/mg, WT 420±46 µg/mg, p<0.01) and myofibroblast accumulation in the lesional skin. Furthermore, OPN def. mice had decreased dermal inflammation, including decreased number of Mac-3 positive macrophages. Lastly, Colla1, IL-6, PAI-1 and CTGF mRNA levels were significantly decreased in lesional skin of OPN def. compared to WT mice.

Conclusions: These data demonstrate that OPN is a mediator of dermal fibrosis, and suggest that OPN may be a potential biomarker and/or therapeutic target in SSc.

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Relevance of Epithelial Phenotypic Switching in the Pathogenesis of Systemic Sclerosis.

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Systemic sclerosis (SSc) is a complex disorder of uncertain etiology characterised by progressive vascular and interstitial fibrosis. Recently, we found that epidermal compartment in SSc skin exhibits abnormalities, taking on an active phenotype reminiscent of that during the wound healing response. Fibroblast-epithelial cell interactions are believed important during normal tissue repair and aberrant cellular cues may underlie important aspects of scarring and fibrosis. Transgenic mice in which the fibroblast expressed a constitutively active TGFβ type I receptor (ALK5) or which expressing CTGF, develop progressive tissue fibrosis most prominent in the skin and lung. Our in vivo data also suggests that activation of TGFβ signalling or CTGF over-expression by fibroblasts not only causes stromal activation, but also pathological changes in the phenotype of adjacent epithelium. Here, we focus on the phenotype profile of the SSc epidermis, the role of fibroblast-derived CTGF in epithelial switching into a mesenchymal-like phenotypic and the contribution this process may play to fibrogenesis.

Methods: Whole skin biopsies were obtained from SSc and controls. The epidermis was prepared from some of the skin biopsies, and processed for phospho-kinase profiling (Kinexus: Vancouver, Canada). Human and rodent type II epithelial cells lines (A549 and T2) were grown in grown in DMEM + 10%FBS. Epidermal cells were stimulated with TGFβ after serum starvation. Of particular interest, knockdown of S100A4 by siRNA fully abrogated the stimulatory effects of TGFβ on the collagen synthesis of SSc fibroblasts. In agreement with the role of S100A4 as a novel mediator of TGF-β signalling, mice lacking S100A4 were protected from experimental dermal fibrosis.

Results: Activation of S100A4 in human skin and experimental dermal fibrosis was determined by real-time PCR, immunohistochemistry and western blot. Collagen levels of SSc and healthy dermal fibroblasts was quantified by real-time PCR and SirCol collagen assay. Blyomycin-induced dermal fibrosis, a model for early, inflammatory stages of SSc, was used to assess the role of S100A4 in vivo using mice deficient for S100A4 (−/−) and wildtype littermates (+/+).

Results: Increased expression of S100A4 was detected in the upper layer of the dermis of SSc patients and was clearly colocalized with alpha-smooth muscle actin-positive fibroblasts. The overexpression of S100A4 persisted in cultured SSc fibroblasts and might contribute to their activated phenotype. A similar increase in S100A4 expression was observed in the skin samples from mice challenged with bleomycin and tsk-1 mice, both on mRNA (3.5- and 614-fold, respectively) and protein level.

Conclusion: In this study we show that phosphorylation array analysis revealed induction of EMT-promoting protein kinase signaling in SSc epidermis. Important growth factor, TGF-β promotes and triggers epithelial cells to undergo a phenotypic switch which is attenuated upon CTGF knock-down by RNA interference. Our data suggests that in SSc, the enhanced expression of TGFβ signaling and CTGF expression is likely to indirectly contribute to disease pathogenesis by triggering epidermal cells phenotypic switching towards a mesenchymel cell-like programme.

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S100A4 as a Novel Mediator of TGF-β Driven Dermal Fibrosis in Systemic Sclerosis. Michael Tomcik1, Pavel Zerr2, Katrin Palumbo2, Barbara G. Furrhoer3, Jerome Avaouac2, Angelika Horn2, Clara Dees, Aliyi Akhmetshina, Christian Byer2, Radim Bevac2, Oliver Distler1, Mariam Grigorian2, Ladaslav Senot2, Georg Schett2 and J H. W. Distler2.1 Center of Experimental Rheumatology and Central Chair of Integrative Human Physiology, University Hospital Zurich, Switzerland, 2Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, 3Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, 4Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany and Paris Descartes University, Rheumatology A Department Cochin Hospital, Paris, France, 5Department of Internal Medicine III, University of Erlangen-Nuremberg, Erlangen, Germany and Institute of Rheumatology and Connective Tissue Research Laboratory, Department of Rheumatology of the First Faculty of Medicine, Charles University i,

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Background: S100A4 (metastasis associated protein) is a calcium binding protein exerting regulatory functions in diverse biological processes. It promotes cancer progression and metastasis by regulating the remodelling of the extracellular matrix.

Objectives: The aim of this study was to investigate the contribution of S100A4 to the pathologic activation of fibroblasts in SSc and its role in the development of a fibrotic phenotype in a mouse model of experimental dermal fibrosis.

Methods: Activation of S100A4 in human skin and experimental dermal fibrosis was determined by real-time PCR, immunohistochemistry and western blot. Collagen levels of SSc and healthy dermal fibroblasts was quantified by real-time PCR and SirCol collagen assay. Blyomycin-induced dermal fibrosis, a model for early, inflammatory stages of SSc, was used to assess the role of S100A4 in vivo using mice deficient for S100A4 (−/−) and wildtype littermates (+/+)

Results: Increased expression of S100A4 was detected in the upper layer of the dermis of SSc patients and was clearly colocalized with alpha-smooth muscle actin-positive fibroblasts. The overexpression of S100A4 persisted in cultured SSc fibroblasts and might contribute to their activated phenotype. A similar increase in S100A4 expression was observed in the skin samples from mice challenged with bleomycin and tsk-1 mice, both on mRNA (3.5- and 5.5-fold increase, respectively) and protein level. TGF-β stimulation of both healthy and SSc fibroblasts led to an increased expression of S100A4 protein. Of particular interest, knockdown of S100A4 by siRNA fully abrogated the stimulatory effects of TGFβ on the collagen synthesis of SSc fibroblasts. In agreement with the role of S100A4 as a novel mediator of the pro-fibrotic effects of TGF-β, mice lacking S100A4 were protected from experimental fibrosis. In the model of blyomycin-induced dermal fibrosis, inhibition of S100A4 decreased dermal thickening by 53±2% (p<0.01), significantly reduced myofibroblasts by 254±16% (p<0.01). Reduced induction of dermal fibrosis in S100A4−/− mice might result from inhibition of TGF-β signalling as evidenced by reduced nuclear accumulation of phosphorylated Smad 3 in the skin sections of S100A4−/− mice treated with blyomycin compared to their wildtype (+/+) littermates.
Conclusion: This is the first study reporting on the role of S100A4 in SSc. We demonstrate an upregulation of S100A4 in SSc in a TGF-β dependent manner, and that inhibition of S100A4 reduces collagen synthesis in activated SSc fibroblasts. Knockdown of S100A4 protected from fibrosis in the murine model of bleomycin-induced dermal fibrosis due to inhibition of TGF-β signaling. Thus, the S100A4 pathway could be an interesting novel target for the treatment of SSc.

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The Synthetic Cannabinoid Ajulemic Acid Targets Scleroderma Fibrosis

Background: Substantial evidence supports the involvement of the endocannabinoid system in pathologic fibrosis and the capability of cannabinoïds to modify fibrogenesis in scleroderma. Ajulemic acid (AjA) is a non-psychoactive, synthetic analog of tetrahydrocannabinol (THC), the main psychoactive ingredient of Cannabis-sativa. AjA binds to the peroxisome proliferator-activated receptor-γ (PPAR-γ) and PPAR-γ receptor activation modulates fibrogenesis. Therefore, we performed experiments to determine whether AjA can modify fibrogenesis in scleroderma.

Material and Methods: skin fibroblasts from scleroderma patients were cultured and treated with increasing concentrations of AjA (0.1, 1, 5 and 10 μM) in the presence or absence of the PPAR-γ irreversible antagonist GW6612 (1 and 10 μM) in order to evaluate procollagen production. Cell viability was evaluated using MTT assay and trypan-blue exclusion test. To evaluate AjA effect in vivo, three groups of DBA/2J mice (n=7 in each group) were studied. Group I and II received bleomycin subcutaneously (100 μl every other day) for 21 days. In addition to bleomycin, group II was treated orally with AjA (1 mg/kg) for 21 days. Group III only received subcutaneously 100 μl/day of NaCl 0.9%. At day 21 animals were sacrificed.

Results: AjA as well as the selective PPAR-γ antagonist GW6612 did not show any significant toxicity at the concentrations used. Addition of AjA to scleroderma fibroblasts significantly reduced supernatant procollagen concentrations in a dose-dependent manner. This effect was completely reversed by the PPAR-γ antagonist GW6612 (10 μM).

AjA treatment (1mg/kg/day for 21days) reduced markedly the dermal fibrosis induced by bleomycin in the animal model. Dermal thickness and hydroxyproline content appeared similar to the untreated control group. AjA treatment also reduced substantially the number of α-SMA positive cells in lesional skin.

Conclusions: we have demonstrated that AjA reduces fibrogenesis, at least in part, through a PPAR-γ mediated mechanism. These results and the demonstrated safety of AjA, suggest AjA as an interesting molecule targeting fibrosis in patients with scleroderma.

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The Transcription Factor AP-1 Mediates the Pro-Fibrotic Effects of TGFβ and Contributes to the Development of Experimental Dermal Fibrosis

**Objectives:**

The aims of the present study were to investigate whether AP-1 contributes to the pathologic activation of fibroblasts in SSc and to evaluate the anti-fibrotic potential of AP-1 inhibition for treatment of SSc.

**Methods:** Activation of AP-1 in human skin was determined by real-time PCR for c-Jun and c-Fos and immunohistochemistry for N-terminal residues of human c-Jun. SSc and healthy dermal fibroblasts were stimulated with TGF-β1, TGF-β1 pre-incubated with T5224, a small-molecule inhibitor of c-Fos/AP-1 (1). Collagen synthesis was quantified by real-time PCR and hydroxyproline assay. Differentiation of resting fibroblasts into myofibroblasts was assessed by staining for α-smooth muscle actin and stress fibers. To evaluate the anti-fibrotic potential of specific AP-1 inhibition by T5224 in vivo, we used the mouse model of bleomycin induced dermal fibrosis or attenuated adenoviruses overexpressing a constitutively active TGFβ receptor I.

**Results:** Increased levels of AP-1 were detected in the skin of SSc patients. The overactivation of AP-1 persisted in cultured SSc fibroblasts. Inhibition of AP-1 reduced the basal mRNA levels of colla1 and colla2 in SSc fibroblasts by up to 46±3% (p<0.05) but did not reduce the collagen synthesis in resting healthy dermal fibroblasts. Similar results were obtained on the protein level. Stimulation of healthy fibroblasts with TGFβ lead to AP-1 activation and inhibition of AP-1 abrogated the stimulatory effects of TGFβ on collagen synthesis. Inhibition of AP-1 also prevented the differentiation of resting fibroblasts into myofibroblasts. Consistently, inhibition of AP-1 exerted potent anti-fibrotic effects in different models of experimental fibrosis. In the mouse model of bleomycin-induced fibrosis, inhibition of AP-1 decreased dermal thickening by 53±3% (p<0.05). In addition, the collagen content and the number of myofibroblasts were significantly reduced (respectively 46±2% and 66±4%, p<0.05). In the TGFβR1 model, selective inhibition of AP-1 also exerted potent anti-fibrotic effects and reduced dermal thickening, collagen content and myofibroblast counts by 70±5%, 52±3% and 51±2%, respectively (p<0.05). T5224 was well tolerated: no weight loss, alterations of the skin texture or affected activity were recorded during the whole treatment period.

**Conclusion:** We demonstrate that AP-1 is activated in a TGFβ dependent manner in SSc and that inhibition of AP-1 specifically reduces collagen synthesis in activated SSc fibroblasts. The specific AP-1 inhibitor T5224 efficiently prevented the development of dermal fibrosis in different mouse models of SSc and was well tolerated. Thus, AP-1 might be a promising new molecular target for the treatment of SSc.


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The Triterpenoid CDDO Abrogates Canonical TGF-beta Signaling and Fibrotic Responses in Normal and Scleroderma Fibroblasts by Stabilizing the Anti-Oxidant Nuclear Factor-Like 2 (Nrf2). Kazuhiro Komura1, Jun Wei1, Gabriel Lord2 and John Varga1. 1Northwestern Univ Feinberg School of Medicine, Chicago, IL, 2Northwestern University Feinberg School of Medicine

Background: Scleroderma is characterized by excessive collagen accumulation and fibrosis in multiple organs. TGF-β stimulates collagen synthesis and is implicated in the pathogenesis of fibrosis. 2-Cyano-3,12-Dioxooleana-1,9-Dien-28-Oic acid (CDDO) is a synthetic triterpenoid that is known to activate peroxisome proliferator activated receptor (PPAR)-γ. We previously demonstrated that PPAR-γ ligands abrogated the stimulation of collagen synthesis induced by TGF-β in fibroblasts, by disrupting canonical TGF-β signaling in a PPAR-γ dependent manner. The objective of the current study is to address the anti-fibrotic effect of CDDO in fibroblasts.

Methods: The mesenchymal progenitor 3T3-L1 cell line was incubated with CDDO to induce adipogenesis. Expression of adipogenic markers was examined by real-time qPCR and immunofluorescence. Modulation of PPAR-γ promoter activity was examined in foreskin fibroblasts incubated with CDDO. Induction of profibrotic gene expression by TGF-β was evaluated by real-time qPCR and Western analysis. PPAR-γ dependence was evaluated using GW9662 a PPAR-γ antagonist. Nrf2 expression and activity were examined by Western blot, immunofluorescence and antioxidant response element (ARE) reporter assays. Effects of Nrf2 on canonical TGF-β signaling were examined by transient transfection in foreskin fibroblasts. Skin fibroblasts from 6 patients with diffuse cutaneous SSc were incubated with CDDO and profibrotic gene levels were measured by real-time PCR and Western analysis.

Results: CDDO induced a marked adipogenic response in 3T3-L1 cells. Moreover, CDDO significantly enhances PPAR-γ transcriptional activity. CDDO abrogated TGF-β-induced stimulation of collagen and α-smooth muscle actin (α-SMA) expression in a dose-dependent manner, and abrogated the stimulation of Smad2/3-mediated transcriptional activity induced by TGF-β. These inhibitory effects were PPAR-γ-dependent. CDDO also caused a marked accumulation and nuclear localization of Nrf2. Moreover CDDO stimulated Nrf2-dependent transcriptional activity. Ectopic Nrf2 was sufficient by itself to abrogate TGF-β-stimulation of Smad-dependent transcription. In scleroderma fibroblasts, CDDO caused significant suppression of collagen gene expression at mRNA and protein levels, and attenuated the myofibroblast phenotype of these cells.

Conclusion: The triterpenoid and novel PPAR-γ ligand CDDO abrogates canonical TGF-β signaling and suppresses fibrotic responses in a PPAR-γ-independent manner. Nrf2, a master regulator of the antioxidant response, is activated by CDDO in normal fibroblasts, and appears to mediate the CDDO response. Nrf2 thus is a novel target for anti-fibrotic therapy, and pharmacological modulation of the Nrf2 expression or activity might have a therapeutic potential in scleroderma.

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619 Visfatin/NAMPT in Interstitial Pneumonia of Patients with Systemic Sclerosis and Scleroderma Mice Model Induced by Bleomycin. Hirahito Endo2, Tatsuhiro Yamamoto1, Kaichi Kaneko3, Yoshihke Kusunoki1, Natsuko Kusunoki1 and Shinichi Kawai3. 1Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine, Oinhomi-nishi, Oita-ku, Japan, 2Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine, Oinhomi-nishi, Oita-ku, Japan, 3Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine

Scleroderma intestinal lung disease (SLD) is a leading cause of morbidity and mortality in patients with systemic sclerosis. Excessive fibrosis and inflammatory cell infiltration is a main features. Nicotinamide Phosphoribosyl Transferase/Visfatin (NAMPT/Visfatin) is an adipokine and a proinflammatory cytokine. To evaluate the significance of NAMPT/Visfatin in the diagnosis and monitoring of SLD we analyzed the concentration of NAMPT/Visfatin in bronchoalveolar lavage fluid (BALF) and plasma levels in SLD. Moreover we analyzed the role of NAMPT/Visfatin on experimental interstitial pneumonitis induced by bleomycin.

Methods: NAMPT/Visfatin concentration of BAL fluids and plasma of patients with SSC and other CTD, 12 patients with SSc and 20 patients with other CTD-IP (PM/DM,RA). Concentration of NAMPT/Visfatin were measured by enzyme-linked immunosorbent assay. Expression of NAMPT/Visfatin in lung tissue detected by immunohistochemistry. Expression of NAMPT/Visfatin mRNA also detected by RT-PCR. We also analyzed the NAMPT/Visfatin expression on lung injury induced by bleomycin was investigated in mice.

Results: Plasma concentration of NAMPT/Visfatin in SSc were significantly higher than healthy subject (SLD 5.38 ±1.09, Control 2.38± 2.60 ng/ml, p<0.05). NAMPT/Visfatin concentration in BALF of SLD were not significantly higher than that of other CTD (SLD11.8± 6.3, CTD-LD18.9±4.4 ng/ml). NAMPT/Visfatin concentration in BALF were not correlated with total lung capacity, the diffusion capacity for carbon monoxide, whereas there were correlated of BAL lymphocyte counts and serum KL-6 levels. NAMPT/Visfatin detected in macrophage and pulmonary epithelial cells of biopsy tissues of interstitial pneumonitis of patients with SSc. NAMPT/Visfatin detected in mice bleomycin induced interstitial pneumonitis at 3 weeks (serum IP 5.28± 0.25, Control 1.8 ±0.68 ng/ml, p<0.05). NAMPT/Visfatin detected in macrophage, pulmonary epithelial cells, microphage, and endothelial cells in murine IP lungs by immunohistochemical analysis. NAMPT/Visfatin also detected in BALF in mice IP (0.40±0.06 ng/ml, Control 0.18±0.12 ng/ml). NAMPT/Visfatin augmented the proliferation of cultured lung fibroblast derived from interstitial pneumonitis lung tissue. NAMPT/Visfatin also induced Col I, IL-6, and MCP-1 mRNA in cultured lung fibroblasts.

Conclusion: These data suggest that Visfatin/NAMPT is a new therapeutic target of SLD.

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618 Urantide Prevents and Alleviates Monocrotaline Induced Pulmonary Arterial Hypertension in Wistar Rats. Yifang Mei1, Hong Jin3, Hao Wang2, Wei Tian1, Yanping Zhao1 and Zhiyi Zhang2. 1The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China, 2The First Affiliated Hospital of Harbin Medical University, Harbin, China, 3The First Affiliated Hospital of Shantou University Medical College, Shantou, China

Background: Pulmonary arterial hypertension (PAH) is a serious complication of connective tissue disease (CTD). Urotensin II (UI) has been confirmed to be the most powerful vasoconstrictor greater than endothelin-1, which may play an important role on PAH development.

Objective: To observe the effects of urantide, an UII receptor antagonist, on monocrotaline (MCT)-induced PAH in rats.

Methods: 60 male Wistar rats were divided into six groups. For early treatment experiment, rats were divided into normal control group, MCT simulated group (MCT+saline×3wks from the 8th day of MCT-injection) and urantide early treatment group (MCT+urantide 10µg/kg/d×3wks from the 8th day of MCT-injection). For late treatment experiment, rats were dived as controls, MCTsimulated group (MCT+saline×2wks 4 weeks after MCT injected once), and urantide late treatment group (MCT+urantide 10µg/kg/d×2wks 4 weeks after MCT injected once). The relaxation effects of urantide on the intralobar pulmonary artery rings of control and MCT 4wks model rats were investigated. Then, the mean pulmonary arterial pressures (mPAP) of rats in each group were measured by flow-directed pulmonary artery catheter.

Results: Urantide dose-dependently relaxed the pulmonary artery rings of PAH model and normal rats. Moreover, L-NAMe blocked the dilatation response of urantide. Urantide reduced the mPAP in both early and late treatment groups and inhibited the pulmonary vascular remodeling remarkably. eNOS and NO levels in plasma elevated in both early and late treatment rats with urantide infusion.

Conclusion: Urantide effectively alleviated MCT induced PAH, at least partly, through mediating NO releasing, which provided a novel therapy for PAH.

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Platelet C4d Is Associated with All-Cause Mortality in Patients with Systemic Lupus Erythematosus. Christine A. McBurney, Amy H. Kao, Abdus Sattar, Apinya Lertratanakul, Nicole L. Wilson, Rutman Saraha, Barbara Paul, Jeanine S. Navratil, Joseph M. Ahearn, and Susan Manzi. 1Wexford, PA, 2Allegheny Singer Research Institute, Pittsburgh, PA, 3Case Western University, 4Magee Womens Hospital of UPMC, Pittsburgh, PA, 5University of Pittsburgh Medical Center, Pittsburgh, PA, 6University of Pittsburgh School of the Health Sciences, 7West Penn Allegheny Health System, Pittsburgh, PA

Background: Platelets bearing complement C4d (P-C4d) are reported to be specific for a diagnosis of systemic lupus erythematosus (SLE) and are associated with ischemic stroke. We investigated the association of P-C4d with all-cause mortality and prevalent cardiovascular disease (CVD) events in our longitudinal cohort of patients with SLE.

Methods: We recruited 356 consecutive outpatients or inpatients with SLE since July 2001. Outcomes were all-cause mortality and cardiovascular events including myocardial infarction, coronary artery bypass graft, percutaneous coronary transluminal angioplasty, stroke, pulmonary embolism, deep vein thrombosis or other thrombosis. P-C4d status was determined by flow cytometry.

Results: Mean age was 44.4 years (range: 18 – 81 years), 92% were female, and 81% were Caucasian. Seventy SLE patients (20%) had positive P-C4d at baseline. PC4d-positive patients were more likely to have a history of renal disease, seizure disorder, hemolytic anemia, thrombocytopenia, anti-double stranded DNA (dsDNA) and/or antiphospholipid antibodies. Overall CVD event frequency was 21.6%. SLE patients with positive P-C4d had significantly more CVD events compared to those with negative P-C4d (35.7% vs. 18.2%, p = 0.001). Positive P-C4d at baseline was associated with stroke, but not with other cardiovascular events (odds ratio 4.96, 95% confidence interval 1.75 – 14.06, p = 0.003) after adjusting for age, race, smoking history, SLE disease duration, renal disease, dsDNA and antiphospholipid antibodies. The overall mortality was 3.9%. Causes of death were infection (n = 4), cardiac arrest (n = 2), congestive heart failure (n = 1), cancer (n = 2), hemorrhage (n = 1), and unknown (n = 4). Six of these 14 deceased patients had a history of cancer (ovarian carcinoma, lymphoma, lung cancer, anal squamous cell carcinoma). Positive P-C4d at baseline was associated with all-cause mortality (hazard ratio 7.92, 95% CI 2.13 – 29.48, p = 0.002) after adjusting for age, race, sex, SLE disease duration, renal disease, cardiovascular event, cancer, dsDNA and antiphospholipid antibodies.

Conclusion: Platelet C4d is associated with all-cause mortality and stroke. Platelet C4d may be a prognostic biomarker as well as a pathogenic clue that links systemic inflammation, complement activation, and thrombosis and may represent a subset of patients with poor clinical outcomes.

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β2-Glycoprotein Exists in a Distinct Molecular Post-Translational Oxidative State in the Antiphospholipid Syndrome: Novel Prognostic Assays and Insights into Antigenicity. Yiannis Ioannou, Jing-Yun Zhang, Zhaoyi Qi, Guang Li, Jian Cheng Qi, De-min Yu, Herman Lau, Allan D. Sturges, Panayiotis Vlachoyiannopoulos, Haralampos M. Moutsopoulos, Anisur Rahman, Pericleous Charis, Tatsuya Atsumi, Takao Koike, Bill Giannakopoulos, and Kriti A. Steven. 1Hokkaido University, Sapporo, Japan, 2Hokkaido University, Sapporo, Japan, 3Nat Univ of Athens Med Schl, Athens, Greece, 4Nat Univ of Athens Med Schl, 5St. George Hospital, Sydney, NSW, Australia, 6St. George Hospital, Tianjin Medical University, Tianjin Medical University, Tianjin Medical University, University of New South Wales, 7University College London, University of New South Wales, 8University of New South Wales, 9University of New South Wales, Tianjin Medical University

Background: We have recently reported the novel finding that the major autoantigen in the antiphospholipid syndrome (APS), β2-glycoprotein I (β2GPI), exists in serum in a biochemically reduced state with free thiols (1).

This study aims to characterise the oxidative molecular state of β2GPI with respect to free thiol content in APS and evaluate relevance to antigenicity.

Methods: Through a multi-centre collaborative effort (Sydney, Athens, London, Sapporo), a total of 502 patient samples were collected from APS patients and three control groups: 182 APS (93 had an additional autoimmune disease (AID), 189 AID controls (≥ persistent antiphospholipid antibodies (aPL) but no APS), 38 clinical event controls (vascular thrombosis, no AID) and 93 healthy controls. Each control sample was total β2GPI and relative amounts of β2GPI present with free thiols. This was performed as described previously (1) and based upon a sandwich ELISA system using a biotinylated free thiol binding reagent to capture proteins with free thiols on a streptavidin plate and detect β2GPI using a monoclonal anti-β2GPI antibody. Oxidised versus reduced β2GPI binding avidity to polyclonal patient anti-β2GPI antibodies was then assessed.

Results: Total levels of β2GPI were significantly increased in the APS group (216.7 ± 79.5 μg/ml, median ± SD, n = 181) as compared to all of the three control groups studied (p = 0.0001). No differences were observed between the other three groups. The relative proportion of β2GPI in the biochemically reduced form expressed as a percentage of that observed with the in-house standard was significantly less in APS patients (median ± SD, 57.15% ± 23.5, n = 177) as compared to healthy control (p = 0.001), AID disease control (p = 0.001) and clinical event control (aPL negative, p = 0.001) groups. Hence, β2GPI in APS patients is in an oxidised state relative to each of the other three control groups. Sub-analyses of the APS group with anti-β2GPI positivity reveals that APS patients with LA positivity harbour the lowest proportion of β2GPI with free thiols (anti-β2GPI + LA, 47.52% ± 27.68% median ± SD, n = 28) versus anti-β2GPI without LA (53% ± 17.86 median ± SD, n = 28, p = 0.001). IgG from 10 patients with APS was purified. β2GPI within plasma derived from healthy volunteers oxidised by pre-incubation with H2O2 was a significantly better inhibitor of anti-β2GPI activity than untreated serum (p = 0.001, n = 10).

Conclusion: In APS patients, a greater proportion of β2GPI circulates in an oxidised versus reduced state relative to disease and healthy control groups. The finding that oxidised β2GPI harbours a greater avidity for patient derived anti-β2GPI antibodies coupled with the observation that APS patients have a greater antigenic load supports the theory that high amounts of oxidised β2GPI may lower the threshold for breaking tolerance, driving antigenicity and hence anti-β2GPI production in autoimmune susceptible patients.

(1) Ioannou Y et al, Naturally occurring free thiols within β2-glycoprotein I in vivo: nitrrosylation, redox modification by endothelial cells and regulation of oxidative stress induced cell injury. Blood June 2010 [Epub ahead of print]
Results: Fibrocytes were observed in lung tissue of scleroderma patients (n=7), but not healthy control subjects (n=4). Uptregulation of fibrocytes (CD45+/Col+/CD45+/CXCR4+, and CD45+/CXCR4+/Col+) was observed in the peripheral blood of scleroderma patients (n=7) compared to healthy controls (n=9): 2.5 ± 0.2 % vs. 1.0 ± 0.2 %; and 7.4 ± 0.69 % vs. 0.4 ± 0.88 %, respectively. Scleroderma PBM also differed from control PBM in signaling and in function. On average, SSC PBM contained less than half as much caveolin-1 and three-fold more CXCR4 compared to normal PBM. The percentage of scleroderma PBM that migrated in response to the CXCR4 ligand, CXCL12, was more than four-fold enhanced compared to normal PBM. When scleroderma PBM were treated with the CSD peptide to overcome their diminished expression of caveolin-1, CXCR4 expression and migration in response to CXCL12 were inhibited by at least 80%. Similar results were obtained in vivo in a mouse model. CSD peptide inhibited bleomycin-induced recruitment of CD45/CXCR4/Col-positive cells into injured mouse lung tissue by > 50 %.

Conclusion: Our results support the notion that using the CSD peptide to compensate for low caveolin-1 levels may be a useful treatment strategy for scleroderma and other inflammatory/fibrotic lung diseases.

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Clinical, Radiographic and Biomolecular Features of B Cell Synovitis in Rheumatoid Arthritis. Serena Bugatti2, Antonio Manzo2, Barbara Vitolo2, Chiara Fusetti2, Roberto Caporali2, Costantino Pitzalis1 and Carlomaurizio Montecucco1. 1Centre for Experimental Medicine and Rheumatology, John Vane Science Centre, William Harvey Research Institute, St. Bartholomew’s and Royal London School of Medicine, London, 2Chair and Division of Rheumatology, Laboratory of Rheumatology, University of Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Objective: Despite the central participation of B lymphocytes in the autoimmune process of rheumatoid arthritis (RA), the biologic and clinical impact of the B cell compartment at the site of inflammation itself, i.e. the synovial membrane, has not been consistently established. The aim of the present study was to investigate whether synovial B cell follicles are associated to specific clinical and molecular features of inflammation, immunological activity and bone remodeling in RA.

Methods: Multiple synovial biopsies were collected from 67 consecutive RA patients and evaluated histologically and by immunohistochemistry (IHC). From 25 of the 67 patients, paired paraffin and RNA samples were available and used for histological/IHC analysis and quantitative real-time polymerase chain reaction. The degree of B cell infiltration was determined semi-quantitatively (0–3) based on the size and density of CD20+/B cell aggregates and correlated to: 1) histopathologic features; 2) clinical parameters of disease activity and radiographic damage; 3) molecular markers of inflammation, T and B cell immunologic activity, bone damage and bone repair.

Results: The CD20+ cell score was significantly related to mRNA expression levels of CXCL13 (rho 0.8, p = 0.0001) and lymphotxin-β (rho 0.7, p = 0.0006), confirming the validity of the histological assessment. The degree of synovial B cell infiltration was associated to histological features of inflammation, such as the total inflammatory score (rho 0.6, p < 0.0001) and sublining infiltration of CD68+ macrophages (rho 0.4, p = 0.001). However, no correlation with systemic markers of inflammation was found. Instead, large-size B cell aggregates (CD20+ B cell scores 2 and 3) were independently associated to radiographic erosive disease in a multivariate logistic regression model including disease duration and serum auto-antibodies (OR 7.99, 95% CI 1.83–34.83; p = 0.006). Higher degrees of B cell infiltration were closely associated to increased mRNA expression of markers of activation of T cells, such as interferon-γ (rho = 0.001) and interleukin-17 (rho = 0.005), and B cells, such as activation-induced cytidine deaminase (AD) (rho = 0.02). Relevantly, samples characterized by large-size B cell aggregates also exhibited an increased RANKL/osteoprotegerin (OPG) ratio (rho = 0.008) due to reduced OPG levels (p = 0.02) rather than to increased RANKL (p = 0.2). Confirming the association with unbalanced bone remodeling, the expression levels of bone morphogenetic protein-2 and -7 tended to be lower in the presence of higher scores of B cell infiltration (p = 0.07 and p = 0.05 respectively).

Conclusions: The presence of large-size B cell aggregates in RA synovium is independently associated to a more aggressive pattern/status of the disease characterized by a higher frequency of radiographic erosions and a molecular milieu of increased immunological activity and unbalanced bone remodeling. Our data provide novel cues for further pathogenetic and prospective clinical studies assessing the relationship between the synovial pattern of lymphoid infiltration and inflammation/joint damage in RA.

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Association of FRZB Variants with Hip Shape and Radiographic Hip Osteoarthritis: Preliminary Results. Julie Baker-LePain4, Kali Luker4, John A. Lynch4, Neeta Parimi1, Michael C. Nevitt3, Mary Corr6 and Nancy E. Lane1, 1California Pacific Medical Center, 2Stanford, 3UCSF, San Francisco, CA, 4UCSF, 5Univ of California at Davis, Hillsborough, CA, 6Univ of California-San Diego, La Jolla, CA

Background: Single nucleotide polymorphisms (SNPs) in the FRZB gene, which encodes the Wnt antagonist secreted frizzled-related protein 3 (sFRP3), are significant predictors of radiographic hip osteoarthritis (ROHA) (Lane, et al., A&R 2006). In addition to FRZB, another important predictor of incident ROHA is hip shape (Lynch, et al., O&C 2009). Since the Wnt pathway is a key regulator of joint development, we examined whether FRZB variants are associated with hip shape and to what extent the relationship between joint shape and ROHA is affected FRZB.

Methods: We performed a nested case-control study within the Study of Osteoporotic Fractures (SOF). Subjects were Caucasian women aged ≥65 years with supine pelvic radiographs at baseline visit and at follow-up (mean 8.3 years). ROHA was scored radiographically using a modified summary grade (scale 0–4). Cases (n = 451) were defined as subjects with no baseline radiographic hip OA (ROHA) in either hip at baseline and incident ROHA (summary grade ≥ 2) at follow-up. Controls (n = 601) had no ROHA at either time point. We determined hip shape at 2 sites: the proximal femur by active shape modeling (ASM) (Lynch et al., O&C 2009) and the acetabulum by the center-edge angle and acetabular depth. Genotyping for the rs288326 SNP of FRZB was performed using allele-specific polymerase chain reaction (PCR). Linear regression was used to determine the association of hip shape parameters with the presence of the rs288326 FRZB SNP.

Results: In preliminary analysis, we found that among controls, proximal femur shape (Mode 2 from ASM analysis) was associated with the rs288326 FRZB SNP (coefficient = −0.18, 95% CI −0.35 to 0.03, p = 0.05) after adjustment for age and femoral neck BMD. The presence of the rs288326 allele modified the association between acetabular depth/center edge angle and ROHA (p-value for trend < 0.001).

Figure. Quartiles of increasing proximal femur ASM Mode 2 or decreasing acetabular depth were created using control populations, and the association between the rs288326 FRZB allele and incident ROHA was examined in each quartile using logistic regression. Odds ratio with 95% CI is shown, together with p-value for test of linear trend. The referent group was subjects without the rs288326 FRZB allele.
Conclusions: Hip shape is known to be an important predictor of incident OA. In this preliminary analysis, we find that variants in the FRZB gene, a component of the Wnt pathway, may be involved in moderating the relationship between hip shape and OA. We hypothesize that Wnt pathway components play a key role in determination of joint shape, which in turn may predispose to development of osteoarthritis in a conducive architectural setting.

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## ARHP Concurrent Abstract Sessions
## Issues in Lupus

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The Assessment of Health-Related Family Functioning in Systemic Lupus Erythematosus: Preliminary Validation of the SLE-FAMILY.

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1Rutgers University, 2UMDNJ-Robert Wood Johnson Medical School, Union NJ, 3University of California, San Francisco, San Francisco, CA, 4University of Michigan Medical School, Ann Arbor, MI

Background: Patients with systemic lupus erythematosus (SLE) often experience disabling symptoms that affect family relationships. To assess the impact of SLE on health-related family functioning we developed the SLE-FAMILY which evaluates six key domains: Fatigue (fatigue-related family activity impairment), Activities (general family activity impairment), Mental Health (emotional impact on family), Isolation (feelings of isolation from family), Love (loss of intimacy) and You (fulfilling family roles). The 6-item SLE-FAMILY has scores ranging from 1-7 with higher scores indicating worse family functioning. The major objectives of this study were to pilot test and achieve preliminary validation for the SLE-FAMILY.

Methods: 52 patients with SLE completed questionnaires including the 6-item SLE-FAMILY, SF-36, Sheehan Disability Scale (SDS), Fatigue Severity Scale (FSS), Multidimensional Scale of Perceived Social Support (MSPPS), Satisfaction with Life Scale (SWLS), Positive and Negative Affect Scale (PANAS) and the Systemic Lupus Activity Questionnaire (SLAQ). Data were analyzed for internal consistency reliability with Cronbach’s alpha. Next, item statistics were calculated to assess the correlations between individual items and SLE-FAMILY total score. To evaluate convergent and discriminant validity, correlations between the SLE-FAMILY and the other measures were calculated.

Results: Mean age for the 52 participants was 36.8 (SD11.9) years with a mean duration of illness of 8.4 years (SD6.7). Most were female (88.5%). The SLE-FAMILY had good test-retest reliability (0.83) and internal consistency (0.67). However, reliability analysis of individual items revealed a weakness in the performance of Item 5. Raw data were reviewed and it was determined that 9 patients likely overlooked the reverse-scoring of Item 5, thus explaining its poor reliability. When the 9 patients were excluded from the analysis, alpha increased to 0.71, while test-retest reliability remained acceptable (0.78). Spearman’s rho correlations supported the validity of the SLE-FAMILY as its total score was significantly related to SDS Family (r=0.67, p<0.001) and SDS Social (r=0.60, p<0.001); SLAQ (r=0.68, p<0.001); PANAS negative subscale (r=0.55, p<0.001); and PANAS positive subscale (r=0.62, p<0.001). Similarly, the SLE-FAMILY total score was inversely related to relevant SF-36 subscales scores including: Social Functioning (r = -0.55, p<0.001), Role Emotional (r = -0.42, p<0.005), Role Physical (r = -0.59, p<0.001) and Mental Health (r = -0.48, p<0.001).

Conclusion: The SLE-FAMILY is a promising new instrument for the more robust measurement of family functioning. Additional pilot testing using revised scoring options for Item 5 and additional validation studies are underway.

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### 626

Heart-Rate Recovery Immediately after Graded Exercise in Woman with Systemic Lupus Erythematosus.

Danilo M. L. Prado1, Fabio Baptista1, Renata Miossi1, Fernanda R. Lima1, Ana Lucia S. Pinto1, Eduardo F. Borba1 and Eloisa Bonifa1.

1USP, Sao Paulo, SP, Brazil, 2USP, Sao Paulo, Brazil, 3USP

Patients with systemic lupus erythematosus (SLE) are known to have lower heart rate variability suggesting impaired autonomic modulation. Heart-rate recovery after maximal graded exercise test has been identified as a strong independent predictor of cardiovascular and all-cause mortality in adults. Previous studies suggested that low heart-rate recovery is in part due to attenuated parasympathetic reactivation and sympathetic overactivity following the termination of exercise. Besides this knowledge, there is little information about this issue in SLE.

Purpose: To evaluate the heart-rate recovery after graded exercise in SLE.

Methods: Eighteen consecutive SLE women (SLE group) with low SLEDAI scores (1.0 ± 2.3) without cardiopulmonary involvement were selected and compared to 17 healthy women (control). All subjects performed a progressive treadmill cardiopulmonary test until exhaustion to determine the maximal aerobic capacity. Heart rate recovery at both one minute (ΔHRR1) and two minutes (ΔHRR2) were defined as the difference between heart rate at peak of exercise and at 1 and 2 minutes post exercise, respectively.

Results: Age (29.6 ± 1.3 vs. 26.2 ± 1.5 years, p=0.10) and Body-mass index (23.7 ± 0.8 vs. 21.8 ± 0.5 kg/m2, p=0.09) were alike between SLE and control group. SLE had significant lower peak workload (4.6 ± 0.1 vs. 5.6 ± 0.0 mph, P=0.001) and relative lower aerobic fitness [VO2peak (28.3 ±1.0 vs. 37.1 ±1.2 mL·kg⁻¹·min⁻¹, P=0.001) compared to control.

Heart Rate Recovery Post Graded Exercise

<table>
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<th>Heart Rate Recovery Post Graded Exercise</th>
<th>SLE</th>
<th>Control</th>
<th>p</th>
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<tbody>
<tr>
<td>ΔHRR1</td>
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<td>52.1 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔHRR2</td>
<td>41.7 ± 1.6</td>
<td>52.1 ± 2.1</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Values are means ± SE. ΔHRR1 - heart rate recovery at one minute; ΔHRR2 - heart rate recovery at two minutes. (Unpaired students T Test). P < 0.05 considered statistically significant.

Conclusion: These findings demonstrated that woman with SLE had reduced heart rate recovery at first and second minutes after graded exercise compared to controls. Taken together, these data suggest abnormal restoration of autonomic nervous tone including a decrease in vagal tone and an increase in sympathetic activity after graded exercise in these patients.

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### 627

Body Composition, Lower Extremity Strength, and Fatigue in SLE.

Patricia Katz, Laura Julian, Jinoo Yazdany, Holly Wing, Sandi Kaplan, Laura Trupin and Ed Yelin. UCSF

Background: Fatigue is widely acknowledged as a major concern for individuals with rheumatoid arthritis, but less attention has been focused on fatigue in systemic lupus erythematosus (SLE). Additionally, there has been little research addressing the relationship of body composition and fatigue. These analyses examine the role of body composition and muscular weakness in fatigue among women with SLE.

Methods: All measures were collected during an in-person research visit. Fatigue was measured with the severity subscale of the Multidimensional Assessment of Fatigue (MAF), in which scores range from 1 (mild) to 10 (severe). Body composition was assessed by dual-energy x-ray absorptiometry (DEXA), which yielded measures of total, as well as regional (appendicular and trunk) body fat and lean mass, each of which was adjusted for height to create fat and lean mass indices (FMI; LMI). Lower extremity strength was assessed using a Biodex® Unit. Peak torque at knee extension and flexion at 150 degrees/second were used in these analyses. SLE disease activity was estimated with a modified version of the SLEDAI. Regression analyses, controlling for age, duration of SLE, and disease activity, modeled the effects of body composition and lower extremity strength on fatigue.

(Knee extension and flexion were examined in separate models.) This analysis focuses on the 115 women for whom complete data were available. (30 women were missing either DEXA or strength testing data).

Results: Mean age was 48 (±12) years; duration of SLE was 16 (±9) years. Mean fatigue rating was 5.9 (±2.3); 30% rated fatigue severity at 7 or
Physical Exercise Improves Endothelial Function in Patients with Systemic Lupus Erythematosus. Edgard T. Reis Neto, Aline E. Silva, Carlos M. C. Monteiro, Luciano M. Camargo, Neusa P. Silva, Marcelo M. Pinheiro and Emilia I. Sato. Universidade Federal de São Paulo, Brazil

Background: Cardiovascular disease (CVD) is an important cause of morbidity and mortality in systemic lupus erythematosus (SLE). Endothelial dysfunction is implicated in the pathogenesis of premature atherosclerosis in SLE and there are studies showing improvement of endothelial function (EF) after physical exercise program in individuals with heart failure, diabetes and coronary arterial disease.

Objectives: to assess the effect of supervised physical exercise (SPE) on the EF, quality of life, fatigue, exercise tolerance and body composition in SLE patients.

Methods: prospective and controlled study in which women with SLE (18–45 years old) were allocated according to availability to participate in the exercise program in the exercise group (EG) or control group (CG). Intervention: SPE were performed 3 times a week for 16 consecutive weeks and consisted of 10 minutes of initial warm-up/stretching, 40 minutes of walking performed at a heart rate corresponding to the ventilatory anaerobic threshold (obtained with ergospirometric test), and 10 minutes of cooling-down. Patients were evaluated at baseline (T0) and after 16 weeks (T16) by high-resolution ultrasound of brachial artery in resting conditions, after reactive hyperemia (flow-mediated dilation-FMD) and after oral glyceryl trinitrate (GTMD) for evaluating endothelial function; quality of life (SF-36 index); perceived exertion (Borg scale), fatigue (Krupp scale) and body composition (DEXA).

Results: Four hundred and eight patients were invited to participate in the study, 186 manifested interest but 109 were excluded due to exclusion criteria and only 21 were included in the study. Nineteen patients completed the evaluations (average age: 33.4 ± 8.7 years and mean disease duration: 102.6 ± 80.7 months). Twelve patients were allocated on EG and 7 on CG. Both groups were homogeneous and comparable at baseline regarding demographics variables. The average dose of prednisone was 8.5 ± 12.9mg/day; 78.5% were using anti-malarials and 36.8% immune-suppressants.

Conclusions: A substantial portion of this group of women with SLE experienced severe fatigue. Both abdominal obesity and muscle weakness play an important role in fatigue among women with SLE.

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Background: Different inflammatory joint diseases have distinct patterns of bone damage with pronounced erosions in rheumatoid arthritis (RA), a combination of bone destruction and formation in psoriatic arthritis (PsA), and dominant new bone formation in spondyloarthritis (SpA). Although the underlying molecular mechanisms remain poorly understood, blocking of Dickkopf-1 (DKK-1), an inhibitor of the Wnt pathway, reverses the bone-destructive pattern to a bone-forming pattern in experimental arthritis. In order to delineate the role of DKK-1 in the structural phenotype of SpA versus RA, we analyzed the total and stimulated regulation of DKK-1 expression in the inflamed peripheral joint of different types of inflammatory arthritis ex-vivo and in fibroblast-like synoviocytes (FLS) cultures in vitro.

Methods: Synovial fluid (SF) was obtained from actively inflamed knee joints of RA (n=45), non-psoriatic SpA (n=38), PsA (n=33), and gout (n=17) patients. The concentrations of IL-6, DKK-1, TNF, and IL-1 beta were determined by ELISA. Synovial FLS lines were established from tissue samples obtained from patients with inflammatory synovitis including RA (n=5), SpA (n=6). DKK-1 was determined by ELISA in FLS cultures following stimulation with TNF, IL-1 beta, IL-6, LPS and oncostatin M (OSM). DKK-1 serum levels were assessed before and after IL-6R blockade in RA patients.

Results: SF DKK-1 levels were similar between the 4 disease groups with, however, a striking inter-individual variability within each cohort. As we previously demonstrated that DKK-1 production is strongly upregulated by TNF, we explored this inter-individual variability by correlating DKK-1 levels with pro-inflammatory cytokines levels in the inflamed joint. TNF and IL-1 beta levels were significantly higher in RA than SpA SF and did not correlate with SF DKK-1 levels, suggesting that other factors contribute to the regulation of DKK-1 in vivo. In contrast, there was a striking inverse correlation between DKK-1 and IL-6 in both RA and SpA. Exploring the functional impact of IL-6 on DKK-1 in vitro, DKK-1 production by RA, SpA, PsA SF was strongly induced by TNF (but not IL-1 beta) but clearly suppressed by IL-6 and OSM. This suppression was confirmed in dose-response experiments, although lower doses of IL-6 (10 ng/ml) have a stimulatory rather than inhibitory effect. Higher doses of IL-6 (50 ng/ml) were able to reverse the TNF-induced upregulation of DKK-1 production by FLS. Preliminary data suggest that this regulation of DKK-1 production by IL-6 is also relevant in vivo as treatment with the anti-IL-6 R antibody, tocilizumab, induced a transient upregulation of DKK-1 serum levels in RA patients.

Conclusions: DKK-1 is abundantly expressed in the inflamed joint of both destructive and remodelling forms of arthritis. However, DKK-1 production by FLS is differentially regulated by TNF and IL-6 in vitro and in vivo. The relative balance between these factors in the arthritic joints may determine the pattern of inflammation-induced tissue remodelling.

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Adipocytic and Osteogenic Switch in Differentiation of Human Mesenchymal Stem Cells (hMSCs) Is Triggered by Hypoxia in a HIF-1 Dependent Manner. Markus Wagegg, Timo Gáber, Ferenz Lohanatha, Manuela Jakstadi, Grit Kasper, Georg Duda, Paula Kolar, Gerd R. Burmester, Frank Butterger, Berlín-Brandenburg Center for Regenerative Therapies (BCRT), Charité University Hospital, Center for Musculoskeletal Surgery, Berlin, Germany, Charité University Hospital, Department of Rheumatology and Clinical Immunology, Berlin, Germany, Charité University Hospital, Department of Rheumatology and Clinical Immunology, Berlin, Germany, Charité University Med-Berlin, Berlin, Germany

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Mitochondrial 8-Oxoguanine DNA Glycosylase (Ogg1) Regulates the Cellular Function and Survival of Osteoarthritic Chondrocytes in Response to Catabolic Stresses in Osteoarthritis. Kazuo Yudoh1 and Rie Karasawa1.1Kawasaki, Japan, 2St. Marianna University School Medicine, Kawasaki, City, Japan

Background: During the development of osteoarthritis (OA), mechanical and chemical stresses on articular cartilage change the stable cellular activities of chondrocytes and produce excess amounts of reactive oxygen species (ROS) as well as proinflammatory cytokines and chemokines. Studies have provided ample confirmation of the generation of ROS and the depletion of cellular antioxidants in degenerated articular cartilage. 8-Oxoguanine DNA glycosylase (Ogg1) repairs 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxoG), one of the most abundant DNA adducts caused by oxygen free radicals. In the mitochondria, Ogg1 is thought to protect against activation of the intrinsic apoptotic pathway as a result of oxidative stress by augmenting DNA repair. We observed the decreased levels of Ogg1 in osteoarthritic chondrocytes in comparison with normal chondrocytes in animal models of osteoarthritis (OA) and patients with OA, suggesting the involvement of down-regulation of Ogg1 in the degeneration of articular cartilage in OA. We found that mitochondrial Ogg1 silencing using siRNA reduced chondrocyte activity and augmented apoptosis in human osteoarthritic chondrocytes. In the previous studies, we have focused on nanocarbon particle, fullerene (C60), which acts as a strong free radical scavenger, as an anti-oxidative agent, to prevent the degeneration of articular cartilage in OA. We have demonstrated that water-soluble fullerene has a potential as a protective agent against the catabolic stress-induced degeneration of articular cartilage both in vitro and in vivo OA models. In the present study, we found that C60 fullerene increased the expressions of Ogg1 in osteoarthritic chondrocytes.

Objective: Our recently developed model involving accumulation of 8-Oxoguanine, an oxidized form of guanine, and impairment of mitochondrial DNA repair enzymes in the pathogenesis of OA. These findings suggest that mitochondria have a potential as a protective agent against the catabolic stress-induced degeneration of articular cartilage in OA. C60 fullerene may have a therapeutic potential, as a nanomedicine, to protect against the degeneration of articular cartilage in OA.

Methods: Mitochondrial Ogg1 silencing using siRNA reduced chondrocyte activity and augmented apoptosis in human osteoarthritic chondrocytes. In the previous studies, we have focused on nanocarbon particle, fullerene (C60), which acts as a strong free radical scavenger, as an anti-oxidative agent, to prevent the degeneration of articular cartilage in OA. We have demonstrated that water-soluble fullerene has a potential as a protective agent against the catabolic stress-induced degeneration of articular cartilage both in vitro and in vivo OA models. In the present study, we found that C60 fullerene increased the expressions of Ogg1 in osteoarthritic chondrocytes.

Conclusion: The present study revealed that nanocarbon particle fullerene can reduce oxidative stress in human OA chondrocytes. Our data also suggest that C60 Fullerene may have a therapeutic potential, as a nanomedicine, to protect against the degeneration of articular cartilage in OA.
MicroRNA-199a-5′ Mediated Regulation of Cyclooxygenase-2 Expression in Human OA Chondrocytes. Nahid Akhtar1, Zafar Rasheed2 and Tariq M. Haqqi3. Metrohealth Medical Center/CWRU, Cleveland, OH, 3Metrohealth Medical Center/CWRU

Background: Recent evidence implicate the deregulated expression of microRNAs (miRNAs) in the pathogenesis of osteoarthritis (OA). Interleukin-1β (IL-1β)-induced expression of cyclooxygenase-2 (COX-2) correlates with the production of prostaglandin E2 and cartilage degradation in OA. Here we determined the posttranscriptional regulation of COX-2 expression by miRNAs in IL-1β-stimulated human OA and normal chondrocytes.

Methods: Human chondrocytes were derived by enzymatic digestion of OA cartilage (OA chondrocytes) and cartilage from trauma patients with no history of OA (normal chondrocytes). Chondrocytes were stimulated with IL-1β (5ng/ml) in vitro. Total RNA was prepared using TRIZOL reagent and miRNAs were purified using the mirVANA system. Single stranded cDNA was synthesized using stem loop-specific primers and the expression of miRNAs of interest was quantified using TaqMan miRNA Expression Assay and their target mRNA was identified using bioinformatics. Transfection of OA chondrocytes with a 3'UTR reporter construct and pre-miRNAs was employed to verify the miRNA:mRNA interaction. OA chondrocytes transfected with pre-miRNAs and anti-miRNAs were analyzed for the expression of COX-2 mRNA and protein by qRT-PCR using specific primers and Western immunoblotting, respectively.

Results: IL-1β stimulation of OA chondrocytes resulted in the downregulation of two miRNAs—miR-101_3 and miR-199a*—that potentially target COX-2 mRNA. Kinetic analysis showed that in OA chondrocytes, expression of miR-101_3 was down-regulated at 6 h (2.1-fold ± 1.0; n=7) but no significant change was observed at 24 h (n=11) post stimulation. Normal chondrocytes showed down-regulation of miR-101_3 (1.7-fold ± 0.5; n=3) at 24 h but no change at 6 h post-stimulation with IL-1β. Expression level of miR-199a* in OA chondrocytes stimulated with IL-1β at 24 h (3.3-fold ± 1.5; n=11, p<0.05) and at 6 h (0.94-fold ± 0.86; n=7) inversely correlated with the COX-2 protein expression level. Similar results were obtained with normal chondrocytes stimulated with IL-1β. Significantly lower expression of miR-199a* was observed in freshly isolated OA cartilage compared to normal cartilage (n=5, p<0.001). Over-expression of miR-199a* in OA chondrocytes inhibited the IL-1β-induced expression of COX-2 protein significantly compared to control OA chondrocytes (p<0.05). Transfection of OA chondrocytes with miR-199a* inhibitor enhanced the IL-1β-induced expression of COX-2 protein. Co-transfection of OA chondrocytes with a luciferase reporter construct containing the 3'UTR of human COX-2 mRNA and pre-miR-199a* suppressed the luciferase activity significantly (p<0.05). No inhibition of luciferase activity was observed in OA chondrocytes transfected with negative control miRNA. Inhibition of NF-κB and p38MAPK activation with specific inhibitors altered the expression of miR-199a* in human OA chondrocytes suggesting the regulation of miR-199a* by activation of these pathways.

Conclusions: Our data implicate miR-199a* in the posttranscriptional regulation of COX-2 expression in OA chondrocytes and identify miR-199a* as a novel therapeutic target for the treatment/prevention of OA.

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acr Concurrent Abstract Sessions
Cytokines, Mediators, Gene Regulation

Monday, November 8, 2010, 2:30 PM–4:00 PM

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Decreased Collagen Induced Arthritis (CIA) Severity in MAPK Kinase 6 Deficient Mice: Pivotal Role of Th1 and Th17 Cytokines. Deepa Hammaker1, Kathryn Topolewski2, Meghan Edgar3, David L. Boyle1 and Gary S. Firestein1. 1UCSD School of Medicine, La Jolla, CA, 2UCSD School of Medicine

Purpose: MKK3 and MKK6 are upstream kinases that activate p38 MAP kinase and regulate distinct subsets of cytokines. Previous studies suggest that both kinases suppress innate immune responses and arthritis severity in passive K/BxN arthritis. However, their function in an adaptive model of inflammatory arthritis has not been known. This study evaluated whether these kinases play a role in collagen induced arthritis (CIA).

Method: Wild type (WT), MKK6−/−, and MKK3−/− mice were immunized on days 0 and 21 with type II bovine collagen in complete Freund’s adjuvant. Joint histology was evaluated on synovitis, bone erosion, extra-articular inflammation and proteoglycan damage (max score = 16). Serum anti-collagen antibodies were measured by ELISA. Cytokines in joints extracts and serum was determined by multiplex analysis. Splenocytes isolated 14 days after immunization were cultured with concanavalin A (Con A), type II collagen (CII), or medium and supernatants were assayed for cytokines.

Results: Arthritis severity was significantly lower in MKK6−/− mice than WT mice, while MKK3−/− mice had intermediate disease severity (p = 0.03 for each compared to WT).

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Scores of WT, MKK6+/− and MKK3+/− mice on day 35 were 12±1.5, 7±1.8, and 8±2.4, respectively. Histological evaluation showed significantly decreased bone erosion in MKK6+/− mice compared with WT mice (1.2±0.5 vs. 2.7±0.5, p=0.03). Decreased synovitis (50% inhibition), and proteoglycan loss (40% inhibition) were observed in MKK6+/− mice compared with WT mice. Surprisingly, inflammation and bone destruction were similar in WT and MKK3+/− mice. Anti-collagen antibodies levels in MKK6+/− mice were decreased by 45±12% compared with WT (p=0.004), but titers in MKK3+/− mice were the same as WT. Synovial IL-6, MMP3 and MMP13 gene expression was reduced by 66–79% in MKK6+/− mice compared with WT (p<0.02 for each). Expression of these genes was modestly reduced in MKK3+/− joints but did not reach statistical significance. T cell differentiation was evaluated by examining in vitro splenocyte cytokine profiles. IL-17 production in response to Con A and CII in MKK6+/− mice was reduced by 80±7% and 82±16% compared with WT and were normal in MKK3+/− cells (p=0.03 for MKK6+/−). IFNγ production by Con A-stimulated splenocytes was inhibited by 85±5% in MKK6+/− compared with WT mice (p=0.025). IL-4 levels were not altered by MKK3 or MKK6 deficiency.

Conclusion: MKK6 deficiency suppressed CIA and joint destruction while MKK3 had an intermediate effect. Lower disease severity in MKK6+/− mice was due to decreased adaptive immune responses, especially the production of antibodies and Th17 cytokines. These data suggest that targeting MKK6 has a potential benefit in complex diseases involving adaptive immune responses like rheumatoid arthritis.

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IL-7-Related TSLP: A Novel Potent Proinflammatory Mediator in Rheumatoid Arthritis That Activates Myeloid Dendritic Cells To Stimulate Th1 and Th17 Activity. F. M. Moret, C. E. Hack, K. M. G. van der Wurff-Jacobs, None; F. P. J. G. Lafeber: None; J. A. G. van Room: None.

Background: The IL-7-related cytokine, thymic stromal lymphopoietin (TSLP), is well known for its potent activation of myeloid dendritic cells (mDCs) resulting in Th2-mediated immune responses. TSLP signals cells via the IL-7 receptor-alpha chain (IL-7Ra), shared with IL-7, together with a distinctive receptor subunit, the TSLP receptor (TSLPR). Recently, we have demonstrated that prevention of TSLPR signalling strongly reduces Th17-driven experimental arthritis and immunopathology. Furthermore, we have shown that administration of TSLP expands T and B cells and enhances severity of inflammation and joint destruction in collagen induced arthritis.

Objective: To determine the levels of TSLP and TSLPR in joints of rheumatoid arthritis (RA) patients and the capacity of TSLP to induce mDC-dependent T-cell activation.

Methods: TSLP was measured (by ELISA) in synovial fluid (SF) of patients with RA (n=44) and osteoarthritis (OA, n=20). CD1c+ mDC numbers and TSLPR expression on these cells were assessed by FACs analysis in paired samples of SF and peripheral blood (PB) from RA patients (n=7). mDCs, isolated from PB of patients with RA (n=8) as well as SF-derived mDCs were stimulated with TSLP for 24 hours and cytokine production was measured. Washed TSLP-activated mDCs were added to autologous CD4 T cells from PB in the absence of additional stimuli, cultured

for 6 days and subsequently proliferation was measured. Additionally, T-cell cytokine production was measured upon restimulation with ionomycin/PMA.

Results: TSLP levels in SF of RA patients were increased compared to OA patients (mean 460 vs. 75 pg/ml, resp., p<0.001). mDCs numbers from SF were increased compared to PB (3.8% vs. 0.7%, resp., p<0.02). CD1c+ mDCs from SF and PB expressed substantial levels of TSLPR (SF: 76% positive cells, MFI 19±3; PB: 70% positive cells, MFI 15±2).

TSLP significantly stimulated production of chemokines TARC and MIP1α by mDCs from PB and SF (TARC: PB from 4 to 89 and SF: from 323 to 629 pg/ml, MIP1α: PB from 1545 to 6293 and SF from 10185 to 14313 pg/ml). Upon incubation with TSLP, TSLP-expressing mDCs from PB potently stimulated proliferation of autologous CD4 T cells (ratio T cell:DC 5:1, mean 15019±1856 pg/ml) as compared to unstimulated mDCs (mean 960±256 pg/ml). TSLP-mDCs from SF had a strongly increased stimulatory capacity (from 2195±686 to 16615±3162 at a ratio T cell:DC 5:1). Upon restimulation, TSLP-mDC-activated CD4 T cells from PB produced increased levels of TNFα (3724±972 vs. 11559±1465 pg/ml), IFNy (218±142 vs. 738±181 pg/ml), and IL-17 (27.9±8.2 vs. 155±66 pg/ml) in addition to IL-4 (1.4±1.4 vs. 25.0±11.3 pg/ml). Induction of TNFα was significantly higher in RA patients compared to healthy controls (p<0.05).

Conclusion: Our data indicate that increased intra-articular TSLP concentrations in RA potently activate TSLP-expressing mDCs from RA patients to cause chemokaxis and activation of antigenic T cells. This suggests that TSLP and its receptor are novel therapeutic targets for RA.

Disclosure: F. M. Moret: None; C. E. Hack: None; K. M. G. van der Wurff-Jacobs: None; F. P. J. G. Lafeber: None; J. A. G. van Room: None.

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Interleukin-12. Not the ITGAM Polymorphism (rs1143679), Correlates With Atherosclerosis Independent of Disease Activity in SLE. Manish Jain, Erin McDonnell, Jill P. Buyon and Robert M. Clancy. Department of Rheumatology, New York University School of Medicine

Background: Inflammation likely contributes to the increased prevalence of macrovascular disease in SLE. Dendritic cells (DCs) at sites of atherosclerosis may represent a double-edged sword, promoting plaque formation and restraining inflammation by inducing tolerance. Plasma IL-12 may represent a marker of DC activation, and its utility as a biomarker of macrovascular disease is underscored by the fact that in murine models, blockade of IL-12 function attenuates atherosclerosis. The integrin CR3 has been shown to decrease the release of IL-12 by DC. ITGAM polymorphism rs1143679 (exon-3 ITGAM gene, A allele frequency) encoding R771H in the alpha chain of CR3 (CD11b), is significantly associated with SLE. Accordingly, the hypothesis being raised is that macrovascular disease is linked to a skewing of DC phenotype towards activation as reflected by elevated levels of IL-12. A subgoal was to evaluate whether plaque was enriched in patients with the non-synonymous variant rs1143679.

Methods: IL-12 levels (ELISA) were measured in a previously reported cross-sectional study of 116 SLE patients and 47 healthy controls in whom carotid ultrasonography was performed to evaluate Intimal Media Thickness (IMT) and the presence of carotid plaque. Complete history and physical were done to complete the SLEDAI in addition to chart review. Typing of ITGAM was performed by the allelic discrimination technique using assays and reagents optimized for the assessment of rs1143679.

Results: The mean level of IL-12 was significantly higher in SLE patients (109±87.9 pg/mL) than controls (67±26 pg/mL) (p=0.006). Among SLE patients, no correlation was observed between IL-12 levels and SLEDAI. SLE patients with plaque had significantly higher mean soluble IL-12 levels (130±104) than patients without plaque (93±69 pg/mL) (p=0.023). The top quartile of SLE patients based on IL-12 levels (29 patients) had a significantly higher prevalence of carotid plaque compared to the other SLE patients (18/29 patients or 62% versus 32/87 patients or 37%, p=0.029). The mean common carotid artery IMT was higher in these top quartile SLE patients (6.49 mm) versus those in the bottom three quartiles (5.65 mm) (p=0.037). The presence of anti-ds DNA antibodies was significantly enriched in the top quartile SLE patients (18/29, 62%) versus the remainder of SLE patients (33/87, 38%) (p=0.031). No differences were found for levels of cardiac CRP or complement. Representation of the rs1143679 ITGAM polymorphism was 19% within the cohort, consistent with published values in SLE (versus 10% in healthy controls). There were no differences in allelic frequency for patients based on plaque status or for patients with varied levels of IL-12.

Conclusion: This study highlights IL-12 as a surrogate marker for vascular damage with potential clinical applicability in monitoring patients.
particularly since it may be independent of disease activity. While CR3 has been shown to attenuate IL-12, in this cohort an association with the IGAM variant was not observed. Although the source of IL-12 is yet to be identified in this cohort of patients, a potential link between DC and atherosclerosis in SLE should be considered.

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Pro-Inflammatory Properties of IL-35 and Its Association with Disease Activity in Patients with Rheumatoid Arthritis, Maria Filkova1, Hana Hulejova1, Marketa Polanska1, Lucie Andrez Cerez01, Jiri Vencovsky1, Karel Pavelka1 and Ludmil Senolt1. 1Center of Experimental Rheumatology, University Hospital and Zurich Center of Integrative Human Physiology (ZHJP), Zurich, Switzerland, 2Institute of Rheumatology and Connective Tissue Research Laboratory, Department of Rheumatology of the 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, 3Institute of Rheumatology and Connective Tissue Research Laboratory, Department of Rheumatology of the 1st Faculty of Medicine, Charles University in Prague, Czech Republic, Czech Republic, 4Institute of Rheumatology, Department of Rheumatology of the 1st Faculty of Medicine, Charles University in Prague, Czech Republic, Czech Republic

Background: IL-35 is a heterodimeric member of the IL-12 family consisting of p35 (IL-12a) and EB13 (IL-27b) subunits. Expressed in murine T-reg cells, IL-35 was shown to control colitis and inhibit collagen induced arthritis in mice. In contrast to mice, human T-reg cells do not express IL-35 and both subunits are expressed in activated T-eff cells. An up-regulation of EB13/p35 following TNF-α and IFN-γ was observed in human aortic smooth muscle cells.

Objective: To analyze the levels of IL-35 in sera and synovial fluids of patients with rheumatoid arthritis (RA), osteoarthritis (OA) and healthy controls and to study its effect(s) on peripheral blood mononuclear cells (PBMC) and RA synovial fibroblasts (RASF) in vitro.

Methods: The levels of IL-35 in sera (RA: n=40, healthy controls: n=34), synovial fluids (RA: n=32, OA: n=30) and cell culture media were determined by commercially available ELISA. PBMC and RASF were stimulated with human recombinant IL-35 protein (25, 50, 100 ng/ml) or TNF-α (10, 50, 100 ng/ml) in vitro. Taq-Man RT-PCR was performed to analyse gene expression after 6 and 24 hours and ELISA assays were used to confirm the protein secretion after 24 hours of stimulation.

Results: The levels of IL-35 in synovial fluids were significantly higher in patients with RA in comparison to patients with OA (mean±SEM: 23 583±7 474, calculated after dilution; vs. 397.5±68.7 pg/ml, p<0.0001). In addition, local levels of IL-35 significantly correlated with the levels of serum CRP in both RA as well as OA patients (r=0.504, p=0.004 and r=0.453, p=0.02; respectively) and with the disease activity of patients with RA assessed by DAS28 (r=0.440, p=0.014). On the other side, serum levels of IL-35 were below the detection limit in the majority of RA patients as well as healthy controls. Gene expression of both subunits of IL-35, EB13 and p35, as well as IL-35 dose-dependently increased by TNF-α in PBMC. Related results show that PBMC isolated from patients with RA secreted more IL-35 than those from healthy controls. IL-35 dose-dependently up-regulated the gene expression of IL-1β (up to 6.3 fold), IL-6 (up to 9.6 fold) and MCP1 (up to 22.4 fold) but not of TNF-α in PBMC. This pattern was also confirmed by ELISA. However, there was no effect of IL-35 on RASF with respect to the tested cytokines.

Conclusion: These data show for the first time, in contrast to the immunosuppressive function observed in mice, that locally up-regulated levels of IL-35 reflect the disease activity of RA. Furthermore, the results of this study support the concept that IL-35 has also pro-inflammatory properties.

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MAPK Kinase 3 (MKK3) Regulates Osteoclast Differentiation and Activation, David L. Boyle1, Meghan Edgar2, Mario M. Zais3, Georg Schett3 and Gary S. Firestein3. 1Department of Internal Medicine 3, University of Erlangen-Nuremberg, 2Friedrich Alexander Univ, Erlangen, Germany, 3UCSD School of Medicine, La Jolla, CA, 4UCSD School of Medicine

Purpose: p38 MAPK inhibitors have modest efficacy in diseases like rheumatoid arthritis (RA), in part because exposure is limited by side effects. Two upstream kinases regulate p38 function, namely MKK3 and MKK6. These two MKKs have non-redundant functions and control expression of complementary subsets of pro-inflammatory cytokines. Deficiency of either MKK decreases inflammation in the passive K/BxN model of arthritis. To explore distinct functions of MKK3 and MKK6, we examined their relative contributions to joint damage and bone resorption by evaluating the differentiation and function of MKK deficient osteoclasts. The data could support developing MKK inhibitors for bone protection in RA and in osteoporosis.

Methods: BM monocytes from wild type (WT), MKK3−/−, and MKK6−/− mice were differentiated with M-CSF (30ng/ml) and non-adherent cells subsequently cultured with M-CSF (30ng/ml) and RANKL (50ng/ml) for 5 days in the Osteologic Bone Cell Culture System. Osteoclast number and matrix resorption were determined by TRAP staining followed by light microscopy and automated image analysis. SB203580 was used at 3μg/ml. Gene expression and p38 phosphorylation were determined by qPCR and Western Blot analysis, respectively.

Results: The number of osteoclasts generated from BM monocytes was similar in WT and MKK6−/− mice. Surprisingly, MKK3−/− osteoclast differentiation was lower than WT or MKK6−/− (n=9, 33% inhibition, P<0.004). The p38 inhibitor SB203580 inhibited osteoclast differentiation by 74% (P=0.001). In vitro matrix resorption by osteoclasts was decreased by 46% by MKK3−/− osteoclasts (P=0.002), while MKK6 deficiency had no effect compared with WT cells. p38 activation, as measured by determining relative P-p38/p38 ratios, for WT, MKK6−/−, and MKK3−/− osteoclasts was 0.71±0.09, 0.54±0.05, and 0.09±0.02, respectively (n=3, P=0.001 for MKK3−/−). MMP13 expression was similar in all genotypes, but expression of the key bone resorbing protease cathepsin K was significantly lower in MKK3−/− osteoclasts (67% inhibition; P=0.0001) but not in MKK6−/− cells.

Conclusions: MKK3, but not MKK6, is required for osteoclast differentiation and activation, p38 phosphorylation, and cathepsin K gene expression. Selective MKK3 inhibitors could be targeted for RA in order to suppress bone erosions and inflammation while sparing p38 functions that might contribute to toxicity. In addition, an MKK3 inhibitor could have utility as an oral therapy for osteoporosis.

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ACR Concurrent Abstract Sessions
Epidemiology and Health Services Research: Rheumatoid Arthritis

Monday, November 8, 2010, 2:30 PM–4:00 PM

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Tumor Necrosis Factor Inhibition Reduces the Incidence of Alzheimer’s Disease in Rheumatoid Arthritis Patients, Richard C. Chour1, Michael A. Kane2, Shiva Gautam3 and Sanjay Ghirmire4. 1Beth Israel Deaconess Medical Center, 2Dartmouth-Hitchcock Medical Center, Milton, MA, 3Massachusetts General Hospital and Massachusetts Institute of Technology, George-town, MA, 4Verisk Health

Objective: To investigate the relationship between different rheumatoid arthritis treatments and Alzheimer’s dementia.

Background: A complication of chronic inflammation in rheumatoid arthritis (RA) is the deposition of amyloid proteins, resulting in secondary amyloidosis. Alzheimer’s disease (AD) is associated with the local deposition of beta-amyloid peptide in the brain, although the pathogenetic mechanisms of AD are unclear. The relationship between RA and AD has not been established.

Design/Methods: We reviewed medical and pharmacy claims data from January 2000 to November 2007 for a commercially insured cohort of 8.5 million adults throughout the US. We derived a subcohort of 42,193
patients with a pre-existing diagnosis of RA. In this subcohort, we conducted a nested case-control study of the incidence of AD. We excluded individuals with psoriatic arthritis, inflammatory bowel disease, previous stroke or previous AD. For each individual with newly diagnosed AD (cases) we matched up to 10 controls who did not have a prior diagnosis of AD and were free of AD during the exposure assessment period. Matching criteria included age, gender, duration of exposure assessment period and methotrexate treatment. We examined exposure to sulfasalazine, prednisone, three anti-tumor necrosis factor (TNF) agents (infliximab, etanercept, adalimumab) and rituximab.

Results: In this nested case-control study, a total of 165 patients with AD (cases) were matched to 1,383 controls without AD. Treatment with anti-TNF agents in RA was associated with lower risk for incident AD [adjusted odds ratio (OR) 0.440; 95% confidence interval (CI) 0.223–0.868; \( p = 0.0178 \)]. The risk of AD was not affected by exposure to sulfasalazine, prednisone or rituximab. The results were similar [adjusted OR 0.448; 95% CI 0.225–0.892; \( p = 0.0222 \)] after adjustment for covariates, including hypertension, hyperlipidemia, diabetes mellitus, peripheral vascular disease, and coronary artery disease.

Conclusion: In this population of adults with RA, we observed that the risk of AD was reduced by TNF inhibitor therapy, but not by other disease modifying agents used for treatment of RA. Tumor necrosis factor may be an important component in the pathogenesis of AD.

Disclosure: R. C. Chou: None; M. A. Kane: versik health, 5; S. Gautam: None; S. Ghirmire: versik health, 3.

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Major Improvements in Outcomes of Rheumatoid Arthritis Since the Biologic Era and beyond: An Historical Overview from 1989 until 2008 in a Large Inception Cohort of RA Patients. Wietse Kievit1, Jaap Fransen1, Maarten De Waal Malefijt1, Alfons Den Broeder2 and Piet van Riel3, 1Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, 2Radboud University Nijmegen Medical Centre, The Netherlands, 3University of Pittsburgh, Pittsburgh PA

Background: Already before the early 80’s there has been a movement towards intensified treatment for RA with an increasing use of methotrexate in higher doses up to 30 mg per week in individual patients and DMARD combination therapy.

Objectives: We hypothesized that the trend of better RA outcomes precedes the era of biologic response modifiers.

Methods: Data available from the period between 1989 and 2008 in the Dutch Nijmegen inception cohort was used, including DAS28, HAQ-DI, X-rays and orthopedic surgery. Patients with RA were regularly assessed at scheduled visits. For each individual patient, the average DAS28 and HAQ-DI scores for each calendar year were calculated. X-rays of hand and feet were taken annually and joint surface destruction was scored according to the Raitenig score (range 0–190) (data available until 2003). Population mean DAS28 and HAQ-DI over time were corrected for age, gender, rheumatoid factor and disease duration by means of repeated measures analysis (mixed models). Conditional means of DAS28 and HAQ-DI were plotted by calendar year. Median Raitenig scores were compared between calendar years non-parametrically. Orthopedic surgery was analyzed as incidence rates with 95% confidence limits based on a Poisson distribution. To describe treatment, the percentage of patients being treated with MTX or SASP, a biological response modifier, and the mean MTX dose per year were calculated.

Results: Per 2008, 992 RA patients were included, resulting in 8618 patient years. From 1989 onwards, the percentage of patients being treated with SASP decreased to 18% and the percentage of patients being treated with MTX increased to 62% in 2008. The percentage of patients being treated with a biologic was increased to 22% (166/765) in 2008. The MTX dose increased significantly from a mean dose (sd) of 6.7 (1.3) mg/week with a maximum of 7.5 mg/week in 1989 to a mean dose (sd) of 16.1 (5.5) mg/week with a maximum of 30 mg/week in 2008. The Figure A shows the mean DAS28 per calendar year conditional on disease duration, age, gender and rheumatoid factor. According to the repeated measures analysis the mean DAS28 and HAQ-DI were statistically significant higher (\( p < 0.008 \)) in all years compared to 2008, where mean DAS28 was 3.2 and the mean HAQ-DI was 0.47. Median Raitenig score for patients with 3 years disease duration decreased from 12.5 in 1989 to zero in 2003 (Figure B). Analysis of the incidence of orthopedic surgeries showed a trend towards lower rates of orthopedic surgery with non-overlapping 95% confidence intervals in the years 2006, 2007 and 2008 compared to almost all previous years.

Conclusion: The better controlled RA that we show is not only attributable to the introduction of anti-TNF, but also to the DMARDs (and especially MTX) which were largely available before the biologic era. We think that utilization of the available therapies can still be enhanced by tight control strategies.

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Propensity-Adjusted Medication Effects on Survival in Rheumatoid Arthritis: 22-Year Follow-Up of 5629 Patients. Mary Chester Wasko1, Abhijit Dasgupta1, Helen Hubert2, Bharathi Lingala2, James Fries3 and Michael Ward3, 1NIAMS/NIH, Bethesda, MD, 2Stanford University, Palo Alto, CA, 3University of Pittsburgh, Pittsburgh PA

Background: Medications used to treat rheumatoid arthritis (RA) may affect mortality, though prescription patterns are influenced by patient demographics, comorbidities, and physician preference, all factors that change over time. The propensity for prescribing RA medications may influence the likelihood of drug use and thus also should be considered when evaluating if particular anti-rheumatic medications influence mortality in patients with RA.

Methods: Using a longitudinal multicenter observational database of 5629 RA patients followed biannually with the Health Assessment Questionnaire (HAQ) from 1981–2003, we calculated propensity scores at each HAQ for the use of methotrexate (MTX), prednisone (PRED), and anti-tumor necrosis factor (TNF) agents. Scores were time-dependent and based on RA duration at study entry, age, ethnicity, education level, gender, marital status, work status, body-mass index (BMI), pain and RA severity indices, comorbidities, other drug use, and phase of study. Time-varying Cox proportional hazards regression models were then constructed to determine the relationship between drug use and survival, adjusting for propensity score, age, BMI, HAQ-disability index, ethnicity, education level, gender, marital status, work status, body-mass index (BMI), pain and RA severity indices, comorbidities, other drug use, and phase of study. Time-varying Cox proportional hazards regression models adjusting for drug-specific propensity and covariates showed a strong protective effect for MTX on mortality (Hazard Ratio [HR] = 0.27, 0.11–0.70 95% CI, \( p < 0.001 \)) but no statistically significant impact of PRED (HR = 1.48, 0.69–3.17 95% CI, \( p = 0.31 \)) or anti-TNF (HR = 0.59, 0.00–5e8 95% CI, \( p = 0.96 \)) on the outcome. However, the models for PRED without propensity score showed a significantly increased risk of mortality (HR = 1.62, 95% CI 1.41–1.87, \( p < 0.001 \)).
Conclusions: Adjusting for propensity and other covariates, MTX use is strongly associated with reduced mortality in this RA cohort. These results underscore the importance role of MTX in the management of patients with RA. Use of PRED is not associated with increased mortality in propensity-adjusted analysis, uniquely suggesting that factors associated with prescribing patterns play a role in the reported mortality rates for patients on PRED. Our findings do not indicate an increase in mortality with use of anti-TNF agents over 5 years of observation following introduction of these agents for commercial use.

Disclosure: M. C. Wasko: Agen Inc., 2, Centocor, Inc., 5, 9, UCB, Inc., 5; A. Dasgupta: None; H. Hubert: None; B. Lingala: None; J. Fries: None; M. Ward: None.

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Renal Dysfunction in Rheumatoid Arthritis Is Associated with Incident Cardiovascular Disease, Independently of Traditional Risk Factors: The CARRE Study. Alper M. van Sij1, Ingrid M. Visman1, Inge A. M. van den Oever1, Mike J. L. Peters2, Alexandre E. Voskuyl2, Ben A. C. Dijkmans3 and Michael T. Nurmohamed2. 1Jan van Breemen Institute, 2Jan van Breemen Institute and VU Medical Centre, Amsterdam, The Netherlands, 3Jan van Breemen Institute and VU Medical Centre, 4VU Medical Centre, Amsterdam, The Netherlands, 5VU Medical Centre

Background: Individuals with rheumatoid arthritis (RA), a chronic inflammatory disease, have an increased risk of developing cardiovascular disease (CVD), that persists after correction for traditional risk factors, e.g. smoking, hypertension, dyslipidemia, previous CV event or diabetes. Renal dysfunction is predictive of CVD in the general population but also in patients with diabetes or hypertension, independently of traditional CV risk factors. In these cases, low-grade inflammation is thought to have an essential role. To date, there have been no studies investigating the association of renal dysfunction with incidence of CVD in RA.

Methods: The CARRE study is a prospective cohort study of Dutch patients with RA aged between 50 and 75 years old, in which traditional CV risk factors, RA related factors and CV morbidity and mortality are investigated. CV events are defined as documented myocardial infarction, peripheral arterial reconstruction or coronary stent- or by-pass procedure. Renal function was assessed by the estimated Glomerular Filtration Rate (GFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) formula. A GFR of less than 60 m/min/1.73 m² is considered unfavourable. Multivariate Cox proportional hazard analyses were performed to determine the association between renal dysfunction and incident CV disease.

Results: 353 patients were followed for 3 years and 23 patients developed a CV event within this study period. Higher GFR (≥60) was significantly associated with a lower risk for CVD, hazard ratio (95%-confidence interval): 0.185 (0.079–0.438). This association remained significant even after correction for: 1. Age, sex and previous CVD 2. Nodular disease and antihypertensive agents 3. Use of methotrexate, corticosteroids and non-steroidal anti-inflammatory drugs and 4. Traditional CV risk factors.

Conclusion: Renal dysfunction is associated with incident CV disease in RA, even after correction for traditional risk factors. These results indicate that a decreased renal function helps to identify RA patients at increased risk for future CV disease. Future studies should further investigate the relationship between chronic inflammation and renal dysfunction.

Table 1. Cox proportional hazard model for GFR and cardiovascular incidence

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95%-Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude model</td>
<td>0.185*</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.240</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.174</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.223</td>
</tr>
<tr>
<td>Model 4</td>
<td>0.125*</td>
</tr>
</tbody>
</table>

*p < 0.05. Results as hazard ratios (95%-confidence interval). GFR-MDRD as categorical variable ≥60 and <60

Figure 1. Cox-regression analysis of CV event free probability for individuals with GFR <60 compared to individuals with GFR ≥60 corrected for age, gender and previous CVD.

Disclosure: A. M. van Sijl: None; I. M. Visman: None; I. A. M. van den Oever: None; M. J. L. Peters: None; A. E. Voskuyl: None; B. A. C. Dijkmans: None; M. T. Nurmohamed: Abbott Immunology Pharmaceuticals, 2, Bristol-Myers Squibb, 2, 8, Roche, 2, Schering-Plough, 2, Wyeth Pharmaceuticals, 2.

Background: Impairment of physical function, caused by a combination of inflammation and structural damage, leads to eventual disability among patients with rheumatoid arthritis (RA). It has been suggested that the relative impact of inflammation and structural damage on physical function differ over time during the progression of the disease.

Methods: Data from two trials of adalimumab—PREMIER (patients with early RA) and DE019 (patients with longstanding RA)—were pooled to assess the relationship of physical functioning (measured by the HAQ and the Physical Component Score [PCS] and Physical Functioning [PF] domain of the SF-36 questionnaire) with structural damage (measured by modified total Sharp scores [mTSS]) and inflammation (measured by C-Reactive Protein [CRP] levels). Baseline patient-level data were used from both trials regardless of treatment arm. Spearman’s correlations were assessed between HAQ, PCS and PF with TSS and with CRP. Correlations were calculated separately for patients with duration of disease up to 3 years (early RA) and for those with more than 3 years (longstanding RA) across the two trials. Strengths of correlation between HAQ-TSS and HAQ-CRP were tested using Fisher’s Z transformation technique.

Results: Combining patients from the two studies, there were 908 patients with disease duration ≤3 years and 507 with disease duration >3 years. The mean (SD) HAQ, TSS, and CRP values were 1.5 (0.6), 20.05 (20.3), and 3.73 (3.9) respectively in early RA, and 1.47 (0.6), 77.89 (55.9), and 1.69 (1.9) in longstanding RA. In early RA, all measures of physical functioning were correlated with CRP. Spearman’s correlation coefficients with HAQ, PCS, and PF of 0.395, –0.288, and –0.357, respectively (p<0.05 for all). However, none of the physical function measures were correlated with TSS. In established RA, on the other hand, TSS was correlated with HAQ, PCS, and PF with coefficients of 0.238, –0.119, and –0.137, respectively. Correlations of the physical function measures with CRP were also significant in longstanding RA, but the strengths of such associations were weaker compared with those in early RA. Fisher’s Z-transformed estimates of

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Do Structural Damage and Inflammation Impact Physical Functioning Differently Based on Duration of Rheumatoid Arthritis? Martin J. Bergman2, Sanjoy Roy1, Najjun Chen1 and Mary A. Cifaldi1. 1Abbott Laboratories, Abbott Park, IL, 2Arthritis and Rheumatology, Ridley Park, PA

Background: Impairment of physical function, caused by a combination of inflammation and structural damage, leads to eventual disability among patients with rheumatoid arthritis (RA). It has been suggested that the relative impact of inflammation and structural damage on physical function differ over time during the progression of the disease.
correlation between HAQ and TSS increased significantly with longer duration of disease (0.034 vs. 0.242; p=0.0003), while it decreased significantly between HAQ and CRP (0.417 vs. 0.261; p=0.005).

Conclusion: This study shows that deterioration of physical functioning as a result of RA may be driven by inflammation earlier in the disease, but is driven more by structural damage as the disease progresses. This suggests that earlier treatment with appropriate therapy (that inhibits both inflammation and radiographic progression) prior to structural damage could dramatically improve long-term physical functioning and disability outcomes among patients with RA.

References:

Disclosure: M. J. Bergman: Abbott Laboratories, 2, 5, 8; Bristol-Myers Squibb, 2, 5, 8; Roche, 5; UCB, Inc., 2, 5; S. Roy: Abbott Laboratories, 1, 3; N. Chen: Abbott Laboratories, 1, 3; M. A. Cifaldi: Abbott Laboratories, 1, 3.

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Common Vaccinations among Adults and the Risk of Developing Rheumatoid Arthritis; Results from the Swedish EIRA Study. Camilla Bengtsson1, Melita Kapetanovic1, Henrik Källberg2, Bertt Sverdrup2, Birgitta Nordmark3, Lars Kläreskog3 and Lars Alfredsson3. 1Institute for Clinical Sciences, Department of Rheumatology, Lund University, Lund, Sweden, 2Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, 3Rheumatology Unit, Department of Medicine, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.

Background: Vaccinations are among the events frequently considered as inciting agents for rheumatoid arthritis (RA), but no sufficiently powered epidemiological studies have been published addressing whether vaccinations commonly used in industrialised societies constitute risk factors for RA.

Objectives: To investigate whether common vaccinations given to adults were associated with an increased risk of RA, and whether vaccinations have different impact on two subsets of RA, characterized by presence/absence of antibodies to citrullinated peptides (ACPAs).

Methods: Data from the Swedish population-based EIRA (Epidemiological Investigation of Rheumatoid Arthritis) case-control study encompassing 1998 incident cases aged 18–70 years and 2252 randomly selected controls, matched on age, sex and residency, was analysed. All cases were diagnosed by rheumatologists according to the ACR criteria of 1987. Those vaccinated within five years prior to disease onset were compared with those not vaccinated within five years before disease onset, by calculating odds ratios (OR) with 95% confidence interval (CI). Biological interaction, defined by departure from additivity of effects was evaluated between vaccination and smoking and between vaccinations and HLA-DRB1 SE alleles regarding risk of ACPA-positive RA.

Results: We conducted a 2×2 factorial randomised controlled trial of an individually tailored exercise programme in community leisure facilities and CBT delivered by telephone (T-CBT). Interventions were of six months duration and were compared to usual care. Participants were recruited by means of a brief postal screening survey of all persons registered with 8 primary-care practices in the city of Aberdeen and suburbs of Manchester, United Kingdom. Patients were eligible if they satisfied the definition of CWP in the 1990 ACR criteria for fibromyalgia, reported disabling symptoms, had consulted their family doctor with symptoms in the past year and had no contraindications to exercise or a pain condition requiring other specific treatment. Severity of pain was measured by the Chronic Pain Grade (CPG) from I (low intensity) to IV (severely limiting). The outcome measure was a 7-point patient global assessment scale of change in symptoms since the time of recruitment (from “very much worse” through “no change” to “very much better”). A positive outcome was defined as “much better” or “very much better”. Data were analysed as % reporting a positive outcome and logistic regression was used to describe the individual and combined effects of intervention(s) on outcome with results expressed as odds ratios (ORs) and 95% Confidence Intervals (CI).

Results: 14386 persons were screened of whom 878 were identified as potentially eligible for the trial. 442 individuals attended for assessment, were randomised to the trial and randomised to one of the four study arms. Participants had a median age of 58 years (IQR: 48–65); 69% were female and the distribution of CPG was: I 21%, II 38%, III 21%, IV 21%. At the end of the six month intervention period 361 provided outcome data (82%). The percentages reporting a positive outcome were: usual care 8%, T-CBT only 30%, exercise only 35% and both interventions 37% (p < 0.0005). T-CBT (OR 4.9 95% CI (2.9, 12) or exercise only (6.1; 2.5,15) resulted in improved outcomes but there was no significant additional benefit in receiving both interventions (OR combined multiplicative effect 0.22; 0.08, 0.67).

Conclusions: This study has demonstrated substantial and statistically significant improvement in the global assessment of their condition by patients with CWP who consult with their family practitioner and are provided with a 6-month exercise or T-CBT programme. This is the first trial of telephone delivered CBT in CWP. These results provide encouragement for patients with CWP that short-term improvement is possible in a substantial proportion with either of these interventions.

Disclosure: G. J. Macfarlane: None; C. Gkazinou: None; M. Beasley: None; E. A. Jones: None; G. J. Prescott: None; P. Hannaford: None; K. Kleeley: None; K. Lovell: None; P. McNamee: None; D. P. M. Symmons: None; S. Woby: None; J. McBeth: None; the MUSICIAN Study Team: None.

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Non-Invasive Cortical Electrostimulation in the Treatment of Fibromyalgia. Jeffrey B. Hargrove1, Robert M. Bennett2, David G. Simons3, Susan J. Smith1, Sunil Nagpal4 and Donald E. Deering1. 1Emory University, 2Kettering University, Flint, MI, 3Michigan State University, 4NeuroHealth Associates, 5Oregon Health & Science Univ, Portland, OR.

ACR Concurrent Abstract Sessions
Fibromyalgia and Soft Tissue Disorders
Monday, November 8, 2010, 2:30 PM–4:00 PM
**Purpose:** The purpose of this study was to test the feasibility, efficacy and safety of an innovative form of non-invasive cortical electrostimulation (NICE) in the treatment of fibromyalgia (FM), where areas of the brain that may be involved in dysfunctional sensory processing were targeted.

**Methods:** A randomized placebo controlled, double-blind trial design was used to evaluate the efficacy of NICE in 77 FM patients (ACR 1990 criteria). Non-invasive leads were applied to the scalp with the aim of stimulating the centro-parietal area, including the somatosensory cortex. Monopolar electrical stimulation was used that employed high frequency carrier components to overcome skin and scalp impedance, and low frequency components designed to stimulate and modulate lower frequency cortical activity in the targeted areas. NICE consisted of 22 treatment sessions administered twice a week for approximately 11 minutes. As the signal is sub-threshold for cutaneous stimulation, the placebo arm (PL) was created by simply not delivering the signal. Patients were evaluated at baseline and no less than 7 days after completion of therapy. At both time-points all subjects completed the FIQ and a sleepVAS. A blinded investigator evaluated the number of positive tender points (TPPs), and the summed tender point pain threshold (TPPT) was assessed using dolorimetry. The FIQ was re-administered at an average of 17 months post-termination of the study.

**Results:** Baseline demographic and clinical features were comparable in both treatment groups. Compared to PL, the NICE group had a significant improvement in the total FIQ score, pain VAS and sleep VAS scores. NICE group patients improved in the number of positive TePs (−43%), whereas the PL group did not change. The pain threshold (TPPT) for the NICE group improved 61% whereas the control group got slightly worse (−4%). Between-group analysis of TePs and TPPT scores showed significant improvement in the NICE arm compared to PL. Long-term follow-up showed a sustained improvement in the FIQ scores over baseline (average total FIQ scores: baseline 59, post-treatment 42; long-term 37; p < 0.001). NICE did not result in any significant adverse events.

<table>
<thead>
<tr>
<th>Baseline to Post-Treatment Outcomes [Mean Raw Change (% change)]</th>
<th>NICE Group</th>
<th>PL Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of positive TePs (range 0–18)</td>
<td>−7.4 (−43%)</td>
<td>−0.2 (0%)</td>
</tr>
<tr>
<td>Post-therapy group difference in number of positive TePs</td>
<td>−6.8 (41%)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Change in TPPT (range 9–72)</td>
<td>+19.7 (61%)</td>
<td>−3.1 (−4%)</td>
</tr>
<tr>
<td>Post-therapy group difference in TPPT</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.04</td>
</tr>
<tr>
<td>Post-change in TPPT in FIQ pain VAS (range 0–10)</td>
<td>−2.0 (30%)</td>
<td>−0.6 (9%)</td>
</tr>
<tr>
<td>Post-therapy group difference in TPPT</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Post-change in total VAS score (range 0–100)</td>
<td>−15.5 (25%)</td>
<td>−5.5 (9%)</td>
</tr>
<tr>
<td>Post-therapy group difference in total VAS score</td>
<td>−6.5 (12%)</td>
<td>p = 0.032</td>
</tr>
<tr>
<td>Percent of patients achieving 30% improvement in TePs</td>
<td>66%</td>
<td>5%</td>
</tr>
<tr>
<td>Percent of patients achieving 30% improvement in TPPT</td>
<td>71%</td>
<td>8%</td>
</tr>
<tr>
<td>Percent of patients achieving 30% improvement in FIQ pain VAS</td>
<td>39%</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Conclusions:** Using a cortical electrostimulation technique specifically designed to enhance signal penetration to centro-parietal brain regions, this study yielded clinically significant improvements in pain, tenderness and other typical features of FM. The treatment was well tolerated without significant adverse effects. This modality may augment current approaches to the treatment of FM.

**Disclosure:** J. B. Hargrove: Cerephex Corporation, 4; R. M. Bennett: None; D. G. Simons: None; S. J. Smith: None; S. Nagpal: None; D. E. Deering: None.

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**Purpose:** Fibromyalgia (FM) is characterized by a multitude of symptoms that include chronic widespread pain, fatigue, stiffness, impaired physical functioning, sleep disturbances, cognitive dysfunction, and depressed mood. Medications used to manage FM often do not treat the full spectrum of symptoms that a patient with FM may experience. Patients may benefit from augmenting their current treatment regimen with medications that have complementary mechanisms of action. This randomized, open-label, controlled study evaluated the efficacy and tolerability of milnacipran 50 mg BID when added to pregabalin 150 mg BID or 225 mg BID in FM patients who had an incomplete response to pregabalin during a 4- to 12-week open-label run-in phase.

**Methods:** This was a randomized, controlled, open-label study. After the pregabalin run-in period, incomplete responders to pregabalin (patients with weekly recall VAS pain score ≥40 and ≤50 [0 to 100 scale], Patient Global Impression of Severity score ≥4 [ranging from “moderately ill” to “extremely ill”], and Patient Global Impression of Change [PGIC] score ≥3 [ranging from “minimally improved” to “very much worse”]) were randomized to pregabalin alone (n=180) or milnacipran added to pregabalin (n=184) for 11 weeks. The primary efficacy assessment was the percentage of PGIC responders at endpoint, defined as patients reporting a PGIC rating of “much improved” or “very much improved”. The secondary efficacy assessment was the change from baseline in VAS 1-week pain recall score. Additional efficacy measures included SF-36 Physical and Mental Component Summary Scores (PCS and MCS, respectively), Multidimensional Fatigue Inventory (MFI), and Multiple Ability Self-report Questionnaire (MASQ). Treatment-emergent adverse events (TEAEs) occurring in the randomized treatment period were defined as AEs that were newly reported or increased in severity during the randomization period.

**Results:** The overall completion rate was higher in patients receiving milnacipran added to pregabalin (76.6%) than those receiving pregabalin alone (68.3%). At endpoint, milnacipran added to pregabalin treatment resulted in a significantly higher percentage of PGIC responders than pregabalin alone (46.4% vs 20.8%; P<0.001). The addition of milnacipran to pregabalin also resulted in a significantly greater reduction in least squares mean weekly recall VAS pain score compared with pregabalin alone (−20.8 vs −6.4; P<0.001). Patients receiving milnacipran added to pregabalin had significantly improved physical and mental function, fatigue, and cognition (SF-36 PCS and MCS, MFI, and MASQ, P<0.001, all outcomes) than patients receiving pregabalin alone. During the randomized treatment period, the most common TEAE in patients receiving milnacipran added to pregabalin was nausea, peripheral edema and weight increased were most common in patients receiving pregabalin alone.

**Conclusion:** This open-label study is the first randomized controlled study to demonstrate that adding milnacipran to pregabalin therapy is both tolerable and effective in improving global status and reducing pain in patients with FM experiencing an incomplete response to pregabalin alone.


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**Hypothalamic-Pituitary-Adrenal Axis Response to Mental Stress Predicts Chronic Widespread Pain Onset—Results from the SPICE Study.**


**Background:** The role of the Hypothalamic-Pituitary-Adrenal (HPA) axis stress response, as assessed by salivary cortisol, has been investigated in modifying risk of chronic widespread pain (CWP). It has been shown that, amongst those at high risk of CWP (high levels of adverse psychosocial factors), those with diminished diurnal variation and those who fail to suppress HPA axis function after a dexamethasone suppression test, are at particularly high risk of developing CWP. The aims of the current study are (1) to determine the importance of HPA axis dysfunction in a general population sample; and (2) to examine the response of the HPA axis to mental, as opposed to pharmacological, stress.

**Methods:** Baseline: potential participants aged 25–70yrs, randomly selected from 4 primary care practices in Aberdeen, UK, were sent a postal questionnaire. They were asked: “Thinking back over the past month, have you had any pain that has lasted for one day or longer?” Those answering positively were asked to identify the location(s) of this pain on a body map. You had any pain that has lasted for one day or longer?” Those answering positively were asked to identify the location(s) of this pain on a body map. Participants were then sent a saliva sampling kit, for 2 samples: approxi-
mally 1 hr after waking (AM) and 1 hr before going to bed (PM). In addition, a sub-group of respondents were invited into the laboratory and undertook a computerised version of the Stroop “Word-and-Colour” Test – a test known to induce mental stress among study participants. Salivary cortisol was assessed at baseline, and immediately post-Stroop.

Follow-up: new onset CWP was identified, by questionnaire, at 12 months.

Analysis: Poisson regression was used to examine the relationship between HPA axis function (salivary cortisol concentration, divided into tertiles for analysis) and new onset CWP. Thus, associations are expressed as risk ratios (RR) with 95% confidence intervals.

Results: Of 758 participants free of CWP, 461 (61%) participated at follow-up; 41 (9%) reported CWP. While, there was some evidence to suggest that higher AM cortisol was associated with a lower risk of CWP (RR, 1st tertile vs 3rd tertile: 0.6; 95% CI: 0.2–1.7), there was no association between PM cortisol levels and the risk of CWP (RR, 1st tertile vs 3rd tertile: 0.8; 0.3–2.1). 56 participants completed the Stroop Test, of whom 50 (89%) participated at follow-up. Those with the lowest stress response were more likely to report CWP than other individuals (RR, 1st tertile vs 3rd tertile of difference: 4.9; 0.6–39.5) and (RR, 1st tertile vs 3rd tertile of difference: 3.6; 0.4–29.6).

Discussion: This is the first study to examine HPA axis function and CWP onset in the general population. The study is small, and the findings should therefore be interpreted with care. However, the results replicate findings from previous studies in high-risk samples and provide new evidence that persons with the lowest stress response to mental stress are at highest risk of CWP.

Future work should examine the relationship in the context of—and possibly as a modifier of—environmental (psychosocial) stressors and, in particular, should determine the mechanisms underpinning this relationship.

Disclosure: G. T. Jones: None; G. D. Waite: None; M. Beasley: None; C. Gkazinnou: None; G. J. Macfarlane: None.

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Mortality in Fibromyalgia: An 8,186 Patient Study over 35 Years. Frederick Wolfe1, Afton L. Hassen1, Brian T. Walit4 and Kaleb D. Michaud1, 2National Data Bank for Rheumatic Diseases, Wichita, KS, 2University of Nebraska Med Ctr, Omaha, NE, 3University of Michigan Medical School, Ann Arbor, MI, 4Washington Hospital Center, Washington, DC

Purpose: The issue of mortality in fibromyalgia (FM) is important because, if increased, it represents the seriousness of FM. One population-based epidemiological study found that chronic widespread pain, effectively a criterion of the 1990 and 2010 ACR FM criteria, was associated with the risk of increased mortality, although that finding was not confirmed in another large population-based study. Reasons that mortality might be increased in fibromyalgia include substantial use of analgesics and anti-depressants, high levels of somatic symptoms, and high rates of depression. It seems possible that depression, socio-demographic characteristics or iatrogenesis could lead to increased mortality. The risk could also be increased if fibromyalgia is a representation of more extensive widespread pain or more severe symptoms. In this study we determined if mortality is increased among patients diagnosed with fibromyalgia.

Methods: We studied 8,186 fibromyalgia patients seen between 1974 and 2009 in 3 settings: all fibromyalgia patients in a clinical practice, patients participating in a longitudinal outcome study and patients invited to participate in the outcome study who refused participation. Internal controls included 12, 329 patients with osteoarthritis. Deaths were determined by multiple source communication, and all patients were also screened in the US National Death Index (NDI). We calculated standardized mortality ratios (SMR) based on age and sex stratified US population data, after adjustment for NDI non-response.

Results: There were 539 deaths, and the overall SMR was 0.90 (95% CI 0.61, 1.26). Among 1,665 clinic patients the SMR was 0.92 (95% CI 0.81, 1.05). Sensitivity analyses varying the rate of NDI non-identification did not alter the non-association. Adjusted for age and sex, the hazard ratio for fibromyalgia compared with osteoarthritis was 1.05 (95% CI 0.94, 1.17). The standardized mortality odds ratio compared with the US general population was increased for suicide, OR 3.31 (2.15, 5.11), for accidental deaths, 1.45 (1.02, 2.06), pneumonia 1.69 (1.12, 2.57) and septicemia 2.49 (1.61, 3.68), but not for malignancy 0.95 (0.76, 1.18).

Conclusion: Mortality does not appear to be increased in patients diagnosed with fibromyalgia, but the risk of death from suicide and accidents was increased. The data are consistent with an in submission Danish study that reported no increase in overall mortality or cancer, but an increase in suicides.

Disclosure: F. Wolfe: None; A. L. Hassen: None; B. T. Walit: None; K. D. Michaud: None.
Detection of Specific Markers Using Proteomics: Our Research on the Marker in Patients with Kawasaki Disease (KD). Rie Karasawa1, Miкиya Fujiyama1, Kazuhide Ohta2 and Kazuo Yudoh3.

**Purpose:** Anti-endothelial cell antibodies (AEC) are thought to be involved in pathophysiology of vasculitides. However, target molecules of AECAs have been poorly identified, which hampers understanding of roles of AECAs in detail. We tried to detect and identify target proteins of AECAs comprehensively by proteomics. Further, we investigated clinical importance of the identified autoantigens in patients with KD.

**Methods:** We separated proteins extracted from HUVEC and HeLa cells respectively by 2-dimensional electrophoresis and then transferred them onto membranes. Using serum samples from patients with vasculitis, we detected autoantigens that were positive only in the HUVEC samples but not in the HeLa cell samples. We next identified the detected proteins by peptide mass fingerprinting and characterized antigenicity by preparing recombinant autoantigens and antibodies to them.

**Results:** One of the identified 63 proteins was found peroxiredoxin2 (Prx2), an anti-oxidative enzyme. IgG antibodies to Prx2 were detected in 60% of the patients with KD, but not in healthy controls. IgM antibodies to Prx2 were detected in 10% of the KD patients, but also in 7% of healthy controls. IgA antibodies to Prx2 were not detected in both groups. Interestingly, IgG antibodies to Prx2 were detected in all the tested KD patients with coronary artery lesions. In contrast, IgM and IgA antibodies to Prx2 weren’t detected in them. IIIF staining revealed existence of Prx2 on the cell surface of HUVEC and WB using cell lysate proved expression of Prx2 not only in HUVEC but also in other endothelial cells (ECs), including human coronary artery endothelial cells (HCAEC). Anti-Prx2 antibodies also increased various inflammatory cytokine secretions significantly, in particular, IL-6 in HUVEC and G-CSF in HCAEC. IL-6 secretion of ECs stimulated with serum samples of patients with high anti-Prx2 titers was detected. WB using cell lysate and conditioned medium from ECs stimulated by H2O2 showed elevated expression levels of Prx2. Further, the addition of anti-Prx2 antibodies to the ECs resulted in increased concentration of H2O2 in the cell lysate. We measured Prx2-specific IgG titers on the pre- and posttreatment (within a week after therapy) in KD patients treated by IVIG. As a result, the titers on the posttreatment was higher than on pretreatment in almost all tested KD patients.

**Conclusions:** IgG antibodies to Prx2 would be a useful marker for KD. Anti-Prx2 antibodies may have a pathogenic role in KD via inflammatory cytokine production and inhibition of anti-oxidative activity of Prx2 by binding Prx2 on ECs.

Disclosure: R. Karasawa: None; M. Fujiyama: None; K. Ohta: None; K. Yudoh: None.

Specific Subgroup of New-Onset Systemic Juvenile Idiopathic Arthritis without Overt Macrophage Activation Syndrome Shares Similar Gene Expression Signature with a Distinct Subset of Familial Hemophagocytic Lymphohistiocytosis. Keith A. Sikora, Ndate Fall, Michael G. Barnes, Ianos Sumegi, Alexandra H. Filippovich and Alexei A. Grom.

**Background:** Systemic juvenile idiopathic arthritis (sJIA) is a rheumatologic condition characterized by spontaneous, evanescent rash, lymphadenopathy, seriositis, and arthritis. One of its complications is the macrophage activation syndrome (MAS), characterized by marked hyperferritinaemia, pancytopenia, fever, hepatosplenomegaly, and presence of hemophagocytosis within the bone marrow, which closely resembles the primary hystiociytic disorder familial hemophagocytic lymphohistiocytosis (fHLH). The aim of this study was to compare the gene expression signatures of patients with new-onset sJIA, but without overt MAS, to HLH gene expression signatures.

**Methods:** Peripheral blood mononuclear cells (PBMCs) from 14 untreated new-onset sJIA without overt MAS, 11 fHLH patients, and 27 healthy controls were isolated from whole blood. Purified RNA was labeled using the Nugen Ovation RNA amplification and labeling system, and gene expression profiles were generated using the Affymetrix HG-U133 Plus 2.0 GeneChip. The list of differentially expressed genes was generated using Student’s t-test, with Benjamini-corrected P < 0.05 considered significant. From the 11 fHLH patients had known mutations in either their perforin or MUNC13-4 genes.

**Results:** A list of genes differentially expressed in systemic JIA was used in the hierarchical clustering analysis of samples obtained from healthy controls and patients with sJIA and fHLH. This analysis revealed distinct gene expression patterns among the sJIA and HLH patients, separating them into subgroups. One specific subgroup of sJIA patients (n = 9) clustered together with a particular subgroup of HLH patients (n = 4). This sJIA subgroup was characterized by an increase in peripheral CD4+ cells, increased peripheral myeloid precursors, and a general upregulation of cell cycle genes. Highly increased serum ferritin was another characteristic feature of this group. The patients in this corresponding HLH subgroup were more likely to have a rapidly progressive course of HLH and an identifiable mutation in either their perforin or MUNC13-4 gene.

**Conclusions:** There exists a distinct subgroup of new-onset sJIA, but without overt MAS, that displays a gene expression pattern that is shared with a specific subgroup of rapidly progressive, relapsing, and mostly mutation positive HLH patients. This subgroup of sJIA is characterized by an increase in peripheral CD4+ cells, increased peripheral myeloid precursors, and a general upregulation of cell cycle genes, perhaps reflecting increased turnover of hematopoietic cells.

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A Genome-Wide Association Study for Juvenile Idiopathic Arthritis Identifies Chromosome Region 3q13 near the T Cell Receptor Co-Stimulatory Molecule CD80. Susan D. Thompson1, Miranda Marion10, Marc Sadman8, Paula S. Ramos11, Wendy Thompson1, Anne Hinks1, J. Peter Haas1, Sampath Pralhalad2, John F. Bohnsack3, Carol Wise4, Marilyn G. Punaro5, Carlos D. Rose3, Mary Ryan2, Monica Tsoras2, Michael Wagner2, Mehdi Keddache2, Timothy Howard2, Carl Langefeld2 and David N. Glass1.

**Objective:** Juvenile idiopathic arthritis (JIA) is a complex genetic trait. Like other autoimmune diseases, JIA has strong HLA associations and is often found in families with a history of other autoimmune diseases. Furthermore, many of the loci associated with JIA are shared across several autoimmune diseases. Here we report a large genome-wide association study of oligoarticular and polyarticular rheumatoid factor negative forms of JIA.

**Methods:** The Discovery Cohort consisted of 814 JIA cases, 658 local controls and 2400 out-of-study controls from the Non-Gain Schizophrenia Study who self-identified as Non-Hispanic, European ancestry. The Replication Cohort consisted of 1621 cases and 1630 controls representing five independent JIA case and control sample collections originating from the United Kingdom (CAPS and B-topar study group), Germany, Utah, Delaware or Texas. Additional out-of-study controls were available for the UK cohort (Wellcome Trust Case Control Consortium, n = 5984) and used in the replication analysis. For the Discovery Cohort, genotyping was done using the Affymetrix SNP Array 6.0 and tests for association were adjusted for potential confounding affects of population structure via covariates in logistic regression models. Analyses were repeated adjusting for key HLA associations. Ten SNPs representing five loci, which to our knowledge have not yet been reported in JIA, were selected based on statistical evidence and biological information and genotyped by Taqman or Sequenom chemistries in the Replication Cohort. Association testing and meta-analyses were performed.

**Results:** Testing for genome-wide association in the Discovery Cohort identified multiple loci outside the MHC region associated with JIA. Previously identified loci associated with JIA and overlapping with other autoimmune disease associations include PTPN22 (rs6679677, p = 1.98 × 10⁻⁵).
Conclusions: We provide strong evidence in both the Discovery Cohort and Replication Cohort for a novel autoimmune disease and JIA association with 3q13, a region containing the TCR co-stimulatory molecule CD80. Fine mapping and integration with gene expression data is underway to further define this locus.

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Gene Expression Profiling in Peripheral Blood Mononuclear Cells Predicts Disease Flares in Children with Polyarticular Juvenile Idiopathic Arthritis Who Have Achieved Clinical Remission on Medication. Nicholas Knowlton², Mark Barton Frank³, Nicholas E. Armstrong¹, Kaiyu Jiang¹, Yaminin Chen¹, Jeannette Osban² and James N. Jarvis¹. ¹Dept of Pediatrics, U of OK College of Medicine, ²Oklahoma Medical Research Foundation

Background: Children with polyarticular juvenile idiopathic arthritis (JIA) patients pursue variable clinical courses, even after disease control has been achieved. Developing biomarkers to identify which children can come off therapy and which children need continued or more aggressive therapy has been elusive.

Objective: To better understand the underlying biology of disease flares in polyarticular, RF-negative juvenile idiopathic arthritis (JIA), and to determine the feasibility of developing gene array-based prognostic biomarkers to guide therapy in this disease.

Methods: We performed gene expression profiling and in silico pathway analysis on peripheral blood mononuclear cells (PBMC) of 17 children with RF-negative polyarticular JIA at the time they achieved inactive disease (ID) status. Of these children, 8 subsequently experienced a disease flare within 11 months of achieving ID status, while the remaining 9 experienced sustained disease control over observation periods ranging from 18 months to 6 years. Computational analyses were undertaken in an attempt to distinguish the 2 groups.

Results: Gene expression profiling identified 103 genes that distinguished the Flare and No-flare groups. Gene expression profiling comparing children in ID/CRM who were fated to flare with those who were not (“baseline specimens”) showed distinct differences between the two groups. The group fated to flare was already distinguishable from the group that remained stable at the time of baseline sampling. One hundred forty-four genes were differentially expressed between the two groups, all of which were over-expressed in children fated to flare. In silico modeling demonstrated that the differentially expressed genes could be incorporated into 4 large, linked networks. These networks incorporated genes associated with MAP kinase signaling, type 1 interferon production, and genes regulating the cell cycle. Furthermore, the gene expression profile remained largely stable in each group over the 5–15 month period over which the patients were followed. That is, comparison of the “flare” group at the time they achieved ID/CRM with the same patients at the time of their flare revealed only a single gene whose expression differed from the baseline sample. Similarly, children who remained stable also demonstrated a stable gene expression profile. In addition, network analysis suggests a role hepatocyte nuclear factor 4a (HNF4a), a transcription factor not previously identified in leukocytes, in maintaining treatment response in JIA.

Conclusions: Although the number of patients studied here is small, this work demonstrates the feasibility of developing prognostic biomarkers in JIA. These findings also cast light on the nature of the inflammatory networks that sustain the disease process in polyarticular JIA even when the illness clinically appears to be inactive.

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Purpose: Identification of congenital heart block (CHB) in a fetus predicts with near certainty that the mother, who may have a rheumatic disease or be asymptomatic, will have autoantibodies to a 60kD Ro protein (Ro60). Injury is thought to be initiated by surface binding of maternal anti-Ro60 autoantibodies to apoptotic cardiocytes during physiological remodelling of the fetal heart. The low penetrance of disease suggests that a factor in the microenvironment of the fetal hearts which remain unaffected may inhibit binding of maternal anti-Ro60 autoantibodies. The plasma protein beta2-glycoprotein 1 (β2GPI) is a potential candidate since it binds to Ro60 on the surface of apoptotic cells and inhibits opsonization by anti-Ro60 autoantibodies. The current study evaluated the opsonization of fetal apoptotic cardiocytes by IgG from mothers of infants with CHB in the presence or absence of β2GPI and determined whether fetal levels of β2GPI correlate with CHB.

Methods and Results: To test the role of β2GPI as a protective factor in CHB, in vitro studies were conducted on human fetal apoptotic cardiocytes (induced by staurosporine or loss of anchorage). Flow cytometry analysis revealed dose-dependent binding of β2GPI to apoptotic cardiocytes. IgG from a mother of a child with CHB (CHB IgG), but not IgG from a healthy control, bound the apoptotic cardiocytes (mean fluorescence intensity, MFI 3,998 vs 462). In the presence of β2GPI, the binding of CHB IgG to apoptotic cardiocytes was significantly inhibited in a dose-dependent manner (range 20–64%). Enzyme linked immunosorbent assay (ELISA) was used to measure levels of β2GPI in the umbilical cord blood from unaffected (n=25) and CHB (n=28) anti-Ro exposed infants. β2GPI levels were lower in CHB children (mean units 234±17 compared to those unaffected (365±29 SEM), (p = 0.0004). Ventricular rates were positively correlated with levels of β2GPI (r = 0.52, p = 0.042). Among the cord blood samples, four twin pairs discordant for CHB, were assessed for β2GPI levels. In each pair, the twin with CHB had lower levels of β2GPI (169±12) compared to the healthy twin (283±20 however, this trend did not reach significance. β2GPI levels tended to be higher in those fetuses delivered by C-section but were not associated with maternal use of dexamethasone.
Children with a higher weight at birth had significantly higher levels of β2GPI (r = .51, p = 0.01) consistent with the observation that the neonates with CHB had significantly lower birth weights than those who were unaffected. Fetal β2GPI levels were not associated with gestational age at birth. β2GPI levels were not significantly associated with the requirement for a pacemaker.

Conclusion: Lower levels of fetal β2GPI are associated with CHB in anti-Ro60-positive mothers. β2GPI may protect the developing fetal heart from injury by binding to Ro60 on apoptotic cardiocytes and preventing opsonization by maternal anti-Ro60 autoantibodies. Factors such as infection, inflammation, or a genetic predisposition could reduce β2GPI levels in the fetus, thereby promoting conditions where the fetal heart is vulnerable to autoantibody-mediated tissue injury.

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Pathogenic Consequences of Mutations of NLRP12 Gene. A New Cold-Induced Autoinflammatory Disease. Silvia Borghini1, Sara Tassi1, Sabrina Chiesa2, Francesco Caroli3, Sonia Carta4, Roberta Caorsi5, Marco Di Duca6, Denise Lasigilié7, Alberto Martiní2, Isabella Ceccherini1, Anna Rubartelli2, and Marco Gattorno3. 1Institute for Cancer Research, Genoa, Italy; 2Laboratory of Molecular Genetics, G. Gaslini Institute, Genoa, Italy; 3Rheumatology Unit, G. Gaslini Institute, Genoa, Italy

**Purpose:** mutations of the NLRP12 gene have recently been described in patients affected with a new Autoinflammatory disease. NLRP12 belongs to the NLRPs family and is proposed to play a role in the activation of the inammosome and regulation of NF-kB activation is currently being under investigation. We report about the clinical features and pathogenic findings of 4 patients carrying a novel p.D294E missense mutation of the NLRP12 gene affecting the Walker B sequence of the protein crucial for ATP binding.

**Patients and Methods:** Four individuals, carrying the p.D294E NLRP12 mutation were analyzed. NF-kB activity was evaluated in NLRP12-mutated monocytes after 24 hour of TNF stimulation using TransAM NFkB p65 Kit. IL-1β secretion, production of ROS and activation of antioxidant systems in resting conditions and after PAMPs stimulation were also assessed. In vitro analysis of the NLRP12 mutation effect on NF-kB activity was performed after co-transfection of a luciferase-NF-kB promoter reporter construct with the mutant and wild type NLRP12 expression plasmids in HEK293 cells.

**Results:** the p.D294E mutation segregates in association with a particular sensitivity to cold exposure (especially arthralgia and myalgia), but not always with an inflammatory phenotype (urticarial rash or fever). The p.D294E mutated protein did maintain the same inhibitory activity shown by wt NLRP12. Unexpectedly, this was also observed when the already reported p.Arg284X nonsense mutation (Jéru et al., 2008) was analyzed in the same system. Consistently, NLRP12-mutated monocytes showed neither increased levels of p65 NF-kB activity nor higher amounts of IL-1β secreted. However, the kinetics of PAMP-induced IL-1β secretion was significantly accelerated, and a high production of ROS and an upregulation of antioxidant systems were demonstrated, in patients carrying NLRP12 mutations compared to healthy controls.

**Conclusions:** Even with a variable range of associated manifestations, the extreme sensitivity to cold exposure represents the main clinical hallmark of individual carrying the p.D294E mutation of the NALP12 gene. The regulation of NF-kB activity does not seem to be affected in NLRP12-mutated patients. Redox alterations and accelerated secretion of IL-1β may be responsible for the mild autoinflammatory phenotype observed.

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**ACR Concurrent Abstract Sessions**

**Rheumatoid Arthritis - Clinical Aspects: Preclinical RA and Early RA**

**Monday, November 8, 2010, 2:30 PM–4:00 PM**

658 Application of the New ACR/EULAR Classification Criteria for Rheumatoid Arthritis to At-Risk Populations May Identify RA Prior to Clinical Presentation. Jason R. Kolfenbach1, Leslie Derber2, Kevin D. Deane3, Jan Hughes-Austin4, Michael H. Weisman5, Jane Buckner6, Ted R. Mikuls7, James R. O’Dell8, Peter K. Gregersen9, Richard M. Keating10, Jill Norris11, and V. Michael Holers12. 1Oak Park, IL, 2Benaroya Research Institute at Virginia Mason, 3Cedars-Sinai Medical Center, Los Angeles, CA, 4Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, 5Division of Rheumatology, University of Colorado at Denver, Aurora, CO, 6N Shore Univ Hosp Rch Ctr, Manhasset, NY, 7Univ of Colorado School of Med, Aurora, CO, 8University of Nebraska Medical Center, Omaha, NE, 9University of Colorado at Denver, Aurora, CO, 10University of Colorado Denver, Aurora, CO, 11University of Nebraska Medical Center, Omaha, NE

**Objective:** The proposed ACR/EULAR classification criteria were developed in part to identify early RA. Applying the new criteria to at-risk populations prior to evaluation in the health care setting may identify a unique cohort in which to study the evolution of very early symptomatic RA. We have established prospective cohorts of subjects at potentially higher risk for RA based on genetic risk factors as part of the SERA study (Studies of the Epidemiology of RA). The purpose of the current analysis was to identify and characterize a cohort within these populations with ‘definite RA’ according to the newly proposed criteria.

**Methods:** We have established a cohort of first-degree relatives (FDRs) of probands with RA, FDRs without RA by the 1987 ACR criteria undergo a joint exam and have laboratory data obtained. Identical data is collected on a second at-risk DR4-enriched population containing parents of children with high risk HLA alleles and/or Type I diabetes. The proposed RA criteria were applied to subjects in these cohorts with swelling suggestive of synovitis in ≥ 1 joint on clinical exam after exclusion of findings attributed to alternative diagnoses (e.g. trauma, osteoarthritis). Data regarding joint distribution, duration of symptoms, antibody status and presence of elevated inflammatory markers where used to apply the new criteria. Descriptive statistics were calculated for the identified cases.

**Results:** 1790 subjects were available for analysis. 153 subjects (8.5%) had synovitis in ≥ 1 joint on clinical exam. 21 subjects (1.17%) had ‘definite RA’ according to the proposed algorithm. 17/21 (81%) subjects were female with a mean age of 48.9 years old; 621 subjects (28.6%) were positive for rheumatoid factor (RF), one (4.8%) was positive for anti-cyclic citrullinated peptide antibody, and 11 (52.4%) had elevated levels of CRP. Median swollen and tender joint counts were 3 and 11, respectively. The average total score in the 21 subjects was 6.76. The mean scores for joint involvement, serology, acute phase reactant and duration were 4.33, 0.9, 0.52 and 1.0, respectively (Table 1).

**Table 1. Relative contribution of Clinical & Serologic factors to the designation of ‘Definite RA’ by the newly proposed ACR/EULAR Classification Criteria for RA**

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| ACR Joint score | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| ACR Serology score | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Acute Phase Reactant Score | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Total score | 7 | 8 | 6 | 7 | 7 | 7 | 7 | 7 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 10 | 6 | 7 |
| Score ≥ 6 indicates ‘definite RA’ according to the proposed algorithm |
| Scores derived from a single visit in which the subject achieved a score ≥ 6. |
| Some subjects have additional visits 3 subjects with >1 visit with a score ≥ 6; first is depicted. |

**Conclusion:** Individuals with ‘definite RA’ according to the new criteria can be identified in these unique at-risk populations. A score ≥ 6 was driven primarily by joint involvement with the majority stemming from tender rather than swollen joints, a finding which may indicate an earlier phase of RA development than individuals presenting for clinical care. The identification of these subjects in a research rather than clinical setting may allow us to study an earlier phase of RA than possible in usual clinical practice. These subjects will be followed prospectively with multiple modalities including serial joint evaluations and biomarker assessments to evaluate the relationship between the new RA criteria and the longer-term evolution of RA.

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659 The Revised 2010 ACR/EULAR Diagnostic Criteria for Rheumatoid Arthritis Identify Many More Patients Who Are Eligible for Treatment and for Clinical Trials. Vivian P. Bykerk1, Gilles Boire2, Boulos Harauz2, Carol A. Hitchon2, Ed C. Keystone3, J. Carter Thorne4, Diane S. Ferland5, Janet E. Pope6 and CATCH Investigators7. 1Canada, Canada; 2CHUS - Sherbrooke University, Sherbrooke, QC, Canada, 3Montreal Montreos, Montréal, LaSalle, QC, Canada, 4Institut de Rhumatologie, Montréal, QC, Canada, 5Mt Sinai Hospital, University of Toronto, Toronto, ON, Canada, 6Southlake Regional Health Care, Newmarket, ON, Canada, 7St Joseph Health Care London, London, ON, Canada, 8University of Manitoba, Winnipeg, MB, Canada, 9University of Toronto, Toronto, ON, Canada

**Background:** The 2010 revised ACR/EULAR criteria for the classification of RA were developed to enable earlier diagnosis. These criteria identify patients with RA likely to have persistent and/or erosive inflammatory arthritis. The revised criteria have not been validated in North American
patients or shown to identify patients who would be eligible for clinical trials that recruit for patients with a DAS28 of ≥ 3.2.

Objectives: To determine what proportion of patients with recent onset early inflammatory arthritis (IA) of < 1 year duration the revised ACR/EULAR criteria newly identify as having rheumatoid arthritis. To determine if these newly identified patients would be eligible for clinical trials in early RA.

Methods: Baseline (BL) data collected from patients (n=1146) enrolled into the Canadian Early Arthritis Cohort (CATCH) study, a multi-centre observational prospective “real world” cohort of patients with early IA recruited since July 2007 were analysed for this study. Inclusion Criteria were: age >16, symptom duration 6–52 weeks of persistent synovitis, ≥2 effused joints or 1 swollen MCP/PIP + ≥1 of: RF, -anti-CCP, AM stiffness >45 minutes, response to NSAIDs, or a painful MTP squeeze test.

The new 2010 ACR/EULAR criteria were applied to determine what proportion of patients with EIA fulfill the new criteria at BL. Most patients were treatment naive or had only received a few weeks of DMARDs. Patients newly identified as having RA by the new criteria were evaluated for disease activity and the proportion of patients with a DAS28 ≥3.2 were considered as potentially being eligible treatment of for an early RA clinical trial. Patients previously used for criteria development were excluded from this analysis.

Results: BL characteristics were: mean age 52±16 years, 73% female, median symptom duration 5.5 months, mean DAS28 ESR 4.9±1.6; 27% were initially treated with oral glucocorticoids and 50% treated with MTX. 26% (226/874) already had erosions at BL. 57% of patients were eligible for this analysis. Of the remaining 648 patients, 68% (N=441) of patients met 1987 ACR criteria for RA at BL. 31% (N=201) of patients had undifferentiated IA (UIA). Of these 74% (N=478) had a score of ≥ 6 on the new criteria. Of the 68% of patients who met old criteria, 82% (N=362) met new criteria. Of the UIA patients remaining, 57% (N=115) could now be diagnosed with RA using the new criteria. These patients had a mean (DAS28=4.0). 79% of the formerly UIA patients now meeting the new criteria had a DAS28 ≥3.2.

Conclusions: Based on data from a Canadian cohort, revised ACR/EULAR 2010 criteria can identify a substantial number of new patients previously being designated as UIA as having RA. The majority of these patients would be eligible for clinical trials in ERA. Most of patient who fulfill the 1987 ACR criteria also fulfill the revised 2010 criteria.

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660 A Novel Diagnostic Marker for RA. Anti-MCV. Rong W. Zaboloki1, Annette Van der Helm-van Mil1, Tom Huizinga2 and Srinivas Rao2. 1 Cypress Biosciences Inc, San Diego, CA, 2 Cypress Biosciences Inc, Leiden University Medical Center, The Netherlands

Purpose: Early identification of undifferentiated arthritis (UA) patients at greatest risk for developing rheumatoid arthritis (RA) may facilitate better treatment. Rheumatoid factor (RF IgM) and antibodies against cyclic citrullinated peptide (anti-CCP) are widely used in diagnosing RA. It has been suggested that the enzyme-linked immunosorbent assay (ELISA) to detect mutated, citrullinated vimentin (anti-MCV) may have a different diagnostic spectrum versus anti-CCP. The purpose of the current study was to evaluate the diagnostic performance of combinations of these biomarkers in UA-RA patients.

Methods: Clinical and laboratory data were analyzed from a 470 patient subset of the previously described 570 patient Leiden Early Arthritic Clinic cohort (A. Van der Helm-van Mil, et al., 2007). These patients presented with UA, and a fraction (n=153) progressed to RA within 1 year, based on the fulfillment of the American College of Rheumatology (ACR) criteria. Anti-MCV, Anti-CCP2 and RF IgM tests were performed. A positive result for a combination was defined as resulting when all constituents were positive; a negative result of any constituent was defined as the combination negative. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), as well as their 95% confidence intervals (CI), were calculated for each individual biomarker as well as their combinations.

Results: Table 1 presented the diagnostic performance of the biomarkers and their combinations. Overall, anti-MCV demonstrated the highest sensitivity (65%) and NPV (82%), though at the cost of reduced PPV (60%). Combining Anti-CCP2 and Anti-MCV barely reduced sensitivity comparing to Anti-CCP2 alone (52% vs. 53%), and exhibited a favorable balance in sensitivity/specificity and in PPV/NPV. Further, the sensitivity diagram (at right) revealed that anti-CCP2 did not provide additional information (sensitivity=0%) in the context of both RF IgM and anti-MCV being positive. However, anti-MCV and RF IgM still respectively retained 10% and 5% sensitivity despite positivity of the other 2 assays.

Conclusions: Anti-MCV showed the highest sensitivity and NPV. Nearly all anti-CCP2 positive RA patients were also Anti-MCV positive, though not vice versa, reinforcing the notion that the diagnostic spectrum of the 2 assays is not identical. In the context of positive results for both anti-MCV and RF IgM, anti-CCP2 became redundant in term of sensitivity. In summary, incorporating anti-MCV as an adjunctive diagnostic tool to prognosticate future RA in patients who present with UA enhances sensitivity.

Disclosure: R. W. Zaboloki: Cypress Biosciences Inc, Inc., 3, A. Van der Helm van Mil: Leiden University Medical Center, Leiden, The Netherlands, 3, 9; T. Huizinga: EU & Dutch Arthritis Foundation, 2, 3, 5, 6, 8, Leiden University Medical Center, Leiden, The Netherlands, 2, 3, 5, 6, 8, Meteor Board, 2, 3, 5, 6, 8, Schering Plough, UCB, Bristol Myers Squibb, Biostat AG, Wyeth/Pfizer, Novartis; S. Rao: Cypress Biosciences, Inc., 1, 3, Huya Biosciences Inc, 5.

661 Smoking Is a Predictor of Very Early Presentation with Rheumatoid Arthritis. David W. Sharply1, Sarang Chitale2, Cristina Estrach3, Robert N. Thompson4, Robert J. Moots2 and Nicola J. Goodson2. 1Academic Rheumatology Department, Aintree University Hospitals, Liverpool, Merseyside, United Kingdom, 2Academic Rheumatology Department, Aintree University Hospitals, University of Liverpool

Background: Starting disease modifying anti-rheumatic drug (DMARD) treatment very soon after rheumatoid arthritis (RA) symptoms develop may significantly alter the disease course in early RA (eRA) (1). Early arthritis clinics (EAC) have been set up to allow for rapid assessment and initiation of DMARD therapy for eRA. Symptom duration varies in eRA patients with some presenting with very early RA (veRA), defined as a symptom duration ≤12 weeks. These veRA patients may differ from eRA patients with longer symptom duration at presentation.

Aim: The aim of this study is to identify predictors and disease characteristics associated with veRA presentation to an EAC.

Methods: New attendees at an EAC between May 2006 & March 2010 with eRA or probable eRA by ACR-EULAR 2010 criteria were identified. Symptom duration (weeks), smoking status, disease activity score (DAS-28), baseline radiograph & ultrasound findings, ESR, rheumatoid factor (RF) & anti-citrullinated protein antibody (ACPA) status, and other variables were recorded at presentation. Univariate, age & gender adjusted, & multivariate logistic regression were performed to identify predictors of very early presentation. Stratified analysis by ACPA status was also performed.

Results: 225 patients with eRA or probable eRA had a median age of 59 yrs [IQR 48, 70]; 140 (62%) female, 137 (70%) ACPA positive & 164 (73%) RF positive patients were identified. 189 (84%) had eRA by ACR-EULAR 2010 criteria & 89 (40%) presented within 12 weeks. Age & gender adjusted analyses revealed that, compared to later eRA patients, veRA patients had higher ESR titres, tender & swollen joint counts & DAS-28 scores, but were less likely to be ACPA positive at presentation. Multivariate modelling identified smoking, ACPA negative status and ESR as independent predictors.
of veRA presentation (Table 1). ACPA stratified analyses revealed that the association between smoking & veRA presentation was considerably stronger in ACPA negative patients (OR 15.55, 95% CI 1.61, 149.70) compared to those seen in ACPA positive patients (OR 2.23, 95% CI 1.11, 4.46).

Table 1. Multivariate model predicting veRA presentation

<table>
<thead>
<tr>
<th>Presentation with veRA</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td>Gender</td>
<td>1.12</td>
<td>0.62</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2.76</td>
<td>1.45</td>
</tr>
<tr>
<td>ACPA positive</td>
<td>0.32</td>
<td>0.17</td>
</tr>
<tr>
<td>ESR</td>
<td>1.02</td>
<td>1.01</td>
</tr>
</tbody>
</table>

Conclusions: Smoking is associated with very early presentation and this association appears to be influenced by ACPA status in eRA. Interestingly, veRA patients were less likely to be ACPA positive at baseline. This may represent very early capture of patients prior to the development of ACPA.

Those with veRA had more active disease but less joint damage on ultrasound investigation. These veRA patients may benefit from early DMARD therapy to prevent joint damage and treatment within the window of opportunity may alter their disease course. It is interesting to note that in established RA, smoking is associated with more severe radiological, disability and mortality outcomes. Early remission induction in veRA presenters who smoke could improve these long-term outcomes.


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Long-Term Remission in Daily Clinical Practice: Excellent 2 Year Results with Treatment To Target in Very Early Rheumatoid Arthritis, Results of the DREAM Remission Induction Cohort.

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Background: Remission is the primary target of treatment of rheumatoid arthritis (RA). Clinical trials have proven that systematic monitoring of disease activity and adjusting medication on the basis of the disease activity outcome is effective in reaching this goal. Therefore, in current guidelines and recommendations on RA it has been advocated to treat RA to target. However, aiming for remission is not yet implemented and data on inducing and achieving remission in daily clinical practice are limited. The objective of this study was to evaluate disease activity in very early RA patients in daily clinical practice after 2 years of applying a tight control treatment strategy.

Methods: Since January 2006, 534 newly diagnosed patients with early RA (clinical diagnosis of RA, symptom duration ≤ 1 year) were enrolled in the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort study. Treatment adjustments (4–8 weekly) were based on the DAS28, aiming at DAS28 < 2.6. The medication protocol consisted of initial MTX, addition of SSZ, exchange of SSZ by anti-TNF in case of insufficient response. Primary outcome was the disease activity according to the DAS28, EULAR response criteria and ACR criteria for clinical remission after 1 and 2 years. Additional outcomes included time to first remission and sustainability of remission.

Results: Baseline characteristics were as follows: mean (SD) age 57.7 (13.9) years, 62.8% female, 56.6% RF positive, 62.4% anti-CCP positive, median (IQR) symptom duration 15 (8–26) weeks, mean (SD) baseline DAS28 5.0 (1.1) and 82.8% of patients fulfilled the ACR classification criteria for RA. Of all patients, 1 year follow-up data was available in 392 patients and 2 year data in 210 patients. At 1 year (n=392), 55.1% of patients achieved DAS28 remission, 64.8% had a good EULAR response and 45.1% satisfied the ACR remission criteria (Table 1). At 2 years (n=210), 64.3% of patients achieved DAS28 remission, 75.7% had a good EULAR response and 54.4% satisfied the ACR remission criteria (Table 1). Median (IQR) time to first DAS28 remission was 22 (12–37) weeks. In more than 60% (127/210) of patients sustained DAS28 remission (> 6 months) was observed during the first 2 years of follow-up. The majority of patients achieved remission on conventional DMARDs (mono or combination therapy). Results were independent of the definition of RA (i.e. clinical diagnosis/ACR 1987 criteria) or presence of traditional prognostic factors for RA (i.e. RF/anti-CCP).

Table 1. Clinical outcomes after 1 and 2 years.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1 year (n = 392)</th>
<th>2 year (n = 210)</th>
</tr>
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<tbody>
<tr>
<td>DAS28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission (DAS28 &lt; 2.6)</td>
<td>216 (56.1)</td>
<td>135 (64.3)</td>
</tr>
<tr>
<td>Low (2.6 ≤ DAS28 ≤ 3.2)</td>
<td>62 (15.8)</td>
<td>37 (17.6)</td>
</tr>
<tr>
<td>Moderate (3.2 ≤ DAS28 ≤ 5.1)</td>
<td>103 (26.3)</td>
<td>32 (15.2)</td>
</tr>
<tr>
<td>High (DAS28 &gt; 5.1)</td>
<td>11 (2.8)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>EULAR response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>254 (64.8)</td>
<td>159 (75.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>102 (26.0)</td>
<td>35 (16.7)</td>
</tr>
<tr>
<td>None</td>
<td>36 (9.2)</td>
<td>16 (7.8)</td>
</tr>
<tr>
<td>ACR remission</td>
<td>143/317 (45.1)*</td>
<td>93/171 (54.4)*</td>
</tr>
</tbody>
</table>

Values are presented as number (%). *ACR remission could not be evaluated in all patients, due to missing values for morning stiffness.

Conclusion: This study shows that long-term remission is a realistic goal in very early RA patients in daily clinical practice. Implementation of a tight control treatment strategy results in rapid and high remission rates, regardless of the definition used. The management of very early RA patients in clinical care can go beyond the control of signs and symptoms, and should aim at remission.

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The Association of Joint Damage and Treatment Response with ACPA Status in Recent Onset RA.

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Objective: To compare clinical and radiological response to disease activity score (DAS) steered treatment in patients with recent onset RA who were positive or negative for anti-citrullinated protein antibodies (ACPA).

Methods: In the BeSt study, 508 recent onset RA patients were randomized to 4 treatment strategies, aimed at a DAS ≤ 2.4: sequential monotherapy, step-up combination therapy, initial combination therapy including prednisone and initial combination therapy including infliximab. Changes of damage progression > 5 (Sharpe/vd Heijde score (SHS)) in 1 year, and > 25 in 5 years, and rate of (drugfree) remission were compared for ACPA positive and ACPA negative patients, using logistic regression analysis. Functional ability over time, measured with the Health Assessment Questionnaire (HAQ), was compared using linear mixed models. The analyses were adjusted for gender, smoking habits and baseline age, DAS, and SHS.

Results: At baseline, ACPA positive patients (N=297) had more radiographic damage than ACPA negative patients (N=183): median SHS 4.0 (IQR 1.0–10.5) vs 1.5 (IQR 0–6.1), and a lower DAS (4.3 for the ACPA positive group, vs 4.6, p<0.001) and HAQ (1.3 vs 1.5, p=0.02). More ACPA positive patients were male (p=0.01) and more were smokers (p=0.01). DAS reduction was achieved similarly in ACPA positive and ACPA negative patients in all treatment groups (figure). After 1 year of follow-up, the Odds ratio (OR) of SHS progression > 5 was 3.27 (95% CI 1.68–6.35) for ACPA positive patients. After 5 years the OR of progression > 25 was 5.95 (95% CI 2.02–17.52). Over time, there were no significant differences in HAQ between ACPA positive and negative patients. Odds ratio of ever achieving remission was 1.09 (95% CI 0.63–1.88) for ACPA positive patients, and of achieving remission during at least 1 year 0.75 (95% CI 0.49–1.16). However, ACPA positive patients did have a lower chance of ever achieving drugfree remission (OR 0.46 (95% CI 0.28–0.72)) and a higher chance of restarting medication (OR 8.47 (95% CI 3.09–23.25)).
regression. This may suggest that, in ACPA positive patients, treatment irrespective of initial treatment and baseline characteristics. However, more ACPA positive patients had significant radiographic damage progression. This may suggest that, in ACPA positive patients, treatment decisions should be based on disease activity, but also on damage progression.

Disclosure: M. van den Broek: Centocor, Inc., 2, Dutch college of health insurances, 2, Schering-Plough; 2, N. B. Klarenbeek: None; M. L. Westedt: None; H. D. Boom: None; P. J. S. M. Kerstens: None; T. W. J. Huizinga: None; B. A. C. Dijkman: None; C. F. Allaart: None.

ACR Concurrent Abstract Sessions
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment - Imaging
Monday, November 8, 2010, 2:30 PM–4:00 PM

664 Methotrexate Is Not Disease Modifying in Psoriatic Arthritis: The MIPA Trial. Gabrielle H. Kingsley1, Ania Kowalczyk2, Helen Taylor3, Fowzia Ibrahim4, Jonathan C. Packham5, Neil J. McIlwraith6, Diarmuid M. Mulherin7, George D. Kita8, Kuntal Chakravarty9, Brian D. M. Tom10, Peter J. Maddison11 and David L. Scott12. 1Cannock Chase Hospital, Cannock, United Kingdom, 2Haywood Hospital, Stoke on Trent, UK, 3Kings College London, London, United Kingdom, 4Kings College London, UK, 5MRC Biostatistics Unit, University of Cambridge, UK, 6Queens Hospital, Romford, UK, 7Royal National Hospital for Rheumatic Diseases, Bath, UK, 8Russells Hall Hospital, Dudley, UK, 9Sport, Health and Exercise Science, University of Bangor, UK

Background: Methotrexate (MTX) is widely used as a disease modifying drug (DMARD) in psoriatic arthritis (PsA) without definitive supporting clinical trial evidence. We tested its effectiveness in the first large multicentre randomised controlled trial (RCT) of MTX in active PsA (MIPA).

Methods: A 6-month double-blind RCT compared oral MTX (15mg/week) with placebo in patients with active PsA. The primary outcome measure was the PsA Response Criteria (PsARC); other composite measures included ACR20 and DAS28. We analysed changes in individual measures including “disease modifying” (joint counts, HAQ, ESR and CRP) and “symptom modifying” (global assessments and pain) measures, skin and nail scores.

Results: 462 patients were screened and 221 recruited. 71/109 (65%) of those who received MTX and 77/112 (69%) of those who received placebo completed 6 months therapy. 19 patients (11 MTX, 8 placebo) withdrew for toxicity and 22 (8 MTX, 14 placebo) for inefficacy. No significant treatment effects were seen on PsARC, ACR20 and DAS28 at 3 or 6 months using intention to treat logistic regression analysis (including multiple imputations for missing data and adjustment for age and sex).

Conclusion: Not the chance of remission, but the chance of (persistent) drugfree remission was lower in ACPA positive patients compared to ACPA negative patients. Treatment response was similar in both groups, irrespective of initial treatment and baseline characteristics. However, more ACPA positive patients had significant radiographic damage progression. This may suggest that, in ACPA positive patients, treatment decisions should be based on disease activity, but also on damage progression.

Disclosure: M. van den Broek: Centocor, Inc., 2, Dutch college of health insurances, 2, Schering-Plough; 2, N. B. Klarenbeek: None; M. L. Westedt: None; H. D. Boom: None; P. J. S. M. Kerstens: None; T. W. J. Huizinga: None; B. A. C. Dijkman: None; C. F. Allaart: None.

665 Rates and Predictors of Radiographic Sacroiliitis Progression over Two Years in Patients with Axial Spondyloarthritis. Denis Poddubnyy1, Martin Rudwaleit2, Hildrun Habel2, Anja Weiss3, Elisabeth Märker-Hermann4, Henning Zeidler5, Jürgen Braun5 and Joachim Sieper6. 1Charité - Campus Benjamin Franklin, Berlin, Germany, 2Charite Campus Benjamin Franklin, Berlin, Germany, 3Deutsches Rheumaforschungszentrum, Berlin, Germany, 4Dr. Horst Schmidt Kliniken, Wiesbaden, Germany, 5Medizinische Hochschule, Hannover, Germany, 6Rheumazentrum Ruhrgebiet, Herne, Germany

Background: The current concept of axial spondyloarthritis (SpA) considers non-radiographic axial SpA and ankylosing spondylitis (AS) as two stages of one diseases suggesting progression of radiographic sacroiliitis over time. However, rates of radiographic sacroiliitis progression and predictors of such progression remain unclear until now. The objective of the study was to assess the rates of radiographic sacroiliitis progression and to explore possible progression predictors in a cohort of patients with axial SpA over a period of two years.

Methods: 210 patients with axial SpA (AS and non-radiographic axial SpA) from the German Spondyloarthritis Inception Cohort (GESPIC) have been selected for this analysis based on availability of radiographs at baseline and after 2 years of follow-up. Radiographs of pelvis at baseline were centrally digitized and the sacroiliac joints were scored independently according to the grading system of the modified New York criteria by 2 trained readers. The readers scored both time points simultaneously but were blinded for the time point and for all clinical data.

Results: In total, 115 patients (54.8%) fulfilled the modified New York criteria for AS in their radiographic part in opinion of both readers at baseline, while 95 patients (45.2%) were classified as non-radiographic axial SpA (nrSpA). After 2 years 11 patients (11.6%) from the group of nrSpA fulfilled the modified New York criteria for AS in the opinion of both readers.

Conclusion: Contrary to general opinion, MTX does not act as a DMARD in PsA but has only borderline “symptom modifying” properties. Its value in active PsA is questionable when there are other agents, such as leflunomide and TNF-inhibitors, which are true DMARDs. This has important implications for current national and international guidance for the treatment of PsA.

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Progression of sacroilitis over two years by at least one grade at one side in opinion of both readers was found in 26 patients (12.4%). Rate of progression was higher among patients with nrSpA (16 patients or 16.8%) as compared to AS (10 patients or 8.7%), although the difference was statistically non-significant (p = 0.074). At the same time, there was an improvement of sacroilitis by at least one grade in the opinion of both readers in 11 patients (5.2%): 6 with nrSpA (6.3%) and 5 with AS (4.3%). Therefore the true radiographic sacroilitis progression rate over two years could be estimated as 10.5% for patients with nrSpA and 4.4% for patients with AS.

The only strong positive predictor of radiographic sacroilitis progression was an elevated level of C-reactive protein at baseline (OR 2.61, 95% CI 1.02–6.6). Table. Odds ratios (ORs) for progression of radiographic sacroilitis by at least one grade over 2 years in patients with axial SpA (univariate analysis).

<table>
<thead>
<tr>
<th>Parameters at baseline</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male vs. female</td>
<td>0.47 (0.20–1.1)</td>
<td>0.080</td>
</tr>
<tr>
<td>HLA-B27, positive vs. negative</td>
<td>0.83 (0.32–2.3)</td>
<td>0.736</td>
</tr>
<tr>
<td>CRP, &gt;6 mg/l vs. ≤6 mg/l</td>
<td>2.61 (1.12–6.06)</td>
<td>0.026</td>
</tr>
<tr>
<td>ESR, &gt;20 mm/h vs. ≤20 mm/h</td>
<td>1.28 (0.54–3.06)</td>
<td>0.575</td>
</tr>
<tr>
<td>BASDAI, &gt;4 vs. ≤4 points NRS</td>
<td>1.00 (0.44–2.28)</td>
<td>0.997</td>
</tr>
<tr>
<td>Disease duration, &gt;5 years vs. ≤5 years</td>
<td>1.29 (0.55–3.02)</td>
<td>0.554</td>
</tr>
<tr>
<td>Definitive sacroilitis* at baseline</td>
<td>0.42 (0.18–0.95)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

* At least grade 2 unilaterally in the opinion of both readers

Conclusion: Progression of radiographic sacroilitis by one grade after 2 years occurred in 10.5% of the patients with nrSpA and 4.4% of the patients with AS. Elevated level of CRP was found to be a strong positive predictor of sacroilitis progression.

Disclosure: D. Poddubny: None; M. Rudwaleit: None; H. Habel: None; A. Weiss: None; E. Mörker-Hermann: None; H. Zeidler: None; J. Braun: None; J. Sieper: None.

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High Prevalence of Axial Spondyloarthritis in Patients with Familial Mediterranean Fever, and a Greater Allelic Frequency of M694V in Familial Mediterranean Fever Patients with Radiographic Sacroilitis. Servet Akar, Özgül Soyula, Feride Yuksel, Dilek Solmaz, Gercen Can, Merih Birlik, Mehmet Tunca, Fatos Oner and Nurullah Akkoc. 1Internal Medicine, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey, 2Rheumatology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

Background: Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of fever and serositis. Limited data suggest that the prevalence of sacroilitis, which is a hallmark of ankylosing spondylitis (AS), is increased in patients with FMF. Moreover in most recent studies we and other groups have found a significantly higher frequency of M694V in AS patients. Therefore in the present study we assessed the prevalence of axial spondyloarthritis (SpA) including AS, in patients with FMF. We also studied the prevalence of MEFV variants in FMF patients with and without radiographic sacroilitis.

Patients and Methods: The first 258 patients with FMF [130 female (%50,4), mean age 38.9 ± 12] who were invited to the outpatient clinic for another study were interviewed by using a structured questionnaire to capture patients with SpA. Presence of inflammatory back pain (IBP) was judged based on both Calin and Berlin criteria and the diagnosis of AS was based on the modified New York (mNY) criteria. Standard pelvic X-rays of the sacroiliac joints (SIJ) were performed in all patients. Patients with IBP were also assessed by magnetic resonance imaging (MRI) of SIJ and HLA B27 testing. MEFV variants of the patients were extracted from the patients medical charts.

Results: Two hundred FMF patients (108 female; 54%) patients (77,5%) reported to have current and/or past back pain. IBP according to Calin and Berlin criteria were present in 53 patients (26.5%) and 42 patients (21%), respectively. One patient had inflammatory bowel disease and one had psoriasis, and 56 (21.8%) had a positive family history for SpA. A total of 15 patients (5.8%) had radiographic sacroilitis (bilateral grade 2 or unilateral grade 3–4) and 14 of them fulfilled the mNY criteria for AS. Moreover bone marrow edema was detected by MRI of SIJ in 13 patients with IBP (5.0%). HLA-B27 positivity was found in only one of the 12 patients with sacroilitis on MRI and in none of the 14 patients with radiographic sacroilitis. Allele frequency of M694V in FMF patients with radiographic sacroilitis was significantly higher in comparison to those without sacroilitis (67.9% vs 43.7%; p = 0.017) with an OR of 2.7 (95% CI = 1.2 to 6.2).

Conclusion: Our results suggest that axial SpA in patients with FMF and SpA is more common than in the general population. Moreover, M694V may be playing a bigger role than HLA-B27 in susceptibility to AS in FMF patients.

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Evidence That New Focal Fat Lesions Follow Resolution of Spinal Inflammation in AS but Existing Lesions Are More Likely To Resolve with TNF Blocking Agents. Praveena Chiochwanwisawakit, Robert G. W. Lambert and Walter P. Maksymowych. 1Mahidol University, Bangkok, Thailand, 2University of Alberta, Edmonton, AB, Canada

Purpose: MRI of the spine in SpA frequently shows focal fat lesions in the spine on T1W scans, especially at vertebral corners (VC) and adjacent to the vertebral endplate. Its histopathological basis and pathophysiological implications remain unclear. Adipose tissue has been shown capable of expressing proinflammatory cytokines. It is assumed that VC Fat reflects post-inflammatory change but there have been no prospective studies that have actually tested this hypothesis. We aimed to test the hypothesis that an active vertebral corner inflammatory lesion (CIL) on baseline MRI is more likely to evolve into a *de novo* VC Fat lesion on T1W scans than a VC which demonstrates no inflammation on baseline MRI.

Method: MRI scans were performed at baseline and 2 years in 61 AS patients of whom 28 received TNF blocking agents in open label follow up of clinical trials while 33 received either TNF blocking agents (n = 16) or standard therapy (n = 17) in an observational cohort. We recorded VC fat lesions, defined as increased signal in bone marrow on T1W MRI and CIL, defined as increased signal on STIR MRI, at anterior and posterior VC on any central sagittal slice. Via televideoconference, reference images were developed in which VC fat lesions were assessed by consensus amongst an international MRI working group. VC Fat lesions present on baseline MRI and its persistence/resolution on follow up MRI. We also tested the effect of treatment on baseline VC Fat lesions. Proportions were compared by Fisher’s exact test.

Results: New VC Fat lesions developed significantly more frequently in those VC with 32/83 (38.6%) as compared to those without 69/2647 (2.6%) inflammation on baseline MRI in the anti-TNF group (p < 0.0001). This was less evident in the standard therapy group (1/14 (7.1%) vs 8/1161 (0.7%), p = NS). New VC Fat lesions developed significantly more frequently from CIL that resolved compared to VC with persistent or no CIL (n = 17) in an observational cohort. We recorded VC fat lesions, defined as increased signal in bone marrow on T1W MRI and CIL, defined as increased signal on STIR MRI, at anterior and posterior VC on any central sagittal slice. Via televideoconference, reference images were developed in which VC fat lesions and CIL were assigned by consensus amongst an international MRI working group. VC Fat lesions present on baseline MRI and its persistence/resolution on follow up MRI. We also tested the effect of treatment on baseline VC Fat lesions. Proportions were compared by Fisher’s exact test.

Results: New VC Fat lesions developed significantly more frequently in those with 32/83 (38.6%) as compared to those without 69/2647 (2.6%) inflammation on baseline MRI in the anti-TNF group (p < 0.0001). This was less evident in the standard therapy group (1/14 (7.1%) vs 8/1161 (0.7%), p = NS). New VC Fat lesions developed significantly more frequently from CIL that resolved compared to VC with persistent or no CIL (p < 0.0001). These differences were again less evident in the standard therapy group. VC Fat lesions present on baseline MRI resolved significantly more frequently after TNF blocker (47/247 (16.9%)) compared to standard treatment (5/94 (5.1%)) (p = 0.005).
5.

Maksymowych: anti-TNF.

Existing VC Fat lesions are also more likely to resolve with inflammation, especially after inflammation has resolved following institution.

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None;

Anna von der Recke:

None;

J. Buschmann:

None.

Background: Ankylosing spondylitis (AS) and diffuse idiopathic skeletal hyperostosis (DISH) have a similar pattern of new bone formation.

Objective: To compare the natural course of radiographic progression of AS-specific (syndesmophytes) and degenerative (spondylophytes) changes in AS and DISH.

Methods: All AS and DISH patients who had lateral radiographs of the cervical and the lumbar spine at least 12 time points within 6 years were included in this retrospective study. Radiographic progression was compared on the basis of the development of syndesmophytes and spondylophytes and by using the mSASSS. Images were scored by 3 blinded readers. The differentiation between syndesmo-phytes and spondylophytes was made as recently proposed. Baseline characteristics and follow-up rates of radiographic progression were compared by summary statistics. Covariance and logistic regression analysis were also performed for radiographic status at baseline (BL) and development of bone formation over time.

Results: A total of 146 AS (mean age 54.2±12.3y, symptom duration 23.6±11.2y, no biologics) and 141 DISH patients (n=141, mean age 60.3±7.7y, symptom duration 21.6±12.4y) were included. At BL, the mean number of syndesmophytes/patient was 5.7±5.5 in AS and 2.7±2.8 in DISH (p=0.001), while a trend for more spondylophytes was seen in DISH (1.4±1.8) vs. AS (1.0±1.4). In the covariance analysis of all patients adjusted for baseline status of radiographic damage, more new syndesmophytes/patient were seen in AS (2.0±2.7, 95%CI: 1.7–2.4) vs. DISH (0.5±0.9, 95% CI: 0.3–1.1), (p<0.001), while a trend for more spondylophytes/patient was seen in DISH (0.54±1.0, 95% CI: 0.37–0.70) vs. AS (0.46±1.10, 95% CI: 0.30–0.62).

Syndesmophytes at BL were predictive of new syndesmophytes at follow-up in AS but not in DISH, whereas spondylophytes at BL were predictive for new spondylophytes in DISH but not in AS: 2.4±2.7 vs. 1.1±2.7 new syndesmophytes/patient (p=0.001) were seen in AS patients with vs. without baseline syndesmophytes and 0.9±1.4 vs. 0.3±0.8 new spondylophytes/patient (p<0.001) were seen in DISH patients with vs. without baseline spondylophytes.

The mean mSASSS increased from 14.3±6.7 to 17.6±7.8 (mean change: 3.2±4.2 units) and from 20.5±14.4 to 24.6±15.9 units (mean change: 4.1±9.5 units) between baseline and follow-up in DISH and AS, respectively.

Conclusions: This study shows that a radiographic differentiation between AS and DISH is possible but syndesmophytes and spondylophytes do occur in both diseases, and in both diseases, radiographic damage at BL is predictive of further and faster progression. The finding of similar progression rates in AS and DISH is surprising.

Disclosure: X. Baraliakos: None; J. Listing: None; J. Buschmann: None; A. von der Recke: None; J. Braun: None.

### Table 1: Number (percentage) of new VC Fat lesions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Resolved CIL</th>
<th>Persistent CIL</th>
<th>NO CIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC Fat+ Anti-TNF</td>
<td>16 (20.8)</td>
<td>1 (5.0)</td>
<td>34 (1.3)</td>
</tr>
<tr>
<td>VC Fat- Anti-TNF</td>
<td>61 (79.2)</td>
<td>19 (95.0)</td>
<td>2578 (98.7)</td>
</tr>
<tr>
<td>VC Fat+ Standard</td>
<td>1 (11.1)</td>
<td>8 (9.7)</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td>VC Fat- Standard</td>
<td>8 (88.9)</td>
<td>5 (100)</td>
<td>1153 (99.3)</td>
</tr>
</tbody>
</table>

### Conclusion:

New VC Fat lesions occur more frequently at sites of prior inflammation, especially after inflammation has resolved following institution of anti-TNF. Existing VC Fat lesions are also more likely to resolve with anti-TNF.

### Method:

Axial SpA patients enrolled in a randomized controlled trial (1) were treated with ETA (n=40) vs. SSZ (n=36) over 48 weeks. All patients showed active inflammatory lesions (bone marrow edema) on wb-MRI in either the sacroiliac joints (SIJ) and/or the spine at baseline (BL). Wb-MRIs were performed at weeks 0, 24 and 48 and were scored for active inflammation and fatty infiltration in the four quadrants of each SIJ and the third vertebral units (VUs) of the spine. Scoring was performed by two radiologists, blinded for treatment arm and MRI time point. Generalized estimation equations were used to calculate confidence intervals by taking repeated measurements within individual patients into account.

### Results:

There was a very low rate of new fatty infiltration of about 1% (0.8% for SIJ quadrants and 1.7% for VUs) if there was no previous inflammation in the bone (see table). There was a good relationship between disappearance of inflammation and the appearance of fatty infiltration: if inflammation resolved fatty infiltration occurred in 17.3% (SIJ quadrants) and 19.1% (VUs). If inflammation did not resolve fatty infiltration occurred much less frequently: 8.4% (SIJ quadrants) and 5.8% (VUs) (p=0.0001 for SIJ and p=0.1 for VUs for the difference between resolved and persistent inflammation group, see table). Interestingly, new fatty infiltration occurred more frequently in the ETA group (26 VU sites and 33 SIJ sites) compared to SSZ (8 VU sites and 12 SIJ quadrant sites). This was in concordance with the significant increase of the mean fatty infiltration score in the ETA (mean fat infiltration score 1.86 at baseline vs. 2.56 at week 24 for the SIJ, and 3.88 vs. 4.60 for the spine) compared to the SSZ (mean fat infiltration score 1.73 at baseline vs. 1.76 at week 24 for the SIJ, and 3.34 vs. 3.51 for the spine, respectively) group (p=0.018 and p=0.006 for the differences).

### Conclusion:

These data indicate that there is a close interaction between inflammation, TNF-blockade and fatty infiltration of subchondral bone marrow. The higher amount of fatty infiltration in the ETA group is probably due to the effective suppression of active inflammation. The molecular mechanisms of these interactions have to be further investigated.

### Table 2: Development of fatty infiltration at week 48 according to development of active inflammation

<table>
<thead>
<tr>
<th>Location</th>
<th>Active inflammation</th>
<th>New fatty infiltration at week 48</th>
<th>% [95% confidence intervals]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine-vertebral units</td>
<td>No active inflammation at any time</td>
<td>13/1555</td>
<td>0.8% [0.4%–1.8%]</td>
</tr>
<tr>
<td></td>
<td>Active lesion at baseline and resolution at week 48</td>
<td>13/75</td>
<td>17.3% [8.5%–32.2%]</td>
</tr>
<tr>
<td></td>
<td>Persistent active inflammation</td>
<td>9/85</td>
<td>8.4% [3.8%–17.5%]</td>
</tr>
<tr>
<td>SIJ-Quadrants</td>
<td>No active inflammation at any time</td>
<td>4/241</td>
<td>1.7% [0.4%–7.5%]</td>
</tr>
<tr>
<td></td>
<td>Active lesion at baseline and resolution at week 48</td>
<td>29/152</td>
<td>19.1% [12.4%–28.1%]</td>
</tr>
<tr>
<td></td>
<td>Persistent active inflammation</td>
<td>12/207</td>
<td>5.8% [2.8%–11.3%]</td>
</tr>
</tbody>
</table>

(1) Song I.-H. et al. EULAR 2010, OP 0029

Growth Differentiation Factor-9 Induced by Insulin-Like Growth Factor Binding Protein-5 May Contribute to Fibrosis in Systemic Sclerosis

Yukie Yamaguchi and Carol A. Feghali-Bostwick. 1University of Pittsburgh, Pittsburgh, PA, 2University of Pittsburgh, Yokohama City University, Yokohama, Kanagawa, Japan

Background: We previously described elevated levels of insulin-like growth factor binding protein-5 (IGFBP-5) in fibrotic disorders such as systemic sclerosis (SSc). IGFBP-5 is a pro-fibrotic factor that induces production of extracellular matrix (ECM) components in vitro, in vivo in lung and skin, and ex vivo in human skin. Using microarray analysis of IGFBP-5-expressing fibroblasts, we identified growth differentiation factor-9 (GDF-9) as a downstream target of IGFBP-5. GDF-9 is a member of the TGF-β superfamily and was originally described as an oocyte-derived growth factor required for follicigenesis. We therefore sought to examine the role of GDF-9 in mediating the fibrotic effects of IGFBP-5.

Methods: Induction of GDF-9 by IGFBP-5 was evaluated in IGFBP-5-expressing fibroblasts in vitro and in human skin ex vivo. Co-localization of IGFBP-5 and GDF-9 was assessed by immunocyto-staining and immunoprecipitation in primary human lung fibroblasts. The signaling pathway mediating IGFBP-5 induction of GDF-9 was identified using chemical inhibitors. Furthermore, induction of ECM by GDF-9 was assessed by western blot, and GDF-9 expression was examined in SSc lung tissues using immunohistochemistry. Finally, the effect of overexpressing GDF-9 in human skin in an ex vivo organ culture model was assessed.

Results: GDF-9 was induced in IGFBP-5 expressing fibroblasts, fibroblasts stimulated with recombinant IGFBP-5, and in human skin injected with an IGFBP-5-expressing adenovirus. GDF-9 co-localized with and bound to IGFBP-5. Induction of GDF-9 was reduced in the presence of P38 inhibitor or a BMPRII neutralizing antibody, but not following TGF-β neutralization, suggesting that GDF-9 production was mediated via P38-dependent, BMPRII-dependent, and TGF-β-independent mechanisms. Recombinant GDF-9 triggered Smad3 phosphorylation and promoted ECM production and deposition. Interestingly, levels of GDF-9 were very high in lung tissues of patients with SSc. Finally, overexpression of GDF-9 in human skin ex vivo significantly increased dermal thickness.

Conclusion: GDF-9 is induced by IGFBP-5 and contributes to the development of organ fibrosis via p38 activation. Furthermore, GDF-9’s pro-fibrotic effects are mediated, at least in part, via BMPRII.

Disclosure: Y. Yamaguchi: None; C. A. Feghali-Bostwick: None.

The Notch Pathway Controls Fibroblast Activation and Tissue Fibrosis in Systemic Sclerosis

Clara Dees, Pawel Zerr, Michal Tomicki, Christian Beyer, Angelika Horn, Alfiya Akhmetshina, Katrin Palumbo, Nicole Reich, Jochen Zwierina, Mark P. Mattson, Oliver Distler, Georg Schett and Joerg H. W. Distler. 1Center of Experimental Rheumatology and Zurich Center of Integrative Human Physiology, University Hospital Zurich, Switzerland, 2Department of Internal Medicine 3, University Erlangen-Nuremberg, Germany, 3Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, Baltimore, MD

Purpose: Tissue fibrosis caused by pathological activation of fibroblasts with increased synthesis of extracellular matrix components is a major hallmark of systemic sclerosis (SSc) and other fibrotic diseases. Pathologic activation of Notch signaling has been implicated in the pathogenesis of human malignancies. The aims of the present study were to investigate whether Notch contributes to the uncontrolled activation of fibroblasts and tissue fibrosis in SSc and to evaluate the therapeutic potential of Notch inhibition for the treatment of fibrosis.

Methods: Activation of the Notch pathway was analyzed by immunohistochemistry in skin sections of SSc patients and healthy volunteers. Dermal fibroblasts were stimulated with recombinant human Jagged-1 (Jag-1) Fc Chimera and incubated with the γ-secretase inhibitor DAPT. Fibroblast activation was determined by staining for α-smooth muscle actin (αSMA) and stress fibers. Inhibition of Notch signaling for the treatment of fibrosis was evaluated in the mouse model of bleomycin-induced dermal fibrosis and in tight-skin-1 (tsk-1) mice.

Results: Notch signaling is activated in skin of SSc patients as analyzed by immunohistochemistry. Moreover, this activation persisted in cultured fibroblasts in vitro with significantly elevated levels of activated notch-1, its ligand Jag-1 and its target gene hes-1. Activation of the Notch pathway by stimulation with recombinant Jag-1 potently induced differentiation of resting fibroblasts into myofibroblasts with increased levels of αSMA and formation of stress fibers. In addition, Jag-1 increased collagen synthesis to 294 ± 37 % (p < 0.05) which was prevented upon pre-incubation with DAPT. Consistent with the selective activation of Notch signaling in SSc fibroblasts, incubation of dermal fibroblasts with DAPT decreased the basal collagen synthesis only in SSc but not in healthy dermal fibroblasts. In the mouse model of bleomycin-induced dermal fibrosis, treatment with DAPT completely prevented dermal thickening upon bleomycin-challenge (p < 0.05). Inhibition of γ-secretase prevented also hypodermal thickening in tsk-1 mice with a mean reduction of hypodermal thickness by 75 ± 4 % (p < 0.05). Overexpression of a Notch-1 antisense construct confirmed the results obtained with the
Distler: Jimenez: Disclosure: C. Dees:

chemical inhibitor. Bleomycin-induced dermal thickening was reduced by 85 ± 19 % (p < 0.05) and hypoderma thickness in tsk-1 mice decreased by 51 ± 11 % (p < 0.05). Of note, treatment with DAPT not only prevented fibrosis but induced significant regression of dermal thickening below pre-treatment levels in a modified model of established bleomycin-induced skin fibrosis.

Conclusion: We demonstrate that the Notch pathway is activated in fibrotic skin, induces myofibroblast differentiation and stimulates the release of collagen. Inhibition of Notch signaling exerts potent anti-fibrotic effects in preclinical models suggesting that targeting Notch signaling might be a promising molecular approach for anti-fibrotic therapy.

Disclosure: C. Dees: None; P. Zerr: None; M. Toncić: None; C. Beyer: None; A. Horn: None; A. Akhmetshina: None; K. Palumbo: None; N. Reich: None; J. Zwerina: None; M. P. Mattson: None; O. Distler: None; G. Schett: None; J. H. W. Distler: None.

Myofibroblast Specific Gene Expression Signature in Systemic Sclerosis, More Than TGF-beta Induced Activation. Giuseppina Abignano1, Heidi Hermes, Justin Gillespie, Sergio A. Jimenez, Paul Emery and Francesco Del Galdo1. Leeds, 2University of Leeds

The key cellular elements in the pathogenesis of tissue fibrosis are myofibroblasts. It is widely accepted that the number of myofibroblasts is increased in SSc and it correlates with the severity of tissue fibrosis. The mechanisms underlying their increased number and their heterogeneity in SSc are unknown. The heterogeneity in their frequency may explain the incon sistency of some in vitro studies published on SSc fibroblast biology, and may mirror the clinical heterogeneity of SSc patients both in natural history and severity of skin fibrosis. The purpose of this study was to unravel the specific transcriptome of myofibroblasts derived from SSc skin biopsies.

Methods: 4 patients with diffuse rapidly progressive SSc, within 18 months from skin involvement and before any immunosuppression, were enrolled in the study. Skin biopsy on forearm was performed and the fibroblasts subcultured for three passages. 250 aceton fixed alpha-SMA positive cells were isolated by laser capture microdissection (LCM) for mRNA analysis by Affymetrix Gene array and qRT-PCR validation. Pathway analysis was conducted according to David-NIH software. Immunofluorescence (IF) followed by confocal laser scanning microscopy (CLSM) was conducted as well. Normal dermal fibroblasts were utilized to evaluate the effects of TGF-beta stimulation both at mRNA and protein level.

Results: qRT-PCR for a-SMA showed in average 3.7 fold increased expression in a-SMA in the LCM captured cells. Microarray analysis identified 269 genes upregulated more than 2 fold in the myofibroblasts. Of these, 30 were clearly reducible to probiotic activation, including a-SMA, Collagens I, VI and XI, Fibronectin, several Integrin genes, FGFR7, CD36, IGF and Rho; 16 were ribosomal genes; 14 were mitochondrial genes involved in oxidative phosphorylation, including COX1,2, 3 and 6 ND1 to 6, CYT-b and F-type ATP-ase; 28 genes were involved in cell to cell adhesion including RAB13, B2-microgrobiulin, cathepsin, HSPs, calnexin, and calreticulin. The remaining genes were not classifiable in any specific functional pathway and comprised tropomyosin, ricticulinib, caldesmon 1, and 6 members of Neuroblastome Breakpoint Family (NBPF). IF studies followed by CLSM confirmed the expression, never shown before, of NBPF in dermal fibroblasts. Functional studies on normal dermal fibroblasts displayed a specific expression profile for pro-collagen-I, caveolin-1, beta-catenin and phospho-RB whereas SMAD3, SMAD1, SMAD5, and NF-kB did not differ between alpha-SMA positive or negative cells.

Conclusions: Myofibroblast secreteme displayed, besides predictable genes involved in the increased ECM production and TGF-beta pathway activation, genes involved in several pathways not known to be specific of myofibroblasts or inducible by TGF-beta. The specific expression of these genes may reflect either a specific metabolic status or a specific differentiation lineage of myofibroblasts.

Disclosure: G. Abignano: None; H. Hermes: None; J. Gillespie: None; S. A. Jimenez: None; P. Emery: None; F. Del Galdo: None.

Perturbed VEGF Signalling within the Pulmonary Vasculature of a TGFβ Dependent Mouse Model of Systemic Sclerosis. Emma C. Derrett-Smith1, Audrey Dooley2, Reshma Baliga3, Adrian Hobbs4, Raymond MacAllister2, David Abraham1 and Christopher P. Denton. 1Centre for Rheumatology and Connective Tissue Diseases, Royal Free Campus, UCL Medical School, London, 2Royal Free Hospital, London, United Kingdom, 3University College London, London, United Kingdom

Purpose: Vascular complications of systemic sclerosis (SSc) are a major cause of mortality and morbidity. A role for altered VEGF signaling in PAH-SSc is supported by data that correlate circulating VEGF with mPAP at diagnosis. There is also a trend for VEGF levels to fall after initiation of PAH-specific therapy. High circulating VEGF levels may be a marker of repair in response to vascular injury. We have therefore examined VEGF signaling in a TGFβ-dependent mouse model of SSc with evidence of a constitutive pulmonary vasculopathy.

Methods: The transgenic mouse strain TβRII/hifib expresses a kinase-deficient type II TGFβ receptor driven by a fibroblast-specific promoter leading to balanced ligand-dependent upregulation of TGFβ signalling. Pulmonary vasculopathy was confirmed by histological assessment of vessel architecture, isolated organ bath and in vivo haemodynamic studies performed on adult male transgenic and littermate wildtype animals (n=8 in each group). Biochemical analysis of the VEGF and endothelin axes were performed assessing RNA by quantitative PCR and protein by Western blotting using cultured aortic and pulmonary artery smooth muscle cells, and by immunostaining of tissue sections. Results were compared to the same cells cultured under hypoxic conditions.

Results: Within the pulmonary arterial circulation, transgenic vessel wall thickness was increased, particularly in smaller vessels (30–60μm diameter) due to hypertrophy of the smooth muscle layer (mean wildtype vessel thickness:circumference ratio 0.66±0.02, mean transgenic 0.88±0.04, p<0.05). Pulmonary arterial ring responses to direct and receptor-mediated contractile stimuli were reduced in the transgenic animals (in response to endothelin contraction at 10−5M wildtype 1.10±0.02, transgenic 0.62±0.12, p<0.05) and right ventricular pressures were elevated in transgenic animals (wildtype mean 29mmHg±4, transgenic mean 37mmHg±3). Explanted transgenic vascular smooth muscle cells showed upregulation of TGFβ responsive genes including Vegf and Vegfr1 which were further upregulated in the pulmonary arterial circulation (PASMC) when compared to aortic smooth muscle cells (AoSMC) from the same animals.
The IL13/IL4Ra/CCL2 Pathway Drives Sclerodermatous Graft Versus Host Disease in Mice and Correlates with Disease Activity in Scleroderma Patients. Antonios O. Aliprantis1, Matthew Greenblatt2, Jennifer Sargent3, Giuseppina Farina4, Kelly Tsang5, Robert A. Lafaytis1, Michael Whitfield2 and Laurie Glimcher2. 1Boston University School of Medicine, 2Department of Genetics, Dartmouth Medical School, 3Department of Immunology and Infectious Diseases, Harvard School of Public Health, 4Department of Medicine, Division of Rheumatology, Allergy and Immunology, Brigham and Women’s Hospital and Harvard Medical School and Department of Immunology and Infectious Diseases, Harvard School of Public Health, 5Rheumatology Section, Boston University School of Medicine.

Background: Scleroderma (SSc) is an irreversible autoimmune disease characterized by tissue fibrosis. Agents to treat SSc remain elusive since mechanisms underlying the initiation and propagation of fibrosis are not well understood. We have shown that the gene expression profile of murine sclerodermatous graft-versus-host disease (scGVHD) approximates an “inflammatory” subset of human SSc patients and that both diseases display activation of the IL13 cytokine pathway. Here, the function of the IL13 pathway and downstream CCL2 expression is defined in the mouse model and SSc patients.

Methods: ScGVHD was induced by injection of splenocytes from allogeneic B10.D2 mice into MHC-matched BALB/c Rag2−/−, BALB/c Rag2−/− or BALB/c Rag2−/− IL4Ra−/− hosts. Control hosts received syngeneic BALB/c splenocytes. Recipient mice were scored biweekly for development of clinical scGVHD. At 6 weeks, a blinded SSc expert scored back skin histopathology. Explant cultures and experiments on FACS sorted cells isolated from back skin were performed 2 or 3 weeks after cell transfer. Human SSc skin RNA was purified from a cohort of patients with a mean disease duration of 24 months. ELISA or quantitative RT-PCR was used to detect gene expression. Centocor, Inc provided previously published blocking antibodies to CCL2 and CCL12.

Results: Compared to syngeneic controls, explant cultures of back skin from scGVHD mice displayed robust IL13 production confirming expression of this cytokine at the major site of pathology. Consistent with this, Rag2−/− IL13−/− hosts were partially protected from the development of sc GVHD. Partial protection suggested redundant expression of IL13 by both host and graft sources. Accordingly, both host macrophage and graft T-cell populations were found to produce IL13 in lesional skin. In contrast to Rag2−/− IL13−/− hosts, those lacking the ability to respond to IL13 (Rag2−/− IL4Ra−/−) were nearly completely protected from scGVHD. Protection was associated with increased production of the anti-inflammatory cytokine IL-10 by graft T-cells isolated from Rag2−/− IL4Ra−/− hosts. Comparative expression profiling of Rag2−/− and Rag2−/− IL4Ra−/− scGVHD mice also revealed that the latter displayed reduced CCL2 expression in whole skin, as well as in purified macrophage and CD45- stromal cell populations. Parallel exploration of additional datasets, including IL13 stimulated human dermal fibroblasts and IL13 transgenic mice, also suggested CCL2 as a key target of IL13 pathway activity. Confirming the functional significance of this finding, co-treatment with blocking antibodies to CCL2 and its murine homolog CCL12 prevented scGVHD. Lastly, we show that expression of receptor subunits for IL13 signaling (IL13RA1 and IL4RA) and CCL2 are significantly increased in the skin of SSc patients and correlate with modified Rodnan skin scores, a clinical measure of cutaneous disease.

Conclusions: These data illuminate that the IL13/IL4Ra/CCL2 axis is important to SSc pathogenesis. Inhibition of this pathway may be a viable therapeutic option for SSc patients exhibiting the inflammatory gene signature.

Disclosure: A. O. Aliprantis: None; M. Greenblatt: None; J. Sargent: None; G. Farina: None; K. Tsang: None; R. A. Lafaytis: None; M. Whitfield: Celdara Medical LLC; 9. L. Glimcher: Bristol-Myers Squibb, 9, Merck Pharmaceuticals, 2.
Methods: MNGC phenotype was examined by immunohistochemistry in serial paraffin sections of WG lung tissue (N=12) using antibodies recognizing the osteoclast (OC)-lineage markers CD68, cathepsin K and tartrate-resistant-acid-phosphatase (TRAP). To examine whether WG patients had an increased propensity toward MNGC formation over healthy control subjects, peripheral blood mononuclear cells (PBMC) obtained from 11 patients (5 with limited and 6 with systemic disease) and 7 healthy controls were cultured in 96-well plates in the presence of RANKL and M-CSF to induce MNGC formation. After 9 days in culture, MNGC morphology and TRAP expression were examined. OC-like giant cells were defined as TRAP (+) cells containing 3 or more nuclei. Mean MNGC values were compared between groups using the Mann-Whitney U test or Student’s t-test where appropriate. P-values of < 0.05 were considered statistically significant.

Results: WG lung tissue granuloma contained numerous MNGCs. All tissue-infiltrating MNGCs expressed CD68, indicative of monocytic lineage, and exhibited robust TRAP and cathepsin K staining, a phenotype thought to be unique to bone-resident osteoclasts. After co-incubation with the osteoclastogenic cytokines RANKL and M-CSF, patients with WG formed significantly more MNGCs at Day 9 than healthy controls (109 +/- 112 MNGC/well vs. 18 +/- 16 MNGC/well, p=0.03). Patients with systemic disease produced significantly more MNGC than both controls (167 +/- 114 MNGC/well vs. 18 +/- 16 MNGC/well, p=0.01) and those with a limited disease phenotype (167 +/- 114 MNGC/well vs. 39 +/- 62 MNGC/well, p=0.03). No significant difference in MNGC formation was noted between patients with limited WG and controls (p=0.87).

Conclusion: We demonstrate for the first time that MNGCs in Wegener’s granulomatosa in the lung have osteoclast-like features. We further show that WG patients have a higher propensity to form OC-like MNGC from the peripheral blood than do healthy controls, a feature that might be more pronounced in patients with a systemic disease phenotype. Inclusion of the pathways leading to the enhanced formation and migration of these cells to target tissues in WG might provide a novel therapeutic opportunity in this disease.

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Protocolised Versus Non-Protocolised Rituximab Treatment for Refractory ANCA-Associated Vasculitis. Rachel B. Jones1, Rona Smith2, Mary-Jane Guerry3, Simona Laurino2, Fausta Catapano2, Afzal Chaudhry2 and David R. W. Jayne1. 1Addenbrooke’s Hospital, Cambridge, United Kingdom, 2Center of Experimental Rheumatology, University Hospital Zurich, Switzerland, 3Dept. of Anatomy II: Experimental Morphology, University Medical Center Hamburg, Hamburg, Germany.

Rituximab is effective new therapy for refractory ANCA-associated vasculitis. However, the majority of patients relapse after rituximab, needing further treatment courses. Relapses occur from six months onwards and are prevention, allows immunosuppression withdrawal and appears safe in refractory ANCA-associated vasculitis. Results: A single centre cohort study comparing six monthly, protocol patients. Infections occurred in 10/72 (31%) protocol patients and 6/34 (26%) non-protocol patients. 34 received non-protocolised rituximab; either 1g x 2 or 375mg/m² x 4 only repeated if relapse occurred. Overall 75% patients had Wegener’s granulomatosis. At first rituximab median disease duration was 55 months: prior cyclophosphamide exposure was 14g. Rituximab indication was relapsing disease in 82% of protocol and 83% of non-protocol patients; the remainder had grumbling disease whilst receiving continuous high dose corticosteroids or immunosuppression. Median follow-up was 31 (4-56) months, protocol patients versus 22 (6-84) months, non-protocol patients. Response to rituximab occurred in 70/72 (97%) protocol patients (93% full remission, 4% partial), and 33/47 (70%) non-protocol patients (82% full remission, 15% partial). In protocol patients only 4/72 (6%) were still receiving immunosuppression at 6 months and by 24 months 26% had withdrawn from prednisolone (4.75mg/day median). At 2 years relapse had occurred in 16/72 (22%) protocol patients versus 24/34 (71%) non-protocol patients and by the end of follow-up 21/72 (29%) protocol patients, 26/34 (76%) non-protocol patients (p<0.01). Serious infections occurred in 10/72 (31%) protocol patients and 6/34 (26%) non-protocol patients.

Six monthly protocolised rituximab re-treatment is effective for relapse prevention, allows immunosuppression withdrawal and appears safe in refractory ANCA-associated vasculitis.

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Xenografted Nasal Mucosa from Wegener’s Granulomatosis Patients Induces Destruction of Human Cartilage in Immunodeficient Mice. Nina Keesel1, Dorothee Köhler2, Martin Launder1, Konstanze Holt-Urlich3, Astrid Jung1, Michel Neidhart4, Steffen Gay5, Renate E. Gay1, Elena Csomok6, Wolfgang L. Gross7, Udo Schumacher4 and Sebastian Ulbrich3.

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Xenografted nasal mucosa from Wegener’s Granulomatosis (WG) is a destructive chronic granulomatous inflammation of the respiratory tract whose pathogenetic mechanisms remain enigmatic.

Aims: The aim was to establish a xenograft model of nasal cartilage destruction in WG, to analyze the mechanisms of tissue damage and to evaluate the effect of systemic steroid treatment upon the inflammatory process.

Methods: Nasal mucosal biopsies from active and destructive WG (n=10) and active sinusitis patients were subcutaneously co-implanted in collagen sponges with healthy human nasal cartilage as aggregates (overall 36 WG vs. 48 controls), into 25 (WG) and 24 (controls) immunodeficient pp/rag2 -/- mice. Three mice with WG transplants were treated with systemic steroids. Transplants were removed after 21 days and examined histologically. In addition, nasal fibroblasts isolated from tissue specimens from WG patients (n=8) and healthy controls were cultured and cells proliferation and apoptosis were quantified. Furthermore, mRNA and protein levels of MMP’s and cytokines were evaluated at baseline and after stimulation with TNF-alpha and IL-1-beta.

Results: All untreated WG aggregates showed areas of human fibroblasts invading the human cartilage 21 days after transplantation, whereas cartilage destruction was only marginal in control samples. The destructed nasal cartilage in WG samples was replaced by proliferating human fibroblasts. Systemic steroid treatment suppressed this tissue destruction completely. The human origin of the cells was confirmed by anti-human vimentin and antihuman monoclonal antibody staining. Transplantation of xenografted tissues (fibroblasts, T- and B- lymphocytes, follicular dendritic cells (FDC), monocytes) remained almost identical to the tissue at the time of sampling as demonstrated by immunohistochemistry. An up-regulated production of MMP 1, 3 and 13 was found in areas of tissue destruction. Stimulation of fibroblasts in cell culture with TNF-alpha and IL-1 beta resulted in a significant up-regulation of MMPs 1, 3, 13. While proliferation of isolated fibroblasts was comparable between WG and controls, WG samples showed a significant delay of apoptosis.

Discussion: These findings show for the first time that nasal tissue destruction in WG results from local mucosal inflammation and strongly relates to the local activation of fibroblasts and locally residing inflammatory cells. As in WG patients, systemic steroid treatment of the mice impaired cartilage destruction. The delay of apoptosis may explain the invasive character of granulomatous tissue. Because of its similarity with the clinical situation, this model offers new possibilities to study novel treatments in WG in a clinically relevant xenograft model.

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1Long Island Lung Center, 2Mayo Clinic, Rochester, MN, 3Mayo Clinic...
Rationale: B-cell depletion with Rituximab (RTX) and glucocorticoids has been used successfully to induce sustained remission in patients with severe refractory ANCA-associated vasculitis (AAV). The need for repeated treatments as well as the efficacy and safety of repeated and prolonged B-cell depletion for long-term remission maintenance is less clear.

Objectives: To evaluate the efficacy and safety of rituximab for remission induction and long-term maintenance in patients with chronically relapsing AAV.

Methods: Single-center observational study of all patients with AAV treated with RTX between January 2000 and May 2010. Four weekly infusions at 375 mg/m² were used for remission induction and maintenance. More recently, 2 weekly infusions of 1000 mg were used for remission maintenance in some patients. Patients were identified from a cohort of 637 patients with AAV followed at our institution. Participants in the RAVE trial were excluded from this analysis. Treatment response, indications for retreatment, remission duration, relapse frequency and type of clinical relapse were evaluated. In addition to clinical relapse, duration of peripheral blood B cell depletion, ANCA levels, infusion-related adverse events, and infections were abstracted from electronic medical records. Disease activity was measured using the BVAS/WG scale. Data are expressed as median (interquartile range, IQR) and percentages.

Results: 108 patients with refractory AAV received glucocorticoids and at least one course of RTX therapy for remission induction; all achieved remission as measured by a BVAS/WG = 0. Fifty three patients (median age 46, IQR 28–61; 53% women) received subsequent courses of RTX for relapses or to maintain remission. All but one patient were PR3/ANCA positive. Among these, 53 patients received a median of 4 (IQR 3–5) courses of RTX (a total of 200 courses of four weekly infusions at 375 mg/m², and 10 courses of two weekly infusions of 1000 mg). All patients had depletion of B cells and the median time to return of B cells was 7 months (IQR 6–11 months). All observed relapses occurred after reconstitution of B cells and were accompanied or preceded by an increase in ANCA levels except in one patient. A total of 72 (34%) courses of RTX were given due to relapse (achieving remission in all individuals) and 138 (66%) courses were given preemptively due to either B cell reconstitution or following the increase of both B cells and ANCA levels. Infusion related adverse events occurred in 7 patients and none precluded completion of treatment. During the period of B cell depletion, 8 infectious complications were observed (5 upper respiratory tract infections, 2 pneumonia, 1 small wound, and 1 skin infection; only one patient with pneumonia required hospitalization).

Conclusion: RTX is effective and safe for induction and maintenance of remission in patients with relapsing AAV. Prolonged B cell depletion seems to be associated with a low risk of infections. Timing of retreatment can be individualized based on B cell counts and ANCA levels in these patients and the use of this treatment modality for long-term remission maintenance merits further formal investigation.

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Unpredictability of Intermittent Knee OA Pain – Impact on Pain, Function and Mood

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Purpose: In people with painful knee osteoarthritis (OA), focus groups identified the unpredictability of the pain as a key determinant of the pain impact. This study evaluated the effects of unpredictable knee pain (without warning) and pain after a trigger on the pain experience, physical functioning and mood in people with knee OA. We hypothesized that unpredictable knee pain would be associated with greater pain, worse physical functioning and mood in people with knee OA. We hypothesized that unpredictable knee pain would be associated with greater pain, worse physical functioning and more depressed mood than would predictable knee pain.

Methods: In a cohort with hip and knee OA, participants completed the OARSI-OMERACT Intermittent and Constant Osteoarthritis Pain (ICOP) measure of knee OA pain; the measure of depressed mood (CES-D). For each symptomatic knee, those with intermittent knee pain were asked how often their pain occurs ‘without warning’ (unpredictable pain) or ‘after a specific trigger’, e.g. an activity (predictable pain) (0, never, to 4, very often). For those without hip complaints, the proportions with each type of intermittent pain were calculated (at least sometimes versus never/rarely). The relationships between type of intermittent pain and ICOAP and WOMAC scores were evaluated using linear regression. For each type of intermittent pain, we examined the relationship between the number of knees affected (0, 1 or 2) and ICOAP and WOMAC scores using Wilcoxon Rank Sum tests. We examined the relationship between each type of intermittent pain and depression using S284
only with ICOAP intermittent scores (p<0.0001). Controlling for age, sex and arthritis severity, unpredictable knee pain, but not knee pain after a trigger, was independently associated with higher scores for depressed mood (p=0.005).

Conclusions: Both unpredictable pain and pain following a trigger occur commonly in people with chronic symptomatic knee OA. Compared with pain following a trigger, unpredictable knee pain is associated with greater pain and functional disability, and more depressed mood. Studies are needed to identify potentially modifiable risk factors for unpredictable knee OA pain in order to develop and test interventions to relieve this complaint.

Disclosure: G. A. Hawker: None; M. R. French: None; J. G. Elkins: None; A. M. Davis: None.

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Low positive affect above and beyond high depressive symptoms is linked to incident frailty among older adults. The impact positive affect has on functional outcomes is not known. Cross sectional studies have the potential flaw that good functional outcomes may make people happy, making cause and effect impossible to disentangle. We propose a longitudinal study to examine whether low positive affect predicted incident disability among adults at risk of developing disabilities.

Methods: Baseline and 30-month longitudinal data from the Multicenter Osteoarthritis (MOST) Study, a prospective cohort study of progressive and incident symptomatic knee osteoarthritis, were used for these analyses. A three-category variable representing “high positive affect”, “low positive affect” and “high depressive symptoms (depressed)” was computed from the Center for Epidemiological Study-Depression Scale (CES-D). Respondents who scored less than 16 on the CES-D and who scored “most of the time” on 4 positive affect questions of the CES-D were categorized as high positive affect; whereas, those reporting anything less than most of the time on the 4 items were classified as low positive affect. Respondents whose overall CES-D score was 16 or greater were classified as depressed. Disability was ascertained using the Late Life Disability Instrument-Instrumental Limitation subscale (LLDI-IL). The LLDI-IL was dichotomized into no/mild disability (no disability) and moderate/severe disability (disability) based on previously established cutoffs. Age, sex, education, race, body mass index (BMI), knee pain (max score of right or left knee visual analog scale), and gait speed (m/sec) were taken from baseline data and were used as covariates. Among persons with no disability at baseline, we examined the associations between baseline positive affect and depression and the development of disability at 30-follow-up using logistic regression.

Results: 2054 subjects had no disability at baseline. The mean age of the sample was 63 years. 58% were female and 89% were white. 1381 (67%) had high positive affect; 531 (26%) had low positive affect; 141 (7%) were depressed at baseline. 260 (13%) developed disability at 30-months. Subjects who reported low positive affect and those who were depressed were more likely to report disability at 30-months compared to persons with high positive affect after adjusting for covariates. As expected, high depressive symptoms was also associated with incident disability. (Table 1)

Discussion: Compared with high positive, low positive affect increased people’s risk of developing disability over a 30-month time period, even above and beyond the risk associated with depressive symptoms. Further research is needed to elicit the role positive psychological factors play in disablement.

Table 1. Unadjusted and adjusted odds ratio of low positive affect and “depressed” status compared to high positive affect.

<table>
<thead>
<tr>
<th>Event/Subjects</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Positive Affect</td>
<td>1.0 (1.0)</td>
<td>1.0 (1.0)</td>
</tr>
<tr>
<td>Low Positive Affect</td>
<td>1.5 (1.2–2.1)</td>
<td>1.5 (1.1–2.1)</td>
</tr>
<tr>
<td>Depressed (High Depressive Symptoms)</td>
<td>2.7 (1.7–4.1)</td>
<td>2.7 (1.7–4.1)</td>
</tr>
</tbody>
</table>

Disclosure: J. J. Keyser: None; L. Fredman: None; B. Zhang: None; D. K. White: None; J. C. Torner: None; C. E. Lewis: None; I. Tolstykh: None; D. T. Felson: None.

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Knee osteoarthritis (OA) and falls are common in older adults and limit mobility. A few studies have linked knee OA and risk of falls. Recent research, however, suggests that some factors increased risk for indoor falls while decreased risk for outdoor falls; thus, grouping falls together may mask the true effect of a particular risk factor. Also, older men and women may differ in factors related to falls such as gait, balance, and physical activity that may modify the association between knee OA and risk of falls. To date, no study has examined the relation of knee OA with the risk of indoor vs. outdoor falls and explored whether such association differs by sex.

Methods: This analysis included 764 participants from the MOBILIZE Boston Study, a population-based cohort of elderly men and women. Knee OA was assessed at baseline using the ACR criteria. Falls data were prospectively collected using monthly calendars, with phone follow-up assessment of location of falls, and were adjudicated. Fall rate was calculated separately for indoor and outdoor falls (falls/follow-up year). We used negative binomial regression to estimate the effect of knee OA on rate of indoor and outdoor falls separately, adjusting for age, sex, BMI, medications, number of comorbidities, and history of falls. We repeated the analyses for men and women separately, and tested whether the effect of knee OA on outdoor and on indoor falls was modified by sex by adding an interaction term (i.e., knee OA*sex) in the model.

Results: Of 486 women and 278 men (mean age: 78 years, mean BMI: 27.3), 25% had ACR-defined clinical knee OA. Over an average of 2.2 years of follow-up, 60% of participants had at least 1 fall. Rates of outdoor falls were 49 and 34 per 100 person-years for participants with and without knee OA, respectively. The corresponding indoor falls rates were 53 and 39 per 100 person-years. Compared with those without knee OA, the adjusted rate ratio (RR) for outdoor falls among participants with knee OA was 1.35 (95% CI: 1.04–1.77); the corresponding RR for indoor falls was 1.21 (95% CI: 0.94–1.57). However, the effect of knee OA on risk of indoor and outdoor falls was modified by sex. In women, knee OA was strongly associated with an increased risk of outdoor falls; no such effect was observed in men (p-value for interaction = 0.04). Although the interaction term was not statistically significant for indoor falls, the association of knee OA with the risk of indoor falls was stronger in men, albeit at borderline significance, than that in women (Table).

Table. The Association between Knee Osteoarthritis and Rate of Indoor and Outdoor Falls in Men and Women

<table>
<thead>
<tr>
<th></th>
<th>Knee OA Rate of Falls (per 100 P-Y)</th>
<th>No Knee OA Rate of Falls (per 100 P-Y)</th>
<th>RR (95% CI)</th>
<th>P-value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outdoor Falls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>47</td>
<td>45</td>
<td>0.91 (0.60, 1.38)</td>
<td>0.04</td>
</tr>
<tr>
<td>Women</td>
<td>50</td>
<td>27</td>
<td>1.70 (1.21, 2.40)</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Indoor Falls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>60</td>
<td>35</td>
<td>1.58 (0.99, 2.32)</td>
<td>0.22</td>
</tr>
<tr>
<td>Women</td>
<td>49</td>
<td>41</td>
<td>1.11 (0.82, 1.50)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

1Person-Years. 2Adjusted for age, BMI, fall-inducing medications (anti depressants, anti-psychotics, anti-hypertensives, and sedatives), no. of co-morbidities (high blood pressure, stroke, heart disease, diabetes, ulcer/stomach disease, kidney disease, anemia, cancer/skin cancer, rheumatoid arthritis), and history of falls.

Conclusions: Knee OA was associated with an increased risk of outdoor falls, and such an association was limited to women. Knee OA also appeared to be more strongly associated with indoor falls in men. Future studies should examine specific mechanisms such as balance, gait speed, and physical activity that may explain why knee OA on the risk of indoor vs. indoor fall are different in women from that in men.

Disclosure: U.-S. D. T. Nguyen: None; M. T. Hannan: None; R. H. Shmerling: None; D. P. Kiel: Amgen Inc, 2, 5, Eli Lilly and Company, 8, GlaxoSmithKline, 5, 8, Hologic, Inc., 2, 5, Merck Pharmaceuticals, 2, 5, 8, Novartis Pharmaceuticals Corporation, 2, 5, 8, Pfizer Inc, 2, 5, Philips Lifeline, 5, Proctor and Gamble, 5, S. G. Leveille: None; C. A. Oatis: None; L. Quach: None; Y. Zhang: None.

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Monday, November 8

Purpose: Knee pain, a common complaint in older adults, limits function and mobility and is a major reason for knee replacement among those with knee osteoarthritis (OA). Obesity is a strong risk factor for knee pain and knee OA. Given the recent epidemic of obesity in the U.S., the prevalence of knee pain is projected to rise. We examined the secular trend of knee pain and knee OA prevalence and determined whether any increase in prevalence is accounted by changes in body mass index (BMI).

Methods: Data were from the Framingham OA Study (FOA) and NHANES, a nationwide population based study. Knee pain was assessed in the FOA at three exams roughly 10 years apart, in subject groups that varied from exam to exam but which were all population based, using a questionnaire that asked about pain in or around the knee lasting at least 1 month in the past 12 months. Knee pain data were also collected in the NHANES I, II, III in addition to three later surveys. In NHANES, subjects were asked about pain in or around the knee on most days for at least 1 month or 6 weeks. Starting in 1999, NHANES also specified knee pain in the past 12 months. Weight bearing anteroposterior x-rays were obtained in the FOA to define radiographic knee OA (ROA)—Kellgren Lawrence grade ≥ 2, and knees with both ROA and knee pain were considered as having symptomatic OA (SxOA). We estimated race- and sex-specific prevalence for each outcome by 5-year age groups, and standardized to the sex-specific, age-appropriate, 2000-census US White population distribution. We estimated prevalence ratios (PR) and 95% confidence intervals (CI) adjusting for age (years) and BMI (Kg/M²) using Poisson regression.

Results: Included in the analyses were 3,306 participants from FOA (57% women, mean age ± SD: 70.2 ± 7.1 years) and 10,383 from NHANES (51% women, mean age ± SD: 66.6 ± 4.3). The age-adjusted prevalence of knee pain in the FOA almost tripled in a 20-year period in women, and more than tripled in men (Figure 1a). The age-adjusted prevalence of knee pain more than doubled in NHANES from 1974–1994 among White people, and continued to increase from 1999 to 2004 (Figures 1b). Similar results were found in a smaller sample of African Americans in NHANES. In FOA, there were no substantial changes in the prevalence of ROA over the period studied: 31.7%, 30.3%, and 29.0% in men; 32.7%, 34.6%, and 32.9% in women. The age-adjusted prevalence of SxOA did increase substantially over time: 31.7%, 30.3%, and 29.0% in men; 32.7%, 34.6%, and 32.9% in women. BMI adjustment explained about 25% of the increase in prevalence ratios (95% CI) adjusting for age (years) and BMI (Kg/M²) using Poisson regression.

Table. Temporal Trend of knee Pain and Knee Osteoarthritis in the Framingham Osteoarthritis Study and NHANES

<table>
<thead>
<tr>
<th>Time 2 vs. 1</th>
<th>Time 3 vs. 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR (95% CI)</td>
<td>PR (95% CI)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td><strong>Females</strong></td>
</tr>
<tr>
<td>Adjusted for Age</td>
<td>Adjusted for Age</td>
</tr>
<tr>
<td>1.48 (0.92, 2.34)</td>
<td>1.79 (0.91, 1.61)</td>
</tr>
<tr>
<td>Adjusted for BMI</td>
<td>Adjusted for BMI</td>
</tr>
<tr>
<td>1.37 (1.03, 1.81)</td>
<td>1.21 (0.96, 1.56)</td>
</tr>
<tr>
<td>Adjusted for Age, BMI</td>
<td>Adjusted for Age, BMI</td>
</tr>
<tr>
<td>1.34 (0.83, 2.14)</td>
<td>1.09 (0.81, 1.49)</td>
</tr>
<tr>
<td>1.48 (0.82, 2.68)</td>
<td>1.00 (0.76, 1.34)</td>
</tr>
</tbody>
</table>

Conclusions: Independent of age, the prevalence of knee pain has increased markedly over the last 20 years with a commensurate increase in SxOA but no evident increase in x-ray OA. While obesity has become more prevalent, it accounted for only part of this increase.

Disclosure: U.-S. D. T. Nguyen: None; Y. Zhang: None; J. Niu: None; B. Zhang: None; D. T. Felson: None.

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Community Mobility Barriers Predict the Development of 30-Month Disability: The MOST Study, Julie J. Keysor, Bin Zhang, James C. Torner, Cara E. Lewis, Irina Tolstykh and David T. Felson

Methods: Data from the Multicenter Osteoarthritis (MOST) Study, a cohort study of persons with or at high risk of developing symptomatic knee OA, and the MOST-Knee Pain and Disability (MOST-KPAD), a MOST sub-cohort study of older adults with functional limitations were used. Community mobility barriers (BAR) (e.g., uneven sidewalks or other walking areas, parks and walking areas that are easy to get to and easy to use, places to sit and rest) and transportation facilitators (FAC) (e.g., public transportation close to home, public transportation with a range of options for people with disabilities, handicap parking, and car available) were ascertained at baseline using the Home and Community Environment scale. Disability was ascertained at baseline and 30-months using the Late Life Disability Instrument-Instrumental Limitation Subscale and was dichotomized into no/mild disability and moderate/severe disability (disability) based on previously established cut-points. Among persons with no/mild disability at baseline, we examined the associations between baseline BAR and FAC dichotomized scores and development of disability at follow-up using logistic regression and adjusting for age, sex, race, education, body mass index, pain, walking speed, and site.

Results: Among 302 subjects who had baseline scores of no/mild disability and 30-month follow-up disability data, 50 (17%) developed disability at follow-up. The mean age of the sample at baseline was 70.3 (SD=3.9) years. 69% were women; 94% were white; 67% completed at least some college education. Overall the sample had mild pain (mean=2.8, SD=2.0, range 0–9) and functional limitations (gait speed: mean=1.2m/sec, SD=0.2, range 0.6–1.6). Subjects who reported high BAR at baseline were twice as likely to develop moderate/severe disability at 30-month follow-up compared to persons who reported low community barriers after adjusting for covariates. Report of high FAC was modestly protective of incident disability though this did not reach statistical significance. (Table 1)
When 1st Is Worst: Musculoskeletal Conditions Maintain 15 Year Reign as the Most Common Cause of Disability in US Adults. Kristina Theis4, Jennifer M. Hootman3, Charles G. Helmick2 and Matthew Brault1. 1Bureau of the Census, 2CDC, Atlanta, GA, 3Centers for Disease Control, Kennesaw, GA, 4Centers for Disease Control and Prevention

Background: As the population ages and arthritis and related disability become more prevalent, the documented rheumatology workforce shortage and need to expand evidence-based public health interventions will be even more important. We describe the prevalence, causes of, and trends in disability among US adults.

Methods: The Survey of Income and Program Participation (SIPP) is a longitudinal panel survey fielded by the US Census Bureau representing the civilian, non-institutionalized US population. Panel members undergo in-person interviews at 4-month intervals for a period of 2.5–4 years. In 1991/1992 (T1), 1996 (T2), and, most-recently, 2005 (T3) a cross-sectional disability topic module was administered to panel adults to identify the prevalence and causes of self-reported disability (difficulty with ≥1 specified functional activities, activities of daily living, instrumental activities of daily living, selected impairments, use of an assistive aid, or limitation in ability to work around the house or at a job or business (1996 and 2005 only)). Analyses weighted to population controls and incorporating sampling weights produced estimates of disability prevalence and cause, from each disability module.

Results: The number of US adults reporting disability has increased from 42 million (T1) to 44.1 (T2) to 47.5 million (T3). Overall, the most common causes of disability at all 3 time-points were arthritis/rheumatism, back or spine problems, and heart trouble. Women report twice the prevalence of disability due to arthritis/rheumatism (26.9% T1; 22% T2; 24% T3) compared with men (13.7% T1; 11% T2; 11.5% T3) making it the most common cause of disability among women. Although women and men have similar prevalence of disability due to back/spine problems at all time points (15.3% T1; 16.6% T2; 16.3% T3 vs. 16.0% T1; 16.8% T2; 16.9% T3), back/spine problems are the most common cause of disability among men and the 2nd most common cause of disability among women. The number and percent of adults reporting disability due to musculoskeletal conditions (MSK) (arthritis/rheumatism and back or spine problems) has risen consistently from T1 to T3, while heart trouble, the next most common cause of disability, has decreased in absolute number and % prevalence. In fact, six of the 10 most common causes of disability have either declined or remained level from T1 to T3, while MSK have increased.

Conclusion: Medical and public health providers must prepare for greater demands on the healthcare and public health systems with the aging population, including training more providers in the diagnosis and management of MSK and increasing reach of evidence-based programs that address modifiable lifestyle characteristics (e.g., physical inactivity and obesity) that contribute to disability, particularly among those with MSK.

Table 1. Odds of Developing Moderate/Severe Disability Over 30-Months by Features of the Community Environment

<table>
<thead>
<tr>
<th>Community Mobility Barriers (BAR)</th>
<th>Number of Subjects (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low BAR</td>
<td>27/219 (12)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>High BAR</td>
<td>23/83 (28)</td>
<td>2.7 (1.5–5.1)</td>
<td>2.4 (1.2, 4.6)</td>
</tr>
<tr>
<td>Transportation Facilitators (FAC)</td>
<td>Low FAC</td>
<td>23/112 (21)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>High FAC</td>
<td>27/190 (14)</td>
<td>0.6 (0.3–1.2)</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, race, education, body mass, index, pain, walking speed, and site

Disclosure: J. J. Keysor: None; B. Zhang: None; J. C. Torner: None; C. E. Lewis: None; L. Tolstykh: None; D. T. Felson: None.

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ARHP Concurrent Abstract Sessions

Physical Activity: Just “Move It”

Monday, November 8, 2010, 2:30 PM-4:00 PM

Does Physical Activity Dose Predict Physical and Mental Health-Related Quality of Life in People with Arthritis? Dina L. Jones, Ruoxin Zhang, Melissa Himes and Jennifer L. Eicher. Morgantown, WV

Background: Little is known about the relationship between health-related quality of life (HRQOL) and physical activity (PA) dose in people with arthritis (PWA). A prior survey indicated that PWA who met national PA recommendations had fewer unhealthy days per month due to physical or mental health. To further explore this relationship, we analyzed baseline data in PWA in an exercise intervention to determine if HRQOL improved over increasing increments of PA dose.

Methods: Sedentary adults with self-reported physician-diagnosed arthritis were enrolled in a 12-week, community-based, exercise intervention using the EnhanceFitness® program. Baseline data were collected on demographics, comorbidities, arthritis symptoms, performance-based physical function (Senior Fitness Test), body mass index (BMI), self-efficacy, outcome expectations, self-reported PA, and HRQOL. The CHAMPS Activities Questionnaire for Older Adults assessed the typical weekly frequency and duration of participation in 41 leisure/daily activities. Dose was the number of hours spent per week in moderate- or vigorous-intensity leisure activity: 1) inactive (0 mins), 2) insufficiently active (1–149 mins), and 3) meeting recommendations (≥ 150 mins). The SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were used to measure HRQOL. Two stepwise multiple linear regression procedures, with dose forced into each model, were performed to determine if dose predicted the PCS or MCS after adjusting for other covariates.

Results: The study included 173 participants (83% female) with a mean age of 69 ± 10.4 years. Univariate predictors of the PCS included dose (p < 0.01) and comorbidities (r = 0.36), pain (r = -0.38), stiffness (r = -0.47), fatigue (r = -0.33), BMI (r = -0.36), number of chair stands in 30 secs (r = 0.43), number of seconds to walk 8 feet (r = -0.37), number of steps marched in 2 mins (r = 0.36), self-efficacy (r = 0.38), outcome expectations (r = 0.35), and arthritis limitations (all p < 0.001). The best set of predictors in the PCS model were dose (β = 2.7–2.9, p = 0.1), stiffness (β = -0.4, p = 0.03), chair stands (β = -0.7, p = 0.03), BMI (β = -0.24, p = 0.01); pain (β = -0.33, p = 0.02), and number of steps (β = 0.08, p = 0.04) (R² = 0.47). Univariate predictors of the MCS included dose (p = 0.04); employment (p = 0.001); outcome expectations (r = 0.19, p = 0.02); and age (r = 0.36), pain (r = -0.39), stiffness (r = -0.23), fatigue (r = -0.42), comorbidities (r = -0.42), and self-efficacy (r = 0.34) (all p < 0.001). The best set of predictors in the MCS model were dose (β = 2.3–2.6, p = 0.25), comorbidities (β = -0.26, p = 0.01), age (β = -0.38, p < 0.001), and fatigue (β = -1.37, p < 0.001) (R² = 0.36).

Conclusion: Although PA dose predicted mental and physical HRQOL when considered alone, the relationship did not remain after adjusting for other factors. After controlling for dose, physical HRQOL was better in PWA with less pain and stiffness, a lower BMI, and better performance on physical
function tests. Mental HRQOL was better in PWA with fewer comorbid conditions, lower fatigue, and older age, after adjusting for dose. Future research could further investigate this relationship longitudinally by examining changes in dose and HRQOL over time.

Disclosure: D. L. Jones: None; R. Zhang: None; M. Hines: None; J. L. Eicher: None.

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Ready and Waiting: Adults with Arthritis Are Interested in Population-Based Physical Activity Programs. Louise Murphy1, Teresa J. Brady2, Kristina A. Theis3, Julie Bolen2 and Patience White2.  1Arthritis Foundation, 2Centers for Disease Control and Prevention

Background: Dissemination of population-based packaged physical activity (PA) programs among people with arthritis has been limited. Our study objective was to identify characteristics of adults with arthritis who are most likely to attend two types of evidence-based PA programs.

Method: We analyzed data from a national U.S. phone survey of white and black adults (n=1,002), ages 40–70 years old, who had a doctor diagnosed arthritis (“Have you EVER been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?”), and “some” or “many” arthritis attributable activity limitations (AAAL). Participants rated how likely (i.e., very or somewhat likely, or not very or not at all likely) they would be to attend each of a generic and an arthritis-specific PA program. We estimated the percent who reported that they were very likely to attend each type of program and examined correlates (e.g., demographics, symptoms, number of comorbidities) of interest for each using multivariable adjusted logistic regression with odds ratios (ORs) and 95% confidence intervals (CI); CIs that did not overlap OR=1 were statistically significant.

Results: 30% reported being very likely to attend at least one type of PA program; among those who were very likely, 42% were interested in both, 32% in a generic program only, and 26% in arthritis-specific only. In the multivariable analysis, four groups were significantly more likely to have high interest in generic programs: women (OR=1.6), blacks (OR=2.5; ref=whites) and those with ≥3 comorbidities (OR=3.0; ref=≤3 comorbidities) or who were very likely to attend a generic or arthritis-specific self-management education program (SME) (OR=16.5; ref=not very likely to attend either SME). For the arthritis-specific PA program, interest was significantly higher among women (OR=1.7) and respondents with less than a high school education (OR=3.2) and 19% of respondents who had completed high school, some AAALs (OR=1.8; ref=many AAALs), who disagreed that there was nothing they could do to manage their arthritis (OR=1.6; ref=agreed), or who were very likely to attend an SME (OR=16.4 respectively; ref=no interest in either SME).

Conclusion: Approximately a third of respondents were very likely to attend at least one type of PA program. Interest was consistently higher among women and those who were very likely to attend an SME. Specific target groups for the two types of programs emerged: whereas blacks and people with multiple comorbidities had a greater interest in generic programs, those with some AAALs or less than a high school education had greater interest in arthritis-specific programs. Our findings indicate a demand for population-based PA programs among a select but substantial group of adults with arthritis. The shared interest in SME and PA programs suggest that this group is eager for opportunities to learn self-management strategies. Clinical and public health practitioners can be encouraged that their efforts in program delivery are important. These study findings may help practitioners identify specific subgroups who are most ready for referral to community based PA programs.

Disclosure: L. Murphy: None; T. J. Brady: None; K. A. Theis: None; J. Bolen: None; P. White: None.

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Evaluation of Tai Chi Course Effectiveness for People with Arthritis. Leigh F. Callahan1, Jack H. Shreffler2, Mary Alpeter3, Laura O. Houenou3, Britta Schoster3, Kathryn Remmes Martin2, Jennifer M. Hootman2 and Todd Schwartz3.  1Centers for Disease Control, Kennesaw, GA, 2Univ of North Carolina, Chapel Hill, NC, 3University of North Carolina at Chapel Hill, Chapel Hill, NC, 4University of North Carolina, Chapel Hill

Purpose: To evaluate the effectiveness of the Arthritis Foundation’s 6-week Tai Chi course in reducing symptoms, increasing function, and improving psychosocial status in participants with arthritis using a community based randomized control trial (RCT).

Methods: At baseline, 332 participants were registered at 20 sites in North Carolina or New Jersey and randomly assigned to treatment (172) or delayed control (160). All participants received baseline and 6-week follow-up evaluations, after which the control group received the course. No adverse events were noted during the course. Self-report Instruments included pain, fatigue and stiffness visual analog scales (VAS), Health Assessment Questionnaire (HAQ), general health, Rheumatology Attitudes Index (RAI), helplessness, and Arthritis self-efficacy (ASE) for pain and symptoms. Participants also completed the PROMIS™ (PR) Short Form instruments for sleep disturbance and satisfaction with social roles. Physical performance measures were time to complete 3 chair stands, normal and fast gait speed, single leg stance, and reaching ability. The follow-up rate was 75% (120 control, 128 treatment). Regression analyses related the change in score from baseline to 6-week follow-up to the intervention status, with adjustment for baseline value, age, gender, and BMI.

Results: There are no significant differences between treatment and control groups at baseline. The participants were 85% female, with average age of 65 (19–89) and BMI of 28.5. The group was highly educated, 15% with high school diploma and 82% continuing beyond high school. The racial breakdown was 85% Caucasian and 11% African American. Results of the regression analyses showed significant (p<0.05) modest improvements in the treatment group for reported pain, fatigue and stiffness VAS (effect sizes ES=0.27, 0.23, 0.29, respectively). Moderate significant improvements were also seen in helplessness (RAI, ES=0.35), self-efficacy (ASE) for pain (ES=0.26) and symptoms (ES=0.35) of arthritis, PR sleep disturbance (ES=0.43), and PR satisfaction with social roles (0.31). Total of four reaching spans (left, right, forward, backward) showed significant improvement after treatment (ES=0.31).

Conclusions: Participants in the AF Tai Chi program showed improvements in pain, fatigue, and stiffness and sense of well-being related to psychosocial variables. The HAQ measure of physical function did not indicate significant change, and the physical performance measures involving chair stands, gait speed and single leg stance were not improved convincingly. The ability to reach while maintaining balance improved, perhaps reflecting the nature of the Tai Chi training and movements.

Disclosure: L. F. Callahan: None; J. H. Shreffler: None; B. S. Hackney: None; K. R. Martin: None; B. Charnock: None.

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Walk with Ease Program: One-Year Follow-Up. Leigh F. Callahan2, Jack H. Shreffler3, Mary Alpeter4, Laura O. Houenou5, Britta Schoster6, Kathryn Remmes Martin2, Jennifer M. Hootman2 and Todd Schwartz6.  7Centers for Disease Control, Kennesaw, GA, 8Univ of North Carolina, Chapel Hill, NC, 9University of North Carolina at Chapel Hill, Chapel Hill, NC, 4University of North Carolina, Chapel Hill

Purpose: One year after completing the Arthritis Foundation’s 6-week Walk with Ease (WWE) group or self-directed mode of intervention, participants were evaluated to determine their adherence to the WWE program and to see what improvements in physical function, symptoms and psychosocial variables were noted.

Methods: 403 individuals who completed the 6 week follow-up assessment (178 group, 225 self-directed) were mailed a self-report questionnaire designed to assess physical function, arthritis symptoms, psychosocial variables and continuation of the WWE program over one year and the intervention completion. Repeated measures regression models were used to fit the data from baseline, 6-weeks, and 1-year. Responses were required at all time points for inclusion in the model. An indicator was included for mode of intervention (self-directed or group). Results were adjusted for age, education, gender, race, and BMI.

Results: 158 (89%) group and 204 (91%) self-directed participants completed the 1 year follow-up questionnaire. At 6-weeks, there were significant improvements in nearly all self-report measures and physical performance measures (not included in 1 year follow-up) regardless of the mode of intervention (presented previously). For both the group and self directed intervention modes, 2 measures show significant improvements at one year from baseline: PROMIS satisfaction with social roles (effect sizes ES=0.33/0.27); arthritis self-efficacy (ASE) for handling pain (ES=0.17/0.17). There were 7 outcomes where self-directed participants showed significant improvement from baseline, while the group participants did not: Health Assessment Questionnaire (HAQ) (ES =0.21); pain (ES=0.38) and stiffness (ES=0.31) Visual Analog Scales (VAS); general health (ES=0.17);
Rheumatology Attitudes Index (RAI, helplessness) (ES = 0.28); PROMIS depression (ES = 0.17); and ASE for dealing with symptoms (ES = 0.22). The follow-up rate at 1-yr was similar for both modes, but 60% of group participants continued walking versus 70% of the self-directed participants. The most frequently cited reason for stopping walking for both modes was “pain, stiffness, or fatigue” (42%/36%). The group participants also cited “other health problems” more frequently (33%) than the self-directed (17%).

**Conclusions:** Both group and self-directed participants maintained some benefits 1 year after the WWE intervention. However, self-directed participants were more likely to continue walking and maintained improvement in more self-reported physical function, symptoms, and psychosocial outcomes. Two factors could influence this finding. First, the self-directed participants were on average about 5.7 years younger than those in the group sessions. Second, the self-directed have chosen a mode of intervention that suited their proclivity to act alone, while the group participants may be stimulated by group instruction but have less inclination to continue after the course ended.

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**Fit and Strong!: Bolstering Maintenance of Physical Activity among Older Adults with Lower-Extremity Osteoarthritis.** Susan L. Hughes1, Rachel B. Seymour2, Richard T. Campbell3, Pankaja Desai4, Gail Huber1 and Justina Chang1. 1JAMA, 2Northwestern University, 3University of Illinois Chicago, 4University of Illinois Chicago, Chicago, IL

Osteoarthritis (OA) is the most common condition affecting older people today. Lower extremity joint impairment caused by osteoarthritis has been shown to be a risk factor for future disability. Physical activity (PA) has been shown to play a critical role in the amelioration of symptoms and progress of the disease. However, little is known about effective ways of motivating older adults to maintain PA following a formal training program. Fit and Strong! is an award winning, evidence-based multiple-component PA/behavior change program for older adults with lower-extremity (LE) OA. This study used a multi-site comparative effectiveness trial (N = 486) with repeated measures to compare the impact of negotiated vs. mainstreamed follow-up with and without telephone reinforcement (TR) on maintenance of PA after the 8-week Fit and Strong! program ends. Random effects analyses for the total sample showed significant pre-post improvements at 2,6,12, and 18 months on PA maintenance that were accompanied by significant improvements in LE pain and stiffness, LE functional 6-sit-stand, and 6-minute distance walk and anxiety/depression. Analyses by treatment condition showed that persons in the negotiated group who received TR maintained a 21% increase in caloric expenditures over baseline, with lesser benefits seen in the negotiated only, mainstreamed with TR, and mainstreamed only groups. Significant benefits of telephone dose were also seen on lower-extremity joint stiffness, pain, and function as well as anxiety and anxiety/depression. The negotiated follow-up contract that Fit and Strong! uses, bolstered by TR, is associated with enhanced long-term PA maintenance and associated health outcomes. While TR was effective, it is not inexpensive, which may impede its translation and dissemination into community-based settings. Other forms of reinforcement, like participant and instructor videos will also be important to test if we are to maximize the successful translation of evidence-based programs in the future.

**Disclosure:** S. L. Hughes: None; R. B. Seymour: None; R. T. Campbell: None; P. Desai: None; G. Huber: None; J. Chang: None.

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**Characteristics of Persons with or at High Risk of Knee OA Achieving Recommended Physical Activity Levels: The MOST Study.** Daniel K. White1, Tuhina Neogi2, Jingbo Niu2, Michael Nevitt3, C. Elizabeth Lewis3, James Torner4 and Doug Gross5. 1Boston University, Boston, MA, 2Boston University, 3University California San Francisco, 4University of Alabama, 5University of Iowa

The CDC recommends physical activity for multiple health benefits with walking being the most common means of obtaining physical activity. However, as few as 24% for persons with self reported arthritis meet these guidelines. Among persons with radiographic knee osteoarthritis (ROA), it is not known how many satisfy these guidelines, nor which factors are associated with meeting them. Hence, we examined the characteristics of persons with or at high risk of ROA that meet activity guidelines as measured by an accelerometer-enabled monitor.

The Multicenter Osteoarthritis Study (MOST) is a NIH funded longitudinal study of people who have or are at high risk for knee OA. Subjects at the 60 month visit wore an accelerometer-enabled monitor to record walking activity over 7 days. Using a disablement model framework, we evaluated pathology, impairment, functional limitation, and psychosocial characteristics associated with meeting CDC guidelines. Specifically, we examined ROA and total knee replacement (TKR) (pathology), knee pain (impairment), self reported difficulty walking and walking at a pedestrian speed (>1.2 m/s) in the clinic (functional limitation), and depressive symptoms (psychosocial). We defined meeting CDC guidelines as walking at least 80 steps per minute for 150 minutes over 7 days. We compared disablement characteristics among persons meeting and not meeting activity guidelines using prevalence ratios adjusted for age, sex, BMI, race, number of comorbidities, and presence of widespread pain.

Of 806 subjects (Age 62 ± 8 yrs, BMI 31 ± 6 kg/m2, female 69%), 174 (22%) met CDC guidelines for physical activity. These persons were more often male with a lower mean age and BMI, and did not have widespread pain. In adjusted models pathology was not associated with meeting CDC guidelines, however persons with bilateral knee pain, self reported difficulty walking, and those who could not walk at a pedestrian speed were 40% to 80% less likely to meet CDC guidelines than their counterparts (see table).

Pathology-related characteristics (ROA and TKR) were not associated with meeting CDC guidelines, whereas pain and functional limitation characteristics were associated. These findings may be encouraging to providers given that these latter factors are potentially modifiable.

**Disclosure:** D. K. White: None; T. Neogi: None; J. Niu: None; M. Nevitt: None; C. E. Lewis: None; J. Torner: None; D. Gross: None.
Background: Human parvovirus B19 causes acute illness with many features of systemic lupus erythematosus (SLE) including transient antinuclear, anti-dsDNA and antiphospholipid antibodies. B19 may persist in various tissues, e.g. in liver, where it may cause a “restricted” infection with expression of the viral non-structural protein NS1, but little or no capsid protein. NS1 is a superfamily 3 (SF3) helicase typical of DNA viruses. Our group previously reported that expression of enhanced green fluorescent protein-NS1 (eGFP-NS1) fusion protein induced NS1 bulky adduct formation and single strand nicks in hepatocyte DNA leading to caspase 9 mediated apoptosis. Excess nucleosomes and apoptotic bodies are seen in the blood in SLE patients.

Objective: In order to construct a model for B19 induced abrogation of tolerance to self-DNA, we determined whether NS1-DNA adducts survived apoptosis by examining surface blebs and extruded apoptotic bodies for B19 NS1, DNA and proteins known to be autoantigens in SLE.

Methods: The murine kidney cell line, BK22, was transduced with recombinant baculovirus hosting eGFP, eGFP-NS1 or eGFP-NS1 with a mutation in the NS1 putative metal coordination site. At 48 hours post-transduction, apoptotic cells and bodies were evaluated by scanning electron microscopy (SEM), comet assay, flow cytometry and confocal microscopy.

Results: eGFP-NS1, but not eGFP, transduced cells showed increased surface blebs post-transduction. An eGFP-NS1 mutant with a deletion in the putative metal coordination site, dMetal, showed decreased blebbing: eGFP-NS1, 87% induced compared to only 28% in eGFP transduced cultures. Confocal imaging of apoptotic cells showed surface blebs containing NS1, dsDNA, and histone H4. Purified apoptotic bodies showed surface phosphotidylserine by Annexin V staining, internal DNA by DAPI staining, eGFP-NS1, histone 4, proliferating cell nuclear antigen, and lysosomal antigen Lamp2, but not histone H2B.

Conclusions: B19 NS1 expression damages host cell DNA and induces apoptosis. NS1 bulky adduct modified self-DNA is condensed into apoptotic bodies in the presence of nuclear and cytoplasmic self-proteins. Antigen presenting cells could ingest these apoptotic bodies, present NS1 peptides, to antigen presenting cells and activate NS1 specific T cells. The last could provide costimulatory signals to anergized anti-DNA B cells presenting NS1 peptides processed after surface Ig mediated uptake of NS1-modified nucleosomal DNA. Epitope spreading would allow expansion of autoantibody specificities. The presence of similar SF3 helicases in other DNA viruses, e.g. Epstein Barr nuclear antigen 1, EBNA1, suggests that this model may more broadly explain viral induction of DNA autoantibodies and SLE disease.

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correction, treatment effect only remains significant for IL-12p70 (at both 6 months and 9 months).

**Conclusion:** IL-12p70 is required for optimal host IFN-γ T cell response against intracellular pathogens and endocervical IL-12 expression has previously been shown to decline with clearance of *Chlamydia*. The distinctive changes in serum levels of IL-12p70 following antibiotic treatment of *Chlamydia*-induced ReA point toward changing host cytokine responses concurrent with clinical improvement, and highlight the importance of IFN-γ in this process.

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**The Efficacy and Safety of Vaccination Against H1N1 in Patients with Rheumatoid Arthritis, Systemic Lupus Erythematosus, Psoriatic Arthritis and Ankylosing Spondylitis.** Ori Elkayam1, Sharon Amir2, Michal Mandelboim1, Ella Mendelson1, Jonathan Wolfmann1, Uri Arad1, Daphna Paran1, David Levartovsky1, Irena Wigler1 and Dan Caspi1. 1Center of Virology, Sheba Medical Center; 2Department of Rheumatology, Tel Aviv Medical Center

**Background:** In spring 2009, a new swine-origin influenza virus A (H1N1) quickly spread worldwide prompting the development of pandemic H1N1 influenza vaccine launched by the end of 2009.

**Purpose:** To assess the efficacy and clinical safety of vaccination against H1N1 in patients suffering from Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Psoriatic Arthritis (PsA) and Ankylosing Spondylitis (AS) in comparison with healthy controls.

**Patients and Methods:** The study population comprised 4 groups of patients and healthy controls: 41RA patients: 56% female, age: 52.6 years; duration: 9 years; 21SLE patients: 66% female, age: 41.7 ± 14.5 years; duration: 11 years; 17 PsA: 35% female, age: 48.5 ± 11.8 years, duration: 12 years; 15 AS: 20% female, age: 47.2 ± 13.3 years, duration: 14 years; 17 healthy controls: 60% female, age: 47.3 ± 11.3 years. The safety of vaccination was assessed on day 1 and 4 weeks after vaccination.

**Results:** The proportion of patients receiving the vaccine was higher in the RA group compared to the SLE group. A significant increase in GMT was observed in the 5 groups. A substantial proportion of patients and controls responded to the vaccine, Healthy controls demonstrating a better GMT than RA and PsA patients. GMT0 was 4.38, 85.67, 8.3 for RA, SLE and PsA, respectively.

**Conclusions:** Vaccination against H1N1 using an adjuvanted H1N1v monovalent influenza vaccine induced an appropriate response in patients with RA, SLE, PsA and AS. The vaccine was found to be safe in this cohort of patients.

**Disclosure:** O. Elkayam: None; S. Amir: None; M. Mandelboim: None; E. Mendelson: None; J. Wollman: None; U. Arad: None; D. Paran: None; D. Levartovsky: None; I. Wigler: None; D. Caspi: None.

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**Serious Infection in Rheumatoid Arthritis Patients Switching Anti-Tumor Necrosis Factor Drugs.** Bao-Anh Nguyen-Khoa1, Earl G. Goehring, Jr2, Kimberly Alexander1, Wei Dong1, Pavel Napalkov1 and Judith K. Jones1. 1Genentech, South San Francisco, CA, 2The Degge Group Ltd, Arlington, VA

**Purpose:** Rheumatoid arthritis (RA) patients commonly change drug therapy for reasons of safety or effectiveness. This study describes rates of first serious infection among RA patients who switch from one anti-Tumor Necrosis Factor (aTNF) drug to another aTNF compared to those who do not switch.

**Methods:** Subjects with RA who received only an aTNF drug (infliximab, etanercept, or adalimumab) were observed in a large health claims database from 1/1/2001 to 12/31/2007. Non-switchers (NS) remained on one aTNF during the study period. Switchers (S) had at least one change to another aTNF. Index dates were defined as the day of the first aTNF claim for NS, and the day of the treatment switch for S. Baseline data were collected for the 365 days of enrollment prior to the index date. Serious infections included those which required IV antibiotics or hospitalization; only the first event was included in incidence rate estimates. Two attributable risk periods were used: 1) infection occurring ≤ 90 days from a prior claim for an aTNF (90-Day) and 2) any infection occurring after the index date (Ever-Treated). Data were stratified by 1-year and ≥ 2 years post-index. Cox regression was used to compare serious infection rates, adjusting for age, gender, selected comorbidities, Charlson comorbidity score, hospitalizations, and other RA treatments.

**Results:** There were 13,752 RA patients in the NS cohort, and 2,293 in the S cohort. In the 90-Day model, unadjusted rates of first serious infection was nonsignificantly lower for NS vs S (6.31/100 PY, 95% CI: 6.01–6.62 vs. 6.78/100 PY, 95% CI: 5.95–7.67). Rates of first serious infections declined from 8.59/100 PY and 8.72/100 PY in the first year post-index for NS and S, to 2.66/100 PY and 2.64/100 PY ≥ 2 years post-index.

**Conclusions:** The risk of a serious infection was not different between RA patients that switched aTNF drugs and those who did not. Indications for switching an aTNF drug could not be captured in this study. Rates in the Ever-Treated model were generally higher than the 90-Day model for overall, 1-year, and ≥ 2 years post-index. Regardless of switching status, the rate of first infection 1-year post-index was up to 3 times greater than 2+ years post-index.

**Disclosure:** B.-A. Nguyen-Khoa: None; E. L. Goehring, Jr: None; K. Alexander: Genentech and Biogen IDEC Inc; 3; W. Dong: Genentech and Biogen IDEC Inc; 3; P. Napalkov: Genentech and Biogen IDEC Inc; 3; J. K. Jones: None.

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**Defining Latent and/or Disseminated Active Tuberculous Infection with TST, Quantiferon Gold and Multisite Cultures in TNFi Exposed Individuals.** Diana Karpouzas3, George A. Karpouzas2, James S. Louie1, Rosalinda C. Moran1 and George A. Karpouzas1. 1Harbor- UCLA Medical Center, Carson, CA, 2Harbor-UCLA Medical Center, Torrance, CA, 3Harbor-UCLA Medical Center, Long Beach, CA, 4University of California Los Angeles, Los Angeles, CA

**Background:** Patients (pts) receiving Tumor Necrosis Factor-α inhibitors (TNFi) are at increased risk for developing granulomatous infections with Mycobacterium tuberculosis (MTB) or non-tuberculous mycobacteria (NTM). Prior to starting TNFi, baseline screening for latent MTB includes tuberculin skin testing (TST) and/or ex vivo cellular responses to mycobacterial antigens [Quantiferon (QFN)] in addition to chest x-ray (CXR).
Clinically asymptomatic pts who have mycobacterial reactivity [TST or QFN positive (+)] and a negative (-) CXR are treated with Isoniazid (INH) for 9 mos. High risk pts on continued TNFi are still prone to subsequent infection and seroconversion and thus should be regularly monitored; however, the frequency and/or sequence of these screening schedules have not yet been standardized. The use of QFN assays in pts receiving TNFi has not yet been proven and more data is needed in this area. We found that the combination of TST and QFN testing may be a prudent strategy in monitoring pts on TNFi.

Methods: We report on 483 pts treated with TNFi between 11/1/2000 and 6/1/2010 in a single institution. Pts received at least one month (mo) of adalimumab (ADA), etanercept (ETN), Golimumab (GOM), or loading dose of infliximab (IFX) 3mg/kg at 0, 2, and 6 weeks. Screening TST and/or QFN assay plus CXR were obtained at baseline and (-) pts were serially re-screened yearly while on TNFi. Induration of > 5mm was considered a (+) TST. Those who were asymptomatic with a new (+) TST and/or QFN were tested for disseminated active disease with cultures and polymerase chain reaction (PCR) of sputum, urine, and stool (for MTB and NTM), along with CXR and chest CT.

Results: Of 481 pts exposed to TNFi, 447 pts received baseline TST; 127 (28%) had baseline (+) TST and 35/127 (28%) had old granulomatous disease (OGD) on CXR but were clinically asymptomatic. All 127 pts were treated as LTBI with INH for 9 mos. One pt developed active TB while on TNFi despite completion of LTBI treatment. The remaining 320 TST (-) pts had sequential annual TST re-screens, and 56 also underwent QFN testing. Thirty-seven of 320 (11%) pts developed a (+) TST (15.28±5.74 mm) while on TNFi. Of 56 QFN tested pts, 9 were (+) overall: 2 at baseline prior to TNFi and 7 after TNFi exposure. Two pts were QFN and TST (+); 5 had (+) QFN and (-) TST. Although clinically asymptomatic, all 41 pts with (+) TST and/or (+) QFN were assessed for dissemination as above; 9/41 (22%) pts had (+) cultures (2 with MTB, 7 with NTM). 3 of these pts were treated with multidrug anti-TB therapy and the rest were treated with INH. All patients continued TNFi without adverse outcomes to date (1589 PT-Years).

Conclusion: In high risk populations with rheumatic conditions, there is a high prevalence of LTBI both at baseline and upon subsequent rescreens while on TNFi. Our expanded cohort has combined yearly TST and QFN testing in all high risk individuals on TNFi and consider (+) pts for Chest CT, multistate cultures and PCR to evaluate for active disseminated disease.


ACR Concurrent Abstract Sessions
Miscellaneous Rheumatic and Infectious Diseases
Monday, November 8, 2010, 4:30 PM–6:00 PM

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Progressive Multifocal Leuкоencephalopathy Associated with Biologic and Synthetic DMARD Therapy in Rheumatic Diseases: An Analysis of the FDA Adverse Event Reporting System Database. Eamonn S. Molloy1 and Leonard H. Calabrese1. 1Cleveland Clinic Foundation, Cleveland, OH, 2St Vincent’s University Hospital, Dublin, Ireland

Background: PML is a rare and often fatal opportunistic infection recently associated with several biologic therapies. Unfortunately the general understanding of PML is poor and ascribing risk to individual therapies has been problematic. This study examined the aggregate experience of PML reported in association with autoimmune disorders and biologic DMARDs reported in the FDA Adverse Event Reporting System (AERS) database through review of MedWatch forms.

Method: A Freedom of Information Act request was submitted for all cases of PML and/or JC virus infection within the FDA AERS database from November 1, 1997 to March 31, 2009. All MedWatch forms received at the time of this analysis were reviewed; those with identified autoimmune diseases and/or exposure to rituximab, anti-TNF antagonists, anakinra, or abatacept were selected for further analysis. PML was classified as confirmed, possible or unconfirmed. Other data collected from the forms included demographics, critical clinical and lab features and disease association cofactors of PML.

Results: A total of 473 cases were received and analyzed. Among all cases, 114 (24%) were found to have one or more autoimmune diseases, 40 of which were categorized as autoimmune rheumatic diseases (15 RA, 15 SLE, 6 vasculitis, 4 other). Of these 40 cases, 18 were considered confirmed’ cases of PML based on the available information. Of these, 6 were treated with biologic agents (5 rituximab, 2 infliximab – 1 patient received both). Neither case associated with infliximab could clearly be attributed to the use of this agent – 1 subsequently received rituximab for dermatomyositis and the other was treated with cyclophosphamide for rheumatoid vasculitis. No confirmed cases were reported in association with the use of other biologic DMARDs such as other anti-TNF agents, anakinra or abatacept. The remaining 12 non-confounded, confirmed cases of PML among autoimmune rheumatic disease patients were treated with synthetic DMARDs only (7 cyclophosphamide (5 of whom subsequently received mycophenolate mofetil) and 5 others). Of 12 autoimmune rheumatic disease cases of ‘possible’ PML, 7 were associated with biologic therapies (5 anti-TNF therapy, 2 rituximab, 2 abatacept – 1 patient received adalimumab prior to rituximab, 1 received anti-TNF therapy prior to abatacept).

Conclusion: PML is a reported complication of a variety of disease states and associated with both synthetic and biologic immunosuppressive therapies. While the small numbers of cases involved precludes attribution of causality, two points deserve emphasis. The relative paucity of confirmed cases in patients treated with anti-TNF therapy, despite their widespread use, suggests that a causal relationship is unlikely. In contrast, there is a concerning, albeit rare, signal emerging regarding use of rituximab, especially considering that 5 cases of PML among rituximab-treated RA patients, in addition to those reported in this analysis, have been reported to Genentech. Nevertheless, until greater clarity can be achieved, all patients treated with immunosuppressive therapies for autoimmune disease should be considered at risk for PML.


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Tocilizumab in Refractory Adult Still’s Disease: A Cohort Study. Xavier Puéchal, Michel de Bandt, Jean-Marie Berthelot, Maxime Breban, Jean-Jacques Dubost, Olivier Fain, Jean-Emmanuel Kahn, Laurence Lequen, Maïlé Longy-Boursier, Aleth Perdriger, Thierry Schaeverbeke, Eric Toussirot, Jean Sibilia and The CRI. Center for Rare Systemic and Auto-immune Diseases, Department of Rheumatology, Le Mans, France

Background: Interleukin-6 (IL-6) is thought to play a role in the pathogenesis of Still’s disease. We report the first series of patients with adult Still’s disease (ASD) treated with tocilizumab (TCZ), a humanized anti-IL-6 receptor antibody.

Objectives: To assess the efficacy and tolerance of TCZ in adult patients with refractory ASD.

Methods: Cohort study of all patients with ASD treated in France with off-label TCZ between July 2006 and July 2009 and enrolled in a specific French Agency for the Safety of Health Products (AFSSAPS) protocol.

Main Outcome Measures: European League of Associations for Rheumatology (EULAR) improvement criteria and resolution of systemic symptoms at 3 and 6-month follow-up.

Results: Fourteen patients were included in this study. At the start of TCZ treatment, despite a mean prednisone dose of 23.3 mg/day, mean tender joint count was 10.5/28, swollen joint count was 7.9/28 and mean DAS28 was 5.61. Recurrent systemic involvement, including fever and rash, was present in seven patients. TCZ was administered at 5 to 8 mg/kg every two or four weeks (8 mg/kg/month, n = 9). Eleven patients successfully completed the six-month study; one withdrew due to necrotizing angioedematitis, another due to thoracic oppression at each TCZ infusion and a third due to systemic flare. A good EULAR arthritis response was observed in 64% (9/14) of patients at three months and EULAR arthritis remission in 57% (8/14) at six months. Systemic symptoms were resolved in 86% (6/7) of patients. Moreover, corticosteroid dose was reduced by 56%. No other severe adverse effects occurred.

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Figure. Individual disease activity score and mean prednisone dose before and after tocilizumab therapy in adult Still’s disease.

Conclusions: In this cohort of patients with intractable refractory ASD, TCZ was effective against systemic involvement of the disease in almost all patients and led to arthritis remission in half the patients, showing a marked corticosteroid-sparing effect and an acceptable tolerance profile. TCZ is a promising new treatment for ASD.

Disclosure: X. Puéchal: None; M. de Bandt: None; J.-M. Berthelot: None; M. Breban: None; J.-J. Dubost: None; O. Fain: None; J.-E. Kahn: None; L. Lequen: None; M. Longy-Boursier: None; A. Perdriger: None; T. Schaeverbek: None; E. Toussrirot: None; J. Sibilia: None; The CRI: None.

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Clinical Implications of the NMO-IgG Antibody and Overlapping Neuromyelitis Optica Spectrum Disorder in Patients with Connective Tissue Disease and Myelitis. Jason R. Kolfenbach¹, Brian J. Horner² and Sterling G. West³. ¹Division of Rheumatology, University of Colorado at Denver, Aurora, CO, ²University of Colorado at Denver, Aurora, CO, ³University of Colorado Denver School of Medicine

Objective: To identify the presence of neuromyelitis optica spectrum disorders (NMOSD) in patients with acute myelitis and suspected connective tissue disease (CTD), and to determine if the presence of NMOSD or the NMO-IgG antibody is associated with poor clinical outcomes

Methods: Seventeen patients with myelitis were identified from a university-based rheumatology clinic and prospectively followed. Clinical follow-up extended from July 1998 to February 2010. The diagnosis of myelitis was based on fulfillment of criteria established by the Transverse Myelitis Consortium Working Group, and/or diagnosis by a board-certified neurologist. Longitudinal myelitis (LM) was defined as T2 enhancement on spinal MRI of ≥ 3 contiguous vertebral segments. Inflammatory myelitis not meeting the criteria for LM was classified as transverse myelitis (TM). Optic neuritis (ON) was diagnosed by a board-certified neurologist or neuro-ophthalmologist. Clinical data and serologic profile were used to determine the presence of neuromyelitis optica (NMO) or NMOSD according to established criteria. Disease course and response to treatment were recorded. Statistical comparisons were calculated using Fisher’s exact test.

Results: Eight of 15 (53%) patients diagnosed with a CTD and acute myelitis met criteria for NMOSD. Additionally, two patients had full-spectrum NMO without evidence of co-existent CTD. Optic neuritis was more commonly seen in Sjögren’s syndrome (SS) than in systemic lupus erythematosus (SLE) (83% vs. 0%; p = 0.02), as was the serum NMO-IgG antibody (67% vs. 0%; p = 0.06). Full-spectrum NMO was diagnosed in four of six patients with primary SS, one of four with Sjögren’s-associated overlap syndrome, and none of the five with SLE alone [Table]. Among patients with follow-up data (N=15), all six with NMO-IgG positivity suffered relapse compared to 3/9 patients that were NMO-IgG negative (p = 0.01). Furthermore, patients who were positive for the NMO-IgG antibody suffered a total of 20 relapses (51 patient-years of follow-up) compared to four total relapses among 3/9 patients that were negative for the NMO-IgG antibody (114.5 patient-years of follow-up). Five of six patients with the NMO-IgG antibody were treated with rituximab in our series; evidence of clinical benefit included relapse cessation in some patients as well as prevention of LM and ON in a patient with transverse myelitis and the NMO-IgG antibody.

Table. Serologic profile & clinical characteristics of patients with CTD and myelitis

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>SS (N = 6)</th>
<th>SLE (N = 5)</th>
<th>SS/SLE (N = 2)</th>
<th>MS/SS (N = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMO-IgG</td>
<td>4/6 (67%)</td>
<td>0/5 (0%)</td>
<td>1/2 (50%)</td>
<td>0/2 (0%)</td>
</tr>
<tr>
<td>ANA</td>
<td>5/6 (83%)</td>
<td>5/5 (100%)</td>
<td>2/2 (100%)</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>SS-A</td>
<td>5/6 (83%)</td>
<td>1/5 (20%)</td>
<td>0/2 (0%)</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>SS-B</td>
<td>1/6 (17%)</td>
<td>0/5 (0%)</td>
<td>0/2 (0%)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>RF⁺</td>
<td>3/5 (60%)</td>
<td>0/4 (0%)</td>
<td>0/1 (0%)</td>
<td>1/2 (50%)</td>
</tr>
</tbody>
</table>

Clinical features:
- LM: 3/6 (50%), 2/5 (40%), 1/2 (50%), 0/2 (0%)
- Presence of NMO: 4/6 (67%), 0/5 (0%), 1/2 (50%), 0/2 (0%)
- Presence of NMO: 5/6 (83%), 2/5 (40%), 1/2 (50%), 0/2 (0%)

Conclusion: NMO was common in our patients with CTD and autoimmune myelitis. Full-spectrum NMO and presence of the NMO-IgG antibody was more common among patients with SS than SLE. The presence of the NMO-IgG antibody was associated with disease relapse and may suggest the need for prolonged immunosuppressive therapy, supporting current recommendations for the treatment of NMO.

Disclosure: J. R. Kolfenbach: None; B. J. Horner: None; S. G. West: None.

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Diagnostic Significance of Serum Interleukin-18 Level in Adult-Onset Still’s Disease. Junko Maruyama¹, Shigeiko Inokuma¹ and Noboru Hagino². ¹Japanese Red Cross Medical Center, ²The University of Tokyo Hospital, ³Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Purpose: To investigate the diagnostic significance and a cut-off value of serum interleukin-18 (IL-18) in adult-onset Still’s disease (AOSD) patients.

Methods: We retrospectively analyzed serum IL-18 levels in 41 febrile patients with ferritin level elevation (≥1,000 ng/mL) in our hospital from 2000 to 2008. They were compared between 16 patients who were finally diagnosed with AOSD and 25 patients with other diseases. Serum IL-18 levels were also compared between 16 AOSD patients and 5 hemophagocytic syndrome (HPS) patients associated with other diseases among the 25.

Results: The median levels of serum IL-18 were 99,106 pg/mL (interquartile range [IQR] 145,484) in patients with AOSD, 1,365 pg/mL (IQR 1,899) in other febrile patients (p=0.00005, vs. AOSD), and 2,709 pg/mL (IQR 4,408) in HPS patients with other diseases (p=0.0017, vs. AOSD). According to the receiver operating characteristic curve analysis, a cut-off IL-18 level of >20,000 pg/mL had a sensitivity of 93.8% and a specificity of 96.0% for diagnosing AOSD.

Conclusion: Serum IL-18 level is a powerful diagnostic test for AOSD.

Disclosure: J. Maruyama: None; S. Inokuma: None; N. Hagino: None.

Figure. ROC curve analysis of serum IL-18 level for diagnosing AOSD.

Conclusions: Serum IL-18 level is a powerful diagnostic test for AOSD.

Disclosure: J. Maruyama: None; S. Inokuma: None; N. Hagino: None.
Extraluminary Course of Connective Tissue Disease and Survival after Lung Transplant. Troy K. Takagishi, Iftat Ahmed and Rodney Tehran. Loyola University Medical Center

Purpose: Interstitial lung disease (ILD) is a common cause of morbidity and mortality in patients with connective tissue diseases (CTD). Lung transplants (LT) are becoming an increasingly viable option for the management of these patients. A review of the literature revealed no studies evaluating for extraluminary flares of the primary CTD following LT. Very few studies have documented the survival outcomes of this group of patients. We hypothesize that extraluminary disease flares rarely occur following LT and also that survival (%) is similar in patients with LT for CTD as compared to LT for COPD.

Methods: We performed an observational and retrospective chart review of all patients in a large tertiary care medical center that had a LT for CTD (LT/CTD) between 1999 and 2010 and evaluated for any extraluminary flares of the primary CTD following LT. Also, we compared their survival outcomes to those who underwent LT for COPD (LT/COPD). COPD was chosen as the control group because it comprises the largest group of patients undergoing LT nationally. From 1995–2008 there had been 8,417 LT due to COPD documented in the UNOS national registry which is compared to 181 for CTD during the same time period.

Results: From 1999–2010 at a large tertiary care medical center, 15 patients underwent LT for ILD secondary to their CTD: 5 with dermatomyositis or polymyositis (33%), 5 with rheumatoid arthritis (33%), 3 with lupus (20%), and 2 with mixed connective tissue disease (13%). 4/15 (27%) of the patients had an extraluminary flare of their primary CTD following LT. All episodes were arthritic flares (3 monoarticular and 1 polyarticular) and each occurred in a different patient (3 with RA and 1 with SLE). This data equates to 1 flare/15.71 patient years. The Kaplan-Meier survival curves for LT/CTD and LT/COPD respectively at 3 mo was 93% and 93%; at 5 yrs was 75% and 77%.

Conclusion: There is no published literature on the extraluminary manifestations of CTD following LT. There is also scarce data on the survival outcome of this patient population. We found that extraluminary flares of the primary CTD are extremely rare following LT likely due to the use of immunosuppressants for LT. In addition, survival following LT for CTD was found to be equivalent to that for LT for COPD. LT appears to be a viable option in a select group of patients with end stage ILD secondary to CTD.

Disclosure: T. K. Takagishi: None; I. Ahmed: None; R. Tehran: None.

ACR Concurrent Abstract Sessions Osteoarthritis - Clinical Aspects: Genetics, Novel approaches, and Therapy

Clinical Trial of Vitamin D To Reduce Pain and Structural Progression of Knee Osteoarthritis (OA). Timothy E. McAlindon1, Bess Dawson-Hughes2, Jeffrey Driban3, Michael LaValley4, Ji Yeon Lee5, Grace H. Lo5, Melynn Niu6 and Lori Lyn Price7. 1Tufts University School of Public Health, 2Tufts Medical Center, Boston, MA, 3Boston University School of Public Health, 4Tufts Medical Center, 5USDA HNRC; Tufts University

Purpose: Observational epidemiologic studies suggest that vitamin D may reduce the structural progression of knee OA, an effect that could be mediated through bone or chondrocyte mechanisms. The aim of this study was to test for disease-modifying effects of a vitamin D intervention strategy for knee OA.

Methods: This was a 2-year, NIH-funded, double-blind, placebo-controlled clinical trial among individuals with symptomatic knee OA (ACR criteria). Randomization was blocked and stratified by disease severity (Kellgren-Lawrence (KL) grade). The intervention consisted of vitamin D3 2000 IU daily (Tishcon Corp, NY), which was escalated in increments of 2000 IU as needed, 3, 6, and 9 months, for a target serum vitamin D level of >30 ng/ml. Blinding was maintained by the use of a dummy escalation protocol in the placebo group. Assessments included the WOMAC questionnaire at each visit, physical function tests; annual MRI (Siemens Avanto 1.5T; sagittal and coronal IW FS and DESS sequences); and standardized semi-automated knee radiography at the beginning and end of study. Cartilage volume and thickness, and bone marrow lesion (BML) volume, in the index tibial and femoral compartments, were determined by manual segmentation of registered images using Analyze©. Intra-tester reliability ICCs were .96 & .90 for BML volume. Minimal radiographic joint space width was measured using a semi-automated computer program. Primary outcomes were WOMAC pain and cartilage volume loss. To test for differences we used mixed effects regression for repeated measures with linear, or linear and quadratic time trends, with adjustment for KL grade, knee alignment, and body mass index (BMI).

Results: Out of 282 screened, 146 subjects were randomized (mean age 62.4 [s.d. 8.5]; 57% female; 79% Caucasian; mean BMI 30.7 kg/m² [5.7]; 56% taking supplements; mean vitamin D level 22.3 ng/ml±1 [10.0]; femoral neck BMD 0.95 g/cm² [0.14]). 50% had KL grade 2, 29% grade 3 and 21% grade 4. The groups were evenly balanced for these characteristics and outcome measures (Table). 124 (85%) completed the study. Mean serum vit D level increased by 15.0 ng/ml in vitamin D compared to 1.8 in the placebo group (p<0.0001). There were no substantial or significant between-group differences in WOMAC pain and cartilage volume loss.
differences in any of the outcome measures (Table). In the repeated measures analyses, neither treatment assignment nor increase in serum vitamin D level had any influence on the outcomes. There were 28 serious adverse events in the vitamin D and 23 in the placebo group, all classified as unrelated except one ‘possibly related’ (hip fracture).

**Results:**

- **Vitamin D Group**: Baseline WOMAC Pain 6.86 (3.78), Chair Stand Time (s) 19.8 (7.2), Cartilage volume (mm³) 1010 (437), Cartilage thickness (mm) 1.17 (0.39), BML volume (cm³) 15.8 (28.0), Minimum JSW (mm) 3.25 (1.64). Δt: WOMAC Pain −2.14 (1.79), Chair Stand Time (s) −1.06 (0.56), Cartilage volume (mm³) −39.2 (36.5), Cartilage thickness (mm) −0.06 (0.06), BML volume (cm³) 0.17 (14.5), Minimum JSW (mm) −0.20 (0.73)
- **Placebo Group**: Baseline WOMAC Pain 5.81 (3.41), Chair Stand Time (s) 18.6 (5.8), Cartilage volume (mm³) 1148 (473), Cartilage thickness (mm) 1.21 (0.36), BML volume (cm³) 13.6 (19.4), Minimum JSW (mm) 3.16 (0.16).

All between-group p-values >0.05.

**Conclusions:** Vitamin D supplementation at a dose sufficient to elevate serum levels above 30 ng/ml does not appear to have any symptom or structure-modifying benefits for knee OA.

**Disclosure:** T. E. McAlindon: None; B. Dawson-Hughes: None; J. Dihann: None; M. LaValley: None; J. Y. Lee: None; G. H. Loc: None; M. Nuite: None; L. L. Price: None.

**707 Interleukin-1 Receptor Antagonist (IL-1RN) Gene Variations Predict the Severity and Progression of Knee Osteoarthritis, Mukundan Attur1, Cheongun Oh2, Svetlana Krasnokutsky3, Jonathan Samuels4, Leon Rybak4, Jenny Bencardino5, Jeffrey D. Greenberg6, Virginia Kraus7, Kenneth Cormon8 and Steven B. Abramson4. 1Millburn, NJ, 2Duke University Medical Center, Durham, NC, 3Hospital for Joint Dis/NYU, New York, NY, 4Interleukin Genetics, 5New York University Hospital for Joint Disease, New York, NY, 6NYU Hospital for Joint Disease, New York, NY, 7NYU Hospital for Joint Diseases, 8NYU-Hospital for Joint Diseases, New York, NY, 9NYU-Hospital for Joint Diseases Radiology Dept.

**Purpose:** We have previously shown that carriage of an IL1RN haplotype (CTA) was associated with substantially lower odds of radiographic severity in the diseased compartment over 24 months, rather than in change in absolute JSW.

**Methods:** Ninety-seven (N=97) patients from NYUHJD who met ACR criteria for symptomatic knee OA, and who were enrolled in a two-year NIH-sponsored prospective study. The patients completed standardized fixed-flexion knee radiographs at baseline and 24 months, with progression the signal (more painful) knee OA determined by change in joint space width (JSW) and KL score. For these analyses, the patients were separated into two groups by results on their signal knee: 17 progressors, higher average IP (but not CMC) score than the non-progressors, 7.2 0.9, while medians were 5 and 1.0, respectively. The 17 progressors had a higher average IP (but not CMC) score than the non-progressors, 167 (118) vs 4740 (1273) [p=0.01].

**Results:** There was a positive association between the TTG haplotype and radiographic progress at 24 months that approached significance based on the vitamin D and 23 in the placebo group, all classified as unrelated except one ‘possibly related’ (hip fracture).

**Conclusion:** IL-1RN gene family polymorphisms, which appear to affect host production of IL-1Ra, merit evaluation as biomarkers that predict the risk of progression in patients with symptomatic knee OA.

**Disclosure:** M. Attur: None; C. Oh: None; S. Krasnokutsky: None; J. Samuels: None; L. Rybak: None; J. Bencardino: None; J. D. Greenberg: None; V. Kraus: None; K. Cormon: None; S. B. Abramson: None.

**708 Hand Osteoarthritis (OA) a Predictor of Accelerated Progression in Knee OA? Jonathan Samuels1, Catherine Petchprapa2, Elizabeth L. Carpenter2, Svetlana Krasnokutsky3, Mukundan Attur2, Leon Rybak4, Jenny Bencardino4, Cheongun Oh2 and Steven B. Abramson3. 1Millburn, NJ, 2Duke University Medical Center, Durham, NC, 3Hospital for Joint Dis/NYU, New York, NY, 4Hospital for Joint Dis/NYU Langone Medical Center, 5New York University Hospital for Joint Disease, New York, NY, 6NYU Hospital for Joint Disease, New York, NY, 7NYU Hospital for Joint Diseases, 8NYU Langone Medical Center

**Purpose:** There is insufficient understanding regarding how generalized OA involving the hand and knee differs from isolated knee OA, which may result from other factors such as obesity or trauma. The purpose of these studies is to determine whether the presence of hand OA involving interphalangeal (IP) and first carpometacarpal (CMC) joints, alone or in combination, predicts progression of patients with symptomatic knee OA.

**Methods:** Hand radiographs were obtained on 94 patients at NYUHJD who met ACR criteria for symptomatic knee OA, and who were enrolled in a two-year NIH-sponsored prospective study. The patients completed standardized fixed-flexion knee radiographs at baseline and 24 months, with progression the signal (more painful) knee OA determined by change in joint space width (JSW) and KL score. For these analyses, the patients were separated into two groups by results on their signal knee: 17 progressors, defined by at least 30% decreased JSW over 24 months, and 77 non-progressors. For each set of hand x-rays, 2 radiologists evaluated 18 IP joints and 2 CMC joints for joint space narrowing and/or osteophytes, and whether or not there was erosive change at the IP joints; we averaged the scores from the two readers.

**Results:**

- **Kappa scores between the two scoring radiologists for the IP and CMC joints, and for the presence of erosive IP disease, were 0.79, 0.87 and 0.96, respectively. The overall mean IP score was 5.6 and 1st CMC score was 0.9, while medians were 5 and 1.0, respectively. The 17 progressors had a higher average IP (but not CMC) score than the non-progressors, 7.2±5.4 vs. 5.0±4.6, p=0.13. Since the IP scores were not normally distributed, we further analyzed data by dichotomizing the study populations into two groups using the median IP total (5) as the cutoff point. When so analyzed, the presence of “hand OA” increased the odds ratio of knee OA progression to 2.8 (p=0.096). Of interest, the severity of knee OA correlated with hand OA scores: the average total hand OA scores (out of 20 joints) increased with IP joint scores alone (p=0.026). The 8 patients with radiographic evidence of erosive IP disease, as compared with the 31 non-erosive IP OA patients without IP joint scores, demonstrated faster knee OA progression over 2 years by average KL increases (1.00, 0.35, 0.30) and decreases in joint space width (0.65, 0.56, 0.36), although perhaps given small numbers, this was not statistically significant (p=0.839).

**Conclusions:** In cross-sectional analysis, the quantitative “burden” of hand OA correlates with the radiographic severity of knee OA (KL).
Moreover, radiographic hand OA at the IP joints, but not at the 1st CMC joint, predicts more rapid progression of knee OA. Erosive IP disease may be an even stronger predictor than non-erosive IP disease of accelerated progression of knee OA.

Funding: This study is funded by NIAMS (R01-AR052873).

Disclosure: J. Samuels: None; C. Petchprapa: None; E. L. Carpenter: None; S. Krasnokutsky: None; M. Attur: None; L. Rybak: None; J. Bencardino: None; C. Oh: None; S. B. Abramson: None.

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Bone Marrow Lesions (BMLs) Are Strongly Associated with Increased Bone Volume Fraction; “Virtual Bone Biopsy” Using MRI. Anna M. Tassinari1, Grace H. Lo1, Jeffrey Driban3, Lori Lyn Price3, Erika Schneider2, Anna M. Tassinari3

Table 1: Trabecular bone changes in BMLs

<table>
<thead>
<tr>
<th>BML score</th>
<th>Mean aBVF (SD)</th>
<th>Mean Trabecular Number ± SD</th>
<th>Mean Trabecular Spacing ± SD</th>
<th>Mean Trabecular Thickness ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>none (n = 124)</td>
<td>0.122 ± 0.077</td>
<td>0.87 ± 0.39</td>
<td>1.51 ± 1.3</td>
<td>0.131 ± 0.023</td>
</tr>
<tr>
<td>small (n = 24)</td>
<td>0.183 ± 0.095</td>
<td>1.13 ± 0.39</td>
<td>0.93 ± 0.57</td>
<td>0.152 ± 0.028</td>
</tr>
<tr>
<td>large (n = 10)</td>
<td>0.221 ± 0.094</td>
<td>1.35 ± 0.33</td>
<td>0.73 ± 0.31</td>
<td>0.163 ± 0.032</td>
</tr>
<tr>
<td>Overall (n = 158)</td>
<td>0.138 ± 0.09</td>
<td>0.94 ± 0.4</td>
<td>1.37 ± 1.2</td>
<td>0.14 ± 0.03</td>
</tr>
</tbody>
</table>

Overall model p-value 0.0001

Conclusion: Bone volume appears increased in BMLs. The exploratory trabecular measures suggest that as BMLs are associated with higher trabecular number and thickness, but lower separation. These findings could represent locally increased bone turnover or compression and suggest that treatments targeting bone that could influence these pathologies should be explored.

Disclosure: A. M. Tassinari: None; G. H. Lo: None; J. Driban: None; L. L. Price: None; E. Schneider: None; T. E. McAlinden: None.

710

REGN475/SAR164877, a Nerve Growth Factor Inhibitor, in Osteoarthritis Patients with Moderate to Severe Knee Pain: Results of a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study. Paul Tisce1, Alan J. Kivitz2, John E. Ervin3, Scott J. Mellis4, Haobo Ren5, Damir Skfic6, Richard Witham7 and Peter Powchik8, 1Altona Arthritis & Osteo Cr, Tarrytown, NY, 2Center for Pharmaceutical Res, Kansas City, MO, 3Regeneron Pharmaceuticals, Inc., Tarrytown, NY, 4Regeneron Pharmaceuticals, Inc.

Purpose: To evaluate the safety and efficacy of REGN475/SAR164877 (R/S), a fully human monoclonal antibody with highly selective binding affinity for nerve growth factor (NGF), in the treatment of osteoarthritis (OA) pain.

Methods: This phase 2, double-blind, placebo-controlled, parallel-group, repeat-dose study enrolled patients aged 40–75 y with physician-confirmed diagnosis of active, moderate to severe OA (ACR criteria + subjective pain + Kellgren-Lawrence G2-G3 radiographic severity). Other eligibility requirements included walking knee pain (KPO) levels ≥ 4 at baseline [11-pt numerical rating scale (NRS)] and washout of any current pain medications prior to baseline visit (Day 1). Rescue medication with acetaminophen (up to 4g per day; no more than 4 consecutive days) was permitted. Patients (N=217) were randomized to receive intravenous (IV) R/S 0.03, 0.1, or 0.3 mg/kg or IV placebo (Pbo) on Day 1 and Day 57, with a 16-wk follow-up period after the second dose. Safety/tolerability [frequency of treatment emergent adverse events (TEAEs)] was the primary endpoint. Efficacy variables included change from baseline on WKP and Western Ontario and McMaster Osteoarthritis (WOMAC) Index.

Results: Baseline characteristics were similar among treatment groups: mean (SD) age 59.3±8.7 yrs; 31.2% male; and 78.1% white. After 24 weeks, the incidence of TEAEs ranged from 66.1–75.0% in the R/S groups vs 63.6% for placebo. The most common TEAEs included headache (R/S range 7.1–7.7% vs Pbo 7.3%), hypoaesthesia (3.8–7.7% vs 0%), musculoskeletal pain (6.6–7.0% vs 5.5%), peripheral edema/joint swelling (3.6–9.6% vs 0–1.8%), and respiratory infections (1.9–8.9% vs 1.8–7.3%). 5.6% of R/S patients and 3.7% of Pbo patients withdrew due to TEAEs; serious TEAEs were infrequent and the incidence of TEAEs was similar between active treatment groups and Pbo. Efficacy of treatment effect was reported in the individual R/S dosing groups vs Pbo; results of the key efficacy evaluations are summarized in the table below. At Week 16, a consistent dose-response relationship was demonstrated in the WOMAC pain and function subscales.

Table 1: Treatment Differences from Baseline at Weeks 8 and 16

<table>
<thead>
<tr>
<th>Key Efficacy Variables</th>
<th>Placebo (n=55)</th>
<th>0.03 mg/kg (n=55)</th>
<th>0.1 mg/kg (n=53)</th>
<th>0.3 mg/kg (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking Knee Pain (NRS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change (SD) from Baseline at Wk 8</td>
<td>−2.01 (2.08)</td>
<td>−2.8 (2.29)</td>
<td>−3.3 (2.61)*</td>
<td>−3.6 (2.48)*</td>
</tr>
<tr>
<td>Mean Change (SD) from Baseline at Wk 16</td>
<td>−2.5 (2.15)</td>
<td>−3.4 (2.49)*</td>
<td>−3.4 (2.59)*</td>
<td>−3.5 (2.55)</td>
</tr>
<tr>
<td>WOMAC Pain Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change (SD) from Baseline at Wk 8</td>
<td>−1.9 (1.74)</td>
<td>−2.6 (2.01)*</td>
<td>−3.4 (2.54)*</td>
<td>−3.5 (2.42)</td>
</tr>
<tr>
<td>Mean Change (SD) from Baseline at Wk 16</td>
<td>−2.4 (2.18)</td>
<td>−2.7 (1.99)</td>
<td>−3.4 (2.53)*</td>
<td>−3.2 (2.24)*</td>
</tr>
<tr>
<td>WOMAC Function Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change (SD) from Baseline at Wk 8</td>
<td>−1.8 (1.95)</td>
<td>−2.8 (2.07)*</td>
<td>−3.4 (2.32)*</td>
<td>−3.4 (2.57)</td>
</tr>
<tr>
<td>Mean Change (SD) from Baseline at Wk 16</td>
<td>−2.3 (2.30)</td>
<td>−2.9 (1.78)</td>
<td>−3.4 (2.28)*</td>
<td>−3.1 (2.18)*</td>
</tr>
</tbody>
</table>

* p < 0.05 (difference vs Pbo).

Conclusions: REGN475/SAR164877 was generally well-tolerated; incidence and type of TEAEs were similar to those previously reported with NGF inhibitor. Preliminary data suggests that nerve growth factor inhibition may be associated with a significant reduction in OA knee pain for up to 8 weeks, with dropouts at the highest dose possibly accounting for the reduced efficacy at 16 weeks.

Disclosure: P. Tisce: Regeneron Pharmaceuticals, Inc., 1, 3; A. J. Kivitz: None; J. E. Ervin: None; S. J. Mellis: Regeneron Pharmaceuticals, Inc., 1, 3; H. Ren: Regeneron Pharmaceuticals, Inc., 1, 3; D. Skfic: Regeneron Pharmaceuticals, Inc., 1, 3; R. Wu: Regeneron Pharmaceuticals, Inc., 1, 3; P. Powchik: Regeneron Pharmaceuticals, Inc., 1, 3.

Objectives: There is a pressing need to develop reliable molecular biomarkers that can inform on the process of joint destruction in osteoarthritis (OA). Such biomarkers could aid in drug development by identifying fast progressors and early response to therapy. Recent advance in metabolomics (the quantitative analysis of all metabolites present within a biological sample) has opened new avenues for biomarker identification. Using targeted metabolomic profiling approach, we have identified that serum branched chain amino acid to histidine ratio is associated with knee OA (Zhai G, et al Ann Rheum Dis 2010). To identify additional novel metabolic biomarkers for OA, we carried out this study using a non-targeted metabolomics approach.

Methods and Subjects: An available fasting serum sample derived from the TwinsUK cohort was utilized. 1052 Caucasian females were profiled metabolomically using non-targeted approach with LC-MS/MS. Among them, 891 individuals with mean age of 58±10.7 years had knee OA data available. 158 were knee OA cases defined as either having total knee joint replacement due to primary OA (n=22), radiographic knee OA if Kellgren-Lawrence score ≥2 (n=72), or self-reported clinical diagnosed knee OA (n=64). 733 were controls with none of these three case definitions. We examined the association between knee OA and the serum metabolic profile using robust linear regression. Their abundance in each individual’s serum sample was measured by the area counts under the MS spectral peak. The area counts were then transformed by natural logarithm to approximate normal distribution and used in the subsequent analysis after correcting for multiple testing with Bonferroni method.

Results: A total of 275 serum metabolites were identified. We examined the association between each of the 275 serum metabolites and knee OA with adjustment for age, and identified four metabolites associated with knee OA (p < 0.00018). γ-glutamyl valine was increased in knee OA patients (β=0.42 SD, p=0.00017), which is a confirmation of our previous findings. In addition, we found that α-tocopherol and bilirubin were negatively associated with knee OA (β=−0.47 SD, p=0.00004, and β=−0.43 SD, p=0.0001, respectively), and hydroxyeicosatetraenoic acid was positively associated with knee OA (β=0.46 SD, p=0.0001).

Conclusion: This novel study using high-throughput metabolomics confirms our previous findings of valine as a marker of OA and identified an additional three novel serum metabolic biomarkers for knee OA, which could have potential clinical utility.

Disclosure: G. Zhai: None; K. Suhre: None; D. Hart: None; C. Gieger: None; N. Soranzo: None; T. D. Spector: None.

ACR Concurrent Abstract Sessions
Rheumatoid Arthritis - Animal Models: Insight in Pathogenesis and Novel Therapeutic Targets
Monday, November 8, 2010, 4:30 PM–6:00 PM

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Anti-CD20 Therapy Inhibits the Progression of Synovitis and Focal Erosion in the Knee Joints but Not in the Ankle Joints of TNF-β mice. Jie Li, Igor Kuzin, Christopher Ritchlin, Ignacio Sanz, Andrea Bottaro, Lianping Xing and Edward Schwarz. University of Rochester, Rochester, NY

Purpose: B cell depletion therapy (BCDT) is effective for some RA patients. However, its mechanism of action and variable efficacy remains an enigma. Previously we utilized contrast enhanced (CE) MRI, micro-CT and near infrared-indocyanine green (NIR-ICG) lymphatic imaging to evaluate arthritis in TNF-β mice, and demonstrated that disease commences in the ankle, which is consistent with reports defining synovitis in the foot as the initiating pathology. We also found that arthritic progression occurs following a sudden decrease in lymphatic flow from the lower limb to the popliteal lymph node (PLN). This decrease leads to a “collapsed” phenotype characterized by the translocation of CD23+CD21hi B cells from the follicles into the sinus space, resulting in “clogging” lymphatic flow of the PLN. Thus, we hypothesize that BCDT ameliorates TNF-induced arthritis by increasing lymphatic flow through the depletion of these B cells, and tested this in our murine model.

Methods: TNF-β mice with collapsed PLNs and ankle synovitis were identified by CE-MRI and followed with scans every two weeks. NIR-ICG footpad clearance (T-clearance) and micro-CT scans were performed before and after treatment with anti-CD20 (n=8; 16 knees) (10mg/kg/i.v. every two weeks) or placebo (n=4; 4 knees) for 6 weeks. PLNs were harvested for flow cytometry or immunohistochemistry (IHC). Ankle and knee joints were harvested for H&E and TRAP histology.

Results: 1) Anti-CD20 significantly decreased knee synovial volume (SynVol=4.55±/-2.39mm³, p<0.002) and synovitis progression (p<0.0003) vs. placebo (SynVol=8.98±/-4.16mm³), and PLN B cells (80–95% depletion). 2) Anti-CD20 significantly increased T-clearance from 82.3±/-0.16% to 90.4±/-0.08% (p=0.02). 3) Anti-CD20 protected the knee from focal erosions, as there was no significant change in patellar bone volume (p=0.1). However, it failed to prevent bone erosion in the ankle joint, as the talus volume dramatically decreased from 0.64+/−0.32mm³ to 0.30+/−0.27mm³ (p=2×10⁻¹⁰) during the 6-week treatment.

Conclusion: Our results show BCDT effectively inhibits progression of arthritis in knee, but not in the ankle, suggesting distinct etiologies for large and small joint pathogenesis. The lack of efficacy observed in the foot is consistent with unabated tenosynovitis in which B cells play little if any role, as evidenced by arthritis in the ankles of TNF-β mice. In contrast, the absence of tendon insertions proximal to synovium in large joints precludes tenosynovitis as a mechanism of inflammatory-erosive arthritis in the knee. Our observations that draining lymph function and the location of B cells in PLNs correlates with disease in the adjacent knee of TNF-β mice is consistent with a novel mechanism of action for BCDT in which removal of the B cells that are “clogging” the lymphatic vessels restores draining function to ameliorate synovitis. Our current clinical pilot to test this hypothesis in anti-TNF refractory RA patients receiving BCDT will be discussed.

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Identifying the TLR4 Bearing Target Cell in Experimental Arthritis. Ben T. van den Brand, Shahila Abdollahi-Roodsaz, Miranda B. Bennink, Onno J. Amrit, Wim B. van den Berg and Fons A. J. van de Loo. Radboud University Nijmegen Medical Centre

Purpose: The IL-1 receptor antagonist (IL-1Ra) knockout mice spontaneously develop T-cell driven arthritis due to excessive IL-1 signalling. Joint destruction is accompanied by increased Th17 cells and elevated IL-17 levels compared to wild type (Balb/c) mice. When crossed bred with TLR4 knock out (TLR4−/−) these animals showed reduced inflammation, joint destruction, and diminished IL-17 levels. To reduce adverse effects of TLR4 inhibition a cell specific targeted therapeutic strategy is desired. Therefore, we set out to identify the TLR4 bearing cells in experimental arthritis responsible for increased IL-17 production and arthritis severity.

Method: A reciprocal sex-mismatched bone marrow transplantation was performed with TLR4−/− and TLR4+/+ mice in the IL-1Ra−/− background and Balb/c bone marrow as control. Y-chromosome staining of bone marrow cells or the radio-resistant cells in the joint did not affect disease incidence. However, animals that lacked TLR4 on the engrafted bone marrow derived cells, radio-resistant cells, or both showed reduced macroscopic arthritis scores. In mesenteric lymph nodes there were no differences observed in percentage of IFNγ and IL-17 producing cells. Neither was there a difference in Th1 cells in the spleen. However, decreased Th17 levels were observed in the spleen when radio-resistant cells lack TLR4.

Conclusion: These data suggest that TLR4 plays a role on both the bone marrow derived and local resident cells in aggravating experimental arthritis. TLR4 plays a role locally on the synovial fibroblasts by creating a more aggressive inflammatory environment in the joint cavity and thereby increases...
ing joint destruction. Conversely, TLR4 activation on the bone marrow derived cells could increase T-cell activation by antigen presenting cells and thereby promoting a more aggressive Th17 phenotype and increase joint swelling.

Disclosure: B. T. van den Brand: None; S. Abdollahi-Roodsaz: None; M. B. Bennink: None; G. J. Arutz: None; W. B. van den Berg: None; F. A. J. van Leeuwen: None.

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Local Expression of IL-27 Reduces Collagen Induced Arthritis through Reduction of Monocyte Migration and Vascularization. Sarah R. Pickens1, Michael V. Volin1, Arthur M. Mandelin2 and Shiva Shahrara3. 1Midwestern University, 2Northwestern University, Chicago, IL, 3Northwestern University

Introduction: To determine the effect and potential mechanism of IL-27 treatment in rheumatoid arthritis (RA), local expression of IL-27 was studied in ankle joints of collagen induced arthritis (CIA) mice compared to control animals.

Methods: Adenovirus containing IL-27 transcript (Ad-IL-27) was constructed and was locally delivered into the ankles of CIA mice. Clinical parameters were assessed histologically and by measuring ankle circumference. IL-17 and its downstream targets, as well as cytokines promoting TH-17 cell differentiation, were quantified by ELISA from CIA tissue homogenates locally expressing IL-27 or Ad-control. Ankles from both treatment groups were immunostained for neutrophils and monocytes and vascularization was determined by quantifying ankle hemoglobin levels and PECAM expression by real-time RT-PCR.

Results: The joint circumference of Ad-IL-27 injected animals was significantly smaller than control animals throughout the study. Histological analysis of ankles from day 41 confirmed that local expression of IL-27 resulted in significantly less inflammation compared to the control group. Further histological studies demonstrated that local expression of IL-27 resulted in a significant decrease (p<0.05) of synovial lining thickness and bone erosion. Next, we found that the cytokines which induce TH-17 cell differentiation (IL-1β and IL-6) and the downstream targets of IL-17 (CXCL1, CXCL5 and CCL2) were significantly decreased in ankle homogenates by local expression of IL-27 compared to control treatment. CIA ankles immunostained for neutrophils and monocytes showed that the local expression of IL-27 greatly decreased the infiltration of these cells into the ankle joints compared to control group. In order to quantify the vascularization changes in the Ad-IL-27 group, ankle hemoglobin and PECAM levels were quantified and compared to control group. Ad-IL-27 treated CIA ankle joints had significantly reduced hemoglobin and PECAM levels compared to control joints.

Conclusion: Our results suggest that increased IL-27 levels relieved arthritis in CIA ankles. This amelioration of arthritis involved a reduction of IL-27-induced TH-17 cell differentiation and resulted in decreased IL-17-mediated monocyte recruitment and angiogenesis. Hence, IL-27 may be a therapeutic target in RA.

Disclosure: S. R. Pickens: None; M. V. Volin: None; A. M. Mandelin: None; S. Shahrara: None.

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Impaired B Cell Immunity in IL-22 Knock-Out Mice in Collagen Induced Arthritis. Odilia Cometh1, Anne-Marie Mus2, Patrick Asmawidjaja3, Laurens Kil2, Wenjun Ouyang3, Rudi Hendriks2 and Erik Lubberts2. 1Worcester, MA, 2Indianapolis, IN, 3Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, IN, 4Department of Medicine and Department of Cell Biology, University of Massachusetts Medical School, Worcester, MA, 5St. Vincent’s Institute, Fitzroy, VIC, Australia

Background: Rheumatoid arthritis (RA) is characterized by chronic synovial inflammation and invasive pannus that drives osteoclast-mediated articular bone erosion. While effective therapies can slow the progression of bone erosion, repair occurs in only a small percentage of RA patients and generally correlates with control of disease.

Methods: To examine the potential for erosion repair and mechanisms driving this process, inflammatory arthritis was induced by transfer of arthrogenic K/BxN serum and articular cartilage from old C57BL/6 mice. Once arthritis was subsequently allowed to resolve. Clinical inflammation peaked at day 10 after initial serum injection and full resolution of clinical inflammation occurred between days 28 and 38. Forefoot bones of the hind paws were evaluated by histology, microCT, and histomorphometry, and quantitative RT-PCR (qPCR) was performed on synovial tissue.

Results: qPCR of synovial tissue confirmed resolution of inflammation, with a 20-fold induction of IL-1β mRNA, 1.5-fold induction of TNF, and 40-fold induction of MMP-13 at day 10, all of which returned to non-arthritic levels by day 28. RANKL/OPG mRNA ratios in synovium also correlated with inflammation, favoring osteoclast-mediated resorption at day 10 and protection from resorption beginning as early as day 15. Serial microCT and histologic analysis of the forefoot bones were consistent with repair of previously established erosions. To quantify bone formation occurring with the resolution of inflammation, dynamic histomorphometric analyses of fluorescence incorporation at sites of erosion were performed on days 10, 28, 38, 48 and 58. Inflammation at the bone interface (day 10) was accompanied by a 20-fold increase in BFR, similar to rates in non-arthritic mice, as we previously reported. In this study, we found that resolution of inflammation from days 28 to 48 was accompanied by a significant increase in BFR and mineral apposition rate (MAR) in arthritic compared to non-arthritic mice, contributing to repair at sites of erosion. Reduction of inflammation was accompanied by striking changes in the expression of modulators of the Wnt/β-catenin pathway, a pathway responsible for bone formation. qPCR revealed that inflammation induced expression of the Wnt antagonist SFRP1.
SB1578, a Novel Selective JAK2 Inhibitor, Is Highly Efficacious in Rodent Models of Rheumatoid Arthritis. 

Kee Chuan Goh, Stefan Hart, Rodent Models of Rheumatoid Arthritis. 

SB1578, a Novel JAK2 Inhibitor which demonstrates a unique kinase spectrum, activity on cellular biomarkers, favorable pharmacokinetic and in vitro safety profile, and promising activity in 2 rodent models of rheumatoid arthritis.

Methods: 

In vitro potency of SB1578 against a diverse panel of kinases was evaluated using recombinant enzymes with synthetic substrates. Potency on intracellular signaling pathways was assessed by Western blot analyses of the phosphorylated substrates in cell lysates. Viability assays were performed on tumor cell lines to investigate potential anti-proliferative activity. 

In vivo efficacy was tested in a rat model of adjuvant-induced arthritis and a mouse model of collagen-induced arthritis. 

Results: 

SB1578 was shown to be a potent inhibitor of JAK2 (IC50 = 46 nM) as well as two other kinases reported to be implicated in human rheumatoid arthritis, namely FLT3 and CSF-1R (IC50 = 62 nM and 69 nM respectively). In a panel of 25 cell lines, SB1578 selectively inhibits proliferation in cell lines with a known dependence on JAK2 or FLT3 signaling, whether wild-type or mutated. These include MV4-11, Molm13, 32D, and 722T, all of which express high levels of JAK2, whereas H9262 and 12/12 and 12/23, these cytokines, in different sequence and combinations with other factors, initiate and/or sustain the T-helper cell subsets activated during autoimmune inflammatory diseases. The JAK2 kinase may therefore serve as a useful target for pharmacological intervention in some of these diseases, including rheumatoid arthritis (RA). We report here SB1578, a novel JAK2 inhibitor which demonstrates a unique kinase spectrum, activity on cellular biomarkers, favorable pharmacokinetic and in vitro safety profile, and promising activity in 2 rodent models of rheumatoid arthritis.

Conclusions: 

SB1578, a novel and selective JAK2 inhibitor, has demonstrated promising anti-tumor activity in JAK2-dependent cell lines and is highly efficacious in two rodent models of rheumatoid arthritis. It is currently undergoing final preclinical development activities to prepare it for clinical studies.

Disclosure: 

Background: The atherosclerotic process is accelerated in patients with rheumatoid arthritis (RA), contributing to higher mortality rates than those found in the general population. Recently, treatment with TNF-blockers has been associated with a lower risk of first-ever CVD events. However, the mechanisms by which TNF-blockers exert this effect is unclear. Adipocytokines have been linked to obesity, insulin resistance, inflammation, and coronary heart disease in the general population and their serum levels are elevated in RA. To explore the relationship between inflammation and atherosclerosis, we investigated the effects of anti-TNF therapy on serum adipocytokine levels (adiponectin, resistin, leptin and visfatin) and known risk factors such as C-reactive protein levels and lipid profile in RA patients.

Methods: 49 patients with active disease (disease activity score evaluated in 28 joints (DAS28)) ≥3.2) were started on adalimumab therapy (40 mg subcutaneously every other week). Blood was drawn from patients while fasting at baseline and 16 weeks after the initiation of therapy. Lipid profiles (total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), lipoprotein (a) (Lp(a)), ApoA-I and Apo B levels), CRP and ESR were determined. Adiponectin, resistin and leptin levels were measured using multiplex analysis and visfatin levels were measured by ELISA.

Results: After 16 weeks of treatment, there was a significant reduction in DAS28 (p<0.001), ESR (p<0.001), and CRP (p<0.001) levels. Of interest, we found a decrease in serum concentrations of resistin (19.2%, p=0.02) and visfatin (17.2%, p=0.09). There were no clear cut changes in serum levels of adiponectin (p=0.91) and leptin (p=0.55). Furthermore, a significant improvement was seen of the TC/HDL ratio (p=0.047), the apolipoprotein A-I ratio (p=0.013) and lip(a) levels (p<0.001). Baseline visfatin levels correlated with ESR. The TC/HDL ratio and LDL/HDL ratio. In addition, the decrease in visfatin levels was related to improvements in LDL/HDL ratio (r=0.32, p=0.05) and TC/HDL ratio (r=0.35, p=0.03).

Conclusions: These data support the downregulation of visfatin as a potential new mechanism by which anti-TNF therapy might reduce vascular inflammation, and as such cardiovascular morbidity in RA patients. These data are in line with recent observations that elevated visfatin levels are related to abnormalities in lipid metabolism.

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Biologies and Risk of Lymphoma in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Lindsay C. Burns1, Mary De Vera1, Vidhula Bhole1, Yanyan Zhu1, Peter Grayson1, W. de Jager2, Kevin Winthrop1 and Elizabeth Delzell2. 1OHSU, 2Univ of Alabama at Birmingham, Birmingham, AL.

Purpose: A previous meta-analysis of biologics trials has reported a three-fold increased risk of malignancies (including lymphoma) (Bongatz et al JAMA 2006), but trials are not designed to capture long-term safety outcomes. To this end, we conducted a systematic review and meta-analysis to determine whether biologic use among RA is associated with risk of lymphoma.

Methods: We searched MEDLINE, EMBASE, and INTERNATIONAL PHARMACEUTICAL ABSTRACTS databases from Jan 1990 to May 2010 for studies that evaluated adverse effects of biologics or evaluated efficacy of biologics with reporting of adverse events. Eligibility criteria were: a) use of an RCT or observational study design (case control, cohort study), b) a study duration of ≥12 weeks, c) sample size of ≥100 for observational studies, d) RA population, or if mixed population, reporting of RA-specific results, e) evaluation of a biologic therapy as mono-therapy or in combination with other RA therapies, f) clearly defined lymphoma outcomes, and g) information on relative risk (RR), odds ratio (OR), and 95% confidence intervals (95% CI). We calculated weighted-pooled summary estimates for lymphoma risk using a random effects model. Then, we combined our results with the previous meta-analysis. We used a random effects model. Then, we combined our results with the previous meta-analysis. We calculated weighted-pooled summary estimates for lymphoma risk using a random effects model. Then, we combined our results with the previous meta-analysis.

Conclusion: Our meta-analysis of the current literature does not support an increased risk of lymphoma with biologic use in RA. The differences between the previous meta-analysis of trials and the current study include study type (trial vs. observational study), durations, and sample sizes.

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The Comparative Incidence of Serious Infections among Rheumatoid Arthritis Patients Who Switch Biologic Agents. Jeffrey R. Curtis1, Feng-Long Xie2, Lang Chen3, John Baddley1, Timothy Beukelman3, Kenneth G. Saag4, Kevin Winthrop4 and Elizabeth Delzell2. 1OHSU, 2Univ of Alabama at Birmingham, Birmingham, AL, 3University of Alabama–Birmingham, Birmingham, AL, 4University of Alabama-Birmingham, Birmingham, AL, 5University of Alabama-Birmingham, Birmingham, AL.

Background: The safety profile of the anti-TNF agents has been well characterized. However, it is unclear whether the comparative safety of newer biologics with different mechanisms of action is similar to the anti-TNF agents. Our objective was to evaluate the incidence of hospitalized infections among rheumatoid arthritis (RA) patients switching to a new biologic.

Methods: Using the administrative databases of a large U.S. healthcare organization from 1/2005-3/2009, we identified enrollees with RA based on having at least 1 physician visit for RA (ICD9 714.X). To control for confounding related to characteristics that cause patients to switch from one biologic to another, eligible patients were those switching to a new biologic who had been treated with a different biologic in the preceding 6 months, defined as the baseline period. Observation time began on the switch date. To further control for confounding, we created pair-wise propensity scores (PS) for each drug contrast using covariates measured at baseline. PS were categorized into quintiles; non-overlapping regions of the PS distributions were trimmed. Exposure was defined as current use of the biologic, allowing for an extension of 90 days. Outcomes of interest were hospitalized infections identified using previously-validated algorithms. Cox proportional hazards models evaluated the incidence rate of hospitalized infections, comparing each biologic to infliximab, selected as a convenient reference standard for average RA duration ranging from 127 to 158 months. A total of 19,323 patients contributed 119,433 person years of follow up, and 129 lymphomas were identified. Using adjusted values, the pooled risk estimate for lymphoma was 1.20 (95% CI, 0.80–1.60) (Figure). Heterogeneity was small (I2-statistic p=0.79) and we did not detect publication bias (Egger test p=0.26). Combining results with recent meta-analysis did not change the pooled risk estimate (1.22; 95% CI, 0.82–1.62) materially.
uniform comparison. Observation time was censored at the first hospitalized infection, end of study, or lack of current exposure.

**Results:** Among a total of 101,906 unique RA patients enrolled in the health plan, 1923 switched to a new biologic and contributed 1915 person-years (py) of observation. Characteristics of these eligible patients were mean ± SD age 49.3 ± 11.2 years, 78% women. A total of 82 fast hospitalized infections were identified; the rate of hospitalized infections ranged from a low of 1.8 (switch to etanercept) to a high of 0.2 (switch to rituximab) per 100py. There was insufficient use of golimumab or certolizumab to evaluate these agents. Refer to infliximab, there were no significant differences between the rates of infection for any biologic after adjusting for age, sex, and PS quintile (Table). There were no cases of active tuberculosis or of hospitalized progressive multifocal leukoencephalopathy (PML).

**Conclusion:** The rate of all hospitalized infections among RA patients switching to a new biologic varies across a relatively small range and was not significantly different between agents.

**Hazard Ratio Comparing the Rate of Serious Infections for Persons Switching to Various Biologics**

<table>
<thead>
<tr>
<th>Drug Switching To</th>
<th>Incidence Rate (per 100 pt-years)</th>
<th>Crude Hazard Ratio</th>
<th>Adjusted for age, sex, propensity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>5.8</td>
<td>1.08 (0.57, 2.04)</td>
<td>0.87 (0.45, 1.70)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>3.8</td>
<td>0.73 (0.40, 1.34)</td>
<td>0.68 (0.36, 1.29)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1.8</td>
<td>0.44 (0.19, 1.05)</td>
<td>0.46 (0.19, 1.12)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>4.8</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>6.2</td>
<td>1.07 (0.56, 2.05)</td>
<td>0.89 (0.43, 1.82)</td>
</tr>
</tbody>
</table>


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**Characteristics of Cases of PML among Patients with Selected Rheumatic and Autoimmune Diseases.** Timothy Beukelman, F. Xie, Lang Chen, John Baddley, Elizabeth Delzell, Carlos G. Grijalva, Nivedita Birmingham, 4University of Alabama - Birmingham, Birmingham, AL, 5University of Alabama-Birmingham, Birmingham, AL, 6University of Alabama-Birmingham, Birmingham, AL, 7Vanderbilt

**Background:** The incidence and antecedent risk factors for infection in rheumatic diseases, particularly PML, are not well understood due to the rarity of the disease. This study aimed to explore the incidence and risk factors associated with PML in a large, real-world cohort of patients with rheumatic and autoimmune conditions.

**Methods:** The study used a retrospective observational design, utilizing data from the National Center for Health Statistics (NCHS) and the Health Information Network (HIN) databases. Patients with a primary rheumatic or autoimmune diagnosis were included. PML cases were identified through a combination of clinical and laboratory data. The primary outcome was the incidence of PML, and secondary outcomes included the identification of risk factors associated with PML.

**Results:** Among 712,708 unique individuals with RA, PsA, PsO, JIA, IBD, or AS, a total of 55 hospitalizations for PML were identified (7.7 per 100,000 individuals). Of these cases, 29 had insurance coverage for at least 6 months prior to the PML case date and had one or more physician diagnoses of a rheumatic disease that occurred before the PML case date. Characteristics of these 29 PML cases include mean ± SD age 46.8 ± 8.8 years, 41% women. There was at least 1 case of PML that occurred among patients with each rheumatic disease studied except for JIA. The most prevalent concomitant comorbidity was HIV (83% of patients). Additional comorbidities present with low prevalence among PML cases included malignancy and concomitant systemic lupus erythematosus. At least one individual with PML had none of these comorbidities nor HIV but was a current user of infliximab.

Among all PML cases, more than 1 patient had antecedent exposure to infliximab in the 6 months prior to the PML case date; the median time from the most recent exposure to infliximab to hospitalization for PML was between 1 and 2 months. No other PML patients had any prior exposure to any other biologic agent. Fewer than 10 patients were using glucocorticoids in the 6 months prior to the PML infection. More than 1/3 of patients died in the 4 months following the PML case date.

**Conclusion:** PML is a rare infection that has been observed to occur among patients with inflammatory and autoimmune conditions, even in the absence of recent biologic drug exposure or other risk factors such as HIV. A better understanding of the epidemiology of PML infections and associated risk factors may be useful to inform patients regarding this rare but serious adverse event.

**Disclosure:** T. Beukelman: None; F. Xie: None; L. Chen: None; J. Baddley: None; E. Delzell: Amgen Inc., 2; C. G. Grijalva: None; N. M. Patkar: None; K. G. Saag: Amgen Inc., 2, 5, 8, AstraZeneca, 5, Aventis Pharmaceuticals, 5, Eli Lilly and Company, 2, 5, Genentech and Biogen IDEC Inc, 5, GlaxoSmithKline, 2, 5, Merck Pharmaceuticals, 2, 5, NovoX, 5, Nitec, 5, Novartis Pharmaceuticals Corp; K. Winthrop: Amgen Inc., 5, Genentech and Biogen IDEC Inc, 5, Oxford Immunotec, 2, Wyeth Pharmaceuticals, 5; J. R. Curtis: Amgen Inc., 2, Centocor, Inc., 2, 5, Corvina, 2, Roche, 5, UCB, Inc., 2, 5, 8.

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**Consequence of Remission Misclassification Due to Reduced Joint Counts Omitting the Feet.** Lilian H. D. van Tulip, a Karin Brissimesser, a David T. Felson, b George A. Wells, c Josep S. Smolen, d Bin Zhang, e Julia Funovits, f Dirkjan van Schaarburg, f and Maarten Boers. f

**Introduction:** With remission in rheumatoid arthritis (RA) as a realistic outcome of treatment, the ACR, EULAR, and OMERACT have joined forces to develop a new definition for remission in RA to be used in clinical trials. One of the issues on the research agenda is the consequence of using a 28- vs a more complete joint count. Several studies report residual disease activity in the feet in patients with a 28-joint count of zero, although this might not be a problem in defining remission if such patients fail to classify because of activity in other measures within the definition.

In an observational early disease cohort we studied the consequences of misclassification due to reduced joint activity in the feet of patients in remission by 28-joint counts.

**Methods:** All patients fulfilling the '87 ACR criteria for RA at inclusion or at 1 year follow up in the early arthritis cohort of the Jan van Breemen Institute (Amsterdam, The Netherlands), not using biologicals were included.

Boolean as well as index-based candidate remission definitions were calculated using the 28- and 38 joint count that includes the 10 metatarsal joints.

Disease stability was defined as stable x-ray scores over 1 year change ≤0 in van der Heijde/Sharp scores AND stable and low scores on the Health Assessment Questionnaire (HAQ change ≤0 AND HAQ score consistently ≤0.5), all during the 2nd year after inclusion.

Analyses comprised: 1) residual disease activity (swollen or tender joints >0) in the feet of patients that fulfilled the candidate remission criteria using a 28 joint count; 2) likelihood ratio’s of remission definitions to predict disease activity in the feet of patients in remission by 28-joint counts.

**Results:** Of a total of 423 RA patients 8 to 30% reached remission at 1 year using a 28 joint count (Table 1).

**Table 1.** Count(%) of patients in remission with active feet

<table>
<thead>
<tr>
<th>Remission definition</th>
<th>Total in remission</th>
<th>Subset with TJC or SJC &gt; 0 in feet</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJC+SJC+CRP+</td>
<td>38 (9)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>PIGA*</td>
<td>36 (9)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>PIGA+PI&lt;1</td>
<td>38 (9)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>PIGA+P&lt;1</td>
<td>34 (8)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>PIGA+P+PI&lt;1</td>
<td>32 (8)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>SDAI ≤3.3</td>
<td>61 (14)</td>
<td>22 (5)</td>
</tr>
<tr>
<td>CDAI ≤2.8</td>
<td>63 (15)</td>
<td>25 (6)</td>
</tr>
<tr>
<td>DAS28 ≤2.6</td>
<td>128 (30)</td>
<td>56 (13)</td>
</tr>
</tbody>
</table>

*New ACR/EULAR preliminary remission definitions in RA
The 6-measure Boolean definition is most strict, the DAS28<2.6 most relaxed. Of these, 26 to 44% showed activity in the feet, ~70% being due to both swelling and tenderness. Misclassification due to reduced joint counts was observed in 2 to 3% of patients measured with a Boolean definition.

A state of remission increased the likelihood of stability of both x-ray and HAQ, with slightly higher LR values for definitions using 38 joint counts vs definitions using 28 joint counts.

Table 2. Likelihood ratio’s of remission definitions with 28 vs 38 joint counts to predict disease activity

<table>
<thead>
<tr>
<th>Remission definition</th>
<th>Joint counts</th>
<th>Total in remission</th>
<th>Stable and:</th>
<th>not in remission</th>
<th>LR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC+JC+SJC+CRP+</td>
<td>28</td>
<td>38</td>
<td>15</td>
<td>70</td>
<td>2.6*</td>
<td></td>
</tr>
<tr>
<td>PtGA ≤1</td>
<td>38</td>
<td>29</td>
<td>12</td>
<td>73</td>
<td>2.8*</td>
<td></td>
</tr>
<tr>
<td>PtGA+PtGA ≤1</td>
<td>28</td>
<td>36</td>
<td>15</td>
<td>70</td>
<td>2.8**</td>
<td></td>
</tr>
<tr>
<td>PtGA+PtGA ≤1</td>
<td>28</td>
<td>37</td>
<td>27</td>
<td>73</td>
<td>3.2**</td>
<td></td>
</tr>
<tr>
<td>PtGA+pain ≤1</td>
<td>28</td>
<td>38</td>
<td>19</td>
<td>66</td>
<td>4.0**</td>
<td></td>
</tr>
<tr>
<td>PtFA+pain ≤1</td>
<td>28</td>
<td>36</td>
<td>14</td>
<td>71</td>
<td>4.6**</td>
<td></td>
</tr>
<tr>
<td>PtGA+pain ≤1</td>
<td>28</td>
<td>34</td>
<td>11</td>
<td>71</td>
<td>7.2**</td>
<td></td>
</tr>
<tr>
<td>PtFA+pain ≤1</td>
<td>38</td>
<td>25</td>
<td>11</td>
<td>74</td>
<td>3.1*</td>
<td></td>
</tr>
<tr>
<td>PtFA+pain+PtFA ≤1</td>
<td>28</td>
<td>32</td>
<td>14</td>
<td>71</td>
<td>3.1**</td>
<td></td>
</tr>
<tr>
<td>PtFA+pain+PtFA ≤1</td>
<td>38</td>
<td>23</td>
<td>11</td>
<td>74</td>
<td>3.7**</td>
<td></td>
</tr>
</tbody>
</table>

*P-value <0.01; **P-value <0.001

Conclusion: A substantial proportion of patients in remission according to 28 joint counts show activity in the feet. Actual misclassification occurs in 2–3% of the total population studied. The ability of remission definitions with 28 vs 38 joint counts to predict long term good radiological and functional outcome is highly similar.

Disclosure: L. H. D. van Tuyl: None; K. Britsensmer: None; D. T. Felson: None; G. A. Wells: None; J. S. Smolen: None; B. Zhang: None; J. Funovits: None; D. van Schaardenburg: None; M. Boers: None.

ACR Concurrent Abstract Sessions
Systemic Sclerosis, Fibrosing Syndromes, and Raynaud’s - Clinical Aspects and Therapeutics
Monday, November 8, 2010, 4:30 PM–6:00 PM

724 Use of Serum Clara Cell 16-kDa (CC16) Levels as a Potential Indicator of Active Pulmonary Fibrosis in Systemic Sclerosis Minoru Hasegawa, Manabu Fujimoto and Kazuhiko Takehara. Kanazawa University

Background: Pulmonary fibrosis (PF) is one of the major systemic sclerosis (SSc)-related causes of death. Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D) are currently considered the best serum markers of PF in patients with SSc. However, these markers are not perfect and an additional serum marker may be helpful for reliable monitoring of PF. Clara cell 16-kDa (CC16, previously named CC10) is a pneumoprotein secreted from the tracheobronchial tree, specifically in the terminal bronchioles where Clara cells are localized.

Objective: To clarify the clinical significance of serum CC16 protein levels in the diagnosis and monitoring of PF in patients with SSc, and to compare CC16 levels with levels of KL-6 and SP-D.

Methods: Serum CC16 levels were determined by competitive enzyme-linked immunosorbent assay (ELISA) and serum levels of KL-6 and SP-D were measured by sandwich ELISA in 92 SSc patients, 20 systemic lupus erythematosus (SLE) patients, and 20 healthy controls. In a retrospective study, correlation of serum CC16 levels with the progression of PF was assessed in 16 SSc patients with elevated serum CC16 levels at their first visit.

Results: Although CC16 levels at the first visit were higher in patients with SSc than in SLE patients or healthy controls, the difference was not significant. Serum levels of CC16 were comparable in limited cutaneous SSc and diffuse cutaneous SSc patients (60.8 ± 109.5 vs. 78.3 ± 124.3 ng/ml) and significantly elevated in SSc patients with PF compared with SSc patients without PF (90.8 ± 110.7 vs. 42.1 ± 80.7 ng/ml, p<0.05). Furthermore, SSc patients with active PF showed significantly elevated serum CC16 levels compared to patients with inactive PF (168.8 ± 161.5 vs. 53.8 ± 95.0 ng/ml, p<0.01). Serum CC16 levels were significantly associated with SP-D (r=0.39, p<0.01), but not with KL-6 (r=0.19, p=0.15). In a longitudinal study, reduced serum CC16 levels were associated with the stabilization of PF activity. Although the serum CC16 levels were less useful for the evaluation of PF severity, CC16 levels were likely as effective for the monitoring of PF activity as KL-6 or SP-D.

Conclusions: Our findings suggest that CC16 levels can be used as a potential serum biomarker for active PF in SSc. Use of this marker in combination with KL-6 and SP-D may be a more valuable as an indicator of PF activity in SSc patients than KL-6 and SP-D alone. Further prospective and comparative studies in larger populations will be needed to confirm these studies.

Disclosure: M. Hasegawa: None; M. Fujimoto: None; K. Takehara: None.


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Background: Scleroderma Renal Crisis (SRC) is a life-threatening complication of systemic sclerosis (SSc). The Major Histocompatibility Region (MHC) showed the strongest association with SSc in a recently published large genome-wide association study, raising the possibility that this gene locus might be also important for biomarker development. The predictive significance of MHC genetic markers for SRC has not been previously investigated. The goal of the current study was to examine the predictive role of MHC genetic markers for the SRC beyond the known clinical correlates in a large population of patients with SSc.

Methods: SSc patients from the Scleroderma Family Registry and DNA Repository, Genetics versus Environment in Scleroderma Outcomes Study (GENISOS) and divisional registry at the University of Texas Health Science Center at Houston were included in the study. Patients, enrolled in more than one of the above mentioned sources, were identified and duplicate entries were omitted. ANA, anticientromere (ACA), anti-topoisomerase (ATA), and anti-RNA polymerase III (ARA) antibodies were detected utilizing commercially available kits. Furthermore, HLA Class II genotyping (DRB1, DQA1, DPB1) was performed on extracted and purified genomic DNA. Multivariate models were constructed following a purposeful variable selection method. First, we evaluated the demographic and clinical variables without genetic risk factors for their multivariable associations with SRC. Subsequently, we conducted a separate purposeful model building analysis after addition of the MHC genetic data. Ethnicities were included in all univariate and multivariable genetic analysis models.

Results: Overall, 1519 patients with SSc were included in this study, from which 90 patients (5.9%) had developed SRC. Of the 90 patients with SRC, diffuse cutaneous subtypes were found in 76%, ATA in 9%, ACA in 2%, and ARA in 50%. ARA and diffuse disease type were independent risk factors for presence of SRC, whereas ACA and ATA were protective in the multivariate model of clinical variables. In the final multivariable analysis after inclusion of HLA alleles, we identified HLA-DRB1*0407 (OR=3.21, 95% CI 1.27–8.08; P=0.013) and *1304 (OR=4.51, 95% CI 1.30–15.68; P=0.018) as independent risk factors for SRC. Only 3 clinical characteristics, ARA, diffuse disease type and ACA remained statistically significant in the final model.

Conclusion: This study suggests that HLA DRB1*0407 and *1304 can be used as biomarkers for identification of SSc patients at risk for developing SRC beyond the information provided by known clinical predictors.

Disclosure: B. Y. Nguyen: None; M. D. Mayes: None; F. C. Arnett: None; D. J. del Junco: None; E. B. Gonzalez: None; H. T. Draeger: None; M. Perry: None; A. Hendifar: None; J. D. Revelle: None; S. Assassi: None.
A Formula To Predict Mean Pulmonary Artery Pressures in Patients with Connective Tissue Disease Based on Echocardiography, NTproBNP and O₂ Saturation. Benjamin E. Schreiber, Christopher J. Valerio, Clive Handler, Greg Keir, Athol U. Wells, Christopher P. Denton and J. Gerry Coghlan. Royal Brompton Hospital, London, Royal Free Hospital, London, United Kingdom.

The area under the curve was 0.84 (95% CI 0.77–0.91). Using a threshold predicted mPAP of 25 it has a sensitivity of 87.3%, specificity of 55.8%, positive LR of 2.0 and negative LR of 0.2. Using a threshold predicted mPAP of 30, it has a sensitivity of 66.2%, specificity of 90.4%, positive LR of 6.9, negative LR of 0.4.

Disclosure: E. W. Hung: None; M. D. Mayes: None; L. Keyses-Elslein: None; L. J. Crofford: None; M. E. Csuka: None; D. E. Furst: None; E. Goldmuntz: None; P. McSweeney: None; R. Nash: None; V. Machico: None; K. Sullivan: None.

**Introduction:** Pulmonary Hypertension (PH) is an important complication of connective tissue disease (CTD). Diagnosis is confirmed by right heart catheter (RHC) but no single non-invasive test accurately predicts PH. To improve selection of patients for RHC, we analysed the relationship between non-invasive tests and mean pulmonary artery pressure (mPAP) at RHC and derived a new formula to predict PAP.

**Methods:** Retrospective analysis of patients with CTD undergoing a first RHC. In our database we have 968 patients (811 SSc, 53 SLE, 15 RA, 42 UCTD, 8 MCTD, 12 DM, 7 PM, 6 Sjogrens, 3 antiphospholipid syndrome, 3 vasculitis). We included for analysis NTproBNP and echocardiography if performed within 3 months of RHC and pulmonary function tests if done within 6 months. Pulse oximetry was measured at the time of the RHC.

**Results:** Regression analysis of these variables individually against mPAP at RHC gave the following results: DLCO (n=469) gave R²=0.87, AUC=0.68; NTproBNP (capped at 300 pmol/litre to reduce the skewing effect of large values) with n=380, gave R²=0.31, AUC=0.74 and echo derived tricuspid valve gradient (n=165) gave R²=0.48, AUC=0.81. Capping NTproBNP gave similar results to a log transformation.

Multivariable linear regression showed significant correlation with mPAP for Echo derived TV gradient (p<0.0005), capped NTproBNP and Oxygen (p=0.004). Addition of predicted DLCO, KCO, FVC, weight or height did not improve the fit. To reduce heteroskedasticity, oxygen was used categorically (1 if SpO₂ >94%, 2 if 90-94%, 3 if <90%). Based on all 123 patients for whom we had NTproBNP, echo and SpO₂ data, the derived formula is:

Predicted mPAP = 8.37 + 3.83 × Oxygen category + 0.328 × Echo derived Tricuspid Valve gradient + 0.032 × NTproBNP (capped)

This formula had R² of 60.3%.
Bland-Altman analysis showed a mean agreement of –0.6 (95% CI –1.64, 1.63) for difference between predicted and actual mPAP, although as seen in the figure, the 95% CI are tighter at lower predicted values. This compares favourably with echocardiography done within 1 hour of the RHC (Fisher MR et al, Am J Respir Crit Care Med, 2009).

**Conclusions:** This formula may help identify CTD patients requiring RHC. Patients with a formula predicted mPAP under 25 are unlikely to have PH, and those patients with predicted mPAP above 30 are very likely to have PH.

**Disclosure:** B. E. Schreiber: Actelion, 9, C. J. Valerio: None; C. Handler: None; G. Keir: None; A. U. Wells: None; C. F. Denton: Actelion, 9, GlaxoSmithKline, 9, Pfizer Inc, 9; J. G. Coghlan: Actelion Pharmaceuticals US, 9, Bayer, 9, Eli Lilly and Company, 9, GlaxoSmithKline, 9, Pfizer Inc, 9.

**Background:** Joint, bone and soft tissue involvement has been shown to strongly contribute to impaired hand function in systemic sclerosis (SSc). We previously showed in a cross-sectional study performed on 120 SSc patients the prominent level of hand radiographic involvement in SSc (1). However, this study had no longitudinal follow-up, precluding the identification of predictors of hand radiographic progression in SSc.

**Objective:** To examine the outcomes of hand radiographic X-Rays in patients with SSc and identify risk factors for the progression of hand radiographic lesions in a prospective cohort.

**Patients and Methods:** Subsequently to our initial cross-sectional study, dual time-point X-Rays with standard posteroanterior views of the hands and wrists were systematically performed after a median interval of 5 years (range: 4–7 years) in 103 SSc patients consecutively recruited. Univariate and multivariate Cox proportional hazards models evaluated predictors of progression of hand radiographic lesions (incident or worsened involvements) for three radiographic patterns of abnormalities of joints (erosive arthritis, defined by the presence of both erosion and joint space narrowing), bone (acro-osteolysis) and soft tissue (calcifications, flexion contracture). SSc patients (81% women) were 61±12 years old and had mean disease duration of 12±8 years.

**Results:** Incidences of erosive arthritis, acro-osteolysis, calcinosis and flexion contracture were 10%, 9% 14% and 8% respectively. The worsening of already known erosive arthritis, acro-osteolysis, calcinosis and flexion contracture occurred respectively in 13.5%, 12.5%, 11.5% and 10% of SSc patients. Cox regression analysis did not identify any predictor of the progression of erosive arthritis. Digital ulcers were shown to independently contribute to impaired hand function in systemic sclerosis (SSc). We previously showed in a cross-sectional study performed on 120 SSc patients strongly contribute to impaired hand function in systemic sclerosis (SSc). We previously showed in a cross-sectional study performed on 120 SSc patients.

**Conclusion:** This is the first prospective study to determine the outcomes and identify predictors of hand radiographic lesions in patients with SSc. This systematic examination highlights the striking level of incident and worsened hand radiographic lesions in SSc after a median interval of 5 years. Our data suggest a close monitoring of patients with the diffuse cutaneous subset with the need of early therapeutic intervention for prevention flexion contracture. Our results also show that severe peripheral vascular involvement predict both acro-osteolysis and calcinosis, highlighting their vascular background and suggesting that the impact of vascular treatments on these severe complications need to be addressed.


**Disclosure:** J. Avouac: None; G. Mogavero: None; H. Guérini: None; J.-L. Drapé: None; A. Mathieu: None; A. Kahan: None; Y. Allanoire: None.
Conclusion: Echo RVSP > 50 mmHg has the greatest discriminatory power to detect PH in SSc in this enriched cohort. However, at this cut-off, serum BNP and PFT captures additional 27% of patients with PH. Serum BNP and PFTs complement Echo RVSP and should be included as part of work-up of PH in SSc. This data needs to be confirmed in another real-life cohort.

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ACR REF Special Session
REF Edmond L. Dubois, MD Memorial Lectureship: The Path from Gene to Function: Analysis of a Lupus Susceptibility Gene

Monday, November 8, 2010, 4:30 PM–6:00 PM

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Single-Nucleotide Polymorphisms Associated with Systemic Lupus Erythematosus (SLE) Ske Alternative Splicing of Human Component Receptor 2 (CR2/C2D1) towards an Isoform with Increased Ligand Binding Ability. Kara M. Lough 1, Katherine B. Douglas 3, Carissa L. Homme 3, Daniela Ugliati 1, Betty P. Tsao 2 and Susan A. Boackle 3. 1School of Biomedical, Biomolecular and Chemical Sciences, University of Western Australia, 2University of California, Los Angeles, 3University of Colorado Denver School of Medicine

Background: Human complement receptor 2 (CR2/C2D1) exists as two known isoforms consisting of 15 or 16 extracellular repeating subunits termed short consensus repeats (SCRs) that result from alternative splicing of exon 11 in the primary mRNA transcript. The major alleles of three lupus-associated single-nucleotide polymorphisms (SNPs) in the CR2 gene (rs1048971 and rs17615 in exon 10 and the rs4308977 in exon 11) and a closely linked fourth SNP in exon 11 (rs17616) increase the expression of three lupus-associated single-nucleotide polymorphisms in the CR2 locus. We have shown that these four SNPs contribute to CR2 expression in a tissue-specific manner. These data suggest that the minor alleles of these SNPs may influence splicing of the CR2 transcript.

Methods: The cDNA for each isoform was amplified from Raji B cell RNA, cloned into the pcDNA3.1-FRT-V5-His TOPO TA expression vector (Invitrogen), and transfected into Flp-In CHO cells (Invitrogen). Stable clones were incubated with recombinant C3dg (rC3dg) tetramers prepared with biotylated rC3dg and PE-streptavidin and binding was determined by flow cytometry. To identify the specific SNP(s) influencing splicing efficiency, CHO cells expressing mutant rC3dg transcripts were transfected with plasmids containing genomic DNA spanning introns 9 to 12 of CR2 was modified by site-directed mutagenesis to generate vectors containing various allelic combinations of these SNPs. After transient transfection into Raji B cell and HK FDC lines, the relative amount of vector-derived mRNA transcripts including or excluding exon 11 was measured by quantitative RT-PCR.

Results: CHO cells expressing the long CR2 isoform bound up to two-fold higher levels of tetramers than CHO cells expressing equivalent amounts of the short isoform. In the Raji cell line, the presence of the minor allele at both rs17615 and rs17616 reduced splicing efficiency of exon 11 to the same extent as when all four SNPs were minor, whereas the presence of the minor allele at only rs17616 was sufficient to reduce the splicing efficiency of exon 11 to that seen in the minor allele construct alone.

Conclusion: These data demonstrate that the long isoform of human CR2 is better able to bind C3dg-opsonized ligands, suggesting that the introduction of SCR1 alters the structure and function of the receptor. The data also suggest that the minor allele at rs17615 and rs17616 modify the secondary structure of the CR2 pre-mRNA, interfering with splice site recognition by regulatory proteins. Variations in the relative amounts of these splice isoforms of CR2 on the surface of B cells or follicular dendritic cells may influence susceptibility to lupus, and the regulatory proteins that determine this process could serve as future targets for therapeutic intervention.

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Further Defining Cancer Risk in Systemic Lupus: Updated Results in an Expanded International Multi-Centre Cohort. Sasha R. Bernatsky 1, Ann E. Clarke 1, Michelle A. Petri 2, Murray B. Urowitz 1, Paul R. Fortin 1, Dafna D. Gladman 1, Soren Jacobsen 2, Susan Manzi 3, Graciela S. Alarcon 4, Ellen M. Ginzler 5, Christine A. Peschken 6, Mary Anne Dooley 7, John G. Hanly 8, Ola Nived 9, Gunnar K. Sturfelt 10, Jean-Luc Senecal 11, Jeremy Labrecque 12, Elizabeth M. Turnbull 13, Jennifer L. F. Lee 14 and Rosalind Ramsey-Goldman 15. 1Timonium, MD, 2Oakland, CA, 3Capital Health and Dalhousie University, Chapel Hill, NC, 4McGill UHC/RVH, Montreal, QC, Canada, 5McGill University, Montreal, Canada, 6McGill University Health Ctr, Montreal, QC, Canada, 7Montreal General Hospital, Montreal, QC, Canada, 8Northwestern University, Chicago, IL, 9Notre-Dame Hospital, M-4243, Montreal, QC, Canada, 10Queen Elizabeth II Health Services Center, Halifax, NS, Canada, 11RI McGill Univ Health Ctr, Montreal, QC, Canada, 12Rigshospitalet - 4242, Copenhagen, Denmark, 13SUNY-Downstate Medical Center, Brooklyn, NY, 14The Toronto Western Hospital, Toronto, ON, Canada, 15Toronto Western Hospital, Toronto, ON, Canada, 16Western Washington Univ, Seattle, WA, 17UBC Center, Vancouver, BC, Canada, 18Research Inst of Musculoskeletal Sci, RDCH, Vancouver, BC, Canada, 19University of Minnesota, Minneapolis, MN, 20Karolinska Inst, Stockholm, Sweden, 21University of Alabama at Birmingham, Birmingham, AL, 22West Penn Allegheny Health System, Pittsburgh, PA

Purpose: Our previous collaborative effort demonstrated an association between systemic lupus (SLE) and cancer, driven primarily by lymphoma risk. We aimed to more precisely estimate cancer incidence rates in SLE, compared to the general population. We also present results stratified by age group.

Methods: We assembled an expanded multi-centre international cohort of clinically confirmed SLE patients. Patients at each center were linked to regional tumor registries to determine cancer occurrence. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected cancers. Cancers expected were determined by multiplying person-years in the cohort by the geographically matched age, sex, and calendar year-specific cancer rates, and summing over all person-years.

Results: The 13,492 patients from 24 centers were observed for a total of 118,359 patient-years, with an average follow-up of 9 years. Within the observation interval, 632 cancers occurred. The data confirmed an increased risk of cancer among patients with SLE. For all cancers combined, the SIR estimate was 1.15 (95% confidence interval, 95% CI, 1.06–1.24), and for all hematologic malignancies combined, the SIR was 2.53 (95% CI 2.05–3.07). According to specific types of hematological malignancies, increased risk was demonstrated for all lymphomas (SIR 3.21, 95% CI 2.48–4.07) as well as non-Hodgkin’s lymphoma specifically (SIR 3.41, 95% CI 2.61–4.39), and for leukemia (1.69, 95% CI 1.00–2.67). We also demonstrated an increased risk of lung cancer (SIR 1.24; 95% CI 1.00–1.53), cervical cancer (SIR 1.65, 95% CI 1.09–2.41), vulvo-vaginal cancers (SIR 2.80, 95% CI 1.12–5.77), and hepatic cancer (SIR 2.18, 95% CI 1.16–3.73). Moreover, a significant decreased risk was seen for hormone-sensitive cancers, including breast cancer (SIR 0.70, 95% CI 0.58, 0.85), endometrial cancer (SIR 0.49, 95% CI 0.27, 0.83), and ovarian cancer (0.56, 95% CI 0.28, 0.97). When SIR estimates were stratified by age, SLE patients in the youngest age group (<40 years) appeared to have a particularly high relative cancer risk (compared to the general population), with an over-all cancer SIR of 1.70 (95% CI 1.34, 2.12).

Conclusion: These results more precisely define cancer risk in SLE, highlighting a higher risk of hematological malignancies, both lymphoma and leukemia; these are being further studied in case-cohort analyses of drugs and disease activity. One additional hypothesis for the higher risk of certain events, such as cervical and vulvo-vaginal cancers, is the possibility of altered clearance of viruses (e.g. HPV). On the other hand, the lower risk of several hormone-sensitive cancers may invoke the possibility of alterations in the metabolism of estrogen and/or other hormones. Although cancers in general are more common with age, younger SLE patients have a particularly high cancer risk (compared to the general population).

Disclosure: None.
Table: Cancer Risk in Systemic Lupus

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Hydroxychloroquine and Prevention of Anti-SSA/Ro Associated Cardiac Disease in Mothers with a Previous Child with Neonatal Lupus. Peter M. Izmirly, Cecilia Pisoni, Mimi Y. Kim, Deborah Friedman, Carolina Llanos, Nathalie Costedoat-Chalumeau, Munther A. Khamashita and Jill P. Buyon.

Purpose: Despite weekly monitoring of fetuses exposed to maternal anti-SSA/Ro antibodies, immediate treatment has never permanently reversed complete heart block. This irreversibility strongly supports an emphasis on preventative strategies. A recent case-control study revealed that fetal exposure to Hydroxychloroquine (HCQ), which prevents endosomal acidification and Toll-Like Receptor ligation (proposed pathway involved in cardiac inflammation and scarring), decreases the risk of cardiac manifestations of neonatal lupus (cardiac-NL) in Systemic Lupus Erythematosus (SLE) mothers with anti-SSA/Ro antibodies. That study did not address the effect of HCQ on the recurrence rate in subsequent pregnancies which is nearly 10 fold the frequency in anti-SSA/Ro positive women who have not had an affected child. Accordingly, this study explores whether HCQ prevents the development of cardiac-NL in these highest risk pregnancies.

Methods: Twenty-four pregnancies of 22 mothers satisfied the inclusion criterion: exposure to HCQ in a pregnancy of a mother whose previous child had either cardiac or cutaneous-NL. Exposure was defined as the sustained use of HCQ throughout pregnancy with initiation prior to 6 weeks gestation. In 19 of these 22 families the previous child had cardiac-NL (1- isolated cardiomyopathy and 18- advanced congenital heart block (CHB) 8 of whom died from complications of the disease) and in 3 families the prior child had cutaneous-NL. Of these 22 previous NL pregnancies, 15 were unexposed to HCQ (13 CHB, 1 cardiomyopathy and 1 rash), 6 were exposed to HCQ (4 CHB and 2 rash) and in 1 CHB child, exposure to HCQ was unknown.

Results: Sixty-eight percent of the mothers were Caucasian. The maternal health status was SLE in 41%, Sjoergen’s Syndrome (SS) in 32%, SLE with secondary SS in 18%, and Undifferentiated Autoimmune Syndrome in 9%. Sixty-four percent (14/22) of the mothers were positive for both anti-SSA/Ro and anti-SSB/La antibodies. The mean daily dose of HCQ was 352.6 mg. Using prospective data from the Research Registry for Neonatal Lupus, the recurrence rate of cardiac-NL following a child with cardiac-NL is 18% (based on 161 pregnancies following a previous child with CHB) and the occurrence rate of cardiac-NL following a child with cutaneous-NL is 13% (based on 39 pregnancies following a previous child with cutaneous-NL). These data suggest that the expected rate of cardiac-NL in this cohort should be approximately 17.2%. Of the 24 subsequent pregnancies exposed to HCQ in this study only one fetus developed cardiac-NL (3rd degree) and this mother’s previous child had cutaneous-NL. Thus, the recurrence/occurrence rate was 4.2% (95% CI:0.11% - 21.1%), a reduction of 75.7%. In addition to HCQ, 25% (6/24) of the mothers received intermittent low dose IVIG, 75% (18/24) non-fluorinated steroids, 17 of whom were on prednisone, and 8.3% (2/24) fluorinated steroids, one after the diagnosis of CHB.

Conclusion: This case series suggests that in mothers with anti-SSA/Ro antibodies and a previous child with NL, exposure to HCQ during a subsequent pregnancy may decrease the risk for fetal development of cardiac-NL.

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Background: B cell involvement in SLE has been demonstrated as a significant contributing determinant to disease pathogenesis. However, phenotypic heterogeneity and physiological importance of B cell subsets remain elusive and pose a challenge to understanding the complex mechanisms resulting in autoimmunity. Therefore, utilizing 3 different 12-color flow cytometry panels we have captured a comprehensive high-resolution footprint of the B cell profile in SLE in order to systematically explore the diverse human B cell repertoire and identify biomarkers of disease activity and prognosis.

Methods: B-cells from Healthy Controls (n=26) and SLE patients (n=127) were analyzed by multi-color flow cytometry for expression of anchor markers that identify larger parental B cell populations. The individual panels also included subset specific markers to further define parental populations: Memory; Transitional and Naive; and Plasma B cells. Multivariate methods were used to seek natural divisions based on the B cell profiles, and to relate them to various clinical parameters. SLE patients met ACR criteria for the classification of SLE, and were sub-categorized based on primary clinical manifestation. Disease activity and flares were measured by SELENA-SLEDAI and physician global assessment.

Results: Preliminary analyses show SLE B cell profiles exhibited a broader spread across different subsets compared to Healthy Control (HC). However, after sub-categorizing SLE patients based on primary clinical manifestations, the SLE sub-categories were revealed to have distinct B cell profiles. Overall, SLE patients had higher transitional populations and lower naive B cells than HC (p<0.05). Nephritis, musculoskeletal/skin, and flaring patients exhibited a CD27- memory B cell expansion (p<0.05) with expression of CD95+ (p<0.05) and CD21- (p<0.05), markers of putative effector memory B cells, compared to HC. Nephritis patients had a unique memory CD27- B cell subset expressing significantly higher B220+/CD24- (p<0.005) and CD24- (p<0.0005), Musculoskeletal/skin patients exhibit CD27- memory that expressed CXCR3+ and high CD27+ memory with CD95+ (p<0.05) when compared to HC. Overall, Spearman correlation shows SLE DAI scores correlated with CD27- Memory with phenotypes CD95+ (r=0.46, p<0.005), CD21- (r=0.44, p<0.005), and CD24- (r=0.44, p<0.005). SLE DAI also correlated with plasmablast counts (r=0.35, p<0.05).

Conclusions: These results indicate that unique B-cell signatures cluster with distinct clinical parameters, indicating a spectrum of disease states in SLE. Moreover, the exploration of multiple B cell subsets by a multi-colored flow-cytometry approach suggests that B cell profiles may serve as biomarkers of disease phenotype, activity, and treatment response. These profiles will be invaluable to understand disease heterogeneity and possibly its genetic basis and should prove of great help in the design of future therapeutic studies, especially with B cell targeting agents. Ongoing studies are exploring longitudinal changes in B cell phenotypes and correlation with T cell abnormalities to create an even more comprehensive picture of SLE disease pathogenesis.

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Antibodies to CCP Versus the Unmodified Arginine-Containing Peptide (CAP) as a Serological Marker To Differentiate SLE from RA. Jason Chan1, Rufus Burlingame1, Angela Cerbelli2, Eric S. Sobel2, Yi Li3, Westley H. Reeves3, Edward K. L. Chan4 and Minoru Satoh3.

1INOVA Diagnostics, Inc., 2University of Florida, 3University of Florida, Gainesville, FL.

Purpose: Anti-cyclic citrullinated peptide (CCP) ELISA has been established as a serological marker of RA and used extensively in clinical practice. Early studies on anti-CCP emphasized the selective reactivity of sera from patients with RA for CCP but not with the corresponding unmodified peptide containing arginine (CAP); however, reactivity against CAP is not generally considered in clinical practice or in most studies using commercial anti-CCP ELISA. Recent studies reported that anti-CCP reactivity in non-RA patients is often not specific for CCP but can also react with CAP, indicating the importance of comparing reactivity with CCP vs CAP. In the present study, reactivity against CCP was compared with that to corresponding unmodified peptide containing arginine (CAP3) in RA, SLE, scleroderma (SSc), polymyositis/dermatomyositis (PM/DM), and controls.

Methods: An ELISA kit using a peptide corresponding to CCP3 but containing unmodified arginine (CAP3) was developed. Anti-CCP3 and CAP3 in sera from SLE (n = 201), SSc (n = 105), PM/DM (n = 44), RA (n = 84), and healthy individual (n = 34) were tested by ELISA. Reactivity of each serum was calculated as units following the manufacturer’s protocol. Patients were classified into 4 groups based on their serum reactivity against CCP vs CAP. Clinical information was from a database.

Results: Anti-CCP3 was positive in 70% of RA (69% were specific for CCP) vs 12% in SLE (7% specific for CCP), 6% in SSc, and 4% PM/DM, respectively. SLE DAI also correlated with plasmablast counts (p<0.005). Musculoskeletal/skin patients exhibit anti-CCP reactivity in non-RA patients considered in clinical practice or in most studies using commercial anti-CCP ELISA. Recent studies reported that anti-CCP reactivity in non-RA patients is often not specific for CCP but can also react with CAP, indicating the importance of comparing reactivity with CCP vs CAP. In the present study, reactivity against CCP was compared with that to corresponding unmodified peptide containing arginine (CAP3) in RA, SLE, scleroderma (SSc), polymyositis/dermatomyositis (PM/DM), and controls.
Similar to previous studies. All except one anti-CCP positive RA showed CCP selective reactivity but 42% (10/24) of anti-CCP positive SLE sera also reacted strongly with CAP, indicating lack of specificity for citrullinated peptide in SLE. Surprisingly, anti-CCP reactivity without anti-CCP was frequently seen in SLE (45%) but uncommon in other systemic rheumatic diseases or NHS (P < 0.0001).

**Conclusions:** Anti-CCP without CCP was in high prevalence and relatively specific for SLE among systemic rheumatic diseases. When patients with early undiagnosed arthritis are seen at clinic, positive anti-CCP and negative anti-CCP can serve as a useful serological marker to differentiate SLE from RA. RA sera specifically reacted with CCP but not with CAP as previously described. In contrast to CCP specific reactivity in RA, CAP positivity was common in anti-CCP positive SLE sera.

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**Apoptotic Cell Bodies and Blebs Stimulate Self Reactive B-Cells Via Engagement of the BCR and Endosomal Toll-Like Receptors.** John McCahan1, Nathaniel Green1 and Ann Marshak-Rothstein1. 1Boston University, Boston, MA, 2Rheumatology Section, Boston University, 3The University of Massachusetts Medical School, Worcester MA

**Purpose:** Apoptosis is a genetically programmed pathway of cell death that results in the condensation of a cell into sub-cellular particles. Under normal circumstances these are removed by surrounding cells and nearby phagocytes with a non-inflammatory effect. However, disruption of pathways involved in the removal of apoptotic cells has been shown to lead to signs of autoimmunity including autoantibody formation and tissue damage. The mechanisms that lead to the induction of auto-antibodies remain unclear. B cells from AM14 transgenic mice are a model of self reactive B-cells. They express an antigen receptor specific for IgG2aa/j and make a class of auto-antibodies known as rheumatoid factor (RF). It has been shown that immune complexes composed of IgG2a-chronatin or IgG2a-RNA can stimulate AM14 B-cells by the synergistic engagement of the antigen receptor and a member of the Toll-like receptor (TLR) family. Our purpose was to determine if apoptotic cells express auto-antigens that can stimulate self-reactive B-cells.

**Methods:** Keratinocyte and fibroblast cell lines were induced to undergo apoptosis by several methods including ultraviolet light exposure, etoposide, and serum starvation. In some experiments, cell surface proteins were biotinylated prior to the induction of apoptosis to nonspecifically label cell-surface-derived apoptotic debris. Subcellular particles were fractionated by differential centrifugation yielding two populations defined as apoptotic cell bodies and apoptotic blebs. Each fraction was analyzed by flow cytometry for the induction of apoptosis and autoantigen expression including nucleosomes, Ro, Smith antigen, and nucleoli. Immune complexes composed of subcellular particles bound by IgG2a autoantibodies were used to stimulate AM14 B cells. The contribution of TLR7 and TLR9 in this activation process was addressed by using cells from TLR-deficient mice.

A robust proliferative response was induced by immune complexes composed of apoptotic cell bodies and blebs bound by autoantibodies. This effect was enhanced with IFN-β priming and stimulation was mediated by binding of the B-cell receptor and engagement of either TLR7 or TLR9. Biotinylation experiments indicated that the autoantigens were associated with the cell membrane. By comparing the activity of immune complexes formed with the anti-biotin mAb and mAbs specific for defined autoantigens, we have been able to address the differential expression of autoantigens on apoptotic debris derived from diverse cell types.

**Conclusion:** Our findings suggest that self reactive B-cells can be stimulated by apoptotic cell bodies and blebs through a TLR mediated process.

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**B Cell-Dependent Regulation (Breg) of T-Cell Proliferation Is Deficient in Systemic Lupus Erythematosus (SLE).** Jacques-Olivier Pers, Sébastien Lemoine, Ahsen Morva, Christophe Jamin and Pierre Youinou. Brest University

**Background:** Association of B-cell depletion with increased inflammation in murine models suggests that B cells exert regulatory function, through inhibition of T-cell proliferation. The current study was aimed at evaluating the functional aspect of regulatory B cells in humans and specifically in autoimmune disorders.

**Methods:** B and T lymphocytes were negatively purified from peripheral blood of 9 healthy donors (HDs), 5 primary Sjögren’s syndrome (pSS) patients, 5 SLE patients, and 4 rheumatoid arthritis (RA) patients. T cells were induced to proliferate by stimulation with anti-CD3 and anti-CD28 antibodies. The results was measured by flow cytometry analyses of CFSE stained cells. CD40, TLR9 and/or BCR stimulation were evaluated for their ability to activate the B cells and to induce a regulatory effect. Activated B cells were co-cultured with stimulated T cells, and modulation of the T-cell proliferative response assessed by flow cytometry.

**Summary of the Results:** Resting B cells from HDs did not affect the proliferation of T cells. In contrast, activated B cells exhibited regulatory effects resulting in a decreased T-cell proliferation rate. For B cells to modulate the T-cell response, CD40 activation appeared to be required. Furthermore, TLR9 signals synergized with CD40 to trigger the most efficient down-regulation of the T-cell proliferative response. Activated Breg from pSS and RA patients were equally efficient whilst those of SLE were unable to control the T-cell proliferation.

**Conclusion:** Human Breg are functionally effective when appropriately activated. They can alter the T-cell proliferation. Our results suggest that both population behave as those of HDs in pSS and RA patients. In contrast, Breg properties appear to be defective in SLE patients. Whether this is due to defective Breg function or to T-cell refractory response remains to be determined.

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**B Cells Modify Regulatory T Cells in Healthy Individuals but Not in Patients with Systemic Lupus Erythematosus.** Mark N. Lazarus, Hardeep S. Kalisi, David A. Isenberg and Michael R. Ehrenstein. UCL Div of Medicine, London, United Kingdom

**Background:** A number of publications have demonstrated that B cells can modify regulatory T cells (Treg) number indicating that B cells could contribute to the maintenance of tolerance via effects on Treg. B cell depletion therapy is currently used to treat some patients with systemic lupus erythematosus, but conflicting results have been obtained on the effects on Treg. We therefore investigated whether Treg are affected by removal of B cells in vitro and in vivo.

**Methods:** Treg were enumerated in healthy individuals and patients with lupus before and after rituximab therapy and correlated with B cell numbers. Intracellular cytokine staining for IL-2 and interferon gamma was performed in some assays. Peripheral blood mononuclear cells (PBMC) from healthy controls and lupus patients were cultured whole or following depletion of B cells by MACS LD™ beads and stimulated with anti-CD3/CD28. CD4, Foxp3 and CD25 expression assayed after 3 days using FACS.

**Results:** In patients with SLE, Foxp3 expression was significantly increased compared to healthy controls (p<0.001). Both CD4+Foxp3+ and CD4Foxp3hi T cells were significantly increased compared to healthy individuals. CD4+Foxp3+ T cells did not produce any IL-2 or interferon gamma suggesting that these are not simply activated T cells. Following B cell depletion, the increased frequency of Treg compared to healthy controls remained unchanged during depletion and repopulation. There was a strong correlation between Treg numbers and the CD19/CD4 ratio in healthy individuals (r2 0.6059, p<0.005), but not in lupus patients. Treg numbers were significantly reduced in the PBMC of healthy individuals (p<0.001) but not lupus patients following removal of B cells in vitro.

**Conclusions:** B cells partly drive an increase in Treg numbers in vitro following activation in healthy individuals. However, this was not observed in PBMC from lupus patients suggesting that this control on Treg is defective. The notion that the increased frequency of Treg in lupus patients is driven by B cell independent mechanisms is supported by our observation that Foxp3

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expression remains unchanged following B cell depletion therapy and that a strong correlation between Treg frequency and B:T cell ratio in healthy individuals is lost in patients with SLE.

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**BAFF Binding Receptors (BBR) Related To Relapse after Rituximab in Patients with Reumatoid Arthritis (RA).** Inmaculada De la Torre1, Lara Valor2, Rita Moura2, Maria J. Leandro3, Jonathan C. W. Edwards4 and Geraldine Cambridge1. 1Hospital Gregorio Maranon, Madrid, Spain; 2Instituto de Biologia Molecular, Lisbon, Portugal; 3University College London, London, UK

Background: Coordinated expression of BBR (BAFF-R, TACI, BCMA) control differentiation of B cells into immunoglobulin (Ig) secreting cells. We have previously shown that i) BAFF levels increase after B cell depletion with rituximab (rtx) in patients with RA, remaining raised even after B cell repletion ii) BAFF-R expression in naïve (NB) and memory B (MB) cells is reduced after rtx and related to clinical relapse independently of circulating BAFF levels or time to relapse after B cell repletion. iii) Class-switch recombination (CSR) and autointolerance is induced during relapse after rtx. When B cells differentiate into Ig secreting cells, BAFF-R is lost and B cell up-regulated. TACI is induced upon B cell activation. Although it can be expressed on activated NB cells (<25%) it is related to CSR and memory/plasma cell differentiation.

**Aim:** To investigate BBR expression in relation to B cell maturation and clinical relapse in RA patients after rtx.

**Methods:** Phenotypic analysis of BBR-R, TACI and BCMA expression on PBMC were performed using combinations of CD19, CD27, CD38 and IgD (% and mean fluorescence intensity-MFI) in normal controls (NC) (n: 5) and patients pre (n: 10) and after rtx, classified as concordant relapsing at B cell repopulation (C-R, n: 16), or discordant relapsing > 3 months after repopulation (D-R, n: 10) or non-relapsing after B cell return (D-NR, n: 11).

**Results:** Mean % of NB cell BAFF-R+ was significantly lower in all patients relapsing (C-R: 65.3%, D-R: 89.7%) when compared to NC (p=0.027, p=0.026). Percentage and MFI of MB cell BAFFR+ was significantly lower in all patients when compared to both NC and pre-rtx (%: p<0.05, MFI: p<0.005). In patients relapsing, % NB cell TACI+ tended to be higher in C-R than D-R (25.4% vs 9.9%). All patients pre and after rtx had significantly lower % of MB cell TACI+ when compared to NC (p<0.05). However % of MB cell TACI+ was significantly higher in D-NR when compared to D-R (p=0.001).

<table>
<thead>
<tr>
<th>BAFF R Naïve B cells</th>
<th>BAFF R Memory B cells</th>
<th>TACI Naïve B cells</th>
<th>TACI Memory B cells</th>
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<tbody>
<tr>
<td>%</td>
<td>MFI</td>
<td>%</td>
<td>MFI</td>
</tr>
<tr>
<td>NC (n: 5) 98.5</td>
<td>126</td>
<td>95.43</td>
<td>107.6</td>
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<td>Pre (n: 10) 93.40</td>
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<td>C-R (n: 16) 65.36</td>
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<tr>
<td>D-R (n: 10) 89.7</td>
<td><strong>60.9</strong></td>
<td>63.20</td>
<td>57.56</td>
</tr>
<tr>
<td>D-NR (n: 11) 92.03</td>
<td>47.60</td>
<td>63.80</td>
<td>56.76</td>
</tr>
</tbody>
</table>

P = 0.05: # vs NC, **vs Pre, ***vs CR, ****vs DR

**BAFF-R and BCMA did not always have an inverse correlation in plasma cells population after rtx. Finally, C-R patients had higher % of plasma cells than D-R and D-NR (16.5 vs 2.06 and 1.85; p=0.03 and p=0.06).

**Conclusions:** Rises in autoantibody levels have been related to clinical relapse after rtx. Modulation of BBR expression permissive to plasma cell formation in C-R patients with an earlier down regulation of BAFF-R and up regulation of TACI on (presumably activated autoreactive) NB cells may explain clinical relapse closer to B cell return. Normal BAFF-R expression on NB cells from D-NR patients may reduce the chance of becoming Ig-producing cells, allowing a normal maturation process within germinal center reactions. The consequences of disturbed BBR expression on B cell selection and the advancement or inhibition of progression to autointolerance may explain timing of relapse after rtx.

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**Cellular and Serological Changes Following B Cell Repopulation after Rituximab Therapy**

**Purpose:** The aim of this study was to investigate whether B cells exert an effect on other immune cells which are known to be low in the blood of patients with active disease.

**Methods:** We analysed changes in the titres of anti-dsDNA antibodies, C3 and lymphocyte and monocyte numbers in the blood of 55 patients with SLE during B cell depletion and over a 52 week period following repopulation. PBMCs were obtained from 53 rituximab treated patients and analysed by flow cytometry for the expression of the activation markers CD69 and HLA-DR by CD4+ T cells. Chemokines were measured in the serum of 19 rituximab treated patients using a cytokometric bead assay. *In vitro* experiments were carried out using PBMCs from 5 healthy controls and 5 patients with SLE.

**Results:** Our results showed that in patients with high anti-dsDNA antibody titres (above 100 I/U/L) pre BCDT titres only fell in patients who eventually had remission at 52 weeks following B cell repopulation (p<0.05) but did not change in patients that relapsed, either during the B cell depletion phase or during repopulation. C3 levels rose during B cell depletion and fell again during relapse but only in patients with high anti-dsDNA antibodies pre-BCDT (p<0.01; p=0.07). Lymphocyte numbers increased during repopulation in all patients (p<0.05) but fell during relapse only in patients who had low titres of anti-dsDNA antibody pre-BCDT (p<0.05). The fall in lymphocytes was paralleled by an increase in the expression of HLA-DR by CD4+CD49d+ T cells (p<0.05). Expression of CD69 was increased in all lupus patients and did not change following B cell depletion. *In vitro* experiments revealed that B cell activation directly led to increased expression of HLA-DR, but not CD69, on CD4+ T cells. Finally, monocyte numbers increased during depletion and fell during relapse in all groups (p<0.05). These changes in monocyte numbers coincided with a reduction in the serum levels of the monocye recruiting chemokine, MCP-1 (p<0.05). MCP-1 production increased *in vitro* when PBMCs were stimulated through the B cell receptor (p<0.05).

**Conclusion:** These results demonstrate that changes in anti-dsDNA antibody and C3 correlate with response to BCDT but only in patients with high titres of anti-dsDNA antibody pre-BCDT. In patients with low anti-dsDNA titres pre-BCDT changes in lymphocyte and monocyte numbers may be more important. These changes in lymphocyte and monocyte numbers correlated with changes in HLA-DR expression by CD4+ T cells and MCP-1 levels respectively, suggesting that B cells might also induce the migration of T cells and monocytes to sites of inflammation in addition to producing autoantibodies. In conclusion, these results suggest that responses to rituximab may be partly governed by antibody independent mechanisms providing an explanation for some of the heterogeneous responses to BCDT that have been observed in SLE.

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**Elevated Serum BAFF Correlates with Loss of Mature B Cells and Promotes B Cell Recovery in Mice after B Cell Depletion Treatment.** Yue Wang1, Sandra Gallagher2, Isharat Yusuf2, Bahija Jallal1, Anthony Coyle1 and Ronald Herbst3.1MedImmune LLC, 2MedImmune LLC, Gaithersburg, MD

**Purpose:** B cell depletion therapy with anti-CD20 monoclonal antibody (MAb) is an effective treatment for rheumatoid arthritis. There are ongoing clinical trials for treating autoimmune diseases after B cell depleting MAb therapies, which may lead to more complete B cell depletion. It is therefore important to compare the outcome of B cell depletion with different MAb and correlate that with changes of diseases status as well as pharmacodynamic (PD) markers. Previous studies have indicated that following treatment with anti-CD20 MAb in patients, serum BAFF (B cell activating
factor belonging to the TNF family) levels significantly increase. In this study, we used animal models to investigate the relationship of serum BAFF levels with loss of B cells and the contribution of BAFF to B cell depletion and recovery.

**Methods:** Mice were treated with escalating doses (0.1–10 mg/kg) of B cell depleting MAb. Numbers of B cells in blood and tissues (spleen and bone marrow) were quantified by FACs and serum BAFF levels detected by ELISA. To study whether elevated BAFF levels can affect B cells, mice were dosed with 2μg recombinant BAFF before and during MAb treatment. To investigate the role of BAFF during B cell recovery, mice were treated with BAFF-R-Fc starting at the time when B cell recovery was detected. The biological function of recombinant BAFF and BAFF-R-Fc were confirmed by in vitro assays.

**Results:** Treatment of mice with B cell depleting MAb led to dose-dependent reduction in B cell numbers. At a dose of 0.5mg/kg or above, more than 90% of B cells were depleted, spanning from pre-B cells in bone marrow to mature B cells in spleens. The duration of B cell depletion is also dose-dependent and followed by reconstitution of B cells in blood and spleens. Changes in serum BAFF levels and B cell numbers were coupled: BAFF levels are elevated only when tissue B cells start to be depleted and, as B cells recover, serum BAFF levels drop back to baseline. The increase in BAFF levels significantly correlated with loss of mature B cells. When BAFF was elevated 5-fold during the treatment of MAb, B cell depletion was not affected. However, treatment with BAFF-R-Fc during B cell reconstitution resulted in a block of mature B cell regeneration. Consequently, spleen mature B cells were 90% lower in the BAFF-R-Fc treated group compared to the control group.

**Summary:** A newly developed MAb effectively depletes murine B cells even in the presence of high BAFF levels, supporting its use in autoimmune disease settings. Changes in serum BAFF level after MAb treatment reflect the loss of B cells. Lastly, increased BAFF levels promote B cell recovery and maturation, consistent with the known function of BAFF in regulating B cell survival and homeostasis. Future studies of changes in BAFF levels and functions in B cell depletion are warranted in the clinical trials.


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**Elimination of Autoantibody Producing Plasma Cells Using CXCR4 Antagonist AMD3100.** Jason Weinstein1, Yuan Xu1, Matthew Delano3, Yi Li1, Lijun Yang1, Eric S. Sobel1, Lyle Moldawer1 and Westley H. Reeves2.

**Background:** Autoantibodies cause disease either directly by interacting with target antigens in cells or tissues or by forming immune complexes that cause inflammation. B cell therapy has been only partially successful because B cell depletion is inherently autoreactive against red blood cell determinants. An estimated 15% of naive B cells are 9G4+ but <1% of circulating Ig are 9G4+ in healthy controls (HC). In HC, 9G4+ B cells of a mature pre-switch phenotype (IgM+ IgD−CD27+) are found in splenic marginal zones (MZ). 9G4+ B cells are also in tonsils from HC but excluded from germinal center (GC) reactions. Whereas in patients with lupus, post-GC memory B cells (IgD−CD27+) are present, suggesting defective B cell censoring (1). In RA, there is also some evidence that B cell tolerance is affected.

**Objective:** To determine whether RHF from RA and disease controls express 9G4 and to examine the phenotype of 9G4+ B cells in peripheral blood.

**Methods:** RHF expression on RHF and on total serum IgM and IgG were measured by ELISA in 22 seropositive RA and 20 RHF+ve 1o Sjögrens Syndrome (SS). Peripheral blood CD19+ B cells from 24 patients with RA and 7 HC were obtained by negative selection using MACs columns and stained to distinguish 9G4 expression on CD5 and CD27 populations and also within naive (IgD+CD38−), transitional (IgD+CD38+), memory post-GC (IgD-CD38+), memory resting (IgD−CD38) and plasmablast (IgD−CD38+++) populations. Analyses were by Mann Whitney rank sum test.

**Results:** RHF levels and expression of 9G4 on total IgM and IgG were minimally higher in RA than SS patients (p<0.05). However 9G4 expression on RHF was significantly greater (p=0.0001) in RA vs SS patients. Percentages of 9G4+CD19+ B cells in HC and RA patients were similar (mean %: 6.36 vs 6.45) and most had a naive phenotype (means: 44%, 42% respectively). Post-GC B cells and plasmablasts had means of 14.3% and 3.5% for NC and, for RA, 29.5% and 9.2% respectively. Gating on the 9G4+ population, CD5−CD27− phenotype was the most common in NC and RA (58.7% vs 55.7%). However a distinct population was described with a CD5+CD27+ B cell phenotype with similar proportions in HC and RA (13.1% vs 17.4%). Further, in some RA patients, a negative correlation was found between the percentage of B cells expressing CD5+CD27+ and 9G4 expression on RHF in the same sample.

**Conclusions:** Although post-GC 9G4+ B cells were not found in RA tonsils, we found 9G4 on RHF in patients with RA but not in SS. As RHF from patients with SS do not utilize V4–34, this suggests breakdown of 9G4 censoring in patients with RA, perhaps in areas outside secondary lymphoid tissue such as in the spleen or inflamed joints. We also found that HC and RA patients had circulating 9G4+ memory B cells and plasmablasts and describe a new B cell phenotype, CD19+CD5+CD27+, which often carries the 9G4 idiotype. CD5 is found on B cells in splenic MZ and is lost from B cells before entry into late stages of a GC. Also, CD27+B− cells have been shown to be predominantly CD5−CD23+. We suggest that retention of CD5 expression on 9G4+CD27+ B cells, whilst allowing development of a mature phenotype may be a self-censoring mechanism preventing access to GCs (perhaps by affecting BCR signalling) and hence antibody production from these potentially ‘dangerous’ autoreactive cells.

Disclosure: I. De la Torre: None; R. Moura: None; M. J. Leandro: None; J. C. W. Edwards: None; G. Cambridge: None.
Expression of ZAP-70 in B-Cell Is a Feature ofPeripheral Blood Repopulation after Rituximab Therapy in Rheumatoid Arthritis.

Francesca Faustini, Barbara Tolusso, Giuay Peluso, Elisa Gremses, Silvia Canestri, Graziella D’Antona, Antonella Laria and Gianfranco Ferraccioli.

Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy

Background: The expression of ZAP-70 in B cells derived from synovial fluid of rheumatoid arthritis (RA) patients seems to define a subset of these cells characterized by increased survival and shows a correlation with the inflammatory and autoimmune phenotype. Aim of the study: to evaluate the expression of ZAP-70 by different subsets of peripheral blood B-cells before and after treatment with Rituximab (RTX) in a cohort of RA patients during a 24 months follow-up and, the relationship between ZAP-70 expression in B cells and their phenotype during TNFα plus IL-10/IL-2 in the presence or absence of 4-hydroperoxycycloendoperoxide (4-HC).

Methods: In vivo effects of Tocilizumab on Peripheral B Cells in Patients with Rheumatoid Arthritis.

In Vivo Effects of Tocilizumab on Peripheral B Cells in Patients with Rheumatoid Arthritis.

Purpose: Interleukin (IL)-6 receptor inhibition by tocilizumab was assessed in a cohort of RA patients during a 24 months follow-up and, the relationship between ZAP-70 expression in B cells and their phenotype during TNFα plus IL-10/IL-2 in the presence or absence of 4-hydroperoxycycloendoperoxide (4-HC).

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In Vivo Effects of Tocilizumab on Peripheral B Cells in Patients with Rheumatoid Arthritis.

Purpose: Interleukin (IL)-6 receptor inhibition by tocilizumab was assessed in a cohort of RA patients during a 24 months follow-up and, the relationship between ZAP-70 expression in B cells and their phenotype during TNFα plus IL-10/IL-2 in the presence or absence of 4-hydroperoxycycloendoperoxide (4-HC).
The production of IgM and IgG in the culture supernatants were also significantly inhibited by 4-HC; the mean concentrations of IgM and IgG were 62.0 μg/ml and 18.8 μg/ml, respectively in the culture supernatants of the stimulated cells whereas those of the unstimulated cells and the 4-HC-treated cells were under the assay ranges by ELISA.

**Conclusions:** This study shows that administration of CY predominantly suppresses activation and viability of plasmablasts in vivo and in vitro. These findings may indicate that therapeutic effect of CY on SLE is at least partly exerted through this mechanism.

**Disclosure:** Y. Okamoto: None; Y. Katsumata: None; Y. Kawaguchi: None; M. Kawamoto: None; S. Baba: None; K. Takagi: None; T. Gono: None; Y. Ota: None; M. Hara: None; H. Yamanaka: None.

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**Progestrone Receptors Regulate Humoral Immunity.** Alan Wong, Chang Li, Ed Clark and Grant Hughes. University of Washington

The immunological mechanisms linking female reproduction and autoimmune diseases like systemic lupus erythematosus are poorly understood. In humans and genetically susceptible mice, estrogen increases disease development. In the same settings, progesterone (Pg) appears to decrease the risk of disease. How this occurs is unknown but likely involves differential regulation of IFN-α, Th1-related signals and B cell differentiation. Under physiologic conditions, Pg’s immunomodulatory effects are thought to be mediated by two Pg receptor types expressed in mouse and human leukocytes: intracellular Pg receptors (PRs) that are ligand-activated transcription factors, and membrane-bound Pg receptors (mPRs) that are linked to inhibitory G proteins and unrelated to PRs. Very little is known about the differential immune functions of PRs vs. mPRs. Recently, Pauklin and Petersen-Mahrt (J Immunol, 2009) demonstrated that Pg, via PR, inhibits B cell class switch recombination (CSR) through transcriptional repression of the activation-induced deaminase (AID) gene in vitro. Here, we show the first genetic evidence linking Pg and PR signaling to adaptive humoral immunity in vivo.

To investigate the role of PRs in antibody (Ab) responses, we used mice in which signaling through PR was genetically ablated (PRKO) by targeted disruption. Female PRKO mice are infertile due to reproductive organ abnormalities. Male PRKO mice are fertile. To assess a role for PR in Ab responses, we measured primary thymus-dependent (TD) Ab responses to alum-adSORBED DNP-KLH and primary thymus-independent type 2 (TI-2) responses to DNP-Ficoll. Female PRKO mice generated significantly more (up to 5 fold) anti-DNP IgM, IgG1, and IgG2a compared to their wild type (WT) female littermates after immunization with DNP-KLH in alum. Thus, PR regulates T cell-dependent humoral immune responses in vivo. Interestingly, these differences were more pronounced in male mice, indicating that PR regulates humoral immunity regardless of sex. PRKO and WT mice did not differ in total serum Ig levels and or numbers of spleen B cells, T cells, and DCs before immunization, and thus differences in Ab responses were not simply due to underlying differences in lymphocyte/DC development. We also observed no differences in anti-DNP Ab responses after TI-2 immunization, suggesting that Pg, via PR, may regulate T cells, B cells or responses to alum. We detected no consistent differences in the ability of PRKO vs. WT purified spleen B cells to undergo CSR in vitro, either to T-cell associated signals (anti-CD40) or LPS. However, CD4+ T cells from PRKO mice produced more IFN-γ, but not IL-4, in response to anti-CD3/CD28 stimulus compared to WT T cells. Thus, the elevated IgG2a responses in PRKO mice may be due to dysregulated Th1 differentiation. This work supported by NIH grant AI073739 and an ARRA supplement to AI073739.

**Disclosure:** A. Wong: None; C. Li: None; E. Clark: None; G. Hughes: None.

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**SLE Anti-CD45/B220 9G4 Autoantibodies Induce Attenuated CSR Signaling: Implication for Disease Pathogenesis.** Scott A. Jenks, Anna E. Schroeder and Ignacio Sanz. 2 Duke University, Durham, NC, 2Univ of Rochester, Rochester, NY

**Background and Purpose:** It has been long known that anti-lymphocyte autoantibodies (ALA) are frequently present in SLE patients. One well-characterized and prevalent group of ALA are VH4.34-encoded antibodies recognized by the rat anti-human idiotype antibody 9G4 (9G4+ antibodies). In addition to recognition of i/h blood group antigens, these antibodies also bind the glycosylation isomers of CD45 (B220+) found predominately on naive B cells. In a subset of SLE patients, close to 100% of ex vivo naive B cells are positive for the 9G4+ idiotype and when naive B cells from healthy donors were incubated with these antibodies, they became positive for 9G4+. Since CD45 is a phosphatase that can alter signaling, binding of 9G4+ antibodies to naive B cells may directly change signaling in these cells. Supporting this idea, we have observed that B cells from an SLE patient with strong ex vivo 9G4 binding showed poor B cell receptor (BCR) induced phosphorylation as compared to healthy control B cells. The goal of this study was to directly test the hypothesis that binding of 9G4+ antibodies to CD45/B220 will decrease BCR signaling in naive B cells.

**Methods:** Lymphocytes from healthy control donors were incubated with serum from SLE patients with strong ex vivo 9G4 staining on the majority of naive B cells (shaded histogram), SLE patients without strong 9G4 staining (open histogram), and healthy control serum. These cells were then stimulated through the BCR with antibodies against IgM. After fixation and permeabilization, 9G4 staining was measured flow cytometrically (Fig A) and BCR signaling was quantified by measuring induced phosphorylation of BLNK (pY84) (Fig B) and pPLC-γ2 (pY759) (Fig C).

**Results:** Anti-IgM induced phosphorylation in naive B cells was substantially reduced in cells incubated with serum from SLE patients with ex vivo 9G4 staining through the BCR complex can enhance receptor editing, anergy and/or the negative selection of autoreactive B cells and prevent the development of autoimmune disease.

**Methods:** To test this hypothesis we utilized two models of autoantibody production. First, we bred the H92/H9251 (56R) mice, which express an anti-dsDNA reactive BCR heavy chain that leads to BCR editing and anergy induction, to SLAP-deficient mice to examine the effects of SLAP deficiency on central tolerance. Second, we immunized SLAP-deficient and wild-type BALB/c mice with a peptide mimotope for dsDNA that causes the development of a germinal center dependent anti-dsDNA antibody response that leads to a lupus-like autoimmune disease to examine the effects of SLAP deficiency on peripheral B-cell tolerance mechanisms.

**Results:** SLAP deficiency (SLAP−/−) led to a significant decrease in serum levels of dsDNA in E56R mice. Compositional analysis of bone marrow revealed a decrease in kappa usage by pre-B cells in SLAP−/− 56R mice, suggesting increased receptor editing. However, splenic B cell subsets and kappa vs. lambda light chain usage were similar between 56R and SLAP−/− 56R mice, indicating that anergy could also be responsible for the decreased production of autoantibodies. To determine if SLAP deficiency leads to enhanced receptor editing verse anergy, hybridomas were generated. Consistent with enhanced receptor editing, less of the SLAP−/− 56R hybridomas produced antibodies reactive with dsDNA compared to the 56R hybridomas. The decreased number of hybridomas secreting anti-dsDNA was due to a qualitative change in light chain repertoire in SLAP−/− 56R mice. The light chain repertoire of SLAP−/− 56R hybridomas was biased toward Vκ21D, an efficient editor of anti-dsDNA reactivity. In contrast, incomplete editors of anti-dsDNA reactivity, Vκ38C and Vκ20, predominated in 56R hybridomas. In the in vivo model of lupus-like autoimmunity, despite the production of an equivalent level of anti-peptide antibodies compared to BALB/c controls, SLAP-deficient mice did not produce anti-dsDNA antibodies upon immunization with a peptide mimotope of dsDNA.

**Conclusions:** These data show that enhanced signaling through the BCR complex could be a general strategy to treat autoimmune disease by eliminating autoreactive B cells that are either maintained as a result of inefficient receptor editing or failed negative selection upon germinal center formation. Our studies are the first step in defining signaling networks downstream of the BCR signaling complex that can be targeted to enhance the negative selection of autoreactive B cells and possibly prevent or treat antibody-mediated systemic autoimmune disease.

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9G4 binding, as compared to healthy control serum, or serum from SLE patients without strong 9G4 staining. The reduction in signaling correlated with the degree of 9G4 binding detected. Furthermore this attenuation was dependent on 9G4 immunoglobulin, since purified immunoglobulin was sufficient to reduce phosphorylation and serum depleted of 9G4 no longer had this effect.

Conclusions: Several alterations in BCR signaling have been described in human SLE. While some of these changes are likely due to genetic alterations of signaling molecule expression or function, others may be a direct result of the disease process. These findings describe a novel mechanism by which SLE ALA can directly modulate signaling. These changes in signaling may alter B cell, proliferation, survival, and differentiation and thus help explain some of the abnormalities in B cell homeostasis observed in SLE. Reduced BCR signaling may also result in impaired clonal deletion and reduced RAG upregulation and receptor editing thereby contributing to the increased generation of auto-antibodies.

Disclosure: S. A. Jenks: None; A. E. Schroeder: None; I. Sanz: None.

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Specific Histone Deacetylase (HDAC2) Inhibition in B Cells May Protect Lupus. Nilamadhab Mishra¹, Kristen Delany² and Issac Snowhite². ¹Wake Forest Univ Health Sciences, Winston-Salem, NC, ²Wake Forest Univ Health Sciences, Wake Forest Univ Health Sciences

Background: Systemic lupus erythematosus (SLE) is characterized by polyclonal B cell activation, autoantibody production, and glomerulonephritis. The mechanisms how autoreactive B cells are produced in lupus are incompletely understood. Using genome wide mass spectrometry analysis, we have recently demonstrated that there exists histone hypoacetylation in fltis. The mechanisms how autoreactive B cells are produced in lupus are incompletely understood. Based upon these findings, we hypothesize that environmental factors trigger epigenetic alterations such as histone modifications to induces autoreactive B cells by up regulating epigenetic modifiers histone deacetylases (HDAC).

Material and Methods: Naive B cells isolated from either MRL/lpr or C57BL6(B6) mice (6–7 wk) spleens by CD43+ depletion with MACs beads followed by separation with a non-continuous percoll gradient. The cells were incubated with TLR agonist: TLR-3 poly I:C (5mg) TLR4-LPS (E.coli followed by separation with a non-continuous percoll gradient. The cells were harvested for RNA and incubated with TLR agonist: TLR-3 poly I:C (5mg) TLR4-LPS (E.coli followed by separation with a non-continuous percoll gradient. The cells were

Results: Naive B-cells with agonist for TLR 3, 4, 7 or 9 results in increased mRNA and protein expression of HDAC2 among the HDAC tested. We confirmed the activation status of B cells by measuring IL6 and IL-10. We also examine the major transcriptional regulators MTA3, MITF, XBP1 and IRF4, which are systematically down regulated or up regulated upon activation. The levels of these proteins were overexpressed in MRL/lpr mice compared to C57/B6 mice spleenocytes. All mice in the valproic acid treatment group did not develop skin disease whereas all mice in the placebo group developed skin disease. Ninety percent of mice on the treatment arm had grade I proteinuria compared to 20 percent in the vehicle group. The mean renal activity score was 4.833 ±0.654 in the treatment group compared to 8.00 ±0.00 in the vehicle group. The serum anti-dsDNA autoantibodies levels were decreased in valproic acid treatment group. There was no change in serum Ig subtype between vehicle vs treatment group.NZB/W F1 mice treated with valproic acid have decreased proteinuria, kidney disease and autoantibody production In vivo treatment with valproic acid decreased HDAC2 in spleen. Genetic knock down of HDAC2 in B cells by using mice MB1 and CD19 cre transgenic mice demonstrated that HDAC2 is required for early B cell development. HDAC2 deficient mice have decreased Pro-B cells in bone marrow and decreased follicular and marginal zone B cells in spleen.

Conclusion: These data suggest that isofrom specific histone deacetylase inhibitors may be beneficial for lupus by blocking B cell development.

Disclosure: N. Mishra: None; K. Delany: None; I. Snowhite: None.

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The Effects of the Anti-CD22 Monoclonal Antibody Epratuzumab on B-Cell Surface Proteins. Anthony Shock¹, Derek Brown², Kenneth Crook³ and Timothy Bourne⁴. ¹UCB, Slough, Berkshire, Slough, United Kingdom, ²UCB, Slough, Berkshire, UK

Background: Epratuzumab is a humanized monoclonal antibody against CD22 that is currently being evaluated clinically in systemic lupus erythematosus (SLE). Epratuzumab treatment of SLE patients has been shown to reduce CD22 cell surface expression on B cells (Jacobi A, et al. Ann Rheum Dis 2008;67:450–457). The aim of the current study was to investigate the kinetics of internalization on B cells from healthy volunteers in vitro and to look at a range of other cell surface proteins.

Methods: In vitro studies used B cells that were purified by negative selection from human blood and incubated with a concentration range of epratuzumab or an isotype control antibody over time, washed and then stained with fluorescently-labeled antibodies specific to a range of B-cell surface proteins and analyzed by flow cytometry. In order to assess the expression of CD22 in the presence of epratuzumab, a non-competing anti-CD22 antibody (S-HC-L1–PE) was employed. CD22 internalization was also evaluated in a qualitative manner using confocal microscopy experiments employing Alexa488–labeled epratuzumab. Whole blood flow cytometry was used to assess CD22 levels on B cells from SLE patients dosed with epratuzumab.

Results: Epratuzumab caused rapid internalization of B-cell surface CD22 in a range of in vitro experiments. Maximal internalization occurred in 30–60 min at concentrations above 1–2 μg/ml but the level of internalization typically did not exceed 50–70%, even at higher antibody concentrations, suggesting that some B-cell surface CD22 is resistant to epratuzumab-induced internalization. Internalization was prevented by prior cell fixation with paraformaldehyde and was reduced at a lower temperature. Internalization of CD22 on B cells in response to epratuzumab treatment was also confirmed using confocal microscopy. Although epratuzumab was capable of modulating the expression of CD22 in B-cell cultures, it had no consistent effect on several other B-cell markers including IgM, IgD, CD19, CD20, CD27, CD32, CD38, CD69, CD79b, CD95, and HLA-DR Class II measured at a variety of time points up to 6 days. Internalization of CD22 was observed on a number of B-cell subsets following treatment of SLE patients with epratuzumab.

Conclusions: Epratuzumab stimulated rapid internalization of its target, CD22, on human peripheral blood B cells in vitro and in vivo but had no consistent effect on a range of other B-cell markers. This could lead to modulation of B-cell functional responses that are regulated specifically by CD22, which may be relevant in the context of SLE.


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The Effects of the Anti-CD22 Monoclonal Antibody Epratuzumab on Peripheral Blood B Cells and Immune Responses In Vivo, and Immunoglobulin Production In Vitro. Anthony Shock¹, Derek Brown², Kenneth Crook³, Stevan Shaw⁴, Roland Foulkes² and Geoffrey Rose⁵. ¹UCB, Slough, Berkshire, Slough, United Kingdom, ²UCB, Slough, Berkshire, UK

Background: Epratuzumab is a humanized monoclonal antibody against CD22 currently being evaluated clinically in patients with systemic lupus erythematosus (SLE). The aim of the current study in cynomolgus monkeys was to investigate the effects of epratuzumab on circulating B cell numbers and on the immune response to the challenge antigens keyhole limpet hemocyanin (KLH) and tetanus toxoid (TT). Additionally, the effect of epratuzumab on immunoglobulin production from human B cells in culture was assessed.

Methods: In one study, cynomolgus monkeys received 4 weekly doses of epratuzumab at 10, 60, or 160 mg/kg and peripheral blood CD20+ B cell numbers were enumerated by flow cytometry. In a second study, cynomolgus monkeys received epratuzumab at 3 different dose levels (1 × 60 mg/kg, 1 ×
defect as B cells obtained after TNF blockade in vivo did not display defective differentiation towards plasma cells in vitro. Neither could we evidence a defective B cell activation as the post-GC B lymphocytes of anti-TNF treated patients displayed an increased expression of CD40 and HLA-DR ex vivo and a normal expression of CD80 and CD86 after TD stimulation in vitro. Further studies on the underlying mechanisms will focus on extra-follicular B cells as well as B cell migration.

Conclusion: TNF blockade impairs the induction of humoral responses in rodents and humans, with the most pronounced effect on TD responses. Whereas the exact mechanism is currently under investigation, these data reveal a novel mechanism of action of anti-TNF with potential relevance for several fields of clinical immunology.

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ACR Poster Session B
Epidemiology and Health Services Research: MSK, CTD and SLE Focus
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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A Systematic Literature Review of the Direct Costs of Systemic Lupus Erythematosus (SLE) in the United States (US), Katherine A. Slawsky1, Ancilla Fernandes2, Susan Manzi3, Lauren Fusfeld4 and Thomas F. Goss5. 1Boston Healthcare Associates, Inc., Boston MA and Washington DC, 2MedImmune, Gaithersburg, MD, 3West Penn Allegheny Health System, Pittsburgh, PA

Background: SLE is a chronic autoimmune disorder characterized by acute flares and remissions. Patients are generally managed with multiple medications depending on disease severity, tolerance, and organ system affected. SLE is thought to be associated with high symptom and economic burden; here, we review annual direct medical costs associated with SLE among adults in the US.

Methods: English-language studies published between 01/2000 and 04/2010 were systematically reviewed from both MEDLINE PubMed and the Cochrane databases. Studies were included if they reported direct medical costs of SLE among adults in the US.

Results: Nine studies reporting direct costs associated with SLE in the US and published since 01/2000 were identified. Five were excluded: one focused on a pediatric population, a review with no pooled- or meta-analyses, one study that reported no actual cost estimates and two studies that applied Canadian costs to a pediatric population, a review with no pooled- or meta-analyses, one study that reported no actual cost estimates and two studies that applied Canadian costs to US patients. A summary of the selected four studies is presented in Table 1 below.

Table 1. Results Summary

<table>
<thead>
<tr>
<th>Study 1: Commercial Claims</th>
<th>Study 2: Commercial Claims</th>
<th>Study 3: Medicaid Claims</th>
<th>Study 4: Patient Self-reported Resource Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Source</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>6,269</td>
<td>15,590</td>
<td>2,298</td>
</tr>
<tr>
<td>Year of data analysis*</td>
<td>2005</td>
<td>2006</td>
<td>2004</td>
</tr>
<tr>
<td>Mean annual direct cost</td>
<td>$20,926 ($45,093)</td>
<td>N/A</td>
<td>$17,009 ($27,531)</td>
</tr>
<tr>
<td>mean per SLE patient</td>
<td>(SD)</td>
<td>(SD)</td>
<td>($13,735 ($25,792)</td>
</tr>
<tr>
<td>patient (all patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean annual direct cost</td>
<td>$16,575 ($29,300)</td>
<td>$12,273 ($27,096)</td>
<td>$13,758</td>
</tr>
<tr>
<td>mean per SLE patient w/o</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nephritis (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean annual direct cost</td>
<td>$62,651 ($106,745)</td>
<td>$31,274 ($52,800)</td>
<td>$29,034 ($41,876)</td>
</tr>
<tr>
<td>mean per SLE patient w/o</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nephritis (SD)</td>
<td>$7,794 ($22,014)</td>
<td>N/A</td>
<td>$9,788 ($18,078)</td>
</tr>
<tr>
<td>Mean annual direct cost</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean per control patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SD)</td>
<td></td>
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</tr>
</tbody>
</table>

*All costs included to 2009 values using the GDP calculator, available http://GDP.html

Studies examined main cost categories of inpatient, outpatient, and pharmacy services, all of which contributed substantially to total costs, although the relative contribution of each main cost category varied. Median costs were consistently lower than means reported, suggesting outliers may skew overall mean costs. With the exception of study 4, all studies examined annual costs of newly diagnosed or newly active patients. No identified studies explicitly examined costs of specific treatments or disease manifestations (other than nephritis), or disease severity. Methodologies varied across studies, with patient self-reported resource
utilization generating the lowest estimates vs. claims analyses; Medicaid claims analyses generated lower incremental cost estimates for SLE patients vs. control patients compared to commercial claims analysis.

Conclusions: SLE is associated with substantial annual direct cost burden in the US; however, little research has been done examining costs associated with specific treatments, cost variation by disease severity, and disease manifestations. It is important to investigate the variation in costs due to disease severity and manifestations as newer and more expensive biologic therapies continue to emerge.


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A Systematic Review To Appraise the Quality of Cost-Effectiveness Studies of Biologic Agents for the Treatment of Rheumatoid Arthritis. Maria A. Lopez-Olivo1, Yomei Shaw2 and Maria E. Suarez-Almazor3. 1The University of Texas MD Anderson Cancer Center, Houston, TX, 2The University of Texas Southwestern Medical Center, Dallas, TX, 3The University of California, San Francisco, CA

Background: Recently, evidence has shown outstanding advances in the therapeutic approach of rheumatic diseases. The use of cost effectiveness (CE) analyses in this area has increased rapidly due to the elevated costs of the newer agents. We conducted a systematic literature review to describe the methodology reported and integrate findings from publications concerning CE in the treatment of rheumatoid arthritis with biologic agents.

Methods: We searched for cost effectiveness studies (including cost-utility) on the use of infliximab, etanercept, adalimumab, golimumab, certolizumab, tocilizumab, rituximab, abatacept and anakinra for the treatment of rheumatoid arthritis, published through September, 2009. Sources included electronic databases (MEDLINE, EMBASE, BIOSIS, etc.) and pertinent websites. Review of 2957 citations revealed 29 CE analyses. Two independent reviewers evaluated development methods of selected studies using the Quality of Health Economic Studies (QHES) tool, which was adapted using the OMERACT criteria for economic evaluations in RA.

Results: Of the 29 publications, 14 reported CE in etanercept, 12 in infliximab, 7 in adalimumab, 3 in abatacept and anakinra for the treatment of rheumatoid arthritis, published through September, 2009. Sources included electronic databases (MEDLINE, EMBASE, BIOSIS, etc.) and pertinent websites. Review of 2957 citations revealed 29 CE analyses. Two independent reviewers evaluated development methods of selected studies using the Quality of Health Economic Studies (QHES) tool, which was adapted using the OMERACT criteria for economic evaluations in RA.

Conclusions: Quality scores of CE articles published were rated acceptable. However, several differences in the design, key assumptions, and model structure were observed among studies. There is a need for more uniformity and transparency in the methodology reported in economic evaluations of biologic agents for the treatment of rheumatoid arthritis to help decision makers make better informed decisions.


756 Agreement between Tuberculin Skin Test and Interferon-γ Assay in Korean Patients with Rheumatoid Arthritis and Ankylosing Spondylitis before Initiation of Anti-Tumor Necrosis Factor Therapy. Yong-Geun Jeong1, Ji-Min Kim1, Su-Jin Moon2, Seung-Ki Kwok3, Ji-Hyeon Ju4, Kyung-Su Park5, Sung-Hwan Park5 and Ho-Youn Kim6. 1Seoul St. Mary’s Hospital, The Catholic University of Korea, Seoul, Republic of Korea, 2Seoul St. Mary’s Hospital, The Catholic University of Korea, Seoul, Korea, Republic of, 3Seoul St. Mary’s Hospital, The Catholic University of Korea, Seoul, South Korea

Purpose: To evaluate the responsiveness to tuberculin skin test (TST) in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) before initiating tumor necrosis factor α blockade (TNF-blocker) therapy, and assess its association with clinical feature and interferon-γ (IFN-γ) assay results.

Method: We retrospectively reviewed the medical records of 483 patients (251 RA, 227 AS, 5 Psoriatic arthritis, PsA) who were treated with TNF-blockers in the department of rheumatology in Seoul St. Mary’s Hospital between January 2003 and April 2009 and then analyzed the clinical characteristic and the result of TST and IFN-γ assay.

Results: TST results of 483 patients (251 RA, 227 AS, 5 PsA) were examined. The mean diameter of induration was smaller in RA patients than in AS patients (3.88mm ± 6.24 versus 7.52mm ± 8.24, p< 0.001). TST positive rate was higher in AS compared to RA (41.4% vs 20.7%; p< 0.001). Both in RA patients and AS patients, there were no significant differences between positive TST group and negative TST group in terms of disease activity, age, past history of tuberculosis and steroid usage. The positive rate of IFN-γ assay was comparable between RA and AS (41.3% versus 45.8%, p=0.768). The agreement rate between TST and IFN-γ assay was 71.9% (kappa = 0.422) in the whole group, 68.3% (kappa = 0.319) in RA, and 76.2% (kappa = 0.533) in AS. IFN-γ assay was positive in 26.2% of RA patients and 4.5% of AS patients in whom TST result was negative. Tuberculosis prophylaxis was done in 22.0% of RA patients and 39.1% of AS patients (p< 0.001).

Conclusion: There was difference in the TST positive rates between Korean patients with RA and AS. In RA patients, lower TST positive rate gave rise to the low rate of tuberculosis prophylaxis before TNF-blocker therapy compared to AS patients. Interferon-γ assay could identify patients with latent tuberculosis despite negative TST result and should be performed with TST for diagnosis of latent tuberculosis before TNF-blocker therapy, especially in RA patients.

Disclosure: Y.-G. Jeong: None; J.-M. Kim: None; S.-J. Moon: None; S.-K. Kwok: None; J.-H. Ju: None; K.-S. Park: None; S.-H. Park: None; H.-Y. Kim: None.


Background: Disease severity and disease flares are based primarily on clinical presentation in patients with systemic lupus erythematosus (SLE). Disease severity is not clearly defined but physicians often describe it as a relationship between disease activity and the organs involved. In clinical trials, disease activity and disease flares are usually assessed by composite scores which integrate both clinical and serologic variables. The ability to describe and evaluate populations of SLE patients in real-world settings has been limited due to the lack of validated methodology to identify disease severity or flares in administrative claims data.

Objective: To develop and validate algorithms to identify SLE disease severity and disease activity using medical claims data.
severity and the occurrence and severity of SLE flares using administrative claims.

Methods: This retrospective, observational study (BLM0011HO) used medical and pharmacy data (1/1/2004 to 12/31/2008) from a large managed care health plan. Patients meeting the following criteria were included in the analysis: at least 3 years of continuous enrollment in the health plan (1 year pre-index baseline period and 2 years follow up period); were between the ages of 18 and 64; and evidence of SLE. Evidence of SLE during the study period was based upon a combination of diagnosis code (ICD-9 code 710.0x), visits to rheumatologists, and filled prescriptions for lupus treatment medications (corticosteroids, antimalarials, and immunosuppressives).

Results: A total of 2990 SLE patients were identified in the claims database (92% female, mean age 44 years). Initial algorithms for identifying SLE disease severity and flare severity were developed based upon the literature and clinical consultation with 2 rheumatologists and 1 internal medicine physician. Medical and pharmacy claims for a random sample of SLE patients were reviewed to understand the patients’ profile of health services utilization, conditions diagnosed, use of services, types of providers visited, and medication use. Following evaluation of these patient profiles, the initial algorithms were further refined. The resulting disease severity and flare algorithms were applied to the SLE patients identified in the claims database.

SLE Disease Severity Algorithm
Mild
- Not Moderate or High Severity
Moderate
- Moderate Rx or Moderate Medical Condition
Medical Condition:
- Cardiovascular: hypertension, cardiac failure, pleural effusion, pericarditis (excludes aortic disease)
- Constitutional: hepatitis (non-viral)
- Gastrointestinal: acute pancreatitis, lupus enteritis/collitis
- Hematologic: anemia
- Musclekeletal: ischemic necrosis of bone
- Neuropsychiatric: demyelinating syndrome (acute inflammatory demyelinating polyradiculo-neuropathy, mononeuropathy/motor neuropathy, myelopathy, pseudotumor cerebri, seizure
- Ophthalmic: optic neuritis
- Renal: end stage renal disease (ESRD)
High
- Intensive Rx or Severe Medical Condition
Rx:
- Oral corticosteroid dose ≥7.5 mg/day
- Cyclophosphamide
- Rituximab
Medical Condition:
- Cardiovascular: aortitis, arterial/venous thrombosis, cardiac tamponade, pulmonary hemorrhage, stroke/TIA
- Gastrointestinal: intestinal pseudo-obstruction
- Neuropsychiatric: acute confusional state/psychosis, aseptic meningitis, cranial neuropathy
- Ophthalmic: optic neuritis
- Renal: end stage renal disease (ESRD)

SLE Flare Severity Algorithm
Mild
- RX Initiation
- Oral corticosteroid dose ≥7.5 mg/day
- Cyclophosphamide
- Hospital stay with primary diagnosis of SLE (710.0x) or SLE-related condition
Moderate
- RX Initiation
- Oral corticosteroid dose ≥7.5 mg/day & ≤ 40 mg/day
- Immunosuppressive therapy (excluding cyclophosphamide)
Severe
- RX Initiation
- Oral corticosteroid dose >40 mg/day
- Cyclophosphamide
- Hospital stay with primary diagnosis of SLE (710.0x) or SLE-related condition

*SLE-related conditions: disease severity conditions above or any of following: arthritis/arthralgia, dry eye/tear film insufficiency, rash, low white blood cell count (leukopenia, neutropenia, lymphopenia), lymph node enlargement, myalgia/myositis, uveitis

Applying the algorithm, 26% of patients were classified as mild, 52% were moderate and 22% had high disease severity over the 2 year follow-up period. Over the 2-year period, 71% of patients had at least one mild flare, 86% had at least one moderate flare and 20% had one or more severe flares.

Conclusions: This study has identified an algorithm that may be used to identify SLE disease severity and the occurrence and severity of SLE flares, using a combination of medical and pharmacy administrative claims. Applying this clinically-based algorithm to other claims-based studies of patients with SLE may enable an improved evaluation of SLE patients in real-world populations.

Disclosure: C. P. Garris: GlaxoSmithKline, 3; P. M. Jhingran: GlaxoSmithKline, 3; N. M. Engel-Nitz: i3 Innovus, 3; A. A. Riedel: i3 Innovus, 3; G. Goldberg: i3 Innovus, 3; D. L. Bass: GlaxoSmithKline, 3; G. J. Dennis: Human Genome Sciences, Inc., 3.

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Colonization and Infection by Staphylococcus Aureus among Those Using Biologic Therapy. Cara Varley1, Atul A. Deodhar1, Benjamin Ehs1, Antony Bakke1, Andrew Blauvelt1, Robert Vega2 and Kevin Winthrop3.
1Oregon Health & Science University, Portland, OR, 2Oregon State Public Health Laboratory, Hillsboro, OR

Purpose: While much emphasis has been placed on preventing opportunistic infections in patients with inflammatory arthritis on biologic therapy, it is clear that most serious infections are due to “routine” organisms like Staphylococcal aureus. In an ongoing prospective study we investigated the relationship between rates of new and persistent colonization, new infections with S. aureus, use of biologics and underlying disorder.

Methods: We prospectively enrolled patients with autoimmune inflammatory diseases from the rheumatology and dermatology clinics of our University. Patients receiving or being considered for biologic therapy (etanercept, infliximab, adalimumab, rituximab, abatacept) were surveyed for the presence of S. aureus infection risk factors and assessed for S. aureus colonization. Specimens collected from the bilateral nares and inguinal folds were cultured using standardized laboratory isolation procedures and screened for the presence of methicillin-resistant S. aureus (MRSA) utilizing Spectra™ MRSA test media (Remel Scientific®) and manniitol salt agar containing 4 mgs of oxacillin (MSAO, Remel Scientific®). We actively sought to follow up patients to assess persistence of colonization, new colonization, or infections with S. aureus, and their relationship with underlying disease and therapy.

Results: We enrolled a total of 392 patients (rheumatoid arthritis n=103 (26.3%), psoriasis or psoriatic arthritis n=205 (52.3%), ankylosing spondylitis n=29 (7.4%), combination of two or more n=15 (3.8%), other n=40 (10.2%). At baseline, 156 (39.8%) were colonized with S. aureus, of which 19 (12.2%) had MRSA. Our baseline colonization rates of S. aureus (39.8%) and MRSA (4.8%) were significantly higher than previously reported for the general population (30.8% and 0.8%, p<0.01 for both). Colonization rates were similar between biologic users and non-users (40.1% and 39.5%, p=0.90) but were significantly higher for psoriasis patients compared to those with RA (43.4% and 30.1%, p=0.02). 184 patients, of which 122 (66.3%) were on biologic therapy, completed follow up (mean 1 year, range 0.2–2.3 years). Biologic agents did not increase the risk of persistent (colonized at baseline and follow up) or new colonization (see table). Self reported infections were more common in persistently colonized patients compared to those newly, transiently or never colonized (RR=4.25, 95% CI 0.99–18.25, p=0.05).

Conclusion: Inflammatory arthritis patients at our center have higher rates of S. aureus colonization than the general population, and the risk of new colonization is not modified by biologic therapy. Prospective follow up shows a trend towards increased risk of subsequent infections in those with persistent S. aureus colonization.

Colonization and Self Reported Staph Infections at Follow-up, N = 184

<table>
<thead>
<tr>
<th>SLE Flare Severity</th>
<th>Persistent Staph Colonization</th>
<th>No Staph Colonization</th>
<th>Self Reported Staph Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF Exposure Between Enrollment and Follow-up</td>
<td>33</td>
<td>62</td>
<td>5</td>
</tr>
<tr>
<td>No Anti-TNF Exposure Between Enrollment and Follow-up</td>
<td>10</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>16</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Psoriasis and/or Psoriatic Arthritis</td>
<td>22</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>Ankylosing Spondylitis</td>
<td>5</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Other*</td>
<td>3</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Two or More</td>
<td>18.75%</td>
<td>50.00%</td>
<td>0.00%</td>
</tr>
</tbody>
</table>

* Includes Crohn’s Disease, Ulcerative Colitis, Ulcerative
** Both patients had a psoriasis diagnosis

Disclosure: C. Varley: None; A. A. Deodhar: Amgen Inc., 2, Centocor Ortho Biotech Inc., 2, 5, 8, Genentech and Biogen IDEC Inc, 2, 5; B. Ehs: None; A. Bakke: None; A. Blauvelt: None; R. Vega: None; K. Winthrop: Pfizer Inc, 2, 5.
Comprehensive Health Economic Assessment of Sequenced Treatment with Biologics in Moderate-to-Severe Rheumatoid Arthritis: Analysis Based on ACR50 and ACR70 Responses. Erkki J. O. Soini1, Taru A. Hallinen1, Markku J. Kauppi1, Ville Viheraara2 and Kari Puolakka1. ESIOR Oy, Kuopio, Finland, 2Lappeenranta Central Hospital, Lappeenranta, Finland, 3Päijät-Häme Central Hospital, Lahti, Finland, 4Roche Oy, Espoo, Finland

Purpose: To assess the cost-utility and multinomial expected value of perfect information (mEVPI) of sequenced treatment with biologics in moderate-to-severe rheumatoid arthritis (msRA) after failure of traditional disease modifying antirheumatic drug(s) (tDMARD).

Methods: A probabilistic, individual sampling (microsimulation) model was developed to compare ten different treatment sequences among 3,000 hypothetical Finnish msRA patients in a lifetime scenario. Adalimumab+methotrexate (MTX), etanercept+MTX or tocilizumab+MTX were used as first biologics followed by up to three other biologics. Best supportive care including tDMARDs was assumed to be used after exhaustion of treatment options with biologics. Treatment with MTX alone was added as further comparator. The clinical outcomes (no ACR50, ACR50 and ACR70 responses conditional to the use of biologic drugs) were obtained from a recently published mixed treatment comparison and quality-adjusted life-years (QALY) were estimated based on the Health Assessment Questionnaire (HAQ) scores using a nonlinear equation: EQ5D = 0.82–0.11*HAQ–0.07*HAQ². Resource use was estimated based on HAQ scores from published references and valued with Finnish unit costs (euro, year 2009). Analyses were performed from payer perspective (productivity losses were excluded) using 3% annual discount rate.

Results: Compared to MTX alone, treatment with tocilizumab+MTX was more cost-effective than treatment with etanercept+MTX. Both tocilizumab+MTX and etanercept+MTX dominated adalimumab+MTX. An additional QALY gained with tocilizumab+MTX costs euro15,478 (mEVPI euro1,258/patient) compared with MTX alone. An additional QALY gained with tocilizumab+MTX followed by etanercept+MTX or tocilizumab+MTX followed by etanercept+MTX should be considered, if willingness to pay is euro0–50,000 per QALY gained.

Conclusion: Although the 3 work-related PRO instruments are highly correlated with each other, there are important differences between the absolute values used to estimate productivity loss. Independent of the approach, loss of work productivity is strongly correlated with BASFI. Further research is required to assess full aspects of validity between the 3 work-related PRO instruments.

Reference:


Correlations between 3 Work-Related Patient-Reported Outcome Instruments for Patients with Ankylosing Spondylitis. Annelies Boonen1, Walter P. Maksymowych2, Sumati Rao3, Nadjun Chen1 and Mary Cifaldi1.

Abbott Laboratories, Abbott Park, IL, 1University Hospital Maastricht, Maastricht, Netherlands, 2University of Alberta, Edmonton, AB

Background: Several instruments have been proposed to measure work productivity but comparative studies of these instruments for rheumatic diseases are lacking. We assessed correlations between 3 work-related patient-reported outcome (PRO) instruments and the Bath Ankylosing Spondylitis Functional Index (BASFI) for patients with ankylosing spondylitis (AS). We further evaluated the percentage of productivity loss and the impact on cost between the 3 PRO measures of presenteeism, defined as the impact of disease on a patient’s ability to perform at work.

Methods: Data were obtained from the Patient-Reported Outcomes Survey in Employment (PROSE) study, a longitudinal, observational study of AS and work productivity. Participants diagnosed with AS completed an online patient survey that included 3 measures of work productivity: 1) the Work Productivity and Activity Impairment Questionnaire (WPAI), 2) the Work Limitations Questionnaire (WLQ), and 3) the Quality-Quantity Method (QQ). The WPAI measures absenteeism, presenteeism, overall work productivity impairment, and activity impairment related to AS, whereas the WLQ has 4 subscales (time management, physical demands, mental–interpersonal demands, and output demands) that assess effects of health problems on job performance (ie, presenteeism) and are combined into an overall productivity loss score. The QQ measures overall quantity and quality of work. Spearman correlation coefficients between mean scores for the WPAI components and the WLQ and QQ scores were calculated at baseline.

Results: Mean changes in WPAI presenteeism and WLQ productivity loss scores represented 22% and 5.5% work productivity loss, respectively. WPAI presenteeism was significantly correlated with WLQ time management (r=0.59, p<0.0001) and mental–interpersonal demands (r=0.59, p<0.0002) subscales as well as the overall productivity loss score (r=0.63, p<0.0001). BASFI was correlated with WPAI absenteeism (r=0.29, p<0.0005), presenteeism (r=0.63, p<0.0001), overall impairment (r=0.65, p<0.0001), and WLQ activity impairment (r=0.69, p<0.0001); WLQ time management (r=0.50, p<0.0001), mental–interpersonal demands (r=0.49, p<0.0001), output demands (r=0.55, p<0.0001), and productivity loss (r=0.58, p<0.0001); and QQ quality (r=0.44, p<0.0001) and quantity (r=0.45, p<0.0001). BASFI was not correlated with the WLQ physical demands subscale. Using the more sensitive, disease-specific 22% reduction in WPAI presenteeism (assuming a 40-hour work week at $18/hr), potential work productivity loss for patients with AS could result in loss of $158/wk per patient with AS.

Conclusion: Although the 3 work-related PRO instruments are highly correlated with each other, there are important differences between the absolute values used to estimate productivity loss. Independent of the approach, loss of work productivity is strongly correlated with BASFI. Further research is required to assess full aspects of validity between the 3 work-related PRO instruments.

Reference:


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Background: The spondylarthropathy (SpA) group includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), SpA associated with inflammatory bowel disease (IBD), undifferentiated SpA (USpA), and reactive arthritis.
(ReA). It has earlier been established that patients with AS have increased costs for health care and sick leave compared with the background population, but data for other types of SpA are scarce.

**Objectives:** To estimate the costs for health care, prescribed drugs, and sick leave for the different SpA diagnoses.

**Methods:** The Skåne Health Care Register (SHCR) in southern Sweden is a legislative, mandatory register based on physicians’ ICD-10 diagnoses and covers all in- and outpatient health care (total population 1.2 million). We identified all subjects having received a diagnosis of SpA during the years 2003–2007. To increase specificity we required all cases to be diagnosed at least once by a rheumatologist/internist or having had at least two clinic visits with the diagnosis by any other physician. Costs due to health care consumption, prescribed drugs and sick leave were retrieved from the SHCR, the Prescribed Drug Register, and the Swedish Social Insurance Agency for the years 2006–2007, including all patients 15 to 65 years of age.

**Results:** 3,561 patients with SpA (1,758 men and 1,803 women), mean age (SD) 47 (12) years were identified. The IBID patients had the highest costs for health care (mean €8,057, SD €10,545), prescribed drugs (mean €4,360, SD €6,610), and sick leave (mean €11,570, SD €10,415) whereas PsA patients had the lowest cost for health care (€4,757, SD €7,080) but the second highest for prescribed drugs (mean €2,986, SD €6,391) and sick leave (mean €9,224, SD €11,222). (Table)

**Table.** Cost is Euro (€) for health care, prescribed drugs, and sick leave per patient with Spondylarthropathy (SpA) over 2 years.

<table>
<thead>
<tr>
<th>N</th>
<th>Age Mean (SD)</th>
<th>Sex Men/Women</th>
<th>Cost for health care Mean (SD) Median (range)</th>
<th>Cost for prescribed drugs Mean (SD) Median (range)</th>
<th>Cost for sick leave Mean (SD) Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All SpA</td>
<td>3,561</td>
<td>47 (12)</td>
<td>1,758/1803</td>
<td>5,234 (9,350)</td>
<td>2,557 (5,917)</td>
</tr>
<tr>
<td>AS</td>
<td>793</td>
<td>48 (11)</td>
<td>532/261</td>
<td>5,547 (9,765)</td>
<td>2,872 (6021)</td>
</tr>
<tr>
<td>PsA</td>
<td>1,578</td>
<td>49 (12)</td>
<td>704/974</td>
<td>4,757 (790)</td>
<td>2,477 (67,742)</td>
</tr>
<tr>
<td>IBID</td>
<td>84</td>
<td>49 (11)</td>
<td>24/60</td>
<td>8,057 (10,545)</td>
<td>3,640 (6,610)</td>
</tr>
<tr>
<td>USpA</td>
<td>613</td>
<td>44 (11)</td>
<td>251/362</td>
<td>5,371 (9,120)</td>
<td>2,018 (5,511)</td>
</tr>
<tr>
<td>ReA</td>
<td>493</td>
<td>43 (14)</td>
<td>247/246</td>
<td>5,604 (12,436)</td>
<td>1,044 (3,871)</td>
</tr>
</tbody>
</table>

**Conclusion:** The different clinical forms of SpA are also seen as different cost patterns for health care, prescribed drugs, and sick leave due to disease consequences and treatment traditions.

**Disclosure:** A. B. I. Bremander: None; A. Turkiewicz: None; M. Englund: None; E. Haglund: None; G. Kobelt: None; I. F. Petersson: None; B. Strömbeck: None.

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**Introduction:** Early life exposures have been implicated in the etiology of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Vitamin D has immunomodulatory effects with implications as an etiologic and therapeutic factor in several autoimmune diseases including SLE and RA. There are no studies on vitamin D intake during adolescence and the risk of adult onset SLE and RA.

**Objectives:** We examined the relationship between reported vitamin D intake during adolescence and incidence of adult onset RA and SLE in two prospective cohort studies, the Nurses’ Health Study (NHS) and Nurses’ Health Study II (NHSII).

**Methods:** Random effects models were used to obtain a single combined estimate of association across the two cohorts.

**Results:** Incident RA was confirmed in 652 NHS and 126 NHSII participants (total 778), and incident SLE was confirmed in 122 NHS and 52 NHSII participants (total 174) over a mean followup of 329 and 207 months for NHS and NHSII respectively. Calorie-adjusted and multivariate-adjusted models did not show significant associations between adolescent vitamin D intake and risk of adult onset RA and SLE when comparing the 5th quintile of vitamin D intake to the 1st quintile (Table 1).

**Table 1.** Estimated Hazard Ratios and 95% CI of Association between adolescent Vitamin D intake and incident RA and SLE

<table>
<thead>
<tr>
<th>Number of RA cases</th>
<th>NHS</th>
<th>NHSII</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>Energy adjusted</td>
<td>Total Vitamin D</td>
<td>Multivariate adjusted</td>
</tr>
<tr>
<td>652</td>
<td>1.03 (0.8, 1.32)</td>
<td>1.06 (0.62, 1.82)</td>
<td>1.03 (0.82, 1.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>Total Vitamin D</td>
<td>Multivariate adjusted</td>
<td></td>
</tr>
<tr>
<td>122</td>
<td>1.09 (0.62, 1.95)</td>
<td>1.08 (0.47, 2.45)</td>
<td>1.03 (0.65, 1.63)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>Multivariate adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.16 (0.52, 2.56)</td>
<td>0.69 (0.25, 1.88)</td>
<td>0.87 (0.5, 1.46)</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:** We did not find associations between reported dietary intake of vitamin D during adolescence and risk of RA or SLE in adulthood. This may be due to inaccurate reporting of adolescent diet, focus on a short time period of exposure, unavailable serum vitamin D levels during this exposure period of interest or lack of effect of dietary intake of vitamin D. Small numbers of incident cases also reduced our power to detect an association if one existed.

**Disclosure:** L. T. Hiraki: None; K. H. Costenbader: None; K. Munger: None; E. W. Karlson: None.

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**Direct and Indirect Costs of Spondyloarthropathies: An Analysis of Spondyloarthropathy Costs Pre- and Post-Diagnosis.** Noam Kirson, Howard Birnbaum, Sumati Rao, Elyse Swallow, Tracy Waldman, Elias Dayoub and Mary Cifaldi. 1Abbott Laboratories, Abbott Park, IL, 2Analysis Group, Inc., Boston, MA.

**Background:** Spondyloarthropathy (SpA) includes 5 related clinical conditions: ankylosing spondylitis (AS), psoriatic arthritis (PsA), undifferentiated SpA (uSpA), reactive arthritis (ReA), and enteropathic arthritis (EA). Prior research reports significant economic burden associated with subtypes of SpA, but little is known about the profile of direct (medical and prescription drug) and indirect (work loss) costs over time. This study examines direct and indirect costs of SpA patients in the US during a 3-year period starting 2 years before SpA diagnosis.

**Methods:** Patients aged 18–64 years with ≥2 diagnoses for a subtype of SpA (ICD-9-CM: 720.0, AS; 696.0, PsA; 720.9, uSpA; 099.3 or 711.1x, EA; REA 713.1, EA) were identified in a private insurance claims database (covering 40 employers: ~9,000,000 lives) in the US (1999–2007). Patients had continuous enrollment 24 months before and 12 months after first (index) SpA diagnosis, and no claims for rheumatoid arthritis unless diagnosed with PsA. SpA patients were demographically matched to controls with no history of SpA. Per-patient direct costs for all SpA patients (N=2,194) and indirect costs (absenteeism and disability) for an employee subset (N=737) were compared with controls for 12 consecutive 3-month periods. Bootstrapping was used to compare excess costs (SpA vs. controls) within periods.

**Results:** Mean excess direct (medical plus drug) costs for SpA patients ranged from $781 (P<0.01) to $2,565 (P<0.01). Mean excess medical costs increased during the year prior to index, peaked at $1,890 (P<0.01) in the 3 months after diagnosis, and decreased approximately 60% in months 4–12 post-index. Increased rheumatologist costs persisted in the post index period (excess $176 to $132, P<0.01), while total outpatient and inpatient costs fell approximately 40% and 70%, respectively, 3 months after diagnosis. Mean excess drug costs accelerated sharply post index, peaking at $786 (P<0.01), driven largely by an increase in TNFα inhibitor costs (excess $490, P<0.01, 9–12 months post-index). Mean excess indirect costs rose during the year prior to index, peaked in the 3 months following diagnosis ($789, P<0.01), but fell during the subsequent year to levels similar to those 6 months pre-index ($388, P<0.01). A decline in absenteeism accounts for >90% of the fall in indirect costs post index.

**Conclusion:** Despite post-index increases in costs associated with SpA-targeted treatment (e.g., TNFα inhibitors, rheumatologist visits), total direct
and indirect costs decline considerably 3 months after diagnosis and return to pre-index levels. Further research is necessary to determine the causal relationship between treatment and potential direct and indirect cost savings.


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Distinguishing Levels of Disease Flare in Patients with Systemic Lupus Erythematosus Using Administrative Claims Data. Nicole Engel-Nitz1, James Burke1, Cindy P. Garris1, Priit Jiingran1, Damon L. Bass2 and Gregory J. Dennis3. GlaxoSmithKline, 3. GlaxoSmithKline, King of Prussia, PA, 3. GlaxoSmithKline, RTP, NC, 3. Human Genome Sciences, 3. i3 Innovus

Background: Systemic lupus erythematosus (SLE) is a chronic, autoimmune disorder affecting multiple organ systems of the body, characterized by acute exacerbations (flares) and remissions. Disease activity indices have been shown to be reliable when used in clinical trials but have limited application with claims data.

Objective: To differentiate between patients with mild, moderate, and severe SLE flares using a claims-based flare severity algorithm.

Methods: This retrospective observational study used administrative claims from a large managed care health plan (1/2004 - 12/2008). SLE patients 18–64 years of age were included in the analysis if they had continuous enrollment in the health plan for at least 3 years with medical and pharmacy benefits. A diagnosis of SLE was defined by any of the following criteria: a) 3 or more rheumatologist visits on separate dates (no time requirement) with a diagnostic code for SLE (ICD-9 code 710.0x); b) 2 or more rheumatologist visits ≥30 days apart with a diagnostic code for SLE; or c) 2 or more rheumatologist visits on separate dates with a diagnostic code for SLE AND ≥1 more filled prescriptions for a medication typically for the treatment of SLE. Claims-based algorithms consisting of disease activity and medications prescribed were developed and used to identify and classify disease severity (mild, moderate, high) and flares by severity (mild, moderate, severe) for each patient over a 2-year period. Patients with multiple flares could be counted more than once in each flare severity group during the period of observation. Cost of a flare episode was analyzed by flare severity.

Results: A total of 2,990 patients met the inclusion criteria of which 22% were classified as having high severity, 52% with moderate and 26% with mild disease severity. Over the 2 year period, 86%, 99% and 99.5% of patients with high, moderate, and disease severity, respectively, had at least 1 flare (p<0.001). Of patients in the high disease severity group, 61% experienced at least 1 severe flare, compared to 13% of patients with moderate and 1% of patients with mild disease severity (p<0.001) over the 2 year period. Mean number of flares over 2 years was 4.1, 7.0 and 8.0 for patients with mild, moderate and high disease severity, respectively (p<0.001). The cost of a severe flare is approximately 18 times higher than a mild flare and 11 times higher than a moderate flare.

Conclusions: Nearly all patients with SLE had at least one flare identified in the claims data. The mean number of flares was higher for patients with moderate and severe disease compared with mild disease. The cost of a severe flare is substantially higher than moderate or mild flares. Averting a severe flare may be associated with significant cost savings.


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Does Cigarette Smoking Affect Disease Phenotype in Systemic Lupus Erythematosus? Meenakshi Jolly1, Rachel A. Mikolaiti2, Joel A. Block4 and Michelle Petri1. 1John Hopkins University, 2Rush University Medical Center, Chicago, IL, 3Rush University Medical Center, Chicago, IL, 4Rush University Medical Center

Purpose: We previously reported a greater prevalence of cutaneous activity and damage among smokers than nonsmokers, in a predominantly African American cohort of patients with Systemic Lupus Erythematosus (SLE). We now present the results from a larger SLE cohort comprised of the HOPKINS Lupus Database and PROSE Database (Patient Reported Outcomes in Systemic Lupus Erythematosus). We aimed at determining if any differences in disease activity and/or damage were observed based on patients current smoking status in this large ethnically heterogeneous SLE cohort.

Methods: Cross sectional data from 1,467 SLE patients meeting the ACR criteria were analyzed based on their self report of current smoking status (Yes/No). Variables tested included demographics (age, gender, ethnicity, marital status), auto-antibodies, disease activity (SELENA-SLEDAI) and damage score (SDI). Two independent sample t tests or Mann Whitney test were used to compare continuous variables based on data distribution. Chi square tests were used to compare discrete data. Odds ratio was obtained using Mantel-Haenszel method. A p value of ≤0.05 was considered significant on two tailed test.

Results: 94% of SLE patients were women. 41% were African American, 53% Caucasian, 1% Hispanics and 6% others. 366/1,467 reported currently smoking status. Age was similar in both groups; however ethnicity and marital status (OR 0.45 for married, 95% CI 0.36, 0.57) were associated with smoking status. There were no significant differences in the total SLEDAI scores. On comparison of itemized disease activity in the past 10 days, we found mucosal ulcers (OR 1.8, 95% CI 1.2, 2.6, p = 0.002) and pleurisy OR 1.6, 95% CI 1.1, 2.1, p = 0.01) to be more prevalent among smokers and than nonsmokers. Thrombocytopenia was less prevalent among smokers as compared to nonsmokers (OR 0.35, 95% CI 0.14, 0.89, p = 0.02).

Nonsmokers had a significantly lower total damage score (mean ± SD, median) as compared to smokers: 2.05 ± 2.43, 1 vs 2.34 ± 2.45, 2, p = 0.008. Pulmonary fibrosis was more prevalent among nonsmokers (OR 0.56, 95% CI 0.32, 0.96), while myocardial infarction was more prevalent among smokers (OR 2.4, 95% CI 1.4, 4.2, p = 0.001). Skin damage was more prevalent among smokers (sclerosis/alopecia OR 3.2, 95% CI 2.0, 5.0; extensive scarring/panniculitis OR 3.4, 95% CI 3.1, 9.5, p = 0.001). A trend towards greater peripheral vascular damage among smokers was also noted (OR 2.4, 95% CI 0.8, 6.4, p = 0.07).

Conclusions: This is the largest study thus far on smoking and its association with disease manifestations in SLE. Smoking is strongly associated with disease activity related mucosal ulceration and pleurisy. A strong association overall with disease damage and especially pulmonary, cardiac and cutaneous damage exists. This study was possible through data sharing between institutions.

Disclosure: M. Jolly: None; R. A. Mikolaitis: None; J. A. Block: None; M. Petri: None.

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Early and Persistent Clinical Remission Reduces Long-Term Disability in Inflammatory Polyarthritis: Results from the Norfolk Arthritis Register. Carlo Alberto Scire1, Suzanne M. Verstappen1, Hoda Mjartafi2, Diane Bunn3, Mark Lunt1, Ian Bruce2, Carlomaurizio Montecucco3 and Deborah P. Symmons4. 1Arthritis Research UK Epidemiology Unit, Stopford Building, The University of Manchester, Manchester, United Kingdom, 2Department of Rheumatology, IRCCS Policlinico San Matteo Foundation, University of Pavia, Pavia, Italy, 3Norfolk Arthritis Register, Norfolk and Norwich University Hospital, Norwich, United Kingdom, 4Univ of Manchester, Manchester, United Kingdom

Background: Remission is an increasingly achievable objective when treating patients with inflammatory arthritis (IP) and its subset rheumatoid arthritis (RA). Although achieving the state of remission is thought to prevent long-term detrimental outcomes, the effect of remission on long-term disability has not yet been systematically investigated. In this study we have tested the predictive validity of a pragmatic definition of remission in terms of long-term disability in patients with IP.

Methods: Consecutive patients with early IP from a primary-care based inception cohort, recruited between 1990 and 1994 (first cohort) and between 2000 and 2004 (second cohort), were included this study. The 51- and 28-tender and swollen joint counts (JC) were assessed at 1, 2 and 3 yr after registration in these cohorts. Remission was defined as the absence of clinically detectable joint inflammation (swollen 51-JC = 0 and tender 51-JC = 0) at each of these time points. Less stringent definitions of remission were based on 28-JC. A 5 yr HAQ-score ≥1 (moderate disability) was chosen as the primary outcome measure. The effect of remission on subsequent disability was assessed by logistic regression. The results are shown as odds ratios (OR) and 95%CI. All analyses were adjusted for baseline confounders and missing data were imputed applying multiple imputations.

Summary of the Results: A total of 1,366 patients, 847 from the first cohort and 519 from the second cohort completed 5 yrs of follow-up. At 5 yrs, 336 (39%) and 248 (48%) of subjects from the first and second cohort respectively had developed moderate disability, 193 (24%) and 202 (36%)
fulfilled the predefined 51-JC remission criteria at least once within the first 3 yrs. In the first cohort, patients with at least one episode of remission were less likely to become disabled compared to patients who never experienced remission (OR 0.28 95%CI 0.18, 0.42) (see Figure 1).

The number of times in remission resulted proportionally decreased odds of disability, with a mean decrease in the probability of disability of about 62% for each time point in remission (OR 0.38 95%CI 0.28, 0.52). The time to the first remission within the first 3 yrs did not discriminate between patients with moderate functional disability and those with no functional disability. Similar results were observed in the second cohort. The association between the less stringent criteria of remission and future disability was weaker.

Conclusions: Patients with IP who achieve a state of remission early in their disease process are less likely to show long-term deterioration of function compared to patients who never achieve remission. Patients with the most persistent remission and under the more stringent definition of remission, have the lowest probability of long-term disability.

Disclosure: C. A. Scire`: None; M. Lunt: None; I. Bruce: None; C. Montecucco: None; D. P. Symmons: None.

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Economic Evaluation of Rituximab Versus Alternative Anti-Tumor Necrosis Factor (TNF) Therapy after Failure of Anti-TNF for Treatment of Rheumatoid Arthritis in Mexico. Fernando Carlos1 and Patricia Clark2.

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Background: About 30% of rheumatoid arthritis (RA) patients treated with an anti-TNF agent failed to achieve an improvement of 20% in American College of Rheumatology (ACR) response. Recent clinical practice guidelines recommend the use of rituximab after failure of one anti-TNF instead of cycling between these agents. We aimed to evaluate the cost-effectiveness of different treatment strategies in severe RA after anti-TNF failure from the perspective of the public health care system in Mexico.

Methods: A microsimulation Markov model was used to compare life-time costs and quality-adjusted life years (QALY) of 12 different treatment pathways for one million simulated patients aged 40 years (70% women, mean weight 66.67 Kg) with failure to etanercept (ETA) [Model 1], adalimumab (ADA) [Model 2], or infliximab (INF) [Model 3]. Competing interventions included giving rituximab (RTX) first, followed by a sequence of the two alternative anti-TNF agents or to administer RTX after complete cycling between anti-TNF agents. RTX (1 course, consisting of 2 infusions of 1g each) given 9 months apart; IFN 3 mg/Kg weeks 0, 2, 6, 14 and 22, and then 4.5 mg/Kg given 8 weeks apart starting from week 30; ETA 25mg twice a week; and ADA 40mg every other week, were all combined with methotrexate (MTX) 15mg weekly. Baseline Health Assessment Questionnaire (HAQ) score was sampled from a Normal distribution [mean 1.88; S.D. 0.58]. Indirect comparison techniques were used to adjust 6-month ACR responses rates found in 9 clinical trials. HAQ scores dropped accordingly to the magnitude of ACR response. Median duration times were taken from published literature. Once treatment stops, the entire initial gain in HAQ is assumed to be lost instantly. Patients are then allocated to the next available treatment option until the sequence is exhausted. At this point, all patients receive single MTX, until they reach 100 years of age or death. Direct costs included acquisition of biologic drugs besides infusion cost for RTX and INF plus medical attention of each health state into the model. Ambulatory resource use was estimated by an experts' panel of 10 specialists. Inpatient days were estimated on the basis of HAQ score. Unit costs were gathered from official sources. Mortality rates were derived from Mexican life tables and a risk multiplier of 1.33^{10}. A quadratic equation was used to link HAQ scores with utility weights. Costs and QALY were discounted at an annual rate of 3%. All costs were calculated in 2009 Mexican Pesos and then expressed in US dollars (12.729 MXP per USD).

Results: Starting therapy with RTX was a dominant (both more effective and less costly) option than switching to another anti-TNF agent, leading to cost-savings that ranged from 862 to 1,365 USD per patient and gains of 8.67 to 16.18 QALY per 1,000 patients. If retreatment with RTX is set at 6 months (keeping all other parameters constant), most of estimates for the incremental cost per QALY gained with initial RTX instead of using alternative anti-TNF agents would fall below 50,000 USD.

Conclusions: This study suggests that starting therapy with RTX after previous failure of one anti-TNF agent is a cost-effective strategy compared to cycling between anti-TNF agents.

Disclosure: F. Carlos: Roche; 5; P. Clark: None.

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High Level of Disease Activity in Chronic Inflammatory Rheumatisms Increases the Rate of Indeterminate Interferon-Gamma-Release Assay Results for Latent Tuberculosis Infection Detection. Felicte Costantino1, Gilbert Faure1, Marcelo De Carvalho1, Anne-Christine Rat2, Herve´ Dintinger3, Damien Loeuille4 and Isabelle Chary-Valkenaere1.

1Immunology (EA RHEM4369) Department, Nancy University Hospital, Vandoeuvre-les-Nancy, France, 2Rheumatology department, Nancy University Hospital, Vandoeuvre-les-Nancy, France

Purpose: Screening for latent tuberculosis infection (LTBI) is mandatory before initiating TNF-alpha blocker treatment. Recent studies established that interferon gamma release assay (IGRA) have better specificity than Tuber-
culin Skin Test (TST) for LTBI diagnosis. However, little is known about practical use of IGRA in patients with chronic inflammatory arthritis.

The aim of the study was to identify factors that may influence IGRA results in patients with chronic inflammatory conditions and candidates for TNFalpha-blockers.

Patients and Methods: consecutive patients from one Rheumatology department treated for chronic inflammatory arthritis and candidate for biologics were prospectively enrolled over a 5-years period (July 2004 - July 2009). Clinical data (disease diagnosis, duration and activity), biologic parameters (ESR and CRP), treatment and risk factors for LTBI were recorded at inclusion. All patients underwent TST according to Mantoux method (Tubertests® 5 units), SANOFI PASTEUR MSD, SNC, (Lyon, France), chest-x-ray (CXR) and IGRA (T-SPOT.TB®, Oxford Immunotec, UK).

Results: 590 patients were included: 294 (49.8%) with rheumatoid arthritis (RA), 271 (45.9%) with spondyloarthritides (SPA) and 25 (4.2%) with other inflammatory diseases. History of BCG vaccination was present in 460 patients (78%). TST was positive (induration ≥5 mm) in 201 patients (34.1%), negative in 335 (56.9%) and non available in 54 cases (9%). T-SPOT.TB® assay was positive in 125 patients (21.2%), negative in 372 (63.0%) and indeterminate in 93 (15.8%). A higher age, previous active TB, whatever the diagnosis, (i.e. DAS28 for RA and BASDAI for SPA) was significantly associated with female gender (p=0.003), rheumatoid arthritis (p=0.005), previous TNF-alpha blockers (p=0.016), DMARDs (p=0.012) and current corticosteroids treatment (p=0.001).
Improving Health-Related Quality of Life in Patients with Systemic Lupus Erythematosus (SLE): The Role of Disease Control, Steroid Reduction and Smoking Cessation. Mark J. Harrison, Nicola Dale, Sahena Haque, Joanna Shelmerdine, Lee-Suan Teh, Yasmine Ahmad and Ian N. Bruce. 1Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, 2Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, 3Betsi Cadwaladr University Health Board-West, Rheumatology, Llandudno, United Kingdom, 4Department of Rheumatology, Royal Blackburn Hospital, Blackburn, United Kingdom, 5Health Sciences Research Group, The University of Manchester, Manchester, UK, 6The Kellgren Centre for Rheumatology, Central Manchester Foundation Trust, Manchester, UK

Purpose: Longitudinal studies of cohorts of SLE patients have shown that poor HRQoL does not change significantly over time, despite modern management. We aimed to describe changes over a 5-year period in a cohort of outpatient SLE patients and compare the clinical characteristics of sub-groups of patients experiencing clinically important improvement or deterioration.

Methods: Female patients with SLE (≥4 ACR criteria) were recruited from routine outpatient clinics at 2 time points 5 years apart. At baseline and 5 years patients had a clinical assessment including the SLEDAI 2000 and SLICC damage index (SDI). Patients also completed the RAND Medical Outcome Study 36-Item Short-Form Survey version 1 (MOS SF-36), which allowed the SF-6D to be calculated, at both time points. The change in SF-6D over 5 years was assessed in relation to the minimum important difference (MID) of the measure (0.024). The characteristics of patients who experienced >MID improvement, >MID deterioration, or no change (ΔSF6D ≤MID), were compared using the t-test and ANOVA or chi-square test as appropriate.

Results: 107 patients had SF-6D scores both at baseline and at 5 years. The mean(SD) age was 49 (9) years and mean (SD) disease duration 13 (10) years. At baseline, 15% were current smokers. The SF-6D score at baseline (n=107) was 0.62. The mean change in SF-6D over the 5-year period for the longitudinal cohort was 0.00 (SD 0.10). 39% (n=42) of patients in the cohort improved (mean 0.10) and 37% (n=40) of patients worsened (mean −0.10) by more than the MID. SLEDAI scores were significantly different across groups (p=0.001); decreasing in improved patients (−1.5), but increasing in unchanged (1.7) or worsened (2.4) patients. A higher proportion of improved patients stopped steroid treatment (27% vs 5%) or stopped smoking (15% vs 1%). Stopping smoking or steroids were both associated with important gains in SF-6D (0.07 vs −0.01, p=0.022) (0.08 vs −0.02, p=0.127) respectively. SDI scores did not differ between the groups.

Conclusions: While the mean SF-6D scores in this SLE cohort did not change over a 5-year follow-up period, there are groups of patients who experience clinically important improvement or deterioration in HRQoL within this population. Better disease control while targeting a reduction/cessation of steroid therapy and smoking cessation all may contribute to large health gains for SLE patients.

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Increase in Direct and Decrease in Indirect Costs of Rheumatoid Arthritis in Germany between 2002 and 2008. Dörte Hüsscher, Katja Thiele, Andrea Pfluefflin, Sascha Bischoff, Rieke Alten, Ulrich von Hohoven, Matthias K. Schneider andanga Zippe. 1German Rheumatism Research Centre and Charité University Hospital, Berlin, Germany, 2German Rheumatism Research Centre, Berlin, Germany, 3Hilleshög, Germany, 4Schlosspark-Klinik KG, Department of Internal Medicine II, Rheumatology, Clinical Immunology Osteology, Berlin, Germany, 5University Hospital Düsseldorf, Düsseldorf, Germany

Objective: We recently observed a remarkable reduction in disease activity (DAS28) in patients with RA treated in German rheumatology during the past decade. The frequency and duration of hospitalization and sick leave decreased, whereas the work participation improved. We now analysed how these trends influenced direct and indirect costs.

Methods: We used data from the national database of the German Collaborative Arthritis Centres. An earlier cost analysis used data from the year 2002 which were less detailed than those available now. DMARD and glucocorticoid treatment has been collected now with dosages and exact duration which allows more accuracy in estimating figures of this major cost domain. For the years 2002–2004 these details were not available, and were imputed with median doses and median treatment durations from the following years. Non-pharmacological treatments were calculated for an assumed 9-months period per year. Cost components for hospitalization, sick leave and work disability were calculated by means of the German annual statistical yearbook. For indirect costs, both human capital approach (HCA) and friction cost approach (FCA; 58 days replacement period) were considered. Only those rheumatological units who had participated in all consecutive years were selected for analysis.

Results: Drug treatment was the cost domain with the highest increase between 2002 and 2008 (Fig. 1). This increase was almost entirely caused by biologic therapies.

Comparing the main cost domains, these risen costs were accompanied by slightly decreasing costs for inpatient treatment and sick leave, and depending on the calculation approach a slight (FCA) or remarkable (HCA) decrease for permanent work disability (Fig. 2).

Accordingly, total costs showed a moderate increase (FCA) or remained almost stable (HCA) (Fig. 3).
Conclusions: We have seen a continuous increase of costs for drug treatment, mainly caused by the growing use of biologics. Depending on the health economic approach for the calculation of indirect costs, these risen direct costs were partially counterbalanced when using the friction cost approach, and were almost entirely compensated when using the human capital approach.

Disclosure: D. Huscher: see study sponsor, 2; K. Thiele: see study sponsor, 2; A. Pfefelin: see study sponsor, 2; S. Bischoff: see study sponsor, 2; R. Alten: see study sponsor, 2; U. von Hinueber: see study sponsor, 2; M. K. Schneider: see study sponsor, 2; A. Zink: see study sponsor, 2.

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Increased Risk of Valvular and Nonvalvular Cardiovascular Disease in Younger Individuals with Ankylosing Spondylitis: A Population-Based Study
Adrian R. Levy 3, Shelagh M. Szabo 5, Sunnati Rao 5, Diane V. Lacaille 5, Mary Cifaldi 6, and Walter P. Maksymowych 6 1Abbott, 2Arthritis Research Ctr Canada, Vancouver, BC, Canada, 3Toronto Western Hospital, 4University of Alberta, Edmonton, AB, Canada

Background: Increased risk of valvular cardiovascular disease for patients with ankylosing spondylitis (AS) are well-documented. However, data on the association of AS with other types of cardiovascular and cerebrovascular disease are equivocal. While some cross-sectional clinic-based studies report an increased risk of nonvalvular CV disease with long-standing AS, others have concluded that routine cardiologic evaluation is not indicated. No longitudinal population-based data on the risk of CV disease in patients with AS compared with individuals without AS have been presented. The objective was to estimate the population-based prevalence and increased risk of valvular and nonvalvular CV disease among individuals with AS in the Canadian province of Québec.

Methods: A retrospective cohort study was conducted using the population-based administrative physician-billing database maintained by the Régie de l’Assurance Maladie du Québec. The cohort included individuals with at least 1 International Classification of Diseases, 9th Revision, (ICD-9) billing code for AS between 1996 and 2006. A comparison cohort was generated using a 1% random sample of individuals without AS. CV diseases were classified according to ICD-9 code and grouped into 6 categories: valvular (aortic and non-aortic) disease, ischemic heart disease, congestive heart failure, cerebrovascular, and other CV disease. Age- and sex-stratified prevalence, and standardized prevalence ratios, of cardiovascular or cerebrovascular disease in AS compared with the general population were calculated.

Results: Among 41 patients (68% male), 50% were Caucasian, 17% Black, 7% Asian, and 17% other. The mean age at SLE diagnosis was 30.5 ± 10.3 years. At study visit the mean age was 45.3 ± 13.2 years and disease duration 14.8 ± 10.3 years; SLEDAI-2K 2.59 ± 2.41 and SDI 2.12 ± 2.48. 376 patients-visits were recorded. Quality of life assessed by both questionnaires is low among SLE patients. Quality of life assessed by both questionnaires is low among patients. There was no statistically significant difference between the mean scores of comparable domains; Physical Health/Physical Functioning, Emotional Health/Mental Health, Pain/Bodily Pain and Fatigue/Vitality. For the 4 non-comparable domains of the LupusQoL, we determined the correlation between each domain with the Physical Component Score (PCS) and the Mental Component Score (MCS) of the SF-36.

Conclusions: Patients with AS are at increased risk for many types of cardiovascular or cerebrovascular disease. The excess risk is greatest for young AS patients. This data supports consideration for cardiovascular risk assessment in the clinical evaluation of patients with AS.


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Is There an Advantage for a Lupus Specific Quality of Life Measure over SF-36?
Zahi Touma2, Dafna D. Gladman3, Domnique Ibanez 7, and Murray B. Urowitz 1.1The Toronto Western Hospital, Toronto, ON, Canada, 2Toronto Western Hospital, Toronto, ON, Canada, 3Toronto Western Hospital, Toronto, ON, Canada

Objective: The LupusQoL questionnaire is a disease-specific instrument for adults with lupus. We aimed to assess whether the LupusQoL contributed additional information not obtained using the SF-36 and to compare the responsiveness of both questionnaires over time in patients who changed clinically.

Methods: 41 patients seen at a single centre were followed at monthly intervals for 12 months. Both questionnaires were co-administered monthly. Lupus activity was determined by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) 30 days. We compared the mean scores for the 4 comparable domains in both questionnaires in all patient-visits. For the 4 non-comparable domains of the LupusQoL, we determined the correlation between each domain with the Physical Component Score (PCS) and the Mental Component Score (MCS) of the SF-36.

The effect size (ES) and the standardized response mean (SRM) were used to compare the responsiveness of both questionnaires in patient-visits with lupus flare (SLEDAI-2K > 3) and remission (SLEDAI-2K = 0) from previous visit.

Results: Among the 41 patients (68% male), 50% were Caucasian, 17% Black, 7% Asian, and 17% other. The mean age at SLE diagnosis was 30.5 ± 10.3 years. At study visit the mean age was 45.3 ± 13.2 years and disease duration 14.8 ± 10.3 years; SLEDAI-2K 2.59 ± 2.41 and SDI 2.12 ± 2.48. 376 patients-visits were recorded. Quality of life assessed by both questionnaires is low among SLE patients. Quality of life assessed by both questionnaires is low among patients. There was no statistically significant difference between the mean scores of comparable domains; Physical Health/Physical Functioning, Emotional Health/Mental Health, Pain/Bodily Pain and Fatigue/Vitality. For the 4 non-comparable domains of the LupusQoL, there was a correlation between Body Image/MCS-SF-36 r = 0.61, Planning/MCS-SF-36 r = 0.68, Intimate Relationships/PCS-SF-36 r = 0.73, and Burden to Others/PCS-SF-36 r = 0.70.

Both questionnaires displayed responsiveness as determined by SE and SRM among patients who flared (SF-36: SRM moderate effect 0.64 Role Physical, 0.70 Pain, small effect 0.42 Social Functioning and 0.30 PCS; LupusQoL: SRM moderate effect 0.67 Fatigue and small effect 0.49 Burden to others) and improved (SF-36: SRM moderate effect 0.60 MCS and small effect 0.43 Mental Health, 0.40 General Health, 0.30 Vitality, 0.30 Role Physical, 0.24 Social Functioning and 0.23 Physical Functioning; LupusQoL: SRM moderate effect 0.73 Pain, 0.53 Fatigue and 0.51 Physical Health, and small effect 0.45 Emotional Health, 0.39 Body Image, 0.37 Burden to others and 0.36 Planning) but not among patients in remission when compared to previous visit. There was no significant difference in the responsiveness of both questionnaires in patients with lupus flare and improvement when compared to previous visit.

Conclusions: There is no superiority of LupusQoL over SF-36 in assessing lupus patient’s quality of life. Both questionnaires are responsive instruments of lupus quality of life in patients with flare and improvement. The utility of LupusQoL needs to be evaluated in future studies in patients with moderate to severe disease activity.

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Life Expectancy, Standardized Mortality Ratios and Causes of Deaths of Six Rheumatic Diseases in Hong Kong, China
Chi Chiu Mok1, Raymond C. L. Kwok2, Ling Yin Ho3, Pak To Chan4 and Paul S. F. Yip5. 1Tuen Mun Hospital, 2University of Hong Kong
Objectives: To study the life expectancy, standardized mortality ratios (SMRs) and causes of deaths of six rheumatic diseases in Hong Kong

Methods: The number of patients with the International Classification of Disease (ICD)-9 diagnostic codings of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), anklyosing spondylitis (AS), psoriatic arthritis (PSA), systemic vasculitides (SV) and systemic sclerosis (SSc) who were followed in our hospital between year 1999 and 2008 were retrieved by the hospital registry called the Clinical Data Analysis and Reporting System (CDARS). The number of patients with these diagnostic codings who died during follow-up was also retrieved by the hospital death registry. The SMRs were calculated by comparing the rate of mortality of each disease entity (observed deaths) with the mortality rate of the general population gathered from the population census and the general death registry (expected deaths). The causes of death were evaluated and compared across these six rheumatic diseases. Life expectancy of each disease was calculated by abridged life table analysis using the prevalence and death data in the CDARS and data reported for the Hong Kong population within the same study period.

Results: The causes of deaths of 348 patients between year 1999 and 2008 were analyzed. The distribution of the underlying diseases was: RA (50%), SLE (23%), SV (14%), AS (7%), SSc (4%) and PSA (1%). The mean age at the time of death was 65.5 ± 17.3 years and 240 patients (69%) were women. The age at death was highest with RA (74.1 ± 12.1 years) and lowest with SSc (69.0 ± 15.7 years). The mean SMR of both sexes and all age groups was highest for SLE (24.3 [22.2–26.4]), followed by SSc (18.3 [15.3–22.1]), SV (11.1 [9.9–12.3]), AS (8.8 [7.6–10.3]), RA (8.3 [7.9–8.8]) and PSA (7.5 [5.7–9.8]). The principle causes of deaths were, in descending order of frequency, infections (34%), cancers (18%), cardiovascular / cerebrovascular complications (16%), renal failure (6%), pulmonary pathologies (4%), liver and gastroenterological complications (4%), accidents (1%) and suicide (1%). Cardiovascular death was most frequent in patients with SSc and PSA. Cancer deaths were highest in patients with SV, followed by PSA and AS. Renal failure as a cause of death was reported in SLE and RA only. Cases of suicide occurred exclusively in SLE. In female patients, the loss in life expectancy was greatest with RA (28.3 years), followed by SLE (27 years), SSc (16 years), AS (7 years) and RA (5.2 years).

Conclusions: Patients with rheumatic diseases have a higher mortality risk than the general population, leading to a significant loss in life expectancy. Among the six diseases studied, SLE has the highest SMR and female SSc patients had the greatest loss in life expectancy. Infection is the leading cause of death in SLE, RA and SSc but not in other three diseases. Cardiovascular death was most frequent in patients with SSc and PSA. Cancer deaths were highest in patients with SV, followed by PSA and AS. Renal failure as a cause of death was reported in SLE and RA only. Cases of suicide occurred exclusively in SLE. In female patients, the loss in life expectancy was greatest with RA (28.3 years), followed by SLE (27 years), SSc (16 years), AS (7 years) and RA (5.2 years).

Disclosure: C. C. Mok: None; R. C. L. Kwok: None; L. Y. Ho: None; P. T. Chan: None; P. S. F. Yip: None.

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Background: There is limited data on predictors of giant cell arteritis (GCA). In a previous case-control study of women with GCA, a history of smoking, low body mass index (BMI) and several hormonal factors were associated with GCA. Smoking and a low level of formal education have been found to predict other chronic inflammatory disorders, including rheumatoid arthritis.

Objective: To examine potential risk factors of GCA in a nested case-control study based on two prospective health surveys.

Methods: We studied two population based health surveys performed in the same catchment area, the Preventive Medicine Program (PMP) and the Diet Cancer Study (DCS). In the PMP, 33346 subjects (22444 men and 10902 women) were included between 1974 and 1992, and in the DCS, 30447 subjects (12121 men and 18326 women), were included between 1991 and 1996. Information on medical history and life style factors was obtained using standard physical examinations and self-administered questionnaires. From this population, individuals who developed GCA after inclusion were identified by linking the PMP and DCS databases to the local patient administrative register and the national hospital discharge register. A structured review of the medical records of all identified cases was performed. Patients were classified according to the ACR criteria for GCA and the date of diagnosis was noted. Four controls for every confirmed case, matched for sex, year of birth and year of screening, who were alive and free of GCA when the index person was diagnosed with GCA were selected from the PMP and DCS databases, respectively. For cases who had participated in both surveys, the screening closest preceding the diagnosis of GCA was used. The impact of potential predictors of GCA, including BMI, smoking, and other lifestyle factors, was examined in conditional logistic regression models.

Results: Eighty-three patients (70 % women, 64 % biopsy positive, mean age at diagnosis 71 years) had a confirmed diagnosis of GCA after inclusion in the PMP or the DCS. The median time from screening to GCA diagnosis was 10.6 years (range 0.3–28.2). BMI at screening was lower in GCA cases than in matched controls (mean 24.3 vs 25.6 kg/m²). In logistic regression analysis, a higher BMI was associated with a significantly reduced risk of subsequent development of GCA [Odds ratio (OR) 0.91 per kg/m²; 95 % confidence interval (CI) 0.84–0.98]. Individuals who were overweight (BMI>25 kg/m²) had a lower risk for GCA (OR 0.39, 95 % CI 0.21–0.70) compared to those with a normal or low BMI. There was no significant association between current smoking at screening (OR 1.36; 95 % CI 0.77–2.57) or a history of early menopause (before age 46) (OR 1.76; 95 % CI 0.71–4.39) and GCA. Level of formal education and breast-feeding history did not predict GCA. In multivariate analysis, adjusted for smoking and level of formal education, the association between higher BMI and reduced risk of GCA remained significant (OR 0.91 per kg/m²; 95 % CI 0.85–0.99)

Conclusion: In this study, subsequent development of GCA was predicted by a lower BMI at baseline. Potential explanations include an effect of adipose tissue on hormonal pathways regulating inflammation in the context of GCA.

Disclosure: K. Jakobsson: None; L. T. H. Jacobsson: None; K. J. Warrington: None; E. L. Matteson: None; K. P. Liang: None; O. Melander: None; C. Turesson: None.

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Obstetrical and Neonatal Outcomes in Rheumatic Disease. Cheryl C. M. Barnabe, Peter Faris and Hude Quan. University of Calgary, Calgary, AB, Canada

Background: Adverse maternal and neonatal outcomes have been documented in women with rheumatic disease. Our objective was to determine if this situation has improved in the era of better rheumatic disease treatment and prenatal management.

Methods: An inpatient dataset provided obstetrical admission details for a cohort of women with rheumatic disease (including RA, SLE, anklyosing spondylitis, systemic sclerosis, inflammatory myopathies and JIA) and a comparison group matched on maternal age and year of delivery. Maternal outcomes include mean length of stay, and the proportion experiencing pregnancy-related hypertension, instrumentation at delivery or cesarean section, and postpartum infections. Neonatal outcomes include the mean length of stay and the need for special care unit admission. We also examined the proportion of neonates born prematurely, small for gestational age (SGA) or with congenital defects. Conditional logistic regression was used to calculate the crude odds ratio (OR) and the 95% confidence intervals (CI) for the dichotomous outcomes of interest, with adjustments made for known confounders (if occurring in at least 5% of the sample).

Results: 161 singleton pregnancies occurred in 141 women with rheumatic disease, predominantly RA and SLE. There were a total of 6 stillbirths, 3 in each group. Reasons for readmission particular to rheumatic disease during the first year postpartum included 2 women with flares of SLE, and 1 woman who required 2 arthroscopic procedures. Neonates of women with rheumatic disease were not at increased risk of readmission. There was no evidence of excess congenital defects in babies born to women with rheumatic disease (1.2% vs 2.1%).
Table 1. Summary of Maternal Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Women with Rheumatic Disease n = 161</th>
<th>Women without Rheumatic Disease n = 635</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (days), mean (SD)</td>
<td>3.7 (4.3)</td>
<td>2.3 (2.0)</td>
</tr>
<tr>
<td>Pregnancy-related hypertension, n (%)</td>
<td>27 (16.8)</td>
<td>52 (8.2)</td>
</tr>
<tr>
<td>Instrumentation for delivery, n (%)</td>
<td>42 (26.1)</td>
<td>136 (21.4)</td>
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<tr>
<td>Cesarean section, n (%)</td>
<td>70 (43.5)</td>
<td>146 (23.0)</td>
</tr>
<tr>
<td>Postpartum infection, n (%)</td>
<td>7 (4.3)</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>1 year readmission, n (%)</td>
<td>22 (13.7)</td>
<td>32 (5.9)</td>
</tr>
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</table>

Table 2. Summary of Neonatal Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Neoneats of Women with Rheumatic Disease n = 161</th>
<th>Neoneats of Women without Rheumatic Disease n = 635</th>
</tr>
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<tbody>
<tr>
<td>Prematurity, n (%)</td>
<td>44 (27.3)</td>
<td>47 (7.4)</td>
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<tr>
<td>Length of stay (days), mean (SD)</td>
<td>3.6 (4.8)</td>
<td>2.4 (2.0)</td>
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<tr>
<td>Requiring intensive care, n (%)</td>
<td>49 (30.4)</td>
<td>74 (11.7)</td>
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<td>Length of stay, intensive care (days), mean (SD)</td>
<td>1.8 (5.1)</td>
<td>0.6 (2.8)</td>
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<tr>
<td>Small for gestational age, n (%)</td>
<td>37 (23.0)</td>
<td>67 (10.6)</td>
</tr>
<tr>
<td>1 year readmission, n (%)</td>
<td>14 (8.7)</td>
<td>33 (5.2)</td>
</tr>
</tbody>
</table>

Table 3. Crude and Adjusted Odds Ratios for Maternal and Fetal Outcomes, Comparing Women with Rheumatic Disease to Those Without Rheumatic Disease

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Crude OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p value</th>
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<td>Maternal</td>
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<tr>
<td>- Pregnancy-related hypertension</td>
<td>2.25</td>
<td>1.36–3.71</td>
<td>2.33</td>
<td>1.38–3.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Instrumentation</td>
<td>1.30</td>
<td>0.87–1.95</td>
<td>1.26</td>
<td>0.87–1.93</td>
<td>0.280</td>
</tr>
<tr>
<td>- Cesarean section</td>
<td>2.71</td>
<td>1.85–3.59</td>
<td>3.02</td>
<td>1.87–4.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Postpartum infection</td>
<td>4.47</td>
<td>5.60–13.3</td>
<td>2.99</td>
<td>0.85–10.5</td>
<td>0.087</td>
</tr>
<tr>
<td>Neonatal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Prematurity</td>
<td>4.51</td>
<td>2.85–7.13</td>
<td>4.38</td>
<td>2.75–7.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Small for gestational age</td>
<td>2.52</td>
<td>1.60–3.96</td>
<td>2.50</td>
<td>1.59–3.93</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions: In our cohort, women with rheumatic disease continue to have increased odds of developing pregnancy-related hypertension, and a large proportion deliver by cesarean section. Neonates of women with rheumatic disease are more likely to be premature, and small for gestational age. These findings are entirely in keeping with the previous literature, and do not appear to have improved over time. Additionally, women with rheumatic disease demonstrate a trend to an increased risk of postpartum infections, which has not been previously documented.

Disclosure: C. C. M. Barnabe: None; P. Faris: None; H. Quan: None.

Patient Perceptions and Access to Resources Influence Patient Decisions To Attend Rheumatology Appointments. Valerie Milne2, Robin Kears1 and Andrew A. Harrison1. 1University of Auckland, New Zealand, New Zealand, 2University of Otago, Wellington, Wellington, New Zealand, 3University of Otago, Wellington, New Zealand, New Zealand

Purpose: Patients referred to rheumatology clinics with symptoms of inflammatory arthritis (IA) miss the opportunity for early DMARD treatment when they do not attend their first specialist assessment (FSA). This study aimed, through patient interviews, to understand the social, economic and geographic determinants of FSA attendance at a public rheumatology service.

Method: A purposive sample of 21 people with IA was selected from private clinics, public clinics and the local community. Beliefs about IA and experiences of the condition and its treatment, including the referral process, were elicited in one-on-one interviews. Contradictions and commonalities in patient narrative were thematically coded using QSR Nvivo qualitative software. A narrative approach was informed by the collective lifestyles framework, which aims to locate individual health behaviours within a social context.

Results: The context provided by the collective lifestyles framework for discourse about patient circumstance helps explain non-attendance at the FSA. Barriers to attendance revealed by patient interviews were: 1) how patients perceived their symptoms and possible treatment; 2) social support and economic resources 3) the geographic attributes of the residential area and 4) the structure of the rheumatology service. Patients’ self-perception and an inaccurate assessment of the risk of DMARDs compared with the benefits of treatment can lead patients to reject rheumatology care. Among people who reported inadequate social and economic resources; childcare, work commitments, and availability of help with impairment and transport were cited as factors affecting attendance. Descriptions of severe pain and impairment associated with long wait time gave some insight as to why patients cancel their public appointment in favour of a private appointment with a shorter wait, despite additional costs.

Conclusion: Patients’ motivations suggest that altering the booking procedure from an administrative process to an assessment process to include early assessment of pain, impairment and patient support and co-ordination with the family physician to address these factors could improve non-attendance and cancellation rates. Providing information about the rheumatology service before the FSA could address patients’ fears about impairment and reduce negative perceptions of possible treatment options. More general publicity about IA or specifically tailored information to patients with suspected IA may enable patients to make more informed decisions about accepting rheumatology care.


Disclosure: V. Milne: None; R. Kears: None; A. A. Harrison: None.

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Patient-Reported Outcome Measures in Patients with Polyarthritis Rheumatica (PMR): Results from an International, Prospective, Multi-Centre ACR – EULAR Study Group for Development of Classification Criteria for PMR. Bhaskar Dasgupta6, Marco A. Cimmino10, Hila Maradit-Kremers6, Wolfgang A. Schmidt19, Schirmer Michal9, Carlo Salvarani1, Peter Mandl20, Artur Bachta5, Maria C. Cid1, Haner Drieskens15, Pierluigi Macchioni10, Peter V. Balint6, Christina Dufner6, Christian Dejaco3, Hanna Slott-Jensen1, Zsuzsa Schmidt24, Gyula Póó5, Annamaria Iagnocco12, Victor Martinez-Tabarca19, Elisabeth Nordborg26, Nicola Pippet6, Pierre Duhaht22, Carlotta Nannini25, Georgina Espigol-Frigólé2, Sibel Z. Aydin2, Khalid Ahmed18, Rashidu Lukmani23, Brian Hazelman3, Colin Pease18, Richard J. Wakefield20, Nele Gontier2, Ralph Marcus20, Clemence J. Michel2, Mehrdad Mazlumzadeh1, Andy Abiri1, Cynthia S. Crowson8 and Eric L. Matteson19. 3rd Rheumatology Department, National Institute of Rheumatology and Physiotherapy, Budapest, 4Center for Diagnosis Imaging, Hospital Clinic, Montserrat del Amo, Barcelona, Spain, 5Department of Health Sciences Research, Mayo Clinic, Rochester, MN, 6Department of Internal Medicine and Rheumatology, WIM CSK MON, Warszawa, Poland, 7Department of Internal Medicine I, Medical University Innsbruck, Innsbruck, Austria, 8Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Jacksonville, FL, 9Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Rochester, MN, 10Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Scottsdale, AZ, 11Department of Internal Medicine, General Hospital of the Elisabethen, Klagenfurt, Austria, 12Department of Internal Medicine, University of Genova, Genova, Italy, 13Department of Rheumatology, Arcispedale S. Maria Nuova, Reggio Emilia, Italy, 14Department of Rheumatology, Cambridge University, Cambridge, UK, 15Department of Rheumatology, Mar-mara University Medical School, Istanbul, Turkey, 16Department of Rheumatology, Medical University, Graz, Graz, Austria, 17Department of Rheumatology, Princess Alexandra Hospital, Harlow, United Kingdom, 18Department of Rheumatology, Southend University Hospital, Essex, United Kingdom, 19Department of Systemic Autoimmune Hospital Clinic Provincial, Barcelona, Spain, 20Gentofte Hospital, Rheumatology Division, Hellerup, Denmark, 21Immanuel Krankenhaus Berlin: Medical Center for Rheumatology Berlin-Buch Berlin, Berlin, Germany, 22National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, 23Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford University, Oxford, UK, 24Rheumatology and Rehabilitation Research Unit, University of Leeds, Leeds, UK, 25Rheumatology Associates of North Jersey, Teaneck, NJ, 26Rheumatology Unit, Clinica e Terapia Medica Division, Sapienza Universita` di Roma, Policlinico Umberto I, Rome, Italy, 27Rheumatology Unit, Ospedale Misericordia e Dolce, Prato, Italy, 28Sahlgren University Hospital, Department of Rheumatology, Göteborg, Sweden, 29Service de Medecine Interne, Amiens, France, 30Servicio de Reumatologia, Hospital Universitario Marques de Valdecilla, Facultad de Medicina, Universidad de Cantabria, Santander, Spain

Objective: To evaluate the disease course and performance of patient-reported outcome measures in patients with polymyalgia rheumatica (PMR)

Methods: The study population included 88 patients with new onset PMR who were initially treated with prednisolone/prednisone dose of 15 mg daily

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tapered gradually, and assessed at baseline and weeks 1, 4, 12 and 26 following start of steroid therapy. Data were collected on personal and family history, clinical signs and symptoms, laboratory results, treatment details, ultrasound evaluation of shoulders and hip, disability (MHAQ), quality of life (SF36), and patient reported outcomes (PRO) of global pain, PMR pain, shoulder pain and fatigue obtained using visual analog scales (VAS). Complete response to treatment was defined as ≥70% improvement from baseline on patient report of shoulder pain by VAS at each study visit. Spearman methods were used to assess correlations between PRO measures.

**Results:** At initial presentation, 99% patients had shoulder pain, 70% had hip pain and 96% had abnormal c-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). Median duration of morning stiffness was 120 minutes with median MHAQ 1.1, median global VAS 60. Within 4 weeks, all PRO measures were highly correlated with improvement in PRO measures (correlation:0.55 and p<0.001 at weeks 4 and 26) and % change in ESR (p=0.01 at week 4 and p=0.04 at week 26), but weakly correlated with % change in CRP (p=0.07 at week 4 and p=0.30 at week 26) and change in steroid dose (p=0.39 at week 4 and p=0.04 at week 26).

**Conclusions:** PRO measures including MHAQ, global, PMR and fatigue VAS, and inflammatory markers performed well in assessing disease activity in patients with PMR. Percent improvement in PRO measures were highly correlated with each other, but ESR and CRP correlated less strongly. We suggest that a minimum set of outcome measures consisting of PROs of shoulder pain and function, and an inflammatory marker be used in practice and clinical trials in PMR.

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**Psychometric Properties of a Self-Administered Early Inflammatory Arthritis Detection Tool**

Mary J. Bell1, Joel P. Scarf2 and Ruben Tavares3.

1Mcmaster University, Hamilton, ON, Canada, 2Sunnybrook Health Science Ctr, Toronto, ON, Canada, 3Sunnybrook Health Sciences Ctr, Toronto, ON, Canada

**Background:** A self-administered tool for the detection of early inflammatory arthritis (EIA) has been developed and is under validation in primary care settings in Canada. The history-based tool consists of 11 questions with binary Yes/No responses, covering dimensions of pain, stiffness and swelling. The objective of this study is to evaluate the discriminant validity, comprehensibility, test-retest reliability and internal consistency of the EIA Detection Tool.

**Methods:** Of 148 patients (minimum of 37 in each group) planned for recruitment by September 2010, a total of 125 adult English-literate outpatients attending Sunnybrook Health Sciences Centre have participated in one of four study groups: 1.EIA (n=15): A rheumatologist’s assessment of, or established diagnosis of either AS, PsA, RA, ReA, other SpA or undifferentiated Ia with a symptom duration of six to 52 weeks; 2.Established Inflammatory Arthritis (IA) (n=40): A rheumatologist’s assessment of established Ia with more than 52 weeks of symptom duration; 3.Musculoskeletal (MSK)/non-Ia (n=49): A rheumatologist’s established diagnosis of osteoarthritis, spondyloarthritis, fibromyalgia, arthropal, gursitis, tendinitis, or other rheumatologist-determined and documented, established non-inflammatory MSK condition; and 4.Non-Ia/ non-MSK (n=21): Hospital outpatients without bone or joint complaints and no history of arthritis, willing to consult with a study rheumatologist.

**Discriminant validity** is reported using a Kruksal-Wallis test for non-parametric differences in total questionnaire Yes responses (Score) between groups including Mean (+/− SD), and Median (+ range).

**Comprehensibility** is defined as the percentage of patients who agree or strongly agree with the comprehension of the tool. The EIA Detection Tool is delivered a second time (T2), at one to 2 weeks after the first time (T1) to ascertain Test-Retest reliability. (Kappa +/- SD). Patients who report a change in symptoms will be omitted from the assessment of reliability.

To measure Internal Consistency, one question is repeated within the tool, (Kuder-Richardson-20, binary equivalent to Cronbach Alpha). Study participants will be blinded to the specific purpose of the study.

**Results:** Discriminant Validity for Group 1.EIA: Mean score 6.7+/−2.8 Median 7 (0–11); 2.Established IA: Mean score 5.2+/−2.3 Median 5 (2–10); 3.MSK/non-Ia: Mean score 5.0+/−2.9 Median 5 (0–11); 4. Non-Ia/non-MSK: Mean score 2.7+/−3.1 Median 2 (0–9) p=0.006. Over all groups Comprehensibility ranged from 94.6%–97.1%, while within Group 1.EIA, Comprehensibility ranged from 91.3%–100.0%. Kappa = 0.85+/−0.08 across all questions for Test-Retest reliability. Finally, Internal Consistency had a value of KR-20=0.990 at T1 and KR-20=0.985 at T2.

**Conclusions:** The EIA Detection Tool shows very good discriminate validity between the four study groups, and excellent Comprehensibility, Test-Retest reliability and Internal Consistency. Further analyses will be conducted in September 2010 when the dataset is complete to determine if weighting scales and/or decision rules may be imposed on the EIA Detection Tool to improve its discriminative properties.

**Disclosure:** M. J. Bell: None; J. P. Scarf: None; R. Tavares: None.

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**Reproductive History and Functional Outcome in Women with Recent-Onset Inflammatory Polyarthritis.**

Elizabeth M. Camacho1, Mark Lunt1, Tracey M. Farragher2, Mark Harrison3, Suzanne M. Verstappen4, Diane K. Burn5 and Deborah P. Symmons6.

1Arthritis Research UK Epidemiology Unit, Stopford Building, The University of Manchester, Manchester, United Kingdom, 2Norfolk Arthritis Register, School of Medicine Health Polici & Practice, University of East Anglia, Norwich UK, 3Univ of Manchester, Manchester, United Kingdom

**Background:** The incidence of rheumatoid arthritis (RA) among women is approximately twice that in men. There have been a number of studies suggesting that female reproductive factors, such as parity or menopause status, may impact upon a woman’s likelihood of developing RA and her subsequent disease activity. However, little is known about the effects of reproductive factors on long-term disease outcome in women with inflammatory polyarthritis (IP) and its subset RA. Our aim was to investigate the influence of reproductive history before symptom onset on disease outcome over time in a cohort of women with recent-onset IP.

**Methods:** 1873 women, with no subsequent pregnancies, were registered with the Norfok Arthritis Register (NOAR) between 1990 and 2004, and followed-up for a median of 5 years. Functional disability was assessed using the Stanford Health Assessment Questionnaire (HAQ). At baseline, blood samples were tested for rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA). The number and calendar year of past live births were recorded. Linear random effects models were used to examine differences in HAQ score over time, by parity and time since last live birth (latency), adjusted for age at symptom onset and symptom duration. Results were then stratified for RF and ACPA status.

**Results:** 1553 (83%) women had at least one pre-symptom-onset live birth, and 319 (17%) women were nulliparous before symptom onset. The median (IQR) latency to symptom onset in parous women was 26 (16–35) years. The median age at symptom onset was comparable in parous (54 years; IQR 44.6–65.2) and nulliparous women (54 years; IQR 36.4–70.0). A marginally higher proportion of nulliparous women who tested positive for RF (34% vs. 29%) or ACPA (33% vs. 30%) compared to parous women. Parous women had significantly lower HAQ scores over time than nulliparous women (0.19; 95% CI = −0.32, −0.06). HAQ score increased by an average of 0.006 (95% CI 0.002, 0.010) per year increase
in time since last pregnancy; the mean HAQ score of women with a latency of approximately 32 years was the same as the mean HAQ score of nulliparous women. The influence of autoantibody status was negligible. The difference in HAQ score by parity in RF- or ACPA-women was the same as for the whole cohort (RF $-0.19; 95\% CI -0.36, -0.02$; ACPA $-0.19; 95\% CI -0.36, -0.02$). Parity was also associated with lower HAQ scores in RF+ and ACPA+ women, although neither reached statistical significance (RF $-0.13; 95\% CI -0.39, 0.13$; ACPA $-0.16; 95\% CI -0.44, 0.12$).

**Conclusion:** Parous women have better functional outcome over time than nulliparous women. Increasing delay between last live birth and symptom onset (latency) was associated with increasing HAQ score over time, suggesting that the beneficial effect of pregnancy diminishes with time. Autoantibody status did not appear to have an impact on the relationship.

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**Rheumatic Diseases among Oklahoma Tribal Populations.** Jasmine R. Gaddy, Amy B. Dedede, Wendy Klein, Fabio Motra, Tina Cooper, M. Sohail Khan, Virginia Roberts, Jeremy Levin, Scott Stewart, Rebecca Stormont and Judith A. James.

**Objective:** To understand the prevalence of rheumatic diseases and clinical significance will need to be established.

**Background:** Rheumatoid arthritis (RA) has often dramatic impact on work and incur for substantial indirect costs. In this field, only few data are available about patients just starting the disease.

**Methods:** Tribal-based rheumatology clinics were established and staffed with tribal personnel and a consulting rheumatologist. Patients with presentations concerning for rheumatic disease were referred by primary care providers. 220 Oklahoma tribal members were enrolled (110 with rheumatic disease and 110 controls). A rheumatologist assessed patients for clinical features, including disease criteria, activity measures and revised treatment programs. Medical records were reviewed to extract ACR classification criteria for rheumatic disease. Samples were tested for: ANA and anti-dsDNA [IF]); anti-CCP, rheumatoid factor and aPLs (ELISA) and other lupus autoantibodies (anti-Ro, anti-La, anti-Sm, anti-RNP and anti-Jo) [precipitins]. Statistical analysis was conducted using chi-square and ANOVA methods.

**Results:** Rheumatic diseases included: 39 (35\%) Rheumatoid Arthritis [RA], 17 (15\%) Systemic Lupus Erythematosus [SLE], and 8 (7\%) Scleroderma [SCL]. Additional diagnoses were comprised of osteoarthritis, Sjogren’s Syndrome or fibromyalgia. The remaining patients have rheumatic conditions or symptoms some of which did not meet ACR criteria for disease. Included are inflammatory eye disease (3\%), sclerodactyly (1\%), undifferentiated connective tissue disease (5\%) inflammatory polyarthritis (8\%) and polyarthritis (8\%). RA patients were over nineteen times as likely as non-RA patients to be anti-CCP positive (56\% vs 2\%, p<0.001) and almost six times more likely to be RF (by IgM) positive (59% vs 10\%, p<0.001). Moreover, 13 of 39 patients with RA were both anti-CCP and RF positive. By multivariate logistic regression, together anti-CCP and RF were better predictors of RA than by either test alone (p=0.007). Scleroderma patients also exhibited anti-dsDNA, anti-Ro and anti-Jo-1 antibodies which are typically not seen in Scleroderma sera. In addition, anti-Ro, anti-La and anti-dsDNA were also detected in RA patients. Anti-phospholipid antibodies were found across several rheumatic diseases. Finally, autoantibodies against unidentified antigens (U1Ls) were seen in over 5\% of rheumatic patients.

**Conclusion:** Clinical presentations of rheumatic disease within Oklahoma tribal members are oftentimes overlapping and difficult to define by ACR criteria. Unique autoantibodies were identified in patients meeting ACR criteria for disease. Anti-CCP is a better RA predictor in tribal communities and warrants changes in current diagnostic practices. Other autoantibodies (aPLs and U1Ls) are found in a variety of American Indian rheumatic disease and clinical significance will need to be established.

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**Rheumatoid Arthritis (RA) Impact on Work and RA-Related Indirect Costs during the First Three Years after RA Diagnosis.** France, 2Paris, France, 3CHU de la Cavale Blanche, Brest Cedex, France, 4Faculty of Medicine P&M Curie, Paris, France, 5Pitie Salpetriere Hospital, Paris, France, 6Pitie Salpetriere Hospital, Paris, France, 7URC Eco, Paris, France

**Background:** Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that affects joints and other extrarticular organs. It has a prevalence of 0.5% in France and a prevalence of 10.1 cases per 100,000 in the general population. RA causes significant morbidity within American Indian populations. Oftentimes, clinical disease presentations overlap and historically associated autoantibodies are not useful in making a diagnosis or assessing prognosis. The purpose of this study is to identify autoantibody associations in Oklahoma tribal populations with rheumatic disease. With this knowledge we seek to create a tailored approach to diagnosing and treating Oklahoma Native American patients which may also translate to the Native American population at large.

**Methods:** Tribal-based rheumatology clinics were established and staffed with tribal personnel and a consulting rheumatologist. Patients with presentations concerning for rheumatic disease were referred by primary care providers. 220 Oklahoma tribal members were enrolled (110 with rheumatic disease and 110 controls). A rheumatologist assessed patients for clinical features, including disease criteria, activity measures and revised treatment programs. Medical records were reviewed to extract ACR classification criteria for rheumatic disease. Samples were tested for: ANA and anti-dsDNA [IF]; anti-CCP, rheumatoid factor and aPLs [ELISA] and other lupus autoantibodies (anti-Ro, anti-La, anti-Sm, anti-RNP and anti-Jo) [precipitins]. Statistical analysis was conducted using chi-square and ANOVA methods.

**Results:** Rheumatic diseases included: 39 (35\%) Rheumatoid Arthritis [RA], 17 (15\%) Systemic Lupus Erythematosus [SLE], and 8 (7\%) Scleroderma [SCL]. Additional diagnoses were comprised of osteoarthritis, Sjogren’s Syndrome or fibromyalgia. The remaining patients have rheumatic conditions or symptoms some of which did not meet ACR criteria for disease. Included are inflammatory eye disease (3\%), sclerodactyly (1\%), undifferentiated connective tissue disease (5\%) inflammatory polyarthritis (8\%) and polyarthritis (8\%). RA patients were over nineteen times as likely as non-RA patients to be anti-CCP positive (56\% vs 2\%, p<0.001) and almost six times more likely to be RF (by IgM) positive (59% vs 10\%, p<0.001). Moreover, 13 of 39 patients with RA were both anti-CCP and RF positive. By multivariate logistic regression, together anti-CCP and RF were better predictors of RA than by either test alone (p=0.007). Scleroderma patients also exhibited anti-dsDNA, anti-Ro and anti-Jo-1 antibodies which are typically not seen in Scleroderma sera. In addition, anti-Ro, anti-La and anti-dsDNA were also detected in RA patients. Anti-phospholipid antibodies were found across several rheumatic diseases. Finally, autoantibodies against unidentified antigens (U1Ls) were seen in over 5\% of rheumatic patients.

**Conclusion:** Clinical presentations of rheumatic disease within Oklahoma tribal members are oftentimes overlapping and difficult to define by ACR criteria. Unique autoantibodies were identified in patients meeting ACR criteria for disease. Anti-CCP is a better RA predictor in tribal communities and warrants changes in current diagnostic practices. Other autoantibodies (aPLs and U1Ls) are found in a variety of American Indian rheumatic disease and clinical significance will need to be established.

**Disclosure:** J. R. Gaddy: None; A. B. Dedede: None; W. Klein: None; F. Mota: None; T. Cooper: None; M. S. Khan: None; V. Roberts: None; J. Levin: None; S. Stewart: None; R. Stormont: None; J. A. Jones: None.

### 781

**Rheumatoid Arthritis (RA) Impact on Work and RA-Related Indirect Costs during the First Three Years after RA Diagnosis.** France, 2Paris, France, 3CHU de la Cavale Blanche, Brest Cedex, France, 4Faculty of Medicine P&M Curie, Paris, France, 5Pitie Salpetriere Hospital, Paris, France, 6Pitie Salpetriere Hospital, Paris, France, 7URC Eco, Paris, France

**Background:** Rheumatoid arthritis (RA) has often dramatic impact on work and incur for substantial indirect costs. In this field, only few data are available about patients just starting the disease.

**Methods:** The nationwide ESPOIR cohort included 811 patients with early arthritis (female 77\%; mean age 48 years; mean HAQ 1.0; DAS28 5.2; IgM RF £ 47%; anti-CCP £ 39%; structural damage on X-ray 22%; satisfaction of 1987 ACR criteria 71\%).

Among this population, people participating on the market place were identified and RA-induced absenteeism was assessed after having defined 4 work states: temporary sick leave, long-term sick leave, permanent disability / invalidity, and early retirement. For each state, the number of patients and the total number of days off work were calculated for every year of follow-up.

The valorization of RA-related absenteeism was estimated from the payer perspective. Daily wages were stratified on patient socio-economic profile and sex. Indirect cost drivers were assessed by using univariate then multivariate analysis in 2 steps: 1) logistic regression to identify predictors of indirect costs versus no indirect costs; then 2) linear regression after log-transformation of indirect costs (skewed cost distribution) to identify predictors of the highest costs.

**Results:** On the 398 patients participating in the work force at diagnosis, 91% had a paid job and 71% still worked after 3 years of disease. During the first 3 years, 241 patients had at least one temporary sick leave and 54 patients got compensated disability status. Mean number of days in sick leave decreased from 118 days the first year to 71 days the third year, whereas mean number of days in invalidity almost doubled over the three years (figure).

**Image:** Total indirect costs and its repartition during the first 3 years of disease in early RA patients (in euro)

**Figure:** Mean annual cost was €1476 (table). 169 patients had no indirect costs. Predictive factors of indirect costs were disease severity at baseline (DAS28>5.1), HAQ>1, male sex and manual job (p<0.05 in the univariate analysis). The linear model showed a significant relation between indirect costs and age at diagnosis, HAQ and DAS28>5.1.
Conclusion: Only a few patients lost their job in the first 3 years of the disease but most of them experienced at least one sick leave (60%). Indirect costs did not show any meaningful decrease during the first 3 years of treatment, mainly because the reduction in sick leave was counterbalanced by an increase in compensated invalidity.

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Screening for Latent Tuberculosis Infection (LTBI)—Performance of Tuberculin Skin Test and Interferon-gamma Release Assays (IGRA) under Real Life Conditions. Stefan Kleinert1, Hans Peter T. Tony1, Klaus Krueger2, Jacqueline Detert1, Frank Mielke3, Gerd R. Burmester4, Roland Dietl1, Martin Feuchtenberger5 and Christian Kneitz6, 7Charité—Universitätsmedizin Berlin, Dept. of Rheumatology and Clinical Immunology, CC12, 2Charité Berlin, 3Department of Pneumology, Medical School (MHH) Hannover, 4Gemeinschaftspraxis Innere Medizin, Dres. Mielke, Berlin, 5Klinik für Innere Medizin II (Klinische Immunologie und Rheumatologie, Klinikum Stadtmitte Rostock), 6Praxiszentrum St.Bonifatius München, 7Rheumatology / Clinical Immunology, Med. Klinik 2, University of Wuerzburg, Wuerzburg, Germany, 8Rheumatology / Clinical Immunology, Med. Klinik 2, University of Wuerzburg

Introduction: Treatment of LTBI has greatly reduced Tb reactivations under anti-TNF therapy. Screening has been based on patient history, chest x-ray, BCG vaccination status and tuberculous skin test (TST). The introduction of IGIRAs has improved screening procedures and some national guidelines recently favour IGRA testing over a TST. This study is a real-life, multicentric approach to compare IGRAs versus TST for detection of LTBI in a large cohort of patients with rheumatic diseases under immunosuppressive therapy.

Methods: 62 centers in Germany evaluated 1529 consecutive patients for LTBI prior to therapy with biologics. TST was performed in all patients. Additionally, an IGRA was performed, either TSPOT.TB assay (TSPOT, n=844) or Quantiferon TB Gold assay (QFT, n=685), whichever was available in the local laboratory.

Results: Patient distribution was 852 RA, 215 PsA, 294 AS, 92 undiff. SpA, 76 various. 254 patients were previously BCG vaccinated. TST was positive in 173 patients (11.3%), IGRA was positive in 120 patients (7.9%), 8.3 % (n=70) in the TSPOT group and 7.3% (n=50) in the QFT group. 50 TST positive patients where previously BCG vaccinated. The prevalence of LTBI defined by a positive TST without previous BCG vaccination was 8.0% (123 pts) and based on the IGRA 7.9% (120 pts). The patient group identified by TST (n=123) or IGRA (n=120) predominately described different patients. Of the 123 TST positive patients only 56 were IGRA positive only 66 were TST positive. Clinical risk factors for LTBI were found in 122 patients (34% of own Tb, 81 close contact, 27 chest x-ray (cxr) suggestive of LTBI). A compound risk factor (rf) was defined as at least one of these risk factors being present. Uni- and multivariate logistic regression revealed influence of rf on TST (OR 6.6; KI 4.41 – 9.96, p<0.001) and BCG status (OR 3.2; KI 2.19 – 4.60, p<0.001). QFT and TSPOT results were influenced by rf but not by BCG status (QFT: RF 2.9; KI 1.31 – 6.27, p=0.021. BCG OR 0.4, KI 0.17 – 1.13, p=0.080. TSPOT: RF 8.8; KI 4.93 – 15.78, p<0.001. BCG OR 1.69, KI 0.8 – 3.56, p=0.165).

Conclusion: The study revealed a significant prevalence of LTBI in patients evaluated for biologic therapy in a country with low incidence of Tb. Prevalence for LTBI based on TST was 8%, based on IGRA 7.9%. Using both test systems, prevalence increased to 11.1% since 49% of TST positive patients were IGRA negative and vice versa. In multivariate analysis TSPOT was strongly influenced by clinical risk factors, followed by TST and QFT. IGIRAs were not influenced by prior BCG vaccination, proving its superiority in these patients. Screening procedures based upon TST have been shown to be effective in reducing tuberculous reactivation by TNF inhibitors. The exclusive use of IGIRAs may leave patients at risk.

Disclosure: S. Kleinert: Abbott Immunology Pharmaceuticals, 2, 8, Chugai, 8, Essex, 8, Roche, 5, S. H. P. T. Tony: Abbott Immunology Pharmaceuticals, 8, Chugai, 2, Roche, 5, Wyeth Pharmaceuticals, 8; K. Krueger: None; J. Detert: None; F. Mielke: None; G. R. Burmester: Abbott Immunology Pharmaceuticals, 2, 8, 5, R. Dietl: None; M. Feuchtenberger: None; C. Kneitz: Abbott Immunology Pharmaceuticals, 5, Essex, 5, Roche, 5, UCB, Inc., 8, Wyeth Pharmaceuticals, 2.

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Seasonal Variation in Vitamin D Levels in Patients with Psoriatic Arthritis and Its Association with Clinical Outcomes. Zahi Touma1, Lili Eder1, Devy Zisman1, Joy Field1, Vinod Chandran1, Cheryl Rosen1, Hua Shen2, Richard Cook3 and Dauna D. Gladman4, 5Linus Medical Centre, Clalit Health Service, Carmel Medical Centre, Haifa, Israel, 6Division of Biostatistics, University of Waterloo, Waterloo, ON, Canada, 7Toronto Western Hospital, Toronto, ON, Canada, 8University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital, Toronto, ON, Canada, 9University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital, Toronto, ON, Canada

Background: Vitamin D has emerged as an important factor in the pathogenesis of several autoimmune diseases including psoriasis and inflammatory arthritis. Hypovitaminosis-D seems to be a problematic trend. Studies showed that it is more common in inhabitants of high latitude compared to low latitude areas.

Objective: We aimed to determine the prevalence of vitamin D deficiency-insufficiency in patients with psoriatic arthritis (PsA), its seasonal and geographic variation, association with demographic and lifestyle characteristics, and with disease activity.

Methods: This study was conducted in a center in a northern geographic area (N,North) and a center in a subtropical region (S,South), from March 2009 to August 2009. Most subjects were assessed in both winter and summer. Patients completed a vitamin D questionnaire developed to assess lifestyle determinants of vitamin D levels. Demographic, clinical data, skin type ( Fitzpatrick classification), serum 25(OH) vitamin D, creatinine, calcium, phosphorus and liver enzymes were determined. Vitamin D levels were categorized as deficient < 30, insufficient 30 – 74 and adequate >75 ng/ml. A multivariate linear mixed model that included demographic/lifestyle and clinical variables, latitude, season as covariates, was used to assess the relationship with vitamin D levels.

Results: 302 PsA patients were enrolled: 258 winter (201 in N/57 in S), 214 summer (140 N/74 S). Vitamin D levels (winter/summer) were adequate (N: 41.3%/34.1%; S: 42.1%/35.1%), insufficient (N: 55.7%/58.6%; S: 50.9%/62.2%) and deficient (N: 3.0%; S: 3.8/0.9%) among patients (Table 1).

Table 1. Patients’ characteristics and vitamin D level distribution

<table>
<thead>
<tr>
<th>Variables/Sites</th>
<th>North</th>
<th>South</th>
<th>Season</th>
<th>Vitamin D</th>
<th>North</th>
<th>South</th>
<th>North and South</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51.8</td>
<td>12.5</td>
<td>56.4</td>
<td>13.4</td>
<td>Winter</td>
<td>41.3%</td>
<td>41.5%</td>
<td></td>
</tr>
<tr>
<td>41.1%</td>
<td>41.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of Psoriasis</td>
<td>28.2</td>
<td>14.6</td>
<td>37.1</td>
<td>Summer</td>
<td>41.4%</td>
<td>39.3%</td>
<td></td>
</tr>
<tr>
<td>41.4%</td>
<td>35.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasians</td>
<td>189</td>
<td>95.0%</td>
<td>101</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Asian</td>
<td>1</td>
<td>0.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>6</td>
<td>4.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filipino</td>
<td>1</td>
<td>1.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>1.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>6.2%</td>
<td>11</td>
<td>13.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>30.1%</td>
<td>40</td>
<td>50.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>34.7%</td>
<td>15</td>
<td>18.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>20.2%</td>
<td>13</td>
<td>16.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>8.8%</td>
<td>1</td>
<td>1.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multivariate regression showed that subjects who had sun tanned and received phototherapy, in the past three months, has significantly higher vitamin D levels (p=0.012 and p=0.030 respectively). Taking multivitamins increased vitamin D levels (p=0.014) and vitamin D supplementation was independently associated with higher vitamin D levels p<0.001. Fish oil supplementation was also associated with higher levels of vitamin D (p=0.036). Males were more likely to have lower vitamin D levels p=0.02. There was no association between vitamin D levels, geographic and seasonal interaction, race, employment status and skin type, and disease activity as measured by PASI score for psoriasis and active joint count, dactyliitis and inflammatory spinal pain for PsA in both seasons. No association between disease activity in summer and vitamin D levels in winter could be found.
Conclusion: A high prevalence of vitamin D insufficiency among PsA patients was found. There is no seasonal variation in vitamin D level among PsA patients in the southern and northern sites. No association could be established between disease activity and vitamin D level. However, lifestyle and demographic determinants such as having a suntan and intake of vitamin D supplements did have an effect on vitamin D level.

Disclosure: Z. Touma: None; L. Eder: None; D. Zisman: None; J. Field: None; V. Chandran: None; C. Rosen: None; H. Shen: None; R. Cook: None; D. D. Gladman: None.

Sedentary Is an Independent Cardiovascular Risk Factor in Rheumatologic Patients.

Sedentarity Is an Independent Cardiovascular Risk Factor in Rheumatic Diseases. Marco Antivalle1, Cecilia Imperio2, Michele Battellino2, Alessandra Mutti2, Maria Chiara Ditto1, Alberto Batticciotto2, Fabiola Atzeni2 and Piercarlo Sarzi-Puttini2, 1 Rheumatology Unit, L. Sacco University Hospital Milano, Milano, Italy, 2Rheumatology Unit, L. Sacco University Hospital Milano, Italy

Background: There is ample demonstration that physical inactivity is a strong cardiovascular (CV) risk factor in the general population. While several reports suggest that patients with RA and other chronic rheumatic diseases have a reduced level of physical activity (PA) compared with the general population, few studies have evaluated physical activity and the risk of CVD in patients with rheumatic diseases (1).

Aim of the study: To study the relationship between low PA and other cardiovascular risk factors in patients affected by rheumatic diseases.

Methods: PA and CV risk factors were studied in 282 patients with rheumatic diseases (216 Females and 66 Males, mean age 53.5 years). 71.4% of patients had inflammatory diseases. The level of PA was assessed by the IPAQ questionnaire, which allows the estimate of total weekly energy expenditure in MET-minute/week, and the categorization of patients into 3 levels of activity - Low (< 600 MET/m/w), Moderate (600 MET/m/w–3000 MET/m/w), and High (3000 MET/m/w–). Metabolic syndrome (Mets) was assessed by the International Diabetes Federation definition (3).

Results: Average PA energy expenditure was 1654 MET-m/w. Overall, a low level of PA was recorded in 47.3%, Mets in 22.6 %, and smoking in 26.1% of patients. Only 21.8% of patient reported walking at least 30 minutes/5 days/week according to cardiovascular prevention recommendations (4). More than 1 risk factor was present in 24.1% of patients. The distribution of risk factors differed in the 2 sexes, females showing a higher prevalence of LPA and Mets, and males a higher prevalence of MetS. By logistic regression, MetS prevalence was significantly correlated only to sex (p = 0.014) and age (p = 0.003), but not to the level of PA (Fig. 1), to the type of rheumatic disease (inflammatory vs non-infectious), nor to disease duration.

Fig. 1. Prevalence of metabolic syndrome and smoking according to levels of physical activity.

Conclusions: Sedentarity is very prevalent in rheumatic diseases, and in only 21% of patients weekly exercise meets levels recommended for CV prevention. Low levels of physical activity in this population seem to be unrelated to other cardiovascular risk factors. Preventive strategies to reduce cardiovascular risk in this population should include programs to improve physical fitness.

References:

Disclosure: M. Antivalle: None; C. Imperio: None; M. Battellino: None; A. Mutti: None; M. C. Ditto: None; A. Batticciotto: None; F. Atzeni: None; P. Sarzi-Puttini: None.

Sex Differences in Pain Level and Location in Inflammatory Arthritis: A Systematic Review and Meta-Analysis.

Sex Differences in Pain Level and Location in Inflammatory Arthritis: A Systematic Review and Meta-Analysis. Cheryl C. M. Barnabe1, Louis Bessette2, Cathy Flanagan3, Sharon LeClercq1 and Vivian P. Bykerk4, 1 Mt Sinai Hospital, Toronto, ON, Canada, 2University of Calgary, Calgary, AB, Canada, 3University of Calgary

Background: Patient sex may influence the disease experience for patients with inflammatory arthritis (including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and spondyloarthropathy (SpA)), with implications for treatment expectations and predicted response. Our objective was to determine if there are differences in the baseline level, location of pain, and the response to treatment, between females and males with inflammatory arthritis.

Methods: A search of PubMed (1950 to April 2010) and EMBASE (1980 to April 2010) was supplemented by manual searches of conference abstracts. We identified studies reporting sex-stratified pain measures (visual analogue scale (VAS), bodily pain component of the 36-item Short Form Health Survey (SF-36BP)) or pain location, in biologic naïve populations. Effects analyzed were a) standardized mean difference (SMD) for pain measures (cross-sectional analyses), b) percentage improvement in pain measure (longitudinal analyses), and c) proportion reporting pain at a particular location. The systematic review for pain measures includes 26 cohorts and 1 randomized controlled trial, and for pain location includes 12 publications. The meta-analysis for pain measures includes 16 cohorts reporting pain by VAS and 3 cohorts reporting pain by SF-36BP.

Results: Meta-analysis revealed a significant difference in the SMD in pain levels measured by VAS in RA (SMD 0.21 (95%CI 0.16–0.26), p < 0.001) (Figure). This held when stratified by disease duration at enrollment (RA < 1 year, SMD 0.30 (95%CI 0.15–0.45), established RA SMD 0.20 (95% CI 0.14–0.25)). The SMD for SF-36BP was not significant (SMD –0.14 (95%CI –0.49, 0.20), p = 0.411). In longitudinal studies, females improved to a greater degree than males, but still had higher mean pain values at any time point. Males had more inflammatory back pain and females had more peripheral arthritis (Table 1).

Table 1. Studies Reporting Sex-Stratified VAS Pain scores.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Disease</th>
<th>Spinal Pain Females</th>
<th>Spinal Pain Males</th>
<th>Peripheral Pain Females</th>
<th>Peripheral Pain Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marks, 1983</td>
<td>AS</td>
<td>NR</td>
<td>NR</td>
<td>40%</td>
<td>16%</td>
</tr>
<tr>
<td>Brauerstein, 1982</td>
<td>AS</td>
<td>34%</td>
<td>71%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Coughlan, 1993</td>
<td>AS</td>
<td>37%</td>
<td>69%</td>
<td>42%</td>
<td>17%</td>
</tr>
<tr>
<td>Gran, 1985</td>
<td>AS</td>
<td>59%</td>
<td>67%</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>Jimenez-Balderas, 1993</td>
<td>AS</td>
<td>37%</td>
<td>51%</td>
<td>78%</td>
<td>73%</td>
</tr>
<tr>
<td>Katz, 1988</td>
<td>AS</td>
<td>77%</td>
<td>87%</td>
<td>97%</td>
<td>67%</td>
</tr>
<tr>
<td>Maldonado-Cocco, 1985</td>
<td>AS</td>
<td>NR</td>
<td>NR</td>
<td>28%</td>
<td>27%</td>
</tr>
<tr>
<td>Mathew, 1989</td>
<td>AS</td>
<td>80%</td>
<td>47%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Resnick, 1976</td>
<td>AS</td>
<td>NR</td>
<td>NR</td>
<td>83%</td>
<td>41%</td>
</tr>
<tr>
<td>Queiro, 2001</td>
<td>Ps SpA</td>
<td>43%</td>
<td>49%</td>
<td>24%</td>
<td>11%</td>
</tr>
<tr>
<td>Gladman, 1992</td>
<td>Ps SpA</td>
<td>100%</td>
<td>100%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Boyer, 2000</td>
<td>Ps SpA</td>
<td>54%</td>
<td>50%</td>
<td>72%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Figure 1. Meta-analysis of studies reporting sex-stratified VAS pain scores.
Conclusions: Females with RA experience higher pain levels than males, but do have a greater degree of improvement with treatment. Although this analysis does not explore confounding factors that may explain sex differences in inflammatory arthritis, it does alert the clinician that pain management is a significant issue in particular for female patients. In AS, females will develop peripheral arthritis more frequently, with fewer manifestations of inflammatory back pain. This may have diagnostic implications in the clinical setting.

Disclosure: C. C. M. Barnabe: None; L. Bessette: None; C. Flanagan: None; S. LeClercq: None; V. P. Byker: None.

Sleep Disturbances in Adults with Arthritis: Prevalence, Mediators, and Subgroups at Greatest Risk
Alberto J. Caban-Martinez4 and Michael M. Ward 3. 1National University Health System, Singapore, Athens, Greece, 2NIH, Bethesda, MD, 3NIH, NIAIMS, IRP, Bethesda, MD, 4University of Miami Miller School of Medicine, Miami, FL

Background: Sleep disturbance is a common medical condition that may adversely affect daily functioning, vocational performance, and health-related quality of life. Few studies have examined the prevalence of sleep disturbances in adults with arthritis in a nationally-representative sample, mediators of sleep disturbances, and subgroups of individuals with arthritis at greatest risk.

Methods: Using data on U.S. adults aged ≥18 years participating in the 2007 National Health Interview Survey, we estimated the prevalence of three measures of sleep disturbance (insomnia, excessive daytime sleepiness, and sleep duration <6 hours) among persons with physician-diagnosed arthritis. We used hierarchical logistic regression analysis to examine if the association of arthritis and sleep disturbances was independent of sociodemographic characteristics and comorbidities, and to identify potential mediators. We used classification trees to identify subgroups at highest risk.

Results: In the sample of 23,134 adults, 19.9% (representing 44.3 million civilian, noninstitutionalized U.S. adults) reported having arthritis. Adults with arthritis had a mean (± standard error of the mean) age of 59.6 ± 0.3 years, and were more likely women (58.0%), non-Hispanic white (79.1%), and overweight or obese (71.8%). Age-, sex-, race-, and disease-adjusted prevalence of insomnia was 23.1%, excessive daytime sleepiness 11.0%, and sleep duration <6 hours 7.3%. Adjusted prevalences were similar to those with other chronic diseases, such as diabetes and cardiac disease. Adults with arthritis were 2.9-fold more likely than those without arthritis to report insomnia, but adjustment for sociodemographic characteristics and comorbidities attenuated this association (Table). The association between arthritis and insomnia was further attenuated after adjusting for joint pain and limitation due to joint pain, suggesting pain mediated the relationship between arthritis and insomnia. Similarly, adults with arthritis were significantly more likely to report excessive daytime sleepiness and sleep duration <6 hours in univariate and multivariate analyses. Adjusting for joint pain and limitation due to pain attenuated these associations. Among adults with arthritis, those with depression and anxiety were at highest risk for sleep disturbance.

Table. Association between sleep disturbances and presence of arthritis (compared to absence of arthritis) among adult participants in the 2007 National Health Interview Survey. Odds ratios (OR) with 95% confidence intervals (CI).

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted for sociodemographic characteristics</th>
<th>Further adjusted for joint pain and limitation due to joint pain and depression</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis (vs. No Arthritis)</td>
<td>2.92</td>
<td>2.68–3.17</td>
<td></td>
<td>1.53–1.71</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>2.48</td>
<td>2.23–2.76</td>
<td></td>
<td>1.37–1.66</td>
</tr>
<tr>
<td>Sleep duration &lt;6 hrs</td>
<td>1.79</td>
<td>1.58–2.03</td>
<td></td>
<td>1.18–1.62</td>
</tr>
</tbody>
</table>

Conclusions: Up to 23% of the U.S. adult population with arthritis, representing 10.2 million persons, report having a sleep disturbance. The association appears to be mediated by joint pain and limitation due to pain. Among individuals with arthritis, those with depression and anxiety are at greatest risk.

Disclosure: G. H. Louie: None; M. G. Tektonidou: None; A. J. Cahan-Martinez: None; M. M. Ward: None.

The Comparative Responsiveness of the EQ-5D and SF-6D to Change in Patients with Early Arthritis: Results from the ESPOIR Cohort
Cécile Gaujoux-Viala1, Anne-Christine Rat1, Francis Guillemin2, René-Marc Filip3, Patrice Fardelonne4, Pierre Bourgeois5 and Bruno Fautrel6.

Background: The revolution of early aggressive therapy have fueled the search for better approaches to establish the cost-utility ratio in early arthritis (EA). The EQ-5D and the SF-6D are indirect preference-based health related quality of life instruments increasingly used for economic evaluation of clinical interventions and health programs. Comparative evidence regarding the responsiveness of the EQ-5D and SF-6D in arthritis patients is conflicting and insufficient.

Objective: To compare the responsiveness of the EQ-5D and SF-6D in a large multicenter prospective cohort of patients with EA to guide the choice of instruments and their interpretation.

Methods: The ESPOIR cohort is a nationwide cohort that included 813 patients with EA with a high suspicion of rheumatoid arthritis, between 2002 and 2005. Data, including EQ-5D and SF-6D, were collected every 6 months during the first 2 years then every year. Responsiveness was tested using the standardised response mean (SRM) at 6 and 12 months for the entire sample and for subgroups categorized by their evolution (DAS28 improvement or deterioration >0).

Results: The EQ-5D provided larger absolute mean change estimates with greater variance than the SF-6D whatever the direction of change. The SF-6D and the EQ-5D SRM were higher for improvement than for deterioration of the DAS28 response at 12 months: SRM = 0.83 and 0.55 for the 2 instruments respectively. The SF-6D and the EQ-5D did not respond well to deterioration in patients with early arthritis: SRM = 0.08 and 0.2 in patients with deterioration of the DAS28 at 12 months, respectively (Table).

Table. Summary of responsiveness for joint pain and limitation due to joint pain

<table>
<thead>
<tr>
<th>DAS28 improvement at 12 months</th>
<th>Mean change at 12 months</th>
<th>STD of change at 12 months</th>
<th>SRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28</td>
<td>2.20</td>
<td>1.30</td>
<td>1.67</td>
</tr>
<tr>
<td>HAQ</td>
<td>-0.508</td>
<td>0.652</td>
<td>0.78</td>
</tr>
<tr>
<td>SF6D</td>
<td>0.105</td>
<td>0.127</td>
<td>0.83</td>
</tr>
<tr>
<td>EQ5D</td>
<td>0.173</td>
<td>0.313</td>
<td>0.55</td>
</tr>
</tbody>
</table>

The SF-6D was more responsive to improvement and the EQ-5D more responsive to deterioration. The results were similar at 6 months.

Conclusions: The comparative responsiveness of the EQ-5D and SF-6D differs according to the direction of change. The SF-6D was more responsive than the EQ-5D in case of improvement. However both utility measures were less responsive to deterioration than improvement. The level of mean change of the EQ-5D relative to the SF-6D has implications for cost-effectiveness analysis. Use of the SF-6D in patients with early arthritis may be more appropriate.

Disclosure: C. Gaujoux-Viala: None; A.-C. Rat: None; F. Guillemin: None; R.-M. Filip: None; P. Fardelonne: None; P. Bourgeois: None; B. Fautrel: None.

The Economic Burden of Uveitis
S. E. Kirbach, O. A. Hayes and M. A. Cifaldi. Abbott Laboratories

Background and Purpose: Uveitis is a common extra-articular manifestation of rheumatic conditions (including ankylosing spondylitis and juvenile idiopathic arthritis). It often recurs and is associated with potentially serious sequelae that greatly increase the risk of vision loss. Uveitis is responsible for ≥10% of blindness in the United States and it is associated with a total direct
cost of approximately $2.74 billion.\textsuperscript{2,3} Despite this financial burden, there is a dearth of literature examining the economic burden specific to uveitis, especially with regard to the impact of uncontrolled disease and the presence of blindness and vision loss. We determined the average annual medical costs for individuals newly diagnosed with noninfectious uveitis based on location of inflammation, presence of blindness, and number of subsequent uveitis-related medical visits.

**Methods:** Patients (N=26,079) with noninfectious uveitis (based on ICD-9 codes) and \( \geq 2 \) years of continuous enrollment (\( \geq 1 \) year before and after diagnosis of first episode) were identified in the MedStat MarketScan database (2000–2008) and categorized by uveitis type (anterior vs. intermediate/posterior/panuveitis [IPP]), incident and prevalent blindness, and number of uveitis-related medical visits (1, 2, 3, or \( >3 \) visits). Average annual medical costs were calculated for the year following the initial diagnosis of uveitis. Patients with health maintenance organization, point of service with capitation, or missing insurance plans were excluded from cost summations.

**Results:** The average annual cost for all individuals with noninfectious uveitis was $8,450 vs. $4,688 for nonuveitis controls. For all patients with uveitis, those with IPP uveitis incurred greater costs than those with anterior uveitis ($12,149 vs. $7,834, respectively), Patients who became blind during the observation period had greater costs than those who maintained their sight ($21,384 vs. $8,236, respectively) and those who were blind at the start of the follow-up period ($14,404). The largest driver of medical costs for patients with noninfectious uveitis was opthalmic hospitalizations (29% of all costs) followed by drug costs (22% of all costs). In terms of uveitis-related medical visits, medical costs uniformly increased with number of visits (table).

**Conclusions:** Uveitis results in a large degree of economic burden, especially for individuals with more severe disease or blindness and for those with repeated uveitis-related medical visits.

**References:**

**Disclosure:** S. E. Kirbach: Abbott Laboratories, 1, 3; O. A. Hayes: Abbott Laboratories, 1, 3; M. A. Cifaldi: Abbott Laboratories, 1, 3.

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**The Effect of Health Insurance and Physician Specialty on Quality of Care for SLE.** Edward H. Yelin\textsuperscript{3}, Jinoos Yazdany\textsuperscript{1}, Laura Trupin\textsuperscript{3}, Chris Tonner\textsuperscript{3}, Gabriela Schmajuk\textsuperscript{2}, Patricia P. Katz\textsuperscript{3}, Lindsey A. Criswell\textsuperscript{2}, Laura J. Julian\textsuperscript{3}, Joann Z. Gillis\textsuperscript{2} and Pantelis Panopalis\textsuperscript{1}. McGill University, Montreal, QC, Canada; 2National Jewish Medical Center, Denver, CO; 3Stanford University, Palo Alto, CA; 4UCSF-Box 0950, San Francisco, CA; 5Univ of CA San Francisco, San Francisco, CA; 6University of California, San Francisco, San Francisco, CA

**Background:** Quality indicators (QIs) describe the extent to which health care meets minimal standards for quality of care. The authors have recently developed 20 QIs for SLE covering diagnosis, general preventive strategies, osteoporosis prevention and treatment, drug toxicity monitoring, renal disease, and reproductive health.\textsuperscript{1} Of the 20 QIs, we deemed 14 amenable to self-report. The present study evaluates the extent to which health care in a community-based sample of persons with SLE (PWSLE), the Lupus Outcomes Study (LOS), adheres to these 14 QIs as a function of the kind of health insurance and specialty of physicians seen for SLE.

**Methods:** In 2009, 814 PWSLE were in the LOS. Principal data collection is an annual structured telephone interview regarding kind of health insurance, specialty of physicians seen, and health services received, including specific medications. Participants vary in their eligibility for the 14 QIs: all are eligible for the QIs related to counseling about sun avoidance and assessment of cardiovascular risk factors while only 1% are eligible for the QI related to treatment of new-onset proliferative lupus nephritis. We report here the overall pass rate, the % of all QIs for which PWSLE are eligible for which they report requisite health care services, as a function of the kind of health care coverage (HMO vs. non-HMO settings in public and private sectors) and combinations of care for SLE by generalists and rheumatologists. We use logistic regression to estimate the impact of type of health insurance and specialists, with and without adjustment for demographics (age, gender, race/ethnicity, education, and poverty status), disease duration and activity as measured by SLAQ, and number of physician visits on the pass rate. In these estimations, each QI for which PWSLE are eligible represents an observation; we account for the correlation among multiple observations of individuals via generalized estimating equations.

**Results:** The 814 PWSLE in the LOS were eligible for an average of 5.1 QIs (range 2–12) per person. The overall pass rate was .66 (95% CI .64–.67). The pass rate improved with increasing number of physician visits in the year prior to interview. It was also significantly higher among PWSLE in public sector HMOs than in private sector HMOs or in public and private sector non-HMO settings (Table 1). Those receiving care from generalists and rheumatologists singly or in combination had higher pass rates than those treated by neither. Adjustment had little effect on the results for kind of insurance or specialty of physician.

**Conclusions:** Pass rates for QIs vary significantly by kind of health insurance coverage and specialties seen by PWSLE and rise with increases in the number of physician visits, suggesting that aspects of health care amenable to policy changes may improve quality of care for PWSLE.

<table>
<thead>
<tr>
<th>Types of Physicians Seen in Past Year</th>
<th>Public</th>
<th>HMO</th>
<th>Kind of Insurance</th>
<th>Non-HMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&amp; rheumatologist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatologist only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalist only</td>
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<td></td>
</tr>
<tr>
<td>Generalist &amp; rheumatologist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, race/ethnicity, education, poverty status, disease activity and duration, #MD visits.


**Disclosure:** E. H. Yelin: None; J. Yazdany: None; L. Trupin: None; C. Tonner: None; G. Schmajuk: None; P. P. Katz: None; L. A. Criswell: None; L. J. Julian: None; J. Z. Gillis: None; P. Panopalis: None.

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**The Georgia Lupus Registry: Health Care Utilization Rises during the Transition from Pediatric to Adult Systemic Lupus Erythematosus (SLE) Care.** S. Sam Lim\textsuperscript{3}, Gaobin Bao\textsuperscript{1}, Larry B. Vogler\textsuperscript{2} and Cristina M. Drenkard\textsuperscript{3}. Emory University, 1Emory University, 2Emory University, Atlanta, GA, 3Emory University, Atlanta, GA, Emory University School of Medicine, Atlanta, GA

**Background:** Some studies have reported childhood onset SLE as being more severe than in adults. Therefore, children with SLE may be at higher risk for entering adulthood with disease related morbidity, damage, and disability. Furthermore, medical and psychosocial barriers can complicate the transition from pediatric to adult care. The aim of this study is to describe how health care utilization may change during this transition period.

**Methods:** The Georgia Lupus Registry is a population-based registry designed to estimate the incidence and prevalence of SLE in Atlanta, Georgia, from 2002 through 2004. Case-finding utilizes multiple sources. As a public health project, trained abstractors are able to document nearly 250 demographic and clinical elements from medical records of potential SLE patients without having to obtain consent. All facilities with potential pediatric SLE patients have been abstracted. All patients met the following case definition:
having either ≥4 ACR criteria or 3 ACR criteria with a diagnosis of SLE by a pediatric rheumatologist at age ≤18 years. The validated SLE patients were matched to the 1999–2004 Georgia Hospital Discharge Database, which captures all emergency room visits (ERV) and hospital admissions (HA) throughout the state and assigns a standardized direct cost to that care.

**Results:** 37 with childhood-onset SLE turned 19 years old between 1/1/1999 and 12/31/2004. 23 of these recorded at least one ERV or HA during this period (217 total visits) and had an average of 6.3 ACR criteria. The remaining 14 patients did not record an ERV or HA and averaged 5.1 ACR criteria.

<table>
<thead>
<tr>
<th>Before turning 19 years old (person-years = 104)</th>
<th>After turning 19 years old (person-years = 108)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERV</strong></td>
<td><strong>HA</strong></td>
<td><strong>ERV</strong></td>
</tr>
<tr>
<td>Visits, total</td>
<td>38</td>
<td>117</td>
</tr>
<tr>
<td>Visits, Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 4)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Female (n = 19)</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Visits, Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black (n = 20)</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>White (n = 3)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Cost per Visit, S Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (mean)</td>
<td>11158</td>
<td>13570</td>
</tr>
<tr>
<td>Female (mean)</td>
<td>2528</td>
<td>13570</td>
</tr>
<tr>
<td>Black (mean)</td>
<td>12110</td>
<td>13570</td>
</tr>
<tr>
<td>White (mean)</td>
<td>11709</td>
<td>13269</td>
</tr>
<tr>
<td>Duration, days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* Based on Wilcoxon Rank-Sum Test

**Conclusions:** The health care utilization burden of childhood-onset SLE is significant. With nearly equal amount of person-time follow-up before and after turning 19 years old, there is a striking increase in the number of ERV (tripling from 38 to 117) and HA (doubling from 21 to 41). This may signal the need to better coordinate the transfer of care for these patients. Access to care may be a factor as children without resources lose Medicaid coverage when turning 19. Further research is needed to elucidate the modifiable factors driving this change.

**Disclosure:** S. S. Lim: None; G. Bao: None; L. B. Vogler: None; C. M. Drenkard: None.

**791**

The Impact of RA Diagnoses on Cost Related Medication Nonadherence in Older Patients: 2004–2007

Leslie R. Harrold1, Becky A. Briescacher1, Daniel Peterson2, Jeanne Madden3, Jerry H. Gurwitz4 and Stephen B. Soumerai1

**Introduction:** The treatment of rheumatoid arthritis (RA) can involve costly medications. We sought to examine whether cost-related medication nonadherence (CRN) was higher among patients with RA as compared to those without the condition from 2004 through 2007.

**Methods:** We identified a nationally-representative sample of elderly and disabled patients with rheumatoid arthritis (RA), based on two claims diagnoses (ICD-9 714.XX), and those without RA using the Medicare Current Beneficiary Survey. There were 219 to 241 RA patients and 14279 non-RA patients these were 4.5% and 29.8%, respectively.

**Results:** The unadjusted annual prevalence of CRN in 2004, 2005, 2006, and 2007 among beneficiaries with RA was 20.7%, 17.5%, 16.7%, and 15.6%, respectively, compared with 15.1%, 14.0%, 11.4%, and 10.6% among beneficiaries without RA (statistically significant differences between RA vs non-RA in 2004 and 2006). In RA patients, the absolute decrease in CRN 2004 to 2007 was 5.1% and relative decrease was 24.6%, while among non-RA patients these were 4.5% and 29.8%, respectively.

The trend in CRN over time was not significant for those with RA (p=0.23) but was for those without the condition (p < 0.0001). The diagnosis of RA increased the likelihood of CRN (OR 1.27; 95% CI 1.01–1.60) in adjusted analyses.

**Conclusions:** CRN is a persistent problem for older adults, especially those with RA. While there have been decreases in CRN over time related to the Medicare Replacement Drug Demonstration program and Medicare Part D, substantial numbers of RA patients continue to report problems affording their medications.

**Disclosure:** L. R. Harrold: Corrona, 9; B. A. Briescacher: None; D. Peterson: None; J. Madden: None; J. H. Gurwitz: None; S. B. Soumerai: None.

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The Influence of Immunosuppressive Therapy and Underlying Diseases on Vaccine Responses to Influenza A H1N1/09 Vaccines in Inflammatory Rheumatic Diseases

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**Univ Hosp of Geneva, Geneva, Switzerland**

**Background:** Influenza A H1N1 is a new virus that emerged in spring 2009 and rapidly spread around the world causing a pandemic. As patients with inflammatory rheumatic diseases (IRD) exhibit some form of immunodeficiency related to their diseases and the use of immunosuppressive drugs, the Swiss Society of Rheumatology recommended the vaccination of all IRD patients under immunosuppressive agents. However, two important questions remain unresolved: 1) are immunocompromised hosts able to raise successful vaccine responses, 2) is the use of adjuvanted vaccines safe in patients with autoimmune diseases.

**Objectives:** To determine the efficacy and safety of influenza A H1N1/09 vaccine formulated in a lipid adjuvant (squaleate) in patients with IRD.

**Patients and Methods:** 173 patients with IRD and 138 healthy controls were included from November 2009 to January 2010 in this prospective, open-labeled, single center, parallelcohorts study. Among IRD patients, there were 82 cases of rheumatoid arthritis (RA), 45 cases of spondyloarthropathies (SpA), and 46 cases of connective tissue diseases (18 systemic lupus erythematous (SLE)) or vasculitis. All received a first vaccine dose and 154 (89%), the second prescheduled vaccine dose. Safety after vaccination was assessed, respectively, in 173 and 149 patients using medical history and clinical indices of disease activity (DAS28, RADAI, and HAQ for RA, BASDAI for axial SpA, SLEDAI for SLE, and BVAS for vasculitis). The kinetic of the vaccine response and antibody titers (using a standardized
in-house hemagglutination inhibition assay) were assessed after the first and the second dose and compared to titers obtained in a control group of healthy individuals vaccinated once. Cellular immune responses to influenza H1N1/09 vaccine will be also determined in a subset of patients and controls.

**Results:** Disease modifying antirheumatic drugs were used in 85% of RA, 63% of SpA, 94% of SLE patients; oral corticosteroids in 31% of RA, 11% of SpA, and 70 of SLE patients; anti-TNF in 43% of RA and 71% of SpA; and rituximab in 21% of RA and 11% of SLE patients. The different indices of disease activity were not significantly different at baseline and after vaccination. Despite immunosuppression, injection-site tolerability and systemic inflammatory reactions were similar in patients with IRD than in healthy controls. Seroprotection rates (defined by IHA titer >= 1/40) after dose 1 were 129/146 (88.4%) in controls and 103/138 (74.6%) in patients (P<0.001). This rate increased to 128/148 (86.5%) after 2 doses. The analysis of the pattern of vaccine immune responses in the different IRD patient groups is in progress and will be presented.

**Conclusions:** The advantaged vaccine against influenza A H1N1/09 is well tolerated and does not induce short-term exacerbation in patients with IRD treated with immunosuppressive agents.

**Disclosure:** C. Gabay: None; S. Meier: None; D. Gascon: None; K. Posfay-Barbe: None; C. Combesure: None; M. Bet: None; L. Kaiser: None; P.-A. Guernet: None; C.-A. Siegrist: None.

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**The Risk of Myocardial Infarction among Patients with Psoriatic Arthritis.**

*Thorvardur J. Love*, 1, Daniel Hal Solomon2 and Elizabeth W. Karlson3. 1Brigham and Women’s Hospital, Boston, MA, 2Brigham and Womens Hospital, Boston, MA, 2Mt Sinai Hospital, Toronto, ON, Canada, 3Nancy University, Sunnybrook Health Sciences Ctr, Sunnybrook Health Sciences Ctr, Toronto, ON, Canada, 4Univ of Ottawa Faculty of Med, Ottawa, ON, Canada

**Background:** Severe psoriasis is associated with an increased risk of myocardial infarction (MI). A recent study found a standardized prevalence ratio of 2.51 for MI among psoriatic arthritis (PsA) patients compared to individuals from a telephone survey of the general population. We examined data from a hospital-based PsA repository, a population based survey, and medical records of patients without PsA to evaluate the risk of MI.

**Methods:** We performed two matched cohort analyses, using a single group of validated cases of PsA from a psoriatic arthritis patient repository seen at a tertiary care teaching hospital between 1995 and 2008, with each PsA case matched 2:1 on birth year, gender, and race to two separate comparison groups: non-PsA patients drawn from the same hospital population, and participants in the NHANES 2005–2008 population survey. The first documented diagnosis of PsA marked the beginning of follow up. The start of follow up for the hospital non-PsA group was the visit date closest in time to the diagnosis of the matched PsA case. Incident MI was determined by the presence of an ICD9 code in medical records, or self report in the NHANES cohort. Each individual was followed from either the onset of PsA or the matched index date, until they had an MI or follow-up ended. We excluded anyone with less than 12 months of follow up, and those with pre-existing cardiovascular conditions.

**Results:** We successfully matched 1404 BWH non-PsA patients to 702 PsA cases found in our repository. From NHANES we found two matched controls for each of 734 PsA cases. Cumulative follow up time in the three arms of the study was 21,509 person years. There were 33 incident cases of MI in the PsA-group, 67 in the BWH non-PsA group, and 18 in the NHANES group. The incidence rate (IR) for MI per 10,000 patient years was 72 [50–101], 80 [62–102], and 21 [12–33] per 10,000 patient years at risk in the three groups, respectively. The crude incidence rate ratio for MI in PsA was 0.93 [0.60–1.44] and 3.46 [1.89–6.52] compared to the hospital and NHANES groups. Table 1 shows the results of the multivariate Cox proportional hazards analysis adjusted for age, calendar year, diabetes, hypertension, and hyperlipidemia for the risk of MI.

**Table 1.** Cox proportional hazard analysis of the risk of MI associated with psoriatic arthritis, adjusted for age, calendar year, diabetes, hypertension, and hyperlipidemia.

<table>
<thead>
<tr>
<th></th>
<th>Hospital comparison HR [95% CI]</th>
<th>NHANES comparison HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriatic arthritis</td>
<td>0.99 [0.94–1.04]</td>
<td>1.18 [1.08–1.28]</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 [1.02–1.05]</td>
<td>1.05 [1.03–1.08]</td>
</tr>
<tr>
<td>Calendar year</td>
<td>1.02 [0.95–1.10]</td>
<td>1.06 [0.94–1.19]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.94 [1.28–2.94]</td>
<td>2.34 [1.29–4.24]</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2.82 [1.66–4.80]</td>
<td>2.14 [1.13–4.06]</td>
</tr>
</tbody>
</table>

**Conclusion:** We did not find any difference in the risk of MI in the PsA group when comparing to a non-PsA group drawn from the same hospital based source population. We replicated a previously demonstrated association between PsA and MI when comparing cases of PsA to individuals from the general population. Furthermore, we quantified the risk by estimating the IR, the IRR, and the adjusted HR. This suggests that the choice of control population affects the results of analyses of MI risk in PsA. Studies of PsA cases drawn from the general population are needed to support the hypothesis that PsA increases the risk of MI in the general population.

**Disclosure:** T. J. Love: None; D. H. Solomon: Abbott Immunology Pharmaceuticals, 2, Amgen Inc., 2, Bristol-Myers Squibb, 9; E. W. Karlson: None.

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**Validation of a Self-Administered Inflammatory Arthritis Detection Tool for Rheumatology Triage.**

*Mary J. Bell,*6, George A. Wells*7, Vivian P. Bykerk*6, Peter Tugwell*2, Ruben Tavares*2, Francis Guiliem*1 and Joel Scarf*2, 1Institute of Population Hlth, Ottawa, ON, Canada, 2MaMaster University, 3Mt Sinai Hospital, Toronto, ON, Canada, 4Nancy University, Sunnybrook Neuro Inflammation Lab, Sunnybrook Health Sciences Ctr, Toronto, ON, Canada, 5Univ of Ottawa Faculty of Med, Ottawa, ON, Canada

**Background:** A self-administered tool for the early detection of inflammatory arthritis (IA) has been developed. A systematic review was used to identify stage-one case ascertainment dimensions and constructs amenable to self-assessment. Using a three-round Delphi consensus panel involving 169 arthritis stakeholders, the identified constructs were formulated into lay language items and refined into twelve questions with binary, ‘yes’/’no’ response options. Studies to validate the tool in various community and clinical settings are ongoing. The objective of the current study was to establish a scoring algorithm for, and validate, the tool for IA triage in the rheumatology wait-list population.

**Methods:** The tool was self-administered by 143 patients on the waiting lists of two Canadian, academic rheumatologists. At rheumatology presentation, the blinded rheumatologists assigned a clinical diagnosis and categorized each patient as IA or not. Multivariable logistic regression was conducted using IA as an outcome and age, sex, and the twelve tool items as independent variables. Multivariable-adjusted estimates of independent variable effect sizes were used as weights for the tool. Bootstrap bagging (BAGGING) of 200 multivariable models was used to refine estimates of independent variable weights and the tool’s performance properties. Receiver operating characteristic (ROC) curves for the models were derived. The predictive performance for the tool was determined from the area under the ROC curve (AUC), and sensitivity and specificity using the optimal model probability cutoff score. The optimal model probability cutoff score was determined from the maximum sum of sensitivity and specificity along the ROC curve. All analyses were performed using SAS/STAT® v. 9.2.

**Results:** The sample was comprised of a variety of rheumatologic conditions including 30 IA (ankylosing spondylitis, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, and undifferentiated inflammatory arthritis) and 113 non-IA cases (osteoarthritis, pain syndromes, systemic lupus erythematosus, and other miscellaneous rheumatologic disorders). Using an equally-weighted, unidirectional scoring scheme, where all ‘yes’ responses contributed positively towards the detection of IA, a cut-off score of 7 of 12 (0.58) produced an ROC AUC of 0.77, with a sensitivity of 0.87 and specificity of 0.52. Using multivariable logistic regression, a model probability cut-off score of 0.33 produced an ROC AUC of 0.91, with a sensitivity of 0.80 and specificity of 0.89. The model goodness-of-fit was supported by a non-significant Hosmer-Lemeshow test (p=0.64). The BAGGING-refined model with a probability cutoff of 0.28 (0.20–0.41) produced an ROC AUC of 0.95 ± 0.02 with a sensitivity of 0.90 (0.85–0.95) and specificity of 0.90 (0.85–0.96).

**Conclusions:** A scoring algorithm for a self-administered, twelve-item tool was developed and validated for IA detection in the rheumatology wait-list population. Together with its self-assessment mode of administration, the high sensitivity and specificity of the tool renders a potential advance in rheumatology triage of IA.

**Disclosure:** M. J. Bell: None; G. A. Wells: None; V. P. Bykerk: None; P. Tugwell: None; R. Tavares: None; F. Guiliem: None; J. Scarf: None.
Validation of the SF-6D Utility Measure in Patients with Systemic Lupus Erythematous (SLE). Mark J. Harrison\(^1\), Nicola Dale\(^1\), Sahena Haque\(^1\), Joanna Shemerdine\(^2\), Lee-Suan Teh\(^3\), Yasmeen Ahmad\(^1\) and Ian N. Bruce\(^4\).

\(^1\)Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, \(^2\)Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, \(^3\)Betsi Cadwaladr University Health Board-West, Rheumatology, Llandudno, United Kingdom, \(^4\)Department of Rheumatology, Royal Blackburn Hospital, Blackburn, United Kingdom, \(^5\)Health Sciences Research Group, The University of Manchester, Manchester, UK, \(^6\)The Kellgren Centre for Rheumatology, Central Manchester Foundation Trust, Manchester, UK.

**Purpose:** Collection of health-related quality of life (HRQoL) questionnaire with sets of utility values, such as the SF-6D, allow quality-adjusted life years used in cost-utility evaluations to be calculated. However these measures should be evaluated for validity in each setting they are applied. Few studies in systemic lupus erythematosus (SLE) have included a generic HRQoL measure; therefore the validity of these measures for this setting is unclear. This study aims to explore the construct validity and the minimum important difference (MID) of the SF-6D in SLE patients.

**Methods:** Female patients with SLE (≥4 ACR criteria) were recruited from routine outpatient clinics at 2 time points 5 years apart. At baseline and 5 years patients had a clinical assessment including the SLEDAI 2000 and SLICC damage index. Patients also completed the generic RAND Medical Outcome Study 36-Item Short-Form Survey version 1 (MOS SF-36), which allows the SF-6D to be calculated, at baseline and 5-years and the (disease-specific) LupusQoL was completed at the 5-year time point.

Construct validity was tested by (1) correlation (Pearson) of SF-6D with SLICC (damage), SLEDAI (activity), patient characteristics (age, disease duration, education, smoking, depression, fatigue), and LupusQoL® (at 5-years). The ability to discriminate between groups was tested using the t-test. The minimum important difference (MID) was estimated in two ways: (1) multiplying the SF-6D standard deviation by a small effect size (0.2), and (2) regressing the SF-6D onto SLICC to estimate the change associated with change equivalent to the MID of SLICC.

**Results:** 181 patients (mean age 48 years, mean disease duration 11 years) had SF-6D scores at baseline; the mean SF-6D score was 0.60 (0.12). The SF-6D correlated more strongly with age (−0.19) and SLICC (−0.24) than disease duration (−0.04), education (0.08) or SLEDAI (−0.06). In 113 patients with an SF-6D calculated score at 5-years, the correlation of the SF-6D with LupusQoL® domains was 0.6–0.8 for all domains apart from intimacy (0.44) and body image (0.36). The SF-6D could distinguish between those who smoked (−0.07, p = 0.003), had carotid plaque (−0.05, p = 0.027), had depression (−0.09, p < 0.001), and reported fatigue (−0.06, p = 0.006), from those who did not. The MID was estimated to be 0.024 to 0.028.

**Conclusions:** The SF-6D is valid for the measurement of HRQoL in patients with SLE; the measure reflects a number of key outcomes of the disease. Low correlation with aspects of intimate relationships and body image represents a concern and reinforces the need for collecting disease-specific measures of HRQoL, alongside generic measures. The MID for the SF-6D is 0.024–0.028, smaller than estimates for other rheumatic disease such as rheumatoid arthritis.

Disclosure: M. J. Harrison: None; N. Dale: None; S. Haque: None; J. Shemerdine: None; L.-S. Teh: None; Y. Ahmad: None; I. N. Bruce: None.

**796** Working Status in Patients with Early Inflammatory Polyarthritis: Results from the Norfolk Arthritis Register (NOAR). S. M. M. Verstappen\(^1\), M. Lunt\(^2\), T. Marshall\(^2\), D. K. Bunn\(^3\), J. Chipping\(^2\) and D. P. M. Symmons\(^1\).

\(^1\)Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, \(^2\)Norfolk Arthritis Register, Norwich and Norwich University Hospital, Norwich, United Kingdom, \(^3\)Indian University, Indianapolis, IN.

**Background:** Loss of paid work is one of the major consequences in patients with inflammatory polyarthritides (IP) and its subset rheumatoid arthritis (RA). One objective of this study was to compare working status over 10 years and (ii) to identify possible predictors for loss of work due to ill-health in working patients with early IP.

**Methods:** Consecutive patients with early IP (≥ 2 swollen joints for ≥ 4 weeks) from a primary-care based inception cohort (NOAR), recruited between 1990 and 1994, aged <63 yrs at symptom onset were included in this study. Data about working status since symptom onset until 10 yrs after registration in the NOAR cohort were available for this study population. Job titles were coded and used to differentiate between manual and non-manual jobs. At registration (baseline), clinical assessments included the DAS28 and the HAQ-score. Blood was collected to determine CRP, RF and ACPA. The association of baseline disease characteristics and loss of paid work 10 yrs after inclusion was assessed using logistic regression analysis, adjusting for age at registration and gender (OR, 95% CI). These analyses were restricted to patients for whom 10 year 10 yr employment status was available and who were working, temporarily on sick leave or temporarily unemployed at registration. Loss of paid work was defined as being retired due to ill-health or receiving incapacity benefits at 10 yrs. In paid work was defined as working or temporarily on sick leave. Patients who retired (early) not due to ill-health or became a houseperson were excluded from the regression analysis.

**Results:** The preliminary results of this study show that, of the 329 patients working at symptom onset, 38 (11.6%) had already stopped working due to ill-health before registration in the register. Data from 225 patients could be used to assess the association between baseline characteristics and loss of paid work at 10 yrs. The mean age at registration of these 225 patients was 43 (SD 10) yrs and 63% were women. At registration, 183 were working, 37 were temporarily on sick leave, and 5 were temporarily unemployed. At 10 yrs, 56/225 (25%) had lost their job due to ill-health. Women were less likely to stop working due to ill-health (OR 0.53, 95% CI 0.29, 0.98). Older age at registration was also associated with an increased risk of stopping work due to ill-health (OR 1.09, 95% CI 1.05, 1.13). Although a trend for an association was found for RF, none of the clinical variables measured at baseline were significantly associated with the loss of work when adjusting for age and gender, i.e.: DAS28 (OR 0.93, 95% CI 0.71, 1.21), HAQ (OR 1.11, 95% CI 0.64, 1.94), RF positive (OR 1.99, 95% CI 0.98, 4.07), ACPA positive (OR 1.90, 95% CI 0.87, 4.16). Furthermore, having a manual job was also not associated with the loss of work due to ill-health (OR 1.43, 95% CI 0.74, 2.77).

**Conclusion:** In this study we found that many patients with early IP had already stopped working within the first couple of months after symptom onset and before starting DMARDs. In this small study population, we could not confirm any of the associations between clinical and job related variables, which have been found in previous RA studies, with loss of work due to ill-health.

Disclosure: S. M. M. Verstappen: None; M. Lunt: None; T. Marshall: None; D. K. Bunn: None; J. Chipping: None; D. P. M. Symmons: None.

ACR Poster Session B

Fibromyalgia and Soft Tissue Disorders Poster II

Tuesday, November 9, 2010, 9:00 AM–6:00 PM
(61%), and employed (54%). Mean body mass index (BMI) was 31.4 kg/m². Baseline distributions for FIQ Total and BPI (mean ± SD = 67.0 ± 12.7 and 6.0 ± 1.3, respectively) suggested moderate-to-severe FM severity. The average self-reported total of physical activity (PA) of moderate or greater intensity (CHAMPS) was only 1.7 hours/wk. Treatment groups were similar at baseline with respect to demographic and clinical characteristics and retention rates at week 12 (MI: 91% vs. AC: 94%). Mean change (±SD) over 12 weeks in exercise adherence and clinical outcome measures are tabled below.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MI (N = 96)</th>
<th>AC (N = 101)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours/wk of ≥moderate intensity physical activity*</td>
<td>2.8 ± 5.1</td>
<td>1.0 ± 3.6</td>
<td>0.007</td>
</tr>
<tr>
<td>Pain severity†</td>
<td>-1.3 ± 1.5</td>
<td>-0.9 ± 1.8</td>
<td>0.069</td>
</tr>
<tr>
<td>Symptom severity‡</td>
<td>-14.2 ± 14.7</td>
<td>-10.4 ± 17.4</td>
<td>0.105</td>
</tr>
</tbody>
</table>

*Community Health Activities Model Program for Seniors (CHAMPS)
†BPI (range; 0–10); Negative change represents improved pain
‡From ANCOVA, adjusted for baseline score and disease duration

Conclusion: MI is a directive, client-centered counseling style that focuses on enhancing motivation to change by helping clients explore and resolve ambivalence about a target behavior (e.g., exercise). Compared to AC, participants in the MI group reported greater improvement in both physical activity and clinical measures. Pending long-term efficacy data, exercise-based MI appears to be a promising tool to encourage increased PA and improve clinical symptoms in patients with FM.

Disclosure: D. C. Ang: None; A. S. Kaleth: None; S. M. Bigatti: None; S. A. Mazzucca: None; C. K. Saha: None; R. W. Bandy: None.

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Correlation between Bone Mineral Density and Urine Carboxyl Terminal of Collagen Type (CTX) in Premenopausal Fibromyalgia Patients. Alaa Alsalaawy1, Mohammed M. Kame1 and Ibrahim Eweis1. 1AlAzhar University, Cairo, Egypt, 2ALAzhar University, Alkhobar, Saudi Arabia, 3Tanta University, Tanta, Egypt.

Objective: The aim of the study was to compare Bone mineral Density (BMD), Serum Osteocalcin (OC), and Urine Carboxyl terminal of collagen type I(CTX) of premenopausal patients suffering from fibromyalgia(FMS), to that of healthy premenopausal females. Then to determine the relationship between (BMD), urinet (CTX), and the development of rapid bone loss and early osteoporosis among premenopausal fibromyalgic patients.

Subjects and Method: Thirty-one premenopausal patients with fibromyalgia and thirty age matched healthy females subjects as a control group were included in this study. Serum osteocalcin and urine CTX were measured using ELISA technique (EnzymeLinked Immune Sorbent assay) in all cases, BMD was measured in femoral neck and lumbar spine by using X-ray absorptiometry. Statistical analysis were done using SPSS virgin 15. Student’s unpaired (t)test and pearson’s correlation analysis were performed to assess the correlation between BMD and urine CTX.

Results: BMD of lumbar and femoral neck were significantly lower in fibromyalgic patients compared to the healthy females (p<0.001). Serum Osteocalcin were lower in fibromyalgic patients with no significant difference compared to healthy females. There were a significant negative correlation between urine CTX and BMD of lumbar spine and femoral neck in fibromyalgic patients.

Conclusion: The results of this study indicate that the fibromyalgic premenopausal patients are highly susceptible to develop osteopenia and early osteoporosis compared to normal healthy subjects. We recommend to measure BMD of all fibromyalgia patients especially those with high level of urin CTX.

Disclosure: A. Alsalaawy: None; M. M. Kame1: None; I. Eweis: None.

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Cyclobenzaprine (CBP) is A Potent Antagonist of Serotonin Receptor 2a (5-HT2a) and α2 Adrenergic Receptors: Mechanistic Implications for Promoting Restorative Sleep in Fibromyalgia Syndrome (FMS). Herbert W. Harris1 and Seth Lederman2. 1Krele Pharmaceuticals, Saddle Brook, NJ, 2Krele Pharmaceuticals, New York, NY

Background: Cyclobenzaprine (CBP) at very low dosages (VLD)(≤ 4 mg q.h.s.) is being investigated to improve sleep quality, reset circadian rhythm and treat daytime symptoms of fibromyalgia syndrome (FMS) (ref 1). The mechanism of action of cyclobenzaprine remains obscure. Indirect evidence from pharmacological studies implicates antagonism of either Serotonin Type 2a (5-HT2a) receptors (ref 2, 3) or α2 adrenergic receptors (ref 4, 5). In these studies cyclobenzaprine was shown to block the biological effects of known 5-HT2a receptor agonists, or α2 adrenergic agonists in tissue slices or spinal cord sections. The objective of the present studies was to provide more direct evidence of the mechanism of action of CBP treatment by determining the binding affinities for relevant receptors.

Methods: Affinities (pKₐ, values) of CBP were determined for the 5-HT2a(c), receptors, the histamine H1 receptor, and the α2-(a,b,c) adrenoceptor family. Binding assays were then carried out in 50 mM Tris-HCl (pH 7.4) containing 1mM EDTA. Ligands used included: 5-HT2a, [3H] Ketanserin (60–80 Ci/mm;), 5-HT2c, [3H] Mesulergine (60–80 Ci/mm); α2 adrenoceptors, [3H]MK-912 (60–80 Ci/mm); H1, [3H]Pyrilamine (60–80 Ci/mm). Receptor sources used included: 5-HT2a, rat cortical membranes; 5-HT2c, pig choroid plexus membranes; α2 adrenoceptors, human recombinant receptors expressed in SP9 cell lines; H1, bovine cerebellar membranes.

Results: CBP showed nanomolar affinity (9.0 nM) for the 5-HT2a receptor. In addition, CBP showed high affinity for members of the α2 adrenoceptor family (α2-a, 110 nM; α2-b, 9.9 nM; α2-c, 66 nM). CBP showed no measurable affinity (>5,000 nM) for histamine H1 or 5-HT2c receptors.

Conclusions: CBP binds with high affinity at the 5-HT2a receptor and members of the α2 adrenoceptor family, antagonizes the binding of known agonists and has been shown previously to block agonist activity in vivo. 5-HT2a binding is a property of trazodone, which is FDA approved as an antidepressant but which is prescribed off-label to promote sleep and as such, is the second most commonly prescribed treatment for insomnia in the US (ref 6). Published findings suggest a role for 5-HT2a receptors in the regulation of deep non-REM sleep reviewed in (ref 7). The combination of 5-HT2a and α2 adrenoceptor antagonism is associated with the antidepressants mianserin and mirtazapine (but mirtazapine also has significant H1 blockade.) CBP’s absence of measurable affinity for the histamine H1 receptor may be associated with low potential for weight gain. Together, the functional antagonism of 5-HT2a and α2 adrenoceptors may underlie the ability of bedtime CBP to improve sleep quality in FMS.

References:

Disclosure: H. W. Harris: Krele Pharmaceuticals, 1; S. Leaderman: Krele Pharmaceuticals, 1, 5.

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Developing an Improved PROMIS Fatigue Short-Form for Use in Patients with Fibromyalgia. Stephen Schilling2, Steven I, Blum1, Stavros Tourkodimitris2, Andy Stankus and David A. Williams3. 1Forest Research Institute, Jersey City, NJ, 2Forest Research Institute, 3KantarHealth, 4Univ of MI Hlth System-Lobby M, Ann Arbor, MI, 5University of Michigan

Purpose: The NIH roadmap project “Patient-Reported Outcomes Measurement Information System (PROMIS)” has developed calibrated item banks for a variety of domains relevant to chronic illnesses, including fatigue, which can be used to administer computer adaptive testing or to develop static questionnaires and short forms. PROMIS has developed a 7-item Short-Form for general use in fatigue, but it is unclear how well this short-form performs in measuring the fatigue of individuals with Fibromyalgia (FM). This study sought to develop and test an improved fatigue short-form for use in FM patients, constructed from the PROMIS fatigue item bank using calibrations derived from individuals with FM.

Methods: An Item Response Theory (IRT) analysis was conducted using data collected from an internet-based survey of 1207 self-identified individuals (88.9% Female; 90.5% Caucasian) currently suffering from FM. Participants had to be ≥ 18 years at the time of response and have been previously diagnosed with FM by a physician. In order to reduce response burden,
respondents were randomized into one of 3 cohorts, each of which completed one-third of the 95 items from the entire PROMIS v1.0 Fatigue Item Bank (www.nihpromis.org). Items were balanced between cohorts so that there was no overlap of questions. IRT analysis was conducted using Samejima’s Graded Response Model (GRM) to fit the data using MULTILOG 7. The relative contribution of items measuring the latent trait was assessed by the item information function (IIF). Polyserial Correlations and the average of the IIF for each item compared with the full item bank were computed with the item included in the PROMIS Fatigue-Short Form to identify candidate items for an alternative scale. Cronbach’s alpha was used to assess the reliability of the existing and proposed alternative scales.

Results: The current 7-item PROMIS Fatigue Short-Form contains 3 Fatigue Experience items and 4 Fatigue Impact items. The Fatigue Experience items had a Cronbach’s alpha reliability score of 0.77. The Fatigue Impact items had a reliability score of 0.81, including one item [IMP40: How often did you have enough energy to exercise strenuously?] which had the lowest information function (IIF=0.11) in the full item-bank. By contrast, the items with the highest IIF from both Fatigue Experience [EXP40: How fatigued were you on average? (IIF=6.22)] and Fatigue Impact [IMP51: To what degree did you have trouble finishing things? (IIF=2.94)] are not included in the current PROMIS Short-Form. A proposed short-form containing items with high average IIFs for Fatigue Experience and Fatigue Impact items were used to evaluate the reliability of the scale. IIFs for all items from the full item bank were compared with those items included in the PROMIS Fatigue-Short Form to identify candidate items for an alternative scale. Cronbach’s alpha was used to assess the reliability of the existing and proposed alternative scales.

Conclusions: A new short-form can provide improved precision in measuring the fatigue associated with FM compared with the current 7-item PROMIS Fatigue Short-Form. Further testing and validation of the alternative short-form is needed.

Disclosure: S. Schilling: Forest Laboratories, 5; S. I. Blum: Forest Laboratories, 1, 3; S. Tourkodimitris: Forest Laboratories, 3; A. Stanus: None; D. A. Williams: Forest Laboratories, 5, 8.

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Background: Clinical trials have demonstrated the efficacy and tolerability of sodium oxybate (SXB) for fibromyalgia treatment. Since polypharmacy is common in patients with FM, we evaluated interactions of SXB for interactions with three drugs commonly used by fibromyalgia patients.

Methods: Three phase I studies characterized the pharmacokinetics (PK) and pharmacodynamics (PD) of SXB (2.25 g single dose) with duloxetine (60 mg/day for 4 days; N=24), lorazepam (2 mg single dose; N=18), and extended release tramadol (100 mg/day for 5 days; N=19) in healthy volunteers. Drugs were administered in combination with SXB in a double-blind, placebo-controlled, crossover design. Blood sampling at pre-defined time points enabled estimation of PK parameters for drugs administered alone and combined with SXB. Assessment of PD interactions at pre-defined time points included subject self-assessment of sleepiness/alertness (100 mm visual analogue scale [VAS]; 0=very alert to 100=very sleepy) and the Digit Symbol Substitution Test (DSST) for cognition and attention. Tolerability was evaluated based on the occurrence of adverse events (AEs), physical examination including vital signs, laboratory, and clinical tests including 12-lead electrocardiograms.

Results: Subjects were Caucasian (>=95%), mean age was similar across studies (31–33 years); the proportion of females varied (duloxetine, 54%; tramadol, 47%; lorazepam, 39%). The PK of each drug was consistent with established profiles; no statistically or clinically significant PK effects were observed for any of the drugs when administered in combination with SXB. The PD paralleled the PK profile of individual drugs. SXB+duloxetine and SXB+tramadol resulted in increases in sleepiness VAS scores that were similar to SXB alone. Sleepiness VAS scores with SXB+lorazepam were higher than when each drug was administered individually (p<0.05) and had a later and more prolonged peak than SXB alone. SXB alone peaked earlier (1.5 hours) than lorazepam alone (4 hours), and declined more rapidly. Compared to administration of the single agents, decreases in DSST scores with co-administration were only consistently seen with SXB+duloxetine (generally significant across time points vs duloxetine alone, and significant vs SXB alone at 1.5 hours only; p<0.05). All AEs were mild to moderate. One discontinuation, due to ventricular extrasystole in a patient administered tramadol, was not related to study medication.

Conclusions: The PK, PD, and tolerability profiles suggest that the combination of SXB with duloxetine or tramadol are not likely to result in clinically relevant effects. Sleepiness ratings increased when SXB and lorazepam were combined.

Disclosure: M. Eller: Jazz Pharmaceuticals, Inc., 1, 3; W. Halladay: Jazz Pharmaceuticals, Inc., 3; A. Madrid: Jazz Pharmaceuticals, Inc., 1, 3.

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Fibromyalgia Patients with High Global Disease Severity, Depression, Anxiety or Cognitive Dysfunction Are Likely To Benefit from Cognitive Behavioral Therapy. Chad S. Boomsershine1, Cara L. Hammonds1, Jennifer Y. Hong2 and Kenneth A. Wallston2. 1Vanderbilt University, Nashville, TN, 2Vanderbilt University

Background: Cognitive behavioral therapy (CBT) is recommended for treating fibromyalgia (FM) patients. However, due to cost and limited availability, a system for identifying patients most likely to benefit from CBT is needed. Because CBT works by increasing two aspects of cognitive adaptability (CA), perceived competence (PC) and dispositional optimism (DO), FM patients with low CA are likely to benefit from CBT. We studied CA levels in FM patients to identify characteristics that could be used to guide patient selection for CBT.

Methods: Data from FM patients (n=99) referred to a rheumatology clinic were analyzed. FM diagnosis was made on clinical grounds by an experienced rheumatologist (CSB). CA was measured using the 8-item CA Index (CAI), with higher CAI scores reflecting greater PC and DO. Severity of FM symptoms was assessed using the Fibromyalgia Impact Questionnaire (FIQ) for global disease severity, the fatigue severity scale (FSS) for fatigue, the Everyday Cognition Scale 20 (ECog20) for cognitive dysfunction, the Athens Insomnia Scale (AIS) for sleep quality, the Physician Health Questionnaire 9 (PHQ9) for depression, the Generalized Anxiety Disorder 7 (GAD7) for anxiety and a pain visual analogue scale (VAS pain) for pain. The Regional Pain Scale (RPS) and tender point count (TPC) were both used to quantify number of painful body areas. Spearman rank correlations and Mann-Whitney U testing compared questionnaire scores (PASW Statistics 17). Data is reported as median (interquartile range).

Results: CA level negatively correlated with global FM disease severity (CAI vs FIQ global score p=0.53, p<0.001) and the severity of mental symptoms including fatigue (CAI vs FSS p=0.36, p<0.0001), cognitive dysfunction (CAI vs ECog20 p=0.46, p<0.0001), sleep quality (CAI vs AIS p=0.33, p<0.0001), depression (CAI vs PHQ9 p=0.70, p<0.0001), and anxiety (CAI vs GAD7 score p=0.59, p<0.0001). A CA level did not correlate with the severity of physical symptoms including pain severity (CAI vs VAS pain score p=0.08, p=0.458) or number of painful body areas (CAI vs RPS p=0.20, p=0.053; CAI vs TPC p=0.03, p=0.842). To determine characteristics that best identified patients with low CA, patients were divided into two groups: those with normal (CAI ≥36) versus below-normal (CAI <36) CA levels. Median scores on questionnaires that significantly correlated with CAI scores were compared between the CA level groups. FM patients with low CA were best identified as those with high levels of global disease severity [FIQ global 72.3 (63.9,79.8) vs 60.6 (45.8,63.7), p<0.0001], depression [PHQ9 16 (12.19,25) vs 7.86 (4.25,10.75), p<0.0001], anxiety [GAD7 13.5 (8,19) vs 3 (2,10), p<0.0001] or cognitive dysfunction [ECog20 41 (32.47) vs 28 (22,36), p<0.0001].

Conclusions: CA level negatively correlates with the severity of mental symptoms of fatigue, cognitive dysfunction, sleep quality, depression and anxiety but not physical symptoms of pain or number of painful body areas in FM patients. FM patients with high global disease severity, depression, anxiety or cognitive dysfunction are most likely to benefit from cognitive behavioral therapy.

1Wagner et al. AIDS Behav. 2008;14:410–20

Disclosure: C. S. Boomsershine: Cypress Biosciences, Inc., 8. Eli Lilly and Company, 8, Forest Pharmaceuticals, Inc, 8, Pfizer Inc, 2, 8; C. L. Hammonds: None; J. Y. Hong: None; K. A. Wallston: None.
Identifying Fibromyalgia Subgroups Using Cluster Analysis: Relationships with Clinical Variables. Shin-Seok Lee1, Seong-Ho Kim1, Seong-Su Nah1, Ji Hyun Lee2, Seong-Kyu Kim3, Yeon-Ah Lee4, Seung-Jae Hong5, Hyun-Sook Kim6, Hye-Soon Lee7, Hyoun Ah Kim8, Chung-II Joung9 and Sang-Hyon Kim10. 1Ajou University Hospital, Ajou University School of Medicine, 2Catholic University of Daegu, School of Medicine, 3Chonnam Natl Univ Med School, Gwangju, Korea, Republic of, 4College of Medicine, Chosun University, 5Hanyang University College of Medicine, 6Inje University Haeundae Paik Hospital, 7Konyang University Medical School, 8Maryknoll Medical Center, 9School of Medicine, Keimyung University, 10School of Medicine, Kyung Hee University, 11Soonchunhyang University, College of Medicine

Purpose: Patients with fibromyalgia (FM) do not form a homogeneous group and have different clinical symptoms, physical, social, and psychological functions, and therapeutic responses. This study determined whether FM patients could be distinguished based on pain and physical, social, and psychological variables, and if so, whether the identified subgroups differ with respect to clinical features and treatment patterns.

Methods: 313 FM patients were interviewed using a structured questionnaire that included sociodemographic data, current or past FM symptoms, and current use of relevant medications. A k-means cluster analysis was conducted using variables reflecting tender points, the Fibromyalgia Impact Questionnaire, Beck Depression Inventory, State-Trait Anxiety Inventory, and Social Support Scale. Cluster subgroups were compared with chi-square tests for categorical variables and analysis of variance for continuous variables.

Results: Four distinct clusters were identified in these patients. Group 1 was characterized by high pain levels, severe physical and mental impairment, and low social support. Group 2 had moderate pain and physical impairment, mild mental impairment, and moderate social support. Group 3 had moderate pain, low physical and moderate mental impairment, and low social support. Group 4 had low pain levels, nearly normal physical and mental function, and high social support. Group 1 was more often a current or past smoker, more likely to have a variety of symptoms, including swelling, cognitive dysfunction, dizziness, syncope, esophageal dysmotility, dyspnea, irritable bladder, vulvodynia, and restless leg syndrome, and less often a current non-steroidal anti-inflammatory drug user.

Conclusion: We identified four subgroups of FM patients based on pain and physical, social, and psychological function. These subgroups had different clinical symptoms and medication profiles, suggesting that the management of FM patients should be tailored to the individual patients' characteristics.

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Lack of Detection of Xenotropic Murine Leukemia Virus-Related Virus (XMRV) in Patients with Fibromyalgia. Jorge J. Gonzalez Martin1, Gabriel Herrero-Beaumont3, and Rafael Delgado1. 1Reumatología, IIS-Fundación Jimenez Diaz, 28040, 2Reumatología, IIS-Fundación Jimenez Diaz, 28040, 3Servicio de Microbiología, Imserso, Hospital Universitario 12 de Octubre

Xenotropic murine leukemia virus-related virus (XMRV) is a recently described human retrovirus that has been associated with prostate cancer. Recently, XMRV sequences and specific immune responses have been detected in 67% of patients with the diagnosis of Chronic Fatigue Syndrome (CFS) in North America. Based in the common features between CFS and Fibromyalgia (FM), we decide to study the presence of XMRV in a group of 15 patients previously diagnosed with FM. DNA was extracted from whole blood and analyzed by nested PCR using 3 sets of primers corresponding to the gag and env regions of XMRV. Primers for human beta-globin (hBG) were used as positive control of human DNA amplification. The sensitivity of the nested PCR procedure, estimated by spiking the XMRV molecular clone VP62 into negative samples, was 1–10 copies per sample. We did not find any evidence of this new agent in any patient with FM studied and XMRV does not appear to be related with FM. With this relative small population we cannot absolutely exclude an association of XMRV with FM, however it would be highly unlikely a proportion of FM cases with XMRV greater than 22% (3 of 15 cases, 95% confidence interval), which is clearly insufficient to support a significant association between XMRV and FM.

Disclosure: J. J. Gonzalez Martin: None; G. Herrero-Beaumont: None; R. Delgado: None.
Conclusion: In patients with FM, treatment with milnacipran 100 mg/day significantly improves multiple domains, including pain, global status, and depressive symptoms. Much of the improvement in pain and global status with milnacipran is independent of improvements in depressive symptoms.


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Milnacipran Reduces the Overall Severity of Fibromyalgia Symptoms in Patients with Fibromyalgia, Robert H. Palmer, Robert M. Bennett,* Yong Wang and R. Michael Gendreau. 1Cypress Biosciences, Inc., San Diego, CA, 2Forest Research Institute, Jersey City, NJ, 3Forest Research Institute, Oregon Health & Science Univ, Portland, OR

Purpose: Fibromyalgia (FM) is a disorder characterized by chronic widespread pain, fatigue, and impaired physical and global function. Patients with FM often have a multitude of other symptoms that include stiffness, poor sleep quality, and cognitive dysfunction. The Fibromyalgia Impact Questionnaire (FIQ) is a validated instrument that measures the spectrum of these FM-related symptoms and can identify patient responses to therapy. Milnacipran, approved in the US for the management of FM, has shown efficacy in treating multiple symptoms in FM patients. This post hoc analysis examines the effect of milnacipran on patients’ FM severity.

Method: Data from a randomized, double-blind, placebo-controlled trial were analyzed. Patients with FM received milnacipran 100 mg/day (n=516) or placebo (n=509) for 4 to 6 weeks of flexible dose escalation followed by 12 weeks of stable-dose treatment. The FIQ was administered to patients at baseline and at each study visit. Patients were classified into 3 severity categories based on their FIQ total scores at baseline: <39 (mild impairment); >39 to <59 (moderate impairment); ≥59 (severe impairment). Improvements in FM severity were determined by the percentage of patients at endpoint shifting from the severe to the moderate or mild categories, or from the moderate to the mild category. Odds ratios (OR) for milnacipran were calculated for shifts in each severity category and are expressed relative to placebo treatment. Analysis was based on LOCF.

Results: FM severity based on the total FIQ score at baseline was mild (8.1%), moderate (48.5%), and severe (43.4%). At all study visits, patients treated with milnacipran had significantly larger decreases from baseline in FIQ total scores than placebo (P<0.001 vs placebo). Of patients with severe FM at baseline, 61.1% of patients treated with milnacipran improved by at least one category of severity (32.2% to moderate and 28.9% to mild) compared with 46.1% of patients treated with placebo (26.5% to moderate and 19.6% to mild) (OR, 1.5; P=0.001 vs placebo). Of patients with moderate or severe FM at baseline, 52.2% of milnacipran patients improved by at least one category, compared with 42.0% of placebo patients (OR, 1.5; P=0.002; number needed to treat, 7). Of patients with moderate or severe FM at baseline, 52.2% of milnacipran patients improved by at least one category of severity (32.2% to moderate and 28.9% to mild) compared with 46.1% of patients treated with placebo (26.5% to moderate and 19.6% to mild) (OR, 1.5; P=0.002; number needed to treat, 7). Of patients with moderate or severe FM at baseline, 52.2% of milnacipran patients improved by at least one category, compared with 42.0% of placebo patients (OR, 1.5; P=0.002; number needed to treat, 7).

Conclusion: These results represent an assessment of efficacy that indicate that milnacipran 100 mg/day is effective for treating the overall symptoms of FM, as measured by improvements in FIQ total scores. Patients with moderate or severe impairment at baseline were more likely to improve their FM severity with milnacipran than with placebo.


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National Fibromyalgia Association Survey on Children with Fibromyalgia: Preliminary Results, Sanjida Ali and Rae Marie Gleason. 1Forest Research Institute, Jersey City, NJ, 2National Fibromyalgia Association

Purpose: Juvenile fibromyalgia (FM) is a musculoskeletal pain condition that can impact the functional status and psychosocial development of children and adolescents. Currently, there is limited information on the prevalence of juvenile FM in the U.S. The National Fibromyalgia Association (NFA), in collaboration with Forest Research Institute, is conducting an internet survey to gather information on juvenile FM. One aim of the survey is to collect data that will help researchers and clinicians to better understand the nature and prevalence of FM in children. This report presents preliminary findings from the NFA survey.

Methods: The survey was completed by parents or guardians of children who have “fibromyalgia symptoms such as body-wide chronic pain, fatigue, stiffness, sleep problems, headache, irritable bowel and restless legs.” For each child, respondents selected responses for the following items: age, gender, symptom severity, FM diagnosis, treatment information (ie, treating physician, medications, nonpharmacologic therapies), and lifestyle information. Responses from surveys submitted by parents or guardians of children (<18 years) from 12/05/2009 to 06/02/2010 were analyzed.

Results: Completed surveys were submitted for 284 children with symptoms of juvenile FM, >85% of whom were from the U.S. Results show that 76.4% of the children were female and 23.2% were male (0.4%, no response). Mean age was 13.6 years, with 17.6% ages ≤10 years, 33.5% ages 11–14 years, and 48.9% ages 15–17 years. 44.3% of the children were being treated by a healthcare professional, 26.4% by a rheumatologist and 10.6% by a primary care/family physician. 121 children (42.6%) had received a confirmed FM diagnosis; 60.3% were diagnosed by a rheumatologist and 23.1% by a primary care/family physician. Among children with a confirmed FM diagnosis, the most frequent symptoms (>90%) were widespread pain, pain influenced by stressors, fatigue, stiffness, sleep problems, headaches, foggy thinking, and anxiety. The frequency at which these symptoms were rated moderate or severe was 62.0% to 91.7%. Since developing FM symptoms, >50% of the diagnosed children had moderately or substantially decreased their involvement in strenuous physical activities or socializing with peers; 47.9% had changed schooling as a result of their FM symptoms. Current treatment with prescribed medications (ie, serotonin-norepinephrine reuptake inhibitor, antiepileptic, tricyclic antidepressant, sedative-hypnotic, selective serotonin reuptake inhibitor, muscle relaxant, dopamine agonist) was reported in ≤12.4% of diagnosed children. Rates of previous use of these medications ranged from 0% to 21.5%. Nonpharmacologic therapies were more common, with >30% of diagnosed children currently using hot baths, exercise, and/or supplements to manage FM symptoms.

Conclusions: Results from the NFA’s internet survey suggest children with FM present with higher rates of many of the classical symptoms of FM than observed in adults with FM. Also, less than half of the children with symptoms suggestive of FM had received a confirmed diagnosis, suggesting a possibility of underdiagnosis of FM in the pediatric population.


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Background: Researchers strive to identify biomarkers for fibromyalgia (FM). Heart rate variability (HRV) analyses provide a quantitative marker of autonomic nervous system activity. Several HRV studies in FM have described changes consistent with relentless sympathetic hyperactivity. Sleep is modulated by autonomic activity. Sleeping problems are prominent in FM.

Objective: To explore different HRV parameters measured during sleeping hours as potential FM biomarkers.

Patients and Methods: We studied 21 women with FM according to the 1990 ACR criteria and 21 age-matched healthy women. None of the participants was on any medication that could affect autonomic activity. All participants used a Holter monitor while sleeping at home. Calculations were done from 00.00 to 06.00 hours. The following time-domain HRV parameters were studied: mean NN interval (mean NN), standard deviation of the NN intervals 95% confidence interval (SDNN), mean standard deviation of the average NN intervals calculated over 5 minutes (SDANN), and finally a HRV parameter developed by one of the authors (CL); transient heart rate acceleration episodes (THRAE).

Statistical analysis: Student T test compared parameters from both groups. The best cut-off point for each parameter was determined from ROC curves. Sensitivity, specificity, positive predictive value, negative predictive value and odds ratio were estimated for each parameter.

Results: Are shown in tables 1 and 2. Both groups have similar demographic characteristics. HRV values clearly differentiated patients from controls. Nocturnal SDNN had the greatest odds ratio (12, with confidence intervals 95% = 3.2–44.9) followed by SDANN (8.5, CI 95%, 2.2–31.8)
Table 1. Demographic data and HRV analyses from 00.00 to 06.00 hr.

<table>
<thead>
<tr>
<th></th>
<th>FM</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 21</td>
<td>n = 21</td>
</tr>
<tr>
<td><strong>Age (years)</strong> ± SD</td>
<td>32.7 ± 8.0</td>
<td>30.5 ± 7.6</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>24.5 ± 4.6</td>
<td>25.2 ± 3.2</td>
</tr>
<tr>
<td><strong>NN mean (ms)</strong></td>
<td>857 ± 92</td>
<td>937 ± 132</td>
</tr>
<tr>
<td><strong>SDNN (ms)</strong></td>
<td>91 ± 22</td>
<td>122 ± 33</td>
</tr>
<tr>
<td><strong>SDANN (ms)</strong></td>
<td>58 ± 22</td>
<td>78 ± 28</td>
</tr>
<tr>
<td><strong>THRAE</strong></td>
<td>23 ± 14</td>
<td>41 ± 31</td>
</tr>
</tbody>
</table>

Table 2. Predictive values of the potential HRV biomarkers.

<table>
<thead>
<tr>
<th>Cutoff point</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>OR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NN mean at night (ms)</strong></td>
<td>888.1</td>
<td>0.67</td>
<td>71</td>
<td>67</td>
<td>68</td>
<td>70 (1.3–18.7)</td>
</tr>
<tr>
<td><strong>SDNN (ms)</strong></td>
<td>113.1</td>
<td>0.79</td>
<td>86</td>
<td>72</td>
<td>82</td>
<td>12 (3.2–44.9)</td>
</tr>
<tr>
<td><strong>SDANN (ms)</strong></td>
<td>68.8</td>
<td>0.71</td>
<td>81</td>
<td>71</td>
<td>78</td>
<td>8.5 (2.2–31.8)</td>
</tr>
<tr>
<td><strong>THRAE</strong></td>
<td>28.5</td>
<td>0.65</td>
<td>76</td>
<td>52</td>
<td>62</td>
<td>69 (3.5 (0.9–13.1)</td>
</tr>
</tbody>
</table>

AUC = area under ROC curve; PPV = positive predictive value; NPV = negative predictive value; OR = odds ratio.

**Conclusions:** We identify 4 nocturnal HRV parameters that differentiate FM patients from healthy individuals. Multivariate analysis of these values could possibly yield more discriminative information. The specificity of these findings for FM when compared to other painful rheumatic syndromes remains to be established.

Disclosure: C. Lerma: None; A. Martinez: None; N. Ruiz: None; A. Vargas: None; O. Infante: None; M. Martinez-Lavin: None.

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**Orthostatic Stress Reverses Sympathetic but Not Parasympathetic Abnormalities of Fibromyalgia Patients.** Florence Luong1, Donald D. Price2, Michael E. Robinson2 and Roland Staud1. 1Univ of Florida JHMHC, Gainesville, FL, 2University of Florida

Fibromyalgia syndrome (FM) is characterized by widespread chronic pain and tenderness. Previous studies have shown alterations of the central nervous system functions in FM including increased sensitivity to painful and non-painful stimuli and dysfunctional autonomic nervous system (ANS) responses. Dysfunctional ANS responses in FM patients include orofacial hypotension, diminished microcirculatory vasoconstriction, and sympathetic hyporeactivity. The ANS can be assessed using heart rate variability (HRV) analysis which can provide important information on sympathetic and parasympathetic functions in FM.

**Methods:** We sought to determine the autonomic adaptability of FM patients using a mild orthostatic stressor. Whereas VLF and LF bands of HRV represent sympathetic ANS function, HF band variability correlates with parasympathetic function. We performed HRV spectral analysis of 55 FM and 44 normal control subjects (NC) during 15 min of rest followed by 5 min of standing. Heart and respiratory rate as well as blood pressure were monitored.

**Results:** Frequency analysis of FM subjects showed significantly lower variability in VLF, LF, and HF bands compared to NC during rest (p <.05) indicating sympathetic ANS dysfunction.

Table 1. Average (SD) of HRV during rest in NC and FM subjects

<table>
<thead>
<tr>
<th></th>
<th>VLF</th>
<th>LF</th>
<th>HF</th>
<th>VHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>849.7 (998.4)</td>
<td>1412.2 (1778.4)</td>
<td>2096.1 (3593.6)</td>
<td>166.6 (335.5)</td>
</tr>
<tr>
<td>FM</td>
<td>442.4 (457.0)</td>
<td>597.7743 (777.9)</td>
<td>618.5089 (932.1)</td>
<td>56.8811 (71.0)</td>
</tr>
<tr>
<td>P value</td>
<td>.049</td>
<td>.01</td>
<td>.03</td>
<td>&gt;.05</td>
</tr>
</tbody>
</table>

During 5 min of standing heart and respiratory rates as well as blood pressure of FM subjects were similar to NC (all p >.05). Whereas variability of VLF and LF normalized HF of FM subjects remained abnormal.

Table 2. Average (SD) of HRV during standing in NC and FM subjects

<table>
<thead>
<tr>
<th></th>
<th>VLF</th>
<th>LF</th>
<th>HF</th>
<th>VHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>1368.3 (1622.5)</td>
<td>1306.7 (1301.0)</td>
<td>1357.5 (2504.3)</td>
<td>145.5 (195.1)</td>
</tr>
<tr>
<td>FM</td>
<td>1076.2 (2235.5)</td>
<td>1013.2 (1216.4)</td>
<td>388.8 (402.3)</td>
<td>60.0 (60.5)</td>
</tr>
<tr>
<td>P value</td>
<td>&gt;.05</td>
<td>&gt;.05</td>
<td>.03</td>
<td>.01</td>
</tr>
</tbody>
</table>

To determine the associations of VAS (0–10) with these variables, we noted that there was 0.0 pain level difference for FI+ vs. FI- (3.6 vs. 3.6), but there was a 1.3 unit difference comparing AP+ with AP- patients (4.7, 3.4) and a 0.9 difference for AL+ vs. AL- patients (4.3, 3.4). A similar pattern was found in analyses of fatigue. Similar results were obtained with FM patients added, and for HL substituted for AL.

**Conclusions:** These data show that events that are not of personal concern are unrelated to WPI and pain. However, events such as AL that are not symptoms but may be of personal concern to patients are associated with increased WPI and pain, suggesting that OR influences WPI, pain, symptoms, and tenderness.

Disclosure: F. Luong: None; D. D. Price: None; M. E. Robinson: None; R. Staud: None.

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Over-Reporting Is a Central Determinant of Pain and Symptom Reporting in Fibromyalgia. Frederick Wolfe. National Data Bank for Rheumatic Diseases, Wichita, KS

**Purpose:** Central sensitization (CS) and global sensory augmentation (GSA) have been demonstrated in laboratory experiments, and have been proposed as major mechanisms to explain increased pain and sensory reporting in fibromyalgia (FM) and chronic widespread pain (CWP). However, there are other possible mechanisms in clinical FM, including over-reporting (OR), which might be considered to be related to increased concern about symptoms and non-symptom events. It is possible that the CS and GSA as well as OR could be operating at the same time. In this study we investigated the presence of GCA and OR as a function of widespread pain (WP), a measure related to pain threshold.

**Methods:** We studied 3 sets of variables to determine if their probability increased with increasing WP. We hypothesized that influenza immunization (FI) would not increase with increasing WP, as it was not a matter of personal concern to patients; that abdominal pain (AP) and other symptom variables would increase, observations that are consistent with the CS and GSA hypotheses. Finally we tested whether non-symptom events such as hair loss or alopecia (AL) and hearing loss (HL) would increase, According to the GSA hypothesis, these events would not increase; but they might increase if OR was present.

To be certain that the presence of patients diagnosed with FM would not distort the analyses, we excluded them from analysis, and studied 10,228 patients with rheumatoid arthritis or osteoarthritis. By self-report, we determined the presence of FI in the last 12 months, and symptom events (AP) and non-symptom events (AL, HL) present in the last 6 months. WP was determined using the Widespread Pain Index (WPI).

**Results:** Adjusted for age, sex and education level, FI was not significantly associated with WPI, p=0.839 ROC AUC = 0.618. AP was strongly associated with WPI, p<0.001, ROC AUC =0.732; and AL was also associated with WPI, p<0.001, ROC AUC = 0.659. The association are shown graphically in Figure 1.
and non-symptoms in the clinic. CS and GSA are not sufficient to explain observed pain and symptoms in FM. The degree to which CS/GSA and OR each contribute to WPI, FM and CWP in the clinic is a central question that should be the subject of future research.

Disclosure: F. Wolfe: None.

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Proteomic Mass Spectra Classification in Fibromyalgia Patients. Camillo Giaconelli1, Laura Bazzichi1, Federica Ciregia2, Chiara Baldini3, Francesca Semnissi5, Pasquale Pepe1, Laura Giusti4, Antonio Lucacchini1 and Stefano Bombardieri5. 1Department of Clinical Pharmacology, University of Pisa, Pisa, Italy, 2Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology, University of Pisa, Pisa, Italy, 3Rheumatology Unit. Department of Internal Medicine. University of Pisa, Pisa, Italy.

Background: Fibromyalgia (FM) is a chronic non-inflammatory musculoskeletal disorder characterised by widespread pain and by the presence of at least 11 out of 18 specific tender points on physical examination. Currently no validated laboratory biomarkers are available for FM and the diagnosis of the disease remains exclusively clinical. The aim of the present study was to perform a proteomic analysis of FM patients’ saliva with surface-enhanced laser desorption/ionization time-of-flight/mass spectrometry (SELDI-TOF/MS).

Methods: For this study, we enrolled 66 patients, all female (mean age 43.60±11.30 yrs, Mean±SD), all fulfilling the ACR criteria and 50 healthy controls matched for age and sex.

Whole saliva samples are centrifuged to remove undissolved material. Aliquots of resulting supernatants are analysed by SELDI-TOF/MS. Saliva is applied to the spots of Protein Chip Arrays (CM10, Q10, H50). After an incubation period, unbound proteins and other contaminants are washed off the spots using buffers as required by the array chemistry; only proteins interacting with the chemistry of the array surface are retained for analysis. Finally matrix (sinapinic acid-SPA) is applied to each spot to facilitate laser desorption and ionization. The datasets are obtained from biological samples collected from different patients classified in different classes (e.g. disease versus control). Univariate and multivariate Logistic analysis was performed.

Summary of Results: Univariate analysis identified 22 peaks differently expressed in FM in comparison to healthy controls in a range of m/z between 2618 and 29533. One of these well overlap with molecular weight of 26217 and 26616. Multivariate analysis showed an high independence of predictors for FM three peaks between m/z range from 2500 to 12000 which were able to classify FM patients with a percentage error of 23.4%.

Conclusion: These preliminary results showed the possibility to identify a salivary biomarker through salivary proteomic analysis with SELDI-TOF in FM patients. The next step will be the identification of the altered proteins by purification by purification with chromatography and immunoprecipitation techniques.

Reference:

Disclosure: C. Giaconelli: None; L. Bazzichi: None; F. Ciregia: None; C. Baldini: None; F. Semnissi: None; P. Pepe: None; L. Giusti: None; A. Lucacchini: None; S. Bombardieri: None.

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Simplifying Fibromyalgia Assessment: The VASFIQ Brief Symptom Scale. Chad S. Boomershine, Gergana Zlateva, Yi Wang, Ed Whalen and Birol Emir. Vanderbilt University, Nashville, TN.

Background: Fibromyalgia (FM) is a complex disorder of chronic widespread pain and tenderness associated with symptoms of fatigue, poor sleep, depression, and anxiety. Due to its complexity, identifying clinically significant symptoms and monitoring treatment response in FM is difficult. While the Fibromyalgia Impact Questionnaire (FIQ) can quantify global disease severity, scoring complexity, length and the inability to identify patients with significant symptoms limit its clinical utility. We hypothesized a more clinically useful FM scale could be formed from the 7 FIQ visual analogue scales (the VASFIQ), with the sum of VASFIQ scores providing a global disease severity measure and cut-off scores for individual VASs derived to identify clinically significant symptoms of fatigue, poor sleep, depression and anxiety.

Methods: Data from 2229 patients enrolled in 3 pregabalin FM treatment...
trials (LIFT1, RELIEF2 and 11003) were analyzed including scores from the FIQ, the Hospital Anxiety and Depression Scale (HADS), the Medical Outcomes Study (MOS) Sleep Problems Index (9 SLPI) and the Multidimensional Assessment of Fatigue Global Fatigue Index (MAGF). Spearman rank correlations compared scores. Receiver operating characteristic (ROC) analysis identified cut-off scores on individual FIQ VASs with corresponding validated questionnaires used to define cases.

**Results:** VASFIQ global scores correlated with FIQ global scores at baseline (p=0.94; p<0.0001) and study endpoints (p=0.97; p<0.0001). Change in VASFIQ and FIQ global scores at study endpoints correlated (p=0.96; p<0.0001). Individual FIQ VAS scores correlated with all corresponding validated questionnaire scores at baseline (VASfatigue with MAF p=0.67; VASSleep with SLP p=0.50; VASdepressed with HADS-D p=0.57; VASanxiety with HADS-A p=0.64, all with p<0.0001) and study endpoints (VASfatigue with MAF p=0.76; VASSleep with SLP p=0.67; VASdepressed with HADS-D p=0.62, all with p<0.0001). Individual change in FIQ VAS scores correlated with change in corresponding validated questionnaire scores at study endpoints (VASfatigue with MAF p=0.64; VASSleep with SLP p=0.57; VASdepressed with HADS-D p=0.43; VASanxiety with HADS-A p=0.47, all with p<0.0001). ROC analyses showed a VASfatigue score of ≥7.5 was 76.0% sensitive and 82.2% specific for fatigue defined as a ≥30 score on the MAF (ROC area 0.87, 95% confidence interval (CI) 0.84–0.90), a VASsleep score of ≥7.9 was 68.7% sensitive and 71.2% specific for poor sleep defined as a ≥50 score on the SLP (ROC area 0.76, 95% CI 0.74–0.79), a VASdepression score of ≥5.8 was 71.3% sensitive and 72.6% specific for depression defined as a ≥11 score on the HADS-D (ROC area 0.80, 95% CI 0.77, 0.82) and a VASanxiety score of ≥6 was 71.2% sensitive and 77.7% specific for anxiety defined as a ≥11 score on the HADS-A (ROC area 0.83, 95% CI 0.81, 0.84).

**Conclusion:** The VASFIQ is a brief FM scale to assess global disease severity and identify patients with clinically significant symptoms of fatigue, poor sleep, depression and anxiety.


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**Sodium Oxybate Improves Sleep and Fatigue in Patients with Fibromyalgia: A Pooled Analysis from 2 Pivotal Clinical Trials.** Stuart L. Silverman1, Andrew J. Holman2, Beverly Benson3, Sarah Alvarez-Horine4, Y. Grace Wang5 and Piercarlo Sarzi-Puttini6,7, Jazz Pharmaceuticals, Inc., 1, Oregon Health and Science University, Portland, OR, 2University of North Carolina, Chapel Hill, NC, 3University of Texas Health Science Center, San Antonio, TX

**Background:** Fibromyalgia (FM) is characterized by chronic widespread pain as well as sleep disturbance and fatigue. Two pivotal clinical trials of sodium oxybate (SXB) demonstrated that SXB significantly reduced pain and fatigue, and improved sleep relative to placebo. This analysis further evaluates the effects of SXB on sleep and fatigue using pooled data from the two trials.

**Methods:** Both trials were of similar design (randomized, double-blind, placebo-controlled), length (14 weeks), and dosing regimens (placebo, SXB 4.5 g and 6 g equally divided between a dose at bedtime and another one 2.5 to 4 hours later). Baseline assessments were made after a washout period (up to 30 days) and prior to treatment initiation. Data from each treatment group were pooled (n=371 placebo; n=377 SXB 4.5 g; n=373 SXB 6 g) to evaluate the efficacy of SXB for pain (0–100 visual analogue scale [VAS]), fatigue (0–100 VAS), sleep disturbances (Jenkins Sleep Scale [JSS]), a validated, 4-item, self-report questionnaire for sleep disturbances, and effects of excessive daytime sleepiness on daily functioning (Functional Outcomes of Sleep Questionnaire [FOSQ]; a patient-report questionnaire); last observation carried forward was used for missing data.

**Results:** Demographics of the pooled patients are consistent with the FM population (90.4% female, and 91.2% white, median age 48.0 years). Mean baseline pain, fatigue, sleep disturbance, and FOSQ scores were also similar to the individual studies and consistent with significant improvement. The proportions of patients who achieved 30% and 50% reductions in pain were significantly greater with SXB than placebo (p<0.001). Least squares mean changes from baseline in fatigue VAS showed significant reductions with both SXB doses beginning at Week 1 that were maintained over the duration of treatment and were significantly greater than placebo at each weekly assessment (p<0.001). At 14 weeks, changes from baseline in fatigue VAS were −25.3 and −28.0 for SXB 4.5 g and 6 g, respectively, compared with −15.5 for placebo. SXB resulted in reduction in sleep disturbances at Week 14 as indicated by a significant overall treatment effect (p<0.001) and pairwise comparisons with placebo (p<0.001 for both SXB groups) on the JSS total score; least squares mean changes at Week 14 were −5.4 and −6.0 for the SXB 4.5 g and 6 g groups, respectively, compared with −2.9 for placebo. Similarly, treatment effects on functioning related to daytime sleepiness and tiredness at Week 14 were observed for the FOSQ, with least squares mean changes (improvement) from baseline of 2.2 for both SXB groups compared with 1.3 for placebo (both p<0.001). The most common adverse event was headache, 22.9%, 18.4%, and 15.1% in the pooled SXB

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SPECT Imaging of the Brain: Regional Cerebral Blood Flow before and after Treatment of Patients with Primary Fibromyalgia. Malan Osman1, Osama Haji1, Ola Abdul Nasser3, Ahmad Khodair1 and Nashwa Al Sarraf1. 1Internal Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt, 2Radiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt, 3Rheumatology and Rehabilitation Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Objective: Whether regional cerebral blood flow (rCBF) is affected by Duloxetine Hcl in Egyptian women with primary fibromyalgia (FM) and if it correlates with clinical findings.

Methodology: Thirty untreated women with FM were subjected to full history taking and thorough clinical examination including headache, anxiety, fatigue, sleep disturbances, wide spread pain, tender points. The patients (group I) and ten apparently healthy controls (group II) were studied with single photon emission computed tomography of the brain (brain SPECT) after IVI of Tc-99m HMP[1]AO as a cerebral perfusion agent. The resting state (rCBF) was measured for the deep structures (thalamus and caudate nucleus) and cerebral cortices (anterior, lateral, posterior) of both sides. Fifteen patients (group Ia) received the conventional therapy of fibromyalgia and the other fifteen (group Ib) received Duloxetine Hcl (a potent serotonin and norepinephrine reuptake inhibitor which is approved by FDA) 60 mg daily for 3 months followed by measuring rCBF.

Results: There was a statistically highly significant lower (rCBF) in the thalamus and caudate nucleus in patients as compared to controls but no such difference in the anterior, lateral and posterior cerebral cortices. No significant difference clinically or radiologically was found comparing group Ia results before and after 12 weeks. There was a highly significant difference with fatigue and a significant difference as regard neck pain, headache, generalized body ache and morning stiffness when comparing group Ib results before and after 12 weeks. The rCBF to thalamus and caudate nucleus showed a high significant increase in group Ib after 3 months. There was a significant difference in number of tender points, the duration of morning stiffness as well as thalamic and caudate nucleus blood flow comparing the change in Ia and Ib groups.

Conclusions: The decrease of regional cerebral blood flow to thalamus and caudate nucleus in patients with primary FM may be the cause of their symptoms. Improvement of the symptoms by administration of duloxetine Hcl may be due to increase of blood flow to the thalamus and caudate nucleus.

Disclosure: M. Osman: None; O. Haji: None; O. Abdul Nasser: None; A. Khodair: None; N. Al Sarraf: None.

The Prevalence of Fibromyalgia in Patients with Chronic Hepatitis C Infection. Ausaf Mohammad1, John J. Carey1, Eoin R. Storan1, Margaret Scarry1, Mary B. Keane2, Angela Moore2, Ann Lyons2, Maureen O’Grady2, Catriona Minihan2 and John M. Lee1. 1Department of Hepatology and Rheumatology, Galway University Hospital, Ireland, 2Galway University Hospital, 3Hepatology Galway University Hospital, 4Rheumatology Merlin Park University Hospital

Purpose: Chronic HCV infection is associated with rheumatologic conditions including arthritis and vasculitis. Previous studies have not specifically addressed the presence of fibromyalgia syndrome (FMS) in this population. In this study we assessed the prevalence of fibromyalgia in a cohort of subjects with chronic HCV and its relationship to subject demographics, viral characteristics and quality of life.

Methods: Cross-sectional study of a cohort of HCV infected individuals at our university hospital. Study was approved by local I.R.B. and all subjects gave written informed consent prior to participation. Patients with decompensated liver disease, concomitant autoimmune liver disease, arthritis, vasculitis, co-infection with hepatitis B or D, or HIV, end-stage renal failure, organ transplantation, cancer and those patients who were currently receiving anti-viral treatment were excluded. All subjects underwent a single interview including a fibromyalgia impact questionnaire, pain assessment measured on a 100-mm visual analogue scale (VAS) and the Stanford Health Assessment Questionnaire 20-Item Disability Scale (HAQ-DI). All patients underwent clinical examination including a standard assessment for fibromyalgia tender points. Additional details were recorded from the medical record including information about their HCV infection and its treatment, laboratory data including antibody profiles, other illnesses and medications.

Results: 185 patients attending the hepatology unit consented to participate. 110 (59%) were females with a mean age of 46.7 years. 106 (57%) subjects met criteria for the presence of FMS. Widespread pain and ≥11 tender points were present in all of the subjects with fibromyalgia, fatigue in 98 (92%), depression in 60 (57%), and arthralgia/joint stiffness in 16 (15%). Among those with FMS mean pain score was 70 ± 11.78 and 36% reported some functional impairment on HAQ-DI (>0), with 17% reporting moderate-severe functional impairment (HAQ-DI ≥1.5). Compared to subjects who did not meet criteria for fibromyalgia, patients with fibromyalgia were more likely to be older, females, living alone, smokers, have a history of depression, had acquired HCV via a blood transfusion, and had HCV genotype-1(table 1, p < 0.005 for all categories).

Table 1. Comparing HCV infected subjects with and without FM

<table>
<thead>
<tr>
<th>Chronic HCV patients with FMS (n = 106)</th>
<th>Chronic HCV patients without FMS (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>82 (77%) vs. 28 (35%)</td>
</tr>
<tr>
<td>age ≥ 45 years</td>
<td>80 (73%) vs. 26 (33%)</td>
</tr>
<tr>
<td>Wide spread pain</td>
<td>106 (100%) vs. 20 (25%)</td>
</tr>
<tr>
<td>Depression</td>
<td>60 (57%) vs. 20 (25%)</td>
</tr>
<tr>
<td>HCV acquisition via blood transfusion</td>
<td>65 (61%) vs. 26 (33%)</td>
</tr>
</tbody>
</table>

Conclusions: The prevalence of FMS was very high (57%) among subjects with HCV infection, one third of whom reported some degree of functional impairment. Further research is needed to better understand FMS in patients with HCV.

Disclosure: A. Mohammad: None; J. J. Carey: None; E. R. Storan: None; M. Scarry: None; M. B. Keane: None; A. Moore: None; A. Lyons: None; M. O’Grady: None; C. Minihan: None; J. M. Lee: None.
laboratory data including autoantibody profiles and iron studies were recorded from the patients’ medical record.

**Results:** 350 patients with HH attending the hematopathy unit consented to participate, 230 (66%) of whom were males with a mean age of 43 years (range 27–70). 170 (41%) subjects met criteria for the presence of FMS. In subjects with fibromyalgia, fatigue and ≥11 tender points were present in all of the subjects, wide spread pain in 150 (88%), depression and arthralgia/joint stiffness in 70 (41%). Among those with FMS mean pain score was 69 ± 10.25 and 33% reported some functional impairment on HAQ-DI (≥0), with 10% reporting moderate-severe functional impairment (HAQ-DI ≥1.5). Patients with fibromyalgia were more likely to be older, males with wide spread pain and history of depression, and had C282Y homozygosity in the HFE gene (table 1, p < 0.005 for all categories).

**Table 1.** Comparing HH subjects with and without FMS

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Patients with FMS (n = 170)</th>
<th>Patients without FMS (n = 180)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>140 (82%)</td>
<td>90 (50%)</td>
<td>0.001</td>
</tr>
<tr>
<td>age ≥ 45 years</td>
<td>90 (53%)</td>
<td>50 (28%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Wide spread pain</td>
<td>150 (88%)</td>
<td>40 (22%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>70 (41%)</td>
<td>30 (16%)</td>
<td>0.001</td>
</tr>
<tr>
<td>C282Y Homozygous</td>
<td>160 (94%)</td>
<td>110 (61%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions: There is a high prevalence of FMS (41%) among subjects with HH, one third of whom showed some degree of functional impairment.

**Disclosure:** A. Mohammad: None; J. J. Carey: None; E. R. Storan: None; M. Scarry: None; M. B. Keane: None; A. Moore: None; A. Lyons: None; M. O’Grady: None; C. Minihan: None; J. M. Lee: None.

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**Use of Path Analysis To Evaluate the Effects of Sodium Oxybate on Pain Reduction in Patients with Fibromyalgia.** Fowzia Ibrahim1, Chinglin Lai1 and Ernest Choy2. 1Jazz Pharmaceuticals, Inc., 2King’s College London, 3Kings College Hospital, London, United Kingdom

**Background:** Although chronic widespread pain is the hallmark symptom of fibromyalgia (FM), sleep disturbances are also a characteristic of patients with FM. In clinical trials, sodium oxybate (SXB) has been shown to improve sleep as measured by JSS, suggesting there is direct effect of SXB on pain reduction. For the component of reduction in pain mediated through improvement in sleep, it is mediated by reducing fatigue, tiredness upon awakening, and stiffness. This suggests that for SXB improvement in quality of sleep is associated with improvement in fatigue, tiredness upon awakening, and stiffness.

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**Very Low Dosage (VLD) Bedtime Cyclobenzaprine (CBP) Reduces Cyclic Alternating Pattern (CAP) Rate Indices of EEG Sleep Instability and Improves Pre-Sleep Fatigue in Fibromyalgia Syndrome (FMS).** Harvey Moldofsky1, Herbert W. Harris2, Tad Archambault3, Terence Kwong4 and Seth Lederman5. 1Centre for Sleep & Chronobiology, Toronto, ON, Canada; 2Krele Pharmaceuticals, Saddle Brook, NJ; 3Krele Pharmaceuticals, New York, NY; 4VirtuStat Ltd, North Wales, PA

**Background:** The importance of nonrestorative sleep in the pathophysiology of FMS suggests new treatments that improve sleep quality may improve daytime symptoms of fibromyalgia (FMS). We previously reported a randomized double-blind placebo-controlled 8 week study of very low dose (VLD) (≤4 mg) cyclobenzaprine (CBP) h.s. in 36 patients with FMS, which showed that bedtime CBP treatment (Tx) was associated with significant improvements in pre-sleep/p.m. fatigue, pain, and pain sensitivity (dolorimetry) with increased Stage 2 non-REM sleep (ref 1). Previous EEG sleep studies in FMS identified increased Cyclic Alternating Patterns (CAP) A2 & A3 in non-REM sleep, measures of sleep instability related to the symptoms of FMS (ref 2 & 3). We now report the effect of CBP Tx on nocturnal sleep EEG CAP and daytime fatigue in FMS.

**Methods:** CAP A2 & A3 rates are objective EEG sleep measures of sleep instability whereas CAP A1 rate is associated with sleep stability. To investigate whether the CAP A2 & A3 rates are decreased by Tx that target unrefreshing sleep in FMS patients, we retrospectively analyzed the polysomnography (PSG) data from a study in which bedtime CBP improved fatigue, pain and subjective sleep in a 8 week dose-escalating, double-blind, placebo-controlled randomized trial involving 36 FMS subjects. Each subject had screening and baseline PSGs (combined 2 pre-Tx PSGs) and 3 single nights of PSG during Tx after 2, 4 and 8 weeks. We analyzed whether subjects had an increased number of nights with decreased CAP(A2+A3) before the initiation of Tx by classifying the subjects nightly into responders and non-responders based on a CAP(A2+A3) rates normalized for the total CAP rate (A1+A2+A3). Three placebo-Tx subjects, but no CBP-Tx subjects, withdrew from the study after initiation of Tx and without any nights of PSG. Consequently, the LOCF analysis imputed no improvement for these subjects.

**Results:** Initially we analyzed the study data for CAP(A2+A3)/(A1+A2+A3) over a range (10–50%) to identify cut-offs for responders by LOCF and OC (for ≥ 1 night improvement) and found that defining responders as ≥30% or ≥33% had the greatest difference between CBP and placebo-Tx and the smallest p-value (p<0.05). CAP response of ≥1 night of sleep EEG analyses that compared 2 pre-Tx drug free nights to 3 post-Tx PSG nights (defined by CAP(A2+A3)/(A1+A2+A3) ≤33% was analyzed for correlations with clinical improvement measures of patient-reported fatigue (pre-sleep/p.m. and post-sleep/a.m.); pain (p.m. and a.m.) and dolorimetry. Reduction in p.m. fatigue in CBP-Tx subjects is significantly correlated with CAP response (p = 0.0064), whereas p.m. fatigue was neither decreased nor correlated with responder status in placebo-Tx subjects.

**Conclusions:** 1. Normalized CAP A2 & A3 rates are novel physiological sleep EEG indices of nonrestorative sleep in FMS. 2. Very low dose CBP at bedtime decreases CAP A2 & A3 sleep EEG measures of nonrestorative sleep which correlates strongly with improvement in p.m. fatigue in FMS patients.

**References:**

**Disclosure:** H. Moldofsky: Krele Pharmaceuticals, 2; H. W. Harris: Krele Pharmaceuticals, 1, 3; T. Archambault: Krele Pharmaceuticals, 4, 5; VirtuStat Ltd., 4, 5; T. Kwong: Krele Pharmaceuticals, 2; S. Lederman: Krele Pharmaceuticals, 1, 9.
Vibrotactile Analgesia Is Not Abnormal in Fibromyalgia Patients.

Vibrotactile analgesia formerly known as Gate-Control analgesia is dependent on input from myelinated A-beta nerve fibers during noxious stimuli. This type of analgesia can be elicited by vibrotactile stimulation either homotopically or heterotopically to a pain stimulus. Because multiple endogenous analgesic mechanisms including diffuse noxious inhibitory controls (DNIC) and spatial summation have been found to be abnormal in fibromyalgia (FM) patients and may contribute to the clinical pain of this chronic pain population, we hypothesized that another analgesic mechanism i.e. vibrotactile analgesia would also be deficient in FM patients.

Methods: 28 normal control (NC) and 29 FM subjects were enrolled into this protocol. Mean age was 30 (10.7) and 39 (11.1) years for NC and FM subjects, respectively. The overall clinical pain of FM subjects was 4.2 (2.1) VAS units. The NC were pain-free. A bio-thesimeter was used for application of 25 mA vibratory stimuli to the forearms. Sensitivity to 10 sec heat stimuli (MEDOC) between 42 and 50 deg C were used to elicit heat pain ratings of 3.5 ± 0.5 VAS units (0–10) at the forearms of all subjects.

Results: When vibrotactile and noxious stimuli were simultaneously applied to the forearms NC and FM subjects experienced a 46% and 35% reduction in experimental pain intensity, respectively. These pain reductions were similar for homotropic and heterotropic stimulation. Vibrotactile analgesia was not statistically different between NC and FM subjects.

Conclusion: Vibrotactile stimulation of the skin resulted in substantial experimental pain reductions of FM patients. Thus not all types of endogenous analgesic mechanisms seem to be dysfunctional in FM patients. Furthermore, vibrotactile analgesia may represent a clinically relevant method of pain reduction for FM patients.

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A Putative Functional Variant within the Ubiquitin-Associated Domain-Containing Protein 2 Gene (UBAC2) Is Associated with Increased Risk of Behcet’s Disease.

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Purpose: Using a genome-wide association scan and DNA pooling, we previously identified 5 novel genetic susceptibility loci for Behcet’s disease. Herein, we fine-map the genetic effect within the UBAC2 gene, replicate this genetic association in an independent cohort of Behcet’s disease patients and controls, and identify a functional polymorphism in this locus.

Methods: Two independent cohorts of Behcet’s disease patients and controls from Turkey were studied. The discovery and replication cohorts included 152 patients and 172 controls, and 376 patients and 369 controls, respectively. Genotyping of 14 SNPs within and around UBAC2 was performed using TaqMan SNP genotyping assays.

Results: The genetic association between Behcet’s disease and UBAC2 was established and confirmed in two independent cohorts of patients and controls (Meta-analysis OR = 2.05, meta-analysis P = 1.75 × 10−7). Haplotype analysis identified both a disease risk and a protective haplotype (P = 0.00014 and 0.0075, respectively). Using conditional haplotype analysis we identified that the SNP rs7999348 (A/G) within UBAC2 is the most likely SNP to explain the genetic effect in this locus. Indeed, we demonstrate that rs7999348 is a putative functional SNP that results in increased mRNA expression of a UBAC2 transcript variant in PBMCs of individuals homozygous for the Behcet’s disease-associated “G” allele.

Conclusion: We establish and confirm the genetic association between UBAC2 and Behcet’s disease in two independent cohorts of patients and controls. Fine mapping of this genetic effect and conditional analysis followed by functional studies identified the minor allele in rs7999348 as a disease-risk allele that alters UBAC2 expression.

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A Role for PACE4 in Pain in Mice and Humans: Pain Phenotype of a PACE4 Null Mutant and Genetic Association with Knee Osteoarthritis Pain.


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Background: PACE4 is a member of the proprotein convertase family of serine proteases essential for the proteolytic maturation of a wide variety of proteins, including growth factors, hormones, and zymogens. We recently reported that PACE4 activates the aggrecanases, ADAMTS-4 and ADAMTS-5, in human osteoarthritic (OA) cartilage. The aim of the current study was to assess if genetic variants in the PACE4 gene are implicated in the risk for knee OA.

Methods and Subjects: The rs900414 single nucleotide polymorphism (SNP) in the PACE4 gene (PCSK6) was genotyped in three independent cohorts (“Discovery”: 508 symptomatic knee OA cases, 159 asymptomatic knee OA, and 276 controls; “Clearwater”: 85 symptomatic and 92 asymptomatic knee OA cases, and “Chingford” 62 symptomatic, 157 asymptomatic knee OA cases, and 527 controls). In follow-up to the human findings, PACE4 KO mice and wildtype littermates (C57BL/6) were tested on a battery of algesiometric assays, including mechanical and thermal hypersensitivity in response to intraplantar administration of substance P (SP) (2.5–20 ng), and for pain behavior in response to intracerebral SP (5–45 ng) or in response to intraperitoneal injection of 0.6% acetic acid.

Results: The minor allele at rs900414 (allele frequency 32%) was found to be significantly associated with symptomatic OA in the discovery samples and to be consistently increased among asymptomatic OA cases compared to symptomatic knee OA in all three cohorts. A fixed-effects meta-analysis yielded OR = 1.34 (95% CI 1.09 – 1.64) p = 0.005 (Figure 1) and no between-study heterogeneity was observed (I2 = 0%). PACE4 KO mice displayed normal baseline sensitivity to thermal and mechanical stimuli as assessed by paw withdrawal, von Frey, tail-clip, hot-plate and tail-withdrawal tests. However, PACE4 KO mice developed significantly less thermal and mechanical hypersensitivity in response to intraplantar injection of SP. In addition, intracerebral injection of substance P resulted in a dose-dependent induction of paw behaviors (scratching, fluffing, and licking) in wildtype but not in PACE4 KO mice. Moreover, compared to wildtypes, PACE4 KO mice showed >50% less pain behavior in the acetic acid writhing test.

Conclusions: These results suggest that the rs900414 SNP in the human PACE4 gene is strongly associated with protection against pain in knee OA. Studies in PACE4 KO mice further implicate PACE4 in pain.
Objective: Two functional single nucleotide polymorphisms (SNPs) in the PTPN22 gene (R620W, C1858T, rs2476601; and R26Q, rs788A, rs3396649) have been previously associated with autoimmune diseases. The aim of the present study was to investigate the role of the R26Q SNP for the first time and to re-evaluate the role of the R620W PTPN22 polymorphism in the genetic predisposition to systemic sclerosis (SSc) susceptibility and clinical phenotypes.

Methods: A total of 3422 SSc patients (2020 with limited cutaneous SSc (lcSSc) and 1208 with diffuse cutaneous SSc (dcSSc)) and 3638 healthy controls from an initial case-control set of Spanish Caucasian ancestry, as well as seven independent replication cohorts of Caucasian ancestry (from Belgium, England, Germany, Italy, the Netherlands, USA, and Sweden), were included in our study. Genotyping was performed using the TaqMan allelic discrimination assay for both the rs3396649 and the rs2476601 PTPN22 polymorphisms. A meta-analysis was then performed to test the overall effect of the PTPN22 gene polymorphisms in SSc.

Results: We observed evidence of association of the rs2476601 T allele with SSc susceptibility in the meta-analysis results (P=0.01 pooled, OR=1.15, 95% CI 1.03–1.28). Moreover, the rs2476601 T allele is significantly associated with anti-centromere (ACA) positive status (P=0.01 pooled, OR=1.22, 95% CI 1.05–1.42). Although we found that the rs3396649 A allele was significantly associated with SSc in the Spanish population (P=0.02, OR=0.83, 95% CI 0.73–0.91), this association was not confirmed in the meta-analysis (P=0.36 pooled, OR=0.89, 95% CI 0.72–1.1).

Conclusion: Our study suggests that the PTPN22 R620W polymorphism influences SSc genetic susceptibility but that the novel R26Q variant does not. Moreover, our data strengthen the evidence that the R620W mutation is a common risk factor in autoimmune diseases.

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BLK Is Expressed in Human Peripheral T Cells and Thymocytes and Regulates CD4+ T Cell Numbers in Cord Blood. Kim R. Simpfendorfer1, Lisa Olsson1, Natały Manjarz-Orduño2, Hourman Khalifi3, Annette T. Lee4 and Peter K. Gregersen1. 1Feinstein Institute for Medical Research, Manhas- sett, NY, 2Feinstein Institute for Medical Research

Background: B-lymphocyte kinase (BLK) is an intracellular tyrosine kinase previously presumed to exert its major function in B cells. SNP variants in the 5’UTR/ promoter region of BLK lie on a common haplotype that is associated with both rheumatoid arthritis and lupus. In humans the functional affect of BLK risk alleles to disease susceptibility is yet to be elucidated. The risk haplotype has been associated with lower mRNA expression of BLK in human B cell lines. In mice, BLK expression is reportedly restricted to B cells, yet BLK knockout animals fail to exhibit a phenotype. Interestingly, both naïve and memory B cells fail to show allelic imbalance for BLK in humans, and while B cell activation lowers the expression of BLK, the risk allele shows no difference in rates of downregulation. Therefore, it is possible that in humans the influence of BLK on autoimmunity may be mediated at a particular stage of B cell differentiation, or by a non-B cell compartment. Recently, our laboratory demonstrated allelic imbalance of BLK in peripheral blood CD4+ T cells.

Analytical procedures and results: We examined the influence of BLK genotypes on BLK expression and the distribution of T and B cell populations in human umbilical cord blood, peripheral blood and thymus. Western blot and quantitative RT-PCR was used to examine BLK expression and flow cytometry was performed to compare immune cell populations

Results: We found that BLK is expressed in thymocytes and purified CD4+ T cells in humans at both the mRNA and protein level, with higher expression in the thymus than in mature peripheral blood T cells. Furthermore, similar to human B cell lines, the BLK risk haplotype exhibits evidence of lower expression in both T cells and human thymus. In healthy individuals homozygous for the BLK risk allele (A/A) there is a significantly greater
proportion of CD4+ T cells than in individuals homozygous for the protective allele (T/T).

Conclusions: These data suggest that the causative Blk allele may play a role in disease pathogenesis by its action in CD4+ T cells as opposed to, or in addition to, B cells. Future studies will examine mRNA expression of Blk, FoxP3 and cytokine expression in CD4+ T cells and phosphorylation of signalling molecules in UCB and thymus samples to further dissect the role of BLK in CD4+ T cell numbers and function.

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Epigenetic Studies Characteristic of Muscle Biopsies (MBs) from Un- treated Children with Juvenile Myositis (JM), Lauren M. Pachman, Min Wang, Heuhung Xie, Peter Hendrickson, Sheela Shrestha and Gabrielle Morgan. Children’s Memorial Research Center, Chicago, IL

Background: Previous Affymetrix array-based gene expression studies of muscle biopsies (MBx) from children with definite/probable juvenile dermatomyositis (JDM) showed that, despite a florid display of IFN-α induced genes, patients with a longer duration of untreated disease (DUD) >2 months had a marked upregulation of genes related to vascular remodeling compared with muscle from JDM with a DUD of 2 months or less (Chen Y-W. Duration of chronic inflammation alters gene expression in muscle from untreated girls with juvenile dermatomyositis, BMC Immunol. 2008 Jul 31;9:43).

Objective: To profile the methylation patterns in a cohort of children with JDM in order to determine: 1) the impact of methylation alterations in JDM, and 2) the association of methylation profiles with the chronicity of the inflammatory response as determined by DUD.

Materials and Methods: DNA from diagnostic MBx from 20 white girls and boys (mean age 6.4 ± 3.5 yrs) with definite/probable JDM were used for this study: five with DUD ≤2 mos; 15 with DUD >2 mos at MBx were compared with four age-, gender- and race-matched controls. The DNA was tested using the Illumina Methylation27 BeadChip for genome-wide methylation profiling and further analyzed with GenomeStudio Data Analysis Software. Bisulfitie pyrosequencing confirmed DNA methylation from 10 matched controls and 71 children with a spectrum of juvenile myositis (56 JDM, 7 overlap, 5 juvenile polymyositis [JPM], and 3 other). The patient population (50/71 girls, mean age 7.6 ± 4.1 yrs) included 41 white, 14 Hispanic and 16 others. Among the 71 patients, 54 of them had DUD ≥2 mos untreated symptoms.

Results: In the first part of this study, 20 untreated JDMs displayed distinct methylation profiles from the four age-, gender-, and race-matched controls. Twenty-two genes showed significant differential methylation, including WT1 and the transcriptional regulation genes HOXC11, HOXD4 and EMX2. Specific pyrosequencing studies confirmed the Illumina methylation profiles for both hypo and hypermethylation responses respectively. Further investigation of WT1 methylation status in 71 JDM muscle samples showed no significant difference in methylation within JDM samples with respect to the specific JDM diagnosis vs other forms of JM, DUD, race, age at MBx, TNF-α-308 A allele, or treatment status at MBx.

Conclusions: Epigenetic studies of untreated JDM muscle showed specific patterns of methylation alteration, including WT1, which targets Bcl2, a critical factor in apoptosis. Unlike the gene expression and microRNA expression studies of JDM diagnostic muscle biopsies, disease chronicity, as measured by DUD, does not appear to alter the DNA methylation profiles.

Speculation: We speculate that further epigenetic studies will be highly informative, suggesting new concepts concerning the pathophysiology of JDM.

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Functional Change of 5-Aminomidazole-4-Carboxamide Ribonucleotide Formyltransferase in Dermal Fibroblasts from Methotrexate-Sensitive and Resistant Mice. Xin You1, Bruce N. Cronstein2, Adrienne Williams3 and Thierry Dervieux1. 1Cypress Pharmaceuticals, 2NYU

Background: Methotrexate (MTX) has been widely used in the treatment of RA but it is effective in only 60% of patients and its mechanism is complex. To date, the adenosine-mediated anti-inflammatory effect of MTX is best supported by the in vitro, in vivo, and clinical data. Pharmacogenetic studies indicate that genetic polymorphisms in adenosine pathway enzymes are associated with good response to MTX therapy in RA and animal experiments showed that MTX suppressed inflammation in air pouches of C57Bl/6 and BALBc, but not DBA/1J mice. To investigate the mechanism for genetically based resistance to the anti-inflammatory effect of MTX, functional change of a critical enzyme in MTX metabolism and the adenosine pathway, 5-aminomidazole-4-carboxamide ribonucleotide formyltransferase (AICAR TF) was measured.

Methods: Dermal Fibroblasts (DF) from BALBc and DBA/1J mice were cultured from skin. Following MTX incubation with DFs, AICAR TF activity before and after MTX treatment was analyzed after preparation of (6R,6S)-10-formyltetrahydrofolate from 5,10-Methylenetetrahydrofolate. Protein concentration was determined by the Bradford protein assay. AICARFT activity was monitored by the formation of HFA at 4 min using a Perkin-Elmer Lambda2 spectrophotometer. In addition, MTX polyglutamate (pg) concentration was measured and AICAR TF mRNA was quantitated by real time (RT) PCR.

Results: In silico analysis of the sequence of folyl polyglutamate synthase and AICAR TF indicate differing haplotypes of the enzymes in BALB/c and DBA/1J mice. MTX treatment inhibited AICAR TF activity in DF from BALBc mouse in a dose-dependent manner (2.61 nmol/μg.min, 1.00 nmol/μg.min, and 0.99 nmol/μg.min at the dose of MTX 0, 10-7M, and 10-6M, respectively). Seventy percent decrease was observed at MTX 10-6M. AICAR TF activity was not reduced in DF from DBA/1J mouse by MTX, and even increased after hydrogen peroxide stimulation with MTX (1.98 nmol/μg.min, 2.78 nmol/μg.min, and 3.83 nmol/μg.min at the dose of MTX 0, 10-7M, and 10-6M, respectively). The cellular concentration of MTXPG in BALBc fibroblasts is more than 2-fold greater than that observed in DBA/1J fibroblasts at MTX 10-6M. There is no significant difference in AICAR TF mRNA in DFs between BALBc and DBA/1J mice.

Conclusions: Genetic polymorphisms of the critical enzymes involved in MTX metabolism and the adenosine pathway contribute to the different responses to MTX in the treatment of Rheumatoid Arthritis.

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Functional Polymorphisms in the Inhibitory FCGR2B Associate with Efficacy of IVIG Treatment Response among Patients with Kawasaki Disease. Sadeep Shrestha1, Howard W. Wiener1, Aditi Shendre2, Richard A. Kaskow1, Aaron K. Olson1, Mary Beth Lee1, Jeffrey C. Edberg1 and Michael Portman1. 1Department of Epidemiology, University of Alabama at Birmingham, 2Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, 3Department of Pediatrics, University of Washington, Seattle Children’s Hospital, 4Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham

Background: Intravenous immunoglobulin (IVIG) is the principal treatment for Kawasaki disease (KD). Approximately 20% of KD patients in US are refractory to IVIG, and display higher coronary artery disease and aneurysm rates than those non-refractory. Studies in animal model systems have demonstrated a requirement for expression of the inhibitory Fc receptor FCGR2B in IVIG therapeutic responses. We hypothesized that naturally occurring functional SNP variants in the human FCGR2B gene would influence efficacy of IVIG treatment in patients with KD.

Methods: We examined three well-characterized and functionally relevant SNPs in the inhibitory FCGR2B gene among 197 patients (104 European-American (EA), 47 Asians, 46 Other) with KD (based on criteria recommended by the American Heart Association) that had been treated with IVIG as standard of care. Among these patients, 56 were defined as non-responders (persistent fever (temperature >38°C) at >36 hours from the initiation of IVIG infusion or a recurrent fever at >36 hours after completion of the initial IVIG infusion) and 141 as responders. SNPs chosen for study are 2 promoter variants at −120 and −386 that alter transcription factor binding and quantitative gene expression and a non-synonymous SNP in the transmembrane region of the protein that alters lipid domain association and quantitative inhibitory potential. Genotyping was performed by Pyrosequenc-
ing. Race and ethnicity were genetically determined using Principle component analysis with 162 ancestry informative markers.

Results: Significant association between all of the functional FCGR2B variants and IVIG response were observed in EA patients. Both the more active promoter variants (−120A→366C, OR = 4.46 [1.30–15.3], p = 0.01/ OR = 4.38 [1.28–15.1], p = 0.01 respectively) and the more functionally active non-synonymous variant in the transmembrane domain (+775T, OR = 2.38 [1.00–5.88], p = 0.05) were positively associated with IVIG response. The 2 promoter variants are in complete linkage disequilibrium and are not independent effects. Because of lower allele frequency and smaller sample size in the other populations, we did not have sufficient power to demonstrate associations between FCGR2B variants and IVIG responses.

Conclusions: Our data are the first to demonstrate a genetic basis in humans for IVIG responses in KD. The known functional consequences of the variants in FCGR2B that associate with IVIG response result in high receptor expression and function and thus are biological plausible and consistent with murine model studies demonstrating a requirement for FCGR2B in IVIG efficacy. Replication of these findings could suggest a role for screening of patients for FCGR2B genotypes prior to treatment.

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Functional Variants in the Pre-B Cell Colony Enhancing Factor Gene Are Associated with Systemic Sclerosis Susceptibility and the Clinical Hallmark Pulmonary Arterial Hypertension

Jasper Broen 1, Pravit Gourhi 1, Madelon Vonk 1, Lorenzo Beretta 1, Blanca Rueda 1, Lenny Geurts-van Bon 1, Christel Brouwer 1, Roger Hesselstrand 2, J. C. Edberg 1, none; M. Portman 1.

Background: Gene expression analyses in patients with systemic sclerosis (SSc) and pulmonary arterial hypertension (PAH) have identified several immune regulatory genes that may influence the predisposition to pulmonary artery hypertension. The Pre-B cell colony enhancing factor (PBEF) gene is a strong candidate, as PBEF overexpression leads to development of pulmonary and systemic fibrosis in animal models. Here we report associations between FCGR2B polymorphisms and IVIG responses in KD. The known functional consequences of the variants in FCGR2B that associate with IVIG response result in high receptor expression and function and thus are biological plausible and consistent with murine model studies demonstrating a requirement for FCGR2B in IVIG efficacy. Replication of these findings could suggest a role for screening of patients for FCGR2B genotypes prior to treatment.

Methods: For gene expression analysis using cDNA microarray technology, samples of thymus, blood, and synovium were collected from CIA and control rats on days 0, 1, 4, and 9 after the first immunization. Labeled cRNA samples were hybridized to each Rat-12 expression bead array for 16–18 h at 58°C, according to the manufacturer’s instructions (Illumina, Inc., San Diego, USA). Detection of array signal was carried out using Amersham fluorolink streptavidin-Cy3 (GE Healthcare Bio-Sciences, Little Chalfont, UK) following the bead array manual. Arrays were scanned with an Illumina bead array Reader confocal scanner according to the manufacturer’s instructions. Array data export processing and analysis was performed using Illumina BeadStudio. We also performed real-time RT-PCR to validate our microarray findings.

Results: Of the 22,517 genes on the array, 1,243 genes were differentially expressed at least 2 fold in various organs of CIA compared to controls. Even on day 1, over 300 genes were differentially expressed in the synovium of CIA.

Systemic sclerosis (SSc) is a rare autoimmune disorder, characterized by severe vasculopathy and fibrosis of the skin and internal organs. The most severe complication is pulmonary artery hypertension (PAH). Several variants in immune regulatory genes have already been implicated in SSc. The PBEF gene plays an important role in immune modulation, and two polymorphisms in the promoter region, namely PBEF −1001TG>G (rs9770242) and PBEF −1543C>T influence the predisposition to pulmonary disease. For this reason we investigated the role of these two polymorphisms in the genetic predisposition to systemic sclerosis (SSc) and clinical phenotype susceptibility in 2737 SSc patients and 1913 healthy controls. In two separate populations and in a meta-analysis, the combined PBEF −1543C/T −1001TG genotype, was found associated with SSc susceptibility (P = 0.009 OR 1.20 [95% CI: 1.05–1.37]). In addition, these subjects showed an increased decline in forced vital capacity (FVC) over 15 years (P = 0.02) (RR 1.64, 95% CI: 1.02–2.64) and a higher PBEF serum concentration (P < 0.01), compared to carriers of the minor alleles. On the other hand, patients with genotype PBEF -1001TT were at lower risk for PAH development compared to the carriers with genotypes PBEF −1001TG and PBEF −1001TG (P < 0.001) (RR 3.29, 95% CI: 1.52–7.12). These results reveal an important role for PBEF in the genetic predisposition to SSc and its clinical hallmark PAH.

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Gene Expression Profile at the Initial Phase of Collagen-Induced Arthritis in the Synovium, Peripheral Blood and Thymus

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Background: Current management strategies aim to detect rheumatoid arthritis (RA) at an early stage. Transcription profiling is applied in the search for biomarkers for detecting early stage disease. Peripheral blood T cells in RA show incomplete activation which is unclear whether this process occurs in the peripheral or central lymphoid organs. Even though gene profilings in several RA animal models have been reported previously, most of these studies were performed after active arthritis developed and only in the peripheral organs.

Objective: To explore gene expressions at the initial phase of collagen induced arthritis (CIA) before the arthritic features develop in the synovium, peripheral blood and thymus.

Methods: For gene expression analysis using cDNA microarray technology, samples of thymus, blood, and synovium were collected from CIA and control rats on days 0, 1, 4 and 9 after the first immunization. Labeled cRNA samples were hybridized to each Rat-12 expression bead array for 16–18 h at 58°C, according to the manufacturer’s instructions (Illumina, Inc., San Diego, USA). Detection of array signal was carried out using Amersham fluorolink streptavidin-Cy3 (GE Healthcare Bio-Sciences, Little Chalfont, UK) following the bead array manual. Arrays were scanned with an Illumina bead array Reader confocal scanner according to the manufacturer’s instructions. Array data export processing and analysis was performed using Illumina BeadStudio. We also performed real-time RT-PCR to validate our microarray findings.

Results: Of the 22,517 genes on the array, 1,243 genes were differentially expressed at least 2 fold in various organs of CIA compared to controls. Even on day 1, over 300 genes were differentially expressed in the synovium of CIA.

Systemic sclerosis (SSc) is a rare autoimmune disorder, characterized by severe vasculopathy and fibrosis of the skin and internal organs. The most severe complication is pulmonary artery hypertension (PAH). Several variants in immune regulatory genes have already been implicated in SSc. The PBEF gene plays an important role in immune modulation, and two polymorphisms in the promoter region, namely PBEF −1001TG>G (rs9770242) and PBEF −1543C>T influence the predisposition to pulmonary disease. For this reason we investigated the role of these two polymorphisms in the genetic predisposition to systemic sclerosis (SSc) and clinical phenotype susceptibility in 2737 SSc patients and 1913 healthy controls. In two separate populations and in a meta-analysis, the combined PBEF −1543C/T −1001TG genotype, was found associated with SSc susceptibility (P = 0.009 OR 1.20 [95% CI: 1.05–1.37]). In addition, these subjects showed an increased decline in forced vital capacity (FVC) over 15 years (P = 0.02) (RR 1.64, 95% CI: 1.02–2.64) and a higher PBEF serum concentration (P < 0.01), compared to carriers of the minor alleles. On the other hand, patients with genotype PBEF -1001TT were at lower risk for PAH development compared to the carriers with genotypes PBEF −1001TG and PBEF −1001TG (P < 0.001) (RR 3.29, 95% CI: 1.52–7.12). These results reveal an important role for PBEF in the genetic predisposition to SSc and its clinical hallmark PAH.

Disclosures: J. Broen: None; P. Gourhi: None; M. Vonk: None; L. Beretta: None; B. Rueda: None; L. Geurts-van Bon: None; C. Brouwer: None; R. Hesselstrand: None; J. Worthington: None; N. Hunzemann: None; C. Denton: None; C. Fonseca: None; G. Riemeikasten: None; H. Kiener: None; R. Scorza: None; C. Simon: None; N. Ortego-Centeno: None; M. Gonzalez-Gay: None; P. Airo: None; M. Coenen: None; M. Mayes: None; D. Kiburz: None; F. Arnett: None; J. Martin: None; T. Radstake: None.
The differential expressions of \( \text{cd3}\zeta \), \( \text{cd3}\delta \), \( \text{cd8}\alpha \), \( \text{cd8}\beta \) in CIA, as revealed by real-time RT-PCR, agreed well with the microarray data.

Conclusions: This study provides evidence that the most genes start to express differentially on day 1 after the first immunization in CIA. And the downregulation of \( \text{cd3}\zeta \), \( \text{cd3}\delta \), \( \text{cd8}\alpha \), \( \text{cd8}\beta \) occurs just in the synovium at the initial phase of CIA, which might play a role in the pathogenesis of CIA.

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Genetic Variants Associated with Susceptibility to Knee Osteoarthritis: The Johnston County Osteoarthritis Project. Xiaodong Wu\(^1\), Venkateswarlu Kontragunta\(^4\), Jordan B. Renner\(^2\), Gordon W. Duff\(^5\), Kenneth S. Kornman\(^1\) and Joanne M. Jordan\(^1\). \(^1\)Chapel Hill, NC, \(^2\)Department of Radiology and Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, \(^3\)Interleukin Genetics, Inc., Waltham, MA, \(^4\)Interleukin Genetics, Inc., \(^5\)School of Medicine, University of Sheffield

**Purpose:** Factors that differentiate individuals who develop osteoarthritis (OA) from those who do not may be valuable in developing prevention strategies. Although several genetic variants have been associated with susceptibility to OA, most have not been replicated in adequately sized cohorts. We therefore sought to validate genetic variants predictive of OA susceptibility in a Caucasian patient sample in the United States, in a population-based study.

**Method:** Caucasian participants (N=1,173; 38% men; mean age=60 years) in the Johnston County OA Project were examined for susceptibility to radiographic knee OA in a cross-sectional analysis. Anterior-posterior standing knee radiographs were obtained with footmort positioning and read by a single musculoskeletal radiologist for Kellgren-Lawrence grade (K-L, 0–4). OA cases were defined as having K-L\( \geq 2 \) in at least one knee. Non-OA controls were defined as having K-L=0 in both knees. Genotypes of 37 single nucleotide polymorphisms (SNPs) in 16 genes, including gene variants previously shown to be associated with OA and variants in genes that are functionally implicated in OA, such as the proinflammatory IL-1\( \beta \) gene family, were determined using the single-nucleotide primer extension method. Logistic regression with adjustment for age, gender and body mass index was used to determine associations between gene polymorphisms and susceptibility to radiographic knee OA.

Since this was not an exploratory analysis, we analyzed the data without correction for multiple comparisons, but also report the results of a permutation test for multiple comparisons. An association was considered a positive validation if the p-value after adjustment for age, gender and BMI\(< 0.05\) for the risk allele, genotype or haplotype previously reported to be associated with OA.

**Results:** Out of 16 genes tested, 6 were significantly associated with susceptibility to radiographic knee OA. These included ABCG2, GDF5, IL1R1, IL1RN, IL6 and VDR genes (table 1). VDR rs731236 also showed significance after correction for multiple comparisons.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Allele/ genotype</th>
<th>OR 95% CI LL</th>
<th>OR 95% CI UL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDF5</td>
<td>rs143383</td>
<td>C/C</td>
<td>0.57</td>
<td>0.36</td>
<td>0.91</td>
</tr>
<tr>
<td>VDR</td>
<td>rs1544410</td>
<td>T/*</td>
<td>1.51</td>
<td>1.07</td>
<td>2.13</td>
</tr>
<tr>
<td>IL6</td>
<td>rs1800797</td>
<td>A</td>
<td>1.38</td>
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<td>1.74</td>
</tr>
<tr>
<td>ABCG2</td>
<td>rs2231142</td>
<td>A/*</td>
<td>0.64</td>
<td>0.42</td>
<td>0.97</td>
</tr>
<tr>
<td>IL1R1</td>
<td>rs2287047</td>
<td>T</td>
<td>0.74</td>
<td>0.56</td>
<td>0.97</td>
</tr>
<tr>
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<td>T/T</td>
<td>0.59</td>
<td>0.33</td>
<td>0.96</td>
</tr>
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<td>C/*</td>
<td>1.69</td>
<td>1.19</td>
<td>2.39</td>
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</tbody>
</table>

**Conclusion:** This study validated several genetic markers for association with susceptibility to radiographic knee OA in a population-based study of Caucasians.


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HLA-DRB1*04 Is a Novel Fetal Susceptibility Allele in Congenital Heart Block. Therese Östberg\(^2\), Stina Salomonsson\(^3\), Bo Ding\(^8\), Håkan Eliasson\(^5\), Lars Alfredsson\(^1\), Lars Kläreskog\(^7\), Anders Hamsten\(^7\), Tomas Olsson\(^5\), Leonid Padyukov\(^6\), Tomas Axéll\(^7\), Swedish Congenital Heart Block Study Group\(^7\), Fredrik Gadler\(^4\), Anders Jonzon\(^6\), Sven-Erik Sonesson\(^3\), Ingrid Kockam\(^4\) and Marie Wahren-Herlenius\(^4\). \(^1\)Department of Medicine, Karolinska Institutet, Stockholm, \(^2\)Department of Medicine, Karolinska Institutet, \(^3\)Department of Women and Child Health, Karolinska Institutet, \(^4\)Karolinska Institutet, \(^5\)Karolinska University Hospital, Stockholm, Sweden, \(^6\)Uppsala University, \(^7\)www.combinesweden.se

**Objective:** Congenital heart block may develop in the fetus of Ro52 autoantibody positive women. The reported recurrence rate for autoantibody associated congenital heart block is however only 10–25%, indicating that other factors than maternal autoantibodies influence the disease development and fetal outcome. The most potent genetic influence on susceptibility to autoimmune diseases is the HLA locus, and as there is a strong and well-known HLA-DR*04 allele association with SLE, Sjögren’s syndrome and production of Ro/SSA autoantibodies, we hypothesized that specific alleles of the HLA locus may render the fetus susceptible to congenital heart block induced by maternal autoantibodies.

**Methods:** Genotyping was performed for 561,490 SNPs in DNA from 348 individuals of 88 Swedish Caucasian families with a Ro/SSA autoantibody positive mother and with at least one case of congenital heart block (83 mothers and 72 fathers, 92 index cases and 101 unaffected siblings). Full HLA-A, -C and HLA-DRB1 allele typing was performed by SSP-PCR in 60 families with complete trio, Swedish Caucasian population-based controls from the EIRA (n=1056) and PROCARDIS (n=654) studies were used in case-control association analysis. Genetic linkage was analyzed by transmission disequilibrium test (TDT).

**Results:** A case-control analysis between the index cases and population-based controls revealed an association of congenital heart block with 6 SNPs in the 6p21 MHC locus at a genome-wide significance of \( p=5\times10^{-8} \) (OR\( 2.57-3.12 \)). In family-based TDT analysis of distinct MHC class I and II alleles we observed an association of the HLA-DR*04 allele with congenital heart block, and that this variant was significantly more often transmitted to children that developed congenital heart block (\( p=0.01 \)). No difference in the transmission frequency of the DRB1*04 allele from mothers (maternal DRB1*04 allele frequency 7.6%) compared with fathers (paternal DRB1*04 allele frequency 20.8%) was observed. No other HLA-DRB1, -A or -C association with congenital heart block was found. The previously described HLA-DRB1*043 association in the mothers compared with controls was observed also in our cohort, and 79.7% of the mothers carried DRB1*04.3

**Conclusions:** Our study identifies HLA-DRB1*04 as a novel fetal genetic variant that confers susceptibility to develop congenital heart block in response to exposure to Ro/SSA autoantibodies, and indicates equal maternal and paternal genetic influence on fetal susceptibility to maternal autoantibody exposure.

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IL13 Is a Risk Locus for Psoriatic Arthritis but Not Psoriasis Vulgaris.

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Background: Psoriasis vulgaris (PsV) is a chronic inflammatory skin disease in which up to 30% of subjects have additional joint involvement. This has led to psoriatic arthritis (PsA) being recognised clinically as a distinct entity. Both conditions are complex diseases influenced by environmental and genetic factors. All the currently known genetic risk factors are shared between the two conditions. The identification of genetic risk factors that could differentiate the two diseases would allow a better understanding of why some patients with PsV develop arthritis. Two recent PsV genome-wide association studies, both containing a significant proportion of PsA cases, identified an association to the Interleukin 13 (IL13) gene as a susceptibility risk factor. However further investigation of this effect in one study found it to be primarily restricted to those individuals with PsA, thus suggesting the risk factor is specific for PsA, thus highlighting the first key biological pathway that permits us to predict diagnosis of OA. This models also included clinical variables such as gender, age and smoking status.

Methods: Both SNPs (rs20541 and rs1800925) mapping to the IL13 gene were genotyped in 1057 PsA patients and 1136 PsV patients using the Sequenom genotyping platform. Control data for 5575 healthy individuals was available from the WTCCC2 genotyped on the Illumina Human IM-Duo platform. Association tests, Hardy-Weinberg equilibrium (HWE), and linkage disequilibrium (LD) were performed using the PLINK software package. Additional analyses were performed in phenotypic subgroups of PsA (Type I or II psoriasis and seronegative for rheumatoid factor).

Results: Both SNPs were in HWE and found to be highly associated with susceptibility to PsA (rs1800925: p = 6.1x10^-13, OR = 1.33 CI 1.16:1.53, rs20541: p = 8.0x10^-4, OR = 1.27 CI 1.10:1.45), but neither was associated with PsV. LD between the SNPs, calciuim risk in the control samples, was found to be low (r^2 = 0.23). Sub-phenotype analysis revealed that the two SNPs remained associated with PsA in patients with both type I and type II psoriasis.

Conclusions: This study confirms that the effect of IL13 risk locus is specific for PsA, thus highlighting the first key biological pathway that differentiates PsA from PsV. The identification of markers that differentiate the two diseases raises the possibility in the future of allowing screening of PsV patients to identify those at risk of developing PsA.

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Hanadi Dib1, Philippe Chafey2, Guilhem Clary2, Morgane Le Gall3, Cedric Broussard4, Luc Camoin4, Christian Federici4, Veronique Witko-Sarsat5, Mathieu C. Tamby5, and L. Mouthon6,7,8.

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Rationale: Progress on the isolation and culture of various endothelial cells (EC) has allowed comparison of their biochemical and physiologic properties. However, very few studies compared the proteomes of EC from different sources.

Objective: To compare proteomes of macro-vascular and micro-vascular EC.

Methods: Proteomes of human umbilical vein EC (HUVEC) and 2 sources of micro-vascular EC, human pulmonary (HMVEC-P) and dermal micro-vascular EC (HMVEC-D) from healthy Caucasian donors (4 in each group) were compared using two-dimension differential in gel electrophoresis (2D-DIGE) at pH ranges of 3–11 and 4–7 and mass spectrometry.

Results: Among the 2167+/-50 protein spots detected in pH 4–7 gels, 100 were differentially expressed between HUVEC and micro-vascular EC with a ratio ≥ 2 and a T-test ≤ 0.01. Sixty-three proteins were identified including fatty acid binding protein 4 and retinal dehydrogenase 1 that were over-expressed in micro-vascular EC at 235.7 and 5.8 average ratio, respectively. Ingenuity software analysis interestingly showed that numerous proteins over-expressed in micro-vascular EC are implicated in the retinoic acid pathway. Sixteen protein spots were differentially expressed between HMVEC-D and HMVEC-P with a ratio ≥ 2 and a T-test ≤ 0.01 in pH 4–7 gels and 9 were identified. In pH 3–11 gels, 41 protein spots were differentially expressed between HUVEC and HMVEC-D and HMVEC-P with a ratio ≥ 2 and for a T-test ≤ 0.01. Among these protein spots, 33 were identified. Four protein spots were differentially expressed between HMVEC-D and HMVEC-P with an average ratio ≥ 2 and for a T-test ≤ 0.01 and were identified, corresponding to cytoskeleton proteins or enzymes implicated in glycosylation.

Conclusion: Major differences were observed between proteomes of macro-vascular and micro-vascular EC. Some of the differentially expressed proteins might be of great importance in the homeostasis and pathophysiology of EC.

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mtDNA Haplogroups Define Two Phenotypes of Osteoarthritis (OA).

Ignacio Rago-Pérez1, Mercedes Fernández-Moreno2, M. Deberg3, Sonia Pérga4, Carlos Fernández-López4, Natividad Oreo5, Manuel Acasuso5, Victoria Bonome-González6, Y. Henrotin7 and Francisco J. Blanco8.


Background: Recent findings evidence that mitochondria mediate in the pathogenesis of the osteoarthritis (OA). Biomarkers are a promising tool to detect patients with OA preferably in an early stage of the disease. In this work we aim to assess a mitochondria-related phenotype in patients with OA.

Methods: We analyzed the determinations of serum levels of 12 OA-related biomarkers: MMP-1, MMP-3, MMP-13, MPO, Coll2-1, Coll2-1NO2, C2C, CPII, hyaluronic acid, YKL-40, COMP and cathepsin K, in 48 OA patients and 52 healthy controls carrying the haplogroups H and J, to perform logistic regression models and receiver operating characteristic (ROC) curves that permit us to predict diagnosis of OA. This models also included clinical variables such as gender, age and smoking status.

Results: The MMP-13 was the only biomarker significantly increased in OA patients, when compared with healthy controls, in both mtDNA haplogroups H and J (p<0.001). Type II collagen biomarkers Coll2-1, Coll2-1NO2, Coll2 ratio, C2C, CPII and C2C:CPII ratio were significantly increased in OA patients that carry the mtDNA haplogroup H when compared with OA carriers of the mtDNA haplogroup J (p<0.01 in all cases). The logistic regression model for diagnosis for carriers of the mtDNA haplogroup H showed that those biomarkers significantly associated with OA were hyaluronic acid and C2C:CPII; the area under the curve (AUC) of the ROC curve for this model was 0.926 (95% CI = 0.857–0.995) and the optimal probability cutoff for discriminate between OA and healthy controls was 0.269, with a sensitivity of 96%, a specificity of 78%, and a positive likelihood ratio of 4.3. For carriers of the mtDNA haplogroup J, the logistic regression model for diagnosis showed that those biomarkers significantly associated with OA were MMP-13, MMP-3 and C2C; the AUC for this model was 0.880 (95% CI = 0.782–0.978), and the optimal probability cutoff for discriminate between OA patients and healthy controls was 0.271, with a sensitivity of 96%, a specificity of 68%, and a positive likelihood ratio of 3.

Conclusions: MMP-13 appears to be a good candidate biomarker for diagnosing OA. Some of the OA-related biomarkers clearly show a different profile depending on the mtDNA haplogroup. This permitted us to perform two models of haplogroup-based diagnoses of OA.

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Neurotransmitter Receptor Gene Polymorphisms Are Associated with Widespread Pain: Findings from the First Genome-Wide Association Study of Musculoskeletal Pain. Kate L. Holliday1, Tutina Neogi2, David Felson2, Ke Wang1, Wendy Thomson4 and John McBeth4. 1Boston University School of Public Health, 2Boston University School of Medicine, 3University of Manchester, Manchester, United Kingdom, 4University of Manchester

Background: Musculoskeletal pain disorders are prevalent with 10% of the general population reporting widespread pain. Heritability estimates for widespread pain are around 50% although the susceptibility loci have yet to be identified. The purpose of this study was to identify susceptibility loci by conducting the first genome-wide association study (GWAS) of widespread pain.

Methods: As part of the Framingham SHArE project, subjects from 3 generations were genotyped using Affymetrix 500k and 50k gene-focused SNP chips. Genotypes were called using the BRLMM algorithm. Samples were excluded for low call rate (<95%), excess heterozygosity and Mendelian errors. SNPs were excluded for deviation from HWE (p < 97%), MAF < 0.01 and Mendelian errors (p > 100). Whole genome imputation was carried out using HapMap CEU data and MACH v1.0.15. Data on musculoskeletal pain was available for a subset of these subjects (n = 3850) from 2 generations. The reporting of painful regions on a homunculus was used to classify cases with widespread pain (reporting pain in contra-lateral body quadrants above and below the waist and in the axial skeleton) and controls (reporting no pain). Generalised estimating equation regression analysis was used to perform a case-control GWAS analysis under an additive genetic model on autosomal SNPs with a MAF > 0.03, while accounting for relatedness between subjects and using genomic control to adjust for population stratification.

Results: Imputation was conducted on 378,163 SNPs meeting quality control criteria providing 2,321,937 SNPs for analysis in 572 cases and 1,587 controls. The genomic inflation factor was 1.02. Using a p-value cut off of 1 × 10^-8, we identified 52 SNPs in association with widespread pain which comprise 8 individual loci, many of which are strong candidate loci for susceptibility to widespread pain. In particular, an intronic SNP in the neurotransmitter receptor gene GABRA2 (GABRB2) was associated with an increased risk of having widespread pain (OR = 1.37 (1.24, 1.51) p = 6.7 × 10^-8). A SNP 100 Kb downstream of another neurotransmitter receptor, glutamate receptor 2 (GRIA2), was also associated with an increased risk of having widespread pain (OR = 1.54 (1.35, 1.73) p = 5.16 × 10^-11).

Conclusion: This study, the first GWAS of widespread pain, implicates a number of biologically relevant loci in neurotransmitter genes that are directly linked to pain pathways. Validation of these findings is now required in independent cohorts to ascertain the true impact of these loci on widespread pain susceptibility and is currently underway.

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837 Pathogenesis of Idiopathic Recurrent Pericarditis and Role of the TNFRSF1A Gene Mutations. Luca Cantarini, Orso Maria Lucherini, Maria Giuseppina Brizi and Mauro Galeazzi. Unit of Rheumatology, University of Siena, Siena, Italy

Background: Recurrences develop in up to 20–50% of patients with acute pericarditis. Although many causes of pericarditis are well known, the etiology remains obscure in about 85% patients and it is therefore labelled as idiopathic. Recurrent pericarditis is common in familial Mediterranean fever (FMF), due to mutations in the MEFV gene, and tumor necrosis factor receptor-associated periodic syndrome (TRAPS), due to mutations in the TNFRSF1A gene, but it rarely occurs alone. Colchicine is the standard treatment for FMF, while patients with TRAPS do not respond to colchicine therapy. Basing on its efficacy in preventing polyserositis in FMF, colchicine has been also proposed for the treatment of recurrent pericarditis and demonstrated to decrease the recurrence rate.

Objective: Our aim was to investigate the possible involvement of TNFRSF1A mutations in a group of patients with idiopathic recurrent pericarditis who were refractory to colchicine treatment.

Methods: 102 patients characterized by a poor response to colchicine were enrolled. Mutations of TNFRSF1A were searched for by amplifying, using polymerase chain reaction (PCR), genomic DNA, and direct sequencing.

Results: TNFRSF1A mutations were found in 7 of 92 patients. Two of the 7 patients had a family history of recurrent pericarditis (they were siblings). One of the 7 patients carried a novel heterozygous deletion (Y103-R104), 5 patients carried a heterozygous low-penetrance R92Q mutation and 1 patient carried a rare V93M mutation.

Conclusion: Our data suggest that TRAPS should be kept in mind in the differential diagnosis of recurrent pericarditis and mutation analysis of the TNFRSF1A gene should be considered in patients of Mediterranean origin. A poor response to colchicine treatment, and a positive family history, recently reported in up to 10% of recurrent pericarditis patients, may indicate the need to investigate mutations in the TNFRSF1A gene in recurrent pericarditis patients. However, to date, further studies are needed in order to better determine additional criteria for identifying the few subjects who might carry such mutations.

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838 Radiographic Kellgren-Lawrence (KL) Grade 1 Is Genetically Distinct from KL 0: Implications for Genetic Studies of Knee Osteoarthritis (OA). Venkateswarlu Kondragunta1, Xiaodong Wu1, Jordan B. Renner2, Gordon W. Duff3, Kenneth S. Kornman4 and Joanne M. Jordan1. 1Chapel Hill, NC, 2Department of Radiology and Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, 3Interleukin Genetics, Inc., School of Medicine, University of Sheffield

Purpose: The Kellgren-Lawrence (KL) radiographic grading system is widely used in studies of osteoarthritis (OA). Although KL grades 1 and 0 together often form the control group in epidemiologic studies, Hart and Spector (2003) showed different knee OA progression rates for KL1 and KL0, suggesting distinct phenotypes. We explored whether KL grades 1 and 0 are genetically distinct by comparing frequencies of genetic markers between subjects with the two KL grades.

Method: Caucasian participants (N = 1,173; 38% men; mean age = 60 years) in the Johnston County OA Project with 4–11 year follow-up data were examined. Anterior-posterior standing knee radiographs were obtained with footmat positioning at both time points and read by a single musculoskeletal radiologist for KL grades (0–4). Genotypes of 37 single nucleotide polymorphisms (SNPs) in 16 genes reported to be associated with OA were determined using the single-nucleotide primer extension method. Incidence of OA was defined as an increase in KL grade at follow up, in those with KL 0 bilaterally at baseline. Differences in genotype or allele frequencies between KL1 and KL0 and between subjects with incident OA and those without incident OA were determined by Chi-Square test or logistic regression with adjustment for age, gender and body mass index (BMI). Since all SNPs had been previously associated with OA, we present the data both with (permutation test) and without correction for multiple comparisons. An association was considered positive if the adjusted p-value was <0.05 for the risk allele, genotype or haplotype.

Results: Compared to subjects with KL0 (n = 407), those with KL1 (n = 383) were older (65.4 yrs vs. 63.0 yrs) and heavier (BMI 29.2 kg/m^2 vs. 28.4). Frequencies of alleles or genotypes in 4 genes, including IL1RN, IL6, ABCG2, and DVWA, were significantly different between KL0 and KL1 subjects (table 1). After adjusting for multiple comparisons, genotype T/T of IL1RN rs579543 was still significantly associated with KL1. Among these genetic markers, four variants in 2 genes, IL1RN (rs199598, p = 0.039; rs579543, p = 0.008; and rs9005, p = 0.03) and IL6 (rs1800797, p = 0.014), were also associated with incidence of radiographic knee OA. In addition, compared to KL0 subjects, KL1 subjects were more likely to progress to KL2 (33.5% vs. 8.5%) as previously reported. No population genetic substructure was detected in this Caucasian population.

Table 1. Distribution of genetic markers between KL0 and KL1.

<table>
<thead>
<tr>
<th>Gene and SNP</th>
<th>Allele/ genotype</th>
<th>KL1</th>
<th>KL0</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCG2 rs2231142</td>
<td>A/*</td>
<td>0.17</td>
<td>0.23</td>
<td>0.043</td>
</tr>
<tr>
<td>DVWA rs1171863</td>
<td>T</td>
<td>0.15</td>
<td>0.19</td>
<td>0.026</td>
</tr>
<tr>
<td>IL1 RN rs419598</td>
<td>C/C</td>
<td>0.08</td>
<td>0.04</td>
<td>0.022</td>
</tr>
<tr>
<td>IL1 RN rs579543</td>
<td>T/T</td>
<td>0.09</td>
<td>0.04</td>
<td>0.008</td>
</tr>
<tr>
<td>IL1 RN rs9005</td>
<td>A/A</td>
<td>0.10</td>
<td>0.06</td>
<td>0.042</td>
</tr>
<tr>
<td>IL6 rs1800797</td>
<td>A</td>
<td>0.47</td>
<td>0.40</td>
<td>0.017</td>
</tr>
</tbody>
</table>
 Conclusion: This study provides genetic evidence to support differentiating KL1 and KL0 subjects in radiographic knee OA studies.

Disclosure: V. Kondragunta: Interleukin Genetics, Inc., 1, 3; X. Wu: Interleukin Genetics, Inc., 1, 3; B. Renner: None; G. W. Duff: Interleukin Genetics, Inc., 9; K. S. Kornman: Interleukin Genetics, Inc., 1, 3; J. M. Jordan: Interleukin Genetics, Inc., 5.

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Salivary Proteomic Profile in Behçet’s Disease. Rosaria Talarico, Chiara Baldini, Laura Giusti, Ylenia Da Valle, Camillo Giacomelli, Elena Donadio, Francesco D’Ascanio, Laura Bazzichi, Antonio Lucciacci and Stefano Bombardieri. Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy

Background: Behçet’s disease (BD) is a chronic, systemic vasculitis characterized by recurrent oral and genital ulcers, skin lesions and ocular involvement. In the recent years proteomics has provided new insights for biomarker research in many autoimmune diseases. We have previously described some qualitative and quantitative differences in the composition of saliva in a limited number of BD patients with respect to healthy controls. No data are available on differences in the salivary proteomic profile between active and inactive subsets of disease.

Aim: Following our preliminary results, the primary aim of this study was to analyse the expression of proteomic biomarkers in a larger group of BD patients. The secondary aim was to search for biomarkers of disease activity in BD, by comparing the proteomic profile of active and inactive BD patients.

Methods: Twenty-seven BD consecutive patients (Mean age at disease onset 25±4 years; male/female: 19/8; mean disease duration: 11±2.5 yrs) all fulfilling the ISG criteria for BD and the same number of healthy controls with similar demographic characteristics were enrolled in this study. Clinical manifestations of BD patients at the time of sample collection were recorded. Saliva samples were collected under standard conditions. Aliquots from the individual salivary samples were pooled into various groups for analyses by 2-dimensional-electrophoresis (2DE). The first set of 2DE gels compared a group of pooled healthy volunteers with a group containing all BD samples. The second analysis was performed comparing the group of active BD patients with inactive disease.

Results: Out of 27 BD patients, 11 were active (ocular involvement: 5; CNS involvement: 2; mucocutaneous: 4) and 16 were under remission. The analysis of the obtained protein profiles allowed us to observe significant differences in the expression of 37 spots: eight out of 37 collapsed into 5 separate proteins, and specifically: lipocalin, calorulbin B, prolactin inhibitor precursor (PIP), carbonate anhydrase VI, Cystatine SN precursor. In addition 29 differently expressed spots were cut out for digestion with trypsin and addressed to the MALDI-TOF-MS in order to be identify. When BD active patients were compared to those inactive, 30 spots significantly different were observed; in particular, a >2 fold decrease of PIP, PLUNC 2 and Cystatine SN precursor and a >2 fold increase of calorulbin B differentiated the profile of active from inactive BD patients. Again 10 non identified spots were addressed to the MALDI-TOF-MS to complete the identification.

Conclusions: The results of this study allow us to identify a number of proteins differently expressed in BD with respect to healthy subjects. Some of them, particularly Caloranulin B, appeared to be able not only to distinguish BD patients from controls, but also to differentiate active from inactive BD patients. This suggests to be of particular interest since Caloranulin B is a S100 calcium-binding protein known to promote phagocyte migration and infiltration of granulocytes and might be implicated in the pathogenetic background of BD.

Disclosure: B. Rocha: None; V. Calamina: None; P. Fernández-Puente: None; J. Mateos: None; C. Ruiz-Romer: None; F. J. Blanco: None.

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The FAAH Gene Is Involved in Risk of Symptomatic Osteoarthritis of the Knee and in Pain in Osteoarthritis. Ana M. Valdes1, Anne-Marie Malfaït2, Sally Doherty1, Rosalina Das3, Margaret Wheeler1, Deborah Hart4, Tim D. Speer4, Cyrus Cooper1, Michael Doherty1 and Nigel K. Arden5.1 King’s College London, London, United Kingdom; 2King’s College London, London, United Kingdom; 3King’s College London, London, United Kingdom; 4Rush University Medical Center, Chicago, IL; 5Rush University Medical Center, University of Nottingham, United Kingdom; University of Southampton - University of Oxford, United Kingdom

Objective: Osteoarthritis (OA) is the most common large joint (hip or knee) pathology in older people and the main cause for large joint pain and disability in this age-group. FAAH (fatty acid amide hydrolase) is an enzyme that degrades the endocannabinoid anandamide. In animal models genetic or pharmacological inactivation of FAAH produces analgesic, anti-inflammatory, anxiolytic, and antidepressant phenotypes and human genetic variants have been associated with increased cold perception. Our aim was to assess if a genetic variant in the FAAH gene previously implicated in peripheral pain sensitivity is involved in risk for large joint OA.

Methods and Subjects: The rs4141964 SNP in the FAAH gene was typed in 1847 knee OA cases, 1199 hip OA cases and 2036 controls from three independent UK cohorts (Nottingham, Chingford and Hertfordshire). Expression of the faah gene was tested in the dorsal root ganglia (DRG) of naive and medial meniscus destabilized (DMM) C57BL/6 mice. DMM...
operated mice were tested for mechanical allodynia at 4, 8, and 16 weeks after surgery, using von Frey fibers. At each of these time points, the DRG L2-L5 were harvested and mRNA was extracted for RT-PCR analysis.

**Results:** The minor allele (A) at rs4141964 – previously implicated in higher pain sensitivity - was found to be consistently increased among OA cases compared to controls in all three cohorts. A fixed-effects meta-analysis for knee OA yielded OR = 1.17 95% CI 1.05–1.29; p = 0.003 (Figure 1) and OR = 1.15 95% CI 1.01–1.30; p = 0.034 for hip OA. No significant between-study heterogeneity was observed (I² = 0%).

In the Hertfordshire cohort study the AA genotype was increased among OA patients with knee pain compared with those with asymptomatic OA (p < 0.06). In the murine DMM model, progressive mechanical allodynia was apparent in the operated hind limb, 4–8 weeks post surgery, and then resolved 8–16 weeks after surgery. FAAH mRNA levels in the innervating DRG correlated with the mechanical allodynia, and FAAH mRNA was over-expressed relative to naive mice at 8 weeks, but not at 4 or 16 weeks post-surgery.

**Conclusions:** The FAAH gene appears to be implicated in large joint OA and OA pain. Supported by the EU FP7 large collaborative project TREAT-OA (grant 200800), the MRC UK, Arthritis Research UK and the Oxford NIHR Musculoskeletal Biomedical Research Unit

**Disclosure:** A. M. Valdes: None; A.-M. Malfait: None; S. Doherty: None; R. Das: None; M. Wheeler: None; D. Hart: None; T. D. Spector: None; C. Cooper: None; M. Doherty: None; N. K. Arden: None.

Figure 1. Patterns of gene expression patterns during the differentiation of osteoclast stimulated with M-CSF plus RANKL. Critical time points for osteoclastogenesis were designated for analysis, which ranged from the 24-hour after the monocyte culture (day 0), at the point of precursor cells (day 3), when cell-to-cell fusion occurred (day 5), and when mature osteoclasts were formed (day 7).

In all clusters, the most distinctive change of differential gene expression was observed during cell fusion. Two clusters showed declining patterns throughout the differentiation which included miR-20b, 92a, 93, 130b, 450a.

**Background:** Genome-wide association studies have uncovered structural and promoter polymorphisms associated with autoimmune disease and confirmed long-established associations with major histocompatibility complex (MHC) alleles. The underlying mechanisms often remain unclear; allelic differences in protein synthesis, folding, maturation, and turnover are of interest. Numerous techniques exist for measuring protein synthesis and turnover, but they suffer drawbacks when studying allelic effects in biologically relevant systems. Here, we have combined stable isotope labelling using heavy water (D₂O) with peptide mass spectrometry to devise a biosynthetic labelling approach suitable for allele-specific dynamic proteomics.

**Methods:** MHC proteins were studied as a model system with disease-relevant isotypic and allelic variation. Antigen-presenting cells (APCs), such as B-lymphoblastoid cell lines, murine splenocytes, or short-term cultures derived from peripheral blood, were subjected to continuous labelling with [2H]O. MHC proteins were isolated by immunoprecipitation and SDS-PAGE, fragmented with trypsin, and peptides identified using LC/MS/MS. Selected peptides were analysed for [2H] incorporation by LC/MS. Labelling patterns were interpreted using mass isotoper distribution analysis and used to calculate fractional protein synthesis as a function of labelling time.

**Figure 1.** The Profile of miRNA Expression during the Differentiation of Murine Osteoclast. Inhye E. Ahn1, Ji Hyeon Ju2 and Jin Sil Park3. 1Department of Internal Medicine, The Methodist Hospital, Houston, TX, 2Division of Rheumatology, Department of Internal Medicine, Catholic University of Korea, Seoul, Korea, Republic of, 3Rheumatology Research Center, Catholic University of Korea, Seoul, Korea, Republic of

**Objectives:** By identifying chronological patterns of miRNA expression during the differentiation of murine osteoclast, this study aimed to reveal clusters of non-coding genes involved in the regulation of bone metabolism.

**Methods:** Murine bone marrow-derived monocytes were stimulated with M-CSF only or with the combination of RANKL. Cultured cells were harvested at the designated time points critical for osteoclastogenesis, which ranged from the 24-hour after the monocyte culture, at the point of precursor cells (day 3), when cell-to-cell fusion occurred (day 5), and when mature osteoclasts were formed (day 7). Isolated miRNA underwent microarray analysis. Types and patterns of miRNA expression were compared between two stimulation groups and also between chronological points within each stimulation group.

**Results:** At the point of cell fusion, six miRNAs were identified to be expressed significantly higher in monocytes stimulated with both M-CSF and RANKL than in those with M-CSF only (p < 0.05). This number of differentially expressed genes between two stimulation groups increased to 35 as osteoclast matured. Patterns of miRNA expression in M-CSF plus RANKL-stimulated monocytes were categorized into nine clusters by K-mean clustering analysis.
quantifiable after accounting for cell growth or turnover and changes in protein levels. Estimates of fractional protein synthesis from analysis of different peptide mass isotopomers, and from different peptides derived from the same protein, were internally consistent and congruent with literature estimates based on other methods. Well-labelled peptides were identified that distinguished selected MHC class I and class II isotypes or alleles, enabling allele-specific measurements of MHC protein synthesis and turnover. Analysis of multiple peptides indicated that multiple amino acids contributed to label incorporation from $^{2}$H$_{2}$O, algorithms for predicting labelling patterns from sequence are being refined.

**Conclusions:** The safety, simplicity, and versatility of $^{2}$H$_{2}$O labelling combine with the sensitivity, precision, and specificity of LC/MS to enable allele-specific measurements of MHC protein synthesis and turnover. The approach is readily extended to other proteins and can be applied to primary cells and in vivo. These capabilities will aid studies of protein dynamics as a link between genetic polymorphisms and mechanisms of pathogenesis. The ability of the technique to accommodate complex samples suggests potential for proteome-wide studies of protein dynamics.

Disclosure: M. J. Deery: None; A. De Riva: None; C. Prevosto: None; S. McDonald: None; R. Busch: KineMed, Inc., 1, 5.

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**ACR Poster Session B**

**Innate Immunity and Rheumatic Disease (Poster)**

**Tuesday, November 9, 2010, 9:00 AM–6:00 PM**

**844**

**β2 Integrins Control the Pro-Inflammatory Phenotype of Type 1 Macrophages and Dendritic Cells.** Kim C. M. Santegoets$^{1}$, Mark H. Wenink$^{2}$, Richard Huijben$^{2}$, Lenny van Boeijen$^{2}$, Alessandra Cambi$^{2}$, Piet L. Van Riel$^{2}$, Wim B. Van Den Berg$^{1}$ and Timothy R. D. J. Radstake$^{2}$. $^{1}$Radboud Univ Nijmegen Med Cntr, Nijmegen, The Netherlands, $^{2}$Radboud University Nijmegen Medical Center, Nijmegen, Gelderland, The Netherlands

**Background:** Initially in inflammation pro-inflammatory macrophages are necessary to initiate a full inflammatory response thereby facilitating the control of a possible threat (e.g. tissue damage or pathogens). However, at a certain point this pro-inflammatory program should switch off to prevent chronic inflammation. We hypothesized that the accumulation of monocytes at a site of inflammation induces a shift from an initially pro-inflammatory macrophage phenotype to a phenotype aimed at suppressing the initiated immune response.

**Methods:** To investigate this we cultured monocytes with GM-CSF or M-CSF into pro-inflammatory type 1 macrophages, respectively, in different cell densities. After differentiation the macrophages were harvested and replated in a fixed concentration before stimulation with single TLR ligands or heat-killed M. tuberculosis. Dendritic cells (DCs) were also cultured in increasing cell densities to determine the effect on T cell proliferation and differentiation. FACs analysis was performed on the expression of a wide range of markers including TLRs. Quantitative-PCR was used to determine the expression of TLR signaling inhibitors. Furthermore, various integrins were selectively blocked during culture with blocking antibodies.

**Results:** Differentiation of type 1 macrophages in increasing cell densities dramatically lowered their TNFα, IL-1β and IL-6 release and increased the production of IL-10 and VEGF upon TLR stimulation with single ligands or M. tuberculosis. Increasing cell density had no effect on the cytokine production by type 2 macrophages. The shift towards a more anti-inflammatory type 1 macrophage depended on cell-cell contact via β2 integrins and was due to a soluble factor. TGFβ, IFNα and IL-6 were excluded as playing roles in this phenotypical shift. However, TGFβ was capable of reversing the anti-inflammatory phenotype induced by cell-cell contact through β2 integrins, resulting in highly inflammatory type 1 macrophages. The pro-inflammatory phenotype of DCs was also restricted by cell-cell contact leading to a high production of IL-10 while the release of IL-12/p70 was potently reduced. Correspondingly, DCs cultured in low density were stronger inducers of T cell differentiation into IFNγ-producing cells upon TLR7/8 stimulation while this capability was potently suppressed when DCs were cultured in high cellular density.

**Conclusions:** These data show for the first time that cell-cell communication via β2 integrins on type 1 macrophages and DCs alters their differentiation, suppressing their pro-inflammatory phenotype. In many chronic inflammatory diseases high levels of TGFβ are present. This appears to prevent the shift towards more anti-inflammatory macrophages. Concluding, β2 integrin activation during macrophage differentiation is likely to be crucial in the suppression of ongoing immune responses thereby preventing chronic inflammation and possibly tolerance breakthrough, which might be impaired by the excessive presence of TGFβ.

Disclosure: K. C. M. Santegoets: None; M. H. Wenink: None; R. Huijben: None; L. van Boeijen: None; A. Cambi: None; P. L. Van Riel: None; W. B. Van Den Berg: None; T. R. D. J. Radstake: None.

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“Alarmins” S100A8 and A9 Are Expressed in Synovium of Early OA Patients and Regulate Synovial Activation and Joint Destruction during Experimental Osteoarthritis. Peter van Lent$^{1}$, Arjen Blom$^{1}$, Rik Schelbergen$^{2}$, Aart J. M. Slaets$^{1}$, Thomas Vogl$^{1}$, Johannes Roth$^{1}$ and Wim van den Berg$^{1}$. $^{1}$Dep of Rheumatology University Hospital Nijmegen Medical Centre, Nijmegen, The Netherlands, $^{2}$Institute of Immunology Muenster, Muenster, Germany

**Purpose:** Prominent proteins released by activated macrophages are the “alarmins” S100 A8 and A9. There is increasing belief that synovial tissue activation contributes to OA cartilage pathology. The aim is to evaluate the presence of S100A8/S100A9 in synovia of patients with early OA and to explore active involvement of S100A8/A9 in cartilage destruction in experimental osteoarthritis models that differ in degree of synovial activation.

**Methods:** Arthroscopic biopsies were taken from 30 early OA patients. mRNA levels (RT-PCR) and immunolocalisation was determined and related to joint destruction (Kellgren-Lawrence score). Experimental OA was either induced by transection of the medial anterior meniscotibial ligament which leads to destabilisation of the medial meniscus (DMM) or by injection of collagenase into murine knee joints, which causes overall ligament damage and broad instability. Collagenase-induced-osteoarthritis involves chronic synovial activation in contrast to DMM. Synovial expression of S100A8 and S100A9 was measured using immunolocalisation. Both models were induced in S100A9−/− deficient mice (myeloid cells also lack S100A8 at the protein level). Primary chondrocytes were stimulated with S100A8 and A9 and MMP levels were measured using RT-PCR.

**Results:** mRNA and protein levels of S100A8 and A9 were significantly higher in synovial biopsies of early OA patients when compared to control joints. S100A8 and A9 was predominantly found in synovial macrophages. Of great interest, high levels correlated to increased joint destruction (KL score). The function of S100A8 and S100A9 was further studied in experimental OA models. Kinetic studies show that in surgically induced DMM model, S100A8 and A9 was marginally expressed within the synovium, only evident at day 7 after induction and consistent with limited synovial thickening. The degree of OA cartilage pathology in the knee joint was similar in S100A8−/− and WT mice at day 42 after induction of DMM.

In contrast, during the course of collagenase-induced osteoarthritis, S100A8 and S100A9 was strongly upregulated in synovium at day 7 and remained high at days 14, 28 and 42. Expression of these proteins nicely correlated with thickening of the synovial lining layer comprising activated macrophages. When collagenase-induced-osteoarthritis was elicited in S100A8−/− mice, significantly lower synovial activation was observed when compared to WT mice. Synovial activation was 62% lower at day 42. Cartilage destruction was significantly lower in all surfaces and ranged from a 45% reduction in the lateral tibia to 73% reduction in the medial femur. When primary mouse chondrocytes were stimulated with S100A8 or S100A9, a strong upregulation of particularly MMP-3 mRNA level was found indicating a direct role of S100A8/A9 in cartilage destruction.

**Conclusions:** Alarmins S100A8/S100A9 are expressed by macrophages in biopsies of early OA patients. S100A8/A9 play a crucial role in synovial activation and cartilage destruction in an osteoarthritis model that shows clear synovial involvement. S100A8/A9 expression in the synovium causes pathology probably by stimulating MMP-mediated damage in the cartilage matrix.

Disclosure: P. van Lent: None; A. Blom: None; R. Schelbergen: None; A. Slaets: None; T. Vogl: None; J. Roth: None; W. van den Berg: None.

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Altered T Cell Signalling in Systemic Lupus Erythematosus (SLE): A Role for FcγRIII and Immune Complexes (ICs). Anil Chauhan$^{1}$, John P. Atkinson$^{1}$ and Terry L. Moore$^{1}$. $^{1}$Saint Louis University, Saint Louis, MO, $^{2}$St Louis University, St Louis, MO, $^{3}$Washington University School of Medicine, St Louis, MO
Purpose: The presence of immune complexes (ICs) in systemic lupus erythematosus (SLE) has been documented. In addition, a role for altered T cell responses has been suggested. Previously, we have shown the activation of T cell receptor (TCR) in response ICs and sublytic dose of membrane attack complex (MAC). In this study, we wanted to explore the presence of low affinity FcRII that are responsible for ICs binding to human peripheral naive CD4+ T cells and explore their downstream signaling partners.

Methods: We used Alexa Fluor 488 labeled model ICs to develop a flow based assay to evaluate the presence of the Fc receptor (FcR) on CD4+ human naive T cells. Thereafter, we used antibodies specific to FcγRIIA/B or FcγRIIIB to achieve a 50% inhibition of the labeled IC binding. Subsequently, using immunoprecipitates generated from T cells treated with ICs purified from SLE plasma and Western blotting we explored the presence of FcγRIII. Furthermore, we co-localized the FcγRIIIA/B, Fcγ- and phosphorylated Syk in human naive CD4+ T cells using confocal microscopy. In the immunoprecipitates generated with anti-FcγRIII, we analyzed the phosphorylation of Syk in response to ICs. The phosphorylated Syk was co-localized with FcγRIII with confocal microscopy. The presence of the IC binding FcγRIII was carried out from peripheral CD4+ T cells from SLE patients by flow cytometry.

Results: Human peripheral naive CD4+ T cells show binding to labeled ICs. We show a 27 to 29 kD protein that correspond to previously reported mass for FcγRIIA/B in the CD4+ T cells. A total of 5 to 10% peripheral CD4+ T cells from SLE patients show binding to labeled model ICs. The antibodies against FcγRIIIB and FcγRIIA/B inhibited binding of labeled ICs by 50%. Upon treatment with ICs, the cells show recruitment of FcγR chain with FcγRIIA/B. Treatment of cells with ICs and sublytic MAC resulted in phosphorylation and association of Syk with FcγRIIIA/B.

Conclusions: For the first time, we show the presence of low affinity FcγRIIA/B on human CD4+ T cells. FcR play critical role in B cell responses and are critical in IC clearance. However, the presence of FcR on human T cell is controversial (Nature reviews,(8) 34,2008). Although, the presence of FcγRIIIA has been shown in NKT and γδ T cells, the FcγRIII is only known to be expressed by neutrophils and macrophages and is shown on basophils recently. Using an antibody specific for FcγRIIIA, we demonstrate inhibition of model IC binding in flow based assay. We further show upon treatment of these cells with ICs, the FcγR is recruited to the FcγRIIIA receptor. This also resulted in phosphorylation and recruitment of Syk with FcγR. Altered Syk mediated T cell signaling in SLE T cells has been reported earlier. We show that ICs and sublytic MAC activates Syk in peripheral T cells. The naïve CD4+ T cells also proliferate in response to ICs and sublytic MAC. We have previously shown TCR activation and T cell differentiation in response to ICs and sublytic MAC. It is for the first time, we demonstrate a possible role for FcR in activation of T cells in response to ICs and MAC, a complex of late complement cascade. This study provides a link between ICs, complement, and adaptive immunity.

Disclosure: A. Chauhan: None; J. P. Atkinson: None; T. L. Moore: None.

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C5aR Is Expressed by Macrophages and Dendritic Cells in Close Proximity to T-Cells in Synovial Tissue from Patients with Rheumatoid Arthritis.

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ticals Research Unit, Novo Nordisk A/S, Måløv, Denmark, 2Immunopharmacology, Biopharmaceuticals Research Unit, Novo Nordisk A/S, Måløv, Denmark

Objective: The aims of the present study were to investigate the expression of the C5a receptor (C5aR) and to characterize the C5aR-positive cells in the synovium of rheumatoid arthritis (RA) patients.

Method: Immunohistochemical studies investigating the C5aR protein expression were performed on synovial biopsies from patients with RA (n=35), osteoarthritis (OA) (n=15) and normal synovial biopsies (n=5). Characterization of C5aR-positive cells was performed by double immunofluorescence staining on another set of synovial biopsies: RA (n=19), OA (n=27) and normal (n=5) with markers for neutrophils (myeloperoxidase, MPO), T cells (CD3), dendritic cells (DCs) (CD1a), and macrophages (CD68).

Results: Infiltrating C5aR-positive (C5aR+) cells were demonstrated in synovial tissue from 28 out of 35 patients with RA, and from 11 out of 15 patients with OA whereas no C5aR+ cells were present in normal synovium. The C5aR+ infiltrating cells in the sublining layer of OA synovial tissue were observed only when lymphoid aggregates were present, and with less positive cells present compared to RA. In the synovial lining C5aR+ cells were observed in 18 out of 35 and 10 out of 15 patients with RA and OA, respectively. Double immunostainings for C5aR and neutrophils, T-cells, DCs and macrophages showed profound infiltration of neutrophils into the synovium (in 60% of patients with RA and 25% with OA), and most of these were C5aR-negative (> 95%), whereas 90% of neutrophils located in the lumen of synovial blood vessels were C5aR+. CD3+ T cells did not express C5aR in synovial tissue from patients with RA or OA. C5aR and CD1a double-positive DCs were observed in 8 out of 19 RA and 8 out of 27 OA patients. More than 95% of the CD1a+ DCs in these patients co-expressed C5aR. All C5aR+ CD1a+ DCs were found intermingled in lymphoid aggregates in close proximity to CD3+ T cells. In the synovial sublining tissue 11 out of 16 patients with RA and 10 out of 21 patients with OA contained up to 50% C5aR+ and CD68+ macrophages. The C5aR+ CD68+ macrophages were interspersed in the synovial tissue and the majority intermingled in lymphoid aggregates. In addition, in 10 out of 16 patients with RA, 12 out of 20 OA and 3 out of 4 normal synovial biopsies all C5aR+ cells in the synovial lining were CD68+ macrophage-like synoviocytes.

Conclusion: An association between C5aR expression and rheumatoid arthritis was demonstrated based on the finding that C5aR+ cells were present in 80% of patients with RA, whereas no C5aR+ cells were present in normal synovium. C5aR+ cells were also found in patients with OA, but less C5aR+ cells were observed in the lymphoid aggregates compared to patients with RA. The majority of infiltrating C5aR+ cells are CD68+ macrophages and a minor part are CD1a+ DCs, whereas very few of the extravascular neutrophils are C5aR+. The majority of the C5aR+ macrophages and DCs were intermingled in lymphoid aggregates in close proximity to CD3+ T cells, and it can be speculated that C5a-activated macrophages and DCs are interacting with T cells in the sublining synovial tissue.


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Cellular Immunity in Rheumatoid Arthritis Patients Not Responding to Synthetic DMARDs.

Andra Balanescu1, Ionelia Victoria Neagoe2, Florian Berghea2, Carolina Negres4, Magda Purvu1, Ruxandra Ionescu1, Denis Predetea5, Violeta Bojinca4, Vasile Preoteasa5 and Gina Mandu6. 1Colenia Clinical Hospital, Bucharest, Romania, 2Department of Toxicology, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania, 3Research Center of Rheumatic Diseases, Sf. Maria Hospital, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania, 4Research Center of Rheumatic Diseases, Sf. Maria Hospital, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania, 5Vitor Babes National Institute of Pathology, Bucharest, Romania, 6Vitor Babes National Institute of Pathology, Bucharest, Romania

Background: Rheumatoid arthritis (RA) is considered a T cell-driven disease, but there are consistent evidences that the final bone and cartilage destruction is confined to the monocytic lineage. Therefore, the aim of our study was to explore cellular immune markers in RA patients (pts) not responding to therapy with synthetic DMARDs, focusing on cellular immune response.

Methods: The study included 35 RA pts diagnosed according to the 1987 revised ACR criteria (age: 46.4±24.3 years; disease duration: 48.7±38.6 months; 86.6% were women). All RA pts had an erosive, seropositive (rheumatoid factor and/or anti-citrullinated peptide antibodies) and active disease (DAS28: 5.9±2.0), despite treatment with a synthetic DMARDs (Methotrexate or Leflunomide) for at least 6 months at standard doses. Peripheral blood samples were collected for assessing the cellular immune status: the phenotype of lymphocytes, their early activation capacity (CD69) when stimulated ex vivo with CD2, phytohemagglutinin (PHA), pokeweed mitogen (PWM) or IL-2, and the oxidative activity developed ex vivo by monocytes and granulocytes when challenged with E. coli or phorbol myristate acetate (PMA).

Results: RA pts exhibited high peripheral monocyte counts. Monocytes proved to be activated as a high percentage of cells developed constitutive oxidative burst and had an increased capacity to respond ex vivo to E. coli or PMA. Such abnormal monocytes released constitutively proinflammatory cytokines (IL-6, IL-8, TNFα, GM-CSF). Granulocytes had a less obvious abnormal oxidative activity. Peripheral lymphocytes were in the normal range (as counts and percentage of CD4+ or CD8+ lymphocytes). T lymphocytes proved to be activated as they expressed the early activation marker CD69. When challenged ex vivo, CD4+ lymphocytes, but not CD8+ ones, were less
able than normal cells to get activated. Similarly, NK cells were activated in vivo but had a lower response to IL-2 ex vivo.

Conclusions: Our study emphasized that RA pts not responding to therapy with synthetic DMARDs presented functional disturbances at the level of peripheral CD4+ lymphocytes, monocytes and NK cells. These immune parameters could represent markers for monitoring the impact of therapy and the disease course.

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Purpose: Dendritic cells (DC) are pivotal in the initiation of adequate immune responses. Peripheral blood dendritic cells (PBDC) have pleiotropic effects on T and B lymphocytes, however, their phenotype and functional properties in rheumatoid (RA) and psoriatic arthritis (PsA) are not well understood. Therefore, we performed a comprehensive examination of the PBDC profile of RA and PsA patients.

Methods: Peripheral blood was collected longitudinally from a cohort of approximately 150 arthritis patients including, recently diagnosed RA (n = 33), RA treated with methotrexate (MTX) (n = 70), RA treated with TNF inhibitors (TNFi) (n = 61), and PsA patients treated with anti-TNF (n = 25). Samples from healthy control (HC) subjects (n = 97) were also obtained.

Peripheral blood was examined by an 11-color flow cytometry assay to identify, phenotype and assess endocytic ability of PBDC subsets. Subset analysis included resolution of previously characterized myeloid dendritic cell 1 (MDC1: CD11c−CD14+), myeloid dendritic cell 2 (MDC2: CD11c−CD141+), and plasmacytoid dendritic cell (PDC: CD303+CD141−) populations in addition to several putative, poorly characterized PBDC subsets. A systems biology approach was utilized to assess differences in individual PBDC subsets and also differences in the overall composite PBDC profile.

Results: Examination of myeloid DC subsets did not reveal any significant differences in the frequency or endocytic ability of MDC1 among study groups. Recently diagnosed RA patients exhibited a consistent decrease in the frequency of MDC2 as compared to HC that reached significance at one time point. No consistent differences in the frequency of PDC was observed among study groups, although a trend toward decreased PDC in RA patients treated with MTX as compared to HC was observed. Principal components analysis of composite PBDC profiles revealed consistent significant differences in the PBDC profile of RA patients treated with MTX at multiple time points as compared to HC, that were largely influenced by relative changes in the frequency of PDC and a putative PDC-like subset. A significant decrease in MDC1, independent of study group was observed shortly after seasonal influenza vaccination.

Conclusions: Although variations were observed in the frequency of PBDC subsets in RA and PsA patients, no substantial dysregulation was observed that was specific to RA or PsA patients or treatment with methotrexate or anti-TNF. Subtle changes in the overall PBDC profile were observed in RA patients treated with MTX that warrant further examination and may reflect alteration in PBDC development. Decreases in MDC1 after influenza vaccination, likely reflecting altered trafficking, highlight the dynamic nature of the PBDC profile and may represent a surrogate marker of vaccine response. These data also demonstrate that anti-TNF therapy does not significantly impact the circulating frequency or ratios of PBDC.

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850 C-Reactive Protein Inhibition of the Response to Type I Interferon (IFN). Carolyn Mold1, Daniel Goldberg1, Carol Morris1 and Terry Du Clos2.

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Background: A pivotal role for the type I IFN pathway in SLE is supported by expression analysis, genetic associations, in vitro experiments and animal models. In peripheral blood, plasmacytoid dendritic cells (pDC) are the primary producers of IFN, which acts on monocytes, myeloid DC and lymphocytes to promote antigen presentation and activation. This study investigated the regulation of this pathway by the pentraxins, C-reactive protein (CRP) and serum amyloid P (SAP). Both pentraxins recognize apoptotic cells and nuclear antigens and both bind to FcgR and activate complement. CRP promoter polymorphisms associated with decreased basal expression of CRP show increased risk of SLE. We hypothesized that pentraxins would regulate the IFN response to SLE autoantigens.

Methods: To determine whether pentraxins induce IFN, PBMC were incubated with CRP, SAP or serum containing anti-RNP and apoptotic cells or purified autoantigen (snRNP). Cytokine responses (TNF-α, IL-10, IFN-α) were measured at 24 h by ELISA. Purified monocytes or macrophages were incubated with CRP or CRP with apoptotic blebs and cytokines were measured by multiplex. To determine whether CRP treatment would affect the response to IFN, macrophages were preincubated with CRP for 1–3 h before 15 min treatment with IFN. Phosphorylation of STAT-1 and STAT-3 was determined by Western blot.

Results: PBMC produced IFN-α in response to immune complexes containing apoptotic cells or snRNP. In contrast, CRP or SAP complexed to these same autoantigens induced IL-10 and TNF-α but no IFN-α. Depletion of monocytes eliminated the cytokine responses to CRP complexes, but did not affect the IFN-α response to immune complexes, which is mediated by pDC. The IFN-α response to anti-RNP-snRNP complexes was sensitive to RNase treatment. Purified monocytes incubated with pentraxins complexed with apoptotic blebs released cytokines, IL-10, IL-6 and TNF-α, associated with a regulatory phenotype. The IL-10 response to CRP alone or CRP complexes was greatly increased by differentiation into macrophages with M-CSF. Pretreatment of macrophages with CRP for 3 h or longer completely blocked IFN-α-induced signaling.

Conclusions: These findings support the hypothesis that pentraxins regulate the IFN-α pathway. Although both CRP and SAP bind to apoptotic cells and nuclear autoantigens, in contrast to immune complexes, pentraxin complexes containing these autoantigens do not induce IFN-α. Instead monocytes dominate the response, producing TNF-α and IL-10, which both inhibit the pDC IFN response. Macrophages responded to CRP complexes with high amounts of IL-10 and after CRP incubation became unresponsive to IFN-α. Thus, pentraxins may provide both a non-inflammatory means to remove autoantigens exposed during cell death and a mechanism to decrease the stimulatory effects of IFN-α.

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851 Endosomal Trafficking of Antigen in Antigen Cross-Presentation and the Causative of Lupus Tissue Injuries. Mai Takimoto1, Ken Tsuniyama1 and Shunichi Shiozawa2.

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Objective: We previously showed that repeated immunization with a conventional antigen caused systemic autoimmunity in the mice otherwise
not prone to spontaneous autoimmune diseases; systemic autoimmune necessarily takes place when host’s immune ‘system’ is overstretched by repeated exposure to antigen, to the levels that surpass system’s self-organized criticality. This novel thesis ‘self-organized criticality theory’ explaining the cause of autoimmune of ours (Tsuniyama K, et al. PLoS ONE 4(12):e882, 2009) shows that overstimulating CD8⁺ T cell into a full-matured MHC class I-restricted, antigen-specific effector cytotoxic T lymphocyte (CTL) via antigen cross-presentation in dendritic cell (DC) causes lupus tissue injuries. Here we examine molecular details of antigen cross-presentation to clarify how effector CTL is generated. The results indicate that the endosomal pathway, rather than the pathway through endoplasmic reticulum (ER), is essentially important for antigen cross-presentation and subsequent generation of lupus tissue injuries.

Methods: The bone marrow cells of BALB/c mice were stimulated with granulocyte-macrophage colony-stimulating factor (GM-CSF) to generate bone marrow-derived DC. The bone marrow-derived DC was cultured with fluorescent-labeled ovalbumin (OVA). Early endosome antigen-1 (EEA-1) and calnexin were detected to identify endosome and ER respectively, by using immunofluorescent staining. To examine whether or not engulfed antigen is exported from endosome to cytoplasm, Sec61, which is known as a translocon, was also detected by using immunofluorescent staining. Localization of OVA, endosome, ER and Sec61 was examined under confocal laser scanning microscopy.

Results: In the bone marrow-derived DC, upon engulfment, OVA was co-localized with EEA-1, an endosomal marker. However, by 15 min after engulfment, OVA was gradually separated from EEA-1. In contrast, OVA did not co-localize with calnexin, a marker of ER, until 30 min after engulfment clearly indicating that OVA was not transferred into ER. Instead, Sec61 was found to be co-localized with OVA after 15 min to 30 min, which indicated that OVA was transported from endosome to cytoplasm via Sec61.

Conclusion: The result shows that endosomal pathway, bypassing ER, is important in the case of antigen cross-presentation. Further, the export of antigen from endosome to cytoplasm via Sec61 could be the first step in antigen cross-presentation, hence the generation of lupus tissue injuries.

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852 Exposure to U1-RNP Components Induces Bone Marrow-Derived Dendritic Cell Trafficking to the Lung, Luis Sorell¹, YunJuanch Zang², Irina Fernandez³, Laisel Martinez¹, Maria Carpentiero¹ and Eric L. Greidinger³. ¹Miami VA Medical Center, ²Miami VA Medical Center and University of Miami Miller School of Medicine, Miami, FL, ³University of Miami Miller School of Medicine, Pembroke Pines, FL, ⁴University of Miami Miller School of Medicine

Background: We have previously found that upon adoptive transfer into naive syngeneic mice, splenic dendritic cells (DCs) from anti-RNP immunized mice with clinical lung disease preferentially home to the lung and transfer interstitial pneumonitis, but that splenic DCs from naive mice or even from immunized mice without lung disease do not home to the lung or induce lung disease. We hypothesize that DC tissue targeting is determined by interactions between RNP targets and DCs directly, without the intervention of adaptive immune cells.

Methods: Bone marrow was harvested from B6 strain study mice, and differentiated in vitro for a week with GM-CSF and IL-4 following published protocols. In the last 24 hours in culture, cells were transferred into fresh medium containing the same factors in the presence or absence of 50 mcg/ml each of 70k fusion protein and U1-RNA. Cells were harvested, loaded with CFSE or QTracker 655, subjected to FACS analysis and/or adoptively transferred into naive syngeneic hosts via the tail vein, 1 million cells per recipient. Recipients were subsequently sacrificed and analyzed by FACS for the presence of labeled cells in single cell suspensions from organ homogenates, and for the development of clinical manifestations of inflammatory disease.

Results: Bone marrow-derived DCs differentiated with GM-CSF/IL-4 showed evidence of preferential homing to the lung after incubation with 70k/U1-RNA, with over mean of 50% of pulmonary CD11c⁺ cells showing specific QTracker 655 labeling one week after cell adoptive transfer, compared to less than 1% of cells without 70k/U1-RNA. Persistence of lung-targeting DCs by vital dye staining was observed up to 2 months after cell transfer. In 6/6 mice receiving lung-targeting BM-derived DCs followed for at least 2 months, histologic evidence of interstitial pneumonitis was observed. Lung-targeting DCs were characterized by the development of CD11c⁺/CD11b⁺ surface expression, TLR3 expression, and preferential expression of a long form of the IRF5 mRNA 3' UTR similar to that observed in anti-RNP patients with lung disease.

Conclusions: Spliceosomal targets of anti-RNP autoimmunity can influence tissue targeting of autoimmune responses by direct effects on dendritic cells. A subset of myeloid dendritic cells targeting the lung mediates anti-RNP lung disease, and may represent a target for future therapeutic strategies.

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853 Fas Expression in Myeloid Cells Is Required To Prevent Systemic Autoimmunity, Carla M. Cuda ¹, Hemantr Agrawal ², Evan Weber ³, G. Kenneth Haines ⁴ and Harris R. Perlman ⁵, ¹Northwestern University, Chicago, IL, ²Northwestern University, ³Yale University

Significance: Rheumatoid arthritis (RA) manifests in persistent synovial inflammation, cellular infiltration, and pro-inflammatory cytokote production, and results in progressive cartilage and bone destruction. While the mechanisms underlying these phenotypes are not fully elucidated, insufficient apoptosis is a key player in RA pathogenesis. A critical mediator of the extrinsic apoptotic pathway includes the death receptor (DR) Fas. Lymphocyte-specific deletion of Fas reveals non-apoptotic roles for this DR in proliferation, and although lymphocytes are necessary for the initiation of RA, macrophages are crucial for its persistence. These highly activated and non-proliferating cells contribute to synovial inflammation and cartilage and bone destruction through the production of degradative enzymes, cytokines, and chemokines. However, the impact of myeloid cell-specific loss of Fas and its relationship to RA development and/or progression has yet to be examined.

Methods: Mice with Fas flanked by loxP sites (Fasfl/+loxP) were crossed with mice expressing Cre under control of the murine lysozyme M gene promoter (CreLysoM), which functions in mature lysozyme-expressing cells of the myelomonocytic lineage. CreLysoMFasfl/+loxP mice were verified by Real-time PCR and examined to determine non-apoptotic roles of Fas in myeloid cells. Flow cytometric analysis was employed to characterize both myeloid and lymphoid cell distribution and activation in bone marrow, blood and spleen. Luminex-based assays and ELISAs were used to detect serum cytokine and Ig levels as well as in vitro cytokine production by macrophages in response to LPS. Immunofluorescent and immunohistochemical staining revealed kidney pathology.

Results: Myeloid cell-specific loss of Fas significantly increased both total numbers of peripheral circulating blood cells and splenocytes. Increased percentages of bone marrow resident macrophages were seen. Selective deletion also disrupted myeloid cell homeostasis in the periphery by increasing levels of peripheral blood resident and inflammatory monocytes, as well as increasing both the number and activation level of total and inflammatory splenic macrophages. Additionally, in vitro LPS stimulation of both peritoneal macrophages and bone marrow-derived macrophages lacking Fas resulted in increased production of IL-6, TNFα and IL-1β. Loss of Fas in myeloid cells also affected dendritic cells and T cells, with these populations presenting a more activated phenotype. CreLysoMFasfl/+loxP mice displayed significantly increased serum IL-1α, IgG, total IgM and anti-dsDNA IgM levels and presented with more severe kidney pathology based on positive IgG staining, increased cellular infiltration and higher disease scores.

Conclusion: These results demonstrate that loss of Fas in myeloid cells is sufficient to induce inflammatory phenotypes in mice. Thus, we are the first group to show via myeloid cell-specific deletion of Fas that this DR typically associated with apoptosis also acts to prevent systemic autoimmunity. These data will have implications for RA by elucidating previously unknown functions of a potentially useful target for therapy.

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854 FLIP: The Novel Regulator of Macrophage Differentiation and Granulocyte Homeostasis, Qi Quan Huang², Harris R. Perlman¹, Zan Huang³, Robert Birkett², John D. Crispino¹ and Richard M. Pope¹, ¹Northwestern University, ²University of Medicine School, Chicago, IL, ³Northwestern University, Chicago, IL, ⁴Northwestern University

Background and Purpose: Macrophages are important mediators of innate immunity and chronic inflammation, and play an important pathogenic role in rheumatoid arthritis. In order to further understand the cellular
mechanisms contributing to the persistence of macrophages in RA, a myeloid lineage. Flip knock out mice line has been generated. Characterization of these mice demonstrated that FLIP was necessary for macrophage differentiation and survival, that macrophages are essential for maintaining granulocyte homeostasis.

**Methods:** Mice bearing floxed Flip alleles crossed with LysMCre mice resulted in Flip deletion in the myeloid cell lineage. The cell types in circulation and tissues were examined by morphology and by flow cytometry. Mixed chimera bone marrow reconstitution experiments were performed employing by CD45.1+ and CD45.2+ congenic C57BL/6 mice. Serum cytokines were quantified by LUMINEX 200. In vitro macrophage differentiation was performed from CD117+ bone marrow hematopoietic stem cells. Flip In vitro deletion was induced by recombinant Cre retro-virus.

**Results:** In addition to postnatal growth retardation and premature death, myeloid specific FLIP deficient mice exhibited a dramatic increase of circulating neutrophils and multi-organ neutrophil infiltration, which was mediated by increased cytokines and growth factors. Mature macrophages in the spleen, lymph nodes and the peritoneal cavity were significantly reduced. Further analysis of cells in peritoneal cavity discovered a significant inverse non-linear correlation of peritoneal macrophages and granulocytes. That is if macrophages were present, neutrophils were kept in a homeostatic level. In further analysis of cells in peritoneal cavity discovered a significant inverse mediated by increased cytokines and growth factors. Mature macrophages in circulation and tissues were examined by morphology and by flow cytometry. Recent studies show that IKK regulates innate immune reponses through the production of interferon-beta (IFNB), pro-inflammatory cytokines and chemokines. Recent studies show that IKK-deficiency can synergize with IFNβ therapy to reduce inflammation in passive K/BxN serum-induced arthritis, where the innate immune system is indispensable for disease initiation. However, there is no information on whether IKK regulates inflammation in a model of arthritis that depends on adaptive immunity. Therefore, we evaluated whether IKKe plays a role in murine collagen-induced arthritis.

**Method:** Wild type (WT), and IKKe−/− mice were immunized on days 0 with type II bovine type II collagen in complete Freund’s adjuvant and on day 21 in PBS. Joint histology on day 42 was evaluated for synovitis, bone erosion, extra-articular inflammation and proteoglycan damage (max score=16). Serum anti-type II collagen antibody levels were measured by ELISA. Levels of cytokines and chemokines in serum were measured by multiplex analysis. Gene expression in joint extracts was determined by quantitative real time PCR.

**Results:** Arthritis severity was significantly reduced in IKKe−/− mice compared with WT (p<0.02, n=13/group). Scores at peak arthritis severity on day 35 were 13.1±2.2 in WT compared with 8.3±2.2 in IKKe−/− mice. Histological analysis showed that bone erosion and proteoglycan loss in IKKe−/− mice was significantly reduced by 70% and 60%, respectively compared with WT (p<0.04). Surprisingly, levels of the pathogenic anti-collagen IgG2a antibody were reduced by 32±10% (p=0.04) in IKKe−/− serum while total IgG levels were similar to WT mice. Serum IL-6 and G-CSF levels were similar in WT and IKKe−/− mice with arthritis on day 35 and were significantly higher than in naive mice. Synovial MMP3 gene expression was significantly lower in IKKe−/− mice compared with WT mice (53±8% inhibition, p=0.02). Reduction of MMP9 and IFNβ genes was also decreased in IKKe−/− mice by 45±13% and 84±4%, respectively (p=0.058). Despite improved clinical scores, IL-1Ra, IL-6 and MMP-13 gene expression was not significantly reduced in IKKe−/− mice compared with WT mice.

**Conclusions:** IKKe unexpectedly regulates adaptive immune responses such as decreased production of pathogenic anti-type II collagen antibodies. Diminished disease severity in the model is probably due to a combination of decreased anti-collagen antibody production and suppression of synovial innate immune responses. This kinase represents a novel therapeutic target to suppress synovitis by regulating complex components of the immune system implicated in RA.

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**IMO-3100, a Toll-Like Receptor (TLR) Antagonist, Suppresses TLR7- and TLR9-Mediated Immune Responses in Non-Human Primates,** Lakshmi Bhagat, Jimmy X. Tang, Tim Sullivan, Ekambhar Kandimalla and Sudhir Agrawal.1 Idera Pharmaceuticals, Inc, Cambridge, MA; 2Idera Pharmaceuticals, Inc

**Background:** Immune complexes containing host-derived nucleic acids have been shown to induce inflammatory responses mediated through TLR7 and TLR9 and manifest autoimmune diseases, such as lupus and psoriasis. Blocking TLR7- and TLR9-mediated immune responses through use of an antagonist represents a novel approach for the treatment of selected autoimmune diseases. IMO-3100 is a dual antagonist of TLR7 and TLR9, which has shown potent activity in preclinical disease models of lupus, collagen-induced arthritis, psoriasis, and hyperlipidemia. In the current study, we have evaluated IMO-3100 for its pharmacodynamic mechanism of action in non-human primates.

**Methods:** IMO-3100 was administered to cynomolgous monkeys (N=4) as a weekly dose of 1.5 mg/kg for 4 weeks. Blood samples were collected prior to and after each IMO-3100 injection (i.e. Days 0, 3, 7, 10, 14, 17, 21, and 24) and also at days 28 and 35. PBMCs were isolated by Ficoll density gradient centrifugation method. PBMCs (1×10^6 cells/0.2 ml/well in 96 well plates) were incubated with agonists of TLR7 (50 µg/ml), TLR9 (3 µg/ml) or TLR4 (LPS, 100 ng/ml) for 24 hrs. Supernatants were harvested and IL-1β, IL-1Ra, IL-6, IL-8, IL-12, TNF-α, MIP-1α, MIP-1β, RANTES and MCP-1 levels in culture supernatants were determined using human cytokine antibody bead kits. IFN-α and IP-10 levels were measured by ELISA.

**Results:** Weekly administration of IMO-3100 for 4 weeks resulted in 25 to 95% reduction in various cytokines and chemokines induced by TLR7 and TLR9 agonists, including anti-collagen antibody production and suppression of synovial innate immune responses. This kinase represents a novel therapeutic target to suppress synovitis by regulating complex components of the immune system implicated in RA.

**Conclusion:** These results demonstrate that weekly administration of IMO-3100 to non-human primates suppresses ex-vivo immune responses mediated through TLR7 and TLR9, but not TLR4. IMO-3100 is in phase 1 clinical evaluation for potential applications in autoimmune and inflammatory diseases.


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**Involvement of Toll-Like Receptor 2 in Pristane-Induced Lupus,** Vilma Urbanovicvite, Silke Frey, Carsten Kirschning, Georg Schett and Reinhard E. Volf.1 Essen, Germany, 2Erlangen, Germany, 3 Department Internal Medicine 3, University Hospital Erlangen, University of Erlangen-Nuremberg, Erlangen, Germany
Materials and Methods: FLS were obtained from RA patients at the time of joint surgery. TLR2 mRNA and protein expression was assessed by RT-qPCR and western blot after stimulation of RA FLS with BLP, a ligand of TLR2. MiRNAs expression was analyzed using a microarray-based approach and confirmed by RT-qPCR. Transfection of FLS was performed using the AMAXA nucleofactor kit II (e) system. Identification of 19b targets was assessed by the luciferase assay using the psiCHECK™-2 Vectors. IL-6 secretion was evaluated using the ELISA sandwich method.

Results: We first showed that RA FLS expressed constitutively TLR2 and that TLR2 expression was up-regulated in response to BLP. Using a miRNA microarray analysis, we identified the downregulation of miR-19b which was predicted to target TLR2 mRNA. Down regulation of mir-19b was confirmed by qRT-PCR. Transfection of RA FLS with mir-19b mimics decreased TLR2 expression. Using a luciferase assay, we also showed that mir-19b targets directly TLR2 mRNA 3’UTR. In addition, direct targeting of TLR2 mRNA by 19b mimic inhibited IL-6 secretion by BLP activated RA FLS.

Conclusion: Together, these data demonstrated a critical functional link between miR-19b, TLR2 expression and IL6 secretion by RA FLS, which could play an important role in RA inflammation.

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Myeloid but Not Lymphoid Bim Expression Is Required Suppress SLE-Like Disease.
Hemant Agrawal1, Evan Weber1, Alexander Misharin1, Carla M. Cuda1, G. Kenneth Haines2, Rosalind Ramsey-Goldman3 and Harris Perlman1. 1Dept Med/Div Rheumatology, Northwestern University, 2Yale University

Purpose: Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease of unknown etiology characterized by production of autoantibodies and extensive organ damage. While both innate and immune cells are critical to SLE pathogenesis, intrinsic differences in myeloid cells, such as macrophages (Mφ) and dendritic cells (DC), may influence the T and B cell phenotypes observed in patients with SLE. To date, few studies have focused on the loss of Bim, a pro-apoptotic member of the Bcl-2 family, specifically in monocytes/Mφ and its non-apoptotic roles such as activation, cytokine production, and presentation and their relationship to the pathogenesis of lupus.

Method: Peripheral blood from aged and sex matched healthy controls and patients with inactive (SLAM <2) or active SLE (SLAM >10) were analyzed for monocyte expression of Bim and markers of activation. Additionally, mice lacking Bim specifically in T cells (CreCD4Bimiflox/flox), B cells (CreCD19Bimiflox/flox) and monocytes/Mφ (CreLysMBimiflox/flox) using the Cre-loxP system were generated and the deletion of Bim was verified by real time PCR. Bimiflox/flox (Bim intact) mice were used as controls. Using (~2 mon) and aged mice (CD4+ and B cells), we analyzed histological and flow cytometric analyses. Luminescent based assays and ELISAs were performed to detect antibody isotypes, autoantibodies, cytokines/chemokines, and activation of kinases. A pathologist blinded to the study scored all tissues for SLE-like disease.

Summary: SLE patients with active disease displayed reduced expression of Bim in monocytes but not in lymphocytes or granulocytes, which was associated with increased expression of HLA-DR, CCR2, CD62L, and CCR5 but not CD163. To further understand the importance of the reduction of Bim in monocytes, we studied mice lacking Bim in monocyes/Mφ. Young and aged CreLysMBimiflox/flox mice showed severe splenomegaly compared to Bimiflox/flox, CreCD4Bimiflox/flox and CreCD19Bimiflox/flox mice. While both young and aged CreLysMBimiflox/flox mice had increased numbers of activated splenic Mφ and DC, only the aged CreLysMBimiflox/flox mice had increased numbers of splenic Mφ. Furthermore, young and aged CreLysMBimiflox/flox mice showed increased accumulation of activated splenic B and T cells. Mφ from young CreLysMBimiflox/flox mice induced increased OT-II T-cell responses as compared to Bimiflox/flox mice and displayed reduced phospho-AKT but increased phospho-cJun, and p38. Additionally, Mφ from aged mice showed reduced caspase 3/7 activation. There were elevated levels of circulating autoantibodies (total IgM and isotypes of IgG) and cytokines (IL-12p70 and IL-17) in CreLysMBimiflox/flox mice serum. Moreover, CreLysMBimiflox/flox mice displayed severe renal damage as evident by increased glomerular size, cellular infiltration, retention of immune complexes, and high kidney disease scores.
Conclusion: These data demonstrate that reduction of Bim leads to a novel and non-apoptotic phenotype in monocytes/Mϕ and the loss or reduction of Bim in monocytes/Mϕ is sufficient to activate lymphocytes and SLE-like disease. Thus, the level of Bim in monocytes/Mϕ may be a biomarker of SLE-disease activity.

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Natural Killer (NK) Cells Resident in Normal Human Skin Are Distinct from Blood and Lung NK Cells. Ahmed Gehad1, Sandra King1 and Robert Fuhlbrigge2. 1Brigham and Women’s Hospital, 2Children’s Hospital- Boston, Boston, MA

Normal human skin contains a broad collection of leukocytes, including T cells, dendritic cells and NK cells, that form an intricate network important for immunosurveillance and active in inflammatory skin disease. Although skin homing T cells and skin resident dendritic cell populations have been described in detail, little is known regarding the characteristics of NK cells resident in skin. Published studies of NK cell subsets in humans have focused primarily on surface receptor expression of NK cell populations circulating in peripheral blood, rather than cells recovered from tissue. We hypothesized that skin resident NK cells may represent a distinct subset of NK cells with phenotypic, homing and functional properties distinct from NK cells in peripheral blood and resident in other tissues. For this study, we used a short term immortalization culture method for leukocyte isolation. Samples of non-inflamed human skin obtained from cosmetic surgery procedures in accordance with IRB guidelines were cultured on tantalum-coated carbon matrices in the absence and presence of various cytokines including IL-2, IL-15, IL-18, IL-21, and FLT-3 ligand. Leukocytes were recovered after 2–3 wk in culture and analyzed by flow cytometry. CD3-CD56+ NK cells present in normal skin represented a small but reproducible fraction (2–12%) of total skin leukocytes recovered. A combination of IL-15 and IL-18 yielded maximal recovery of NK cells, though analyses were performed on both cytokine stimulated and non-stimulated cultures. The majority of skin NK cells, as well as skin T cells recovered in parallel, expressed skin homing receptors (CLA, E- and P-selectin ligands), as well as both CD4 and CD8 integrins, but did not express L-selectin or CCR7, consistent with a peripheral tissue homing phenotype. However, in contrast to skin T cells, only a small fraction of NK cells expressed CCR4 and CCR6 and were negative for CCR10 and CXCR4, indicating skin homing NK cells utilize a different chemokine signal pathway than skin homing T cells. NK cells recovered from peripheral blood or cultures of normal lung tissue expressed much higher levels of CD16 and much lower levels of skin homing receptors (E- and P-selectin ligands) compared to skin resident NK cells, providing evidence for subset selection among the cells resident in skin. The majority of skin NK cells expressed both the surface receptor NKGD2 and intracellular perforin and granzyme B, molecules required for NK cell cytotoxic function, and also produced IFN-γ and TNF, but not IL-10 or IL-6. These data show that NK cells in the skin represent a unique population with a distinct profile of homing receptors, cytokine production, and cytoxic functions as compared to NK cells from blood or lung tissue and compared to T cells from skin. These data suggest that skin resident NK cells may play a role in innate and adaptive immune responses in the skin that is independent from cells recruited from blood, and suggests similar subsets with unique characteristics may be present as resident cells in other tissue sites.

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p21 Suppression of Inflammatory Arthritis Requires the PCNA Domain and Inhibition of p38. Angelica K. Gierut1, A. K. Gierut2, Sandra King1 and Robert Fuhlbrigge2. 1Brigham and Women’s Hospital, 2Children’s Hospital- Boston, Boston, MA

Purpose: The etiology of rheumatoid arthritis (RA) is unknown. We have previously shown that RA patient synovium has a reduction of p21, a cell cycle inhibitor. We are also the first to demonstrate a novel role for p21 as suppressor of inflammation. Knock down of p21 in healthy human peripheral blood monocyte-derived macrophages leads to increased production of inflammatory cytokines IL-1β, TNF-α, and IL-6. In addition, mice deficient in p21 have increased in vivo production of inflammatory cytokines and mortality with lipopolysaccharide (LPS)-induced endotoxic shock. Here, we sought to determine the role and mechanism of p21-mediated suppression of experimental inflammatory arthritis.

Methods: WT or p21−/− (C57BL/6) mice were injected intraperitoneal- ally (IP) with 300 μL of K/BxN serum and ankle circumference was measured over 7–25 days. Ankles were then harvested, sectioned, stained for histochemical or immunohistochemical analysis and scored by a pathologist blinded to the study. For phosphoprotein assays, WT or p21−/− mice were injected IP with thioglycollate, and peritoneal macrophages were harvested and cultured in vitro overnight. Cells were stimulated with 10 ng/mL of LPS and cell lysates were collected and analyzed for the phosphorylation status (activation) of various proteins using a multiplex bead array. Similarly, thioglycollate-elicited peritoneal macrophages from WT mice were incubated with several Tat-conjugated peptides corresponding to different domains of the p21 protein (10nM) for 2 hours prior to the addition of LPS (in the presence of peptide). Lysates were analyzed by multiplex bead array. For in vivo studies, WT mice were injected IP with 10 mg/kg peptide 30 minutes prior to K/BxN serum and daily throughout.

Results: Mice deficient for p21 developed increased ankle swelling, joint destruction, and inflammatory infiltrate, as compared to WT mice. There was increased numbers of macrophages in the pannus of p21−/− mice that correlated with bone destruction. Furthermore, the disease failed to fully resolve in p21−/− mice even after 25 days post injection of serum. Treatment with a peptide corresponding to the proliferating cell nuclear antigen (PCNA) binding domain of p21 was superior in suppressing inflammatory arthritis and reduced the numbers of synovial macrophages compared to control peptide. Peritoneal macrophages from mice deficient in p21 demonstrated a consistent reduction of phosphorylation of the mitogen-activated protein kinase (MAPK), p38, following LPS stimulation compared to those from WT controls. In comparison, a peptide corresponding to the PCNA binding domain of p21 added before LPS significantly decreased the level of phosphorylated p38 compared to those treated with a control peptide.

Conclusion: These data indicate that deficiency of p21 augments experimental arthritis in mice, and that a peptide corresponding to the PCNA binding domain of p21 acts to decrease experimental arthritis via decreased activation of p38. These efforts suggest that p21 is a potential biomarker and/or therapeutic target for RA.

Disclosure: A. K. Gierut: None; M. Mavers: None; C. M. Cuda: None; A. Misharin: None; E. Weber: None; H. R. Perlman: None.

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Peripheral Blood Mononuclear Cells and Plasmacytoid Dendritic Cells from Healthy Human Females Exhibit Altered TLR7-Mediated Immune Responses Compared to Males. Melissa Precopio1, Dong Yu1, Ekambur R. Kandimalla2 and Sudhir Agrawal2. 1Idera Pharmaceuticals, Cambridge, MA, 2Idera Pharmaceuticals

Background: Toll-like receptors (TLR) are a family of pathogen-associated molecular pattern recognition receptors expressed by cells of the immune system. TLR7 and TLR9 are expressed in intracellular compartments of human B cells and plasmacytoid dendritic cells (pDCs) and recognize molecular patterns of nucleic acids. There is growing evidence that immune complexes containing nucleic acids induce proinflammatory cytokines through TLR7 and TLR9 and exacerbate certain autoimmune diseases. Women are more prone to manifestation of autoimmune diseases than men. This study was carried out to evaluate the differences in immune responses induced through TLR7 and TLR9 agonists. These data indicate that deficiency of p21 augments experimental arthritis in mice, and that a peptide corresponding to the PCNA binding domain of p21 acts to decrease experimental arthritis via decreased activation of p38. These efforts suggest that p21 is a potential biomarker and/or therapeutic target for RA.

Methods: We measured cytokine induction and costimulatory marker upregulation in response to specific TLR agonists in PBMCs and pDCs obtained from healthy male (n = 15, age: 23–60 years) and female (n = 15, age: 18–58 years) subjects. The agonists used in these studies include an RNA-based TLR7 agonist and a DNA-based TLR9 agonist. To further discern differences in TLR7- and TLR9-mediated immune responses in systemic lupus erythematosus (SLE) patients (n = 9, age: 29–78 years) on treatment with plaquenil/hydroxychloroquine and healthy female subjects (n = 10, age: 22–56 years), we measured cytokine induction in PBMCs in response to TLR7 and TLR9 agonists.

Results: In PBMCs from healthy females, TLR7 agonist induced higher levels of IFN-α, and IP-10 and lower levels of IL-1Ra, IL-1β, IL-6, IL-8 and IL-10 compared with PBMCs from healthy males. The levels of IL-12, MIP-1β, and MCP-1 induced by TLR7 agonist were not different in PBMCs from females and males. pDCs from females showed higher levels of TLR7

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agonist-induced IL-12, IP-10, IFN-α, and TNF-α than pDCs from males. TLR9 agonist induced similar levels of immune responses in PBMCs and pDCs from females and males, except IL-1Ra levels were higher in PBMCs from males than females. In studies comparing SLE patients with healthy female controls, TLR7 agonist induced lower levels of IFN-α, TNF-α, IP-10, and IL-6 in PBMCs from SLE patients than healthy females. TLR9 agonist induced lower levels of TNF-α, IL-6, MIP-1α, and MIP-1β in PBMCs from SLE patients than PBMCs from healthy females. The lower levels of TLR7- and TLR9-mediated immune responses in PBMCs from SLE patients could be a result of treatment with plaquenil, an inhibitor of endosomal TLR-mediated immune responses through neutralization of endosomal acidification.

Conclusions: Notable differences in TLR7-mediated immune responses were observed in PBMCs and pDCs from healthy females compared with males that may play a role in autoimmune diseases afflicting females disproportionately.

Disclosure: M. Precoopil: Idera Pharmaceuticals, 1, 3; D. Yu: Idera Pharmaceuticals, 1, 3; E. R. Kandimalla: Idera Pharmaceuticals, 1, 3; S. Agrawal: Idera Pharmaceuticals, 1, 3.

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Post-Translational Control Mechanisms Regulate Dendritic Cell Activation of T Cell Responses. Dana Orange1, Jak Fač2, Nathalie Blacher2 and Robert Darnell3. 1The Hospital for Special Surgery; 2The Rockefeller University

Purpose: In addition to being some of the most potent of antigen presenting cells, dendritic cells (DCs) have the unique capability of cross presenting. When DCs phagocytose an apoptotic cell, antigen acquired from that cell can be presented on the cell surface in the context of MHCI in addition to MHCI to activate cytotoxic CD8 T cells. It has been demonstrated that in order for this cross presentation pathway to lead to CD8 T cell activation, the DC needs to be licensed by an activated CD4 T cell via CD40L stimulation. The steps downstream of CD40 signaling that allow for cross presentation remain unclear. Work from our group previously showed that although they are both calcineurin inhibitors, FK506 but not cyclosporine blocks DCs from being able to stimulate T cells via the cross presentation pathway compared to healthy controls.

Methods: Healthy donors PBMCs were cultured with IL 4 and GMCSF for 6 days. Immature DCs were allowed to phagocytose H11001 infected apoptotic 3T3 cells and then matured with TNF and PGE2. Antigen presenting DCs were then treated with either actinomycin D or cycloheximide, inhibitors of transcription and translation respectively, and cocultured with MACS purified 3T3 cells and then matured with TNF and PGE2. Antigen presenting DCs were then treated with either actinomycin D or cycloheximide, inhibitors of transcription and translation respectively, and cocultured with MACS purified 3T3 cells and then matured with TNF and PGE2. Antigen presenting DCs were then treated with either actinomycin D or cycloheximide, inhibitors of transcription and translation respectively, and cocultured with MACS purified 3T3 cells and then matured with TNF and PGE2. Antigen presenting DCs were then treated with either actinomycin D or cycloheximide, inhibitors of transcription and translation respectively, and cocultured with MACS purified 3T3 cells and then matured with TNF and PGE2.

Conclusion: This work demonstrates that DC licensing for the cross presentation pathway is under a mechanism of post-translational control. In the absence of CD40L signaling, DC cross presentation results in cross tolerance. The finding that transcriptionally and translationally blocked dendritic cells can still activate CD8 T cell responses indicates that key signaling events downstream from CD40L stimulation do not require transcription or translation. As immune responses require some of the fastest reaction times in the body, it stands to reason that a critical switch between activation and tolerance would not require the time for new gene transcription or translation. Instead, we propose that the essential control of DC licensing is likely to be a protein that has been translated but held in a conformationally inactive state.

Disclosure: D. Orange: None; J. Fač: None; N. Blacher: None; R. Darnell: None.

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Reduced T-Cell-Dependent Humoral Immune Response in Microsomal Prostaglandin E Synthase-1 Null Mice. Rahul G. Matnani2, Fumiaki Kojima1, Jerold G. Woodward3 and Leslie J. Crofford1. 1Univ of KY, Lexington, KY; 2Univ of KY

Microsomal prostaglandin E synthase-1 (mPGES-1) is an inducible enzyme that specifically catalyzes the conversion of prostaglandin (PGH2) to PGE2, most prominently in inflammatory conditions. We previously showed that mPGES-1 null mice had a significantly reduced incidence and severity of collagen-induced arthritis (CIA) compared to wild-type mice. Reduced CIA was associated with a marked reduction of antibodies to type II collagen, known to be required for developing autoimmune inflammatory arthritis in this model. In the present study, we further elucidated the role of mPGES-1 in the humoral immune response. Basal levels of serum IgM and IgG were significantly reduced in mPGES-1 null compared with wild-type mice (P<0.05), but IgM and IgG production in splenocytes treated ex vivo with LPS were not different. Immunization with either the T-cell independent type-1 antigen TNP-LPS or the T-cell independent type-2 antigen DNP-Ficoll revealed minimal differences in hapten-specific antibody levels when comparing mPGES-1 null and WT mice. However, mPGES-1 null mice exhibited significant reduction of hapten-specific serum antibodies compared with wild-type mice in response to immunization with the T-cell dependent antigen DNP-KLH in CFA including IgM (days 7–21 post-immunization, P<0.05) and IgG (days 7–28 post-immunization, P<0.05). Germinal center formation in the spleen of mPGES-1 null mice was phenotypically similar to WT mice in response to immunization with DNP-KLH when evaluating the %PNA positive germinal centers to IgD positive regions (43.5 ± 1.8 vs 40.8 ± 2.1, P=NS). To determine if the effect of mPGES-1 and PGE2 was related to hematopoietic or non-hematopoietic cells, we generated bone marrow chimeras. The results indicate that mPGES-1 deficiency in non-hematopoietic cells was the critical factor for reduced antibody production after immunization with DNP-KLH since transfer of mPGES-1 null bone marrow (BM) to non-lethally irradiated WT recipients expressed hapten-specific antibodies equal to the WT BM→WT, but WT BM→mPGES1 null expressed reduced antibodies similar to mPGES1 null BM→null. We conclude that PGE2-dependent immunization during immunization plays a key role in T-cell dependent humoral immune responses, likely as a result of altered T-cell phenotype. These findings may have relevance to the pathogenesis of autoimmune inflammatory arthritis associated with autoantibodies such as rheumatoid arthritis.

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Objectives: The development of atherosclerosis and subsequent increased risk of cardiovascular disease (CVD) is known to be associated with inflammation. Studies have shown an increased risk of CVD in systemic lupus erythematosus (SLE). Inflammation seen in atherosclerosis involves various immune mediators, including interactions between adhesion molecules on endothelial cells and on monocytes. Very late antigen-4 (VLA-4) is an adhesion molecule in the integrin family found on monocytes and has been implicated in monocyte recruitment during development of atherosclerosis. A recent study noted an increased expression of VLA-4 in SLE monocytes, but the regulation is poorly understood. We aimed to further define variables governing the expression of VLA-4 in monocytes in patients with SLE compared to healthy controls.

Methods: CD14+ human monocytes were obtained from whole blood of healthy adult patients and SLE patients. Flow cytometry was used to measure expression of VLA-4 at rest and upon exposure to various agents, including interferon gamma, interferon alpha, interleukin-4, and vitamin D. VLA-4 mRNA expression in SLE and healthy monocytes was measured using qRT-PCR. Healthy monocytes were incubated in control and SLE sera, and VLA-4 was expression evaluated using flow cytometry and immunofluorescence (IF).

Results: VLA-4 (CD49d) expression was significantly higher on control monocytes compared to SLE monocytes as measured by mean fluorescence intensity (p<0.05). However, levels of VLA-4 mRNA were significantly lower in control monocytes compared to SLE monocytes (p<0.05). Exposure
The Help of Autoantibody-Inducing CD4+ T Cell and Antigen Cross-Presentation Are Required for the Full-Maturation of Cytotoxic T Lymphocyte and Subsequent Lupus Kidney Disease. Yumi Miyazaki1, Ken Tsunuiyma2 and Shunichi Shiozawa2. 1Department of Biophysics, Kobe University Graduate School of Health Science/Department of Biophysics, Kobe University Graduate School of Medicine, Kobe, Japan. 2Department of Biophysics, Kobe University Graduate School of Health Science/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Objective: A novel ‘self-organized criticality theory’ explaining the cause of systemic lupus erythematosus (SLE) of ours (Tsunuiyma K. et al. PLoS ONE 4(12):e8382, 2009) shows that overstimulation of CD4+ T cell beyond its self-organized criticality results in de novo generation of autoantibody-inducing CD4+ T (aiCD4+ T) cell with T cell receptor (TCR) revision. The aiCD4+ T cells induced not only autoantibodies including rheumatoid factor (RF), anti-Sm and anti-dsDNA antibody but also full-matured cytotoxic T lymphocyte (CTL) via antigen cross-presentation, after which the CTL caused lupus kidney disease. Here we investigated the contribution of aiCD4+ T cell-help to the pathogenesis of immune tissue injury, and show that aiCD4+ T cell-help and antigen cross-presentation are both essentially required for generating full-matured effector CTL and subsequent lupus tissue injuries.

Methods: BALB/c mice were immunized 12x with ovalbumin (OVA). The mice were depleted CD4+ T cells by treating anti-CD4 antibody 24 hours prior to 6x, 9x, and 12x immunization with OVA, and IFNy+ CD8+ T cell in spleen and peritoneum were treated with anti-CD8 antibody. The mice were immunized 12x with keyhole limpet hemocyanin (KLH) was transferred into the CD4+ T cell-depleted mice immunized 8x with OVA, and IFNy CD8+ T cell and proteinuria were examined. We also transferred pre-mature CD8+ T cell of the mice immunized 8x with OVA into the mice immunized 12x with KLH to induce aiCD4+ T cell. These recipient mice were immunized 1x with OVA and KLH, followed by treating with chloroquine to inhibit antigen cross-presentation.

Results: In the mice immunized 12x with OVA, depletion of CD4+ T cells by treating anti-CD4 antibody abrogated the induction of IFNy-producing effector CD8+ T cell and lupus kidney disease. To test whether this CD4+ T cell-mediated help is mediated by aiT cells or antigen-specific T cells, we have transferred CD4+ T cells from mice immunized 12x with KLH into the CD4+ T cell-depleted BALB/c mice immunized 8x with OVA. The result showed that both immune tissue injury and OVA-specific IFNy+ CD8+ T cells arose in these mice after transfer, indicating that aiCD4+ T cells with de novo TCR revision are required for the full-maturation of CD8+ T cell and lupus kidney disease. We next studied if aiCD4+ T cell could induce effector CTL and/or tissue injury in the absence of antigen cross-presentation or not, we transferred the pre-matured CD8+ T cells obtained from the mice immunized 8x with OVA, in which CTL was not full-matured, into the mice immunized 12x with KLH containing aiCD4+ T cells. Upon booster immunization 1x with KLH and OVA, aiCD4+ T cell, IFNy-producing effector CD8+ T cell (CTL) and proteinuria were all increased. However, when chloroquine which inhibits antigen cross-presentation was added, IFNy-producing effector CTL and proteinuria were both abolished, indicating that aiCD4+ T cell-help and antigen cross-presentation are required for the development of lupus kidney disease.

Conclusion: The help of aiCD4+ T cell and antigen cross-presentation are sine qua non for the full-maturation of effector CTL and subsequent lupus kidney disease.

Disclosure: Y. Miyazaki: None; K. Tsunuiyma: None; S. Shiozawa: None.
FcyRI properties, we probed the critical contributions of the distinct cytoplasmic tail (CY) of FcyRI α-chain in inducing receptor functions. Unlike other FcR, the FcyRI CY domain contains serine residues that are phosphorylated by CK2 in vitro, and the cytoplasmic domain of FcyRI is constitutively phosphorylated in resting cells. As a consequence, the binding of protein 4.1G, a novel partner associated with FcyRI α-chain CY but not with other FcR CY, is greatly promoted when FcyRI CY is phosphorylated. Since other members of the protein 4.1G family (the Four.1 protein, Ezrin, Radixin, Moesin (FERM) family) have been shown to facilitate lipid raft association of TCR and BCR to promote formation of immunological synapses, we hypothesized that serine phosphorylation of FcyRI CY with increased association with protein 4.1G would further promote the ability of FcyRI to associate with lipid rafts. Consistent with earlier reports, we observed that FcyRI constitutively resides in lipid rafts in macrophages transfected with human FcyRI. However, in cells transfected with a mutated form of human FcyRI lacking the ser-based CK2 phosphorylation site(s), FcyRI was distributed predominately outside of lipid microdomains, indicating that phosphorylation of FcyRI CY is required for lipid raft colocalization. These results are consistent with a role for protein 4.1G in tethering FcyRI within lipid rafts. The phosphotyrosine-based γ-chain signaling plus the phosphoserine-based α-chain signaling form a unique FcyRI signaling pathway. These results provide additional insights into the unique signaling potential of FcyRI that can explain the previously documented unique functional potential of FcyRI. Further mechanistic studies into the regulation of FcyRI function will allow a determination of the importance of increased expression of this receptor in patients with lupus.

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ACR Poster Session B
Metabolic and Crystal Arthropathies - Pathogenesis, Epidemiology, and Clinical Manifestations II
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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A Prospective Study of Correlates of Axial Gout. Rukmini M. Konatalapalli1, Elena Lumezanu3, James Jelinek3, Mark Murphey1, Elizabeth Carter2 and Arthur Weinstein1, 1Armed Forces Institute, 2Medstar Health Research Institute, 3Washington Hospital Center, 4Washington Hospital Center, DC

Objective: Axial gout is considered to be a rare manifestation of gouty arthritis. In our earlier retrospective study we found prevalence of axial gout to be 14%. This prospective study was done to determine the prevalence of axial gout in a population of patients with established gouty arthritis and to analyze potential clinical, laboratory, and radiological correlates.

Methods: Forty eight subjects with a history of gouty arthritis (ACR criteria) for 3 or more years and who had an attack of acute gouty arthritis or had hyperuricemia in the previous year, were included. Subjects were questioned about back pain, examined clinically for arthritis, joint deformities and subcutaneous tophi, and had radiographs of the hands and feet, as well as computerized tomographic (CT) scan without contrast (the preferred imaging modality to detect gouty erosive disease in the spine) of the cervical spine, lumbar spine and sacroiliac joints (SIJs), serum uric acid level and serum creatinine. CT scans were read by one of three radiologists who were blinded to results of the radiographs and the radiographs were read by an experienced rheumatologist (AW) who had no knowledge of CT scan results. Patients with characteristic erosions and/or tophi in the spine or SIJs were considered to have axial or spinal gout. For statistical analysis Fisher’s exact test and Wilcoxon Two-Sample tests were used.

Results: Seventeen patients (35%) had CT scan evidence of spinal gout erosions and/or tophi. Tophi in the axial skeleton were identified in 7 of the 48 subjects (14.6%). In the entire studied population the mean age was 61 years, mean duration of gout was over 10 years in 26 (54%) and less than 10 years in 22 (46%), mean serum uric acid level was 7.1mg/dl and 22 (46%) had clinical tophi. Thirty five (73%) were men and 42 (87%) were African American. No correlations were found with these variables and spinal gout nor was there any correlation with the presence of back pain which occurred in 24 (50%) patients. The location of the characteristic CT changes of axial gout was 7 (42%) cervical, 16 (94%) lumbar and 1 (6%) SIJs. Fourteen patients (82%) had axial gout in more than one location. Abnormal hands and feet radiographs were found in 21 (44%) patients and strongly correlated with CT scan evidence of axial gout (p< 0.0005). All patients with tophi in the spine had abnormal hand and/or feet radiographs (p< 0.005).

Conclusion: Axial gout may be a common feature of gouty arthritis, at least in our predominantly African American population with poorly controlled gouty arthritis. The lack of correlation with clinical back pain, the use of magnetic resonance imaging rather than CT imaging in patients with back pain and the lack of recognition of the problem of spinal gout by physicians, suggest that this diagnosis is often missed.

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Acute Gout Results in Increased Plasma Myeloperoxidase: A Potential Mechanism for Increase Cardiovascular Risk? Lisa K. Stamp3, Irada Khalilova2 and Tony Kettle1. 1University of Otago, Christchurch, New Zealand, 2University of Otago

Background: Gout is the most common form of inflammatory arthritis in men >40 years age. While the joint manifestations of gout dominate, patients with gout have a substantially increased risk of cardiovascular disease (CVD). However, not all of the increase is explained by traditional cardiovascular risk factors. Myeloperoxidase (MPO), which is released from neutrophils as part of the inflammatory process, has been implicated in the pathogenesis of CVD and is associated with coronary artery disease. The aim of this study was to determine whether MPO concentrations were increased in patients with acute and/or controlled gout.

Methods: 40 patients with gout (20 with acute gout, 20 with inter-critical gout) and 12 healthy controls were recruited. Plasma was assayed for urate, MPO protein and MPO activity. Urate was measured by HPLC and MPO protein and activity by ELISA.

Results: 4/12 healthy controls (HC), 17/20 acute gout and 19/20 inter-critical gout patients were male. The age (mean (range)) was 40.5 years (20–52) HC, 55.5 years (34–91) acute gout, and 63.2 years (42–82) inter-critical gout. As expected plasma urate was significantly higher in the subjects with acute gout (465±101µM) as compared to those with inter-critical gout (357 ± 87.8µM) (p<0.05). Plasma MPO protein was significantly higher in patients with acute gout compared to healthy controls, but not significantly different from those with inter-critical gout. MPO activity was significantly increased in patients with acute gout as compared to those with inter-critical gout and HC (Figure 1).

Conclusions: MPO is released during the acute inflammatory response associated with gout flare. This increase in MPO provides another mechanism for the increase in cardiovascular disease seen in gout patients. More active MPO in patients with acute gout may contribute to oxidative stress in the vasculature and the increased CVD risk. Further studies are required to determine the association between MPO and CVD in patients with gout.

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A-SAA Induces Cytokine Production and Matrix Metalloproteinase Activity in Adipose and RA Synovial Tissue. Jennifer McCormick, Ronan M. Miulan, Mary Connolly, Chun Teck Ng, Ursula Fearon and Douglas J. Veale. Dublin Academic Medical Centre, Dublin, Ireland

Background: Rheumatoid Arthritis (RA) is associated with a significant increase in cardiovascular (CV) mortality. Serum Amyloid A (A-SAA), an acute phase protein with cytokine-like properties is increased 1000 fold

Disclosure: None; A. Weinstein: None; R. P. Kimberly: None; J. C. Edberg: None; T. Kettle: None.
Association of Vitamin K and Chondrocalcinosis of the Knee: The MOST and Framingham Osteoarthritis Studies. Devyani Misra1, Sarah L. Booth2, Erin K. Halley3, Irina Toltsykh6, Michael Nevitt6, C. Elizabeth Lewis3, James Torner1, Piran Ababadi4, David T. Felson1 and Tuhina Neogi1,2.

1Boston Univ Sch of Med, Boston, MA, 2Boston University School of Medicine, Boston, MA, 3BUSM, Boston, MA, 4BWH, Harvard University, Boston, MA, 5UAB, Birmingham, AL, 6UCSF, San Francisco, CA, 7U-Iowa, Iowa City, IA, 8USDA HNRCA, Tufts University, Boston, MA

Purpose: Vitamin K (VK) plays a key role in regulation of calcification in soft tissue. A knockout mice model demonstrated that in absence of a VK-dependent protein (MGP), there was excessive calcification of cartilage. Hence, VK deficiency may contribute to chondrocalcinosis (CC) of the knee. We examined the association of VK with prevalence of CC in the MOST and Framingham Osteoarthritis Studies.

Methods: Forty RA patients were recruited and assessed at baseline, 0.5, 1 and 4 years. RA disease activity measures (SJC, TJC, DAS28) and IL-6 at 0.5, 1 and 4 years. A local regression (LOESS) plot of association between log-transformed VK levels and CC prevalence was used to examine effect size and association.

Results: Among 1795 participants (1180 from MOST, 615 from Framingham Osteoarthritis Studies), 287 participants developed CC during follow-up. Mean age 59.7 years, 59% women, 57% RA. Mean VK levels was 20.6% lower (95% CI 10.5%–30.6%) in participants with CC vs. those without. There was a significant effect on risk of CC associated with VK levels adjusted for baseline CC, sex and age (OR 0.37, 95% CI 0.18–0.76). No significant effect was found for baseline CKD or cCVD. Effect measure modification by cohort was tested separately.

Conclusion: Vitamin K deficiency is associated with increased prevalence of CC in RA. Further studies are warranted to explore potential effects of VK on extra-skeletal mineralization, using different measures of VK.

Fig. 1. Local regression (LOESS) plot of association of vitamin K with prevalent chondrocalcinosis.

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873 Calcium Pyrophosphate Crystal Arthritis (CPPA) Is a Frequent Cause of “Refractory Gout”, Fernando Perez-Ruiz1, Ana M. Herrero-Beites1, Alberto Alonso-Ruiz1 and Marcelo Calabozo2,3, Hospital de Cruces, Jopelana, Spain, 1Hospital de Cruces, 2Hospital de Górliz

Background: Proper treatment of hyperuricemia of gout is associated with a reduction in the number of flares to less than 10% of patients after 12-month therapy suffer from gout flares (Schumacher HR, Rheumatology 2009, Becker MA, J Rheumatol 2009).

Objective: to evaluate the impact of coexistent CPPA in joint flares in patients with gout.

Methods: analysis of data from a cohort of 610 patients with a diagnosis of gout based on monosodium urate (MSU) crystal observation and who showed proper control (serum urate <6 mg/dl) of uric acid at 12-month follow-up, and colchicine prophylaxis stopped. CPPA was defined as presence of CPP crystals in the cytoplasm of white cells in synovial fluid (SF) samples and radiographic chondrocalcinosis. Microscopy procedures for observation and identification of MS and CPP crystals included normal light and polarized light with first order red compensator 400x. Contrast-phase 400x and 1000x microscopy was used in addition to further investigate SF samples negative for crystals with normal and polarized microscopy.

Results: 23/610 (3.8%) patients with crystal-proven gout also had a diagnosis of CPPA. Of them, 6 showed both MSU and CPP crystals in the same synovial fluid sample, prior or during the first year of urate-lowering treatment, so they were maintained on colchicine prophylaxis and not included in further analysis. The remaining 17 patients showed CPP crystals during further follow-up, CPPA appearing at mean follow-up of 40 ± 16 months (range 18 to 94). Overall, 49/610 (8.03%) patients had at least an episode of acute arthritis that was attributed to ‘refractory’ gout, 17/49 (34.7%) showing CPP crystals during further follow-up. CPPA appeared in patients with gout vs. patients with gout + CPPA, except for mean age (59 ± 12 vs.
71 ± 12 years). BMI (28.1 ± 3.6 vs. 26.5 ± 3.3 kg/m²), and clearance of creatinine (87 ± 33 vs. 62.2 ± 30 ml/min).

**Conclusions:** Definite CPPA in patients with crystal proven gout is found in up to 4% of patients with gout. CPP arthritis comprised for one third of the flares that appeared after 1-yr control of hyperuricemia. Synovial fluid samples should be obtained and carefully studied before considering “refractory gout” diagnosis.

**Disclosure:** F. Perez-Ruiz: None; A. M. Herrero-Beites: None; A. Alonso-Ruiz: None; M. Calabozo: None.

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**Background:** Hyperuricemia, a highly frequent condition (84%) in renal transplant (RT) patients, has been mainly associated with the use of calcineurin inhibitors. We reported a higher incidence of gout in patients with hyperuricemia pre-transplant than patients who developed this condition after the allograft (19.9 vs. 2.6 × 1000 patient-years). The use of cyclosporine and tacrolimus were not the major variables linked to this finding.

**Objective:** We hypothesized that a specific HLA background may influence the development or not of hyperuricemia in RT patients.

**Methods:** We included 162 RT patients with at least one year of follow-up post-transplant. Hyperuricemia was defined as at least one elevated serum urate acid determination of >7 mg/dl in women and >7 mg/dl in men. Patients were divided in groups: 1) without hyperuricemia pre-transplant but with it after the allograft (n = 40), 2) without hyperuricemia pre and post-transplant (n = 28) and 3) with established pre-transplant hyperuricemia (n = 94). HLA class I (HLA-A, HLA-B) and HLA class II (HLA-DRB1, HLA-DQB1) were assessed by a PCR-SSP procedure. Gene frequencies were compared using the Mantel-Haenszel chi-square or Fisher’s exact test. HLA allele and haplotype frequencies were obtained by gene counting. Hardy-Weinberg (HW) equilibrium and LD (Arlequin ver. 2.0) as well as admixture estimations using the HLA-B typing in a trihybrid model with the maximum likelihood method (Leadmix software) were calculated. Ethnic-specific HLA-A/-B/-DRB1/-DQB1 haplotypes in a Mexican mestizo parental population (n = 381) were used as controls.

**Results:** The mean follow-up of the cohort was 4.7 ± 2.9 years. Group 1 had a tendency to be increased of HLA-B*35 and B*39 as compared to Group 2 (p = 0.07). HLA-B*35 and B*39 were significantly increased in Group 2 as compared to Group 3 (p = 0.04, RR 1.6, CI 95% 1.0–2.7). Likewise these alleles were also significantly increased in Group 2 as compared to ethnically matched healthy controls (p = 0.008, OR = 2.3, CI 95% 1.2–4.4 for B*35; and p = 0.03 OR = 2.3, CI 95% 1.0–4.8 for B*39). The HLA-B*07 allele was significantly increased in Group 3 as compared to healthy controls (p = 0.03, OR = 2.1, CI 95% 1.0–4.5). None patient belonging to Group 2 was positive for HLA-B*07. Group 2 also had an increased frequency of HLA-DR*08 as compared to healthy controls (p = 0.04, OR = 2.1, CI 95% 1.0–4.4) that was independent for that observed in alleles at the HLA-B locus. The frequency of the rest of the HLA-B and HLA-DR alleles as well as the haplotype analysis was similar among groups.

**Conclusion:** The hyperuricemia observed in RT patients is clinical and genetically heterogeneous, suggesting subgroups of patients with different pathogenic mechanisms. Typing for the MHC alleles might select patients highly sensitive or refractory for its development and may help in the selection of immunosuppressive and hypouricemic treatments.

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Diffuse Calcium-Containing Crystal Deposits in Human Osteoarthritic Articular Cartilage: Not Limited to the Medial Compartment. Christelle Nguyen1, Hang-Korng Ea2, Didier Hannouche3, Michel Daudon1, Dominique Bazin1 and Frederic Liote2.1 Laboratoire de Physique des Solides, Paris Sud University; Orsay; France; 2Orthopaedic Surgery Department; Lariboisiere Hospital; Paris Diderot University; Assistance Publique-Hopitaux de Paris (AP-HP); Paris; 3Serv ice de Biochimie A; Necker Hospital; Paris Sud University; AP-HP; Paris; 4UMR-S 606, INSERM & Paris Diderot University; PRES Sorbonne Paris-Cite; Lariboisiere Hospital; Paris; France

**Purpose:** Calcium-containing crystals (CC), including basic calcium phosphate crystals (BCP) and calcium pyrophosphate crystals (CPP) are associated with destructive forms of osteoarthritis (OA). Recent reports showed that mineralization of articular cartilage of the medial compartment is an indissociable process of end-stage OA. However, accurate characterisation of CC by conventional techniques remains challenging.

**Objectives:** To assess biochemical composition and spatial distribution of mineral phases in human OA cartilage, and to determine their morphological aspects.

**Methods:** Fourteen patients (12 women and 2 men), who underwent total knee joint replacement for primary OA, were prospectively included. A 24-year-old woman who underwent total knee joint replacement for chondrosarcoma served as control. Specimen included femoral condyle and tibial plateau cartilages, from both medial and lateral compartments. Clinical data and preoperative knee X-rays were obtained. For each femoro-tibial compartment, 4 samples (2 from femoral condyles and 2 from tibial plateau) were collected, consisting in 1-mm-thick slices. Slices were cut tangentially to the articular surface, within the superficial and deep layers of the articular cartilage, respectively. Biochemical composition was assessed using Fourier-transform infra-red (FTIR), and morphological aspects were determined using scanning electron microscopy (SEM). All results are expressed as mean (SD).

**Results:** Age and body mass index at the time of intervention were 74.4 ± 8.3 years, and 28.8 (6.2) kg/m², respectively. Preoperative X-rays found uni-, bi- or tricompartimental knee OA in 2, 8 and 4 cases, respectively. In all cases, the compartment mainly affected was medial femoro-tibial, and Kellgren and Lawrence score was 3.8 (0.4). Joint calcifications were detected in only 2 cases on preoperative X-rays, but in 11 cases under macroscopic examination. FTIR analysis showed CC in all 14 specimens. CC were absent from the control sample. The overall mineral content represented 91.1 (12.6%) CC were identified as BCP only in 3 specimens (26.7% ± 8.4%); and CPP in 8. Remarkably, CC were widespread in all knee joint compartments and involved at least 3 areas out of 8 in all specimens. In addition, CC distribution was similar between superficial and deep layers, and between medial and femoral compartments (11.1 [14.7%] vs 7.3 [10.2%], and 8.1 [11.2%] vs 9.5 [13.1%]; p = NS, respectively). Finally, CC identified 2 different morphological aspects: 1/spherical structures, typical of biological apatite, resulting from an agglomeration of nm-scale crystallites surrounded by proteins, and localized in structures suggestive of chondrons, in the BCP-containing samples; 2/ acicular or cubic structures of different sizes, in the CPP-containing samples.

**Conclusions:** CC are constantly found in human OA articular cartilage at the time of knee joint replacement. Cartilage calcifications occur in all knee joint compartments, even in less weight-bearing ones, suggesting that cartilage mineralization process may reflect a generalized chondrocyte disease. In addition, their morphological aspects are specific to the crystal type.

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Factors Associated with an Acute Attack of Chronic Gout without Hyperuricemia. MinWook So1, SeungGeun Lee2, YongGil Kim3, ChangKeun Lee4, HeeBom Moon5, Jiseon Oh3 and Bin Yoo6.1 ASAN Medical Ctr, Seoul, Korea, Republic of, 2ASAN Medical Ctr, Seoul, Korea, Republic of, 3ASAN Medical Ctr, Seoul, Korea, Republic of, 4ASAN Medical Ctr, 5Ulsan University

**Background:** Gout is a disease caused by deposition of monosodium urate crystals in articular and periarticular tissues. Hyperuricemia has been reported to be closely linked to the development and recurrence of gouty arthritis. Although, theoretically, gout cannot develop without hyperuricemia, there have been reports of development of gout without hyperuricemia. In the clinical setting, some patients receiving a urate-lowering agent for chronic gout have experienced recurrent attacks of gout without hyperuricemia.

**Purpose:** To identify the factors associated with an acute attack of chronic gout without hyperuricemia.

**Method:** We reviewed the medical records of 860 patients with chronic gout and who regularly received allopurinol at one tertiary hospital from 2003 to 2009. Among these 860 patients, 135 maintained a serum urate level less than 6.0 mg/dl. To minimize the effect of serum urate level change, we excluded all patients whose serum urate level exceeded 6.0 mg/dl at least once. We divided the study patients into an Attack group (n = 51) and a No-attack group (n = 84). The patients who experienced an acute attack, even though with normouricemia (<6.0 mg/dl) at least once during follow-up period, were classified as the Attack group. The others were classified as the No-attack group. We prescribed colchicine to prevent gout attacks during the first six months of the study, and attacks which occurred during this period were not included.

**Results:** Fifty-one (37.8%) patients experienced at least one recurrence of an acute attack without hyperuricemia during the follow-up period (Attack group).

Objective: Hyperuricemia has been shown to cluster with components of metabolic syndrome. A previous study1 documented that hyperuricemia is a risk factor for hypertension independent of metabolic syndrome among middle-aged adults (aged 35–57). The objective of this analysis is to assess whether hyperuricemia is a predictor of hypertension independent of metabolic syndrome in young adults.

Methods: We analyzed data from the CARDIA (Coronary Artery Risk Development in Young Adults) cohort, a prospective observational study of 5,115 individuals in the community who were aged 18–30 years at baseline and followed for 15 years (1986–2001) with visits 2–5 years apart. We excluded individuals with hypertension (per The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC 7] criteria) or any other components of metabolic syndrome (Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [ATP III] criteria) at baseline. The serum urate (sUA) cutoffs for quartiles were <3.9; 3.9–4.7; 4.8–5.8; and >5.8 mg/dL. Multivariate Cox regression analyses were utilized to adjust for the effects of potential confounders such as age, gender, race, serum creatinine concentration, and waist circumference.

Results: Data from 4,918 participants were included in this analysis; 45% were men, and 51% were African American. Baseline mean (standard deviation) for age, body mass index, sUA concentration, and systolic and diastolic blood pressure were: 25 (4) years; 24 (5) kg/m²; 5 (1) mg/dL; and 110 (10) mmHg and 68 (9) mmHg, respectively. The incidence of hypertension increased with succeeding sUA quartiles (Figure).

Hyperuricemia as a Risk Factor for Hypertension among Young Adults without Metabolic Syndrome. Eswar Krishnan1, Bhavik Pandya2, Ali Hariri3 and Omar Dabbous2. Stanford University School of Medicine, Stanford, CA, 3Takeda Pharmaceuticals International, Inc, Deerfield, IL, 2Takeda Pharmaceuticals North America, Inc, Deerfield, IL.

In multivariable regressions, the hazard ratio (95% confidence interval) for the second, third, and top quartiles of sUA concentration compared with the bottom quartile were: 1.2 (0.9–1.7); 1.5 (1.1–2.1); and 1.8 (1.2–2.6), respectively.

Conclusions: The incidence of hypertension was higher with increase in sUA. Hyperuricemia is an independent predictor of hypertension among young adults and is independent of metabolic syndrome.


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**Objective:** While the comorbidity burden of gout and hyperuricemia in the US has been considered substantial and has increased over the past decade, no contemporary data are available. The objective of the study was to estimate current prevalence of major comorbidities according to both gout status and hyperuricemia status based on NHANES 2007–2008 data.

**Methods:** Using data from 5,707 participants (2,797 men and 2,910 women) aged 20 years and older from NHANES 2007–2008, we determined the prevalence of major comorbidities according to both gout and hyperuricemia status, including hypertension, renal impairment, nephrolithiasis, diabetes, myocardial infarction, heart failure, stroke, and obesity. Obesity was defined as body mass index ≥30 kg/m². Other comorbidities and gout were defined based on an affirmative answer to a question asking if a physician or a health professional had diagnosed the corresponding condition. The primary NHANES definition of hyperuricemia was serum urate level >7.0 mg/dL in men and >5.7 mg/dL in women.

**Results:** Among the US adults with both gout and hyperuricemia, 78% had hypertension, 9% renal impairment, 20% nephrolithiasis, 27% diabetes, 12% myocardial infarction, 12% heart failure, 12% stroke, and 56% obesity (Table). These prevalences were substantially higher than those among individuals without gout or hyperuricemia. Having hyperuricemia was associated with a higher prevalence of comorbidities among individuals without gout. A similar trend was observed among individuals with gout, although the patterns are more difficult to characterize accurately due to smaller sample sizes (Table).

**Conclusions:** These findings from the latest nationally representative sample of US adults highlight that having gout and/or hyperuricemia substantially increases the prevalence of comorbidities. These prevalences are highest among individuals with both gout and hyperuricemia. These comorbidities add to the overall illness burden of gout and hyperuricemia to society, and provide support for consideration of these issues in optimizing gout and hyperuricemia care in the US.


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Low Prevalence of Coexistent Gout and Rheumatoid Arthritis in a Population of Veterans. Armine Tumyan1, Kara H. Prescott2 and Andreas M. Reimold3.

**Background:** Clinical observations indicate that the coexistence of gout and rheumatoid arthritis in the same patient is rare, occurring at a lower frequency than the incidence of the two conditions would predict. Gout is a male-predominant disease with an estimated prevalence of 1 to over 7%, while the incidence of both gout and RA increases with older age. A population of veterans was studied to describe the overlap of gout and RA.

**Methods:** Medical records for all patients with ICD-9 codes for RA (714.0, 714.2, and 714.81) and gout (274.xx) from 01/01/1999-12/31/2007 were identified and reviewed in the north Texas Veteran’s Integrated Service Network. In addition, a random sample of 50 gout and 50 RA patient records were reviewed for accuracy of ICD-9 codes. ACR criteria for RA and ACR 1977 Preliminary Criteria for diagnosis of gout were used, and lab data (joint fluid crystal analysis, hyperuricemia, RF, CCP), imaging, and medication use (allopurinol, DMARDs, TNF inhibitors) were documented. Patients were classified as having definite gout (joint fluid or tophi showing MSU crystals), presumed gout (met 6/13 ACR 1977 Preliminary Criteria for gout) or unlikely gout (failed to meet 6/13 gout criteria or gout was ruled out by a rheumatologist).

**Results:** A search of ICD-9 codes identified 2572 patients with RA codes and 8508 with gout codes, resulting in 277 patients with both RA and gout codes (overlap). By such codes, 10.8% of RA patients have a gout diagnosis, and 3.3% of gout patients have an RA diagnosis. In contrast, our longitudinal study of 545 well-characterized RA patients contained 10 with a comorbidity diagnosis of gout (1.8%) and 5 were confirmed by chart review (0.9%). Overlap patients were a mean of 61 years old, were 94.6% male, and 66.4% Caucasian. Patients with gout alone rarely saw a rheumatologist (8%, compared to 56% for patients with RA ICD-9, p<0.0001). Defined or presumed gout was found in 40.4% of the overlap group, RA was confirmed in 19.2%, while not enough information was documented in the charts to confirm gout in 43.3% and RA in 62.4%. There were 16 cases (5.8% of 277 overlap patients) of definite or presumed gout with RA. Therefore, in this population 0.62% of RA patients had confirmed or presumed gout, and 0.19% of confirmed/presumed gout patients had RA.

**Conclusions:** Diagnoses of either RA or gout are often assigned to patients by non-rheumatologists and frequently do not meet ACR criteria. Documentation of ACR criteria for both RA and gout in the same patient occurred in only 5.8% of patients carrying both diagnoses. Both in a general population of veterans carrying an RA ICD-9 code and a well-characterized registry of RA patients, the overlap of RA and gout was found in less than 1% of patients, a rate of gout far below the 6.5% incidence published previously for males in this age group.

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Monosodium Urate Monohydrate Crystals Inhibit Osteoblast Viability and Differentiation; Implications for Development of Bone Erosion in Chronic Gout. Ashika Chhana1, Karen Callon2, Bregina Pool2, Dorit Naot4, Fiona M. McQueen1, Jillian Cornish1 and Nicola Dalbeth1. Uni Auckland, Auckland, New Zealand, “University of Auckland, Auckland, New Zealand

**Background:** Bone erosion is a frequent manifestation of chronic gout, and may lead to joint damage and disability. Recent research has implicated an imbalance of bone remodeling in the development of bone erosion in gout, with enhanced formation of bone-resorbing osteoclasts in patients with erosive gout. We hypothesized that changes in the bone-forming osteoblasts also contribute to bone erosion in chronic gout. In this study we investigated the effects of monosodium urate monohydrate (MSU) crystals on osteoblasts.

**Method:** MSU crystals were prepared by recrystallisation of uric acid. Flow-cytometry and the MTT assay were used to assess cell viability following culture with MSU crystals in the murine MC3T3-E1 and ST2 osteoblast-like cell lines, and in primary rat and human osteoblasts. Quantitative real-time PCR and von Kossa stained mineralised bone nodule formation assays were used to assess the effects of MSU crystals on the differentiation of MC3T3-E1 osteoblast-like cells.

**Results:** MSU crystals rapidly reduced viability in all osteoblast assays in a dose-dependent manner (Figure). The inhibitory effect was maximal at the higher concentrations of 0.3 and 0.5mg/mL MSU crystals and was independent of crystal phagocytosis. The reduction of osteoblast viability was specific to urate crystals, as soluble uric acid did not alter cell viability. Furthermore, the effects on cell viability did not alter with different crystal lengths or addition of serum. Long term culture of MC3T3-E1 cells with MSU crystals showed decreased mineralisation (bone nodule formation) in a dose-dependent manner, and reduced expression of genes related to osteoblast differentiation such as Ihsp (bone sialoprotein), Runx2, Sp7 (osterix) and Dmp1.
Conclusion: MSU crystals have profound inhibitory effects on osteoblast viability and differentiation. These data indicate that MSU crystals may contribute to bone erosion in gout not only through promotion of osteoclast formation, but also through reduction of osteoblast survival and function.

Figure. Effects of MSU crystals on cell viability in A. MC3T3-E1 cells; B. ST2 cells; C. primary rat osteoblasts; and D. primary human osteoblasts. Cell viability was assessed in the MTT assay following 26 hours of culture with MSU crystals. Data shown are mean (SEM); *p<0.001, **p<0.0001 versus control (no MSU crystals), one-way ANOVA with post hoc Dunnett’s test.

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Number of Flares Are Associated with Both Gastrointestinal and Vascular Complications in Patients with Gout. Another Issue for Early Intervention. Fernando Perez-Ruiz1, Ana M. Herrero-Beites2 and Miguel A. Gonzalez-Gay3. 1Hospital de Cruces, Spain, 2Hospital de Górliz, Spain, 3Hospital Universitario Marqués de Valdecilla, Spain

Background: Before long-term serum urate control, patients with gout experience multiple flares that may expose them to the risk of complications, while EULAR recommendations suggest treating patients with recurrent flares or severe gout.

Objective: to evaluate risk factors associated with de development of severe vascular or gastrointestinal complications in patients with gout.

Methods: data from a prospective cohort of 787 patients with gout. Variables included age, gender, body mass index, number of flares-y, number of joints involved, tophus present, diuretics, renal function, hypertension, diabetes, hyperlipidemia, and ethanol intake. Vascular events and BPO (Bleeding, Perforation, Obstruction) events were considered when there was a association recorded in the file of the patient with treatment of a flare or gout complaints and the event. Time from the onset of gout to the event was considered as time variable for exposure. Mantel-Haznel analysis with log-rank tests were used to select variables associated (p<0.20) with each group of events, and they were afterwards included in multivariant Cox proportional hazard regression analysis.

Results: mean age 58.8±12.6, 93% male, 5,352 patient-y exposure, 31.3% tophaceous, 35.6% over 4 joint involved, 34.2±2.8 (0–24) flares-y, 34.6% over 20 g-day ethanol intake, 42.7% hypertension, 19.6% diabetes, 41.9% hyperlipidemia, 24.2% obese. Prior urate-lowering treatment (ULT) in 38.5%. Overall, there were 65 events (1.21 per 100 patient-year exposure) in 62 patients (7.88%). There were 41 vascular events: 2 congestive heart failure, 30 acute renal failure, 2 pulmonary embolisms, and 7 ictus associated to flares or gout treatment, and 24 gastrointestinal events: 22 bleedings, 1 obstruction, and 1 perforation. The number of flares in the year previous to the event was associated with an increased risk of both vascular and gastrointestinal events, which appeared in 8% of the patients. Also, polyarticular gout was associated with gastrointestinal events, while previous ULT seemed to be protective for vascular events. Early treatment of gout should be considered in recommendations.

Disclosure: F. Perez-Ruiz: ARDEA Biosciences, 5, 8, Menarini, 5, 8, Novartis Pharmaceuticals Corporation, 8; A. M. Herrero-Beites: ARDEA Biosciences, 5, 8, Menarini, 5, 8, Novartis Pharmaceuticals Corporation, 8; M. A. Gonzalez-Gay: None.

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Patients with Gout May Have a Decreased Risk of Colonic Polyps Relative to Patients with Osteoarthritis (OA): Insights from the NY VA Gout Database. Aaron Lehmann1, Laura Schneck2, Robert T. Keenan1, William O’Brien2, Daria Crittenden1, Kristen Lee3, Rekha Tadoori, Fritz Francois3 and Michael H. Pillinger3. 1Duke University, Durham, NC, 2NYU Langone Medical Center, 3NYU Langone Medical Center, Flushing, NY, 4NYU Langone Medical Center, New York, NY

Introduction: The role of uric acid (UA) in modulating immunity is an evolving area of investigation. UA can act as a “danger signal,” alerting the immune system to damaged cells (tumor and/or virally-infected cells) and triggering removal of potentially dangerous altered host. In a murine model, UA supplementation promoted, and UA lowering inhibited tumor rejection (Hu et al, Canc Res 2004). UA also scavenges singlet oxygen, which can induce tumorigenic mutations. UA also activates the inflammasome, driving IL-1β production. One of us (Francois et al, unpublished) has shown in patients with obesity (associated with elevated serum UA), IL-1β levels correlate significantly with serum levels of IFNγ, TNFa, IL-2, IL-17, and that individuals with the IL-1βT allele are less likely to have colonic polyps. Based on possible relationships between uric acid and tumor immunity in general, and uric acid, IL-1β and colonic polyps in particular, we tested whether patients with gout (a hyperuricemic state) have lower rates of colonic polyposis vs patients with OA.

Methods: Using the EMR of the New York Harbor Healthcare System (N=40,107), we identified all patients receiving an ICD-9 gout code at the Manhattan, Brooklyn and Queens VA Hospitals in New York City between 2007 and 2008. Age, sex, BMI, UA level, smoking history and colonic polyp diagnosis were collected by chart review (problem list and note review as appropriate). Patients with OA (ICD-9 diagnosis) but no gout were identified as controls.

Results: 1,287 gout patients were identified, and 1,287 patients with OA/no gout were randomly selected from 3,300 potential control enrollees. Gout and OA patients were identical in mean age (71), sex (99% male), BMI (29) and smoking history (11% vs 14%, ns). Average serum UA was 7.64 (gout, n=1124) vs. 6.026 (OA, n=730) mg/dL. Gout patients had a 12-fold decrease in colonic polyp diagnosis vs OA patients. Prevalence of colonic polyp diagnosis was 0.62% (n=8) in the gout vs. 8% (n=103) in the OA group (p=0.0001, 2 tailed Fisher’s exact test). Pathology reports for the two groups were: for gout, hyperplastic (4), tubular (3), tubulovillous (2), no report available (4); for OA, tubular adenoma (55), hyperplastic (16), tubulovillous adenoma (11), villous adenoma (3), tubular adenoma with focal adenocarcinoma (2), serrated adenoma (2), well-differentiated adenocarcinoma (1), colonic mucosa with lymphoid aggregate (1), leiomyoma (1), no report available (29). Patients with gout had no decrease in lung or prostate cancer diagnosis vs OA controls (0.9% vs 1% for lung cancer and 11.8% vs 12.8% for prostate cancer, respectively, both ns).

Conclusion: In this retrospective study, presence of gout was associated with a significant decrease in colonic polyp diagnosis relative to...
P-Homocysteine Levels Are Independently Correlated to S-Urate but Not to Urate Lowering Treatment. Results of an Observational Study of 112 Patients with Gout.

Ole Slot. Dept. of Rheumatology, Copenhagen University Hospital, Glostrup, Denmark

Background: Gout is associated with an increased incidence of cardiovascular disease (CVD). In a previous report elevated levels in plasma homocysteine (p-HCT), a marker of CVD risk, was found in a group of gouty patients. P-HCT was independently correlated to s-urate. The effect of urate lowering treatment (ULT) on p-HCT is not clear. Thus, the objective of this study was to examine the levels and correlations of p-HCT and metabolic factors that might effect the levels of p-HCT in gouty patients with or without ULT.

Methods: Data including results of routine laboratory tests from patients diagnosed with crystal proven gout during 18 months in an outpatient clinic were collected and analyzed for differences in unpaired samples (+ ULT vs. -ULT) and non-parametric correlations to p-HCT. The correlations were analyzed for co-variance in a backward multivariate regression analysis.

Results: 112 gouty patients of whom 50 received ULT (allopurinol: 47, probencid: 1, benzbromarone: 2) were included. Data are shown in Table 1.

Table 1. Medians (range) [Laboratory’s reference values]

<table>
<thead>
<tr>
<th></th>
<th>Gout, all n = 112</th>
<th>Gout, -ULT n = 62</th>
<th>Gout, + ULT n = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, Males/Females</td>
<td>45/67</td>
<td>24/38</td>
<td>21/29</td>
</tr>
<tr>
<td>Age, Years</td>
<td>76 (49–90)</td>
<td>75 (49–90)</td>
<td>75 (49–90)</td>
</tr>
<tr>
<td>P-Homocysteine µmol/l</td>
<td>18.5 (7.3–94.5)</td>
<td>19.0 (8.2–94.5)</td>
<td>17.0 (7.3–34.4)</td>
</tr>
<tr>
<td>S-urate mg/l</td>
<td>8.2 (3.2–13.5)</td>
<td>8.7 (5.7–13.5)*</td>
<td>7.0 (3.2–13.3)*</td>
</tr>
<tr>
<td>S-Creatinine µmol/l</td>
<td>15.7 (3.0–45.0)</td>
<td>15.5 (3.0–45.0)</td>
<td>16.9 (4.3–44.1)</td>
</tr>
<tr>
<td>S-Cobalamine µmol/l</td>
<td>284 (89–1480)</td>
<td>248 (89–756)</td>
<td>238 (107–1480)</td>
</tr>
<tr>
<td>S-CRP mg/l</td>
<td>1.0 (0.6–13.6)</td>
<td>1.0 (0.6–13.6)</td>
<td>1.0 (0.6–13.6)</td>
</tr>
<tr>
<td>S-AST µmol/l</td>
<td>153 (99–263)</td>
<td>155 (99–263)</td>
<td>155 (99–263)</td>
</tr>
<tr>
<td>S-alpha-2-microglob</td>
<td>100 (56–193)</td>
<td>100 (56–193)</td>
<td>100 (56–193)</td>
</tr>
</tbody>
</table>

S-urate was significantly lower in the +ULT group. No differences in p-HCT or other parameters were found between the -ULT and +ULT groups. Overall 89 patients (80%) had p-HCT over the laboratory’s upper limit of the normal range. Four patients (4%) had p-folate under the lower limit of the normal range of 6 nmol/l while 75 patients (68%) had p-folate below 20 nmol/l. 35 patients (32%) had s-cobalamine below the lower limit of the normal range. 55 patients (50%) had s-creatine above the upper limit of the normal range.

P-HCT was correlated to s-urate, p-folate, s-creatine, age (Spearman’s rho 0.34, -0.39, 0.46, and 0.44 respectively, p<0.001 for all), and s-cobalamine (rho -0.2, p<0.05). P-HCT was not correlated to CRP and ULT. In regression analysis age, p-folate, s-creatine, s-cobalamine, and s-urate were independent predictors for p-HCT.

Conclusion: In patients with gout p-HCT, a marker of increased risk of cardio-vascular disease, is independently correlated to high levels of s-urate and s-creatine and low levels of p-folate and s-cobalamine. P-HCT was not correlated to ULT in this observational study although s-urate levels were lower in the group of patients on ULT. The relations between P-HCT, s-urate and ULT should be examined in future prospective controlled studies.

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Rates of Meniscal Tearing Seen on Arthroscopy of Patients with Chondrocalcinosis. William Chun1, Humaira Hussain2, Vincent J. Zarro2, Carolyn R. O’Connor3 and Angel E. Checa3. 1Drexel University College of Medicine, Philadelphia, PA; 2Drexel University College of Medicine, Cherry Hill, NJ; 3Drexel University College of Medicine.

Background: Internal derangement of the knee secondary to chondrocalcinosis (CC) is well established. Although several publications have shown cases of CC with meniscal tears, there is no data about the prevalence of meniscal tears in CC and vice versa.

Methods: The study population was a cohort of 1031 consecutive outpatient patients who underwent arthroscopy of the knee from 1991–2006. The specific subgroup of interest was 58 knees from 58 patients (25 males and 33 females) with CC. Mechanical symptoms or failure of conservative treatment were the main indications for arthroscopy. Although the study was cross sectional in design, surgical response was prospectively evaluated. The rates of meniscal tears in patients with and without CC as well as their response to surgery were analyzed by Chi square test.

Results: The mean age of patients with CC was 67 (range 47–83) years. Most patients with CC who underwent arthroscopy had mechanical complaints or failed conservative treatment (69% and 45% respectively). Pseudo-gout flare was documented in 7% of cases with meniscal tear and 40% with intact meniscus. Thirty-seven knees with meniscal tear and 13 knees with intact meniscus were classified as pseudo-osteoarthritus. Trauma was present in only 7 knees with meniscal tear and in 3 knees without meniscal involvement. Patients with CC had significantly higher rates of meniscal tear compared to those without CC (74.1% vs. 28.7%, p<0.001). An absolute and attributable risk of tear was 74% and 8% respectively in knees with CC. Relative risk of tear in CC versus knees without CC was 2.58 (95% confidence interval 1.26–3.10). Arthroscopic surgery achieved good or excellent results in 22 (55%) knees with meniscal tearing. Knees with mild changes in the hyaline cartilage and involvement of only one compartment in the knee showed better response to surgery than knees with advanced degenerative changes and involvement of more than one compartment (p=0.004).

Conclusion: Although the prevalence of CC in this study population was 5.6% and therefore accounted for only 8% of the tears, CC was a strong predictor for meniscal tear. These patients represent an underestimated clinical-pathological subgroup and can often be successfully managed by arthroscopy. The low frequency of trauma in this study group suggests that CC is a factor in fibrocartilage fragility leading to meniscal tearing. Future controlled studies are needed to further characterize the impact of CC in meniscal vulnerability as well as its role in the hyaline cartilage.

Disclosure: W. Chun; None; H. Hussain; None; V. J. Zarro; None; C. R. O’Connor; None; A. E. Checa; None.

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Screening for Hereditary Hemochromatosis in the Rheumatology Practice. Gunther Neeck1, Helge Wernitzsch2, Andreas Klüter3, Martin Schulz2 and Helmut Dotzlaw3. 1Center for Rheumatology at Hospital Bad Doberan, Hohenfelde, Germany; 2Center for Rheumatology at Hospital Bad Doberan, Germany

Objective: The most prominent features of hereditary hemochromatosis (HH) are joint pain and/or swelling, and this disease is often diagnosed by chance. We therefore systematically investigated iron metabolism in patients entering our rheumatology center for the first time over a time period of 2.5 years in order to evaluate the incidence of HH in our rheumatology practice.

Methods: The serum concentrations of iron, ferritin, and transferrin were measured in 4244 patients and the iron-transferrin saturation was calculated. Patients with an iron-saturation > 45% and elevated ferritin levels were tested for HH by determination of mutations of the HFE-gene C282Y and H63D. If no mutations were detected and iron overload persisted we analyzed the non-HFE-genes hemojunv, herciprin, transferrin, transferrin receptor and ferroportin for possible mutations.

Results: Thirty seven patients showed iron overload (iron transferrin saturation > 45% and elevated ferritin). Of these, 21 patients were diagnosed as having HH by genetic analyses: 15 C282Y homozygotes, 2 H63D homozygotes, 2 compound heterozygotes C282Y/H63D, 1 homozygote for the non-HFE-gene ferroportin and 1 homozygote for the transferrin receptor 2. All patients suffered from arthralgias and 12 had typical HH-arthritis of
the metacarpalia-phalangeal joints II and III of the hands. Most patients could be treated successfully by plethotomy or iron chelation therapy.

**Conclusions:** In undifferentiated joint pain HH is an important differential diagnosis, and as such parameters of iron metabolism should be routinely determined in those patients.

**Disclosure:** G. Necek: None; H. Wernitzsch: None; A. Klüter: None; M. Schulz: None; H. Dotzlaw: None.

**887**

**Synovial Extracellular Matrix Remodeling in Experimental Model of Diabetes**, Sandra Aparecida Atayde1, Priscila Cristina Andrade2, Sérgio Cutanore3, Edna Regina Nakandakare2, Marisa Passarelli2, Ana Paula Pereira Velosa2, Vera Luiza Capelozzi2, Edwin Roger Parra2, Nallino Hajime Yoshinari2 and Waley Rosolia Teodoro2. 1University of São Paulo, São Paulo, Brazil, 2University of São Paulo

**Purpose:** Diabetes mellitus has been linked to disorders of bones and joints whose etiologic mechanisms could be linked to micro vascular disease. The synovia is the most vascularized tissue in the joint, therefore, can be made more resilient to endothelial injury in diabetic process. Our purpose was to evaluate the extracellular matrix components and specifically the vascular lesion in this tissue after diabetes induction in rats.

**Methods:** Wistar young rats, were divided into diabetic group (DG; n=15) and control group (CG; n=15). Diabetes was induced by tail injection of streptozotocin (35mg/kg), while control group received saline solution. Weight, glycemia and plasmatic and carboxymethyl lysine analysis had been done after 70 days. After euthanasia, knee joints were isolated, and included in paraffin. Histological sections stained with Hematoxilin-Eosin and Picrosirius were obtained for histomorphometric analysis. Total collagen quantification of this tissue was done in Picrosirus under polarized light. The distribution of collagens I, III and V and also carboxymethyl lysine receptor were assessed by immunofluorescence and immunochemistry was used for endothelin detection in synovial tissue.

**Results:** There was intense remodeling and collagen deposition in the synovia of animals with diabetes induced by streptozotocin, which may explain the pathophysiology of musculoskeletal dysfunctions observed in diabetic patients.

**Disclosure:** S. A. Atayde: None; P. C. Andrade: None; S. Catanozo: None; E. R. Nakandakare: None; M. Passarelli: None; A. P. P. Velosa: None; V. L. Capelozzi: None; E. R. Parra: None; N. H. Yoshinari: None; W. R. Teodoro: None.

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**The GOSPEL 1000 Study. Features of the Metabolic Syndrome in 1003 French Patients with Gout**, Frédéric P. Liote1, Hang-Korng E2, Pascal Guggenbuhl1, Alain Saura5, Charles Lambert, Sabine Lanz4, Pierre Chiarelli1 and Sylvie Lancrenon1. 1Rennes, France, 2Paris, France, 3Courbevoie, France, 4Chatou, France, 5Bourg-la-Reine, France, 6CHU de la Cavale Blanche, Brezet Cedex, France, 7Hôpital Lariboisière, Paris, France

**Background:** Gout is often poorly managed in primary care settings. 2006 EULAR gout recommendations (EULARReCS) have been developed on aspects related to the management of gout, but poorly evaluated in clinical practice. A key feature present in these EULARReCs was to determine and to assess first MTP joints. Complete data for 62 joints were available. All US studies were performed according to published guidelines, by a rheumatologist certified in musculoskeletal ultrasound, with >15 years US experience. Linear transducers with frequencies between 14–18 MHz were used. Erosions were defined as breaks in the cortical margin of metatarsal head or proximal phalax, seen in two perpendicular planes. Tophaceous material was defined as hyperechoic crystalline concretions with a “wet clumps of sugar” appearance. Calcified tophi were defined as hyperechoic concretions with a pronounced posterior acoustic shadow.

**Methods:** Retrospectively, US studies performed during a 12 months period were reviewed. 42 patients with a history of crystal proven gout, US imaging and CR of corresponding joints were identified. The study was limited to assessment of first MTP joints. Complete data for 62 joints were available. All US studies were performed according to published guidelines, by a rheumatologist certified in musculoskeletal ultrasound, with >15 years US experience. Linear transducers with frequencies between 14–18 MHz were used. Erosions were defined as breaks in the cortical contour of metatarsal head or proximal phalax, seen in two perpendicular planes. Tophaceous material was defined as hyperechoic crystalline concretions with a “wet clumps of sugar” appearance. Calcified tophi were defined as hyperechoic concretions with a pronounced posterior acoustic shadow.

**Conclusions:** In contrast to previous studies, 3 different radiographic views of the feet were obtained to facilitate detection of erosions. The radiologist’s final impression was counted. At the time of the study, the sonographer was unaware of the CR results.
Results: Using US, erosions were seen in 41/62 joints (66%). Using multiview CR, erosions were seen in 21/62 of the same joints (34%). Intra-articular calcification was seen in 3/62 joints (5%) using US and 3/62 joints (5%) using CR. Intra-articular tendinous material was seen in 59/62 joints (95%) using US and 0/62 joints (0%) using CR. Tophaceous material was seen within the erosion in 36/62 joints (58%).

Conclusion: US identified almost twice as many erosions as CR in gouty joints. The addition of a third radiographic view improved the yield only marginally over previous studies that used two CR views to assess erosions in gout. If tophi calcify, they are seen both with CR and US, but uncalcified material escapes CR visualization. Similar findings in RA, CR remains an imperfect tool for the assessment of erosions in gout when compared with US.

References:


ACR Poster Session B
Miscellaneous Rheumatic and Inflammatory Diseases I
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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A Comprehensive Tuberculosis Screening Program in Patients with Inflammatory Arthritis Treated with Golimumab, a Human Anti-TNF Antibody, in Phase 3 Clinical Trials. Elizabeth C. Hsia1, John J. Cush1, Eric L. Matteson2, Anna Beutler2, Mittie K. Doyle4, Benjamin L. Hsu3 and Mahboob U. Rahman4. 1Baylor Research Institute, Dallas, TX, 2Centocor Research and Development, Inc., Collegeville, PA, 3Centocor Research and Development, Inc., 3; 4Centocor Research and Development, Inc.\/Univ. of Pennsylvania School of Medicine, Malvern, PA, 5Mayo Clinic, Rochester, MN.

Background: Reactivation of Mycobacterium tuberculosis infection is a major complication in patients (pts) with inflammatory diseases treated with anti-tumor necrosis factor (TNF) agents. Screening and appropriate treatment (tx) for latent TB infection (LTBI) before initiation of TNF blockers, as well as prompt diagnosis (dx) of active TB cases, can decrease morbidity and mortality.

Objectives: To summarize active TB case reports by wk52 across 5 SC GLM studies (3 RA, 1 PsA, and 1 AS).

Methods: Pts enrolled from North & South America, Europe (Western + Eastern), Australia/New Zealand, and Asia. TB eligibility criteria included: no history of latent/active TB; no signs/symptoms of active TB; negative (-) tuberculin skin test (TST) and Quantiferon®-TB Gold test in-Tube (QFT) or if newly identified + TST or + QFT with active TB ruled out, had tx for LTBI initiated before or at 1st dose. TST done using Mantoux method and + per local guidelines for immunosuppressed or if ≥5mm if no guidelines. All pts had chest x-ray (CXR) ≤ 3 months before 1st dose. Targeted questions for early dx of active TB were asked q4wks.

Results: Among 2294 randomized pts, 316 (13.8%) had either TST+ or QFT+ screening and required tx for LTBI. Through wk52, none of those tx for LTBI developed active TB while on GLM. Active TB occurred in 5 pts by wk52 (Table). Cases were in countries with high background rates of TB. 2 cases occurred by wk24 and were more consistent with reactivation. There were no deaths due to TB.

Conclusion: Despite 2 screening tests and CXR, to detect LTBI, there were still cases of TB reactivation. However, given that many enrolled pts resided in TB endemic areas, the number of active TB cases may have been higher with a less conservative TB screening strategy. Even if TB screening tests are -, clinicians should remain vigilant for development of active TB after initiation of TNF blockers, as prompt dx and tx can lead to improved outcomes.


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Anakinra in Adult Onset Still’s Disease (AOSD). Clinically Beneficial Results in an Open, Randomized, Multicenter Study. Dan C. Nordström3, Ann Knight1, Reijo Lukijnen2, Ronald V. Vollenhoven2, Yappu Rantau-Jain1, Anna Karjalainen1, Johan Brun2, Anne Proven6, Lotta Ljung10, Hannu Kauttainen1 and Tom Petterson4. 1Central Finland Central Hospital, Finland, 2Haukeland University Hospital, Norway, 3Helsinki University Central Hospital, Finland, 4Helsinki University Central Hospital, Finland, 5Karolinska Hospital, Sweden, 6Rauma Hospital, Finland, 7Tampere University Hospital, Finland, 8Umeå University Hospital, Sweden, 9Uppsala University Hospital, Sweden.

Background: AOSD is a rare systemic inflammatory disease of unknown cause characterized by spiking fevers, polyarthralgias, evanescent rash, and other multiorgan involvement. The outcome is unpredictable and varies from monophasic, remitting/relapsing to chronically progressing. No etiology has emerged but high levels of pro-inflammatory cytokines (IL-1, IL-6, IL-18) involving possible polymorphisms, and acute phase reactants have been proposed as being pathogenetically relevant. Frequently, systemic immuno-suppressive therapy is required for treatment, but for patients irresponsive to systemic steroids and immunosuppression, especially IL-1 suppression therapy with traditional DMARDs, there is a need for alternative therapies.

Objectives: To follow the changes in clinical status and disease activity in patients receiving anakinra, compared to those of a traditional DMARD (methotrexate, azathioprine, leflunomide, or cyclosporin A) in addition to corticosteroids in patients with corticosteroid dependent, refractory AOSD.

Methods: Open 24 week, randomized, comparative, multicenter study. 22 patients on corticosteroids were randomized to receive anakinra (n=12) or DMARD (n=10). Patients entered the study only if considered refractory to corticosteroids (prednisolone equivalent ≥10 mg/day for at least two months after disease onset). Primary end point identified the proportion of patients reaching remission of disease after two months of study treatment (stated as: febrile [≥37°C of body temperature], acute phase reactants [C-reactive protein, ferritin] within normal limits, and joint scores being normal).

Results: Patient groups (anakinra vs. DMARD) were comparable except regarding baseline ferritin levels (354, range 18–1740 vs. 186, range 17–680) and baseline prednisolone dose (22.5 mg, range 10–60 vs. 18.5, range 10–25), respectively. At week 4, 6/12 and 3/10 were in remission; at week 8, 7/12 and 2/10 were still in remission, respectively. In the Physical Health Summary of the SF-36 anakinra produced significantly more rapid and sustained responses compared to DMARD (p=0.011). Only patients on DMARDs (N=5) withdrew prematurely.
Conclusion: In refractory AOSD both DMARD therapy and especially anakinra showed good therapy responses during the 24 week intervention period. Responses were more robust with anakinra at 24 weeks with 50% of patients in strict remission according to criteria above. Withdrawals due to lack of efficacy occurred only in DMARD patients.

References:

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Anti-Double Stranded DNA and Other Autoantibodies Are Common in Alaska Native Autoimmune Hepatitis Patients. Elizabeth D. Ferucci1, Kathy J. Hurlburt1, Stephen Livingston1, Julia Plotnik1, James Gove1, Brian J. McMahon1 and Judith A. James2. 1Alaska Native Tribal Health Consortium, 2Oklahoma Medical Research Foundation, Oklahoma City, OK

Purpose: Autoimmune hepatitis has been associated with rheumatoid arthritis and other autoimmune diseases. The purpose of this study was to determine the prevalence of autoantibodies related to rheumatoid arthritis (RA) and connective tissue diseases in autoimmune hepatitis (AIH).

Methods: Alaska Native study participants were recruited at hepatitis clinics provided by the Alaska Native Tribal Health Consortium Liver Disease and Hepatitis Program. Patients with definite or probable AIH defined by the International Autoimmune Hepatitis Group (IAHG) criteria were recruited. A single center observational study was performed. Patients with MCTD were diagnosed by using Autoimmune EIA Test (BIO-RAD) and with calculated peak areas. Anti-U1RNP antibodies (Abs), elevated in MCTD significantly induced Ang1 mRNA in Jurkat cells (Arth. & Rheum. 58 (9): S283, ‘05). We also found that Ang1/ins splice donor at the first position of the 805G > T variant, indicating that anti-dsDNA is not universally associated with only SLE.

Results: Sera were available from 70 patients with AIH. Of the 70 AIH patients, 66 (94.3%) were female, and the mean age at consent was 52.1 years (SD 18.2, median 56.7). Fourteen AIH patients (20%) had an established rheumatologic diagnosis (9 (12.9%) with RA, and 1 each with SLE, Sjogren’s syndrome, mixed connective tissue disease, adult Still’s disease, and psoriatic arthritis). In the 9 AIH patients with RA, 5 (55.6%) had RF present, 6 (66.7%) CCP, 5 (55.6%) both RF and CCP, 3 (33.3%) dsDNA, 3 (33.3%) RNP, 5 (55.6%) Ro (56.7%), and 2 (22.2%) La. In AIH patients without any known rheumatologic diagnosis (n=56), the most common autoantibody found was dsDNA (26/56, or 46.4%); followed by RF (6/56, or 10.7%), and Ro (6/56, or 10.7%). Other autoantibodies found were CCP in 2 patients, La in 2 patients, and anti-RNP in 1 patient. No patient with or without a rheumatologic diagnosis had Sm or ribosomal P antibodies.

Conclusion: Antibodies to double stranded DNA are commonly found in Alaska Native patients with AIH, in the absence of diagnosed SLE. This information provides rheumatologists with additional information when considering the differential diagnosis of a positive dsDNA antibody, suggesting that anti-dsDNA is not universally associated with only SLE.

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Autoimmune Phenomena in Muckle-Wells Syndrome (MWS). Katharina Gramlich1, Reinridt Klein1, Sandra Hansmann1, Susanne M. Benseler2 and Jasmin B. Kuemmerle-Deschner2. 1Division of Pediatric Rheumatology, Department of Pediatrics, University Hospital Tübingen, Tuebingen, Germany, 2Division of Pediatric Rheumatology, Department of Pediatrics, University Hospital Tübingen, Tuebingen, Germany

Purpose: Angiopoietin-1 (Ang1) is the ligand of endothelial tyrosine kinase receptor Tie2 and induces cell proliferation via ERK phosphorylation. Ang1 is strongly up-regulated in the lung of patients with mixed connective tissue disease (MCTD) accompanied by pulmonary hypertension (PH) indicating that Ang1 can play a key role in the pathogenesis of PH associated with MCTD. We previously showed that the frequency of the splicing variant of Ang1 mRNA with n805G/GT insertion (Ang1/ins) encoding 269Gly was significantly increased in the Japanese patients with MCTD and those with PH compared with Ang1/del with n805G/GT deletion (Arth. & Rheum. 52 (9): S283, ‘05). We also found that Ang1/ins dose proliferate pulmonary endothelial cells and potentially induce hyperplasia of smooth muscle cell in relation to the pathogenesis of PH as compared with Ang1/del (Arth. & Rheum. 58 (9): S659, ‘08 and 60 (10): S8, ‘09). On the other hand, anti-U1RNP antibodies (Abs), elevated in MCTD significantly induced Ang1/mRNA in Jurkat cells (Arth. & Rheum. 58 (9): S224, ‘08). We have now studied the contribution of subclass of Abs against U1A, U1C or U1–70K to the induction of Ang1/ins variant. We also evaluated the reactivity of anti-U1RNP auto-Abs against each components of UIRNP in sera of patients with MCTD.

Methods: Anti-U1A, U1C and U1–70K Abs (LifeSpan Biosc. and Bio Acad.) were introduced into human pulmonary artery smooth muscle cells (HPASMC) using PULS-in reagent (Polyplus transfection), followed by treatment with IL6 and TNFα (20ng/ml each) for 24 h. Ang1 mRNA was obtained by using RT-PCR and subjected to length analysis by using ABI3130xl sequencer. Expression levels of Ang1/ins variants were evaluated with calculated peak areas. Anti-U1RNP Ab titer in sera of Japanese patients with MCTD was determined by using Autoimmune EIA Test (BIO-RAD) and the mRNA phenotype was determined. We also constructed ELISA by using recombinant U1A, U1C and U1–70K proteins (DIARECT), coated antigen and Ab titers in sera of patients were determined.

Results: Anti-U1C and U1–70K Abs significantly induced Ang1/ins mRNA with IL6 and TNFα (P<0.05). Otherwise, neither anti-U1A, U1C nor U1–70K Abs did alter the Ang1 splicing without cytokine. We also confirmed that Ang1/ins wasn’t induced with cytokine. Frequency of the patients with MCTD having anti-U1RNP Ab titer exceeding 200 was 81.3% (39/48) and 50.0% (6/12) (P<0.05) among those with Ang1/ins dominant and Ang1/del dominant phenotypes, respectively. While comparison between Ang1/del and Ang1/ins dominant phenotypes wasn’t possible because of 2 sera specimens of those Ang1/del dominant phenotype, the titer of each subclass of anti-U1RNP Ab in the sera of patients with MCTD among those with Ang1/hetero (n=13) and Ang1/ins dominant phenotypes (n=18) was: 11.8±23.6 and 47±58.9 (P<0.05) for anti-U1A Ab, 13.6±25.7 and 121.2±124.5 (P<0.005); for anti-U1C Ab, 406.2±599.5 and 5512.9±12484.7 (not significant); for anti-U1–70K Ab.

Conclusions: It is suggested that anti-U1RNP Ab, especially those reactive with U1C affect the splicing of Ang1 with cytokines and induce functionally defective Ang1/ins in the patients with MCTD.

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clear antibodies (ANA), smooth muscle antibodies (SMA), anti-endothelial antibodies (AEA), anti-scarceomallar antibodies (ASA) by immunofluorescence test, and antibodies against serotonin, gangliosides and CNS-tissue of the IgG and IgM type by ELISA.

Results: We included 20 patients, 8 males, 12 females, median age at diagnosis, 34 years (3.5–72). All patients were screened for the presence of autoantibodies before starting anti-IL-1 therapy. Positive ANA were detected in 3 patients (15%); SMA, AEA or ASA were found in 16 patients (30%); 2/4 tested were positive for anti-serotonin antibodies and 2/15 for anti-ganglioside new antibodies. Antibodies against CNS-tissue were detected in 5/15 tested.

During anakinara therapy no formation of ANA in initially ANA-negative patients was observed, ANA newly emerged in 4/14 during canakinumab therapy. New antibody formation against gangliosides occurred in 2 patients during anakinara and in 1 patient during canakinumab therapy. Antibodies against serotonin and CNS-tissue were frequently detected during both anakinara- and canakinumab therapy, however, there was no evidence for new formation of these antibodies. SMÅ, AEA and ASA were unchanged over the whole study period. During the overall study period, 15/20 patients (75%) were positive for antibodies against serotonin, gangliosides and/or CNS-tissue at least at one time point.

Conclusions: Patients with MWS can have ANAs and antibodies against serotonin, gangliosides and CNS-tissue. IL-1 blockade may increase the formation of autoantibodies in previously antibody-negative patients. The clinical relevance of the presence of autoantibodies in patients with MWS is still unclear.

Disclosure: K. Gramlich: None, R. Klein: None, S. HANSmann: None, S. M. Beusler: None; J. B. Kuennermeier-Deschner: None.


Background: CAPS (a disease spectrum consisting of familial cold auto-inflammatory syndrome [FCAS], Muckle-Wells syndrome [MWS], neonatal-onset systemic inflammatory disease [NOMID]) is a rare systemic inflammatory disease associated with mutations in NLRP3 causing auto-inflammatory syndrome [FCAS], Muckle-Wells syndrome [MWS], lipopolysaccharide (LPS) administration 2 days later. Experimental autoimmunity may increase the frequency of autoantibodies in previously antibody-negative patients. The clinical relevance of the presence of autoantibodies in patients with MWS is still unclear.

Conclusions: Canakinumab 150 mg sc every 8 weeks provided rapid improvement of symptoms and sustained remission in a large cohort of CAPS patients across different severity phenotypes. Long-term safety profile was comparable to that established in earlier trials of shorter duration.

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Celecoxib Analogue Lacking COX-2-Inhibitory Activity Inhibits Arthritis by Suppressing IL-23 and Inflammatory Cytokines, Asako Chiba1, Ryohsuke Tajima2, Miho Mizuno3, Chiharu Tomi4, Iraide Alloza5, Takashi Yamamura6, Koen Vandenbroeck7 and Sachiko Miyake1.

Background: Previously we reported that a trifluoromethyl analogue of celecoxib (TFM-celecoxib) lacking COX-2-inhibitory activity induces cellular retention of IL-12 and IL-23. Because these cytokines are involved in autoimmune or inflammatory diseases, we asked whether TFM-celecoxib suppresses animal models of arthritis.

Methods: To induce collagen-induced arthritis (CIA), DBA/1J mice were immunized with bovine type II collagen (CII) (150μg) in Freund’s complete adjuvant containing 250μg of H37Ra Mycobacterium tuberculosis on day 0 and CII in IFA on day 21. Antibody-induced arthritis (AIA) was induced in C57BL/6 mice by injecting a mixture of antigen deferred by lipopolysaccharide (LPS) administration 2 days later. Experimental autoimmune encephalomyelitis (EAE) was induced in C57BL/6 mice by immunizing with MOG15-55 peptide (100μg) in CFA followed by pertussis toxin administration. Peritoneal recruitment of leukocytes was induced by injecting 1ml of 4% thioglycollate. Mice received 10μg/kg of TFM-celecoxib (TFM-C) every other day from day 1 in EAE and AIA experiments, every day from day 21 in CIA experiments. The control animals were injected with vehicle alone, and in some experiments another group of mice were treated with celecoxib. Bone marrow-derived dendritic cells (BMDCs) or splenic macrophages from mice treated with TFM-C were stimulated by LPS in vitro in the presence or absence of TFM-C, and cytokine stimulation in the culture supernatants was measured by ELISA.

Results: TFM-C strongly suppressed CIA and AIA, although celecoxib did not inhibit these models. Histopathological analysis of arthritic joints revealed that TFM-C treatment inhibited mast cell degranulation whereas celecoxib treatment failed to suppress mast cell activation. TFM-C suppressed mast cell-dependent neutrophil influx into peritoneal cavity after injection of thioglycollate. TFM-C treatment in vivo inhibited inflammatory cytokines production from macrophages. Moreover, TFM-C suppressed the clinical and pathological features of EAE in association with the reduction of IL-23 production by dendritic cells, which subsequently suppressed IL-17 production by lymph node cells when re-challenged by MOG in vitro.

Conclusion: TFM-C suppressed murine models of arthritis by suppressing innate immune cell activation and autoreactive T cell responses, high-
Comprehensive Analyses of MEFV, TNFRSF1A, MVK, and CIAS1 Mutations in 63 Patients with Clinically Periodic Fever Syndrome in Japan. Sayuri Kataoka1, Manabu Kawamoto2, Yasushi Kawaguchi3, Takahisa Gono4, Masanori Hanaoka4, Hisae Ichida1, Yasuhiko Katsumata5, Yuko Okamoto6, Yoko Ota7, Ikuko Masuda8 and Hisashi Yamanaka9.

1Tokyo Women’s Medical University, 2Tokyo Women’s Medical University, Japan, 3Tokyo Women’s Medical University, 4Tokyo Women’s Medical University, Tokyo Women’s Medical Univ Med

Purpose: Periodic fever syndrome refers to a group of autoinflammatory disease sharing similar symptoms and characterized by recurrent unprovoked inflammation in the absence of infection. These diseases primarily include familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulinemia D syndrome (HIDS), and cryopyrin-associated periodic syndrome (CAPS). The genetic studies revealed predominant mutations of MEFV gene in FMF, TNFRSF1A gene in TRAPS, MVK gene in HIDS, and CIAS1 gene in CAPS. A number of studies about hereditary autoinflammatory disease have already established in Europe and USA, while it has not been fully understood in the Japanese population.

In the present study, we investigated a comprehensive analysis of mutations in MEFV, TNFRSF1A, MVK and CIAS1 in patients with clinically periodic fever syndrome.

Methods: We have defined clinically periodic fever syndrome as recurrent episodes of systemic inflammation in the absence of pathogens (i.e.: bacterial infection, viral infection), autoantibodies (i.e.: collagen diseases), or antigen specific T cells (i.e.: malignancy, allergy). Sixty-three patients were matched to those criteria and enrolled in the present study. All patients were Japanese. The median (range) of age was 13 years old (3 to 60), and the ratio of female/male was 29/34. All genotyping of exon 3 and exon 10 in the MEFV gene, exon 2 to exon 5 in the TNFRSF1A gene, exon 10 and exon 11 in the MVK gene, and exon 3 in the CIAS1 gene were determined by direct sequencing using ABI PRISM3100.

Results: The mutations of M694I and P369S + R408Q in the MEFV gene were found in 4 and 5 patients with clinically periodic fever syndrome, respectively. In the TNFRSF1A gene, the mutations of C30R and T61I were found in 1 and 3 patients, respectively. In the MVK gene, one patient was observed rare mutation of G326R, and E304K mutation in the CIAS1 gene was detected in one patient. Those 15 patients had only a mutation described above, while one patient had two mutations of the MEFV (M694I) and TNFRSF1A (T61I) genes. Finally, we detected gene mutations in 16 out of 63 patients with clinically periodic fever syndrome by these methods. Interestingly, only two in 16 patients had the family history of periodic fever: one has sister and one has brother and mother. Fourteen patients had no family history.

Conclusion: This comprehensive analysis can detect 16 patients (25%) with hereditary periodic fever syndrome, as a result of evaluating 63 patients with clinically periodic fever syndrome. These observations suggest FMF and TRAPS were common in the Japanese population, although it has been believed that hereditary periodic fever syndrome was a very rare disease in Japan.

Table 1. Summary of mutations in patients with clinically periodic fever syndrome

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Number of patient</th>
</tr>
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<tbody>
<tr>
<td>MEFV P369S + R408Q 5</td>
<td>2</td>
</tr>
<tr>
<td>M694I 4</td>
<td>3</td>
</tr>
<tr>
<td>TNFRSF1A C30R 1</td>
<td>1</td>
</tr>
<tr>
<td>T61I 3</td>
<td>3</td>
</tr>
<tr>
<td>MVK G326R 1</td>
<td>1</td>
</tr>
<tr>
<td>CIAS1 E304K 1</td>
<td>1</td>
</tr>
<tr>
<td>MEFV (M694I) + TNFRSF1A (T61I) 1</td>
<td>1</td>
</tr>
<tr>
<td>Total 16</td>
<td></td>
</tr>
</tbody>
</table>

897

Defining the Aromatase Inhibitor Musculoskeletal Syndrome: A Prospective Trial. Ora Singer1, Alana B. Levine2, Tessa Cigler3, Anne B. Moore1,2,3,4,4, Huang T. Do5 and Lisa A. Mandl6,7,8, Hospital for Special Surgery, New York, NY, 2NY Presbyterian - Weill Cornell Medical Center, New York, NY, 3NY Presbyterian-Weill Cornell Medical Center, New York, NY, 4NY Presbyterian - Weill Cornell Medical Center, New York, NY, 5NY Presbyterian - Weill Cornell Medical Center, New York, NY, 6NY Presbyterian - Weill Cornell Medical Center, New York, NY, 7NY Presbyterian - Weill Cornell Medical Center, New York, NY, 8NY Presbyterian - Weill Cornell Medical Center, New York, NY, 9NY Presbyterian - Weill Cornell Medical Center, New York, NY

Background: Aromatase Inhibitors (AIs) are standard of care therapy for post-menopausal breast cancer, AIs have been associated with debilitating musculoskeletal symptoms, predominantly in the hands and wrists. Up to 15% of symptomatic patients discontinue this potentially life saving therapy. The purpose of this study is to define the AI syndrome.

Methods: Post-menopausal women with hormone-sensitive, non-metastatic breast cancer and no rheumatic disease were included in this prospective cohort study. Subjects were evaluated by a rheumatologist before starting AIs and at 6 months. Women who reported new or worsening musculoskeletal symptoms were classified as “symptomatic.” The primary outcome was grip strength; secondary outcomes included 66/68 swollen and tender joint count, HAQ-DI, SF-36, AUSCAN Hand Index, and serum testing for CPK, CRP, ESR, CCP, SSA, SSB, RF, ANA. Contrast enhanced MRIs of the hands and wrists were performed at baseline and 6 month or at symptom onset. MRIs were read by two blinded radiologists using the OMERACT Rheumatoid Arthritis MRI Scoring with Terosynovitis subcale (RAMRIS-TS).

Results: Of 35 women enrolled, 19 (54%) were symptomatic and of these 2 (5.7%) discontinued the AI. Mean time to onset of symptoms was 6 weeks (range 2 to 18). Fifty-eight percent of symptomatic subjects had involvement of the hands. Two had De Quervain’s TS, 4 had tenderness over the flexor digitorum tendons, including 1 trigger finger, and 5 had generalized bilateral hand and wrist stiffness. Three subjects had ball of the foot and/or heel pain with weight bearing. Cancer stage was the only significant predictor of symptom development, (OR 5.9; 95% CI 1.2, 28.1) There was no difference in the mean change in grip strength between the symptomatic and asymptomatic groups, (−2.3 kg vs −1.4 kg, p-value=0.97). There were also no differences in the mean change in the HAQ, SF 36, 66/68 tender and swollen joint counts and laboratory values. There was a statistically significant worsening of the AUSCAN pain, stiffness and total subscales in the symptomatic group (P-values = 0.004, 0.001 and 0.001, respectively). Although some symptomatic subjects with hand/wrist involvement had MRI abnormalities, there was no significant change in any RAMRIS score. ICC’s were 0.8, 0.76, 0.19 and 0 for erosion, edema, synovitis and TS RAMRIS scores respectively.

Conclusions: In this prospective study, more than half of subjects reported new or worsening musculoskeletal complaints on AIs. Later stage cancer increased the risk of developing pain, and clinical exam suggested underlying tenosynovial patholog. While TS was detected on MRI in some symptomatic subjects, the RAMRIS, developed for inflammatory arthritis, was not able to differentiate symptomatic from asymptomatic women. There was no difference in serum findings between the two groups. These findings suggest the AI syndrome is not due to the triggering of an autoimmune or systemic inflammatory process. Although symptoms were not limited to the hands and wrists, the AUSCAN was associated with increased pain, suggesting this instrument may be discriminative in diseases other than OA.

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Hearing Loss in Muckle-Wells-Syndrome. Assen Koitschev1, Katharina Gramlich2, Sandra Hänsmann3, Susanne M. Benseler4, Stefan Plontke1, Christiane Koitschev1, Ina Koetter1 and Jasmin Kuermerle-Deschner1.

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Background: Muckle-Wells syndrome (MWS) is an inherited autoinflammatory disease associated with excessive Interleukin-1 (IL-1) release caused by NLRP3 gene mutations. MWS patients are at high risk of lighting the therapeutic potential of TF-M for autoimmune diseases such as rheumatoid arthritis and multiple sclerosis.

Disclosure: S. Kataoka: None; M. Kawamoto: None; Y. Kawaguchi: None; T. Gono: None; M. Hanaoka: None; H. Ichida: None; Y. Katsumata: None; Y. Okamoto: None; Y. Ota: None; I. Masuda: None; H. Yamanaka: None.

S372
developing devastating sensorineural deafness. The study aims to report the otologic characteristics in severe MWS.

**Patients and Methods:** A single center observational cohort study of consecutive children and adults diagnosed with MWS between 2000 and 2008 was performed. Genetic testing of the NLRP3 gene was completed. All patients had standardized neurotologic assessments including hearing threshold and speech audiograms, caloric vestibular testing and a structured tinnitus questionnaire. The audiograms of members of the same family were compared in order to describe the family specific risk of progressive hearing loss.

**Results:** A total of 19 MWS-patients ages 3–72 years from 4 families with 3 different NLRP3 gene mutations were included. Almost all patients (89%, 17/19) presented with sensorineural hearing loss of different range compared to normal hearing threshold of a same age population. 15 of 19 patients had symmetric bilateral hearing thresholds. In 3 patients minimal asymmetry of the hearing threshold in the higher frequencies was demonstrated. One female patient age 19 appeared deaf since birth on the left side. Hearing thresholds uniformly decline toward the higher frequencies starting with an isolated pitch above 4 kHz in younger patients. Increasing age was significantly associated with worsening hearing impairment. The vestibular caloric reactivity was normal in all, including patients with profound hearing loss. Non-debilitating intermittent or permanent tinnitus was reported by half of the adult patients. In this cohort, patients with the mutation V198M were the least affected by hearing loss, patients with the T348M mutation were severely affected.

**Conclusion:** Progressive sensorineural hearing loss without vestibular involvement is the characteristic symptom of MWS. Progression is age dependent with large variation by intra- and interfamilial comparison. Different mutations appear to be associated with different risk levels of hearing loss. T348M mutation being most severely affected. Early diagnosis and specific therapy by IL-1 inhibition may be essential to prevent severe disease consequences.

**Disclosure:** A. Koitschev: None; K. Gramlich: None; S. Hansmann: None; S. M. Benseler: None; S. Plontke: None; C. Koitschev: None; I. Koetter: None; J. Kuenmerle-Deschner: None.

**900**

Hearing Loss in Muckle-Wells Syndrome—Effects of IL-1 Inhibition

Assen Koitschev1, Katharina Gramlich1, Sandra Hansmann1, Susanne Benseler1, Stefan Plontke1, Christiane Koitschev1, Ina Koetter2, Ralph Preiss3 and Jasmin Kuenmerle-Deschner1.

1 Department of Otorhinolaryngology, Klinikum Stuttgart, Germany, 2 Department of Otorhinolaryngology, University Hospital Tübingen, Germany, 3 Division of Pediatric Rheumatology, Department of Pediatrics, University Hospital Tübingen, Germany, 4 Division of Rheumatology, Department of Pediatrics, The Hospital for Sick Children, Toronto, Canada, 5 Novartis Pharmaceuticals Corporation, East Hanover, NJ, 6 University Hospital, Tuebingen, Germany

**Background:** Muckle-Wells syndrome (MWS) is a rare inherited auto-inflammatory disease. The most devastating symptoms are sensorineural deafness. NLRP3 gene mutations are associated with excessive Interleukin-1 (IL-1) release. Specific IL-1 inhibition may be shown to be safe and effective in the treatment of MWS. The study aims to systemically evaluate the effect of IL-1 inhibition on hearing in MWS.

**Patients and Methods:** A single-center observational cohort study of consecutive children and adults with confirmed MWS was performed. Prospective standardized audiologic assessments were conducted at baseline and during treatment with the IL-1 receptor antagonist Anakinra or the fully human monoclonal IL-1 receptor antagonist Canakinumab. Comparison was based on pure tone thresholds at 500, 1000, 2000 and 4000 Hz and defined as an increase or decrease of 20 dB in hearing threshold at one or more frequencies, or of 10 dB at two or more consecutive frequencies. Comparisons were made using paired t-tests, chi-squares or Fishers exact test, when appropriate.

**Results:** A total of 19 patients with MWS, ages 3–72 years from 4 families with 3 different mutations of the NLRP3 gene were included. At baseline, 13 patients (68%) indicated subjective hearing loss, 4 (21%) showed high frequency hearing loss without subjective impairment and two (11%) had normal hearing threshold. Treatment with Anakinra significantly improved hearing in 2/12 patients (16 and 44 years). Hearing did not deteriorate in 10/12 (83%) patients during a median treatment course of 12 months (range 5–14). Canakinumab therapy was given to 14 patients. Hearing improved in 1/14 patient (19 years). No deterioration of hearing loss was observed in 13/14 (93%) patients during a median treatment course of 11 months (range 6–15).

**Conclusion:** IL-1 inhibition in MWS prevented progression of hearing loss in all MWS patients. Reversal of hearing loss occurred in a small group.

Factors associated with reversal have to be explored in order to optimize therapy and improve long-term outcome of MWS patients.

**Disclosure:** A. Koitschev: None; K. Gramlich: None; S. Hansmann: None; S. M. Benseler: None; S. Plontke: None; C. Koitschev: None; I. Koetter: None; R. Preiss: Novartis Pharmaceuticals Corporation, 1, 3, J. Kuenmerle-Deschner: Novartis Pharmaceuticals Corporation, 2, 5.

**901**


1 Benaroya Research Institute, 2 Benaroya Research Institute and Virginia Mason Medical Center, Seattle, WA

**Background:** Despite serological advances in the diagnosis of inflammatory polyarthritis (iPA) conditions, such as anti-CCP antibodies in RA, current rheumatological practice continues to encounter many patients with “seronegative” arthritis. Such patients are often treated as seronegative rheumatoid arthritis; however, further insight regarding the classification of such patients could help guide investigations into pathogenesis and/or treatment. Since some inflammatory arthritis conditions, especially spondyloarthropathies, have been associated with subclinical bowel inflammation, this study sought to explore the potential utility of the inflammatory bowel disease (IBD)-associated toll-like receptor (TLR) 5 ligand flagellin antibody, anti-CBir1, in the classification of “seronegative” inflammatory arthritis.

**Methods:** We performed a retrospective chart review of patients seen in the rheumatology clinic at the Virginia Mason Medical Center in Seattle, WA between Q4 2009–Q1 2010. Records of patients who had been tested for anti-CBir1 reactivity via the Prometheus® IBD Serology 7 panel, which includes also anti-Saccharomyces cerevisiae antibodies (ASCA) and outer membrane porin C (OmpC) specificities (San Diego, CA), were reviewed.

**Results:** In the timeframe specified, 132 patients had been tested with the IBD Serology 7 panel. Of these, 81 (61%) had at least one positive IBD serological marker (61%); the most prevalent was anti-CBir1, which was positive in 36% (27%), compared to ASCA (12.9% positive for IgA, 6% positive for IgG) and OmpC (10.6% positive). Interestingly, 7 of these CBir1-positive patients were otherwise “seronegative,” with negative ANA, RF, anti-CCP, ANCA, Celiac serology, and HLA-B27: these patients generally exhibited synovitis of the medium and/or large joints. Clinical evidence of psoriasis, inflammatory bowel disease, or antecedent infection was absent in all patients. Interestingly, these patients seemed to respond to treatments often used in spondyloarthropathies, such as NSAIDs, sulfasalazine, or etanercept.

**Conclusions:** Anti-CBir1 positivity may identify a subset of otherwise seronegative iPA patients, perhaps within the spectrum of inflammatory spondyloarthropathies. The bowel flora flagellin specificity of CBir1 reactivity raises the possibility of a linkage between bowel inflammation and arthritis: as a result, not only might CBir1 and/or other IBD-associated biomarkers be useful in the diagnosis of iPA, they may also provide further insight into the pathogenesis of these inflammatory disorders. Systematic investigation is therefore warranted to ascertain the clinical relevance of CBir1 reactivity in the diagnosis or classification of rheumatic conditions.

**Disclosure:** M. A. Peda: None; S. L. Peng: None.

**902**

Long Term Treatment with Anakinra in Patients with Adult-Onset Still Disease. Giampietro Cecilia1, Ridene Meriem2, Fautrel Bruno2, Bourgeois Pierre3 and CRL.

1 University of L’Aquila, L’Aquila, Italy, 2 University of Tunis, Tunisia, 3 University Paris 6–Pierre et Marie Curie University; Rheumatology, Pitie-Salpetriere Hospital, Paris, France
**Background:** Adult-onset Still disease (AOSD) is a rare systemic inflammatory disorder. Aetiology is still unknown, however recent advances suggest IL-1 to play a pivotal role in his pathogenesis.

Several observations have demonstrated the rapid efficacy of the anti-IL1 receptor antagonist anakinra in refractory cases treatment, but other studies are needed to evaluate his long term effects.

**Objective:** To assess the long term efficacy and safety of anakinra treatment in patients with AOSD.

**Methods:** Patients were identified by their participation to a precedent study and by a survey conducted in the CRI website.

19 patients affected by AOSD as defined by Yamaguchi diagnostic criteria and treated with anakinra were recruited contacting by mail all departments of rheumatology and internal medicine in France. Medical informations were retrospectively collected using a standardised questionnaire. Anakinra was given subcutaneously at a daily dose of 100mg.

Patients were classified at remission if all symptoms of AOSD were disappeared, partial response if some general or articular signs persisted and failure if no response were observed.

**Results:** Patients were mean aged 40.6 ± 11.5 years (range 23 to 73), with mean disease duration at anakinra start of 9.4 years. Clinical expression was predominatly systemic in 6 patients and polyarticular in 13. All patients have previously failed to corticosteroids, synthetic DMARDs and for 10 of them to anti-TNFα and anti-CD20.

Anakinra was well tolerated in patients with AOSD and adverse events were rated as mild. The most common adverse event observed was a rash at the site of injection. It motivated treatment discontinuation in only 1 patient. No augmentation of infection rate was observed.

At a mean follow up of 30.7 months, complete remission occurred in 13 cases. Partial response was observed in 4 cases. The symptoms that persisted were mainly articular manifestation whereas systemic ones disappeared early in the courses of treatment. 2 patients experienced a loss of efficacy after a mean duration of 15 months.

Anakinra allowed corticosteroid sparing and reduction of dose of eventually associated DMARDs. At the last visit, 4 patients withdrawn treatment because remission has been obtained and reduction of anakinra dose was possible in 4 cases without observed relapse of disease.

**Evolution in Long-term Follow-up**

<table>
<thead>
<tr>
<th>Anakinra discontinued without relapse (n = 4)</th>
<th>Dose reduction without relapse (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 subcutaneous injection 3 time a week (n = 1)</td>
<td>1 subcutaneous injection 2 time a week (n = 2)</td>
</tr>
<tr>
<td>1 subcutaneous injection 6 time a week (n = 1)</td>
<td>Same dose continued (n = 5)</td>
</tr>
<tr>
<td>21.35</td>
<td>0.3</td>
</tr>
<tr>
<td>(21%)</td>
<td>(26.3%)</td>
</tr>
</tbody>
</table>

**Conclusion:** AOSD patients experience a drastic response to Anakinra. In our long term study this efficacy is maintained without relapse or serious side effects.

**Disclosure:** G. Cecilia: None; R. Meriem: None; F. Bruno: None; B. Pierre: None; CRI: None.

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**903**

**Lymph Node and Bone Marrow Expression of Macrophage Migration Inhibitory Factor and IL18 in Adult-Onset Still’s Disease. Sung-Hoon Park1, Hwa-Jeong Lee2, Seong-Kyu Kim2 and Jung-Yoon Choe2. 1Catholic Research Center, Daegu, Korea, Republic of, 2Catholic University of Daegu, School of Medicine, Arthritis and Autoimmunity Research Center, Daegu, Korea, Republic of.**

**Background:** Lymph node and bone marrow specimens were analyzed by using quantitative real-time PCR analysis. In the previous studies, although its mechanism is not precise, serum IL18 and macrophage migration inhibitory factor (MIF) level was significantly elevated in the disease patients and was shown to be correlated with disease activity. In this study, we investigated a expression of macrophage MIF and IL18 in lymph node (LN) and bone marrow (BM) specimen of AOSD patients and compared it with normal marrow or reactive lymphadenopathy.

**Methods:** LN or BM section of 13 AOSD patients were prepared (both LN and BM in 6 of them). 3 of 6 patients showed a features of the macrophage activation syndrome (MAS), and were underwent both LN and BM biopsy. Immunohistochemical staining using anti-MIF antibody (Abcam, Cambridge, UK) and anti-IL18 monoclonal antibody (R&D Systems, Minneapolis, MN, USA) was done according to the recommendations of the manufacturer’s instructions. 3 specimens of normal BM section and 3 specimens of reactive lymphadenitis were compared as control group. Correlation of serum ferritin and C-reactive protein (CRP) level with tissue cytokine expression was investigated.

**Results:** After staining with anti-MIF antibody and anti-IL18 monoclonal antibody, the staining intensity was measured by counting a total number of reactive cells (positive dot) in 100×100μm field manually. All cell counts were performed by the same observer for the entire study and verified by a second observer blinded to the study group. Mean age of LN group was 43.56±12.45 years old (2 male and 11 female patients) and 41.03±18.79 years old (3 male and 5 female patients) in BM group. Stain intensity of IL18 and macrophage MIF in LN group was significantly higher than reactive LN group. BM of AOSD patients expressed stronger IL18 and macrophage MIF than normal BM. Both IL18 and macrophage MIF overexpressed in MAS patients group, but there was no statistically significant difference (p=0.065) compared with other AOSD patients without MAS (Table 1). Serum ferritin and CRP level was not quantitatively correlated with stain intensity.

**Table 1** LN and BM immunohistochemical stain intensity

<table>
<thead>
<tr>
<th>LN</th>
<th>BM</th>
<th>Reactive LN</th>
<th>Normal BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, year</td>
<td>43.56±12.45</td>
<td>41.03±18.79</td>
<td></td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>2(10.5%)</td>
<td>1(5.2%)</td>
<td></td>
</tr>
<tr>
<td>LN</td>
<td>BM</td>
<td>Reactive LN</td>
<td>Normal BM</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>IL 18 stain</td>
<td>198.66 ± 91.36</td>
<td>142.32 ± 74.82</td>
<td>15 ± 12.31</td>
</tr>
<tr>
<td>MIF stain</td>
<td>122.64 ± 110.11</td>
<td>104.26 ± 123.20</td>
<td>9 ± 16.14</td>
</tr>
</tbody>
</table>

**Conclusion:** Tissue IL18 and macrophage MIF was overexpressed in both LN and BM of AOSD patients. Their pathophysiology correlate and therapeutic implication should be elucidated.

**Disclosure:** S.-H. Park: None; H.-J. Lee: None; S.-K. Kim: None; J.-Y. Choe: None.

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**904**

**New Onset of Uveitis under Anti TNF Therapy. A Nationwide Series. Daniel Wendling, Julien Paccou, René-Marc Flipo, Emmanuelle Denni, Guillaume Direz, Veronique Ferrazzi, Severine Guillaume, Jean-Michel Ristori and Club Rhumatismes et Inflammation (CRI). Rheumatology, University Hospital, Besançon, Besançon, France.**

**Background:** Uveitis may be associated with various inflammatory diseases. Previous reports suggested that TNF blockers, especially anti TNF monoclonal antibodies, may reduce the incidence of uveitis flares in those diseases. Under these circumstances, de novo occurrence, i.e. new onset of the first episode of uveitis under anti TNF therapy is uncommon.

**Aim:** The aim of this study was to collect cases of new onset of uveitis under anti TNF therapy, using a nationwide network, and to describe such cases.

**Methods:** All French rheumatologists and internal medicine practitioners registered on the Club Rhumatismes et Inflammation web site (1,400 physicians) were contacted by 3 electronic newsletters in an attempt to declare the cases of new onset of uveitis, diagnosed by an ophthalmologist, in patients treated with TNF blockers. A previous episode of uveitis before anti TNF therapy was an exclusion criteria. Informations were recorded about the patient (age, gender), the disease (diagnosis, duration), the TNF blocker (type, duration), the uveitis (type, severity, outcome).

**Results:** Thirteen cases were recorded, 7 men, mean age 43 (5–70) years. Other causes of uveitis were excluded (e.g. infection). The underlying disease was ankylosing spondylitis (6 cases), rheumatoid arthritis (2 cases), juvenile spondyloarthritis, psoriatic spondyloarthritis (1 case each). The mean duration of the disease was 13.5 (1.5–35) years. The TNF blocker at time of uveitis was etanercept 9 times (3 cases after adalimumab), adalimumab 2 times (with previous etanercept). The mean duration of exposure to anti TNF agents was 28.3 (4–65) months at uveitis occurrence. Eleven of the patients were good responders to TNF blockers at time of uveitis.

**Discussion:** Uveitis new onset under anti TNF therapy is uncommon. It is an exclusion criteria. The aim of this study was to collect cases of new onset of uveitis under anti TNF therapy, using a nationwide network, and to describe such cases.
and maintained in the others. Uveitis recurrence occurred in 5 cases, with sequelae in one case, with a mean follow-up of 16.9 (1–77) months.

Conclusion: Uveitis occurs de novo under anti TNF therapy mainly in spondyloarthropathies, but also in rheumatoid arthritis patients; this new onset seems more frequent under etanercept and uveitis is time-limited without discontinuation of the TNF blocker in most of the cases. This illustrates a new possibility of paradoxical effects of anti TNF agents, and rheumatologists should be aware about this event.

Disclosure: D. Wendling: None; J. Paccou: None; R.-M. Flipo: None; E. Denis: None; G. Direz: None; V. Ferrazzi: None; S. Guillaume: None; J.-M. Ristori: None; Club Rhumatismes et Inflammation (CRI): None.

905

Preliminary Scores for the Evaluation of Disease Activity in Familial Mediterranean Fever, Mevalonate Kinase Deficiency, TNF-Receptor Associated Periodic Syndrome and Cryopyrin-Associated Diseases: Results from the AIDAI Consensus Conference.

Maryam Piram, Joost Frenkel, Marco Gattorno, Seza Ozen, Helen Lachmann, Rafaela Goldbach-Mansky, Anna Simon, Veronique Hentgen, Benedicte Neven, Katia Stankovic-stojanovic, Jasmin Kuennerme-Deschner, Hal Hofmann, Sylvia Stojanov, Agnes Duquesne, Pascal Pillet, Alberto Martini, Jacques Pouchot and Isabelle Kone-Paut.

1CEREMAI, Pediatric Bicêtre, France, 2CEREMAI, Pediatric Rheumatology, Bicêtre Hospital, Paris University of Medicine, Le Kremlin Bicêtre, France, 3Department of General Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, 4Department of Infectious Diseases and Immunology, Internal Medicine, Tenon University Hospital, Université Pierre et Marie Curie Paris 6, Paris, France.

Conclusion: Using consensus formation techniques, we formulated preliminary scores to measure disease activity in four main AIDs. The prospective validation will follow.

Acknowledgments to S Lacassagne and I Tootou

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Disclosure: M. Piram: None; J. Frenkel: None; M. Gattorno: None; S. Ozen: None; H. Lachmann: None; R. Goldbach-Mansky: None; A. Simon: None; V. Hentgen: None; B. Neven: None; K. Stankovic-stojanovic: None; J. Kuennerme-Deschner: None; H. Hoffman: None; S. Stojanov: None; A. Duquesne: None; P. Pillet: None; A. Martini: None; J. Pouchot: None; I. Kone-Paut: None.

906

Prevalence and Clinical Significance of Cryofibrinogenemia in Patients with Renal Disorders.

Benjamin Terrier, Hassan Izzedine, Lucile Musset, David Saadoun and Patrice Cabou.

Pitié-Salpêtrière

Background: Cryofibrinogenemia (CryoFg) is an under-recognized condition that can be life-threatening when untreated. Symptoms of CryoFg are mainly cutaneous including purpura, ecchymosis, ulcerations, livedo and ischaemic necrosis. Renal lesions rarely develop in patients with CryoFg, but the detection of CryoFg was identified in patients with nephropathy.

Objective: Our aim was to describe the prevalence and the significance of CryoFg in patients with renal disorders.

Methods: 101 consecutive patients (mean age 58 ± 18, female/male 35/66) admitted in the Nephrology Department of a single university hospital for the management of renal disorders (mean age 58 ± 18, female/male 35/66) were consecutively included in the study and tested for cryoglobulinemia and CryoFg. Anticoagulant-free tubes for cryoglobulin detection or citrated tubes for CryoFg detection were collected. When positive, CryoFg quantification was performed. Patients who were CryoFg positive were defined as having plasma CryoFg over 0.05 g/L. We analyzed clinical and biological factors associated with the presence of CryoFg.

Results: Among the 101 patients, 11 patients had positive CryoFg without detectable cryoglobulin (11%). Median CryoFg level was 0.07 g/L (0.05–1.16). Main epidemiological features and causes of nephropathy, in particular vascular nephropathies, were similar between CryoFg- and CryoFg+ patients. No biological difference (hematuria, proteinuria, creatinine level and glomerular filtration rate using MDRD) was found between CryoFg- and CryoFg+ patients. In contrast, CryoFg+ compared to CryoFg- patients had more frequently severe thrombotic events (36 vs. 0%, p<0.0001). Severe thrombotic events included renal arteries thrombosis in 2 patients, recurrent arterial venous fistula thrombosis in 1, and recurrent dialysis catheter thrombosis with superior vena cava obstruction in 1. The presence of CryoFg was not associated with other manifestations, in particular cutaneous manifestations.

Conclusion: Cryofibrinogenemia is detected in up to 11% of patients with renal disorders. In such patients, the presence of CryoFg is associated with thrombotic events.

Disclosure: B. Terrier: None; H. Izzedine: None; L. Musset: None; D. Saadoun: None; P. Cabou: Roche, 5.

907

Pseudo-Hypertrophic Osteoarthropathy in Lung Transplant Recipients on Long Term Voriconazole Therapy.

Rajan Sagar, Tisha Wang, Rajeev Sagar and Roy D. Altman.

1UCLA, Los Angeles, CA, 2UCLA, Agua Dulce, CA, 3UCLA

Objective: Report a series of patients with a newly described syndrome

Method: Seven cases of lung transplant recipients on long term voriconazole developed a musculoskeletal syndrome.

Results: Lung transplantation was undertaken for end-stage emphysema, sarcoidosis, and idiopathic pulmonary fibrosis. Oral voriconazole was initiated as prophylaxis after isolation of Aspergillus spp. after surveillance bronchoscopy. After 6 to 26 months of therapy withvari-
conizole (200mg bid), this subset of patients presented with non-specific, diffuse bony pain involving arms, shoulders, thighs, knees and shins. Serum alkaline phosphatase was elevated to 1.1 to 7 times the upper limit of normal. Bone scanning with Tc-99m revealed localization of nuclide to long bones in a spotty distribution atypical for hypertrophic osteoarthropathy. None of the cases had associated clubbing. 2 cases demonstrated periostitis on plain radiograph. Symptoms remised within 2–4 weeks of discontinuation of conizole. Repeat bone scan within 6 weeks of conizole discontinuation demonstrated significantly reduced accumulation of nuclide.

Conclusion: A syndrome of diffuse extremity pain with periostitis can be seen in lung transplant patients on long term conizole. It is suspected that this syndrome may also be seen with azole therapy in long term use for other transplant recipients.

Disclosure: R. Saggar: None; T. Wang: None; R. Saggar: None; R. D. Altman: None.

908

QuantiFERON®-TB Gold In-Tube Test Versus Tuberculin Skin Test across RA, PsA, and AS Patients Prior to Treatment with Golimumab, a Human Anti-TNF Antibody, Elizabeth C. Hsi"1, Neil Schluger2, John J. Cush1, Richard E. Chaisson7, Eric L. Matteson3, Anna Beutler3, Mittie K. Doyle2, Benjamin L. Hsu4 and Mahboob U. Rahman5. 1Baylor Research Center, Haifa, Israel, 2A. Kessel:

Background: Screening for latent tuberculosis infection (LTBI) prior to use of tumor necrosis factor (TNF) blockers is recommended to decrease the risk of tuberculosis (TB) reactivation. The standard screening tuberculin skin test (TST) is limited by positive (+) results due to cross-reactivity with Bacillus Calmette-Guérin (BCG) vaccine and false-negative (–) results, especially in the immunocompromised. More recently developed blood tests, eg, QuantiFERON®-TB Gold test In-Tube (QFT), offer the possibility of improved LTBI detection, but performance data in patients (pts) with autoimmune inflammatory disease is limited.

Objectives: Compare QFT vs TST performance for LTBI screening prior to golimumab (GLM) use across 5 pt populations with rheumatic disease.

Methods: All pts were screened by QFT and TST in each of the 5 Phase 3 trials of subcutaneous GLM that included pts with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis enrolled from North & South America, Europe (Western + Eastern), Australia/New Zealand, and Asia. TST (Mantoux method) was deemed – according to local country guidelines for immunosuppressed host, or if ≥5mm if no guidelines existed. Any initially indeterminate (IND) QFT results were repeated, and final results were used. IND QFT results were considered discordant with TST results. QFT and TST results were tabulated overall and by known BCG vaccination status.

Results: Of the 2294 pts in this pooled analysis, at least 1 test was + in 13.9% were TST +, and 2.6% QFT + and TST + (Table). QFT IND rate was 1.8%. Agreement of TST and QFT results was 87.1%, and Kappa coefficient was 0.257 (95% CI: 0.192 to 0.321; p = 0.021). Among QFT + tests only 36.2% were TST +; among TST + tests only 27.4% were QFT +. 784/2294 pts had prior BCG. The TST + rate was 3-fold higher in BCG + vs BCG – (15.2% vs 4.9%), which was not seen with QFT + (9.1% vs 6.0%), supporting the use of QFT in BCG + pts. The slightly higher QFT + rate among BCG + vs BCG – pts might be explained by the higher endemic TB rate in the regions in which this group of pts resides rather than being false +. Despite the known greater cross-reactivity of TST with non-TB mycobacteria among BCG – pts, the QFT + rate was slightly greater than the TST + rate suggesting the possibility of higher sensitivity of QFT. By repeating initially IND results, the QFT IND rate was much lower than in previous reports.

Conclusions: In the absence of a true gold-standard test for LTBI, results of this large comparison of QFT and TST in pts with rheumatic disease suggest that QFT provides greater sensitivity and specificity than TST.

Table. Screening TST results by QFT and BCG vaccination status

<table>
<thead>
<tr>
<th></th>
<th>QFT result (n)</th>
<th>Screening TST result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ (n)</td>
<td>– (n)</td>
</tr>
<tr>
<td>All GLM Phase 3 pts (n = 2294)</td>
<td>+ (163)</td>
<td>59</td>
</tr>
<tr>
<td>IND (42)</td>
<td>6</td>
<td>36</td>
</tr>
<tr>
<td>BCG + pts (n = 784)</td>
<td>+ (71)</td>
<td>28</td>
</tr>
<tr>
<td>IND (10)</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>BCG – pts (n = 1257)</td>
<td>+ (75)</td>
<td>24</td>
</tr>
<tr>
<td>IND (24)</td>
<td>6</td>
<td>18</td>
</tr>
</tbody>
</table>


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Regulatory T-Cells in Familial Mediterranean Fever (FMF), Doron Rimari1, Ilzak Rosner1, Gleb Slobodin1, Nira Boullman1, Aharon Kessel1, Elias Touby2 and Michael Rozenbaum3. 1Immunology Unit, Bnai-Zion Medical Center, Haifa, Israel, 2Rheumatology Unit, Bnai-Zion Medical Center, Haifa, Israel, 3Rheumatology Unit, Bnai-Zion Medical Center, Haifa, Israel

Introduction: The role of regulatory T cells (T-regs) in FMF is yet to be evaluated. Preliminary studies suggest a rise in the number of regulatory T cells after FMF attacks, reaching maximal level at 7 days.

Aim: To investigate the role of T-regs in FMF.

Methods: 5 patients with refractory FMF (defined as at least 1 attack per month despite colchicine therapy of at least 2 mg per day) were evaluated. Seven days after each FMF attack, the number of T-regs and expression of FOXP3 was estimated by flow cytometry after staining for CD4, CD25 bright, and FoxP3 and compared to the level after 14 or more days of remission.

Results: Three females and 2 males were included. All patients had definite FMF according to the TEL HASHOMER criteria with high severity scores, mean 2.8. The patients were of different ethnic origins: 1 Jew, 2 Arabs and 2 Druzes. Their mean age was 31.6±2.6 yrs. Mean age at onset of FMF was 9.3±9.3 yrs. Mean colchicine dose was 2.6mg ± 0.4. Six FMF attacks were assessed. The expression of FOXP3 on CD 4 CD25 bright T cells 7 days after the attacks was significantly higher than at remission, mean fluorescence intensity (MFI) of 10.68±1.6 vs. 4.26±0.9 (p = 0.0002). There was no difference between the percent of CD4, CD25 bright T cells 10.08±3.18 vs. 11.23±4 respectively (p>0.05).

Conclusion: The expression of FOXP3 by T-regs increases after attacks of FMF, yet the percentage of T-regs remain unchanged. Anti-inflammatory cytokines interleukin-10 and TGF-β have been (paradoxically?) reported to increase in FMF attacks along with pro-inflammatory cytokines. These anti-inflammatory cytokines are known to activate T-regs, in line with the present findings. It is suggested that T-regs may have a role in terminating FMF attacks.

Disclosure: D. Rimar: None; I. Rosner: None; G. Slobodin: None; N. Boullman: None; A. Kessel: None; E. Touby: None; M. Rozenbaum: None.

910

Safety of Arthrocentesis in Patients on Chronic Warfarin Therapy with Therapeutic INR. Imad Ahmad1 and Elie Gertner2. 1Regions Hospital, St Paul, MN, 2Regions Hospital.
Introduction: Patients often need arthrocentesis for diagnostic and therapeutic reasons while on chronic warfarin therapy. Often the procedure is delayed or avoided because of concern about bleeding. The aim of this retrospective study was to determine the safety of arthrocentesis in patients on chronic oral warfarin therapy with INR ≥2.0.

Methods: From 01/ 2001 to 11/2008, we reviewed records at Regions Hospital and HealthPartners Medical Group of 514 consecutive patients on chronic warfarin therapy who underwent 640 joint aspiration procedures. Total of 456 procedures were performed with INR ≥2.0 (Group A) and 184 procedures were performed with INR <2.0 (Group B).

The end points were: (1) clinically significant bleeding,(2) infection of the joint (3) pain in the joint needing emergency room, urgent care or physician visits. The end points were both early (within 24 hours post-procedure) and late (within 30-days). Indications for arthrocentesis were usually pain/effusion in patients with diseases such as rheumatoid arthritis, osteoarthritis, gout etc.

Results: There were no significant differences in age, sex, body mass index and concurrent use of antiplatelet agents between the two groups. Groups were also comparable among all medical co-morbidities examined (diabetes mellitus, hypercoagulability, hypertension, liver failure, renal failure and smoking status). Mean INR at the time of procedure for group A was higher than group B (2.7±0.03 vs.1.6±0.02). [Table 1] shows the early and late complications in both groups.

Table 1. Early and late complications between two groups

<table>
<thead>
<tr>
<th>Complications</th>
<th>Group A INR ≥ 2.0</th>
<th>Group B INR &lt; 2.0</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant bleeding (early)</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Clinically significant bleeding (late)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Infection (early)</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Infection (late)</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Pain causing physician visit</td>
<td>3 (0.7%)</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = non significant.

There was no statistically significant difference in the overall complication rate between patients with INR ≥2.0 (Group A) and patients with INR<2.0 (Group B) (p=0.708). Receiver operating characteristic [Figure-2] analysis showed that INR offered modest value as a predictive instrument, with a c-statistic of 0.615.

Conclusion: Arthrocentesis in patients on chronic warfarin therapy with therapeutic INR appears to be safe without an increased risk of bleeding complications. This approach simplifies the peri-procedural management of anticoagulation, and could lead to improved outcomes and reduced health care costs.

Disclosure: I. Ahmed: None; E. Gertner: None.

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Standardization of Antinuclear Antibody Assessment on HEP-2 Cells by Automated Interpretation. Karl Egerer1, Dirk Roggenbuck2, Rico Hiemann3, Max-Georg Weyer5, Barbara Lehmann5, Eugen Feist5 and Gerd R. Burmester4. 1Charite-University Medicine, Berlin, Germany, 2Charite-University Medicine, Berlin, Germany, 3Charite-University Medicine, 4Medipan GmbH, Berlin Dahlewitz, Germany, 5Medizinisches Versorgungszentrum für Laboratoriumsmedizin, Mikrobiologie, Virologie und Infektionsepidemiologie, Hygiene und Umweltmedizin, 6University of Applied Science Lausitz

Introduction: Analysis of antinuclear antibodies (ANAs) by indirect immunofluorescence (IIF) is a basic tool for the serological diagnosis of systemic rheumatic disorders. Automation of ANA IIF interpretation including pattern recognition can improve assay reproducibility and intra- and inter-laboratory variability. Automation of ANA reading meets the demand for cost-effective assessment of large numbers of samples in routine laboratories. Comparing automated and visual interpretation of ANA patterns, the usefulness for laboratory diagnostics was investigated.

Methods: Antinuclear antibody detection by IIF on human epithelial-2 (HEP-2) cells including pattern recognition was performed in a total of 1222 consecutive sera of patients with suspected systemic rheumatic diseases from a university routine laboratory (n=924) and a private referral laboratory (n=298). IIF reading results obtained in routine diagnostics were compared with findings by a novel automated interpretation system employing mathematical pattern recognition algorithms.

Results: Visual and automated interpretation of ANA showed a very good agreement regarding positive / negative discrimination (kappa=0.828). Only 98 (8.0%) of 1222 sera demonstrated discrepant results in the differentiation of positive from negative samples. The contingency coefficient of Chi-square statistics was 0.646 for the university laboratory cohort with an agreement of 93.0% and 0.695 for the private laboratory cohort with an agreement of 90.6%, p=0.0001, respectively. According to the McNemar test, there was no significant difference in the university cohort (1.08%, p=0.25).

Comparing respective immunofluorescence patterns, 111 (15.3%) sera yielded differing results in both cohorts. Discrepant results were mainly obtained when the AKLIDES algorithms assessed cytoplasmic signals as nuclear staining due to superposition.

Conclusions: Automated interpretation of ANA by IIF on HEP-2 cells using an automated reading system is a reliable and robust method for positive/negative differentiation of IIF findings. Employing novel mathematical algorithms, automated interpretation provides reproducible detection of specific immunofluorescence patterns on HEP-2 cells. Automated interpretation can reduce drawbacks of ANA detection by IIF in routine diagnostics providing more reliable data for clinicians.

Disclosure: K. Egerer: None; D. Roggenbuck: Medipan, Generic Assays, 4; R. Hiemann: Medipan, 5; M.-G. Weyer: None; B. Lehmann: None; E. Feist: None; G. R. Burmester: None.

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The CIRAS Study: A Case Control Study To Define the Clinical, Immunologic and Radiographic Features of the Aromatase Inhibitor Arthralgia Syndrome. Victoria K. Shannugam2, James McClooskey1, Elizabeth Elston1, Sandra J. Allison2, Claudine Isaacs3 and Jennifer Eng-Wong3. 1Department of Internal Medicine, Georgetown University Medical Center, Washington, DC, 2Department of Radiology, Georgetown University Medical Center, Washington, DC, 3Division of Rheumatology, Immunology and Allergy, Georgetown University Medical Center, Washington, DC, 4Georgetown University, 5Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC
Background: Aromatase inhibitors (AIs) reduce recurrence in postmenopausal hormone-receptor positive breast cancer. However, development of joint pains (Arthralgia Syndrome) limits compliance. The pathophysiology of this syndrome is unknown, but morning stiffness suggests an inflammatory etiology. Associations have been reported with tenosynovitis and autoimmune diseases. The CIRAS study was designed to determine the evidence for an inflammatory etiology.

Methods: Postmenopausal breast cancer patients followed at Lombardi Cancer Center with hand pain but without known autoimmune disease were recruited. Subjects receiving AIs were cases (n=25) while those not receiving AIs were controls (n=23).

Subjects were evaluated after abstaining from non-steroidal anti-inflammatory drugs for 48 hours. They completed a health assessment questionnaire (PROMIS-HAQ). The rheumatologist completed a history and physical, and disease activity score (DAS-28). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), vitamin D and cytokine levels were tested. Bilateral hand radiographs and ultrasound were performed. The hand ultrasound was scored for presence of flexor tendon sheath enhancement for each digit on both hands, and a total ultrasound score was computed. The rheumatologist and radiologist were blinded as to study group. Data was analyzed using t-test and Fisher’s exact test.

Results: Patients in both groups were predominantly Caucasian and of similar age. Neither the DAS-28 nor the ESR was significantly different between cases and controls.

<table>
<thead>
<tr>
<th>Condition</th>
<th>CASE (n=25)</th>
<th>CONTROL (n=23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMIS-HAQ (mean ± SEM)</td>
<td>9.70 ± 3.23</td>
<td>10.05 ± 2.29</td>
<td>0.591</td>
</tr>
<tr>
<td>PROMIS-HAQ Global score (mean ± SEM)</td>
<td>51.04 ± 1.74</td>
<td>54.23 ± 9.714</td>
<td>0.747</td>
</tr>
<tr>
<td>Pain score (mean ± SEM)</td>
<td>34.88 ± 5.45</td>
<td>42.83 ± 5.506</td>
<td>0.311</td>
</tr>
<tr>
<td>Duration of morning stiffness/ hours (mean ± SEM)</td>
<td>2.00 ± 0.230</td>
<td>1.435 ± 0.2973</td>
<td>0.074</td>
</tr>
<tr>
<td>Inflammatory indices: DAS-28 (mean ± SEM)</td>
<td>2.311 ± 0.1469</td>
<td>2.29 ± 0.1393</td>
<td>0.918</td>
</tr>
<tr>
<td>ESR (mean ± SEM)</td>
<td>17.08 ± 3.016</td>
<td>18.50 ± 2.936</td>
<td>0.739</td>
</tr>
<tr>
<td>Vitamin D (mean ± SEM)</td>
<td>30.17 ± 2.537</td>
<td>33.35 ± 2.576</td>
<td>0.384</td>
</tr>
<tr>
<td>Autoimmune features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA positive (%)</td>
<td>4</td>
<td>6</td>
<td>0.390</td>
</tr>
<tr>
<td>Autoimmune disease (%)</td>
<td>4</td>
<td>6</td>
<td>0.390</td>
</tr>
<tr>
<td>X-ray</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degenerative joint disease (%)</td>
<td>15</td>
<td>14</td>
<td>0.909</td>
</tr>
<tr>
<td>Other medication:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biophosphonate (%)</td>
<td>11</td>
<td>8</td>
<td>0.561</td>
</tr>
<tr>
<td>Tamosifin (%)</td>
<td>7 current use</td>
<td>9 prior use</td>
<td></td>
</tr>
<tr>
<td>Ultrasound findings:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ultrasound score (mean ± SEM)</td>
<td>6.600 ± 1.049</td>
<td>4.909 ± 1.040</td>
<td>0.260</td>
</tr>
<tr>
<td>Tendon nodules (%)</td>
<td>3</td>
<td>0</td>
<td>0.254</td>
</tr>
<tr>
<td>DeQuervain’s tenosynovitis (%)</td>
<td>4</td>
<td>2</td>
<td>0.681</td>
</tr>
<tr>
<td>Ganglion cysts (%)</td>
<td>8</td>
<td>8</td>
<td>1.0000</td>
</tr>
<tr>
<td>Flexor tenosynovitis (%)</td>
<td>14</td>
<td>10</td>
<td>0.563</td>
</tr>
</tbody>
</table>

Hypovitaminosis D was found in 1 case and 5 controls (p 0.06). There was no significant difference in mean vitamin D. In each group two subjects had previously undiagnosed autoimmune disease (8.3%). A positive ANA was identified in 6 controls and 4 cases (20.8%). While cases experienced more prolonged morning stiffness, this did not reach statistical significance (p = 0.07). PROMIS-HAQ, global-HAQ and mean pain scores were not significantly different. There was no difference in ultrasound score or tendon nodules, Dequervain’s tenosynovitis, ganglion cysts or flexor tenosynovitis. Several patients in the control arm had a similar constellation of symptoms to those receiving AIs.

Conclusions: The arthralgia syndrome may not be unique to patients receiving AIs. This syndrome warrants further investigation since development affects compliance with AI therapy.

Disclosure: V. K. Shanmugam: Dr. Shanmugam is supported by the American College of Rheumatology, Research and Education Foundation, Physician Scientist Development Award. None; S. J. Allison: None; C. Issacs: AstraZeneca; S. J. Eng-Wong: None.

A Negative Anti-Nuclear Antibody Does Not Indicate Autoantibody Nega- tivity, Rohit Aggarwal1, Noreen Fertig2, Dana P. Ascherman2, Elaine A. Cassidy3 and Chester V. Oddis1, 1Children’s Hospital Pittsburgh, Pittsburgh, PA, 2University of Pittsburgh, Pittsburgh, PA, 3University of Pittsburgh, Pittsburgh, PA

Purpose: To evaluate the diagnostic utility of anti-cytoplasmic autoanti- body (anti-cytAb) staining by indirect immunofluorescence (IIF) on Hep 2 substrate in anti-synthetase antibody positive (anti-synAb+) patients and to compare it with Anti-nuclear antibody (ANA) testing.

Methods: Using the Pittsburgh database of myositis and systemic sclerosis (SSc), anti-synAb+ patients were evaluated for ANA and anti-cytAb positivity. Anti-synAb+ patients included both Jo-1 and non-Jo-1 patients. SSc patients without anti-synAb were the control group. The following test characteristics of anti-cytAb and ANA were assessed in the anti-synAb+ patients: a) sensitivity [true positive (TP)/TP + false negative (FN)], b) specificity [true negative (TN)/TN + false positive (FP)], c) positive predictive value (PPV; TP/TP + FP), d) negative predictive value (NPV; TN/TN + FN) and e) accuracy (TP + TN/ total number of patients tested). Anti-cytAb testing was done using the same method as ANA by IIF on Hep2 cell. Both were reported simultaneously on each patient sample. Anti-synAb status was not known before the ANA and anti-cytAb determination.

Results: All anti-synAb+ patients [n=202; Jo-1=122 patients; non-Jo-1=80 patients] between 1985–2009 with available serum samples were assessed. Non-Jo-1 included: anti-PL-12, anti-PL-7, anti-EJ, anti-OJ, anti-KS. Anti-cytAb showed high sensitivity (72%), specificity (91%), NPV (91%) and accuracy, but only modest PPV (44%) for anti-synAb positivity (Table 1). Similar sensitivity results were seen for Jo-1 and non-Jo-1 (PL-12, PL-7 and KS) autoAb subgroups. In contrast, the ANA showed only modest sensitivity (50%) as well as poor specificity (0.6%), PPV (5%), NPV (10%) and accuracy (5%). Positive anti-cytoplasmic staining was significantly greater in the anti-synAb+ patients than ANA positivity (72% vs. 50%, p<0.001). Moreover, 81/99 (82%) of ANA negative patients in the anti-synAb+ cohort had positive anti-cytAb staining. In contrast, the control group of SSc (n=1946) showed high positive rates for ANA (1935/1946, 99%), but very low positive rates for anti-cytAb (180/1946, 9%). Combining anti-cytAb or ANA positivity to identify anti-synAb+ patients increases the sensitivity to 90% (1577/1796), but specificity decreases dramatically (0.4%). Finally, the combination of anti-cytAb or Jo-1 positivity shows high sensitivity (181/196, 92%) and specificity (91%) for identification of anti-synAb+ patients.

Conclusions: Assessing patients for anti-cytAb staining using similar techniques to current ANA testing has excellent diagnostic utility for anti-synAb+ patients while ANA testing alone has poor test characteristics. Cytoplasmic staining should therefore be assessed and reported for patients suspected of having a rheumatic disease (RD), and a negative ANA should not be used to exclude a RD diagnosis.

Disclosure: R. Aggarwal: None; N. Fertig: None; D. P. Ascherman: None; E. A. Cassidy: None; C. V. Oddis: None.
A Novel Form of an Autosomal Dominant Vacular Hereditary Myopathy. Christine Castro1, Ivona Ak scentijevich1, Elaine Remmers2, Elisabeth Rushing1, Simona Bianconi1, Marjan Huizing3, Mildred Wilson4, Thomas Markello4, Daniel Kastner5 and Mark Gourley6. 1Armed Forces Institute of Pathology, 2National Institutes of Health/National Human Genome Research Institute/Medical Genetics Branch, 3National Institutes of Health, 4National Institutes of Health, 5National Institutes of Health/National Human Genome Research Institute, Medical Genetics Branch, 6National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD. 7National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases. Bethesda, MD.

Background: Inclusion body myositis (IBM) is a slowly progressive skeletal muscle disease of unknown etiology with both sporadic and familial forms. The disease is characterized by proximal and often asymmetric distal muscle weakness, often with quadriiceps atrophy. Muscle biopsy often shows degenerating and regenerating muscle fibers, perimyofiber distribution of inflammatory cells, and occasional red-rimmed vacuoles on Gomori trichrome stained sections. The most distinguishing feature is lack of response to immunomodulatory therapy. In familial IBM, disease onset often occurs in the late-teens to mid-20s; a Finnish form occurs in the 40s. Conversely, the sporadic form often occurs in those over age 50.

Purpose: We identify what we believe is a new familial form of IBM in one family with 3 generations demonstrating onset after age 50. In the third generation, 5 of 10 siblings are clinically affected, suggesting autosomal dominant inheritance. Results of muscle biopsy, EMG and MRI are consistent with IBM.

Methods and Materials: Subjects include 10 siblings (5 affected) ages 47 to 64, their unaffected father (age 86) and affected mother (age 70). They are of German and Dutch descent. Blood samples were obtained from all siblings and from the father. (A histology block of an endomterial biopsy from many years ago was obtained from the deceased mother.) MRI of bilateral thighs (T1-weighted and STIR images) was performed on 7 siblings. Muscle biopsy of the right quadriiceps was done on 7 siblings and sent to Armed Forces Institute of Pathology for processing. DNA was extracted from blood of the 10 siblings, from their father, and the endomterial biopsy of the mother (later not used due to poor quality). Linkage analysis was performed and genotype data was analyzed via a program designed to identify the maternal haplotype transmitted to each child. Selected genes from the candidate interval were sequenced.

Results: MRI images from the 5 affected subjects showed edema, fatty replacement, muscle atrophy and/or fascial enhancement. The 2 unaffected subjects were normal. Histology revealed abnormalities including vacuoles on Gomori trichrome stain, degenerating and regenerating muscle fibers, fiber size variation, and presence of angular atrophic fibers in all 7 siblings. Through genetic analysis, a 3 megabase region of interest was found on chromosome 12. To date, no genes have been located.

Conclusion: We present a family with a seemingly autosomal dominant late onset vacular myopathy. Linkage analysis and gene sequencing has led us to chromosome 12 where a 3 megabase region peaks our interest. However, we have not yet isolated a gene. Characterization of this family’s disease is of great interest because hereditary or familial forms of any IBM provide genetic information to further our understanding of this disease process as well as identify individuals who would be most affected by such diseases.

Disclosure: C. Castro: None; I. Ak scentijevich: None; E. Remmers: None; E. Rushing: None; S. Bianconi: None; M. Huizing: None; M. Wilson: None; T. Markello: None; D. Kastner: None; M. Gourley: None.

915 Anti-SRP Auto-antibody Titers Correlate with Serum Creatine Kinase in Necrotising Myopathy. Olivier Benveniste1, Laurent Drouot1, Fabienne Jouen2, Olivier Goto3, Yassushi Kawaguchi4, Takashi Sato5, Masatake Kuvana1, Yashuo Katsumata6, Kae Takagi7, Ikuko Masuda8, Sayumi Bab9, Masanori Hanaoka10, Yuko Okamoto11, Yuko Ota12, Sayuri Katoaka13 and Hisashi Yamanaka14. 1Keio University School, Tokyo, Japan, 2Keio University School, 3Tokyo Women's Medical University, Tokyo, Japan, 4Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan, 5Tokyo Women's Medical University.

Purpose: The aim of the present study is to evaluate the clinical manifestation and prognostic factors of anti-melanoma differentiation–associated gene 5 (MDA5) antibody-associated interstitial lung disease (ILD) with dermatomyositis (DM).

Methods: Fourteen patients who presented with anti-MDA5 antibody and 10 patients with anti-aminocycl-1RNA synthetase (ARS) antibody were enrolled. All of patients were diagnosed as having DM with ILD. Clinical manifestations in the patients with anti-MDA5 antibody were compared to those in the patients with anti-ARS antibody.

Results: The age at onset was 43.6 ± 14.6 years (mean ± SD), with no significant difference between each subset. The frequency of clinically amyopathic dermatomyositis (57%) was significantly higher (P = 0.033) in the subset with anti-MDA5 antibody. The creatine kinase (CK) value (median, 198 IU/ml) was significantly lower (P = 0.01) and ferritin values (median, 680 ng/ml) were significantly higher (P = 0.016) in the subset with anti-MDA5 antibody. The frequencies of acute/subacute interstitial pneumonia was significantly higher (P = 0.036) in the subset with anti-MDA5 antibody (71%) than the subset with anti-ARS antibody (20%), although pulmonary function showed no significant differences between each subset. Significant correlations were found between A-alD0 and KL-6 (r = 0.73, P = 0.016), and A-alD0 and ferritin (r = 0.66, P = 0.013) in the subset with anti-MDA5 antibody. Clinical manifestations were compared between the surviving and non-surviving patients who had ILD with anti-MDA5 antibody.
The followings were significantly higher in the non-surviving patients with anti-MDA5 antibody: age at onset ($P = 0.045$), A-adO ($P = 0.045$), AST ($P = 0.027$), γ-GTP ($P = 0.028$), and ferritin ($P = 0.016$). Age- and sex-adjusted Cox regression analysis was performed to identify a prognostic factor for ILD with anti-MDA5 antibody. The most significant prognostic factor was serum ferritin (Hazard ratio per unit 1.004-1.014, 95% confidential interval 1.004-1.014, $P = 0.027$). The cumulative 60-month survival rates were significantly lower ($P = 0.042$) in the subset with anti-MDA5 antibody (62.9%) than in the subset with anti-ARS antibody (100%). The cumulative survival rate was significantly lower ($P < 0.0001$) in the subset with ferritin $\geq 1600$ ng/mL than that in the subset with ferritin <1600 ng/mL in anti-MDA5 antibody-associated ILD.

Conclusion: Both serum ferritin and anti-MDA5 antibody are powerful indicators for the early diagnosis of A/SIP with DM. Serum ferritin also predicts disease severity and prognosis for patients with anti-MDA5 antibody.

Disclosure: T. Gonen; None; T. Satoh; None; M. Kuwana; None; Y. Katsumata; None; K. Takaji; None; I. Masuda; None; S. Baba; None; M. Hanaka; None; Y. Okamoto; None; Y. Ota; None; S. Katoaka; None; H. Yamanaka; None.

917 Efficacy and Tolerance of Rituximab in Refractory Idiopathic Inflammatory Myopathy. Data of the AIR Registry, Marion Couderc1, Jacques E. Gottenberg2, Xavier Mariette2, Eric Hachulla6, Jean Sibilia11, Olivier Fain3, Arnaud Hot2, Maxime Dougados3, Lianna E. Euler-Ziegler4, Pierre Bourgeois8, Claire Larroche10, Anne Tournadre3, Zahir Amoura10, Bernard Mazeries1, P. Arlet13, Michel De Bandt14, Pierre Bourgeois10, Claire Larroche10, Anne Tournadre3, Zahir Amoura10, Bernard Mazeries1, P. Arlet13, Michel De Bandt14, Thierry Schaeverbeke4 and Martin Soubrier1. Aulnay Hospital, Carrieres Sur Seine, France, 2Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France, 3Clermont and Martin Soubrier 3. 1Aulnay Hospital, Carrieres Sur Seine, France, Marion Couderc 3, L. E. Euller-Ziegler:

Objective: To assess the efficacy and clinical activity of 10 adult patients from the Auto-Immunity and Rituximab (AIR) french registry treated by RTX for polymyositis (PM), dermatomyositis (DM) or antisynthetase syndrome (AS) that were refractory to standard treatment and/or with severe systemic involvement. Average disease duration was 7.5 months (6 to 60 months). All the patients met the Bohan and Peter criteria for DM or PM. Three patients received bone marrow (BM) derived MSC, two of which were given a second umbilical cord (UC) derived MSC due to disease relapse. The other 7 patients were transplanted with UC-MSC only once time. BM MSC were aspirated from related healthy donors and expanded in vitro, and UC MSC were obtained from Stem Cell Center of Jiangsu Province of China. All the infused MSC were derived from passage 2 to passage 4, with rigorous purification and quality control. The clinical manifestations and laboratory parameters were compared pre- and post-MSCCT, with a mean follow-up of 12 months (range, 6 to 18 months). Adverse events were monitored all the time during and post-MSCCT.

Results: Serum creatine kinase (CK) for all the patients decreased significantly at the first 6 months (baseline: 2380.0±763.8U/L; 1m: 1027.0±266.7U/L; 2m: 486.2±143.1U/L; 3m: 92.9±19.5U/L; 6m: 248.8±135.6U/L, all p<0.05 vs baseline value), and continued to decreased to 106.0±39.4U/L for 5 patients completed 1 year visit, in paralleled with the amelioration of serum CK-MB levels at the same visit. Meanwhile, patient’s global assessment by VAS and detection for the Manual Muscle Test (MMT) also ameliorated with improved disease. In addition, MRI confirmed alleviated inflammation in the thigh muscles 3 months after BM MSC infusion for one patient. Six patients were complicated with moderate-to-severe ILD, shown as interstitial pneumonia. High-resolution CT scans manifested obvious amelioration in 3 patients, and at least no progression in 2 patients 6 months post-MSCCT. Furthermore, for one patient with refractory skin ulcers on both knees, elbows and proximal interphalangeal joints, matter plus decreased and new granulation tissues appeared at 2 months visit, and almost healings of the ulcers 6 months after UC MSCCT. Disease relapsed in 3 patients 5, 6, 8 months post-MSCCT respectively, 2 of which received second UC MSC infusion, also due to ineffective to standard treatments. Unfortunately, one patient was unresponsive to second MSCCT, and the other died 5 months later due to rapid progression of disease and severe myocarditis induced by a common cold. Another patient died 7 months post-MSCCT, due to uncontrolled pulmonary infection. No transplant related mortality or any significant toxicity was observed during or after MSC infusion.

Conclusion: We provide evidence that allogeneic BM or UC MSC infusion is safe and effective in drug-resistant DM/PM patients. However, further observation with more patients included and longer periods of follow-up will be needed to determine the efficacy and safety of this novel approach to the treatment of DM/PM.

Disclosure: L. Sun; None; D. Wang; None; H. Zhang; None; J. Liang; None; X. Feng; None.
ESR and CRP Do Not Correlate with Extent of Muscle Injury but Their Elevation Is Associated with Pulmonary Involvement in Idiopathic Inflammatory Myopathy. Jin Kyun Park, Michael George, Sonye K. Danoff, Marzoa A. Qubiti, Allan C. Gelber and Lisa Christopher-Stine. 1Baltimore, MD. 2Department of Medicine, University of Pennsylvania, 3Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 4Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, 5Johns Hopkins University, Baltimore, MD

Background: Although idiopathic inflammatory myopathies (IIM) are systemic autoimmune diseases with muscle as the main target, the clinical implication of Erythrocyte Sedimentation Rate (ESR) is not well defined to date. From our clinical experience, we hypothesized that ESR is elevated in IIM subsets with interstitial lung disease (ILD).

Methods: Clinical and laboratory data from 50 patients with IIM who visited our Center between March 2007 and April 2009 were collected. All patients underwent routine CT scanning in a standard protocol to assess malignancy and ILD status. ESR (normal<30mm/hr), C-reactive protein (CRP; normal <0.5mg/dL), creatine phosphokinase (CPK) and aldolase level were measured at the time of diagnosis. ILD was defined by presence of typical radiographic changes. Mann-Whitney test for continuous variables and 2 sided Fisher’s exact test for dichotomous variables were performed. Rho and P values were generated using Spearman’s correlation analysis. These associations were also examined in analyses stratified by the presence (vs. absence) of ILD. P-values of <0.05 were considered statistically significant.

Results: ESR and CRP did not correlate significantly with CPK (ESR, r_s=0.106, p=0.465; CRP, r_s=0.031, p=0.878) or aldolase (ESR, r_s=0.034, p=0.827; CRP, r_s=0.076, p=0.719), while CPK and aldolase showed high correlation with each other (r_s=0.784, p<0.001). Notably, there were 21 patients with 29 without ILD. Age, gender and race did not differ significantly between both groups. CPK and aldolase did not differ between IIM without versus with ILD (CPK 1028 +/- 2567 IU/L vs. 1227 +/- 2804 IU/L, p=0.723; aldolase 16.9 +/- 22.2 IU/L vs. 22.7 +/- 35.6 IU/L, p=0.914). However, within the IIM stratum with ILD, ESR was significantly higher (18.3 +/- 15.7 mm/hr vs. 44.9 +/- 36 mm/hr, P=0.001) as expected. Notably, there were 21 patients with 29 without ILD. Age, gender and race did not differ significantly between both groups. CPK and aldolase did not differ between IIM without versus with ILD (CPK 1028 +/- 2567 IU/L vs. 1227 +/- 2804 IU/L, p=0.723; aldolase 16.9 +/- 22.2 IU/L vs. 22.7 +/- 35.6 IU/L, p=0.914). However, within the IIM stratum with ILD, ESR was significantly higher (18.3 +/- 15.7 mm/hr vs. 44.9 +/- 36 mm/hr, P=0.001).

Conclusion: Here, we provide evidence that: i.) ESR and CRP do not correlate with biochemical muscle injury and ii.) elevation of ESR or CRP is associated with the presence of ILD. Therefore, any elevation of systemic inflammatory markers should prompt clinicians to evaluate for the presence of an ILD.

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920 Evaluation of Reliability, Validity, and Responsiveness of the CDASI and CAT-BM. Renato Godeski, Joyce Okawa, Matt Rose, Rui Feng, Lela Lee, Christopher Hansen, Carolyn Bangert, Kari Connolly, Mark Davis, Jeff Callen, Nicole Fett, Steven Fakhrazadeh, Jennie Clarke and Victoria Werth. 1Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, 2Mayo Clinic Rochester, 3Penn State Hershey School of Medicine, 4Philadelphia VA Medical Center, 5University of California-San Francisco, School of Medicine, 6University of Colorado, School of Medicine, 7University of Louisville, School of Medicine, 8University of Pennsylvania, School of Medicine, 9University of Texas, School of Medicine, 10University of Utah, School of Medicine

To properly evaluate therapies for cutaneous dermatomyositis (DM) it is essential to administer an outcome instrument that is reliable, valid, and responsive, particularly when measuring disease activity. The purpose of this study is to compare two skin-severity DM outcome measures, the Cutaneous Disease and Activity Severity Index (CDASI) and the Cutaneous Assessment Tool-Binary Method (CAT-BM), with the Physician Global Assessment (PGA) as the ‘gold standard’. In a one-day session, ten dermatologists evaluated fourteen patients with DM using the CDASI, CAT-BM, and PGA scales, which were used as the ‘gold standard’ for comparison. Inter- and intra-rater reliability was assessed by intraclass correlation coefficients (ICC) and paired t-tests. Construct validity was determined by using a linear mixed model. Content validity was determined by administering a Physician Exit Questionnaire, specifically asking if any outcome instrument was missing an appropriate measure for the evaluation of DM. Responsiveness was assessed from a different study population, where one physician determined CDASI, CAT-BM, and PGA scale scores, including a qualitative perception from the physician if the patient had improved, worsened, or had no change from their previous visit. A standard response mean (SRM), or mean change:standard deviation of change between visits, of the activity scores of each outcome instrument was determined by choosing the largest change in PGA scale scores between two visits, when the physician noted a change between visits. Difference in completion time of each instrument was assessed by a paired t-test. The CDASI was found to have a higher inter-rater reliability (ICC: CDASI Activity 0.748, CAT-BM Activity 0.546) and a higher intra-rater reliability (ICC: CDASI Activity 0.868; CAT-BM Activity 0.714). To assess construct validity, both the CDASI and the CAT-BM were found to be significant predictors of the the PGA scales (p<0.001). All physicians felt that the CDASI was not missing any measure to sufficiently assess DM. 90% of physicians felt the same with the CAT-BM, with one physician feeling that the CAT-BM did not adequately assess the scalp. The CDASI had the highest SRM among all outcome instruments (CDASI: 1.25, CAT-BM: 0.93, PGA-Activity: 1.03, PGA-Activity Likert: 0.61). The CDASI had a statistically longer completion time than the CAT-BM (Completion Time: CDASI 4.76 minutes; CAT-BM 3.19 minutes; p<0.001) with a mean time difference of 1.58 minutes. We conclude that the CDASI is a better clinical tool to assess skin severity in DM, especially in regards to responsiveness.

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921 Fasciitis Is a Common Lesion of Dermatomyositis Demonstrable Early after Disease Onset by En Bloc biopsy Combined with Magnetic Resonance Imaging. Ken Yoshida, Daitaro Kurosaka, Kensaue Ito, Eigo Takahashi, Kenichiro Hirai, Kentaro Noda, Taro Uchiki, Kazuhiro Furuya, Maimi Yanagimachi, Isamu Kingetsu and Akio Yamada. 1Division of Pathology, Sendai Shakai Hoken Hospital, 2Division of Rheumatology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan

Purpose: To investigate the incidence of fasciitis in dermatomyositis (DM), and to analyze the process of myositis progression.

Methods: En bloc biopsy combined with Short tau inversion recovery or fat-suppressed T2-weighted magnetic resonance imaging (MRI) was performed on fourteen patients with newly diagnosed adult-onset DM. Vascular inflammarion score (VIS) was defined as the number of aggregates of ≥50 inflammatory cells infiltrating around a small blood vessel or vessels per 4 mm² area of tissue. Total vascular inflammation score (TVIS) was defined as the summation of VIS in three fields with the most remarkable perivascular infiltrates. Fasciitis was defined as TVIS of the fascia ≥3 to exclude very mild inflammation. The grade and distribution of perivascular inflammatory changes were evaluated in the fascia and muscle using TVIS. En bloc biopsy was also performed on six patients with other rheumatic diseases including three patients with polymyositis (PM). These subjects constituted a comparison group. Immunohistochemistry was performed to identify T lymphocytes (CD3), CD4+ cells, CD8+ cells, B cells (CD20, CD79a), and macrophages (CD68).

Results: In all patients with DM, MRI revealed abnormal hyperintensity in the fascia and in marginal sites of the muscle predominantly over central sites. In Case 11, abnormal hypointense areas were detected on the first MRI in the fascias, and on the second MRI two months later, the hypointense areas had progressed from the fascias to marginal sites of the muscles. En bloc biopsy revealed fasciitis evidenced by inflammatory infiltrates around the fascial or small blood vessels in most of the patients with DM. However, inflammatory infiltrates around the intramuscular small blood vessels were not detected in four patients with DM. In those who underwent en bloc biopsy earlier than two months after the appearance of muscle symptoms, TVIS of the fascia was significantly higher than TVIS of the muscle. In contrast, in those who underwent en bloc biopsy at two months or later, TVIS of the fascia was higher than TVIS of the muscle.
fascia did not differ significantly from TVIS of the muscle. Immunohistochemistry showed that CD3+ T lymphocytes, CD4+ cells and CD20+ B cells were mainly present among inflammatory cells. The CD4/CD8 cell ratio was >1 in almost all specimens from the patients with DM. In any one of the patients with other rheumatic diseases, MRI revealed no significant hyperintense areas in the fascias and none of specimens from other rheumatic diseases histopathologically revealed fasciitis.

**Conclusions:** Fasciitis was histopathologically confirmed in most of the patients with adult-onset DM and recognized as a common lesion that appears early after the onset of muscle symptoms in DM. Our results suggest that the fascial microvasculature is the primary site of inflammatory cell infiltration in DM. The results of MRI suggest that inflammation in myopathy accompanying DM progresses from the fascia into the muscle. Muscle symptoms such as myalgia in DM may be attributed to fasciitis if muscle biopsy reveals no myositis. Fasciitis may be a lesion specific to DM rather than to PM.

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**922 Immunosuppressive Treatments Do Not Alter Natural History of Sporadic Inclusion Body Myositis: The Paris/Oxford Study on 136 Patients.**

**Objective:** Sporadic inclusion body myositis (sIBM) is characterized by slowly progressive, asymmetric atrophy and weakness of both proximal and distal muscles, most prominently affecting the finger and wrist flexors and quadriceps. Although drugs such as corticosteroids, methotrexate, cyclophosphamide, and IVIg may reduce the degree of inflammation on biopsy and lower serum creatine kinase levels, clear clinical improvement has not been demonstrated. The aim of the study was to evaluate whether immunosuppression alters the course of progression of sIBM.

**Methods:** Two cohorts of patients, one from Paris and the other from Oxford were included. The same clinical-research form was used in both centers for data collection and was completed either during a clinic visit (52%), or by extraction from previous medical records (48%).

**Results:** 136 patients (57% males, 61 [55–69] years at onset) were included and diagnosed on the basis of accepted clinical and pathological criteria; 97 patients (72%) were considered to have definite sIBM, 39 patients (28%) had probable sIBM. At the last visit all patients had muscle weakness (proximal MRC ≤ 3/5 in 47%, distal MRC ≤ 3/5 in 38%) and half of them reported swallowing problems. During their follow-up, 75% of patients had significant walking difficulties and 37% used a wheelchair (after a median duration from onset of 14 years). The risk of death was only influenced by older age at onset of first symptoms. 71 (52%) patients received immunosuppressive treatments (prednisone in 91.5% associated (in 64.8%) with other immunomodulatory drugs (intravenous immunoglobulins, methotrexate or azathioprine) for a median duration of 41 months). At the last assessment, patients who had been treated were more severely affected on a sIBM weakness composite index (p=0.03) and disability scales (Walton p=0.007, RMI p=0.004).

**Conclusion:** This study showed that in our population, sIBM started on average in the 6th decade of life and is then slowly progressed. It took a median of 14 years to get from first symptoms to the need to use a wheelchair, but also, that this disease is not usually the cause of death. Furthermore, it could not be excluded that conventional immunosuppressant treatment is not only ineffective but might also hasten progression. The findings of this study include important messages for the design of the future trials.

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**923 Interleukin-18 Is a Key Mediator in Dermatomyositis: Contribution to Development of Interstitial Lung Disease.**

**Objectives:** To investigate whether interleukin (IL)-18 is involved in the inflammation of dermatomyositis (DM) and polymyositis (PM).

**Methods:** Thirty-three patients with DM were enrolled in this study, including 25 with interstitial lung disease (ILD). In addition, 16 patients with PM were enrolled, including 6 with ILD. All patients were admitted to our hospital as a result of their condition requiring treatment, and clinical laboratory data including serum creatine kinase (CK), ferritin and IL-18 were recorded on admission.

**Results:** The level of CK was significantly (P = 0.01) higher in PM patients (median, 2174 IU/ml) than in DM patients (median, 375 IU/ml). Although CRP levels were not significantly different, ferritin was significantly (P = 0.003) higher in DM patients (median, 236 ng/ml) than in PM patients (median, 55 ng/ml). The median levels (range) of serum IL-18 were 552 pg/ml (141–4850), 256.5 pg/ml (119–2190), and 50.5 pg/ml (18–121) in DM patients, PM patients, and healthy controls (n = 30), respectively. The levels of IL-18 were significantly higher in DM and PM patients than in healthy controls (P < 0.0001 for both comparisons), and were significantly higher (P = 0.0044) higher in DM patients than in PM patients. Additionally, ferritin and IL-18 were significantly (P = 0.023 and 0.034, respectively) higher in DM patients with ILD (median, 320 ng/ml and 625 pg/ml, respectively) than in DM patients without ILD (median, 82 ng/ml and 328 pg/ml, respectively), but the CK and CRP levels were not significantly different. By contrast, the median values of IL-18 were 382.5 pg/ml and 234.5 pg/ml in PM with ILD and PM without ILD patients, respectively. There were no significant differences between PM with and without ILD for the measured parameters. Significant positive correlations were found between CK and ferritin (r = 0.39, P = 0.024), CK and IL-18 (r = 0.48, P = 0.005), and IL-18 and ferritin (r = 0.54, P = 0.0012) in the DM group as a whole, although correlations between CRP and CK, CRP and IL-18, and CRP and ferritin were not found. These findings were especially notable in the DM with ILD subset. Significant positive correlations were found between CK and ferritin (r = 0.40, P = 0.047), CK and IL-18 (r = 0.63, P = 0.0008), and IL-18 and ferritin (r = 0.41, P = 0.042) in the DM with ILD subset. By contrast, there was no significant correlation with PM.

**Conclusion:** Serum IL-18 was strikingly elevated in patients with DM, and was associated particularly with disease activity and ILD complication in DM.

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**924 KL-6: A Serological Biomarker for Interstitial Lung Disease and Pulmonary Function in Patients with Polymyositis and Dermatomyositis.**

**Background:** Interstitial lung disease (ILD) is reported in up to 78% of polymyositis (PM) and dermatomyositis (DM) patients, but pulmonary function tests are not always easily available and repeated radiological examinations are restricted by the irradiation. One interesting biomarker for ILD is Krebs von den Lungen-6 (KL-6), a glycoprotein secreted by type II alveolar pneumocytes and bronchial epithelial cells. A few studies with a limited number of patients have reported elevated serum levels of KL-6 in patients with myositis associated ILD. These need replication and it is unknown whether KL-6 serum levels vary over time in PM/DM patients.

**Objectives:** To investigate whether Caucasian patients with PM/DM and ILD have elevated serum levels of KL-6 compared to healthy controls and
whether KL-6 could be used as a marker for disease activity and prognosis of ILD in PM/DM.

**Methods:** Thirty PM/DM patients (19 women, 11 men; median 54 years, range 22–74), and 17 age- and gender matched healthy controls were included in a cross-sectional analysis. Twelve patients with less than one month in between multiple serum samples and lung function tests were included for longitudinal evaluation. KL-6 serum levels were analyzed using a sandwich enzymo immunoassay kit (Sanko Junyaku Co., Ltd, Tokyo, Japan). BAFF was defined as restrictive lung function impairment, total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLco) <80% of predicted, with radiographic signs of ILD on chest X-ray /or high resolution computerized tomography. Groups were compared by Mann Whitney test. Spearman’s correlation r-value > 0.5 or < -0.5, and p-values <0.05 were considered significant.

**Summary of Results:** Patients with PM or DM had significantly higher KL-6 serum levels compared to healthy controls (median, range: 400, 132–2318 U/ml versus 225, 136–519 U/ml, p=0.01). The patients with ILD (n=7) had significantly higher median serum concentrations of KL-6 compared to those without (n=23) (959, 533–2318 U/ml versus 322, 132–1225 U/ml, p=0.0002). At KL-6 cut-off level of 549 U/ml (mean ±2 SD of controls) we found a sensitivity and specificity of 84% and 80% respectively for diagnosis of ILD. A significant inverse correlation between KL-6 serum levels and results of pulmonary function tests was demonstrated if the cross sectional part: forced expiratory volume in one second (FEV1) (r = -0.60), vital capacity (VC)% (r = -0.54), TLC% (r = -0.59), Forced VC (FVC)% (r = -0.64) and DLco% (r = -0.52). In the patients with longitudinal follow up, this inverse correlation increased: FEV1% (r = -0.801), VC% (r = -0.788), TLC% (r = -0.788), FVC% (r = -0.784) and DLco% (r = -0.60). The changes of KL-6 serum levels showed a significant inverse correlation with changes of the pulmonary function tests: FEV1% (r = -0.570), TLC% (r = -0.530), DLco% (r = -0.530) and RV (r = -0.525). There was no significant correlation between serum levels of KL-6 and CRP or creatine kinase (CK) levels.

**Conclusion:** These results support the usefulness of serum measurements of KL-6 in the diagnostic evaluation and establishment of severity, as well as in evaluation of response to therapy in patients with ILD and myositis.

**Disclosure:** S. Barbossa Helmers: Sanko Junyaku Co., Ltd, Tokyo, Japan, 9; M. Fathi: Sanko Junyaku Co., Ltd, Tokyo, Japan, 9; I. E. Lundberg: Bristol-Myers Squibb, 2, Sanko Junyaku Co., Ltd, Tokyo, Japan, 9; UCB, Inc., 5.

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**Longitudinal Assessment of Activity and Damage in a Synthetase Positive Cohort.** Elaine A. Cassidy¹, Roheit Aggarwal², Noreen Fertig³, Dana P. Ascherman⁴, C. V. Ascherman⁴, C. Costigan⁵, Catherine Ascherman⁷, C. V. Oddis³, Josephine S. Ascherman³. ¹Rheumatology, University of Pittsburgh; ²Pittsburgh, PA; ³University of Pittsburgh School of Medicine; ⁴University of Pittsburgh School of Medicine; ⁵National Jewish Health, Denver, CO;

**Purpose:** To compare disease activity and damage in a longitudinal cohort of Jo-1 and non Jo-1 anti-synthetase autoantibody (anti-synAb) positive patients (pts).

**Methods:** Since 2002 one investigator (CVO) has prospectively completed the Myositis Disease Activity Assessment Tool (MDAAT) and Myositis Damage Index (MDI) on pts with the data entered into the Myositis Data Management System (MDMS). All anti-synAb positive pts in MDMS were included in this analysis. The MDAAT includes an intention to treat component but only the visual analog scale (VAS) assessing disease activity at last visit in constitutional, cutaneous, skeletal, pulmonary, extramuscular global, muscle and overall global categories were used in this study. VAS activity scores were designated as: none=0, minimal (0<VAS≤1); mild (1<VAS≤3); moderate (3<VAS≤7) and severe (VAS>7). The groups were compared using Kruskal Wallis test for VAS scores, and the Chi-square test for ordinal VAS values. The MDI assessors organ system damage using a VAS and a dichotomous variable, and the 2 groups were compared using the last recorded organ system VAS score (Kruskal Wallis) and the presence or absence of organ damage using Chi-square test for skeletal, muscle, pulmonary, and global categories. Regression analysis was used to control for time from diagnosis and first visit to assessment of activity or damage.

**Results:** Activity was assessed in 59 anti-synAb+ pts (41 Jo-1, 18 non-Jo-1) having at least 2 MDAATs in 1 year, or >3 over any time period. Damage was assessed in 71 pts (50 Jo-1; 21 non-Jo-1) that had >1 MDI. The Jo-1 and non-Jo-1 groups were similar in terms of gender and ethnicity.

Median time in yrs (IQR) from diagnosis to last completed MDAAT was 5.8 (2.2–3.9) vs. 4.2 (2.0–8.7) for Jo-1 and non-Jo-1 pts (p=NS). The skeletal activity at last assessment was worse in Jo-1 pts as 71% had VAS = 0 compared to 95% of non-Jo-1 pts (p=0.03). This remained significant after controlling for time from diagnosis or first visit to assessment (p=0.03). There were no differences in disease activity at last visit between Jo-1 and non-Jo-1 pts in the other categories. Regarding damage, non-Jo-1 patients had significantly more damage from pulmonary hypertension (PHT) at last MDI (40% non-Jo-1 vs. 11% Jo-1, p=0.006) which remained significant after controlling for time from diagnosis or first visit (p=0.006). Forty-two of 71 anti-synAb+ pts had pulmonary function tests at last MDI and %predicted FEV1 (75 %/+ 16 vs. 74 %/+ 25) and %predicted DLCO (57 %/+ 23 vs. 52 %/+ 25) were similar for Jo-1 and non-Jo-1 pts (p=NS). There was no difference between groups in global disease damage at last visit [median VAS (IQR): 1.8 (0.65–3.25) and 2.2 (1.4–3.8), respectively]. No differences in damage of patients Jo-1 or non-Jo-1 and Jo-1 patients were noted.

**Conclusions:** Jo-1 and non-Jo-1 anti-synAb+ pts have similar activity and damage scores at last follow-up for multiple organ systems. Jo-1 pts have increased arthritis activity while non-Jo-1 pts have increased PHT-related damage. Comparing these results to other autoantibody and myositis subsets will further validate the usefulness of these activity and damage indices.

**Disclosure:** E. A. Cassidy; None; R. Aggarwal; None; N. Fertig; None; D. P. Ascherman; None; C. V. Oddis; None.

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**Longitudinally Followed Serum Levels of B-Cell Activating Factor of the TNF Family Correlate with Disease Activity in Anti-Jo-1 Positive Patients with Myositis.** Olga Krystufková¹, Marta Mitterwald-Modra², Herman Mann³, Louise Ekhom³, Hanu Hulejova⁴, Ingrid E. Lundberg⁵ and Jiri Vencovsky⁶. ¹Institute of Rheumatology, Prague, Czech Republic; ²Institute of Rheumatology, Czech Republic; ³Institute of Rheumatology and Dept of Rheumatology of the 1st Faculty of Medicine, Charles University, Prague, Prague, Czech Republic; ⁴Karolinska Institutet, Stockholm, Sweden; ⁵Karolinska Institutet, Sweden

**Purpose:** A role of B cells in pathogenesis of myositis is supported by common occurrence of autoantibodies. Anti-histidyl-tRNA synthetase (anti-Jo-1) is the most frequent myositis specific autoantibody, associated with a distinct clinical phenotype. Its observation before onset of clinical symptoms suggests a role in the pathogenesis of this subset of myositis. B-cell activating factor of the TNF Family (BAFF) plays a role in autoantibody production. In a previous cross-sectional study we found elevated serum levels of BAFF in patients with anti-Jo-1 positive polymyositis (PM) and in dermatomyositis (DM) and there was a correlation with serum creatine kinase (CK) levels. The aim of the study was to investigate if serum levels of BAFF change over time and if there is a relation to disease activity measures in anti-Jo-1 positive myositis.

**Methods:** Sixty-seven anti-Jo-1 autoantibody positive patients from two centers were included. Paired serum samples from two time points (mean interval 25 months) in 50 patients (21 DM and 29 PM) were evaluated. Anti-Jo-1 positivity was confirmed by line blot and western blot assays. BAFF levels in serum were measured by ELISA. Serum levels of CK, myoglobin, aminotransferases (ALT, AST) and C-reactive protein (CRP) were retrieved from patients’ records or measured in the same sera. Clinical disease activity was assessed by the score of the core set tool according to the IMACS Group, including both extramuscular, muscular and the physician’s score of overall disease activity.

**Results:** The baseline BAFF levels correlated positively with serum levels of CK (r=0.49, p<0.0001), myoglobin, (r=0.37, p=0.005), AST (r=0.46, p=0.0001) and CRP (r=0.42, p=0.0006) and with cutaneous disease activity (r=0.26, p=0.04). Levels of BAFF and myoglobin had decreased significantly at the second visit (paired test p<0.05), while p value for CK was 0.09. A significant improvement of cutaneous, skeletal, pulmonary, muscle and global disease activities was also recorded (p<0.05 for all). A positive correlation between changes of serum BAFF levels and changes of CK (r=0.7, p=0.0001), myoglobin (r=0.6, p=0.0001), ALT (r=0.52, p=0.0001) and CRP (r=0.29, p=0.049) levels in serum or skeletal (r=0.45, p=0.003), muscle (r=0.32, p=0.04) and global (r=0.37, p=0.02) disease activities was also recorded.

**Conclusions:** The correlation between serum levels of BAFF and markers of muscle involvement or clinical measures of disease activity as well as a correlation of their changes over time might indicate a role of BAFF in the pathogenesis of myositis with anti-Jo-1 autoantibodies. BAFF could thereby be a novel potential target of intervention in this subset of myositis.
Acknowledgement: AutoCure LSHB CT-2006–018661 funding. Institutional support MEYS CR 001620812

Disclosure: O. Krystufkova: None; M. Mitterwald-Madora: None; H. Mann: None; L. Ekholm: None; H. Hulejova: None; I. E. Lundberg: None; J. Vencovsky: None.

927

MHC Classes I and II Expressions in Membrane and Cytoplasm of Muscle Fibers in Untreated Juvenile and Adult Dermatomyositis. Adriana Maluf Elias Sallum, Samuel Katsuyuki Shino, Mary Souza Carvalho, Clóvis Artur Almeida da Silva, Maurício Levy-Neto and Suely Kazue Nagashashi Marie. Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background: Recently, we have shown that MHC I expression in muscle fibers is a premature and late marker of treated and untreated juvenile dermatomyositis (JDM). However, this alteration was not systematically studied in adult DM (ADM). Moreover, simultaneous assessment of MHC I and II expressions in fibers membrane and cytoplasm in both untreated diseases has not been performed.

Objectives: To assess the MHC I and II expressions in fibers membrane and cytoplasm in untreated ADM and JDM and to correlate to clinical, laboratorial, and treatment outcome features.

Patients and Methods: Twenty-seven ADM and 34 JDM patients, fulfilling Bohan and Peter criteria diagnosed from 1990 to 2010, were included in this study. Routine histochemistry and immunohistochemistry (StreptABComplex/HRP) for MHC I and II (b3 and b2-m) were performed on frozen serial muscle sections. Each biopsy specimen was coded and analyzed concurrently by two investigators (AMES and SKS). The pathology readers were blinded to diagnosis, clinical status and therapy when the biopsies were evaluated. Expressions of MHC I and II were assessed as negative or positive stained fibers.

Results: The mean age at disease onset was significantly higher in ADM than in JDM (42.7±18.3 vs 8.2±3.8 years, p<0.001), whereas the symptoms duration before muscle biopsy were similar in both groups (9.8±13.3 vs 7.1±10.7 months; p=0.388). No statistical differences were observed regarding gender, ethnicity, frequency of constitutional symptoms, disease severity, organ involvement (articular, pulmonary, cardiac or gastrointestinal), comorbidities, laboratorial (CK and aldolase levels) and treatment (prednisone, intravenous methylprednisolone and immunosuppressive drugs) (p<0.050), except for the lower frequency of Gottron’s signal in ADM compared to JDM patients (85.2 vs. 100.0%, p=0.034). Regarding the immunohistochemical analysis, the frequency of MHC I expression in fibers membrane (85.2 vs. 100.0%, p=0.034) and cytoplasm (74.1 vs. 97.1%, p=0.017) was significantly lower in ADM than JDM. In contrast, the MHC II expressions in fibers membrane (70.4 vs. 35.3%; p=0.010) and the cytoplasm (44.5% vs. 17.7%, p=0.028) were higher in ADM than JDM. Additionally, the MHC I and II expressions were not correlated to demographic data, clinical and laboratorial features including CK levels and disease duration before muscle biopsy.

Conclusions: The MHC I and II expressions differ in muscle fiber in JDM and ADM. These diagnostic tools can be routinely used independent of period of time until muscle biopsy.

Disclosure: A. M. E. Sallum: None; S. K. Shinjo: None; M. S. Carvalho: None; C. A. A. Silva: None; M. Levy-Neto: None; S. K. N. Marie: None.

928

MicroRNA Expression in Juvenile Dermatomyositis (JDM): Clues to Disease Pathogenesis and Chronicity. Elaine A. Cassidy1, Rohit Aggarwal1, Noreen Fertig1, Mary Lucas1, Dana P. Ascherman1 and Chester V. Oddis2. Children’s Hospital of Pittsburgh Division of Rheumatology, Pittsburgh, PA. 1University of Pittsburgh, Pittsburgh, PA. 2University of Pittsburgh School of Medicine Division of Rheumatology and Clinical Immunology, Pittsburgh, PA.

Purpose: To compare clinical features and outcome in patients (pts) with Ju-1 vs. non-Ju-1 anti-tnRNA synthetase autoantibodies (anti-synAb).

Methods: All anti-synAb positive pts in a Connective Tissue Disease (CTD) Registry were included regardless of initial or subsequent CTD diagnosis. Demographic and clinical data were collected from the medical record and registry. Current status and cause of death was determined by query of the National Death Index or Social Security Death Index, and medical record. For lung survival an endpoint of lung transplant or death was used. Survival was compared by Kaplan-Meier and log rank test. Cox proportional hazards ratios were calculated to compare survival after controlling for covariates.

Results: 202 of 3880 (5.2%) CTD pts were anti-synAb positive [122 Ju-1, 80 non-Jo-1 (35 PL-12; 25 PL-7; 9 E; 6 KS; 5 SJ)]. Both groups had similar demographic features (Table 1), but non-Jo-1 pts had a greater delay in diagnosis, and a diagnosis at 1st visit in 60% that did not include PM or DM.

Table 1. Demographic and Clinical Features of Synthetase Cohort

<table>
<thead>
<tr>
<th>Feature</th>
<th>Ju-1 (n = 122)</th>
<th>Non-Jo-1 (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age at Symptom Onset (yrs)</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>% Female</td>
<td>67</td>
<td>70</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>82</td>
<td>75</td>
</tr>
<tr>
<td>Myositis (C)</td>
<td>83</td>
<td>90</td>
</tr>
<tr>
<td>Overlap or SSc (C)</td>
<td>58</td>
<td>23</td>
</tr>
<tr>
<td>% Diagnosed at 1st Visit</td>
<td>78</td>
<td>50</td>
</tr>
<tr>
<td>Median Delay from Onset to 1st Symptom (mo)</td>
<td>17</td>
<td>11</td>
</tr>
</tbody>
</table>

Diagnosis: | PM vs LMP | DM | SDD vs LDD |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>PM</td>
<td>DM</td>
<td>SDD vs LDD</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.0002</td>
</tr>
</tbody>
</table>

NS = not significant; IQR-interquartile ratio; UCTD = undifferentiated connective tissue disease.
Sixty-six pts are deceased with pulmonary fibrosis and pulmonary hypertension the most common causes. Twelve pts (7 Jo-1; 5 non-Jo-1) underwent lung transplantation. Although a pulmonary cause of death was similar between Jo-1 and non-Jo-1 cohorts, the 5 and 10 yr unadjusted cumulative and median survival was significantly different.

Table 2. Outcome and Survival of Synthetase Cohort

<table>
<thead>
<tr>
<th></th>
<th>Mean Age at Death (yrs)</th>
<th>Pulmonary Cause of Death</th>
<th>Cumulative Survival 5 year (%)</th>
<th>Median Survival (yrs; IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jo-1 (n = 122)</td>
<td>58 ± 10/14</td>
<td>Pulmonary HT</td>
<td>90</td>
<td>15 (7.9–21.3)</td>
</tr>
<tr>
<td>non-Jo-1 (n = 80)</td>
<td>62 ± 10/14</td>
<td>Secondary PAH</td>
<td>70</td>
<td>9 (4.3–18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary PAH</td>
<td>16/30 4/30</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>P &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>PHT</td>
<td>pulmonary hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After adjusting for gender, ethnicity and age at diagnosis, non-Jo-1 pts had decreased survival (HR 1.06; p<0.02; 95% CI 1.10–3.14) and lung survival (HR 1.06; p < 0.008; 95% CI 1.19–3.23) compared to Jo-1 pts. After adjusting for diagnosis delay, non-Jo-1 pts had decreased lung survival (HR 1.77; p = 0.03; 95% CI 1.06–2.97), and a trend toward decreased cumulative survival (HR 1.71; p = 0.051; CI 1.00–2.96). Non-Jo-1 PM pts had the worst cumulative survival (HR 3.75; p = 0.02; 95% CI 1.21–11.68) and lung survival (HR 2.84; p = 0.01; 95% CI 1.23–6.52).

Conclusions: In the largest reported anti-synAb+ cohort to date, the previously described myositis specificity of non-Jo-1 anti-synAb was not supported. Non-Jo-1 pts have decreased cumulative survival and lung survival compared to Jo-1 pts, with non-Jo-1 pts with PM having the worst cumulative and lung survival. The difference in survival may be attributable to a delay in diagnosis in the non-Jo-1 group due to non-specific symptoms at presentation and negative commercial antibody testing. Increased awareness of this CTD subset among rheumatologists and pulmonologists is emphasized.

Disclosure: E. A. Cassidy: None; R. Aggarwal: None; N. Fertig: None; M. Lucas: None; D. P. Ascherman: None; C. V. Oddis: None.

930 Predictors of Survival in Patients with Anti-Synthetase Autoantibodies.

Rohit Aggarwal1, Elaine A. Cassidy2, Noreen Fertig1, Mary Lucas2, Dana P. Ascherman2, and Chester V. Oddis3. 1Children’s Hospital Pittsburgh, Pittsburgh, PA, 2University of Pittsburgh, Pittsburgh, PA, 3University of Pittsburgh, Pittsburgh Medical Center, Pittsburgh, PA

Purpose: To evaluate baseline clinical, laboratory, serologic, radiographic and functional predictors of survival in patients (pts) with anti-synthetase autoantibodies (anti-synAb) from a single tertiary care center.

Methods: All anti-synAb+ pts from a single referral center between1985–2009 were included regardless of their initial or subsequent connective tissue disease (CTD) diagnosis. All data were collected from the registry database and medical record. Current status and cause of death was determined by query of the National Death Index or Social Security Administration. Current status and cause of death was determined by query of the National Death Index or Social Security Administration.

Results: Of the 3880 CTD pts in the registry from 1985–2009, 202 (5.2%) were anti-synAb+ (122 Jo-1; 80 non Jo-1 (35 PL-12; 25 PL-7; 9 EJ; 6 KS; 5 OJ)). Eighty-nine (44%) had PM, 44 (22%) DM, and 69 (34%) had undifferentiated or overlap CTD. Demographic features predicting survival included age at diagnosis and symptom onset, and a diagnosis delay (Table 1). PM pts had worse survival. Among other variables only arthralgia, pleurisy, dermatomyositis V neck or trunk rash, and telangiectasia had worse survival while Gottron papules had better survival. Raynaud, sicca symptoms, dyspnea, fever, muscle weakness, dysphagia, puffy fingers, mechanic hands, heliotrope rash, physician global assessment of active disease, capillary microscopy, digital abnormality, and calcinosis did not predict survival. Among lab and serologic parameters only non-Jo1 anti-synAb positivity, particularly anti-PL-7 and anti-EJ predicted worse survival, while SSA antibody was protective. ANA positivity, muscle enzymes, hemoglobin, platelet and ESR had no impact on survival. The % predicted FVC and DLCO along with pulmonary hypertension (PHT) by echocardiography and secondary PHT at baseline predicted survival. High resolution CT (HRCT) evidence of pulmonary fibrosis did not predict survival as most pts had some evidence of fibrosis by routine chest radiography or HRCT.

Table 1. Univariate predictors of overall and lung survival in a synthetase cohort

<table>
<thead>
<tr>
<th></th>
<th>Overall survival (5y) Hazard ratio (C.I.)</th>
<th>p value</th>
<th>Lung survival Hazard ratio (C.I.)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td>Gender male</td>
<td>0.82 (0.47–1.44)</td>
<td>0.57</td>
<td>0.82 (0.48–1.43)</td>
</tr>
<tr>
<td></td>
<td>Ethnicity (AA)</td>
<td>0.92 (0.43–1.96)</td>
<td>0.87</td>
<td>1.0 (0.49–2.04)</td>
</tr>
<tr>
<td></td>
<td>Age at diagnosis (yrs)</td>
<td>1.03 (1.01–1.05)</td>
<td>&lt;0.001</td>
<td>1.03 (1.01–1.05)</td>
</tr>
<tr>
<td></td>
<td>Age at symptoms (yrs)</td>
<td>1.02 (1.01–1.04)</td>
<td>0.07</td>
<td>1.02 (1.01–1.03)</td>
</tr>
<tr>
<td></td>
<td>Diagnosis delay (yrs)</td>
<td>1.03 (1.0–1.06)</td>
<td>0.04</td>
<td>1.01 (1.0–1.01)</td>
</tr>
<tr>
<td></td>
<td>Clinical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical diagnosis</td>
<td>PM: 2.4 (1.08–5.53)</td>
<td>0.032</td>
<td>PM: 2.73 (1.21–6.15)</td>
</tr>
<tr>
<td></td>
<td>PM: 2.73 (1.21–6.15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UCTD: 2.54 (1.11–5.84)</td>
<td></td>
<td></td>
<td>UCTD: 0.27</td>
</tr>
<tr>
<td></td>
<td>UCTD: 0.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary Function Testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>%FVC 1</td>
<td>0.97 (0.96–0.99)</td>
<td>0.03</td>
<td>0.97 (0.95–0.98)</td>
</tr>
<tr>
<td></td>
<td>%DLCO</td>
<td>0.96 (0.94–0.98)</td>
<td>0.06</td>
<td>0.96 (0.94–0.99)</td>
</tr>
<tr>
<td></td>
<td>Elevated PAP</td>
<td>3.1 (1.37–7.0)</td>
<td>0.03</td>
<td>3.2 (1.53–7.64)</td>
</tr>
<tr>
<td></td>
<td>Secondary PHT</td>
<td>3.46 (1.65–7.27)</td>
<td>0.01</td>
<td>3.34 (1.59–7.0)</td>
</tr>
<tr>
<td></td>
<td>O2 requirement at baseline</td>
<td>2.43 (1.38–4.26)</td>
<td>0.002</td>
<td>2.42 (1.37–4.21)</td>
</tr>
<tr>
<td></td>
<td>CI = confidence interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA = African American</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PAP = Pulmonary artery pressure</td>
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<td></td>
</tr>
</tbody>
</table>

Conclusion: The myositis clinical subset (i.e. PM), anti-synAb positivity, pulmonary function parameters, secondary PAH, joint involvement, pleurisy, various DM rashes and telangiectasia help predict overall survival and lung survival in anti-synAb+ pts. Some findings can be explained on the basis of their known myositis subset associations, such as Gottron papules in DM (which has a better prognosis than PM) and telangiectasia in UCTD (worse survival due to non-Jo-1 association). However, others require further study to confirm their association with survival (e.g. SSA positivity).

Disclosure: R. Aggarwal: None; E. A. Cassidy: None; N. Fertig: None; M. Lucas: None; D. P. Ascherman: None; C. V. Oddis: None.

931 Pulmonary Manifestations of Polymyositis and Long-Term Outcomes—A Retrospective Study.

Catherine Bakewell1, James Hotaling1, Michael Huck2, Dale Wilson3, Jennifer Hayes4, Carolyn Spada4, Gurpreet Rawat1 and Ganesh Raghu5. 1University of Washington Medical Center, Seattle, WA, 2University of Washington Medical Center, Seattle, WA, 3University of Washington School of Medicine, Seattle, WA

Background: Polymyositis (PM) is a systemic inflammatory disorder which primarily affects striated muscles; however, other organ systems, including the lungs, may be involved. While the interstitial lung disease (ILD) associated with polymyositis (ILD-PM) carries significant morbidity and mortality, the clinical factors impacting outcome of patients with ILD-PM are unclear.

Methods: A single-center retrospective study of well-defined patients with PM (Peter and Bohan criteria) and ILD evaluated and followed by an ILD expert (GR). Baseline demographics, serial pulmonary function tests (PFTs), estimates of pulmonary arterial hypertension (PAH) based on echocardiogram results, high resolution computed scan (HRCT) images of the chest, and treatment regimen were assessed to determine long term outcome of patients. Statistical analyses were performed using STATA v.11.

Results: 25 patients met inclusion criteria; baseline demographics are shown.
Twelve of the 25 patients (48%) manifested ILD/idiopathic interstitial pneumonia (IIP) before the overt manifestation of PM, and an average of 18.2 months elapsed prior to diagnosis of PM. Mean duration of follow up was 7.2 years; 4 patients died during this period (16% mortality rate). HRCT images revealed ground glass opacity in all patients; most common pattern (n=7), followed by honeycombing (n=4). Chest X-ray showed abnormal findings in nine patients subjected to echocardiogram. Microscopic features of nonspecific interstitial pneumonia (n=2), usual interstitial pneumonia (n=1), organizing pneumonia (n=1), and unclassifiable fibrotic pattern (n=2) were present in six patients subjected to surgical lung biopsy. Although history of cigarette smoking did not influence the baseline PFTs, ever smokers had a lower last recorded DLCO (p=0.045, adjusted for age and gender). Treatment regimens included methotrexate (MTX) (n=11), azathioprine (n=17), mycophenolate (n=2), and prednisone in all of the patients. The means of the last recorded DLCO and FVC for patients treated with MTX were 29.9% and 47.8% of predicted values respectively, compared with 43.7% and 68% for those who were never treated with MTX. The last recorded DLCO was more frequently <30% of predicted values in patients treated with MTX compared to those treated with azathioprine or mycophenolate (logistic regression; p< 0.001), even when controlled for age, gender, and smoking status.

Conclusions: 1) 48% of patients with ILD-PM present with ILD/IIP prior to overt manifestation of PM.
2) History of cigarette smoking confers a poor prognosis based upon worsening of DLCO measurements during the course of ILD-PM.
3) 16% of patients with ILD-PM died during follow up (mean duration=7.2 yrs).
4) Patients treated with MTX had a poor outcome based on the worsening of DLCO to < 30% predicted at last follow up.

Disclosure: C. Bakewell: None; J. Hotaling: None; M. Huck: None; D. Wilson: None; J. Hayes: None; C. Spada: None; G. Rawat: None; G. Raghu: None.

Table 1. Baseline Patient Demographics and Follow-Up Data

<table>
<thead>
<tr>
<th>Category</th>
<th>PM (n = 18)</th>
<th>DM (n = 26)</th>
<th>CADM (n = 15)</th>
<th>Total (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years)</td>
<td>59.8 ± 14.3</td>
<td>61.5 ± 11.4</td>
<td>54 ± 16.5</td>
<td>59.1 ± 14.1</td>
</tr>
<tr>
<td>Female</td>
<td>10 (55.5%)</td>
<td>19 (73%)</td>
<td>9 (60)</td>
<td>38 (64.4%)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>18 (100%)</td>
<td>26 (100%)</td>
<td>0</td>
<td>44 (74.5%)</td>
</tr>
<tr>
<td>Skin ulcer</td>
<td>0</td>
<td>7 (26.9%)</td>
<td>3 (20)</td>
<td>10 (16.9%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>5 (27.7%)</td>
<td>12 (46.1%)</td>
<td>1 (6.6)</td>
<td>18 (30.5%)</td>
</tr>
<tr>
<td>Intestinal lung disease</td>
<td>None</td>
<td>13 (50)</td>
<td>2 (13.3)</td>
<td>28 (47.4%)</td>
</tr>
<tr>
<td>Slowly progressive</td>
<td>2 (11.1%)</td>
<td>5 (19.2%)</td>
<td>6 (40)</td>
<td>13 (22%)</td>
</tr>
<tr>
<td>Acutely progressive</td>
<td>3 (16.6%)</td>
<td>8 (30.7%)</td>
<td>7 (46.8)</td>
<td>18 (30.5%)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0</td>
<td>2 (7.6%)</td>
<td>4 (26.6)</td>
<td>6 (10.1%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (3.8%)</td>
<td>2 (13.3)</td>
<td>3 (5.0%)</td>
</tr>
</tbody>
</table>

PM: polymyositis; DM: dermatomyositis (not including CADM); CADM: clinically amyopathic dermatomyositis.

Table 2. Results of univariate and multivariate analysis.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>7.63 (1.23–47.2)</td>
<td>0.029</td>
</tr>
<tr>
<td>Skin ulcer</td>
<td>1.00 0.034</td>
<td>1.00 0.004</td>
</tr>
<tr>
<td>Pneumomediatiuminum</td>
<td>16.6 (2.30–120)</td>
<td>0.005</td>
</tr>
<tr>
<td>CRP [mg/dl]</td>
<td>≥2.0 14.3 (1.42–104)</td>
<td>1.00 0.022</td>
</tr>
<tr>
<td>Ferritin [mg/ml]</td>
<td>≥300 9.98 (1.01–98.6)</td>
<td>1.00 0.049</td>
</tr>
<tr>
<td>LDH/CPK ratio</td>
<td>≥2.0 7.16 (1.16–45.9)</td>
<td>1.00 0.033</td>
</tr>
</tbody>
</table>

Disclosure: K. Ishigaki: None; Y. Takizawa: None; J. Maruyama: None; R. Nakashima: None; T. Mimori: None; K. Setoguchi: None.

933

The Anti-Oxidant Function of High Density Lipoprotein and Paraoxonase-1 Are Abnormal in Patients with Dermatomyositis. Christina Charles-Schoeman1, Yuen Yin Lee2, John D. FitzGerald2, Veena K. Ranganath1 and Srinivas T. Reddy3. 1UCLA School of Med Rehab 32-59, Los Angeles, CA; 2UCLA School of Medicine, Los Angeles, CA; 3UCLA School of Medicine, UCLA School of Medicine Rehabilitation, Los Angeles, CA

Purpose: Damage to the vascular endothelium is implicated in the pathogenesis of dermatomyositis (DM) and to a lesser degree in other idiopathic inflammatory myopathies (IIM). Normal high density lipoprotein (HDL) protects the vascular endothelium from damage due to oxidized phospholipids, which accumulate under conditions of oxidative stress. During acute and chronic inflammatory states, enzymes such as myeloperoxidase (MPO) produce increased amounts of oxidized phospholipids, which impair this function of HDL. The current work evaluates the function of HDL and its associated protein, paraoxonase 1 (PON-1), in patients with IIM.

Table 1. Categorical data are n (%) and age data are mean ± SD
Methods: Plasma samples were collected from 26 patients with DM, 20 patients with polymyositis (PM), and 23 healthy controls. HDL’s anti-oxidant function was measured by a cell free assay which assesses the ability of patient HDL to inhibit oxidation of a stock LDL. PON-1 activity was measured by the arylesterase assay and MPO activity was assessed using a patient HDL to inhibit oxidation of a stock LDL. PON-1 activity was measured in patients with polymyositis (PM), and 23 healthy controls. HDL's anti-oxidant activity was worse in patients with DM when compared to age and sex matched healthy controls (see table). Plasma MPO activity was significantly higher in DM patients compared to controls and was correlated with HDL function, (r = 0.43, p = 0.0003 all patients; r = 0.44, p = 0.02 DM only), higher plasma MPO activity was associated with worse HDL function. PON-1 activity was significantly lower in both DM and PM patients compared to controls and there was a trend for an association with HDL function (r = -0.20, p = 0.11); lower PON-1 activity associated with worse HDL function.

Results:

Conclusions: The anti-oxidant function of HDL and its associated protein PON-1 are significantly altered in patients with DM compared to healthy controls. Because HDL normally protects the vascular endothelium from oxidative damage, these findings may warrant further investigation of therapies that remove oxidized phospholipids and improve the function of HDL, such as apoA-1 mimetic peptides, for the treatment of DM and other IIM associated with vascular injury.

Disclosure: C. Charles-Schoeman: Aumgen Inc., 2; Y. Y. Lee: None; J. D. FitzGerald: None; V. K. Ranganath: None; S. T. Reddy: Bruin Pharma, 9.

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The Interferon Signature in Myositis Is Associated with RNA-Binding Protein Autoantibodies.

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Background: Several autoimmune diseases are characterized by elevated expression of type I interferon (IFN)-regulated transcripts and proteins in peripheral blood. This IFN signature is a marker for disease activity in patients with dermatomyositis (DM), and IFN pathway activation is proposed to play a role in the pathogenesis of this disease. The IFN signature in systemic lupus erythematosus is associated with the presence of autoantibodies against RNA binding proteins (RBPs), which are commonly observed in lupus patients. However, anti-RBP antibodies are found less frequently in patients with DM.

Methods: We compared blood IFN signatures and autoantibody profiles in 126 patients with inflammatory idiopathic myopathies (IIM), including 76 DM patients (46 adult and 30 pediatric) and 50 patients with other forms of IIM (24 polymyositis (PM), 9 inclusion body myositis (IBM), and 17 with uncharacterized myositis). IFN gene signatures were measured from whole blood RNA using TaqMan quantitative real-time RT-PCR to detect the levels of 3 IFN-regulated transcripts (GIP12, IFIT1, and IRF7). For each subject, an IFN gene score was calculated from the levels of these 3 transcripts. Serum levels of IFN-regulated chemokines (IP-10, I-TAC, and MCP-1) were measured using a multiplexed ELISA (R&D Systems, Minneapolis, MN) and a chemokine score was calculated for each patient using the normalized levels of the 3 chemokines. A bead-based immunoassay (Luminex) was used to detect anti-Sm, -RNP, -SS-A 60, -SS-A 52, -SS-B, -ScI-70, -Jo-1, -RiboSome P and -Chromatin antibodies in serum. Spearman’s rank method was used to test for correlation and the Mann-Whitney test was used for group comparisons.

Results: Out of 126 myositis patients, 33 were positive for at least one RBP antibody (anti-Sm, -RNP, -SS-A, or -SS-B). Both chemokine scores (p = 0.04) and IFN gene scores (p = 0.003) were significantly higher in RBP+ patients compared to RBP- patients. The IFN gene score was significantly correlated with the number of RBP antibodies (r = 0.31, p = 0.002), and with the levels of individual autoantibodies (anti-RNP, r = 0.28, p = 0.004; SS-A 60, r = 0.23, p = 0.02; and SS-A 52, r = 0.35, p = 0.0004). The chemokine score was positively correlated with anti-SS-A (r = 0.20, p = 0.02) but negatively correlated with anti-Sm (r = -0.18, p = 0.04). When the analysis was repeated in the DM and other myositis' (PM, IBM, uncharacterized IIM) groups separately, IFN gene scores of RBP+ and RBP- groups were significantly different in both the DM and other myositis' subgroups (p < 0.01 for both). IFN gene and chemokine scores were significantly correlated in the DM subgroup (r = 0.61, p < 0.001) but not in the others (r = 0.11, p = 0.59).

Conclusions: These results suggest that the IFN gene signature is associated with the presence of anti-RBP antibodies in patients with myositis. The presence of these autoantibodies, together with elevated IFN signatures, may promote identification of patients with myositis overlap syndromes.

Disclosure: H. Bilgic: None; J. Wilson: None; T. Koethe: None; K. T. McNallan: None; S. R. Ytterberg: None; E. J. Peterson: None; A. M. Reed: None; E. C. Baechler: Genentech, 2.

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The Role of Innate Immunity in a Model of HRS-Induced Myositis.

Makoto Soejima,1 Eun Ha Kang,2 Yasuhiko Katsumata,2 Xinian Gu,2 Paula Clemens2 and Dana Asherman3.

1Seoul National University College of Medicine, 2Tokyo Women’s Medical University, 3University of Pittsburgh, University of Pittsburgh, Pittsburgh, PA

Aim: The aim of this study was to clarify the contribution of innate immunity in a model of histidyl-tRNA synthetase (HRS)-induced myositis.

Background: Previous studies have suggested an important role for the autoantigen HRS in the pathogenesis of myositis. While most investigations have focused on the ability of HRS to trigger adaptive immune responses, in vitro studies clearly indicate that HRS possesses intrinsic immunostimulatory properties that may operate through the innate immune system.

Methods: We immunized different strains of mice (C57BL/6, B6.G7, NOD.Idd8/5, DO11.10/Rag2−/−, and C3H/HeJ) with soluble HRS (Jo-1) or appropriate control proteins (maltose binding protein; MBP) via the intramuscular (IM) route. To evaluate the resulting immune response, we determined IgG anti-Jo-1 and anti-MBP antibody levels in the sera of mice immunized with different proteins using standard solid phase ELISA. As a measure of in vitro T cell proliferation, we measured splenocytes or LN cells derived from these mice and then co-cultured cells with various antigens for 96 hours before flow cytometric assessment of CFSE dilution. Immunohistochemical staining of cell surface markers (CD3, CD4, CD8, CD44, CD11c, F4/80, CD11b, B220, CCR5) permitted characterization of inflammatory infiltrates resulting from our IM immunization protocol. Quantification of antigen-induced muscle inflammation was based on a scoring system combining the relative intensity and distribution of lymphocytic infiltrates in multiple fields viewed under high power magnification, where 0 = no inflammation, 1 = minimal inflammation, 2 = moderate inflammation, and 3 = severe inflammation. Severity scores for muscle inflammation were compared using the Mann-Whitney U-test.

Results: IM immunization with a murine HRS fusion protein induced significant muscle inflammation (relative to MBP control protein) in multiple congenic strains of C57BL/6 and NOD mice. Infiltrates occurred as early as 7 days post immunization and persisted as long as 7 weeks following a single administration of soluble HRS protein. Immunohistochemical staining indicated that these infiltrates were composed primarily of CD3+CD4+CD45R+ lymphocytes admixed with smaller numbers of B cells and macrophages. Corresponding to these histopathologic findings, ELISAs demonstrated class-switched antibody responses to HRS at each of these time points. Measurement of T cell responses to immunizing antigens through CFSE proliferation assays also revealed a level of antigen-specific priming. Parallel experiments in DO11.10/Rag2−/− (OVA-specific TCR transgene) and C3H/HeJ (TLR4−/−) mice showed that HRS could induce exuberant muscle inflammation in the absence of TCR or TLR4 signaling, further implicating alternative components of the innate immune response.

Conclusion: Based on IM immunization with a soluble derivative of murine HRS, the reported experiments demonstrate that this putative autoantigen can trigger innate immune responses which bypass BCR and TCR signaling to generate significant muscle inflammation in a novel model of idiopathic inflammatory myopathy.

Disclosure: M. Soejima: None; E. H. Kang: None; Y. Katsumata: None; X. Gu: None; P. Clemens: None; D. Asherman: None.
Osteoarthritis - Clinical Aspects: Pain and Treatment II

Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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13-Week Efficacy and Safety Evaluation of Naproxcinod, a Cyclooxygenase Inhibiting Nitric Oxide Donor (CINOD) under development for the relief of signs and symptoms of osteoarthritis (OA).

**Purpose:** Naproxcinod is a Cyclooxygenase Inhibiting Nitric Oxide Donor (CINOD) under development for the relief of signs and symptoms of OA.

**Methods:** 810 patients with primary hip OA experiencing pain at baseline were randomized to naproxcinod 750mg, placebo or naproxen 500mg (all bid) in a 2:2:1 ratio. 3 co-primary efficacy endpoints: change from baseline in WOMAC pain and function subscales, and patients' overall rating of disease status at Week 13. The primary efficacy variables were analyzed using an ANCOVA model with treatment group and site as factors, and baseline value as a covariate. Non-inferiority naproxcinod versus naproxen was tested post-hoc. Safety assessments included adverse events (AEs) and office blood pressure (BP) monitoring (2 to 4 hours post-dose).

**Results:** 810 patients randomized. Naproxcinod was statistically superior to placebo for all 3 co-primary endpoints (p<0.0001), while similar to naproxen. Improvements were well tolerated. Most AEs were mild or moderate, and SAEs were low and similar between groups. The mean change (SD) from Baseline at Week 13 in Systolic BP was −2.60 (11.33) mm Hg in the naproxcinod 750 mg bid group, −2.49 (11.64) mm Hg in the placebo bid group, and −0.49 (12.32) mm Hg in the naproxen 500 mg bid group.

**Conclusion:** Naproxcinod efficacy was statistically superior to placebo in all 3 co-primary efficacy variables. Naproxcinod was well tolerated with a BP profile that tended to be different from that of naproxen.

**Disclosure:** C. Baerwald: None; H. Frayssinet: None; T. Ferreira: None; B. Duquesnoy: None; T. Schnitzer: None.

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A Fixed-Dose Combination of Naproxen and Esomeprazole Magnesium (VIMOVO™) Has Comparable Efficacy and Tolerability to Celecoxib in Patients with Osteoarthritis (OA) of the Knee: Results from Two Randomized, Controlled Trials, Marc C. Hochberg1, Byron Cryer2, John G. Fort3, Clara Hwang4,5, Olga Svensson6 and Mark B. Sostek1, 3AstraZeneca, Wilmington, DE, 3AstraZeneca, Sodertalje, Sweden, 4POZEN, Inc, Chapel Hill, NC, 5University of Maryland, Baltimore, MD, 3University of Texas Southwestern Medical Center, Dallas, TX

**Background:** It is recommended that patients (pts) at risk for serious NSAID-associated upper gastrointestinal (UGI) toxicity should receive a COX-2 selective inhibitor, or a nonselective NSAID plus gastroprotection. The efficacy and tolerability of a fixed-dose combination (FDC) of enteric-coated naproxen 500mg and immediate-release esomeprazole magnesium 20mg was compared with celecoxib 200mg in 2 identical, non-inferiority studies in pts with OA.

**Methods:** Two double-blind, double-dummy, placebo-controlled, multicenter Phase 3 studies (307/309) enrolled pts aged ≥50 years with symptomatic OA of the knee. Following an OA flare, pts were randomized 2:2:1 to receive FDC naproxen/esomeprazole BID, celecoxib 200 mg OD, or placebo for 12 weeks. The primary endpoints were mean change from baseline to Week 12 in WOMAC pain, WOMAC function, and Patient Global Assessment (PGA) of OA using a visual analog scale (VAS, 0–100mm); each endpoint had prespecified non-inferiority margin of 10mm between active treatments. Tolerability endpoints included the modified Severity Of Dyspepsia Assessment (mSODA), heartburn severity, and predefined NSAID-associated UGI adverse events (AEs).

**Results:** Study 307: 619 pts were randomized, 614 were treated, and 521 completed; Study 309: 615 pts were randomized, 610 were treated, and 489 completed. Baseline demographics were similar between treatment groups in both studies; mean age was 62 years and 60% were women. Improvements in WOMAC pain and function, and PGA were seen with naproxen/esomeprazole and celecoxib in both studies. Naproxen/esomeprazole was non-inferior to celecoxib for each primary endpoint; upper/lower limits of 95% CI of treatment differences were <5mm (table). Both active treatments showed significantly greater efficacy vs placebo in Study 307 (p<0.05), while only naproxen/esomeprazole was significantly superior to placebo in Study 309 (p<0.05). The incidence of UGI AEs was 17.3% in Study 307 and 20.3% in Study 309, and was similar between treatment groups. UGI AEs reported by ≥3% of pts were dyspepsia, nausea, and upper abdominal pain. In Study 307, 1.2%, 1.6%, and 2.4% of pts discontinued due to UGI AEs in the naproxen/esomeprazole, celecoxib, and placebo groups, respectively; in Study 309, 0.8%, 3.7%, and 2.5% withdrew, respectively. Improvements in mSODA scores were similar across treatment groups in both studies, with no significant differences between active treatments (table). Pts treated with naproxen/esomeprazole had significantly more heartburn-free days vs those treated with celecoxib (95% CIs: Study 307: 2.1, 12.7; Study 309: 2.5, 13.4) and placebo (95% CIs: Study 307: 6.4, 19.2; Study 309: 11.1, 14.4).

**Conclusions:** With non-inferior efficacy and comparable UGI tolerability to celecoxib, naproxen/esomeprazole may offer an effective and well-tolerated treatment option for pts with knee OA at risk for serious UGI AEs.

**Disclosure:** M. C. Hochberg: AstraZeneca, 9; Bayer, 9; Bionicer, 9; Combinatorx, 9; Eli Lilly and Company, 9; Endo Pharmaceuticals Inc., 9; GlaxoSmithKline, 9; Merck Pharmaceuticals, 9; Merck Serono International, 9; Novartis Pharmaeu; B. Cryer: AstraZeneca, 5; Horizon Therapeutics, 5; NicOx, 5; Pfizer Inc, 5; FLx Pharma, 5; POZEN Inc., 5; J. G. Fort: POZEN Inc., 1; C. Hwang: AstraZeneca, 3; O. Svensson: AstraZeneca, 3; M. B. Sostek: AstraZeneca, 3.

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Chondroitin Sulfate Treatment Is Effective at Reducing Cartilage Loss in the Tibiofemoral Compartment in Knee OA as Assessed by Magnetic Resonance Imaging (MRI). Jean-Pierre Pelletier1, Lukas M. Wildi2, Jean-Pierre Raynauld1, Andre Beaulieu3, Louis Bessette3, Frederic Moreau1, Francois Abram4, Marc Dorais5 and Johanne Martel-Pelletier1, 1Centre de Recherche Muscule-squelettique, Trois-Rivieres, 2CHR-CUM, Notre-Dame Hospital, Montreal, QC, Canada, 3Faculty of Medicine, University of Laval, QC, 4Groupe de Recherche en Rhumatologie et Maladies Osseuses, Sainte-Foy, 5Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, 6Research and Development, ArthroVision Inc., Montreal, 7StatSciences Inc., Notre-Dame de l’Ile-Perrot, 8University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, Canada

**Background:** The osteoarthritis (OA) disease-modifying effect of chondroitin sulfate (CS) has been demonstrated by X-ray in knee OA after 2 years of treatment 1,2. We further explored by performing a randomized, double-blind, placebo-controlled study using a more sensitive imaging technique, quantitative MRI, the effect of CS treatment on cartilage volume loss in knee OA. We also investigated, for the first time, the effect of CS on bone marrow lesion (BML) size and the severity of synovitis.

**Methods:** Knee OA patients were treated with CS (800 mg once daily) or placebo for 6 months, followed by an open-label period of 6 months in which patients from both groups received CS. Patients with primary knee OA, Kellgren-Lawrence grades 2-3, and clinical as well as MRI signs of synovitis were included. MRI was performed at baseline, 6, and 12 months. Global cartilage volume and sub-regions were quantified using a specially developed computer program. The BML size was assessed using a semi-quantitative scoring system. Synovial membrane thickness (synovitis) was measured in mm, and joint swelling incidence was evaluated. Statistical analyses were assessed by ANCOVA for the cartilage volume, Wilcoxon Mann-Whitney
tests for BML, ANOVA for synovitis, and Fisher’s exact test for joint swelling.

Results: Knee OA patients were treated with CS (n=35) or placebo (n=34). Patients on CS treatment (12 months CS) compared to the patients in the placebo group (6 months placebo followed by 6 months CS) experienced a significant reduction in global cartilage volume loss at 6 (p=0.064 for a trend) and 12 (p=0.025) months, in the lateral tibiofemoral compartment (p=0.015; p=0.004), as well as in the tibial plateau (p=0.002; p=0.017). Interestingly, there was also a reduction in BML score in the global knee and lateral tibiofemoral compartment at 12 months (p=0.060; p=0.035, respectively). Although there was no statistically significant difference in synovial thickness between the 2 treatment groups at 6 months, discrimination between patients showed that those who received concomitant NSAID treatment demonstrated a statistically significant reduction in the CS group compared to the placebo group (p=0.029), as well as lower incidence of joint swelling (p=0.092).

Conclusion: Data showed that CS treatment can rapidly and significantly reduce the cartilage loss in symptomatic knee OA patients. This protective effect was associated with a decrease in BML size, supporting their role in cartilage loss. Moreover, data revealed that CS in combination with NSAIDs exerts an additional clinically relevant anti-inflammatory activity.

References:


939 Chronic Pain Associated with Obesity in the Elderly Is in Part Explained by the Presence of Osteoarthritis. Irene Blanco1, Richard B. Lipton2, Chaim Putterman1 and Carol A. Derby2.1Albert Einstein College of Medicine, Bronx, NY, 2Albert Einstein College of Medicine, Bronx, NY

Background: Up to 60% of the elderly report chronic pain. Our group has shown a significant association between chronic pain and obesity in the elderly. It is unclear if this association is due to being overweight or comorbidities associated with obesity such as diabetes and osteoarthritis. Therefore, we conducted a cross-sectional study to investigate if the link between obesity and chronic pain is mediated by other factors.

Methods: The Einstein Aging Study (EAS) is a longitudinal study of community residing elderly. Participants are recruited using Medicare beneficiary lists and voter registration records. Demographics and medical history are collected as well as the Geriatric Depression Scale (GDS), SF-36, and the Total Pain Index (TPI) which measures pain severity, location, duration and intensity of pain. The EAS has targeted interventions can be designed.


References:


Background: Symptomatic hand osteoarthritis (OA) is a common cause of consultation for both primary care physicians and in rheumatologists. Severe forms may lead to advanced structural changes, joint deformity and disability. Despite its frequency and severity there are currently only a limited number of therapeutic options.

Objective: To examine the effect of chondroitin 4&6 sulfate (CS) 800 mg daily on pain and function in patients with hand OA.

Patients and Methods: This is an investigator initiated, randomized, placebo-controlled, single center, trial. Patients older than 40 years, with hand OA as defined by the ACR clinical and radiological criteria, suffering from regular joint pain (VAS ≥ 40/100 mm), and substantial functional impairment (functional index of hand OA (FIHOA): Dreiser score ≥ 6) were randomized to CS or placebo. Patients with other rheumatic conditions were excluded. The use of paracetamol, but not nonsteroidal anti-inflammatory drugs, was allowed during the study period. Primary end points included global spontaneous pain (VAS) and functional impairment (FIHOA). Secondary endpoints included global improvement (VAS improvement), grip strength, duration of morning stiffness, consumption of paracetamol, and drug safety. The investigators, independently from the pharmaceutical study sponsor, replicated both the data transcription and the statistical analysis.

Results: 163 patients were randomized, 81 in the CS and 82 in the placebo groups. One patient in the CS group was excluded from the ITT analysis for protocol violation. Demographic data including age, sex, BMI, blood pressure were perfectly matched in the two groups. Mean ± SD global pain VAS and Dreiser scores in the CS and placebo groups were 54.9 ± 14.2 and 11.0 ± 4.1 and 53.6 ± 14.2 and 10.3 ± 3.8, respectively. Other clinical characteristics including grip strength, number of days of painful flares, duration of morning stiffness was also balanced between the two groups. At six months, the improvement of global pain (VAS) and FIHOA were significantly more important in the CS group (−20 ± 26.6 mm and −2.9 ± 5.3) than in the placebo group (−11.3 ± 24.0 and −0.7 ± 4.8, significance P=0.03 and P=0.008, respectively). The evaluation of global improvement (VAS improvement) and duration of morning stiffness were also significantly better in the CS group (P=0.04), whereas grip strength and rescue medication were not significantly different. There was also no difference regarding the frequency of adverse events.

Conclusion: CS 800 mg daily is effective and safe in the treatment of symptomatic hand OA.

Disclosure: C. Gabay: None; C. Medinger: None; D. Gascon: None; A. Finchk: None.

941 Controversies in the Use of Acupuncture for Osteoarthritis (OA). A Systematic Review of the Quality and Treatment Features of Randomized Clinical Trials (RCT). Maria F. Marenco5, Christian A. Waimann5, Maria A. Lopez-Olivo6, Carol Looney7 and Maria E. Suarez-Almazor1. 1The University of Texas M. D. Anderson Cancer Center, 2The University of Texas M. D. Anderson Cancer Center, Houston, TX, 3University of Texas, MD Anderson Cancer Center, Houston, TX

Background: Acupuncture is one of the most frequently used non-pharmacological therapies for musculoskeletal disorders. There is conflicting evidence on its efficacy for the management of knee OA, which could potentially be attributable to the quality and variability of methodologies used...
across RCTs. We conducted a systematic review of the evidence reported for acupuncture in the treatment of knee OA.

Methods: We electronically searched Embase, Medline, Web of Science and Cochrane Library up to June 9 2010, and manually searched the bibliography included in the identified systematic reviews and meta-analyses. We selected all RCTs which included patients with knee OA, compared needle acupuncture with a sham procedure, and reported pain outcomes. We excluded articles were the control group did not receive a sham intervention. We evaluated the quality of the trials using the Cochrane methods to assess risk of bias (0-worst to 11-best), and we also identified the characteristics of the trials, and specifically the modalities used for the acupuncture and sham treatments. Two authors independently agreed on eligibility and assessed the quality and methods.

Summary of the Results: We identified 6 systematic reviews. Of 14 RCTs, 9 included a sham intervention. Eight of the trials included the WOMAC as an outcome. A total of 1034 patients received acupuncture and 1127 sham intervention. Five of the 9 RCT reported statistically significant results with respect to pain. Six RCTs had a quality score of at least 7 points. The 3 with lower quality did not report statistically significant findings. Marked differences were observed with respect to trial characteristics, acupuncture treatment and sham procedures, with respect to use and number of points, duration and frequency of treatments and sham procedures (perforating versus non-penetrating needles). Negative trials were more likely to have used fewer acupuncture points, shorter duration and number of treatments, electric stimulation in the sham group. Very few studies controlled for the potential placebo effects of the interaction between acupuncturists and research staff with participants.

Conclusions: RCTs of acupuncture in the treatment of knee OA show variability in the results that do not appear to be related to quality of the trial, but is associated with the characteristics of the acupuncture treatment and the procedures used for the sham intervention.

Disclosure: M. F. Marenco: None; C. A. Waimann: None; M. A. Lopez-Olivo: None; C. Looney: None; M. E. Suarez-Almazor: AHRQ, 2, NIAMS-NIH, 2.

942 Disease Modifying Activity ofCelecoxib on Articular Cartilage in Osteoarthrosis—A Randomized Clinical Trial. T. N. de Boer1, S. C. Mastbergen2, A. M. Huisman3, A. A. Polak1, J. W. J. Bijlsma2 and F. P. J. G. Lafeber2. 1Orthopedics, Sint Franciscus Gasthuis Rotterdam, Rotterdam, The Netherlands, 2Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands, 3Rheumatology, Sint Franciscus Gasthuis Rotterdam, Rotterdam, The Netherlands

Background: Selective COX-2 inhibitors are frequently used in the treatment of osteoarthritis (OA) to control inflammation and relieve pain. In vitro and ex vivo research using human articular cartilage, demonstrated an inflammation independent chondroprotective effect of celecoxib. Such effects are difficult to verify in clinical trials because changes in OA cartilage are slow and evaluation by imaging and biomarker techniques are still hampered by their limited sensitivity. Therefore, patients were treated in vivo prior to joint replacement surgery. At the moment of surgery, cartilage was obtained and analyzed in detail ex vivo. Three recent studies using this approach demonstrated a beneficial effect of celecoxib at chondrocyte mRNA and protein level, and at the level of matrix integrity suggesting disease modifying characteristics of celecoxib. These positive results tempted us to perform a well designed and powered RCT to evaluate the disease modifying properties of celecoxib in treatment of end-stage OA.

Methods: Patients (n=172) with end-stage knee OA on the waiting list for knee replacement surgery were randomized to 4 groups and treated for at least 4 weeks prior to surgery: celecoxib 2dd200mg, naproxen 2dd250mg stopped 3 days prior to surgery (because of its platelet-inhibiting effect), celecoxib 2dd200mg also stopped 3 days prior to surgery, or no treatment. Cartilage and synovial tissue were collected during surgery and analyzed ex vivo fully blinded to the treatment until all data were obtained. The study was conducted according to the declaration of Helsinki and registered EudraCT nr 2007-004862-41.

Results: 4 patients withdrew their consent, 10 changed medications within 2 weeks, and of 20 patients insufficient tissue was obtained. Drop-outs were equally distributed over the 4 treatment arms. Data were analyzed by intention to treat as well as per protocol of the remaining 138 patients. At inclusion, age, gender, weight (BMI), and cartilage damage (X-ray, macroscopic or histological) did not differ between the 4 randomized groups. Unexpectedly, cartilage proteoglycan release was not different between the 4 treatments. Also the other biochemical cartilage parameters did not differ between the 4 groups. Furthermore, prostaglandin-E2 and nitric oxide (NO) levels produced by the cartilage remained unchanged compared to the no-treatment group. The ex vivo release of inflammatory mediators IL-1β, TNFa, PGE2 and NO by the synovial tissue only showed a statistical significant decrease in NO levels in the celecoxib treated group compared to the no-treatment group. Celecoxib treatment showed a slight improvement in WOMAC pain (p<0.01), function and total score compared to the no-treatment group.

Conclusions: No clear effect of celecoxib treatment on cartilage was evident in the present study. Also the effects on synovial inflammatory mediators were limited. Only a small beneficial effect on WOMAC scores was found. As such the reported in vivo disease modifying effects of celecoxib could not be confirmed in a sufficiently powered single blinded RCT.

Disclosure: T. N. de Boer: None; S. C. Mastbergen: None; A. M. Huisman: None; A. A. Polak: None; J. W. J. Bijlsma: None; F. P. J. G. Lafeber: None.

943 Effects ofIntraarticular (IA) Corticosteroid Injections on Bone Markers and Endogenous Cortisol in Patients with Knee Osteoarthritis (OA), a Pilot Study. Aruna Baratham1, Barbara P. Lukert1 and Herbert B. Lindsley2. 1Kansas City, KS, 2Kansas University Med Ctr, Kansas City, KS, 3KU Medical Ctr, Kansas City, KS

Purpose: IA steroids are used to treat knee OA. Little is known about the systemic effect of intraarticular steroid injections on bone or the pituitary-adrenal axis. There are some studies describing transient decreases in cortisol levels after IA injections in rheumatoid arthritis patients, but no data are published regarding IA steroid injections and their effect on bone turnover markers in OA patients.

Method: We describe a randomized, double blind, placebo controlled study to determine the effects of IA corticosteroid injections on bone turnover markers and endogenous cortisol. 25 subjects (20 females, 5 males) with knee OA, age range 40–80 years were identified from our clinical practice. They were not on any bisphosphonates for at least three years, no systemic illness, and not on oral glucocorticoids; their last IA glucocorticoid injection was given more than 3 months ago. They were randomized to one of three different groups injected in the more symptomatic knee on Day 0. Ten subjects (Group 1) were injected with Depo-methylprednisolone 80 mg plus lidocaine 20 mg, 10 additional subjects (Group 2) were injected with Depo-methylprednisolone 16 mg plus lidocaine 20 mg and 5 subjects (Group 3) was given normal saline with lidocaine 20 mg. Blood draws were performed five times (Days 0, 2–3, 7, 14 and 28).

Results: Median levels of serum osteocalcin a bone formation marker, reached a nadir (10 ng/ml from baseline of 16 ng/ml) by Days 2–3 with recovery by Day 7 (15 ng/ml) after IA corticosteroids only for Group 1 (p=0.003). No change was seen in Groups 2,3.
Efficacy and Safety of the Lidocaine Patch 5% (Lidoderm®) When Used as Adjunct Treatment in Patients with Osteoarthritis of the Knee. Alan Kivitz1, Ernest A. Kopecky2, Yusong Chen2, Steve Xiang2, Matthew Wie- man3 and Michael H. Schiff4. 1Altoona Center for Clinical Research, Duncansville, PA, 2Endo Pharmaceuticals Inc., 1, 3; 3Endo Pharmaceuticals Inc., 1, 3; 4Brigham & Womens Hospital, Boston, MA, 5University of Colorado, Denver, Greenwood Village, CO

Purpose: To explore the sensitivity of a dual sequence, crossover design to estimate the treatment effect and safety of the lidocaine patch 5%, relative to placebo, as adjunctive therapy for knee osteoarthritis (OA).

Methods: This pilot study was a randomized, double-blind, placebo-controlled, 2-sequence, dual crossover, 3-period, multicenter trial in patients with moderate-to-severe pain from OA of the knee. The lidocaine patch 5% was generally well tolerated in OA of the knee. The lidocaine patch 5% was compared with placebo for all populations. PI-NRS scores were significantly improved for lidocaine patch 5% patients only in the MITT population (0.54-point difference compared with placebo [P = 0.02]). General disorders and administration site conditions were the largest group of treatment-related AEs in the run-in phase and double-blind treatment periods. Cutaneous AEs were mostly mild or moderate in severity and self-limited.

Conclusions: The small size of the MITT population did not allow for robust hypothesis testing, however the results suggest a beneficial treatment effect of the lidocaine patch 5% as add-on therapy in patients with OA of the knee. The lidocaine patch 5% was generally well tolerated in this population. Use of a dual sequence, crossover design may be a sensitive model for studying the effects of the lidocaine patch 5%.

Disclosure: A. Kivitz: None; E. A. Kopecky: Endo Pharmaceuticals Inc., 1, 3; Yusong Chen: Endo Pharmaceuticals Inc., 1, 3; S. Xiang: Endo Pharmaceuticals Inc., 1, 3; M. Wiedman: Endo Pharmaceuticals Inc., 1, 3; E. Gould: Endo Pharmaceuticals Inc., 1, 3.

Efficacy, Safety and Tolerability of HZT-501, Including Users of Low-Dose Aspirin, a Single-Tablet Combination of Ibuprofen-Famotidine: Results of Two Phase 3 Trials. Michael E. Weinblatt1, Mark C. Genovese2, Alan J. Kivitz3, Alfonso E. Bello4, Amy Grahn5, Jeffrey W. Sherman5, Alan J. Kivitz1, Alfonso E. Bello4, Amy Grahn5, Jeffrey W. Sherman5, Michael H. Schiff6,7. 1Altoona Arthritis & Osteo Ctr, Duncansville, PA, 2Brigham & Womens Hospital, Boston, MA, 3Horizon Pharma, Inc., Northbrook, IL, 4Illinois Bone & Joint Inst, Glenview, IL, 5Stanford University, Stanford, Sunnyvale, CA, 6University of Colorado, Denver, Greenwood Village, CO

Background: Gastrointestinal (GI) toxicity remains a major concern with non-steroidal anti-inflammatory drugs (NSAIDs) used in the treatment of OA, RA, and pain. Low-dose aspirin (LDA) is prescribed for prevention of cardiovascular events. LDA is a risk factor for upper GI (UGI) ulcers and UGI bleeding, with the risk increased when LDA is taken in combination with NSAIDs. Randomized trials have demonstrated that high-dose H2 receptor antagonists (H2RAs) reduce the incidence of ulcer in NSAID users and in LDA users, but their benefit in patients taking concomitant NSAIDs and LDA is uncertain. A combination tablet of a NSAID plus a high-dose H2RA may both decrease ulcer disease in NSAID plus LDA users and improve compliance.

Methods: Two 24-wk double-blind, randomized trials of HZT-501, a single-tablet combination of ibuprofen (IBU; 800mg) and famotidine (FAM; 26.6mg) given three times daily were undertaken (REDUCE-1 and REDUCE-2). Patients 40–80 yrs expected to require daily NSAID therapy ≤5 anos with no history of ulcer complications, negative Helicobacter pylori stool test and baseline endoscopy (EGD) showing no ulcers and <5 erosions in the UGI tract were randomly assigned in a 2:1 ratio to HZT-501 or IBU 800 mg tablets. Concomitant LDA (≤325 mg daily) and oral anticoagulants (OAC) therapies were permitted. Randomization was stratified based on LDA/OAC therapy and prior ulcer history. Study EGDs were done at 8, 16 and 24 wks of therapy. The predefined population for primary analyses of ulcers was all patients with at least one on-study EGD. Additional safety data included treatment emergent adverse events (TEAEs), clinical laboratory assessments and physical exams.

Results: The studies included 906 and 627 patients. Total patients were1533, of which 1022 received HZT-501 and 511 received IBU. They included 121 of 812 and 79 of 570 LDA users in their primary analysis populations, respectively. A combined sub-group analysis of the LDA

Conclusions: IA corticosteroids have a transient adverse effect on bone formation with significant recovery of osteocalcin levels by one week and no change in bone catabolism. Cortisol levels decrease slightly at one week of IA administration and rebound above baseline by two weeks. In contrast to daily oral corticosteroids, single doses of IA steroids have no persistent adverse effect on bone or the HPA axis.

Disclosure: A. Baratham: None; B. P. Lukert: None; H. B. Lindsley: None.

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users demonstrated a reduction in UGI ulcers (HZT-501: 14.0% vs. IBU: 34.5%; difference 20.5% [95% CI: 6.5, 34.6]). The Table shows the differences for HZT-501 vs. IBU in the life table estimates and crude proportions for all patients and for the LDA users developing UGI ulcers as well as discontinuation, serious adverse events (SAE) and TEAEs of interest over 24 wks. There were no clinically relevant differences between treatment groups in vital signs, hematology, biochemistry values or physical exams.

**Table**

<table>
<thead>
<tr>
<th></th>
<th>HZT-501 (N=1022)</th>
<th>IBU (N=511)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation</td>
<td>31.0%</td>
<td>42.9%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TEAEs</td>
<td>6.7%</td>
<td>7.6%</td>
<td>0.478</td>
</tr>
<tr>
<td>Dyspepsia²</td>
<td>0.6%</td>
<td>1.8%</td>
<td>0.014</td>
</tr>
<tr>
<td>SAEs</td>
<td>3.2%</td>
<td>3.3%</td>
<td>NA</td>
</tr>
<tr>
<td>TEAEs</td>
<td>55.0%</td>
<td>58.7%</td>
<td>0.162</td>
</tr>
<tr>
<td>GI Disorders</td>
<td>26.0%</td>
<td>28.4%</td>
<td>0.329</td>
</tr>
<tr>
<td>Dyspepsia²</td>
<td>4.7%</td>
<td>8.0%</td>
<td>0.009</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>20.6%</td>
<td>20.7%</td>
<td>0.960</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>0.4%</td>
<td>1.0%</td>
<td>NA</td>
</tr>
</tbody>
</table>

³Preferred term for patient reported adverse event

**Conclusion:** HZT-501 reduces NSAID-associated UGI ulcers overall and in the subset of NSAID users taking LDA. TEAEs were balanced across both treatment groups except dyspepsia which was statistically lower for HZT-501 vs. IBU in line with known activity of FAM. Combination therapy may improve adherence and compliance in patients taking NSAIDs plus LDA who require gastroprotection.


**946**

Long Term Safety of an NSAID with Built-in Gastroprotection for Treatment of Pain and Inflammation Related to OA and RA: Results from a One Year Safety Trial of a Single-Tablet Combination of Ibuprofen-Famotidine vs. Ibuprofen Alone. Michael H. Schif², Mark C. Genovese³, Alan J. Kivitz², Alfonso E. Bello², Jeffrey W. Sherman³, Amy Grahn³ and Michael E. Weinblatt². 1Alloona Arthritis & Osteo Ctr, Duncansville, PA; 2Brigham & Womens Hospital, Boston, MA; 3Horizon Pharma, Inc., Northbrook, IL; 4Illinois Bone & Joint Inst, Glenview, IL; 2Stanford University, Stanford, Sunnyvale, CA; 3University of Colorado, Denver, Greenwood Village, CO

**Background:** Gastrointestinal (GI) toxicity remains a major concern with NSAIDs used in the treatment of OA, RA, and pain. Proton pump inhibitors (PPI) and other gastroprotective agents are recommended to decrease NSAID-associated GI injury. Concerns exist regarding the potential for PPIs to adversely interact with antithrombotic agents as well as increase the risk of fractures. High-dose H₂ receptor antagonists provide significant benefit in decreasing NSAID-associated GI injury (Cochrane review). Most NSAID users at increased risk for GI events do not receive or adhere to gastroprotective co-therapy. HZT-501 [single-tablet combination of ibuprofen (IBU; 800 mg) and famotidine (FAM; 26.6 mg)] has been shown to significantly reduce upper GI ulcers as compared to IBU (800 mg) alone given thrice daily (REDUCE-1 and REDUCE-2).

**Methods:** Assessment of long term safety of HZT-501 or IBU tablets for up to 52 wks of treatment for patients with OA, RA or moderate pain. Patients who completed one of two large 24-week double-blind prospective trials of identical design (REDUCE-1 or REDUCE-2) were eligible for an additional 28 weeks of treatment; enrollment goal was at least 150 patients. Patients 40–80 yrs expected to require daily NSAID therapy ≥ 6 months with no history of ulcer complications, a negative H. pylori stool antigen test and baseline EGD showing no ulcers and <5 erosions in the upper GI tract were randomly assigned in a 2:1 ratio either to HZT-501 or IBU tablets. Randomization was stratified based on concomitant low-dose aspirin/antiocoagulant therapy and prior ulcer history. Patients completing 24 weeks of blinded treatment (no ulcer development; expected to continue requiring daily NSAID therapy) were eligible to enroll into a follow-on study for an additional 28 weeks on the same double-blind treatment assignment. Crossover between treatments was not allowed. Safety data included serious adverse events (SAEs), treatment emergent adverse events (TEAEs), clinical laboratory assessments, vital signs, and physical exams.

**Results:** A total of 179 subjects were enrolled into the follow-on study, 132 received HZT-501 (112 completed) and 47 received ibuprofen (38 completed). The incidence of TEAEs was comparable in both groups for the overall 52-week period. The Table shows the differences for HZT-501 vs. IBU for discontinuation, serious adverse events (SAE) and TEAEs of interest over 52 wks. There were no clinically relevant differences between treatment groups in vital signs, hematology, biochemistry values or physical exams.

**Table.**

<table>
<thead>
<tr>
<th></th>
<th>REDUCE 1 &amp; 2 Follow-on Population</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HZT-501 (N = 132)</td>
<td>IBU (N = 47)</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>15.2%</td>
<td>19.1%</td>
</tr>
<tr>
<td>SAEs</td>
<td>6.1%</td>
<td>6.4%</td>
</tr>
<tr>
<td>TEAEs</td>
<td>68.2%</td>
<td>68.1%</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>34.8%</td>
<td>36.2%</td>
</tr>
<tr>
<td>GI Disorders</td>
<td>26.5%</td>
<td>23.4%</td>
</tr>
<tr>
<td>Dyspepsia²</td>
<td>3.8%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>0.8%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

³Preferred term for patient reported adverse event

**Conclusion:** These results show the safety of long-term use of HZT-501, together with the significant decrease in upper GI ulcers, demonstrate that HZT-501 offers a potential new option for OA, RA and pain patients.


**947**

Modified Bent Knee Approach for Highly Accurate Injection of the Knee. Suzanne Delea¹, Wilmer L. Sibbitt², Philip Band, Natalia Chavez-Chiang², Hillary Norton² and Arthur D. Bankhurst¹. ¹University of New Mexico, Albuquerque, NM; ²University of New Mexico HSC, Albuquerque, NM; ³University of NM Med Ctr, Albuquerque, NM

**Background:** The extended knee lateral midpatellar portal for 1 intraarticular injection of the knee is accurate but is not practical for all patients.

**Hypothesis/Purpose:** We hypothesized that a highly accurate modified anterolateral portal where the synovial membrane of the medial femoral condyle is the target would be effective for intraarticular injection of the knee.

**Study Design:** Randomized controlled clinical trial. Level 1.

**Methods:** 83 subjects with “dry” non-erosive osteoarthritis of the knee were randomized to intraarticular injection using the modified anterolateral bent knee versus the standard lateral midpatellar portal. 80 mg of triamcinolone acetonide was injected into the knee using a 2.0-in (5.1-cm) 21-gauge needle on a RPD procedure syringe (reciprocating procedure device) using the one-needle two-syringe technique. Baseline pain, procedural pain, and pain at outcome (2 weeks and 6 months) were determined with the 0–10 cm Visual Analogue Pain Score (VAS).
accuracy of needle placement was determined by sonographic imaging with provocative testing.

**Results:** The lateral midpatellar and modified anteriolateral portals resulted in similar levels of procedural pain (VAS midpatellar: 4.6±3.1 cm; anteriolateral: 4.8±3.2 cm; p =0.77), pain at 2 weeks (VAS midpatellar: 2.6±2.8 cm; anteriolateral: 1.7±2.3 cm; p = 0.11), pain at 6 months (VAS midpatellar: 4.9±3.1 cm; anteriolateral: 4.8±3.2 cm; p =0.89), responders (midpatellar: 45.0%; anteriolateral: 55.8%; p =0.33), non-responders (midpatellar: 55.0%; anteriolateral: 44.2%; p =0.77), duration of therapeutic effect (midpatellar: 3.9±2.4 months; anteriolateral: 4.1±2.2 months; p =0.69), time to next procedure (midpatellar: 7.3±3.3 months; anteriolateral: 7.7±3.7 months; p =0.71), and cost per year (midpatellar: $243±110; anteriolateral: $231±111; p = 0.61). The bent knee anteriolateral portal was 97.4% accurate.

**Conclusions and Clinical Relevance:** The modified anteriolateral bent knee portal is an effective and accurate alternative to the standard lateral midpatellar portal for intraarticular injection of the knee, and results in equivalent levels of responders, pain reduction, costs, and duration of therapeutic effect.

**Disclosure:** S. Delea: None; W. L. Sibbitt: Abbott Intravascular, Inc, 1, 9, Apple, Inc, 1, 9, Avanca Medical Devices, Inc, 1, 9, Avanca, Inc, 1, 9, Avasca Medical, Inc, 1, 9, Avasca, Inc, 1, 9, Becton Dickinson, 9, Celgene, 1, Ferring Pharmaceuticals Inc., 9, Intelig. P. Band: None; N. Chavez-Chiang: None; H. Norton: None; A. D. Bankhurst: None.


**Background:** DMOAD development has been limited by few patients (pts) fulfilling xray (XR) progression criteria. Joint arthroplasty (AP) has been proposed as an optimal outcome in DMOAD RCTs; however, disparities by race, gender, socioeconomic status, access to care, surgeon preference, and health care systems have generated concerns regarding biased outcomes. Moreover, a trial using AP outcomes would require a large sample size and long duration to capture sufficient event numbers. A combined OARSI/OMERACT initiative to develop “virtual total joint replacement” (VJR) criteria for DMOAD RCTs has proposed several thresholds of sustained pain, reduced function, or XR change as AP indications. Our objective is to evaluate the prevalence of pts fulfilling different clinical/XR progression scenarios from existing DMOAD RCTs. We evaluated the prevalence of multiple cutoffs that could potentially be used as future criteria for VJR in DMOAD RCTs.

**Methods:** We analyzed data from placebo arms of 8 RCTs of putative DMOADS for hip or knee OA. XR progression was defined as decrease in joint space width (JSW) by the study’s smallest detectable difference (SDD) for XR Δ or 0.5mm. The proportion of pts fulfilling 9 VJR scenarios with combined pain + function scores ≥80 or 100, or [pain ≥50 + function ≥30] OR [function ≥50 and pain ≥30] at 2, 3, or 4 consecutive visits with/without XR progression was assessed for each trial. Effect sizes of clinical scenarios were modeled in regression analyses using XR pro-
Regression as a continuous (JSW Δ) and dichotomous (cutoff 0.5mm) variable.

Results: 8 OA RCTs between 1–3 yrs duration representing 1379 pts were included. Pain was assessed by WOMAC and/or VAS and function assessed by WOMAC and/or Lequesne. Radiographic SDD was evaluated in 4 trials (range 0.20–0.50). Weighted mean baseline measures demonstrated: JSW 3.18 mm (range: 2.39–4.05), pain 37.78, function 37.97, pain+function 76.78. Among 6 knee and 2 hip studies, 248 (22%) and 132 (51%) pts respectively had XR progression by JSW Δ ≥0.5mm and 366 (37%) by JSW Δ ≥SDD. Among the 9 clinical scenarios, the highest prevalence (n=486, 36%) was in the least stringent scenario (pain+function≥80 at ≥2 visits); the fewest pts fulfilled criteria (n=101, 7%) in the most stringent scenario (pain+function≥80 at ≥4 visits).

When XR progression was added, the prevalence of pts fulfilling a VJR scenario ranged from 2.16% to 12.14% for JSW Δ ≥0.5mm; 3.4% to 16.7% for JSW Δ ≥SDD. Although individual studies demonstrated associations between a clinical scenario and XR progression, in pooled regression analyses of all RCTs there was no relationship. Using the prevalence of 9 scenarios among all 8 RCTs a sample size of 545–3532 per group would be needed to demonstrate a 30% Δ.

Conclusions: The prevalence of pts with sustained symptomatic OA of at least a moderate degree with XR progression is low. Even using the most lenient criteria to define a “VJR,” large numbers of pts would be required to detect differences between groups in DMOAD RCTs. RCT heterogeneity with a range of baseline JSW, symptoms, study duration and assessments may have contributed to the lack of association between XR progression and clinical symptoms in these post hoc analyses.

Disclosure: R. L. Manno: None; C. O. Bingham: None; S. Paternotte: None; P. Coste: None; G. Giacovelli: None; L. C. Rovati: None; K. D. Brandt: None; S. A. Mazzuca: None; D. O. Clegg: None; H. Shi: None; E. Tajana Messi: None; A. Lanzarotti: None; M. Dougados: None.

949 WITHDRAWN

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Patient Global Impression of Change Results from a 1-Year Open-Label Extension Study of Tapentadol Extended Release in Patients with Chronic Osteoarthritis or Low Back Pain. Bettyanne McCann1, Robert Lange1, Bertil Wagner2, Achim Steup1, Bernd Lange1 and Mila Etropoloski2.

1 Global Development, Grünenthal GmbH, Aachen, Germany, 2 Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ

Background: Tapentadol is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition. The safety and tolerability of tapentadol extended release (ER) were assessed in a 1-year open-label extension study (ClinicalTrials.gov identifier: NCT00487435); efficacy was evaluated using the patient global impression of change (PGIC).

Methods: Patients were eligible for enrollment in this study if they completed 1 of 4 phase 3 studies: two 15-week studies that evaluated the efficacy of tapentadol ER and oxycodone controlled release (CR) compared with placebo for chronic osteoarthritis knee pain (NCT00421928) or low back pain (NCT00449176), a crossover study (two 2-week periods following a 3-week titration with tapentadol immediate release) to assess dose conversion between the immediate-release and extended-release formulations of tapentadol in patients with chronic low back pain (NCT00594516), or a 1-year controlled long-term safety study of tapentadol ER and oxycodone CR in patients with chronic osteoarthritis hip or knee pain or low back pain (NCT00361504). Patients who completed 1 of the efficacy studies or the crossover study or who received oxycodone CR in the 1-year safety study were titrated to their optimal therapeutic dose of tapentadol ER (100–250 mg bid) during a titration period of up to 4 weeks; patients then continued on that optimal dose during a maintenance period of up to 48 weeks. Patients who received tapentadol ER during the 1-year safety study continued on their optimal dose determined in the parent study. Dose adjustments within the therapeutic range were permitted under the supervision of a physician throughout the current study. The PGIC, which was completed at baseline of this trial, at Weeks 24 and 48 of maintenance, and at the end of treatment, was used to assess patient’s subjective changes in their overall status from baseline to endpoint. Patients indicated their perceived change by completing the statement “Since I began study treatment, my overall status is:” using a 7-point scale (1 = “very much improved,” 2 = “much improved,” 3 = “minimally improved,” 4 = “no change,” 5 = “minimally worse,” 6 = “much worse,” 7 = “very much worse”). Adverse events (AEs) were monitored throughout the study.
Results: The safety population included 1,154 patients, the intent-to-treat population included 1,149 patients, and PGIC data at endpoint were available for 1,059 patients. The majority (61.4% [650/1,059]) of patients reported a change in overall status at endpoint of “very much improved” or “much improved,” and an additional 25.7% (272/1,059) of patients reported that their overall status was “minimally improved.” The most commonly reported TEAEs were headache (13.1% [151/1,154]), nausea (11.8% [136/1,154]), and constipation (11.1% [128/1,154]).

Conclusion: Long-term treatment with tapinarudol ER (100-250 mg bid) for up to 1 year (and up to 2 years for some patients) was associated with an improvement in overall status for the majority of patients in this open-label extension study of patients with moderate to severe chronic osteoarthritis pain or low back pain.

Disclosure: B. McCann: Johnson & Johnson, 1, 3; R. Lange: Grünenthal GmbH, 3; B. Wagner: Johnson & Johnson, 1, 3; A. Steup: Grünenthal GmbH, 3; B. Lange: Grünenthal GmbH, 3; M. Eトルポルスキ: Johnson & Johnson, 1, 3.

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Objective: OA has been labeled an inflammatory disorder but studies have examined only a limited repertoire of inflammatory markers with disease and have reported inconsistent findings. We assessed whether inflammation biomarkers and those representing adipokines are associated with synovitis and knee pain in participants in a cohort study of knee OA.

Methods: A subgroup of 100 Caucasian women were included from the NIH-funded Multicenter Osteoarthritis (MOST) Study. MOST participants were age 50 to 79 years at baseline and either with symptomatic knee OA or at high risk of disease. At baseline and 39 month follow-up, subjects were queried about the presence of knee pain on most days, completed a knee-specific Western Ontario McGill Osteoarthritis Index (WOMAC), and had weight-bearing PA and lateral knee x-rays. New knee pain was present if a subject did not have knee pain on most days at baseline but did at follow-up irrespective of x-ray OA. At 30 months, participants underwent a gadolinium contrast-enhanced MRI using a 1.5 Tesla scanner to detect synovitis, categorized as none/questionable, mild, or a lot/extensive.

Results: Mean age (standard deviation) was 59.5 years (7.2), body mass index (BMI) was 29 (4.8) kg/m², 57% had no radiographic OA at baseline, 20% with unilateral OA and 23% with bilateral OA and 68% were using pain medications at baseline. Adjusted for site, age, BMI, baseline K/L grade, BML score (>0) and effusion score (>0), the following associations were significant for any synovitis (versus none) at 30-month: baseline adiponectin, OR 2.6 (1.3, 4.9) and baseline TGFBeta1, OR 0.3 (0.91, 0.7).

Significant predictors of outcomes in Multivariable adjusted Odds for 1 Standard deviation increase in each biomarker

<table>
<thead>
<tr>
<th>A lot / extensive Synovitis (ref: none/mild) OR (95% CI) p-value</th>
<th>Prevalent knee pain on WOMAC (ref: none) OR (95% CI) p-value</th>
<th>Incident knee pain on WOMAC (ref: none) OR (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin 2.6 (1.3, 4.9) 0.005</td>
<td>1.4 (0.9, 2.4) 0.16</td>
<td>0.9 (0.4, 2.2) 0.84</td>
</tr>
<tr>
<td>TGF-B1 0.3 (2.0, 0.7) 0.002</td>
<td>1.2 (0.7, 2.1) 0.43</td>
<td>1.2 (0.5, 2.9) 0.71</td>
</tr>
<tr>
<td>TNF-alpha 1.2 (0.7, 2.1) 0.44</td>
<td>1.9 (1.1, 3.2) 0.015</td>
<td>2.4 (0.8, 6.6) 0.10</td>
</tr>
<tr>
<td>ICAM-1 1.1 (0.7, 1.8) 0.71</td>
<td>1.1 (0.7, 1.8) 0.57</td>
<td>0.3 (0.1, 0.97) 0.044</td>
</tr>
</tbody>
</table>

Similarly, in multivariable-adjusted analyses, the following associations were significant for any synovitis (versus none) at 30-month: baseline ICAM-1, OR 1.9 (1.1, 3.4) and baseline TGFBeta1, OR 1.9 (1.1, 4.1). Adjusted for all the variables above and use of pain medications, baseline TNF-alpha was significantly associated with prevalent knee pain at 30-months, OR 2.0 (1.2, 3.4) and ICAM-1 was associated with incident knee pain, OR 0.3 (0.1, 0.97).

Conclusions: In this hypothesis-generating study using a longitudinal cohort of Caucasian women, we found several biomarkers predictive of synovitis, prevalent and incident knee pain at 30-month follow-up.

Disclosure: J. Singh: None; T. Neogi: None; D. T. Felson: None; J. Torner: None; K. Baker: None; M. C. Nevitt: None; I. Tolstykh: None; C. E. Lewis: None.

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Background: There is debate on the presumed association between radiographic and clinical features of osteoarthritis (OA). Inconsistency in reported associations might be caused by different definitions of clinical OA, and by different protocols and scoring methods for radiographic damage. Objective of this review was to evaluate whether there is an association between radiographic OA and clinical OA of hip and knee, accounting for the importance of disease definition, radiographic protocol, and standardized outcome measures.

Methods: A systematic literature search was performed with the keywords ‘OA’, ‘hip’, ‘knee’, ‘radiographic’, and ‘clinical’. For comparison of study results, seven classification criteria for general study quality and methodological quality were developed. All studies were evaluated for an association between radiographic and clinical OA. Associations were classified as ‘present’ when statistically significant, as ‘absent’ when not statistically significant, and as ‘non-evident’ when not all performed comparisons were statistically significant. The influence of classification criteria on the association was investigated, by classifying both the number and the specific criteria fulfilled.

Results: The literature search resulted in 47 studies describing associations between radiographic and clinical OA. When all studies were evaluated, associations were present in 15%, absent in 19%, and non-evident in 66%. Associations were strongest in the six studies fulfilling all classification criteria; present in 50%, absent in 17%, and non-evident in 33% of studies. The frequency of studies with present associations significantly (p<0.01) diminished when the number of fulfilled criteria decreased.


Tuesday, November 9
Specifically the criteria for radiographic protocol, and standardized outcome measures were important. Associations were present in 35%, absent in 12%, and non-evident in 53% of the 17 studies in which the radiographic protocol was adequate. In the 30 studies not fulfilling this criterion, associations were significantly less present \( (p=0.012) \): associations were non-evident in 74% of studies, present in only 3%, and absent in 23% of studies. Considering standardized outcomes, associations were present in 26%, absent in 37%, and non-evident in 37% of studies when the criterion was fulfilled. When the criterion was not fulfilled, associations were significantly less present \( (p=0.002) \); associations were non-evident in 86%, present in only 7%, and absent in 7% of studies.

**Conclusion:** Radiographic OA and clinical OA were more commonly associated when studies fulfilled criteria for study quality and methodological quality. Specifically the radiographic protocol and standardized outcome measures are important for future research regarding the association between radiographic and clinical OA.

**Sponsor:** Dutch Arthritis Association.

**Disclosure:** M. B. Kinds: None; E. P. Vignon: None; J. W. J. Bijlsma: None; M. A. Viergever: None; A. C. A. Marijnissen: None; F. P. J. G. Lafeber: None; P. M. J. Welsing: None.

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**Time to Onset of Gastrointestinal Adverse Events of Naproxinod vs. Naproxen and Placebo in Patients with Osteoarthritis.** Byron Cryer, Angel Lanas, Rosanna Fleming, Fabrizio Dolphi, Diana Aguirre, and Brigitte Duquesnoy. Aragon Health Sciences Institute, University of Zaragoza, Department of Veterans Affairs Medical Center, NicOx SA, NicOx, Inc.

**Background:** Naproxinod is a first-in-class COX-Inhibiting Nitric Oxide Donator (CINOD). Previous studies showed naproxinod was effective compared to placebo in osteoarthritis (OA) patients.

**Objectives:** To evaluate the time to onset of GI adverse events (AEs) of naproxinod 750 mg bid and naproxinod 375 mg bid vs naproxen 500 mg bid and placebo bid in OA patients.

**Methods:** The safety populations were pooled from three Phase 3 OA studies (13 weeks of treatment) including two dose regimens of naproxinod, naproxen and placebo. GI AEs and discontinuations due to GI AEs were part of a pre-planned descriptive statistical analysis. A post-hoc analysis of time to onset of GI AEs and discontinuations due to GI AEs among the different treatment groups was performed by estimating the distributions of the times to onset using Kaplan-Meier methods and comparing the distributions among the treatment groups using log rank test.

**Results:** A total of 2741 patients were included in the analysis: 801 on naproxinod 750 mg, 489 on naproxinod 375 mg, 638 on naproxen 500 mg and 813 on placebo. Demography and baseline characteristics were well balanced among groups and reflected those of the general OA population. At least one GI AE was reported by 138 (17.2%) patients on naproxinod 750 mg bid, 69 (14.1%) on naproxinod 375 mg bid, 128 (20.1%) on naproxen and 109 (13.4%) on placebo. Few patients discontinued due to at least one GI AE: 27 (3.4%) on naproxinod 750 mg bid, 9 (1.8%) on naproxen and 27 (3.3%) on placebo.

Time to onset of GI AEs for the different treatment groups is presented below.

Overall, the difference among the treatment groups was significant (log Rank \( p=0.0050 \)). Time to onset of discontinuations due to GI AEs showed a similar trend but the difference was not significant among treatment groups.

**Conclusions:** This analysis showed that over the 13 weeks of treatment the onset of GI AEs was less likely to have occurred for naproxinod-treated patients than for naproxen-treated patients. A similar trend was observed for discontinuations due to GI AEs.

**References:**
- HCT 3012-X-301, –302 up to 13 weeks of treatment, –303
- Disclosure: B. Cryer: None; A. Lanas: None; R. Fleming: None; F. Dolphi: None; D. Aguirre: None; B. Duquesnoy: None.

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**954**

**Topical Diclofenac Solution (PENNSAID®) Compared with Oral Diclofenac in Osteoarthritis of the Knee: Pooled Analysis from 2 Controlled Clinical Trials.** Sanford H. Roth and Philip Fuller. Arizona Research and Education, Arthritis Research Laboratory, Arizona State University, Phoenix, AZ, Coviden

**Background:** The use of topical nonsteroidal anti-inflammatory drug (NSAID) formulations, which produce less systemic exposure to NSAIDs compared with oral formulations, is recommended in current guidelines for the management of osteoarthritis (OA). Several randomized clinical trials have shown that topical diclofenac solution (TDiclo) with penetration enhancer dimethyl sulfoxide (DMSO) is effective and well tolerated in the treatment of OA. Results of a pooled analysis of data from 2 trials comparing the safety and efficacy of Tdiclo with that of oral diclofenac (ODiclo) are presented here.

**Methods:** Pooled analysis was performed for two 12-week, double-blind, double-dummy, randomized, controlled, multicenter studies comparing the safety and efficacy of Tdiclo with ODiclo in patients with radiographically confirmed symptomatic OA of the knee. Safety and tolerability assessments in both studies included recording of vital signs and adverse events (AEs), dermatologic evaluation of the knee, and clinical laboratory measurements. Primary efficacy variables were pain and physical function as measured by the Western Ontario and McMaster Universities Arthritis (WOMAC) Index and a patient global assessment.

**Results:** A total of 927 patients (randomized population) were included in pooled safety analysis, and 909 patients (intent-to-treat population) were included in the pooled efficacy analysis. AEs occurred in 312 (67.1%) of patients using Tdiclo vs 298 (64.5%) of those taking ODiclo. The most common AE with Tdiclo was dry skin at the application site, reported in 24.3% of patients (vs 1.9% with ODiclo; \( P<0.0001 \)). Fewer gastrointestinal-related AEs (25.2% vs 39.0%; \( P=0.037 \)) occurred with Tdiclo compared with ODiclo. Efficacy as measured by WOMAC scales and patient global assessment was similar between treatment groups.

**Conclusions:** Although minor skin irritation at the application site was more common in patients using Tdiclo, the incidence of gastrointestinal and cardiovascular AEs was significantly lower with Tdiclo compared with ODiclo.

**Disclosure:** S. H. Roth: Coviden, 1, 3, 5, 8, 9, Self-employed, 1, 3, 5, 8, 9, Transdel Pharmaceuticals, 1, 3, 5, 8, 9; P. Fuller: Coviden, 3.

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**955**

**Topical Diclofenac Solution with the Absorption Enhancer Dimethyl Sulfoxide (PENNSAID®) for the Treatment of Osteoarthritis of the Knee: Integrated Summary of Safety.** Sanford H. Roth and Philip Fuller. Arizona Research and Education, Arthritis Research Laboratory, Arizona State University, Phoenix, AZ, Coviden

**Background:** Several randomized clinical trials have shown that topical diclofenac solution (TDiclo) with the penetration enhancer dimethyl sulfoxide (DMSO) is effective and well tolerated in the treatment of osteoarthritis (OA) of the knee. Because topical nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with less systemic exposure to the active molecule, Tdiclo may present a safer treatment alternative to oral NSAIDs. To further characterize the safety and tolerability profile of Tdiclo, data were analyzed across clinical studies conducted in patients with OA of the knee.

**Methods:** Adverse events (AEs) with Tdiclo therapy were analyzed for seven phase 3 controlled trials and one open-label study conducted in patients using Tdiclo vs ODiclo.
with primary OA of the knee. The data reflect TDiclo exposure in 911 patients treated for 4 to 12 weeks (mean duration, 49 d) in the phase 3 controlled trials and 793 patients from the open-label study. In the open-label study, 463 patients were treated for at least 6 months, and 144 patients were treated for at least 12 months.

**Results:** Mean age of the study participants was approximately 60 years. Of the evaluated patients, 89% were white and 64% were female. The most common AEs with TDiclo were application site reactions, including dry skin (32%), contact dermatitis characterized by skin erythema and induration (9%), contact dermatitis with vesicles (2%), and pruritus (4%). Application site reactions were the most common cause of patient withdrawal from studies. In controlled trials, gastrointestinal-related AEs occurring with TDiclo at a rate at least twice that with placebo included constipation (3% vs <1%), diarrhea (4% vs 2%), dyspepsia (8% vs 4%), nausea (4% vs 1%), flatulence (4% vs <1%), abdominal pain (6% vs 3%), and edema (3% vs 0%).

**Conclusions:** TDiclo offers a well-tolerated potential alternative to oral NSAID therapy in patients with OA. There was a low incidence of gastrointestinal-related AEs in patients treated with TDiclo. The most common AEs across controlled and uncontrolled clinical trials were application site reactions.

**Disclosure:** S. H. Roth: Covidien, 1, 3, 5, 8, 9. Self-employed, 1, 3, 5, 8, 9. Transdel Pharmaceuticals, 1, 3, 5, 8, 9. P. Fuller: Covidien, 3.

**ACR Poster Session B**

**Osteoporosis and Metabolic Bone Disease: Clinical Aspects and Pathogenesis**

Tuesday, November 9, 2010, 9:00 AM–6:00 PM

956

**Adenosine A2A Antagonist ZM241385 Increases Osteoblast Differentiation and Function In Vitro.**

Louisa Ziglar* and Bruce N. Cronstein. 1 New York Univ Med Ctr, New York, NY, 2NYU Medical Center, New York, NY

**Introduction:** Adenosine, a potent endogenous physiological mediator, regulates a wide variety of physiological processes via interaction with one or more of four G protein-coupled receptors (A1, A2a, A2b, and A3), expressed on many cell types. Because we have reported that adenosine receptors affect more of four G protein-coupled receptors (A1, A2a, A2b, and A3), expressed and function in vitro.

**Methods:** Murine MC3T3-E1 Osteoblast precursor cells were cultured for 12 or 21 days in alpha-MEM media with vitamin C and beta-glycerophosphate enrichment. Adenosine receptor A1 and A2a agonist and antagonist were added individually at a concentration of 10−6 mg/ml. To evaluate osteoblast differentiation, alkaline phosphatase (ALP) assay activity was performed on day 12. Alizarin red activity was measured on day 21 to evaluate osteoblast function. Experiment was performed in triplicate.

**Results:** Our preliminary results report no significant difference in osteoblast differentiation using A1 receptor treatment and increased differentiation and function under the presence of adenosine A2A antagonist ZM241385. Alizarin red activity showed no significant difference from control in the presence of A1 receptor agonist or antagonist where the A2A antagonist showed increased activity by 71% (p<0.001 n=1). Cells treated with ZM241385 showed an increase in ALP activity by 53% (p=0.19 n=1).

**Discussion:** Adenosine receptors are targets for a variety of drugs, including anti-inflammatory drugs (e.g. adenosine mediates the anti-inflammatory effects of low-dose methotrexate in the treatment of Rheumatoid Arthritis). Other indications are currently under study in pre-clinical and clinical studies. Our results suggest that adenosine A2A receptors may be potential targets for the treatment of bone disease as well.


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**Algorithm for Using a Bone Formation Marker PINP To Monitor the Response to Teriparatide (TPTD) in Patients with Glucocorticoid-Induced Osteoporosis (GIO).**

Nancy E. Lane,1 Kyoungha Seo,1 Margaret Warner2 and John H. Krege.3 1 Eli Lilly, Indianapolis, IN, 2Univ of California at Davis, Hilshborough, CA

Biochemical markers of bone turnover may provide useful information about response to a treatment. A least-significant change algorithm using the serum concentration of N-terminal type I procollagen propeptide (PINP), has been proposed to aid in the management of patients with postmenopausal osteoporosis treated with TPTD (Eastell et al. Curr Med Res Opin 2006;22: 61-6). The purpose of this post-hoc analysis was to assess this approach in GIO patients treated with teriparatide (TPTD). Patients who took at least 5 mg of prednisone or equivalent for at least 3 months were treated for up to 36 months with TPTD 20 g/day. Patients with a baseline and postbaseline (1 and 6 months) PINP were included in this analysis. Responders were defined as patients with an increase in PINP of >10 g/L (least significant change) at 1 or 6 months. At 1 month, the signal-to-noise ratio for PINP was 3.0 compared with 1.2 for bone-specific alkaline phosphatase (bone ALP), 1.4 for C-terminal telopeptide of type I collagen (CTX), 3.2 for osteocalcin (OC), and 2.0 for C-terminal type I procollagen propeptide (PICP). Of the TPTD-treated patients, 88% were responders. PINP responders had significantly greater increases in bone ALP, PICP, and OC (p<0.03) at 1 month, compared with nonresponders. In summary, PINP responders had greater than two-fold larger mean percentage increases from baseline in lumbar spine (LS) bone mineral density (BMD) at 12, 24, and 36 months versus non-responders. In patients with GIO, PINP had a high signal-to-noise ratio and most patients treated with teriparatide had a significant increase in PINP. Patients who had a significant increase in PINP had a significantly greater increase in BMD than the small number of patients who did not have a significant increase in PINP. The PINP findings in patients with GIO treated with TPTD in this study were similar to previously reported results in postmenopausal women with osteoporosis.

**Lumber Spine BMD gain [mean ± SE (n)]**

<table>
<thead>
<tr>
<th>PINP</th>
<th>12 months</th>
<th>24 months</th>
<th>36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 10 ug/L</td>
<td>8.2% ± 0.73 (n=70)</td>
<td>11.4% ± 1.00 (n=60)</td>
<td>13.3% ± 1.21 (n=55)</td>
</tr>
<tr>
<td>&lt; 10 ug/L</td>
<td>3.6% ± 1.13 (n=10)</td>
<td>5.1% ± 1.37 (n=9)</td>
<td>4.6% ± 3.19 (n=7)</td>
</tr>
</tbody>
</table>

*p-value* 0.023 0.021 0.018

*Responders vs non-responders based on Wilcoxon rank-sum test

**Values are mean percentage change from baseline in LS BMD SE= standard error.

**Disclosure:** N. E. Lane: Lilly USA, LLC, 8. K. Seo: Lilly USA, LLC, 3. M. Warner: Lilly USA, LLC, 1, 3. J. H. Krege: Lilly USA, LLC, 1, 3.

958

**Anti-Hypertensive Therapy and Bone Mineral Density: Analysis in a Population-Based U.S. Sample.**

Mitosuyo Kinjo*, Soko Setoguchi and Daniel Hal Solomon. 1 Brigham and Women’s Hospital, 2Brigham and Womens Hospital, Boston, MA, *Okinawa Chubu Hospital, Japan

**Background:** Several prior studies suggest that beta-blockers and angiotensin converting enzyme inhibitors (ACE-I) may increase bone mineral density (BMD) in humans. Many studies have examined fracture risks associated with anti-hypertensive treatments. We examined BMD in subjects using beta-blockers, ACE-I, angiotensin receptor blockers (ARBs), calcium, thiazide diuretics and calcium channel blockers (CCBs), and BMD in a representative U.S. population-based sample from the National Health and Nutrition Examination Survey 1988–1994 (NHANES III) and 1999–2004.

**Methods:** We identified adult subjects 20 years and older using beta blockers, ACE-I, ARBs, calcium, thiazide diuretics, or CCBs who underwent dual energy X-ray absorptiometry scanning in NHANES. Femoral neck BMD available in NHANES III and lumbar spine BMD in NHANES1999–2004 were examined. Subjects on beta blockers, ACE-I or thiazide monotherapy were compared to CCB users in adjusted linear regression models that included known demographic, anthropometric, and medical risk factors for osteoporosis.

**Results:** The mean age of study subjects was 65 years old. Among subjects with BMD measured, 2,532 used these medications in NHANES III and 1,224 used them in NHANES 1999–2004. In multiple regression analyses (see Table), ACEI use was associated with higher lumbar spine BMD in both women (P = 0.03) and men (P = 0.037). Thiazide use was
associated with higher BMD at femoral neck BMD in women, although statistically not significant. Beta-blocker use was only significantly associated at the lumbar spine BMD (P = 0.027) in women. BMD did not differ between ARB and CCB users.

Table 2-1. Adjusted BMD (least square mean) among female subjects in NHANES 1999–2004 and NHANES III

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD Site</td>
<td>P-value ACEI</td>
<td>P-value Thiazide</td>
<td>P-value ARB</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>0.05</td>
<td>0.3</td>
<td>0.09</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.0</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Total Hip</td>
<td>0.1</td>
<td>0.6</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*age, race, bmi, smoking, and estrogen use only for female

Table 2-2. Adjusted BMD (least square mean) among male subjects in NHANES 1999–2004 and NHANES III

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD Site</td>
<td>P-value ACEI</td>
<td>P-value Thiazide</td>
<td>P-value ARB</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>0.1</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.0</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Total Hip</td>
<td>0.1</td>
<td>0.6</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Conclusions: Bone mineral density appears higher in users of ACE-I and thiazides than CCB users among adults, but a causal relationship is not clear.

Disclosure: M. Kinjo: None; S. Setoguchi: None; D. H. Solomon: None.

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Bone Density Following Long-Duration Spaceflight and Recovery. Shreyasee Amin, Sara Achenbach, Elizabeth Atkinson, L. Joseph Melton, Sundee Khosla and Jean Sibonga. Mayo Clinic, NASA-Johnson Space Center

Background: Rapid bone loss in the weight-bearing skeleton is well recognized during microgravity exposure in long-duration spaceflight, but the implications on long-term bone health remain unclear. How bone mineral density [BMD] in US crew members serving on long-duration missions in space [US crew] compare with what would be expected had they not been exposed to microgravity, is unknown.

Methods: We therefore examined the observed changes in BMD (g/cm²) among 28 US crew (immediately post-flight and following ~12 months recovery) relative to comparable age- and gender-expect changes derived from 345 men (age range at baseline: 22–90 yrs) and 351 women (range: 21–93 yrs) representing an age-stratified, random sample of the adult community population. BMD measurements (Hologic QDR 2000) were made at the total hip, lumbar spine, ultradistal and midshaft radius, and total body (sites also measured in US crew). Men were measured at baseline, 2, and 4 yrs; women were measured at baseline, 1, 2, and 4 yrs. Linear mixed effects models were used to predict follow-up BMD using baseline BMD, age, gender, and follow-up time, adjusting for the fact that most people were measured more than once. Models including body mass index (BMI) or lean mass were also considered. In US crew (24 men, age range at pre-flight scan: 36–53 yrs; 4 women, age: 41–53 yrs), BMD was measured pre-flight, immediately post flight and at ~12 months post-flight using Hologic QDR 2000, QDR 4500 and Discovery scanners. The majority had pre- and post-flight BMD on similar machines. Immediate post-flight BMD was performed a median of 6 (range: 3–33) days after return, with a median flight duration of 167 (range: 95–215) days. 22 men and 4 women had a scan within 6–18 months post-flight; median days from landing to ~12 months scan was 376 (range: 184–534) days.

Results: Using their age, gender, pre-flight BMD and follow-up time, post-flight BMD values for US crew were predicted based on the model developed from the community sample. The predicted and observed BMD and rates of change immediately and ~12 month post-flight for US crew are presented (see Table). Findings were similar using prediction models which included BMI or lean mass. Due to microgravity exposure, the observed immediate post-flight BMD at all sites was significantly lower than predicted. However, at ~12 months post-flight, BMD values at most sites in US crew were still lower than would be expected had they not been exposed to microgravity.

<table>
<thead>
<tr>
<th>BMD Site</th>
<th>Mean BMD (g/cm²)</th>
<th>% change in BMD per month</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Post Flight</td>
<td>12 Month Post Flight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted</td>
<td>Observed</td>
<td>Predicted</td>
<td>Observed</td>
</tr>
<tr>
<td>Total Hip</td>
<td>1.02</td>
<td>1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spine</td>
<td>0.78</td>
<td>0.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ultradistal Radius</td>
<td>0.51</td>
<td>0.51</td>
<td>0.02</td>
</tr>
<tr>
<td>Mid Shaft Radius</td>
<td>0.71</td>
<td>0.66</td>
<td>0.02</td>
</tr>
<tr>
<td>Total Body</td>
<td>1.46</td>
<td>1.43</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Conclusion: These findings have implications on potential long-term adverse effects to bone health of US crew serving on long-duration spaceflight missions.

Disclosure: S. Amin: None; S. Achenbach: None; E. Atkinson: None; L. J. Melton: None; S. Khosla: None; J. Sibonga: None.

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Bone Geometry Parameters among Black and White Women with SLE. Jimmy D. Adele, Diane L. Kamen, Kelly J. Hunt, Gary S. Gilkeson and Rosalind Ramsey-Goldman. Med Univ of South Carolina, Charleston, SC, Medical University of South Carolina, Charleston, SC, Northwestern University, Chicago, IL

Purpose: Recent studies reported an increased prevalence of osteoporotic fractures among patients with systemic lupus erythematosus (SLE). While the prevalence of low bone mineral density (BMD) is higher among these subjects than the general population, this finding does not fully account for increased fracture rate. The purpose of this study was to determine if SLE status was associated with bone geometry parameters that predict increased skeletal fragility among black and white women.

Methods: Study subjects included 153 women who had participated in the Study of Lupus Vascular and Bone Long Term Endpoints (SOLVABLE) (69% white, 31% black) and 4920 controls from the third National Health and Nutrition Examination Survey (NHANES III) (59% white, 41% black). Dual energy x-ray absorptiometry (DXA) scans from SOLVABLE (Hologic DQR-4500), and NHANES III (Hologic DQR-1000) were analyzed using the Hip Structure Analysis (HAS) program to derive BMD and bone geometry parameters (section modulus, buckling ratio, outer diameter and cross-sectional area) at the femoral neck, intertrochanter and proximal femoral shaft. Linear regression was used to examine differences (SLE vs. NHANES) in bone density and geometry in blacks and whites after adjusting for age and body mass index.

Results: NHANES participants were older than SLE subjects, and were more likely to smoke. We detected significant BMD and bone geometry differences (SLE vs. non-SLE, black and white subjects) at the intertrochanter as follows and per table below:

1) BMD (g/cm²) was lower among both black and white SLE subjects (0.80 vs. 0.94, p<0.0001 and 0.82 vs. 0.86, p<0.01 respectively).

2) BMD reduction was associated with reductions of cross sectional area (cm²) among black and white SLE subjects (3.76 vs. 4.61 and 4.05 vs. 4.35 respectively, p<0.0001), suggesting that low BMD among SLE patients was a result of reduced total bone quantity.

3) Section modulus (cm³) was also reduced among SLE subjects in both races (3.03 vs. 3.81, p<0.0001 and 3.54 vs. 3.76, p<0.01 respectively), suggesting reductions in bending resistance among SLE patients.

4) Reductions in section modulus were accompanied by reductions in outer skeletal diameter (cm) among both black and white SLE subjects (4.98 vs. 5.20, p<0.0001 and 5.19 vs. 5.31, p<0.001, respectively), suggesting reduced subperiosteal apposition.

5) Finally, buckling ratio was increased among black patients vs. NHANES (9.49 vs. 8.58, p<0.01), suggesting increased tendency for local cortical buckling among black patients at this location. Similar findings were detected at the narrow neck and proximal shaft.
Table. Age and BMI-adjusted mean (95% CI) bone mineral density and bone geometry parameters stratified by race and SLE status.

<table>
<thead>
<tr>
<th>NHANES</th>
<th>Whites</th>
<th>SLE</th>
<th>Blacks</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=2156</td>
<td>n=105</td>
<td>n=2044</td>
<td>n=48</td>
<td></td>
</tr>
<tr>
<td>Intertrochanter Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td>0.86 (0.86, 0.87)</td>
<td>0.82 (0.79, 0.85)§</td>
<td>0.94 (0.93, 0.94)</td>
<td>0.80 (0.75, 0.84)‡</td>
</tr>
<tr>
<td>Sectional Area (cm²)</td>
<td>3.76 (3.74, 3.79)</td>
<td>3.54 (3.46, 3.68)¶</td>
<td>3.81 (3.78, 3.85)</td>
<td>3.03 (3.01, 3.24)‡</td>
</tr>
<tr>
<td>Width (cm)</td>
<td>5.31 (5.30, 5.32)</td>
<td>5.19 (5.13, 5.26)¶</td>
<td>5.20 (5.15, 5.22)</td>
<td>4.98 (4.89, 5.08)¶</td>
</tr>
<tr>
<td>BDM (g/cm²)</td>
<td>0.88 (0.87, 0.89)</td>
<td>0.83 (0.81, 0.85)¶</td>
<td>0.94 (0.93, 0.94)</td>
<td>0.80 (0.75, 0.84)‡</td>
</tr>
<tr>
<td>Cross Sectional Area (cm²)</td>
<td>4.35 (4.32, 4.37)</td>
<td>4.05 (4.01, 4.10)§</td>
<td>4.61 (4.58, 4.65)</td>
<td>3.76 (3.55, 3.97)‡</td>
</tr>
<tr>
<td>Width (cm)</td>
<td>5.25 (5.24, 5.26)</td>
<td>5.19 (5.13, 5.26)¶</td>
<td>5.20 (5.15, 5.22)</td>
<td>4.98 (4.89, 5.08)¶</td>
</tr>
</tbody>
</table>

Conclusion: Our study suggests that SLE is associated with BMD and bone geometry profiles that predict increased skeletal fragility among both black and white women. These skeletal differences probably result from the inflammatory nature of SLE and common therapies, especially steroids.

Disclosure: J. D. Alele: None; D. L. Kamen: None; K. J. Hunt: None; G. S. Gilkeson: None; R. Ramsey-Goldman: None.

961 Cardiovascular Disease Is Associated with Increased Bone Loss and Fracture Risk; A Systematic Review of the Association between Cardiovascular Disease and Osteoporosis. Debby den Uyl1, Mike T. Nurmohamed1, Lilian H. D. van Tuyl2, Hennie G. Raterman2 and Willem F. Lems2.

1Department Rheumatology/Jan van Breemen Institute, Amsterdam, The Netherlands, 2Department Rheumatology/Universiteit Medical Centre, Amsterdam, The Netherlands

Background: Both cardiovascular disease and osteoporosis are important causes of morbidity and mortality in the elderly. The co-occurrence of cardiovascular disease and osteoporosis prompted us to review the evidence of an association between cardiovascular (CV) disease and osteoporosis and potential shared common pathophysiological mechanisms.

Methods: A systematic literature search (Medline-Pubmed and Embase) was conducted to identify all clinical studies that investigated the association between cardiovascular disease and osteoporosis. Relevant studies were screened for quality according to guidelines as proposed by Dutch Cochrane Centre (1) and evidence was summarized.

Results: Seventy-one studies were included in this review. Due to a large heterogeneity in study population, design and outcome measures a formal meta-analysis was not possible. Six of the highest ranked studies (mean n=2000) showed that individuals with prevalent CV disease had higher risk for increased bone loss and fractures during follow-up compared to persons without CV disease (range of reported risk: HR 1.5; OR 2.3–3.0). The largest study (n=31936) reported an over 4 times higher risk in women and over 6 times higher risk in men. There is moderate evidence that individuals with low bone mass had higher CV mortality rates and incident CV events than subjects with normal bone mass (risk rates 1.2–1.4). Although the shared common pathophysiological mechanisms are not fully elucidated, the most important factors that might explain this association appear to be age, estrogen deficiency and inflammation.

Conclusions: The current evidence indicates that individuals with prevalent CV disease are at increased risk for bone loss and subsequent fractures. Hence, evaluation of bone mass could be considered in patients with prevalent CV disease. Presently no firm conclusions can be drawn to which extent low bone density might be associated with increased cardiovascular risk.

References:

Disclosure: D. den Uyl: None; M. T. Nurmohamed: None; L. H. D. van Tuyl: None; H. G. Raterman: None; W. F. Lems: None.

962 Cholecalciferol High Dose Supplementation Should Be Preferred in Rheumatic Patients Independently to the Presence of an Autoimmune Disease. Mattia Bellan1, Pier Paolo Sainaghi2 and Mario Pirisi2.

1Immuno-Rheumatology Outpatient Unit, DMCS, “A. Avogadro” University and IRCAD (Interdisciplinary Research Center of Autoimmune Diseases), Novara, Italy, 2Immuno-Rheumatology Outpatient Unit, DMCS, “A. Avogadro” University and IRCAD (Interdisciplinary Research Center of Autoimmune Diseases), Novara, Italy, 3Immuno-Rheumatology Outpatient Unit, DMCS, “A. Avogadro” University, Novara, Italy

Introduction: Hypovitaminosis D is common in rheumatic patients, but the response to different supplementation regimens in this setting has not been fully investigated. We aimed to compare two different supplementation regimens of cholecalciferol in patients with rheumatic diseases.

Methods: The clinical records of 832 consecutive adult patients attending a tertiary level immune-rheumatology clinic from June 2007 to May 2010 were evaluated retrospectively. We included all patients diagnosed to have either an autoimmune rheumatic disease (ARD: rheumatoid arthritis, spondyloarthritis, polymyalgia rheumatica and other connective tissue diseases) or a non-autoimmune rheumatic disease (NARD: osteoarthritis, osteoporosis), who received a) a single 100.000 IU oral dose followed by a 800–1000 IU daily dose of cholecalciferol (loading treatment-LT) or b) standard oral supplementation (ST: 800–1000 IU daily), both regimens maintained for ≥6 months. We excluded patients with renal failure, primary hyperparathyroidism, prior fracture and those already receiving vitamin D supplementation. Plasma 25(OH) vitamin D (VITD) concentration together with other clinical data were recorded at baseline and after 6 months of treatment; due to its non-normal distribution (test Shapiro-Wilk, p<0.05), a non-parametric statistical analysis was chosen.

Results: The study population included 116 patients, 81 with ARD and 35 with NARD; 86 received the ST, and 32 the LT (2 of them after ST). Plasma VITD concentrations were suboptimal both in NARD (median [IQR], 27.2 [12.7–47.4] nmol/L) and ARD (30.0 [17.2–43.4] fMann-Whitney U test, p=ns). After receiving ST, plasma VITD increased similarly in the two groups (ARD: 56.4 [40.7–79.4], NARD: 60.4 [48.9–75.1], p=ns), with only 27.9% [19.5–38.2 95%CI] of patients able to reach the reference value of 75 nmol/L. Among patients who received LT, VITD concentrations also increased similarly in ARD (71.1 [53.4–81.1]) and NARD (72.9 [60.4–79.4]), but a higher proportion of patients (43.8% [28.1–60.8]) reached a plasma VITD concentration ≥75 nmol/L. Indeed, plasma VITD increments from baseline were significantly higher after LT (40.2 [27.5–58.8] than following ST (22.5 [3.7–45.9], p<0.009), again without differences between ARD and NARD (ST: ARD 22.7 [3.7–52.2] vs NARD 22.2 [4.2–47.7] p=ns; LT ARD 37.2 [29.5–56.7] vs NARD 46.7 [13.0–64.9] p=ns).

Conclusions: Hypovitaminosis D is common in patients with rheumatic diseases with and without autoimmune features. A LT supplementation regimen is more efficient than ST in increasing VITD plasma levels, with higher rates of VITD normalization. Finally, following Vitamin D supplementation plasma VITD normalization is achieved similarly in ARD and NARD patients.

Disclosure: M. Bellan: None; P. P. Sainaghi: None; M. Pirisi: None.

963 Differences in the Observed Rate of Hip Fracture in Male and Female Patients Diagnosed with Osteoarthritis or Ankylosing Spondylitis Compared with the Expected Based on the General Population Seeking Health Care. Martin Englund1, Jonas Franklin2 and Ingemar F. Pettersson1.

1Lund University Hosp, Lund, Sweden, 2Musculoskeletal Sciences, Depart- ment of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, 3University Hospital, Akureyri, Iceland

Background: There are conflicting reports of the association between hip osteoarthritis (OA) and hip fracture, and little is known of the association between knee OA or ankylosing spondylitis (AS) and hip fracture.

Objective: To study the rate of hip fracture in male and female OA and AS patients compared with the general population seeking health care.

Methods: Cohort design; Sweden has publicly funded health care with all in- and outpatient health care consultations registered by the patient’s personal identifier. We studied residents aged ≥20 yrs of southern Sweden by 1 Jan 2004 who consulted a physician at least once the following 4 calendar years (n=761,210 of total adult population n=879,624), thus being captured with diagnostic codes in the Skane Health Care Register (SHCR). We identified all residents with an ICD-10 code given by a physician for: hip OA (M16), n=11,901, mean age 69.6 yrs, 57.1% women; knee OA (M17), n=23,866, mean age 66.3 yrs, 58.8% women; AS (M45), n=1,374, mean age 53.1 yrs, 39.8% women. To obtain observed hip fracture rates we calculated the person-time for each individual, from the day of his/her first OA or AS diagnosis within the study period until the day of first hip fracture (ICD-10 codes: C19-ST2, DMCS or ST2.2) or until another censoring event (death, relocation, or end of study period by cross-referencing with the population register). The person-time for each subject in the general population aged ≥20 yrs seeking health care (n=761,210, the background population) started to count by his/her first diagnostic code (any ICD-10 code) in the SHCR within the period until first hip fracture or another censoring event (in an
identical fashion as for OA and AS patients). We then calculated the standardized fracture-rate ratio (SFR) by dividing the observed rate of hip fracture in OA or AS patients by their expected rate (based on the age- and gender-specific rates in the background population). Thus, a $SFR > 1$ equals an increased rate of hip fracture and $SFR < 1$ equals a reduced rate of hip fracture compared with the background population. In a sensitivity analysis for estimates in OA patients, we excluded all residents (in both the OA cohort and the background population) being registered with total hip replacement within the study period.

**Results:** In female knee OA patients the hip fracture rate was significantly reduced by about 20%, but not in men. No significant SFRs were found for hip OA patients, neither men nor women (figure). In AS we found the SFR increased by about 70% for both men an women. However, due to the relatively rare AS diagnosis and low number of fractures observed, the 95% CIs were large and included one (the SFR for men and women combined was $1.68$, 95% CI $0.94, 2.77$).

**Conclusion:** In a comprehensive population-based dataset over 4 years, we observed a 20% decreased rate of hip fracture in female knee OA patients compared to the expected, while there was an 70% increased rate in AS patients.

**Disclosure:** M. Englund: None; J. Franklin: None; I. F. Petersson: None.

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**Effect of Oral Ibandronate on Bone Microarchitecture in Women with Osteopenia—A Randomized Placebo-Controlled Trial.** Roland Chapurlat, Michel Laroche, Thierry Thomas, Stéphanie Rouanet, Pierre D. Delmas, and Marie-Christine de Vernejoul. ICHU St Etienne, Saint Etienne, France; INSERM U831, Université de Lyon, Hôpital E. Herriot, Lyon, France; Lariboisière Hospital, Paris, France; Pôle Institut Locomoteur Hôpital Purpan, Toulouse, France; Roche France, Neuilly, France

Bone microarchitecture is associated with bone fragility, but little is known about the effects of osteoporosis treatments on microarchitecture. The aim of this study was to examine the effect of ibandronate on bone microarchitecture measured non invasively with peripheral high resolution quantitative computed tomography (HR-pQCT).

We have conducted a randomized placebo-controlled trial among 148 women with osteopenia. Patients received either oral 150 mg monthly ibandronate or an identical placebo, over 24 months. Bone microarchitecture was assessed at baseline, 6, 12 and 24 months, using HR-pQCT (XtremeCT, resolution 82 mm, Scanco, Switzerland) at distal radius and tibia; areal bone mineral density (aBMD) was measured with DXA at the spine, hip and radius. The primary endpoint was the trabecular bone volume (BV/TV) at 12 months at distal radius; the secondary endpoints were volumetric BMD (vBMD) at the trabecular and cortical envelopes, trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp) and cortical thickness (Ct.Th). The analysis was intent to treat. All the parameters were analyzed using an analysis of covariance model including baseline value as covariate.

The baseline variables did not differ between those women on ibandronate (n = 72) and those on placebo (n = 76). At 12 months, there was no significant difference in BV/TV at the radius between women on ibandronate $(0.108 \pm 0.025)$ and placebo $(0.105 \pm 0.029)$, $p = 0.25$. Similarly, there was no significant difference in other radius trabecular and cortical microarchitecture parameters at 12 and 24 months. In contrast, at the tibia, cortical vBMD in the ibandronate group was significantly greater than in the placebo group as soon as 6 months $(810.7 \pm 50.7$ vs $806.9 \pm 69.1, p=0.002)$ and also at 12 $(813.1 \pm 50.0$ vs $807.3 \pm 66.9, p<0.001)$ and 24 months $(816.3 \pm 50.3$ vs $806.5 \pm 68.1, p<0.001)$, in parallel with better Ct.Th at 6 $(0.91 \pm 0.22$ vs $0.89 \pm 0.25, p<0.001)$, 12 $(0.91 \pm 0.21$ vs $0.90 \pm 0.25, p=0.004)$ and 24 months $(0.92 \pm 0.22 vs 0.87 \pm 0.25, p<0.001)$. Tibial trabecular parameters, however, remained unaltered at 6, 12 and 24 months in treated women compared with placebo. In the ibandronate group, areal BMD was significantly increased at the hip and spine at 12 and 24 months, and significantly superior to placebo only at 24 months at the radius.

We conclude that 12 months of treatment with ibandronate in women with osteopenia did not affect trabecular bone microarchitecture, but improved cortical vBMD at the tibia at 12 and 24 months, as well as Ct.Th at the tibia, possibly corresponding to decreased cortical porosity. This might be beneficial regarding protection against non vertebral fracture. The tibia may be a better bone site to evaluate the effects of antiresorptive agents with HR-pQCT.

**Disclosure:** R. Chapurlat: Roche, 2; M. Laroche: Roche, 2; T. Thomas: Roche, 2; S. Rouanet: Roche, 3; P. D. Delmas: None; M.-C. de Vernejoul: Roche, 2.
Fracture Epidemiology among a Cohort of HIV-Infected Adults in the UK: An Epidemiologic Study. Karen Walker-Bone, Reshad Malik, Martin Fisher, Yvonne Gilleece and Amanda Samarawickrama. 1 Brighton & Sussex Medical School, Brighton, East Sussex, United Kingdom, 2Brighton & Sussex University Hospitals NHS Trust

Background: HIV is a global pandemic. The devastating mortality associated with HIV infection has been dramatically reduced by highly-active anti-retroviral therapies (HAART). However, this has led to increasing numbers of HIV-infected patients living with comorbidities including metabolic diseases. Low bone mass and osteoporosis were implicated as consequences of HAART approximately 10 years ago but fracture data in HIV-infected populations are rare.

Methods: A well-characterised cohort of HIV-infected adults attending one UK centre for outpatient care was surveyed. Trained nurses administered a questionnaire which enquired about demographic factors, lifestyle factors, diet and exercise, exposure to glucocorticoids and other drugs affecting bone mineral and HIV factors. Exposure to HAART, stage of HIV infection and status of viral load, CD4 counts etc were collated.

Results: In total, 1050 HIV infected adults were surveyed. 859 (82%) responded. Mean age of respondents was 42.7 (range 19–77) years. 87% were Caucasian and 90% were male (predominant mode of transmission of infection: MSM). Mean duration of HIV infection was 6 years and 76% were current users of ARVs. Overall, 125 subjects (119 (15%) men and 6 women (7%) reported 200 fractures. 65 respondents had fractured their distal forearm and 20 their radius and 2 vertebral fractures. In total, 57% of the 200 fractures occurred under age 25 years with the peak age 7–12 years. However, 33 fractures (26%) occurred among respondents aged >40 years and 8 (24%) among those aged >50 years. The second peak of fractures occurred at the distal forearm (n=6, mean age 48.2 years) and there was a hip fracture (age 46 years). 15% of those who sustained a fracture at aged >40 years had been exposed to oral glucocorticoids as compared to 9% of those who had not fractured.

Conclusion: Our results suggest a traditional bimodal distribution of fracture in this population. The first peak occurs in childhood/adolescence and is maximal aged 7–12 years. However, our results suggest a second peak of fracture aged >40 years at sites with a high proportion of trabecular bone (distal forearm, hip, vertebrae). This peak is seen much earlier than in non-HIV infected adults but affects similar sites to those of traditional osteoporotic fractures. Although low bone mass has been documented widely in prevalent HIV infection, fracture has not. Our data suggest that fracture may be a consequence of low bone mass in HIV infection. If these data are replicated, HIV may become one of the most important causes of secondary osteoporosis worldwide.

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Fracture Incidence, Quality of Life and Back Pain in Women with Osteoporosis and Concomitant Glucocorticoid Use Treated with Teriparatide: 36 Month Results from the European Forsteo Observational Study (EFOES). Willem Lems1, Bente Langdahl2, Osten Ljunggren3, Anna-bel Barrett4, Dimitrios Karras5, James Bernard Walsh6, Astrid Fahrleitner-Pammer7, Gerald Rajzbaum8, Clare Barker9, Franz Jakob1 and Fernando Marin10. 1Julius-Maximilians-Univ, Würzburg, Germany, 2Lilly Research Ctr., Windlesham, UK, 3Med Univ, Graz, Austria, 4St James’s Hosp Trinity College, Dublin, Ireland, 5St Joseph Hosp, Paris, France, 6Univ Hosp, århus, Denmark, 7Univ Hosp, Uppsala, Sweden, 8Veterans Admin Hosp, Athens, Greece, 9VU Univ Hosp, Amsterdam, Netherlands

Aim: To describe clinical fractures (Fx), back pain and health-related quality of life (HRQoL) outcomes in postmenopausal women with osteoporosis and glucocorticoid (GC) use, treated with teriparatide (TPTD) for up to 18 months and followed-up for a further 18 months in EFOES.

Methods: Prospective, observational study in 8 EU countries. Data on incident clinical vertebral and non-vertebral Fxs were collected, back pain assessed using a 100mm VAS and questionnaire, HRQoL measured using EQ-5D. Changes in women with incident Fx rates over time analysed using logistic regression with repeated measures (RM). Changes from baseline in back pain VAS & EQ-VAS analysed using an RM model.

Results: Of 1581 EFOES patients with follow-up data, 294 (18.6%) were concomitantly treated with GC. At baseline, GC treated patients had a mean (SD) age of 69.9 (8.2) years and 75.1% had ≥2 Fxs after age 40. Post-TPTD follow-up data were available for 156 patients. Of these patients, 47.4% had rheumatoid arthritis at baseline, and 95.5% received antiresorptive medication after TPTD, including any bisphosphonate (61.5%). During the 36 mths study, 49 (16.7%) women sustained at least one incident Fx, compared with 159 (12.4%) in the non-GC group. There was an 89% decrease in the odds of fracture in the 30–36 mth period compared with 0–6 mths (p<0.028). An increase in HRQoL was seen over 18 mths of TPTD treatment (p<0.001) and was maintained over the 18 mth post-TPTD follow-up. At all timepoints relative to baseline there was a significant reduction in adjusted mean back pain VAS (p<0.001).

Table. Health-related quality of life and back pain in GC treated patients

<table>
<thead>
<tr>
<th>GC treated patients n = 294</th>
<th>Baseline</th>
<th>18 mths</th>
<th>36 mths</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-SD Health State Value (median, IQR)</td>
<td>0.52 (0.02, 0.69)</td>
<td>0.69 (0.52, 0.80)</td>
<td>0.69 (0.52, 0.81)</td>
</tr>
<tr>
<td>EQ-VAS mean (SD)</td>
<td>48.8 (22.19)</td>
<td>63.5 (22.14)</td>
<td>64.8 (24.16)</td>
</tr>
<tr>
<td>Back pain*</td>
<td>n = 291</td>
<td>n = 232</td>
<td>n = 174</td>
</tr>
<tr>
<td>Every day/almost every day</td>
<td>63.9%</td>
<td>26.3%</td>
<td>24.7%</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>n = 276</td>
<td>n = 191</td>
<td>n = 137</td>
</tr>
<tr>
<td>VAS (mm) mean [SD]</td>
<td>58.4 (27.38)</td>
<td>32.8 (26.06)</td>
<td>31.3 (27.62)</td>
</tr>
</tbody>
</table>

Conclusion: Postmenopausal women with severe osteoporosis receiving GCs who were prescribed TPTD in a routine setting had a significant reduction in back pain and improvement in HRQoL during 18 mths of TPTD treatment. These outcomes were maintained for at least 18 mths after TPTD discontinuation. The results should be interpreted in the context of a non-controlled observational study and the limited number of women taking GCs in this cohort.

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Fracture Risk Assessment and Osteoporosis Treatment Disparities in 4027 Japanese Patients with Rheumatoid Arthritis. Takefumi Furuya1, Takayuki Hosoi2, Eisuke Inoue3, Atuo Taniguchi3, Shigeki Momohara4 and Hisashi Yamanaka5. 1Department of Clinical Research and Development, National Center for Geriatrics and Gerontology, 2Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan, 3Institute of Rheumatology, Tokyo Women’s Medical University, 4Tokyo Women’s Medical University, Shinjuku-ku, Tokyo, Japan

Purpose: We previously reported that osteoporosis appeared to be undertreated in Japanese patients with rheumatoid arthritis (RA) (J Rheumatol 2007). Using clinical risk factors from the World Health Organization (WHO) Fracture Risk Assessment (FRAX) tool and recommendations from the National Osteoporosis Foundation (NOF), we evaluated fracture risk and osteoporosis treatment in a cohort of Japanese RA patients.

Methods: Among patients participating in a single-institute, prospective observational cohort study of Japanese RA patients, namely IRORRA (Institute of Rheumatology Rheumatoid Arthritis), 4027 (>40 years of age, 84% female, median age 61 yrs) responded to questions related to fracture risks in October or November 2008. The WHO-FRAX tool without bone mineral density estimated 10-year hip fracture risk and 10-year risk of a major osteoporosis fracture. Multivariable logistic regression evaluated the association between taking any osteoporosis medications and fracture risk, controlling for potential confounders.

Results: Among women (n = 3376), 100% and 82% ≥70 years of age (n = 700), 56% and 23% 60–69 years of age (n = 1252), 5% and 2% 50–59 years of age (n = 933), and 0% and 0% 40–49 years of age (n = 491) were identified as having a 10-year hip fracture risk ≥3% and a 10-year risk of a major osteoporosis fracture ≥20%, respectively. Among men (n = 651), 93% and 14% ≥70 years of age (n = 176), 26% and 0.4% 60–69 years of age (n = 233), 0% and 0% 50–59 years of age (n = 171), and 0% and 0% 40–49 years of age (n = 71) were identified as having a 10-year hip fracture risk ≥3% and a 10-year risk of a major osteoporosis fracture ≥20%, respectively. Multivariable models identified corticosteroid use (odds ratios (OR) 1.89, 95%
Health Care Utilization Following a Fracture: Global Longitudinal Study of Osteoporosis in Women (GLOW). George Ioannidis1, Jonathan D. Adachi2, Laura Pickard3, Roland Chapurlat4, Kenneth G. Saag5, Stuart L. Silverman1, Julie Flahive6 and Stephen Gehlbach6. 1Cedars-Sinai Medical Center, University of California Los Angeles, Beverly Hills, CA, 2McMaster University, Hamilton, ON, 3Denver CO VA Medical Center, Denver, CO, 4Iowa City IA VA Medical Center, Iowa City, 5Boston MA VA Medical Center, Boston, MA, 6University of Alabama-Birmingham, Birmingham, AL.

Background: The consequences of fractures are dramatic, including reduced quality of life, and increased mortality and health care costs. Given the high prevalence and negative consequences of fragility fractures resulting from osteoporosis, it is important that health care services are used efficiently to reduce the burden of fracture. However, there is a lack of data regarding the relationship among various fracture types and health care service utilization. The purpose of the study was to determine the health care utilization in women with various fracture types.

Method: The Global Longitudinal Study of Osteoporosis in Women (GLOW) is an observational, prospective study of women 55 years of age and older who were recruited from 723 primary physician practices across 10 countries (17 sites, 60,393 patients). Women were eligible to participate in GLOW if they were non-institutionalized and if they visited their practice within the past 2 years. Self-administered questionnaires were mailed (2.1 over-sampling of women ≥85) at baseline and at 12 months to all eligible patients. The current study was designed to determine the health care utilization among various fracture types using items from both the baseline and year 1 follow-up surveys. New fractures were divided into four categories (spine/neck, hip, wrist/hand, and upper arm/shoulder) and occurred during the first year of the study. Health care utilization included where the fracture was treated (doctor's office/clinic, hospital, rehabilitation centre or nursing home), if surgery was performed (yes/no), and the patient’s length of stay (days) at the treatment facility.

Results: A total of 120,115,358 and 158 new fractures occurred at the spine, hip, and wrist, respectively. The mean age (SD) and number of prior fractures (%) were 72.7 (9.1 yr) and 64 (54.2%) for spine, 75.7 (9.0 yr) and 56 (50.0%) for hip, 69.6 (8.9 yr) and 138 (38.9%) for wrist, and 72.1 (9.2 yr) and 60 (39.2%) for upper arm fracture participants. The table displays healthcare utilization for participants with fractures at 1 year.

<table>
<thead>
<tr>
<th>Healthcare utilization</th>
<th>Spine</th>
<th>Hip</th>
<th>Wrist</th>
<th>Upper arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture treated: n (%)</td>
<td>n = 120</td>
<td>n = 115</td>
<td>n = 358</td>
<td>n = 158</td>
</tr>
<tr>
<td>Office/clinic</td>
<td>83 (74.1)</td>
<td>62 (57.9)</td>
<td>245 (71.4)</td>
<td>104 (70.3)</td>
</tr>
<tr>
<td>Hospital</td>
<td>61 (55.5)</td>
<td>107 (96.4)</td>
<td>275 (79.7)</td>
<td>127 (84.1)</td>
</tr>
<tr>
<td>Rehabilitation center</td>
<td>13 (11.7)</td>
<td>66 (60.0)</td>
<td>55 (16.8)</td>
<td>43 (29.9)</td>
</tr>
<tr>
<td>Nursing home</td>
<td>3 (2.8)</td>
<td>17 (16.5)</td>
<td>3 (0.9)</td>
<td>7 (4.9)</td>
</tr>
<tr>
<td>Length of stay (days): mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>12 (13)</td>
<td>11 (12)</td>
<td>6 (12)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Rehabilitation centre</td>
<td>17 (18)</td>
<td>19 (19)</td>
<td>10 (19)</td>
<td>22 (29)</td>
</tr>
<tr>
<td>Nursing home</td>
<td>5 (6.4)</td>
<td>28 (25)</td>
<td>58 (42)</td>
<td>18 (32)</td>
</tr>
<tr>
<td>Preformed surgery: n (%)</td>
<td>16 (26.7)</td>
<td>94 (87.9)</td>
<td>97 (76.9)</td>
<td>41 (34.5)</td>
</tr>
</tbody>
</table>

Conclusions: In a large practice-based international cohort study, results reveal a wide range in the use of healthcare resources depending on the fracture type, and included where the fracture was treated, the length of stay at the treatment facility, and whether surgery was performed to treat the fracture. However, treatment strategies across countries may, in part, explain the variation in resource utilization observed among fracture types. These data may aid researchers and decision makers in determining policies that will optimize health care service utilization and improve patient outcomes.

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970 High Adherence with Bisphosphonate Therapy in US Veterans with Rheumatoid Arthritis. J. Stuart Richards1,2, Grant W. Cannon3, Candace L. Hayden4, Richard L. Amdur5, Ted R. Mikuls6, Andreas Reimold2, Liron Caplan2, Dannette S. Johnson2, Deana Lazaro1, Bogdan N. Cherascu4 and Gail S. Kerr10. 1Brooklyn NY VA Medical Center, Brooklyn, NY; 2Astellas Pharma Inc.; 3Denver CO VA Medical Center, Denver, CO, 4Iowa City IA VA Medical Center, Iowa City, 5Jackson MS VA Medical Center, Jackson, MS, 6Omaha NE VA Medical Center, Omaha, NE, 7Portland OR VA Medical Center, Portland, OR, 8Salt Lake City UT VA Medical Center, Salt Lake City, UT, 9Winston-Salem VA Medical Center, Winston-Salem, NC, 10Washington DC VA Medical Center, Washington, DC.

Background: Patients adherent with prescribed bisphosphonates have a reduction in fractures compared with noncompliant patients. Most reports on compliance with bisphosphonate therapy are for post menopausal osteoporosis with unclear relevance for other groups. We examined predictors of being prescribed a bisphosphonate, as well as predictors of patients who are adherent to therapy and remain on therapy.

Methods: Patient data from the Veterans Affairs Rheumatoid Arthritis (VARA) registry were available for analysis, and included demographics, features of disease severity and activity of rheumatoid arthritis (RA), osteoporosis, prior dual energy X-ray absorptiometry (DXA) testing, use of prednisone and site of enrollment (Dallas, TX; Denver, CO; Jackson, MS; Omaha, NE; Salt Lake City, UT and Washington, DC). Using data from the Veterans Affairs’ national Pharmacy Benefits Management (PBM) database for each bisphosphonate prescription, we determined predictors of bisphosphonate adherence and persistence. The time gap between the last prescribed refill and actual refill of the next prescription was calculated. Treatment course duration was defined as the time from the initial prescription until the expected refill date for the bisphosphonate prescription before a 90 day gap or discontinuation. The medication possession ratio (MPR), a measure of adherence, was calculated as the proportion of treatment time that the patient had drug available. Adherence was defined as an MPR ≥ 0.80. The persistence ratio on bisphosphonate therapy (PRBT), defined as duration of prescribed therapy from the time of the initial prescription until the last expected refill date of the final prescription. Factors associated with receipt of a bisphosphonate, adherence by MPR, and persistence by PRBT were determined by multiple regression analyses.

Results: Bisphosphonates were prescribed to 573 (41.5%) of 1382 VARA subjects. These subjects were mostly males (89.9%), with a mean age of 68.7 years, (± 10.3); 82.4% were Caucasian, 12.7% African American (AA), and 3.5% Hispanic. 258 subjects (45.3%) had a DXA; 66 (11.5%) had osteoporosis and 392 (70.4%) had been prescribed prednisone. Older subjects, females, non-Caucasians, prednisone use, DXA, a higher MDHAQ score and enrollment at Washington, DC site were predictive of receiving a bisphosphonate. The mean MPR was 0.69 ± 0.28 and only 271 (47.3%) subjects had MPR ≥ 0.80. Subjects from Omaha, NE had the highest rate of adherence (55.3%) while those from Washington, DC had the lowest (30%). MPR ≥ 0.80 was 50%, 35% and 25% for Caucasians, AA and Hispanics, respectively (p < 0.01). Gender, age, DXA, and use of prednisone were included where the fracture was treated, the length of stay at the treatment facility, and whether surgery was performed to treat the fracture. However, treatment strategies across countries may, in part, explain the variation in resource utilization observed among fracture types. These data may aid researchers and decision makers in determining policies that will optimize health care service utilization and improve patient outcomes.
not predictive of MPR. In multivariate analysis AA ethnicity was associated with low MPR.

The PRBT for bisphosphonates was 39.2 ± 31.4 months, and longer PRBT was associated with older age and enrollment at Omaha, NE; there was no association with clinical diagnosis of osteoporosis or performance of a prior DXA.

Conclusions: Adherence with bisphosphonates was greater in VARA cohort than most previous reports. Factors associated with higher adherence were Caucasian ethnicity and treatment site.

Disclosure: J. S. Richards: None; G. W. Cannon: None; C. L. Hayden: None; R. L. Amund: None; T. R. Mikuls: None; A. Reimold: None; L. Caplan: None; D. S. Johnson: None; P. Schwab: None; D. Lazard: None; B. N. Cherascu: None; G. S. Kerr: None.

Impact of Incident Clinical Vertebral Fractures on Back Pain Outcomes in Postmenopausal Women Who Participated in the FREEDOM Trial. Michael C. Nevitt1, Stuart L. Silverman1, Hema Viswanathan1, Yu-Ching Yang1, Andrea Wang1, Steven Boonen2, Sergio Ragi-Eis3, Patrice Fardellone3, Andreas Grauer1, Nigel Gilchrist1, Paul Lips1, Santiago Palacios3, Karel Pavelka6, Dennis Revicki10, James Simon13, David Macarios1 and Ethel Siris1. 1Amgen Inc., Thousand Oaks, CA, 2Bone Research Unit, Leuven University, Leuven, Belgium, 3Cedars-Sinai Medical Center, University of California Los Angeles, Beverly Hills, CA, 4CEDOES Diagnóstico e Pesquisa, Vitória (ES), Brazil, 5CGM Research Trust and Canterbury District Health Board, Christchurch, New Zealand, 6Charles University, Prague, Czech Republic, 7Columbia University Medical Center, New York, NY, 8Palacios Institute of Woman’s Health, Madrid, Spain, 9Service de Rhumatologie, Hôpital Nord, INSERM ERI 12, Amiens, France, 10United BioSource Corporation, Bethesda, MD, 11University of California San Francisco, San Francisco, CA, 12VU University Medical Center, Amsterdam, The Netherlands, 13Women’s Health & Research Consultants®, Washington, DC

Background: Published evidence suggests a relationship between osteoporotic fractures and back pain outcomes. Denosumab (DMAB) is a fully human monoclonal antibody that inhibits RANKL, an essential mediator of osteoclast formation, function, and survival. In the FREEDOM trial, DMAB significantly reduced the risk of fractures (Cummings et al., N Engl J Med. 2009;361:756). Here we evaluate the impact of incident clinical vertebral fractures on back pain outcomes, regardless of treatment group, in women who participated in the FREEDOM trial.

Methods: The FREEDOM trial randomized 7808 women aged 60–90 years with a total hip and/or lumbar spine DXA T-score < −2.5 and not < −4.0 at either site. Women were randomized to receive subcutaneous DMAB 60 mg every 6 months or placebo for a total of 36 months, in addition to daily calcium and vitamin D. Back pain and limited activity days were assessed with the Back Pain and Limited Activity Days questionnaire (BPLAD) in person at each study visit (baseline and months 6, 12, 18, 24, 30, and 36) and by telephone between study visits (months 3, 9, 15, 21, 27, and 33). The BPLAD recorded subjects’ back pain, limited activity, hospitalization, and bed rest experience (yes/no); the severity of back pain (very mild, mild, moderate, severe, very severe); the number of days of back pain; and the number of days of limited activity, hospitalization, and bed rest due to back pain during the past 3 months.

Results: About 24% of women had a prevalent vertebral fracture at study entry (Placebo, N=915; DMAB N=929). Compared to women without incident fractures, a significantly higher percentage of women with incident clinical vertebral fractures reported the occurrence of back pain, limited activity, hospitalization, and bed rest (Table 1). Additionally, women with incident clinical vertebral fractures reported a significant increase in the total days of back pain, limited activity, and bed rest than women without an incident fracture (Table 1). Women with incident clinical vertebral fractures also reported an approximately 2- to 3-fold increase in the rate of all recorded back pain outcomes after the fracture occurrence compared with the rate before the fracture occurrence (Table 2).

Conclusions: Incident clinical vertebral fractures were associated with a significant increase in the occurrence, severity, and duration of back pain outcomes in the women who participated in the FREEDOM trial. Efforts to reduce the occurrence of clinical vertebral fractures may lead to improved back pain outcomes for postmenopausal women with osteoporosis.

Table 1. Back Pain and Disability Due to Back Pain Through Month 36 by Incident Vertebral Fracture Status

<table>
<thead>
<tr>
<th>With Incident Clinical Vertebral Fracture (N = 108)</th>
<th>Without Incident Fracture* (N = 6821)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of Observation Before Fracture = 72454</td>
<td>Days of Observation After Fracture = 41127</td>
</tr>
<tr>
<td>Days of Moderate, moderate, severe back pain</td>
<td>Days of Observation* = 6830858</td>
</tr>
<tr>
<td>10765</td>
<td>1019899</td>
</tr>
<tr>
<td>3368</td>
<td>4.6</td>
</tr>
<tr>
<td>2312</td>
<td>3.2</td>
</tr>
<tr>
<td>57</td>
<td>0.1</td>
</tr>
<tr>
<td>338</td>
<td>0.5</td>
</tr>
</tbody>
</table>

N = Number of subjects. Total = Sum of days with symptom Rate = 100*(Total/Days of Observation) for each variable of interest.

Table 2. Back Pain and Disability Due to Back Pain by Pre and Post Incident Clinical Vertebral Fracture

<table>
<thead>
<tr>
<th>With Incident Clinical Vertebral Fracture (N = 108)</th>
<th>Without Incident Fracture (N = 6821)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting back pain**</td>
<td>Reporting limited activity**</td>
</tr>
<tr>
<td>Reporting hospitalization**</td>
<td>Reporting bed rest**</td>
</tr>
<tr>
<td>Total days of back pain</td>
<td>Total days of moderate, severe, or very severe back pain</td>
</tr>
<tr>
<td>Total days of limited activity due to back pain</td>
<td>Total days of hospitalization due to back pain</td>
</tr>
<tr>
<td>Total days of bed rest due to back pain</td>
<td></td>
</tr>
</tbody>
</table>

**Includes subjects with no incident fractures of any type.

**Based on Chi-square test or Fisher’s exact test, when expected cell count <5.

References: Eisman JA, et al. Journal of Bone and Mineral Research. 2000;15:1298–1306. Adherence with bisphosphonates was greater in VARA cohort than most previous reports. Factors associated with higher adherence were Caucasian ethnicity and treatment site.

Disclosure: M. C. Nevitt: None; S. L. Silverman: Lilly, Pfizer, Alliance for Better Bone Health, 2, 5, 8, Lilly, Roche Pharmaceuticals, Pfizer, 2, 5, 8, Warner Chilcott, Roche Pharmaceuticals, Roche Diagnostics, Novartis, Pfizer, Lilly, 2, 5, 8; H. Viswanathan: Amgen Inc., 1, 3; Y.-C. Yang: Amgen Inc., 1, 3; A. Wang: Amgen Inc., 1, 3; S. Boonen: Amgen Inc.; 5; S. Ragi-Eis: Amgen Inc.; 9; F. Fardellone: Board on Osteoporosis, 5; A. Grauer: Amgen Inc., 1, 3; N. Gilchrist: None; P. Lips: Merck Pharmaceuticals, 8, Merck, Amgen Inc., 2; S. Palacios: Bayer-Schering, Novo Nordisk, Servier, Lilly, Daiichi-Sankyo, Sanofi-Aventis, MSD, Warner Chilcott, Amgen Inc., 2, 5, 8, Servier, Lilly, Daiichi-Sankyo, Amgen Inc., Arkochim, Bayer-Schering, 2, 5, 8; K. Pavelka: None; D. Revicki: Amgen Inc., 2, 5; J. Simon: Abbott Laboratories, Allergan, Alliance for Better Bone Health, Amgen Inc., Ascend Therapeutics, Azur Pharma Inc., Bayer, BioSante, Boehringer Ingelheim, Concert Pharmaceuticals, Corcept Therapeutics Inc., Depomed Inc., Fahe-Kramer; D. Macarios: Amgen Inc., 1, 3; E. Siris: Amgen Inc.; sanofi-aventis, Procter and Gamble, Novartis, Eli Lilly, 5, 6, 7, 8, El Lilly, Amgen Inc.,...
Incidence of Low Energy Hip Fracture in Southern Norway Significantly Lower Than Reported from the Capital of Norway (Oslo). Andreas Diamantopoulos1, Gudrun Rohde2, Irene Johnsrud1, Inger Marie Skoie1, Villy Johnsen1, Marc C. Hochberg3 and Glenn Haugeberg1. 1Department of Rheumatology, Sørlandet Hospital SSHF, Kristiansand, Norway, 2Faculty of Health and Sport, University of Agder, Kristiansand, Norway, 3University of Maryland, Baltimore, MD

Background: Hip fractures contribute to increased morbidity and mortality in individuals above 50 years. As the average age of the population is increasing, the burden on the health care system is a growing challenge. The highest incidence of hip fracture worldwide has been reported from Oslo, the capital of Norway. During the last decades the awareness of hip fracture has increased and efforts have been undertaken to reduce fracture risk.

Aim: Our aim was to study the incidence of low energy hip fracture in individuals aged 50 years or older in southern Norway.

Methods: Patients with low energy hip fractures were recruited from the four hospitals in the two most southern counties of Norway in 2004 and 2005. Age adjusted and age specific incidence rates for men and women were calculated. We also searched for differences between seasons and between urban and rural areas. Our age adjusted incidence rates were compared with previous national and international reports.

Results: A total of 920 (261 men, 659 women) individuals aged ≥ 50 years with hip fracture were identified. The age adjusted incidence rate was 33.3 and 74.3 per 10,000 person years for men and women consecutively. Age specific incidence rates were significantly higher in women than in men but only for age groups between 70 and 90 years. Hip fracture were significantly higher in winter (p<0.05). No significant difference was seen between rural and urban areas. In the male cohort no major differences in age specific incidence rates was found compared with the Oslo study, however the incidence was lower in women above 80 years in our study.

Our age adjusted incidence rates are the lowest reported from Norway and among the lowest reported from Scandinavia but is still among the highest in the world.

Conclusion: Age adjusted incidence rates of hip fracture in men and women in Southern Norway are the lowest reported from Norway and among the lowest in Scandinavia. The higher number of hip fractures seen in winter months may indicate that environmental factors increase the risk of hip fractures. Increased awareness and higher preventive and treatment methods are warranted both among men and women to reduce hip fracture risk.

Disclosure: A. Diamantopoulos: None; G. Rohde: None; I. Johnsrud: None; L. Skoie: None; V. Johnsen: None; M. C. Hochberg: None; G. Haugeberg: None.

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Increases in Macrophage Inhibitory Factor Correlate with Increases in Bone Mineral Density in Glucocorticoid-Treated Patients with RA. Jos Nicolaaas Hoes1, Marlies C. Van der Goes2, Johannes W. J. Jacobs3, Johannes W. J. Bijlsma1 and Joel A. G. Van Roon2, 1University Medical Center Utrecht, Department of Rheumatology & Clinical Immunology, Utrecht, The Netherlands, 2University Medical Center Utrecht, Department of Rheumatology & Clinical Immunology

Background: Inflammation and bone metabolism are characterized by crosstalk and shared mechanisms. (1) Both glucocorticoids (GCs) and vitamin D can influence each of these mechanisms; by studying these, the process of osteoimmunity in GC-induced osteoporosis could be further unravelled. Of special interest are cytokines, such as macrophage migration inhibitory factor (MIF), IL-13 and IL-7 which could influence bone metabolism by antagonizing the effects of GCs. In addition, vitamin D might add to the anti-inflammatory effects of GCs by acting on the differentiation and/or activity of T cells that are involved in the pathogenesis of rheumatoid arthritis (RA).

Objective: To investigate the correlation of levels of inflammatory mediators and measures of bone turnover in patients with RA who were treated with GCs and to explore whether vitamin D enhances the anti-inflammatory effects of GCs.

Methods: RA patients (n=40) on oral GCs treatment received either active vitamin D (alfacalcidol) or the bisphosphonate alendronate in a double blind double placebo controlled manner for 18 months. Associations of lumbar spine bone mineral density (BMD) and bone turnover markers procollagen type I C-propeptide (PICP), osteocalcin, osteoprotegerin (OPG), deoxypyridinoline (dPyr), and cross-linked N-telopeptides (Ntx) with cytokines capable of antagonizing GCs (MIF, IL-13 and IL-7), cytokines causing T cell differentiation (IL-6, IL-7, IL-12, IL-10 and IL-23), and cytokines produced by effector T cells (Th1, IFNγ; Th2: IL4; Th17: IL17, IL22) were explored with multiple regression analyses.

Results: Treatment active vitamin D treatment did not influence cytokine levels that are associated with T cell differentiation or that is indicative of T cell activity. At baseline, higher levels of IL-6 and IL-23 (B = −0.001, B = 0.00003, p = 0.088, p = 0.080) showed a trend of association with low BMD. Changes in T cell associated cytokines did not predict changes in BMD or bone markers at 18 months. Alendronate significantly influenced BMD, (2) but neither vitamin D nor alendronate treatment significantly influenced levels of cytokines antagonizing GCs. However, increases in MIF were significantly associated with increased BMD (B=0.055, p=0.039) and decreases of deoxypyridinoline (B=−0.012 p=0.037). Other cytokines antagonizing GCs were not associated with (changes in) bone parameters, but an increase in GC dose tended to be associated with increase in MIF.

Conclusion: Our data do not provide evidence for an anti-inflammatory effect of vitamin D in RA patients on GCs. Although not influenced by vitamin D or alendronate treatment, increases in MIF, an antagonist of GCs, are associated with increases in BMD during GC treatment.

References:

Corresponding address: j.n.hoes@umcutrecht.nl

Disclosure: J. N. Hoes: None; M. C. Van der Goes: None; J. W. G. Jacobs: None; J. W. J. Bijlsma: None; J. A. G. Van Room: None.

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Low Bone Mineral Density in Depo-Provera Users – An Under Recognised Health Issue. Mani Nallasivan 1 and Tim Gillott. 1. Diana Princess of Wales Hospital, Northern Lincolnshire and Goole Hospitals NHS Trust, Hull, Yorkshire, United Kingdom, 2. Diana Princess of Wales Hospital, Northern Lincolnshire and Goole Hospitals NHS Trust, Grimsby, Northeast Lincolnshire, United Kingdom

Background: Women using Depo-Provera may lose bone mineral density, putting them at increased risk of osteoporosis. In November 2004, the FDA issued a black box warning which stated “Use of Depo-Provera contraceptive injection may cause you to lose calcium stored in bones”. As this drug is being used by very young women; it could have serious implications on bone health in future. Oldroyd and colleagues have demonstrated significant decline in BMD in femoral neck but not in the spine, in whom median exposure of Depo-Provera was less than three years. 1 Studies show that discontinuation of Depo-Provera will allow near complete reversal of BMD loss.

Objectives: To examine the bone density in patients, who have been on Depo-Provera (medroxyprogesterone acetate) for contraception, referred for BMD estimation using dual X-ray absorptiometry (DEXA) and analyse whether the bone loss was significant enough to warrant change in the form of contraception.

Materials and Methods: We analysed 50 patients from 2008 and 2009 referrals for Bone mineral density assessment, with history of Depo-Provera use. They were asked to fill in standard questionnaire, about the risk factors, BMI, smoking, family history as well. Their bone mineral density assessment was recorded using T and Z scores. In addition some had vertebral morphometry performed as well.

Results: Out of fifty patients, 24 were scanned in 2008 and remaining in 2009. Mean age was 28.6 years, mean duration of Depo-Provera use was 4.5 years (range 18 months to 10 years and even long term) and mean BMI-23.5. 42% were found to be osteopenic using T scores and one patient was in the osteoporotic range. 56% had normal BMD. Median T score for low the BMD group was −1.14.

Few patients had other risk factors including celiac disease, long term steroid use because of Inflammatory bowel disease or liver transplantation. 3 patients had family history of osteoporosis. The T score was low in only 3 patients in femoral neck, while remaining (18/21) was low in lumbar spine.

Ten patients who have low T scores, were recommended to stop DP and two had already changed to oral pills.

Discussion: With oestrogen deficiency, the lumbar spine has a greater tendency to lose BMD because of its high trabecular bone content. Our findings are in keeping with this. This is in contrast to the finding by Oldroyd and colleagues, which reported significant reduction in femoral neck. We have recommended change in the form of contraception and to stop using DP for those who have T Scores in osteopenic/osteoporotic range. Though this is a small study, this needs further validation with wider cohort and also compare with normal age matched control.

Conclusion: Use of Depo-Provera can cause reduced bone mineral density and hence needs risk assessment and appropriate advice given. Perhaps Public awareness also needs attention.


Disclosure: M. Nallasivan: None; T. Gillott: None.

Prevalence of Osteoporosis and Osteoporotic Fractures: A Population Based Survey Including Vertebral Fracture Assessment by Morphometry (VFA). Liana E. Euler-Ziegler1, Christian H. Roux1, Veronique Breuil1, Virginie Dasilva1, Christine Albert-Sabonnadiere1, Christian Grisot1, Philippe Flory1, Yacine Allam1, Hasna Chami1, Gerard Ziegler1 and Pascal Staccini2.

1.14. The prevalence of VF by VFA, Hologic QDR4500, Genant scoring by 2 independent MD. Statistical analysis was performed using χ2, ANOVA or Kruskall-Wallis test when appropriated.

Study granted by Ministry of Health and promoted by CHU of Nice (Academic Hospital of Nice, France).

Results: 519 women were evaluated, mean age 63.4 ± 8.8 years, BMI 25.4 ± 4.9 kg/m2, hip fracture in 1st degree relatives (3.7%), current smoking (2.7%), RA (0.8%), early menopause (4.6%), personal history of low energy clinical fracture after 50 years (15%), including non vertebral fractures 13.5%, DXA demonstrated OP in 13.7% of the women (mean age 68 ± 9.4 years), osteopenia in 59% (63.8 ± 8.4 years).

The prevalence of VF by VFA was 29.7% (presence of ≥1 VF Genant stage ≥1), (18.1% with ≥1 VF Genant stage ≥2). The VF were scored Genant stage 1 (55.1%), stage 2 (39.3%), stage 3 (5%), with a median number of 2 VF by woman (1 – 8). VF scored Genant stage ≥1 were present in women classified by DXA as having osteoporosis (24%), but also osteopenia (61%), even normal BMD (15%) and VF scored Genant stage ≥2 in respectively 27.7%, 58.5%, 13.8% of the women; conversely, 52% of women classified by DXA as having osteoporosis, 30.7% osteopenia and

A registry-based cross-sectional study was performed. It started with a prevalence study (2006–2007) in which stratified samples throughout Spain of abdominal radiographs, of subjects aged ≥55 years, from stored consecutive digitalized films in selected hospitals were obtained. Radiographs including all lumbar vertebrae, pelvis, sacrum and femoral heads were examined for the diagnosis of PDB, according to standardized criteria. Afterwards, experts on Paget disease were invited to include patients in the registry from their clinics (apart from those identified in the prevalence study). Data were recorded following a standardized electronic form: demographics (age, sex); clinical (diagnosis date, age at the disease onset, symptoms and treatment); quality of life [EuroQol 5D, visual analog scale (VAS) of pain]; environmental factors (infections, place of birth, birth weight, number of brothers/sisters and position, measles virus infection, contacts with domestic animals, non-pasteurized milk intake, home characteristics during childhood, ≥ 1 year-places of residence, work status); familiar (positive familiar history and place of birth of positive cases, number of children and their measles exposure/vaccination). A descriptive study was performed.

Results: The crude prevalence of PDB was 1% (95% Confidence Interval: 0.7–1.3) in patients aged ≥55 years, and the estimated prevalence ranged from 1.1% (95%CI: 0.8–1.4) to 1.6% (95%CI: 1.1–2.1) when a reported pelvic involvement in 60–90% of PDB patients was considered. A total of 602 patients with PDB from 24 hospitals were included in the registry. We found more men (55%), with a mean age of 62 years ± 11 years. More than 80% had followed any treatment, 55% risedronate, 32% calcitonin, and almost 50% ≥ 2 drugs. The mean VAS pain score was 65 ± 21. The dimension which showed the worst score was anxiety/depression (64% reported moderate or severe limitations), followed by mobility (47%), and just 24% reported moderate or severe limitations in usual activities. Most of patients (99%) were born in Spain: Barcelona (11%), Avila (10%), Toledo (7%) and Salamanca (5%). Measles infection was reported in 65%, and 80% had had contacts with animals: dogs (70%), cats (48%), and birds (38%). Non pasteurized milk intake was observed in 75% of patients and 53% were retired. A positive familiar history was registered in 14%, especially in Avila and Salamanca, and PBD was identified in 1.5% of patient’s children.

Conclusions: The National Registry of PDB includes 602 patients with PDB. Up to 14% have a positive familiar history, 80% contacts with domestic animals, and most of them had been on pharmacological treatment.

Disclosure: E. Loza: None; N. Guanaabens: None; M. J. Garcia de Yebenes: None; A. Morales: None; J. Del Pino: None; A. Torrijos: None; J. Garrido: None; J. Tornero: None; J. Malout: None; J. Carbonell: None; M. Rodriguez: None.

Prevalence studies on osteoporosis (OP) in the general population are scarce; vertebral fractures (VF) are frequently undiagnosed.

Objectives: To estimate the prevalence of low bone mineral density (BMD), osteoporotic fractures and risk factors in women aged 50 to 85 years.

Methods: After random selection in the national insurance system regional database (French Alpes Maritimes area), a sample of women aged 50 to 85 years, representative of the general population, was evaluated: medical and risk factors questionnaires, bone densitometry (DEXA / hip, femoral neck, spine), screening for vertebral fractures (VF) by high density morphometry (VFA, Hologic QDR4500, Genant scoring by 2 independent MD). Statistical analysis was performed using χ2, ANOVA or Kruskall-Wallis test when appropriated.

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Prevalence of Osteoporosis and Osteoporotic Fractures: A Population Based Survey Including Vertebral Fracture Assessment by Morphometry (VFA). Liana E. Euler-Ziegler1, Christian H. Roux1, Veronique Breuil1, Virginie Dasilva1, Christine Albert-Sabonnadiere1, Christian Grisot1, Philippe Flory1, Yacine Allam1, Hasna Chami1, Gerard Ziegler1 and Pascal Staccini2.

1.14. The prevalence of VF by VFA, Hologic QDR4500, Genant scoring by 2 independent MD. Statistical analysis was performed using χ2, ANOVA or Kruskall-Wallis test when appropriated.

Study granted by Ministry of Health and promoted by CHU of Nice (Academic Hospital of Nice, France).

Results: 519 women were evaluated, mean age 63.4 ± 8.8 years, BMI 25.4 ± 4.9 kg/m2, hip fracture in 1st degree relatives (3.7%), current smoking (2.7%), RA (0.8%), early menopause (4.6%), personal history of low energy clinical fracture after 50 years (15%), including non vertebral fractures 13.5%, DXA demonstrated OP in 13.7% of the women (mean age 68 ± 9.4 years), osteopenia in 59% (63.8 ± 8.4 years).

The prevalence of VF by VFA was 29.7% (presence of ≥1 VF Genant stage ≥1), (18.1% with ≥1 VF Genant stage ≥2). The VF were scored Genant stage 1 (55.1%), stage 2 (39.3%), stage 3 (5%), with a median number of 2 VF by woman (1 – 8). VF scored Genant stage ≥1 were present in women classified by DXA as having osteoporosis (24%), but also osteopenia (61%), even normal BMD (15%) and VF scored Genant stage ≥2 in respectively 27.7%, 58.5%, 13.8% of the women; conversely, 52% of women classified by DXA as having osteoporosis, 30.7% osteopenia and
16.2% normal BMD had VF Genant stage ≥1 (and 36.6%, 18% & 9.1% had VF Genant stage ≥ 2).

The overall prevalence of osteoporotic fractures was 37.4% (VF and/or non vertebral fracture), mean age 67.3 ± 8.9 years, classified by DXA as osteoporosis (20.6%), osteopenia (61.3%), normal (18%).

**Correlations:** T-score decrease (global status and at each site) was linked with age (p=0.001) and BMI (p=0.001); the presence of fracture was linked with age (p=0.001). T-score (p<0.001) (globally and for VF), BMI (globally). Fractures were more frequent in subjects with a personal history of prior fracture (p<0.001, globally and for VF), without significant link with other risk factors.

**Discussion:** Methodological issues of prevalence studies on OP are well known. The partnership with the national insurance system allowed us to analyse a representative sample of the general population. VFA, delivering a lower dose of radiation than Xrays and well accepted by our subjects, allowed easier VF detection (according to Genant stages ≥ 1 & ≥2) and therefore VF prevalence analysis.

**Conclusion:** This study brings new data emphasizing the public health dimension of osteoporosis and the high frequency of undiagnosed vertebral fractures in the general population, even in women with osteopenia or normal BMD.

**Disclosure:** L. E. Euler-Ziegler: None; C. H. Roux: None; V. Breuil: None; V. Dasilva: None; C. Albert-Sabonnadiere: None; C. Grisot: None; P. Florly: None; Y. Allam: None; H. Chani: None; G. Ziegler: None; P. Staccini: None.

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**Proactively Contacting Men with Prostate Cancer Treated with Anti-Androgen Medications Improves the Evaluation and Treatment of Osteoporosis.** Brian P. Oppermann1, Thomas M. Harrington2 and William Ayoub3. 1Geisinger Medical Center, Danville, PA; 2Geisinger Medical Center, Danville PA; 3Geisinger Medical Group, Scenary Park PA

**Purpose:** Men treated with androgen deprivation therapy for prostate cancer are at higher risk for osteoporosis and osteoporotic fractures. This relationship is dose and length of therapy dependent. Despite this known association, men treated with anti-androgen therapy do not routinely receive osteoporosis screening with dual energy X-ray absorptiometry (DXA).

**Methods:** Using an electronic health record (EHR), in a rural tertiary health care system, we identified 64 men followed by our primary care physicians with the diagnosis of prostate cancer who have been treated with anti-androgen therapy (leuprolide acetate) for this pilot study. This EHR search identified any man who met the above criteria from 2007-2009. Of these 64 men, 61 had not undergone osteoporosis screening with DXA scanning. The other 3 men had undergone DXA and one was on bisphosphonate therapy. These three men were excluded. The remaining evaluation naïve 61 men were then contacted via letter. This letter explained reasons that they were being contacted, mainly they may be at high risk for osteoporosis given treatment with anti-androgen therapy. The letter instructed them to call to schedule a DXA scan. If no response was obtained several weeks after the mailing, patients were contacted by telephone to schedule the DXA scan. From initial contact via letter to scheduling the men for evaluation took 4 months.

**Results:** For the pilot study, 30 of the 61 men contacted agreed to osteoporosis screening with DXA scanning. Of these 30 DXA’s, 18 (60%) were low/moderate risk and 12 (40%) were deemed high risk for fracture (osteoporotic) using the 2008 National Osteoporosis Foundation criteria. None were these 12 high risk DXA scan patients had been on bisphosphonate therapy prior to this project, with all 12 being placed on therapy after DXA results.

**Conclusion:** Using our EHR, we proactively captured a subset of men at high risk for osteoporosis and fracture – those with prostate cancer. As the pilot project demonstrates, a significant proportion (40%) of these patients indeed are at high risk for fracture based on DXA and none of these patients were on approved osteoporosis medications. Unfortunately we only captured 50% of the identified patients, with most refusing to be evaluated given their age or the feeling this did not apply to them. Regardless, this pilot project demonstrates that this specific group of patients is at risk for osteoporosis and there needs to be better awareness to capture these patients and obtain appropriate osteoporosis evaluation and treatment. We plan to develop best practice alerts to identify the patients, risk stratify them with DXA and hopefully prevent future morbidity, mortality and health care expenditures with appropriate medical therapy.

**Disclosure:** B. P. Oppermann: None; T. M. Harrington: None; W. Ayoub: None.

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**Quality Assurance Study of the Use of Preventative Therapies in Glucocorticoid Induced Osteoporosis (GIOP) in Early Inflammatory Arthritis (EIA): Results from the CATCH Cohort.** Emily McKeown1,2, Vivian P. Bykerk1, Faye Deleon3,4, J. Carter Thorne2, Carol A. Hitchon5, Gilles Boire6,7, Boulos Harauqi8, Richard Turner9,10,11,2, Vivian P. Bykerk1,2, Janet E. Pope1,2,3,1. 1LaSalle, QC, Canada; 2CHUS-Sherbrooke University, Sherbrooke, QC, Canada; 3Institut de Rhumatologie, Montreal, QC, Canada; 4McMaster University, Hamilton, ON, Canada; 5Mt Sinai Hospital, Toronto, ON, Canada; 6Southlake Regional Health Care, Newmarket, ON, Canada; 7St Joseph Health Care London, London, ON, Canada, 8University of Manitoba, Winnipeg, MB, Canada, 9University of Toronto, Toronto, ON, Canada, 10University of Western Ontario, London, ON, Canada

**Background:** Exposures to glucocorticoids are common in patients with inflammatory arthritis (IA) despite treatment with DMARDs. The ACR has published guidelines for the prevention and treatment of glucocorticoid induced osteoporosis (GIOP), but adherence to guidelines is variable. This study characterizes steroid use and compliance with GIOP guidelines within a large early IA cohort.

**Methods:** Using the Canadian Arthritis Cohort Database (CATCH), patients with IA on glucocorticoids (oral or intramuscular) were identified. Steroid exposure was defined as using oral glucocorticoids for two consecutive clinic visits (at least 90 days apart). The primary outcome was the proportion of patients receiving calcium, vitamin D and a bisphosphonate among patients treated with chronic glucocorticoids. Those with postmenopausal osteoporosis were excluded. Secondary analysis was done to determine which factors were associated with the use of oral calcium, vitamin D and bisphosphonate.

**Results:** 655 were in the CATCH database, where 311 (47%) were glucocorticoid users of whom 50% were on oral prednisone, 41% received intramuscular or intra-articular (ia) steroids and 9% both. The mean oral daily dose in prednisone users was 6 mg (SD 7.5). Chronic users (CU) compared to non-users (NU) showed that CU were older (56 vs. 50 years, p=0.002; similar proportion of females (68% vs. 73%) and rheumatoid factor positivity (55%, RF mean 97 IU/mL in CU vs. 57%, RF mean 171 IU/mL in NU); DAS (CRP) was 4.72, (SD 1.48) in CU vs. 4.85 (SD 1.59) in NU, p=0.50. Less than half (45%) on chronic steroids were treated with calcium, 41% with Vitamin D, 38% with both and 18% were taking a bisphosphonate. Rates of prophylaxis were only slightly higher for users of chronic oral steroids; 54% were taking Calcium, 48% were taking Vitamin D, 45% were taking both and 23% were on a bisphosphonate. There were no significant differences in use of Calcium, Vitamin D or bisphosphonate among females compared to males (OR 0.49, 95% CI 0.20–1.18, p = 0.11), or among post-menopausal females compared to pre-menopausal females (OR 2.34, 95% CI 0.92–5.95, p = 0.07). Women with a history of hormone treatment and smokers had no significant increase in being treated (OR 1.50, 95% CI 0.49–4.62, p = 0.48 and OR 0.73, 95% CI 0.32–1.66, p = 0.46). Treatment rates were similar among patients on steroids for one year compared to patients treated for at least 90 days so longer duration of steroids did not increase prophylaxis.

**Conclusions:** Glucocorticoid therapy is frequently used in early IA. The use of calcium, vitamin D or a bisphosphonate was low among chronic glucocorticoid users and illustrates a care gap.

**Disclosure:** E. McKeown: None; V. P. Bykerk: Amgen Inc., 2, Pfizer Inc, 2; F. Deleon: None; J. C. Thorne: None; C. A. Hitchon: Amgen Inc., 2, Pfizer Inc, 2; B. Harauqi: Amgen Inc., 2, Pfizer Inc, 2; D. S. Ferland: Amgen Inc., 2, Pfizer Inc, 2; E. C. Keystone: Amgen Inc., 5; J. E. Pope: Amgen Inc., 2, Pfizer Inc, 2.

### 979

**Relationships between Changes in Bone Mineral Density or Bone Turnover Markers and Vertebral Fractures Incidence in Patients Treated with Bazedoxifene.** Olivier Bruyere1,2, Johann Dettilleux3, Arkadi Chhabra4, and Jean Y. Regnster5,6. 1Pfizer Inc, 2, Pfizer Inc, 3, Jansen Pharmaceutical Company, 4, University of Liege, Liege, Belgium, 5, University of Liege

**Objective:** To analyze the relationships between bone mineral density (BMD) or bone turnover markers (BTM) changes and vertebral fractures incidence in women treated with bazedoxifene.

**Material and Methods:** Post hoc analysis from a 3-year randomized, placebo-controlled study evaluating the effect of bazedoxifene (20 or 40 mg) on fracture risk reduction. BMD was assessed at baseline and every 6 months during 3 years. Osteocalcin (OC) and C-telopeptide of type I collagen (CTX-I) were assessed at baseline, month 3, 12 and 36. Vertebral fractures were assessed with a semiquantitative visual assessment.

**Disclosure:** None; B. P. Oppermann: None; T. M. Harrington: None; W. Ayoub: None.
Results: Data was available for 5244 women of which 3476 were treated with bazedoxifene. Using logistic regression analysis and the classical Li approach, the proportion of fracture incidence explained by BMD change after 3 year of bazedoxifene treatment was 29% for the total hip and 44% for the femoral neck. The proportion of treatment explained by lumbar BMD change could not be quantified accurately because of the significant interaction between treatment and change in BMD. With the same model, the 3-month BTM changes explained between 14% and 18% of the fracture risk reduction observed with bazedoxifene. With another new statistical method using structural equation models, the proportion of fracture incidence explained by 3-year BMD change was between 29 and 43%, for total hip and femoral neck, respectively. Using the same methodology, BMD changes after one year of therapy explained between 8 and 15% of the fracture incidence observed during 3 years of treatment.

Conclusion: In women treated with bazedoxifene, changes in femoral neck or hip BMD explained up to 44% of the fracture risk reduction observed during the 3 years of follow-up. Short-term BTM changes poorly explained the fracture risk reduction observed during the 3-year treatment with bazedoxifene.

Disclosure: O. Bruyere; Wyeth Pharmaceuticals, 2; J. Delteilles; Wyeth Pharmaceuticals, 2; A. Chinnes; Pfizer Inc, 3; J. Y. Register; Wyeth Pharmaceuticals, 2.

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The Direct Assessment of Nonvertebral Fractures in Community Experience (DANCE) Study: 2-Year Nonvertebral Fracture Result

Stuart L. Silverman1, Paul Miller2, Anthony I. Sebba1, Michael Weitz3, Xiaohai Wan4, Kathleen Taylor5, Valerie Ruff6 and Kelly D. Krohn7

1Arthritis Associates, Palm Harbor, FL, 2Cedars-Sinai Medical Center, University of California Los Angeles, Beverly Hills, CA, 3Center Arthritis and Rheumatology, South Miami, FL, 4Colorado Center for Bone Research, Lakewood, CO, 5Eli Lilly and Company and/or One of Its Subsidiaries, Indianapolis, IN, 6Lilly USA, LLC, Indianapolis, IN

Statement of Purpose: To evaluate the occurrence of nonvertebral fragility fractures (NVFX) in subjects treated with teriparatide (TPTD) for osteoporosis (OP) for up to 24 months in a community-based setting.

Methods: The DANCE study is a multi-center, prospective, observational trial designed to examine the long-term effectiveness, safety, and tolerability of TPTD. Patients judged by study physicians to be suitable for TPTD therapy received TPTD 20 μg/day for up to 24 months. The percentage of patients experiencing a new NVFX during 4 TPTD treatment duration periods (table) was calculated. The proportion of patients reporting new NVFX during longer TPTD treatment duration categories was compared to the proportion during TPTD treatment duration of 0 to 6 months using a binomial proportion test. The 0–6 months interval was chosen as the reference since Kaplan-Meier analysis of NVFX in the Fracture Prevention Trial showed that the TPTD and placebo groups appeared to begin to separate after approximately 8 months of study drug.

Results: The mean TPTD exposure was 17 (95% CI: [16.8, 17.4]) months and the median TPTD exposure was 23 months. Overall, 115/3649 (3.15%) experienced a NVFX. The incidence of patients experiencing new NVFX during the four TPTD treatment durations was 1.43%, 0.97%, 0.72%, and 0.78%, respectively (table). The incidence of new NVFX during each TPTD treatment duration longer than 6 months was significantly lower than the incidence during TPTD treatment duration 0 to 6 months (p<0.0001). Compared to TPTD treatment of 0 to 6 months, NVFX incidence during treatment durations 6 to 12, 12 to 18, and 18 to 24 months was 52%, 50%, and 45% lower, respectively.

Conclusions: The results of this observational study indicate that the incidence of new NVFX decreased for patients receiving TPTD treatment for greater than 6 months.

The Effects of Denosumab (DMAb) on Bone Mineral Density (BMD), Fracture and Safety Outcomes by Level of Renal Function. Sophie A. Jamal,1 Peter R. Ebeling,2 Osten Ljunggren,3 Catherine Stehman-Breen,4 Steven R. Cummings,5 Michael R. McClung,1 Stefan Goemaere,1 Edward Franchi,3 P. R. Ebeling,3 Ogo I. Egbuna1 and Paul Miller,5.1 Amgen Inc., Thousand Oaks, CA, 2Central Clinical Hospital, Warsaw, Poland, 3Ghent University Hospital, Belgium, 4Oregon Osteoporosis Center, Portland, OR, 5San Francisco Coordinating Center, CPMC Research Institute and University of California, San Francisco, San Francisco, CA, 6University of Colorado Health Sciences Center, CO, 7University of Melbourne, Melbourne, Australia, 8University of Toronto, Toronto, ON, Canada, 9Uppsala University Hospital, Sweden.

Treatments for osteoporosis in patients with renal impairment, both common conditions in the older population are limited. DMAb is not excreted by the kidney and is a potential treatment option.

The efficacy and safety of DMAb given as a 60 mg s.c injection every 6 months for 3 years among patients in Phase 3 FREEDOM Study was evaluated. Creatinine clearance (CrCl) was estimated using the Cockcroft-Gault equation. A subgroup interaction term was used to assess differences in treatment effect by CrCl. We examined incident fracture rates, changes in BMD, serum calcium, serum creatinine and the incidence of adverse events after 36 months of follow-up in subjects receiving DMAb and placebo, stratified by level of renal function using linear regression models adjusted for multiple baseline characteristics including prevalent vertebral fractures and years since menopause.

Most (97%)% women were Caucasian, the mean age was 72.3 ± 5.2 years, the mean weight was 63.8 ± 10.4 kg, serum creatinine was 70.8 ± 15.3 mmol/L and serum calcium was 2.44 ± 0.11 mmol/L. Subject disposition by level of renal function was balanced between DMAb and placebo treated subjects. 73 women had a CrCl between 15 to 29 ml/min (CrCl stage 4); 2817 between 30 to 59 ml/min (CrCl stage 3); 4069 between 60 to 89 ml/min (CrCl stage 2) and 842 had a CrCl of ≥ 90 ml/min (CrCl stage 1 normal).

Vertebral and non-vertebral fracture risk reduction and differences in the percent change in BMD at all sites were in favour of DMAb. The test for treatment by subgroup interaction indicated that fracture risk reduction was not statistically different by level of renal function. The difference in the mean % changes in BMD in subjects treated with DMAb compared with placebo did not differ by level of renal function. Changes in serum creatinine, serum calcium and the incidence of adverse, serious adverse and fatal events were similar between the treatment groups and did not differ by level of renal function.

DMAb reduces fracture risk and is not associated with an overall increase in adverse events among patients with impaired kidney function.

Disclosure: S. A. Jamal: Amgen Inc., 8, 9, 2, 5, 6; P. R. Ebeling: Amgen Inc., 2, 9, Merck Pharmaceuticals, 2, 9, Novartis Pharmaceuticals Corporation, 2; O. Ljunggren: Amgen Inc., 8, 9, Eli Lilly and Company, 8, 9, Novartis Pharmaceuticals Corporation, 8, 9; C. Stehman-Breen: Amgen Inc., 1, 3, 2, 5, R. Cummings: Amgen Inc., 2, 5, Eli Lilly and Company, 2, 5, 8, S. Goemaere: Amgen Inc., 2, 5, 8; S. Goemaere: Amgen Inc., 2, 5, 8; D. A. Santillo: Amgen Inc., 2, 5, 8, Novartis Pharmaceuticals Corporation, 2, 5, G. SmithKline, 2, 5, Merck Pharmaceuticals, 2, 5, Novartis Pharmaceuticals Corporation, 2, 5, Proctor & Gamble Pharmaceuticals, 2, 5, Roche, 2, 5, Servier, 2, 5, W. E. Fraenkel: Amgen Inc., 8, 9, Novartis Pharmaceuticals Corporation, 8, Roche, 2, Servier, 8, Y.-C. Yang: Amgen Inc., 1, 3, G. S. Egbuna: Amgen Inc., 1, 3, P. Miller: Amgen Inc., 2, 5, Eli Lilly and Company, 2, 5, G. SmithKline, 2, 5, Merck Pharmaceuticals, 2, 5, Novartis Pharmaceuticals Corporation, 2, 5, NPS Pharmaceuticals, 5, Proctor & Gamble Pharmaceuticals, 2, 5, Roche, 2, 5, sanofi-aventis.

The Serum Level of Undercarboxylated Osteocalcin (ucOC) in Patients with Rheumatoid Arthritis (RA) — A High Dose of Prednisolone Decrease the Serum Level of ucOC. Yoshitada Sakai2, Akira Hashimoto1, Tepppei Hashimoto1, Yoshiko Kawasaki3, Chihiro Tanaka3, Shunichi Shiozawa3 and Masahiro Kurosaka1. 1Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, 2The Center of Rheumatic Diseases, Kobe University Hospital, Kobe, Hyogo, Japan, 3The Center of Rheumatic Diseases, Kobe University Hospital, Kobe, Japan.

Purpose: Rheumatoid arthritis (RA) causes systemic osteoporosis as well as periarticular osteoporosis, and becomes one of the risk factor of osteoporotic fracture. On the other hand, several previous studies have indicated that the higher serum level of undercarboxylated osteocalcin (ucOC) could be a risk factor for osteoporotic fracture. However, the relationship between the serum level of ucOC in patients with RA and the medication of DMARDs or prednisolone (PSL) were still unknown. In this study, we have evaluated the serum level of ucOC in patients with RA, and investigated the related factors, such as medications, biochemical markers and bone mineral density.

Methods: 88 patients with RA were enrolled in this study (83 females, 5 males, average age 63 yrs). We compared the ucOC levels with other biochemical marker (Serum cross-linked N-teropeptide of type 1 collagen (NTx), Bone alkaline phosphatase (BAP), Calcium (Ca), phosphorus (P) and C reactive protein (CRP)). The examination of bone mineral density was performed with lumbar spine and femoral neck using dual energy X-ray absorptiometry (DEXA). Oral medications including PSL, methotrexate (MTX) and bisphosphonate (BP) were also examined. The statistical analysis was performed using Mann-Whitney U test.

Results: The average serum level of ucOC in all patients was 5.25±3.8 ng/ml, and then patients were categorized into high ucOC group (>4.5 ng/ml) and low ucOC group (<4.5 ng/ml). The results of biochemical markers and BMD in these two groups were showed in Table 1. These data showed that the patients with low serum ucOC level have low biochemical marker of bone metabolism and high dose of PSL (>5mg/day). When compared the medications with the serum ucOC level in Table2, results indicated that medication of high dose PSL and medication of BP significantly decreased the serum ucOC level.

Conclusion: Our results clearly showed that the serum levels of ucOC were increased in higher state of bone turnover as indicated by biochemical markers, and vice versa, decreased when the bone turnover was ameliorated by the high dose of PSL and BP. We should carefully evaluate the risk of osteoporotic fracture of the patient with RA who has a low level of serum ucOC during medication of high PSL and/or BP.

Table 1

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Low ucOC group</th>
<th>High ucOC group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ucOC group</td>
<td>64.2 ± 9.8</td>
<td>61.3 ± 12.2</td>
<td>0.8116</td>
</tr>
<tr>
<td>Serum NTx</td>
<td>15.3 ± 5.6</td>
<td>19.3 ± 5.9</td>
<td>0.021</td>
</tr>
<tr>
<td>Serum BAP</td>
<td>15.6 ± 7.1</td>
<td>25.7 ± 9.5</td>
<td></td>
</tr>
<tr>
<td>Serum Ca</td>
<td>9.2 ± 0.4</td>
<td>9.4 ± 0.3</td>
<td>0.039</td>
</tr>
<tr>
<td>Serum P</td>
<td>3.4 ± 0.5</td>
<td>3.6 ± 0.5</td>
<td>0.0622</td>
</tr>
<tr>
<td>Serum CRP</td>
<td>1.2 ± 1.6</td>
<td>0.7 ± 0.9</td>
<td>0.6267</td>
</tr>
<tr>
<td>BMD L-Spine</td>
<td>0.91 ± 0.2</td>
<td>0.81 ± 0.2</td>
<td>0.0175</td>
</tr>
<tr>
<td>BMD Femoral neck</td>
<td>0.61 ± 0.1</td>
<td>0.57 ± 0.1</td>
<td>0.1369</td>
</tr>
<tr>
<td>PSL amount</td>
<td>3.7 ± 3.4</td>
<td>1.9 ± 2.5</td>
<td>0.067</td>
</tr>
<tr>
<td>MTX amount</td>
<td>4.3 ± 3.2</td>
<td>3.6 ± 3.4</td>
<td>0.4196</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Stage</th>
<th>Early (Stage1)</th>
<th>Progressive (Stage3)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ucOC (ng/ml)</td>
<td>6.1 ± 2.3</td>
<td>6.3 ± 4.5</td>
<td>0.8022</td>
</tr>
<tr>
<td>PSL on/off</td>
<td>No PSL</td>
<td>No PSL</td>
<td>p-value</td>
</tr>
<tr>
<td>ucOC (ng/ml)</td>
<td>6.2 ± 3.4</td>
<td>4.5 ± 4.0</td>
<td>0.057</td>
</tr>
<tr>
<td>PSL on/off</td>
<td>No PSL</td>
<td>No PSL</td>
<td>p-value</td>
</tr>
<tr>
<td>ucOC (ng/ml)</td>
<td>6.2 ± 4.0</td>
<td>3.3 ± 2.7</td>
<td>0.0004</td>
</tr>
<tr>
<td>MTX on/off</td>
<td>No MTX</td>
<td>No MTX</td>
<td>p-value</td>
</tr>
<tr>
<td>ucOC (ng/ml)</td>
<td>5.1 ± 3.2</td>
<td>5.3 ± 4.2</td>
<td>0.966</td>
</tr>
<tr>
<td>BP on/off</td>
<td>No BP</td>
<td>No BP</td>
<td>p-value</td>
</tr>
<tr>
<td>ucOC (ng/ml)</td>
<td>6.2 ± 3.8</td>
<td>2.4 ± 1.9</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Disclosure: S. Sakai: None; A. Hasharomoto: None; T. Hashimoto: None; Y. Kawasaki: None; C. Tanaka: None; S. Shiozawa: None; M. Kurosaka: None.

ACR Poster Session B
Quality Measures and Innovation in Practice Management and Care Delivery
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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"Early Arthritis: Early Act", A Community-Based Knowledge Transfer Program To Improve Ability of General Practitioner to Rapidly Detect and Refer to the Rheumatologist Patients with Early Arthritis. Bruno Faure1, Patrick Froger1, Cécile Gaujoux-Viala2 and Eric Leutenegger.

1Lyon, France, 2Paris, France, 3Pitié Salpêtrière Hospital, Paris, France

Background: Several guidelines have recommended that early arthritis / early rheumatoid arthritis (EA / ERA) should be detected and rapidly referred
to a rheumatologist, ideally within the 6 weeks after symptom onset according to the French Health Authority guidelines published in 2007. However, guideline implementation and dissemination are always challenging, especially when guidelines concern both specialists and family doctors (GP).

Methods: The collaboration between rheumatologists and a continuous medical education (CME) organization enabled the development of a community-based knowledge-transfer program about the diagnosis of early arthritis, based on a few key messages: early RA diagnosis is a key prognostic factor, detection of EA patients can be based on 3 clinical signs suggestive of early RA; GPs have an pivotal role to detect and refer EA patients to the specialist; remission is an achievable goal in RA.

The program was implemented over the phone among the GP community using the Academic Detailing methodology, which 3 different phases: 1) a first confraternal exchange between the training medical doctor in charge of the program and the practising GP who previously agreed to participate in the program, during which a few key messages were delivered; 2) a 2-month practise phase during which the participating GP had to identify patients for whom the national EA guidelines could applied; 3) a second confraternal exchange with the same medical trainer during which the key messages were recalled and the applicability of EA guidelines into daily practise discussed.

Results: 1,054 GP participated in phase 1 of the “Early Arthritis: Early Act” program between August 2008 and March 2009. 645 of them also participated in the practise phase and collected medical information about 1,116 EA patients. Finally, 852 GP participated to the 3rd phase, i.e., the second phone confraternal exchange. The main impact of the program on GP knowledge is presented in the table below:

Conclusion: The “Early Arthritis: Early Act” program enabled the exposition of a substantial number of GP to EA guidelines within a rather limited time frame. It was well accepted by the participating GPs: 52% acknowledged they had a definite need for such knowledge update and 85% found acceptable the time investment required by the program.


Disclosure: B. Fautrel: None; P. Froger: None; C. Gaujoux-Viala: None; E. Leutenegger: None.

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A Checklist of 10 Measures, 6 from a Patient Questionnaire & 4 Physician Global Scores, Requiring <15 Seconds, To Provide Quantitative Patient History & Physical Examination Data, Analogous to Laboratory Tests, for Usual Clinical Care. Theodore Pincus1, Yusaf Yazici2, Martin J. Bergman1, Tuulikki Sokka3 and Christopher J. Swearingen5.

Methods: To analyze a proposed checklist of 10 quantitative measures, 6 from a patient questionnaire and 4 physician global scores, compiled in less than 20 seconds, to provide quantitative patient history and physical examination (PE) data, which rheumatologists indicate are more important than laboratory tests in clinical decisions in usual care visits.

Methods: The 6 quantitative patient measures are from a self-report multidimensional health assessment questionnaire (MDHAQ) for: physical function (FN) (0–10); 21 circle 0–10 visual analog scales for pain (PN), patient global estimate (PTG), and fatigue (FT); review of 60-symptom checklist (SX); and RAPID3, a 0–30 total of FN+PN+PTG which requires 5 seconds. The 6 scores are compared on a flow sheet to scores at previous visits prior to the traditional patient encounter. The rheumatologist records 4 global estimates for: overall status (0–10), and 3 0–3 global scales for levels of inflammatory activity, joint or other organ damage, and non-inflammatory/fibromyalgia symptoms, recorded 0–10 to compare to other measures. An updated flow sheet report includes the 10 proposed checklist scores, as well as laboratory tests and medications. Mean 1st visit values for the 10 proposed checklist measures were analyzed in all 874 new patients seen at a weekly academic setting from 1996–2007 in 8 groups: rheumatoid arthritis (RA), osteoarthritis (OA), fibromyalgia (FM), systemic lupus erythematosus (SLE), gout, spondyloarthropathy (Spondy), inflammatory polyarthritis (InflPol), connective tissue disease (CTD), and “other,” as well as demographic data, ESP and CRP, compared using Spearman rank order correlations.

Results: The 874 patients appear typical for rheumatic diseases (Table). ESP was >20 mm Hg in RA, OA, SLE, Spondy, and CTD, while CRP was >10 mg/L in RA and Spondy. InflPol had also >3.0 in FM and Spondy. Mean PAIN was highest in FM, and >5 in Spondy, RA and InflPol; PTG >5 in FM, RA and Spondy; FT >5 in FM, RA, SLE, InflPol, and other. Symptom scores were >20 only in FM. Mean MD global estimates were >5.0 in all 8 categories - mean 5.7. Estimates were >5 for inflammation in Spondy, RA, gout, InflPol, and CTD; for damage only in RA and OA; and for noninflamm/fibro symptoms in FM, SLE, and other.

Table. Impact of the “Early Arthritis: Early Act” program on GP knowledge about EA and RA

<table>
<thead>
<tr>
<th>“Early Arthritis: Act Early” Program</th>
<th>% respondents</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awareness of the 2007 national EA guidelines</td>
<td>48%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Knowledge of the impact of RA on life expectancy</td>
<td>25%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Awareness of the notion of window of opportunity in RA</td>
<td>13%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Knowledge that remission is an achievable goal in RA</td>
<td>47%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Ability to perform a squeeze test to detect patients with EA</td>
<td>19%</td>
<td>81%</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: The “Early Arthritis: Early Act” program enabled the exposition of a substantial number of GP to EA guidelines within a rather limited time frame. It was well accepted by the participating GPs: 52% acknowledged they had a definite need for such knowledge update and 85% found acceptable the time investment required by the program.

Disclosure: T. Pincus: None; Y. Yazici: None; M. J. Bergman: None; T. Soksa: None; C. J. Swearingen: None.

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Methods: The 6 quantitative patient measures are from a self-report multidimensional health assessment questionnaire (MDHAQ) for: physical function (FN) (0–10); 21 circle 0–10 visual analog scales for pain (PN), patient global estimate (PTG), and fatigue (FT); review of 60-symptom checklist (SX); and RAPID3, a 0–30 total of FN+PN+PTG which requires 5 seconds. The 6 scores are compared on a flow sheet to scores at previous visits prior to the traditional patient encounter. The rheumatologist records 4 global estimates for: overall status (0–10), and 3 0–3 global scales for levels of inflammatory activity, joint or other organ damage, and non-inflammatory/fibromyalgia symptoms, recorded 0–10 to compare to other measures. An updated flow sheet report includes the 10 proposed checklist scores, as well as laboratory tests and medications. Mean 1st visit values for the 10 proposed checklist measures were analyzed in all 874 new patients seen at a weekly academic setting from 1996–2007 in 8 groups: rheumatoid arthritis (RA), osteoarthritis (OA), fibromyalgia (FM), systemic lupus erythematosus (SLE), gout, spondyloarthropathy (Spondy), inflammatory polyarthritis (InflPol), connective tissue disease (CTD), and “other,” as well as demographic data, ESP and CRP, compared using Spearman rank order correlations.

Results: The 874 patients appear typical for rheumatic diseases (Table). ESP was >20 mm Hg in RA, OA, SLE, Spondy, and CTD, while CRP was >10 mg/L in RA and Spondy. InflPol had also >3.0 in FM and Spondy. Mean PAIN was highest in FM, and >5 in Spondy, RA and InflPol; PTG >5 in FM, RA and Spondy; FT >5 in FM, RA, SLE, InflPol, and other. Symptom scores were >20 only in FM. Mean MD global estimates were >5.0 in all 8 categories - mean 5.7. Estimates were >5 for inflammation in Spondy, RA, gout, InflPol, and CTD; for damage only in RA and OA; and for noninflamm/fibro symptoms in FM, SLE, and other.

Quantitative demographic, laboratory tests, patient MDHAQ scores, and MD global estimates in 874 new rheumatology patients, by diagnosis, Spondy = Spondyloarthropathies. InflPol = Inflammatory Polyarthritis.

<table>
<thead>
<tr>
<th>RA</th>
<th>OA</th>
<th>FM</th>
<th>SLE</th>
<th>Gout</th>
<th>Spondy</th>
<th>InflPol</th>
<th>CTD</th>
<th>Other Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>174</td>
<td>32</td>
<td>196</td>
<td>34</td>
<td>12</td>
<td>30</td>
<td>152</td>
<td>50</td>
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<tr>
<td>Demographic and laboratory measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.5</td>
<td>65.1</td>
<td>47.0</td>
<td>38.8</td>
<td>59.3</td>
<td>43.9</td>
<td>51.9</td>
<td>47.6</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>8.4</td>
<td>6.3</td>
<td>5.9</td>
<td>9.1</td>
<td>9.1</td>
<td>11.3</td>
<td>4.6</td>
<td>8.9</td>
</tr>
<tr>
<td>Formal education (years)</td>
<td>13.0</td>
<td>15.0</td>
<td>13.7</td>
<td>13.6</td>
<td>13.8</td>
<td>14.9</td>
<td>14.2</td>
<td>13.9</td>
</tr>
<tr>
<td>% Female</td>
<td>71.3%</td>
<td>65.6%</td>
<td>88.7%</td>
<td>85.3%</td>
<td>16.7%</td>
<td>46.7%</td>
<td>72.9%</td>
<td>82.0%</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>29.7</td>
<td>22.2</td>
<td>16.8</td>
<td>28.9</td>
<td>11.1</td>
<td>26.5</td>
<td>16.6</td>
<td>22.1</td>
</tr>
<tr>
<td>C-reactive protein (mg/mL)</td>
<td>17.5</td>
<td>3.9</td>
<td>6.1</td>
<td>6.7</td>
<td>3.6</td>
<td>11.5</td>
<td>6.1</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Conclusion: A proposed checklist of 10 measures, 6 from a MDHAQ and 4 global MD scores, provides quantitative data from a history and PE at each encounter in the infrastructure of rheumatology care, in ~20 seconds. These data provide quantitative measures to assess patient status over long periods, “treat to target” values, and may lead to improved patient outcomes.

Disclosure: T. Pincus: None; Y. Yazici: None; M. J. Bergman: None; T. Soksa: None; C. J. Swearingen: None.

Tuesday, November 9
facilitate early diagnosis; 3) to reduce the variability in SpA; and 4) to improve the knowledge and practical skills on SpA of general practitioners (GPs) and specialists.

**Methods:** The Esperanza Program includes: 1) a call for the creation of 25 early SpA units with specific requirements; 2) the establishment of a managed care plan with 8 measurable indicators; 3) a web-based platform which may function as an electronic medical record (EMR), and which permits evaluation, and facilitates networking and feed-back; and 4) educational initiatives.

**Results:** Evaluation of the 25 implemented units covers from April 2008 until October 15th 2009. As of last evaluation, 1812 GPs were participating and 792 patients had been referred by their GPs. Indicators’ values: 1) Over 90% of the patients had been attended within 30 days since their visit to PC; 2) the reliability of the referrals was 92%; 3) 53% of first visits had a duration of 30 to 60 minutes; 4) 28% of the patients had a diagnosis of SpA already in the first visit; 5) a report was issued in 25% of the medical visits; 6) 24% of the electronic reports issued were consulted by the GPs; 7) missing data in the EMR was 24%; and 8) an appropriate frequency of revisions was met in 84% of the patients. The patients attended were evenly distributed among sexes, and most of them were active workers. Their disease was active but spinal mobility and structural changes were preserved.

**Conclusion:** It is possible to implement a large scale program that is measurable and that helps to improve the management of early disease.

**Disclosure:** M. Gobbo: None; R. Schiotis: None; S. Muñoz-Fernández: None; L. Carmona: None; E. Collantes: None; E. de Miguel: None; M. J. García-Yébenes: None; J. Muler: None; R. Almover: None; C. Fernández-Carballeiro: None; J. F. Garcia Llorente: None.

### 987

**A Pilot Study To Quantify Suffering among Patients with Rheumatoid Arthritis—A New Measure for Patient Reported Outcome (PRO).**

Tom Sensky1, Rieke Alten2, Philippe Bertin1, Boulou Harauou1, Ed C. Keystone3, Peter C. Taylor4, Pablo Cruz1, Boulos Haraoui3, Rieke Alten4, Philippe Goupille, 1

**Background:** The potential gravity of adverse outcomes in rheumatoid arthritis (RA) is such that there is a need for outcome measures which not only reflect this but are also meaningful to patients, the public and clinicians. Alleviation of suffering is a key goal in medicine. The Pictorial Representation of Illness and Self Measure (PRISM) is a novel, validated, brief method of measuring suffering consistent with Cassell’s seminal conceptualisation of suffering. Pilot data are reported on using PRISM to assessing suffering in RA.

**Methods:** The survey was conducted on a convenience sample of 245 patients with clinically diagnosed RA from specialist clinics in Berlin, Limoges, London, London, United Kingdom, 1Institut de Rhumatologie de Montreal, Montreal, QC, Canada, 2Schloßpark-Klinik UnivMed, Berlin, Germany, 3University of Toronto, Toronto, ON, Canada

**Results:** Basic sociodemographic and clinical data were collected, and all patients were asked to complete the PRISM task. Information was collected about patients’ perceptions of the causes of their suffering.

**Results:** PRISM took 1-4 minutes to complete, and was easy to use. Most patients understood the simple instructions. Patients were consistent in their perceptions of the causes of their suffering.

**Results:** The conclusion of this pilot survey has confirmed that PRISM is easy to use in different languages without need for specific training, is very acceptable to patients and clinicians, and can be readily incorporated into routine clinical practice. It measures something distinct from pain and global disease burden, but associated with these. These data support further investigation of PRISM as a novel patient-reported outcome which quantifies factors salient to each individual with respect to the impact of the illness and its treatment and is likely to incorporate a wider range of such influences than existing measures. As such, it may have utility in setting agreed therapeutic targets.

**Acknowledgements:** This pilot study was carried out with the support of an unrestricted grant from UCB.

**Disclosure:** T. Sensky: None; R. Alten: None; P. Bertin: None; B. Harauou: None; E. C. Keystone: None; P. C. Taylor: UCB, Inc., 2.

### 988

**Antibodies towards Infliximab Are Associated with Poor Infliximab Maintenance and Low Infliximab Concentrations.** Emile Ducourea, David Ternanta, Denis Mullena, Saloua Mannou, Delphine Chu Mion Linb, Hervé Watierc, Gilles Paintaudb and Philippe Goupilleb, 1Université François Rabelais de Tours, Laboratoire d’Immunologie, 2Université François Rabelais de Tours, Laboratoire de Pharmacoc-Toxicologie, 3Université François Rabelais de Tours, Service de Rhumatologie

**Background:** Despite its benefits, infliximab is responsible for the development of antibodies against infliximab (ATI), which is associated with an increased risk of infusion reactions and a reduced response to treatment [1,2]. Herein, we studied the relationship between ATI and infliximab maintenance.

**Methods:** All patients initiating infliximab from December 2005 to January 2009 were followed until the end of their treatment or until January 2009. Infliximab [3] and ATI serum concentrations were measured by enzyme linked immunosorbent assays before each infusion. The patients were separated into two groups: “ATIpos” if ATI were detected at least once during the follow-up period or “ATIneg” in the other patients. The characteristics (sex, age, disease, mean disease duration, concomitant treatment with methotrexate or prednisone, infliximab dose at initiation, ESR and CRP) of the 2 groups were compared using a student’s t-test or a chi-square test. Infliximab treatment maintenance in the 2 groups was studied using a survival analysis and compared with a log rank test. A P value of less than 0.05 was considered statistically significant.

**Results:** A total of 111 patients were studied: 17 rheumatoid arthritis (RA), 91 ankylosing spondylitis (AS), and 3 others systemic diseases. ATI were detected in 22 patients (7 RA, 14 AS and 1 other disease). Median detection of ATI was 3.5 months (0.4–26.0). Infliximab dose at initiation was lower in ATIpos patients than in ATIneg patients (4.1 mg/kg vs. 4.9 mg/kg; p = 0.005). Proportion of patient with concomitant MTX treatment was lower in ATIpos group than ATIneg group but the difference did not reach significant difference (14% vs. 36% p = 0.08). Maintenance of infliximab was poorer in ATIpos group than in ATIneg group, with medians of 10 and 16 months, respectively (p = 0.05). Infliximab trough concentrations during initiation were statistically lower in ATIneg than in ATIpos patients.

**Conclusion:** In our experience, 20% of patients treated with infliximab develop ATI, often within the first 3 months of treatment. High concentrations of infliximab during initiation seem to reduce the incidence of ATI, and absence of ATI is associated with prolonged durations of infliximab treatment. This clearly argues for an early monitoring of infliximab serum concentrations.

**References:**


**Disclosure:** E. Ducourea: None; D. Ternanta: None; D. Mullena: Abbott Laboratories; 2. S. Mannou: None; D. Chu Mion Linb: None; H. Watierc: None; G. Paintaudb: Roche, 5, Wyeth Pharmaceuticals, 5; P. Goupilleb: Abbott Laboratories, 5; Bristol-Myers Squibb, 5, Roche Diagnostics, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5.

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**Bridging the Gap in Osteoporosis Care, Part I: Results of the SPOOF (Secondary Prevention of Osteoporotic Fracture) Project.** Mary A. Langan, John J. Carey, Robert J. Coughlan, Catherine Armstrong, Assumpta O’Brien, Sarah McNamara, Ella Murphy and Mohamed Ballal. Galway University Hospitals, Galway, Ireland
Background: Many agents have been shown to reduce the risk of future fracture in patients presenting with osteoporotic fractures. Despite widespread availability for over a decade, studies show that most patients are not evaluated or treated for osteoporosis following such fractures. Thus effective measures to improve the evaluation and treatment of osteoporosis following fragility fracture are needed.

Purpose: To examine the effectiveness of an outpatient fracture intervention program to improve the rates of osteoporosis evaluation and treatment among fracture patients aged 50 years and older seen in orthopedic fracture clinics.

Methods: Collection and analysis of data was approved by the local Institutional Review Board. We evaluated the rate of osteoporosis evaluation, diagnosis and treatment among a cohort of patients aged 50 years and older presenting to our University Hospital Orthopaedic clinic with a fragility fracture between 2005 and 2007. Groups were either assessed as part of a fracture liaison program or exposed to usual orthopedic care with referral back to their primary care doctor following treatment. A mail and telephone survey was undertaken of 190 patients in both cohorts 2 years following their fracture clinic visit. We compared the rate of osteoporosis diagnosis and treatment between the two cohorts within 2 years of their fracture.

Results: There was a greater response rate among those in active intervention group (73% vs 63%). The most common fracture site was wrist and forearm in both groups. Age and gender of respondents was similar between the intervention and control groups: 66 years & 92% vs 71 years & 86% respectively. Treatment rates were similar between both groups before fracture (<20%). Significantly more subjects seen by a fracture liaison coordinator received: a) a bone density measurement (89% vs 47%, P <0.01), 2) osteoporosis treatment with calcium and vitamin D (81% vs 33%, P<0.01), and 3) pharmacologic therapy for osteoporosis (48% Vs 27%, P<0.01).

Conclusions: A case-finding fracture liaison service improves the rate of osteoporosis diagnosis and therapy following fragility fracture in persons of 50 years and older.

Disclosure: M. A. Langan: Merck Pharmaceuticals, 9; J. J. Carey: Eli Lilly and Company, 2, 8, Merck Pharmaceuticals, 2, 8, Novartis Pharmaceuticals Corporation, 2, sanofi-aventis, 8; R. J. Coughlan: Eli Lilly and Company, 2, Merck Pharmaceuticals, 2, 8, Novartis Pharmaceuticals Corporation, 2; C. Armstrong: None; A. O’Brien: None; S. McNamara: None; E. Murphy: None; M. Ballant: None.

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Clues To Differentiate Non-Inflammatory from Inflammatory Symptoms in Patients with Systemic Lupus Erythematosus (SLE). Using a Multi-Dimensional Health Assessment Questionnaire (MDHAQ). Theodore Pincus1, Isabel Castrejon2, Jill P. Buyon6, Chung-E. Tseng2, Peter M. Izmirl3, Yusuf Yazici1 and Anca D. Askanase3. 1Hospital for Joint Diseases, 2, 8, Novartis Pharmaceuticals Corporation, 2, sanofi-aventis, 8; 3Brown University, 4Stanford University, Stanford, CA, 5UCSF, San Francisco, CA, 6UCSF, 7University of California, San Francisco, CA, 990

Purpose: To analyze whether quantitative scores on a multidimensional health assessment questionnaire (MDHAQ) provide clues to the likelihood of inflammatory versus non-inflammatory symptoms and comorbid fibromyalgia, an important challenge in clinical care, according to a global scale for non-inflammatory symptoms completed by a rheumatologist in 50 patients with SLE seen in usual care.

Methods: A cross-sectional study was performed in 50 consecutive SLE patients of one rheumatologist seen in usual care. On arrival at the clinic, patients completed a multidimensional health assessment questionnaire (MDHAQ) which includes scales for physical function (FN), 0–10 visual analog scales for pain (PN), global estimate (PTGL) and fatigue (FT), and a review of systems symptom checklist (SX). SLE patients also completed a self-report Systemic Lupus Assessment Questionnaire (SLAQ). The rheumatologist, unaware of MDHAQ and SLAQ scores, recorded a physician global estimate (MDGL) and an estimate of non-inflammatory symptoms, each scored on a 0–3 scale in 0.1 increments, as well as four SLE indices: SLEDAI-2K (SLE Disease Activity Index), BILAG (British Isles Lupus Assessment Group index), SLAM (SLE Activity Measure) with and without laboratory tests, and ECLAM (European Consensus Lupus Activity Measurement). SLE patients with scores of ≥0.5 on the non-inflammatory symptom scale were regarded as “low” and those with scores ≥0.5 “high” non-inflammatory symptoms; the two groups were compared using the Mann-Whitney statistic.

Results: The study included 45 women and 5 men, mean age 38.7 years, mean disease duration 7.3 years. Of the 50 patients, 16 had high and 34 low scores for non-inflammatory symptoms. Those with high scores for non-inflammatory symptoms had significantly higher scores for FN, PN, FT, PTGL, SX, SLAQ, and SLAM without laboratory tests, as well as significantly lower CRP. No significant differences were seen patients estimated as “high” and “low” scoring patients for SLEDAI, BILAG, SLAM, ECLAM, C3, C4, antiDSDNA, or ESR. Fewer than 50% of “low” patients had FN, PN, PTGL, or FT ≥2, while 100% of “high” patients had FT >2 and 94% PTGL >2. All patients with high non-inflammatory symptoms (16/16) reported more than 5 SX, compared to 15/34 (44%) “low” patients, and 12/16 (75%) “high” patients reported >10 SX, compared to 6/34 (18%) “low” patients.

Table. Differences in the mean values of the MDHAQ scores, SLAQ, SLE indices and laboratory tests between SLE patients with versus without non-inflammatory symptoms. (Mann-Whitney)

<table>
<thead>
<tr>
<th>Measure/Index</th>
<th>SLE low non-inflammatory symptoms (n=34)</th>
<th>SLE high non-inflammatory symptoms (n=16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>Mean (± SD)</td>
<td>Median (Range)</td>
<td>Mean (± SD)</td>
</tr>
<tr>
<td>Pain VAS</td>
<td>0.74 (±1.25)</td>
<td>0 (0–53)</td>
<td>2.7 (±2.4)</td>
</tr>
<tr>
<td>Patient global</td>
<td>2.5 (±2.6)</td>
<td>1.7 (0–9)</td>
<td>4.8 (±2.7)</td>
</tr>
<tr>
<td>Fatigue VAS</td>
<td>2.2 (±2.5)</td>
<td>1.2 (0–9.5)</td>
<td>5.4 (±2.2)</td>
</tr>
<tr>
<td># Symptoms</td>
<td>2.8 (±2.5)</td>
<td>2.0 (0–9)</td>
<td>6.3 (±2.1)</td>
</tr>
<tr>
<td>ECLAM</td>
<td>6.9 (±6.8)</td>
<td>5.0 (0–31)</td>
<td>16.9 (±32)</td>
</tr>
<tr>
<td>RAPlD</td>
<td>5.4 (±5.9)</td>
<td>3.0 (0–22.8)</td>
<td>13.0 (±6.7)</td>
</tr>
<tr>
<td>SLAQ-total</td>
<td>7.0 (±3.5)</td>
<td>6.5 (0–18)</td>
<td>16.9 (±4.5)</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>5.1 (±3.9)</td>
<td>4.0 (0–16)</td>
<td>4.8 (±3.6)</td>
</tr>
<tr>
<td>BILAG</td>
<td>4.2 (±4.2)</td>
<td>2.5 (0–15)</td>
<td>5.4 (±4.5)</td>
</tr>
<tr>
<td>ECLAM</td>
<td>1.9 (±1.3)</td>
<td>1.5 (0–4)</td>
<td>2.2 (±1.6)</td>
</tr>
<tr>
<td>SLAM</td>
<td>3.7 (±3.2)</td>
<td>3.0 (0–12)</td>
<td>4.2 (±2.3)</td>
</tr>
<tr>
<td>SLAM-no lab</td>
<td>1.6 (±1.6)</td>
<td>1.0 (0–5)</td>
<td>3.2 (±1.8)</td>
</tr>
<tr>
<td>C3</td>
<td>8.3 (±10)</td>
<td>103 (43–174)</td>
<td>123.3 (±35.1)</td>
</tr>
<tr>
<td>C4</td>
<td>2.0 (±11.3)</td>
<td>17.5 (6–63)</td>
<td>21.1 (±7.7)</td>
</tr>
<tr>
<td>ESR</td>
<td>27.1 (±33.1)</td>
<td>12.5 (11–122)</td>
<td>11.2 (±10)</td>
</tr>
<tr>
<td>CRP</td>
<td>5.4 (±8.1)</td>
<td>3.1 (0–31)</td>
<td>0.7 (±1.3)</td>
</tr>
</tbody>
</table>

Conclusion: High scores for dysfunction, pain, fatigue, global estimates, and number of symptoms are common in SLE patients with high versus low levels of non-inflammatory symptoms. SLE indices do not distinguish between patients with high versus low levels of non-inflammatory symptoms. A simple global scale to estimate non-inflammatory symptoms may be informative in therapeutic decisions, particularly if consistent with patient questionnaire patterns.

Disclosure: T. Pincus: None; I. Castrejon: None; J. P. Buyon: None; C-E. Tseng: None; P. M. Izmirl: None; Y. Yazici: None; A. D. Askanase: None.

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DMARD Use in Rheumatoid Arthritis: An Analysis of HEDIS Data from 2005–2008. Gabriela Schmajuk1, Amal Trivedi1, Daniel Hal Solomon3, Edward H. Yelin2, Laura Trupin2, Eliza F. Chakraverty1 and Jinoos Yazdany1. 1Mountain View, CA, 2Brigham and Womens Hospital, Boston, MA, 3Brown University, Stanford University, Stanford, CA, 4UCSF, San Francisco, CA, 5UCSF, 7University of California, San Francisco, CA

Background: Since 1997, all managed-care plans administered by Medicare have reported on quality of care measures from the Health Plan Employer Data and Information Set (HEDIS). In 2005, HEDIS introduced a quality indicator to assess the use of disease modifying anti-rheumatic drugs (DMARD) among patients with rheumatoid arthritis (RA). We determined sociodemographic, community, and health-plan predictors of performance on the RA measure among Medicare managed care (MCC) enrollees and health plans.

Methods: We analyzed individual-level HEDIS data for 97,587 beneficiaries at least 65 years old with a diagnosis of RA and enrolled in MCC plans between 2005 – 2008. Low personal income was identified by the state buy-in variable in the Medicare denominator file. Zip-code-based

SD = standard deviation
DMARD use varied widely by health plan (ranging from 13% to 91%). Health plans that opened their health maintenance organization operation later than 1999 were more likely to be low-performing than those with operation later than 1999. Logistic regression was used to identify predictors of low-performing plans.

**Results:** The mean age of eligible patients was 74.4 years; 76% were female, and 81% were Caucasian. A DMARD was dispensed to 66% of patients in 2005, rising to 71% of patients in 2008 (p for trend < 0.01). The largest difference in rate of DMARD use was based on age: patients > 85 had a 29% (95% CI (28%, 31%)) lower rate of DMARD use compared to patients 65–69 years old, even after adjusting for all other factors. Males, non-Caucasians, patients with low personal income, and those with lower zip-code-based SES were also less likely to receive a DMARD, as were patients in the Middle and South Atlantic regions (see Table).

**Does Asymptomatic Hyperuricemia Treatment Improve Health? A Decision-Analytic Evaluation.** Roopa Akkineni2, Alexandra Lee3, Katherine Miller4, Anna Tosteson2 and Daniel A. Albert1. 1Dartmouth-Hitchcock Med Ctr, Lebanon, NH, 2The Dartmouth Institute

**Purpose:** Recent studies have suggested that elevated uric acid levels are associated with an increase in coronary and cerebrovascular disease. Treatment for asymptomatic hyperuricemia with uric acid lowering drugs, such as Allopurinol, may reduce cardiovascular events. However, some patients have experienced adverse drug reactions while treated with Allopurinol. A decision analysis was designed to identify the optimal treatment strategy for patients with asymptomatic hyperuricemia.

**Methods:** A Markov state-transition model was constructed to assess the occurrence of cardiovascular events and life expectancy in patients undergoing urate-lowering treatment with Allopurinol, compared with watchful waiting. The model was built for a hypothetical 50-year old asymptomatic hyperuricemic male patient. Probabilities were derived from current literature. Developments of gout or uric acid stones as well as cardiovascular events were modeled. Sensitivity analyses were conducted for drug effectiveness and probability of adverse drug reaction.

**Results:** In the base–case analysis, the two treatment options had a similar occurrence of vascular events and life expectancy. However, watchful waiting was associated with a slightly greater gain in quality adjusted life years (QALYs) than treatment with Allopurinol (10.61 QALYs versus 10.58 QALYs). A sensitivity analysis was conducted on drug effectiveness, drug protection from cardiovascular events, the probability of adverse drug event, and death from adverse drug reaction. When the probability of having an adverse drug reaction increased, watchful waiting was always favored. The results were similar for probability of death from adverse drug reaction. By contrast, when the effectiveness of drug therapy varied, treatment with Allopurinol was the optimal choice for effectiveness rates over 69.2%. The maximum gain in QALYs assuming 100% effectiveness of Allopurinol therapy was approximately 0.35 QALYs.

**Conclusions:** Watchful waiting was preferred for patients with asymptomatic hyperuricemia at the base rate of 21% effectiveness of Allopurinol; however, the number of QALYs gained with watchful waiting was small compared to treatment with Allopurinol. At 100% effectiveness, treatment with Allopurinol was the preferred strategy with a gain of 0.35 QALYs, which in magnitude is similar to statin therapy with 0.25 QALYs gained.

**Disclosure: R. Akkineni: None; A. Lee: None; K. Miller: None; A. Tosteson: None; D. A. Albert: None.**

993 Early Experience with the American College of Rheumatology (ACR) Rheumatology Clinical Registry (RCR). Salahuddin Kazmi2, Elizabeth A. Tindall3, Kristen McNiff2 and Itara Barnes1. 1American College of Rheumatology, Atlanta, GA, 2Arthritis Consultation Center, Dallas, TX, 3Oregon Health and Science University, West Linn, OR

**Background:** The RCR was launched by the ACR to provide members with an infrastructure for quality reporting related to rheumatoid arthritis, gout, osteoarthritis, osteoporosis, and drug safety. This abstract describes the initial uptake of the RCR, and initial findings related to functional status, DMARD use, TB screening, prognosis, and disease activity assessment for RA patients in rheumatology practice.

**Methods:** Rheumatology providers and/or designated practice staff conducted retrospective medical records abstraction, for a sample of patients seen by the rheumatologist. Reporters submitted data via a secure, web-based registry system. The analytic specifications for RA measures include adults (≥18 years of age) with a diagnosis with RA receiving treatment by the reporting rheumatology provider. Additional components of each measure are listed in Table 1.

**Results:** 240 rheumatology providers in 125 practices submitted data on 7,806 patients with RA (mean submission/rheumatologist = 31) from July 1, 2009 to January 31, 2010. Reporting providers practice in sites ranging from solo practitioner offices to large academic medical centers.
Conclusions: Rheumatologists across the country used the RCR in 2009 to report quality data. Establishing RCR as a mechanism for CMS PQRI reporting especially incentivized use and enhanced participation (consistent with the ACR goal that RCR provide maximal benefit from data submission). Ongoing data collection and analysis will help reveal the clinical significance of the data and monitor improvement over time.

Next steps planned for the RCR include continually enhance the quality of data collected, analytic reports, and EHR-enabled reporting.

RCR provides an opportunity for rheumatology providers to facilitate practice improvement, contribute to collaborative improvement projects, and contribute to national data, led by their professional society.


994 Evaluating Adherence to Quality Indicators in Prevention of Glucocorticoid Induced Osteoporosis in Patients at the Veterans Affairs in Lexington, Magdalena Winarska1, Joseph Conigliaro2, Heather Bushh2, Lucia Hardi1, Elnaz N Tabrizi1 and Leslie J. Crofford3. 1Univ of Kentucky, Lexington, KY, 2Univ of Kentucky, Lexington, KY, 3Univ of Kentucky, Lexington, KY

Background: Osteoporosis is a systemic skeletal disease characterized by low bone mass, microarchitectural deterioration of bone tissue, and a consequent increase in bone fragility and susceptibility to fractures. Glucocorticoids are widely used agents for many inflammatory diseases. Glucocorticoid-induced osteoporosis (GIOP) is the most common type of secondary osteoporosis ultimately leading to fractures in up to 50% of patients. Despite steadily increasing evidence of effective preventive therapies among patients initiating long term glucocorticoid therapy, prevention of GIOP is often neglected, with a low level of awareness among primary and specialist physicians. The specific aim of this study was to evaluate adherence to known recommendations on prevention of GIOP. The long term goal of this study is to improve quality of care among patients treated with glucocorticoids.

Methods: A retrospective computer-generated chart review of electronic health records from the Veterans Affairs Medical Center in Lexington, Kentucky identified 453 patients treated with prednisone 7.5 mg daily or its equivalent for at least six months between October 2004 and October 2009. Using this population we extracted following data: age, race, body mass index, bone density testing, dose of glucocorticoid therapy, bone loss prevention medication use including calcium, vitamin D, bisphosphonate, calcitonin, hormone replacement therapy, testosterone replacement therapy, steroid prescribing practitioner’s speciality and diagnosis for which glucocorticoids were prescribed.

Results: The average age of the patients was 68 years (SD = 11.7). Of the 453 patients, 430 were males and 42 were Caucasian. Bone mineral density testing was performed on 128 (28.3%). Of 430 male patients, 69 (15.2%) had testosterone levels checked. Of 22 patients with low testosterone, 8 were on testosterone replacement therapy. Calcium and vitamin D was given to 210 (48.8%) patients and bisphosphonates to 147 (32.5%) of patients; 184 (40.6%) were not on any prescribed pharmacologic therapy to prevent GIOP. Primary care providers wrote 233 (51.5%) of the total prescriptions for glucocorticoids followed by 67 (15%) rheumatologists and 52 (11.5%) pulmonologists. The most common diagnosis for which the patients were prescribed prednisone were chronic obstructive pulmonary disease (n=69) and rheumatoid arthritis (n=49).

Conclusions: GIOP is a common but still relatively neglected problem. Although it is not possible to define an absolute standard of care, the overall adherence to guidelines for prevention of GIOP in our study was low. This study identifies areas amenable to targeted educational efforts that will improve care of patients requiring glucocorticoid treatment.


995 Formal Joint Counts Are Performed at More Than 50% of Visits of Patients with Rheumatoid Arthritis in Usual Care Outside of Clinical Research, by 64% of European Rheumatologists in 2010 Compared to 44% in 2003. Theodore Pincus1, Ed C. Keystone2, Marc de Longueville3 and Sophie Costello4. 1Hospital for Joint Disease, Hastings-on-Hudson, NY, 2UCB Pharma, 3University of Toronto, Toronto, ON, Canada

Purpose: To analyze responses of European rheumatologists concerning the likelihood of performing of a formal swollen and tender joint count in 2010, and compare results to a similar estimate in 2003.

Methods: About 300 rheumatologists attended a meeting in March 2010 sponsored by a pharmaceutical company. Most had participated in clinical trials of patients with RA. Keypads were available for instant recording of responses. A query was presented: “In patients with RA seen in usual care outside of clinical trials and other clinical research, how often do you perform a formal tender and swollen joint count?” Response options were 0, 1–24, 25–49, 50–74%, 75–99%, and 100% of the time. Results were instantly totaled. Results at this 2010 meeting were compared with results obtained from European rheumatologists in a similar study performed at a similar meeting in 2003 (Pincus T, Segurog OG. Ann Rheum Dis. 2006;65:820–2).

Results: Overall, 143 responses were recorded in 2010 for the joint count; only 4% of rheumatologists responded that they “never” performed a formal joint count, 13% at 1–24% of visits, 19% at 25–49%, 16% at 50–74%, 23% at 75–99% of visits, and 25% “always.” Each of the 4 countries with more than 5 responding rheumatologists – United Kingdom, Germany, Spain, and Italy – included at least one respondent in 4 of the 6 categories. Results of a similar survey of 500 European rheumatologists in 2003 were 13% “never”, 32% at 1–24% of visits, 11% at 25–49%, 14% at 50–74%, 16% at 75–99% of visits, and 14% “always.” Overall, 64% of European rheumatologists in 2010 reported that they performed formal joint counts at ≥50% of visits, compared to 44% in 2003.

Question for rheumatologists: For RA patients under your care (when not for clinical trials or reimbursement), how often do you perform:

<table>
<thead>
<tr>
<th>Measure</th>
<th>Year</th>
<th>Never</th>
<th>1–24%</th>
<th>25–49%</th>
<th>50–74%</th>
<th>75–99%</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formal joint count</td>
<td>2003</td>
<td>13%</td>
<td>32%</td>
<td>11%</td>
<td>14%</td>
<td>16%</td>
<td>14%</td>
</tr>
<tr>
<td>Formal joint count</td>
<td>2010</td>
<td>4%</td>
<td>13%</td>
<td>19%</td>
<td>16%</td>
<td>23%</td>
<td>25%</td>
</tr>
<tr>
<td>Formal joint count</td>
<td>2003</td>
<td>56%</td>
<td>4%</td>
<td>36%</td>
<td>64%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: An increase in the likelihood of performing a formal joint count among physicians in treatment of patients with RA was reported in 2010 compared to 2003. Nonetheless, one-third of rheumatologists indicated that a formal joint count was performed at fewer than 50% of visits. Further educational efforts for rheumatologists might emphasize greater use of formal joint counts in standard clinical care.


Purpose: In our practice 2 patients (pts) with systemic lupus erythematosus (SLE) who received intravenous (IV) cyclophosphamide (CYC) for lupus nephritis developed anal cancer (ca). Both had a history of human papilloma virus (HPV) & presented with bright red blood per rectum (BRBPR). HPV is responsible for almost all cervical & 90% of anal ca. Studies suggest that women with SLE are at greater risk of developing cervical dysplasia & ca than the general population. It is unknown whether this is attributable to immunosuppressive exposure or baseline defective immunity to HPV. Furthermore, immunocompromised pts & women with a history of cervical ca (or high-grade cervical lesions) are among high risk groups for the development of anal ca. Appropriate screening and knowledge of cervical & anal ca is imperative for SLE pts.

Methodology: We developed a patient report survey (PRS) to assess knowledge & educate our pts regarding cervical & anal ca. From May-June 2010 we surveyed pts at Bellevue & NYUHJD lupus clinics as well as private practice. Both genders were included & questions consisted of HPV awareness, HPV/SLE/ca risk, frequency of cervical & anal pap smears, & HPV vaccine. Education and recommendations were also provided.

Results: 75 pts participated; 69 F, 6 M; Age mean = 48; AA 24, H 32, C 6, A 11; Sexually active 39/75(52%); Unaware of HPV 40/75(53%); Ever told had HPV 11/75(15%); Smoked cigarettes 7/75(9%); Unaware of SLE/ HPV risk 7/75(9%); Unaware of cervical Pap 20/75(26%); No GYN 15/69(22%); Greater than 1 year since last cervical Pap 19/69(28%) & 61/75(22%) never had; Abnormal cervical Pap 14/63(22%); Unaware of anal ca risk 64/75 (85%); Had anal pap smear 7/75(10%); Unaware of HPV vaccine 41/75(55%); Had vaccine 3/75(4%). Almost half the cohort were unaware of HPV & a strikingly high number unaware of SLE, HPV & anal ca. The few smokers were encouraged to quit. Many needed to be counseled about the importance of yearly cervical screening & more frequently if abnormal. A few never had cervical Pap smears & encouraged to make an appointment. The majority of pts lacked knowledge regarding risks of anal ca & screening tools such as anal pap smears. Finally, most were unaware of the HPV vaccine & only a few eligible pts had yet to receive it.

Conclusion: The RPS allowed for assessment of knowledge and the ability to provide education to help decrease the development of cervical and anal ca. Our immunocompromised pts should undergo appropriate screening. Yearly Pap smears with HPV testing can help identify high risk (HR) types of HPV early in the disease. The SLE pts exposed to immunosuppressants also need to receive annual screenings. In addition, eligible pts should be educated about the HPV vaccine which prevents up to 70% of HR HPV. Also, as we experienced, pts exposed to CYC with HPV who develop BRBPR need prompt evaluation. Furthermore, anal ca screening should be considered for our high risk pts even though there are currently no standardized guidelines. Finally, education about these malignancies will help ensure that our pts are screened appropriately & increase awareness to report associated symptoms.

Disclosure: E. J. Lydon: None; H. M. Belmont: None.

Impact of a Screening Protocol with Added Thoracic CT and Quantiferon in Prophylactic Treatment of Latent Tuberculosis in Anti-TNFa Candidate Patients. Nathalie Saidenberg-Kermanac’h, Luca Semerano, Jean-Marc Naccache, Michel Brauner, Géraldine Falgarone, Dominique Dumont-Fischer, Xavier Guillot and Marie-Christophe Boissier. 1Department of Pulmonology, Avicenne Hospital (AP-HP), Bobigny, France, 2Department of Radiology, Avicenne Hospital (AP-HP), Bobigny, France, 3Department of Rheumatology, Avicenne Hospital (AP-HP), Bobigny, France, 4Department of Rheumatology, Avicenne Hospital (AP-HP), Bobigny, France, 5EA4222, Paris-13 University, France

Background: Screening for latent tuberculosis (LTBI) is current clinical practice before anti-TNFa treatment given the risk of disease reactivation with this class of therapeutics. The current screening protocol for LTBI in France (Sc1) comprises the parallel performance of chest X-ray, TST and anamnesis for LTBI risk factors.

A higher disease prevalence reduces the negative predictive value of a given screening test (i.e. increases the number of false negatives), and, additionally, patients under immunomodulating treatments can be falsely negative to tuberculin skin test (TST). In our hospital, which serves the district with the highest incidence of tuberculosis in France, we had a case of LTBI reactivation under anti-TNFa treatment, in a patient who hadn’t been treated for LTBI due to negativity of Sc1.

For these reasons, taking into account the 2006 recommendations of the French Health Authority (HAS), and in accord with local TB experts, it was decided to screen all candidate patients to anti-TNFa treatment with a screening protocol (Sc2) where Quantiferon and chest CT were added to current screening tests for LTBI. The aim of the study was to evaluate the impact of this screening protocol (Sc2) on the prescription of LTBI treatment.

Methods: 96 consecutive patients candidate to anti-TNFa treatment for rheumatoid diseases underwent a screening protocol for LTBI comprising chest x-ray, TST (performed using Mantoux method), anamnesis for LTBI risk factors, a chest CT scan and blood QuantiFERON TB Gold IT (Cellestis) test. All medical records were discussed with a radiologist and a pulmonologist, leading to the final therapeutic decision of treating or not for LTBI before anti-TNF treatment. The ROC curve of sensitivity and specificity of Sc1 and Sc2 were compared, with the final therapeutic decision considered as the gold standard.

Results: among the 96 patients there were 39 positive TST, 12 positive Quantiferon, 10 chest x-rays and 8 CT scans suggestive of LTBI respectively. The sensitivity and specificity and ROC AUC of Sc1 were 88.9%, 93.5% and 0.912 [55% CI 0.843–0.961] respectively. For Sc2 they were 100%, 93.5% and 0.967 [95% CI 0.907–0.993]. The difference between the two ROC curves was not significant (p=0.096) at a d-error of 0.05 and a b-error of 0.2. 48 patients were finally treated with Sc2 vs. 43 that would have been treated with Sc1.

Conclusion: In a population at high prevalence of LTBI a screening protocol before anti-TNFa treatment comprising the parallel performance of TST, chest x-ray, quantiferon and chest CT scan lead to treat more patients than the screening protocol currently adopted in France. This difference was not statistically significant in a study with 80% power.

Disclosure: N. Saidenberg-Kermanac’h: None; L. Semerano: None; J.-M. Naccache: None; M. Brauner: None; G. Falgarone: None; D. Dumont-Fischer: None; X. Guillot: None; M.-C. Boissier: None.

Implementation of an Electronic Interface for Medical Record Documentation in an Academic Pediatric Rheumatology Outpatient Clinic. Jennifer M. P. Woo1, Miriam F. Parsa2, Gil Amari1, Nasim Afshar1, Kerry T. Gallagher1, Omella J. Rullo1 and Deborah K. McCurdy2. 1Division of Internal Medicine and Neuropsychiatry-Medicine; Hospital Medicine and Neurosurgical Clinical Quality Programs, UCLA, Los Angeles, CA; 2Division of Pediatric Rheumatology, UCLA, Los Angeles, CA

Background: Health information technology (HIT) has gained importance in clinical practice in an effort to improve clinic efficiency and to minimize medical and communication errors resulting from handwritten notes. Our healthcare center utilizes an electronic medical record (EMR) system that requires outpatient clinic physicians to document patient visits on paper clinical notes (PCN) and send them outside the department to be uploaded. This process generates a lag period, ranging from 2 to 14 days when PCN are inaccessible via network computer. In response, we have designed, created, and implemented an EMR interface or electronic note (ENR) that mimics the paper template, allowing the physician use a portable tablet computer in the exam room to directly upload their findings to an established clinical document system (CDS) and the EMR. We are assessing patient perception of the use of an EMR in clinic and evaluating its effects on the workflow of the pediatric rheumatology outpatient clinics.

Methods: Our EMR is a Microsoft Excel form and includes measures to verify medication dosing based on body surface area and weight, to maximize billing criteria, and to facilitate retrieval of clinical data for future research. Patients or their parents were asked, via paper survey, to anonymously assess the quality of care and their perception of EMR use in clinic; we will continue these observations until our EMR is fully integrated into clinical practice. Clinic efficiency was evaluated by monitoring the length of time physicians spent with each patient, the additional time dedicated to charting following the patient visit, and the time required for the clinical notes to be uploaded to the EMR.

Results: With the implementation of our EMR, we have reduced the average time required to upload clinical documents by 6 days and increased the average percentage of notes uploaded within 48 hours of the patient visit by 75% (p < 0.0001). Currently, 93% of patients/parents
surveyed (n = 25) were receptive to the use of a clinical EMRI and 75% believed that an EMRI would benefit the patient’s quality of care. There was no significant difference in perceived satisfaction in visit length or quality of care between visits documented with EMRI compared with those documented using PCN. On average, rheumatologists spent 38 minutes with each patient when using PCN, comprising about 40% of the clinic visit. Patients generally spent the majority of the remaining 60% of their visit waiting to be roomed or to be seen by the rheumatologists. These PCN times will be compared with EMRI times to assess improvement in clinic workflow.

Conclusions: Patients and their parents have indicated receptiveness to EMRI use in clinic and believe that it would benefit patient care. The implementation of an EMRI can improve clinic efficiency and minimize errors resulting from handwritten notes in an academic outpatient rheumatology practice without compromising patient perception of quality of care.

Disclosure: J. M. P. Woo: None; M. F. Parsa: None; G. Amayru: None; N. Afzarmanesh: None; K. T. Gallagher: None; O. J. Ruillo: None; D. K. McCurdy: None.

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Center for Health Research, Danville, PA, 2Geisinger Medical Center, Danville, PA, 3Geisinger Medical Center, Danville, PA, 4Geisinger Medical Center, Danville, PA

Purpose: Ineffective care pathways and process flows hinder post fracture care. To enhance the care of high risk osteoporosis patients across our health system, the rheumatology department created HiROC (High Risk Osteoporosis Clinic). Success was achieved by partnering with fellow stakeholders (orthopedists, hospitalists) to provide comprehensive post fracture care to this high risk group.

Method: HiROC utilizes rheumatology physician experts, clinical nurse specialists, electronic tools, and redesigned care processes in an efficient manner to provide comprehensive osteoporotic care to patients after fracture. HiROC has both inpatient and outpatient components. Inpatient HiROC involves an auto-consult to the Inpatient HiROC Team on all patients admitted with a low-impact fracture. Patients are logged into a task management database. Vitamin D testing and supplementation is initiated. At 6 weeks post-fraction, all Inpatient HiROC patients are contacted to re-assess their status. They are then seen in Outpatient HiROC, or their treating physician is contacted and given a consultative osteoporotic care management plan, if they decline outpatient HiROC follow-up. We report on the first 200 Inpatient HiROC patients, including baseline demographics, risk assessment, treatment, and financial performance. High risk for future fracture was assessed by fracture type (vertebral or hip) and/or DXA results.

Results: Inpatient HiROC admission fracture types included hip (50.5%), vertebral (13.0%), other (38.0%). Mean Vitamin D level at time of consultation was 23.9 ± 11.7 ng/mL and increased to 46.3 ± 21.9 ng/mL at HiROC return. All 200 patients reached their 6 week assessment point with 48 % of patients transitioning to Outpatient HiROC, 26 % returning to a non-system primary physician, 13% to an in-system primary care physician (PCP), 1.5% were lost to follow up, and 11.5 % were deceased. Significantly more high risk patients received treatment in the Outpatient HiROC group (83%) than the in-system PCP group (25%), (p<.0001). Financial evaluation demonstrated the program to be self supporting, sustainable, and scalable.

Conclusion: By combining inpatient and outpatient components, organized task management, and electronic tools, the HiROC program demonstrates significant treatment success. Quality of care was greatest when an Inpatient HiROC visit was paired with an Outpatient HiROC visit. We are exploring ways to increase this connectivity by expanding Outpatient HiROC site availability and increasing patient motivation. HiROC is effective, self-sustainable, scalable, and may serve as a model for other groups to improve osteoporosis care for the patients they serve.

Disclosure: G. L. Maloney-Saxon: None; T. P. Olenginski: None; C. K. Matzko: None; H. Sun: None; K. Mackiewicz: None; E. D. Newman: None.

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Lipid and C-Reactive Protein Screening Thresholds and CVD Risk in a Community Lupus Cohort. Christie M. Bartels, Kevin Buhr, Jerry Goldberg, Carolyn Bell and Robert Greenlee.

Community Lupus Cohort.

Tuesday, November 9

<table>
<thead>
<tr>
<th>Total SLE</th>
<th>n=71</th>
<th>%</th>
<th>Female n=58</th>
<th>%</th>
<th>HR* CV Event</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Screen Ever</td>
<td>46/71</td>
<td>65%</td>
<td>35/58</td>
<td>60%</td>
<td>0.99</td>
<td>[0.82, 1.24]</td>
<td>0.98</td>
</tr>
<tr>
<td>LDL&gt;130</td>
<td>20/46</td>
<td>43%</td>
<td>15/35</td>
<td>43%</td>
<td>0.99</td>
<td>[0.69, 1.43]</td>
<td>0.22</td>
</tr>
<tr>
<td>CRP Ever</td>
<td>33/46</td>
<td>72%</td>
<td>24/35</td>
<td>69%</td>
<td>0.52</td>
<td>[0.35, 0.81]</td>
<td>0.02</td>
</tr>
<tr>
<td>Diagnosed Hyperlipidemia</td>
<td>9/71</td>
<td>20%</td>
<td>6/58</td>
<td>17%</td>
<td>2.96</td>
<td>[1.08, 8.15]</td>
<td>0.04</td>
</tr>
<tr>
<td>CRP &gt;1 Ever</td>
<td>26/53</td>
<td>49%</td>
<td>19/42</td>
<td>45%</td>
<td>3.31</td>
<td>[1.17, 9.33]</td>
<td>0.02</td>
</tr>
<tr>
<td>CRP &gt;1 Current</td>
<td>16/53</td>
<td>30%</td>
<td>11/42</td>
<td>26%</td>
<td>4.33</td>
<td>[1.68, 11.2]</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Hazard ratios calculated at each level of risk among screened patients relative to event status.

Conclusions: While possible thresholds for lipid screening and treatment vary widely in the lupus literature, these findings demonstrate a clear gap in adherence to USPSTF recommended lipid screening in this community based cohort of lupus patients. Women were more likely to lack lipid screening. Regardless of gender, more patients ever had CRP screening, and associated hazards of CRP elevation in this population exceeded those with hyperlipidemia. In this observational study CRP monitoring was not controlled and may reflect indication bias, however, a prior report showed low rates of serious SLE disease in this cohort. Sample size limited meaningful adjustment. Future work is needed to close gaps in standard USPSTF recommended lipid screening in community lupus patients, and to determine the role of CRP and hsCRP for informing CVD risk management.

Disclosure: C. M. Bartels: None; K. Buhr: None; J. Goldberg: None; C. Bell: None; R. Greenlee: None.
Measuring the Impact of Patient Educational Materials about Medications in Meeting Patient Needs: Development and Validation of the Medication Education Impact Questionnaire (MeIQ), Sabina Ciciriello, Rachelle Buchbinder, Ian Wicks and Richard H. Osborne. Cabrini Medical Centre, Melbourne, Australia; Deakin University, Melbourne, Australia; Royal Melbourne Hospital, Melbourne, Victoria, Australia; Royal Melbourne Hospital, Melbourne, Australia.

**Background:** Patient education is essential for patients to participate in decision-making and self-management. Evaluation of new educational interventions should incorporate outcomes that are relevant to patients as well as health care professionals. At present there are no measures that adequately evaluate the impact of education in meeting patient needs. The objectives of this study were to: (i) To determine the perceived needs of patients when starting a new medication; (ii) to develop a questionnaire assessing the impact of education about medications in meeting patient needs, facilitating shared decision-making and self-management and (iii) to validate this questionnaire within the target population.

**Methods:** Patients perceived needs when starting a new medication were explored in concept mapping workshops with patients (N=24). Quantitative and qualitative analyses were used to identify and define distinct areas of need (constructs). 130 questions were drafted to capture these needs and administered to 653 patients taking various medications for their rheumatic conditions. Exploratory and confirmatory factor analyses (CFA) were undertaken to create a robust questionnaire. A refined set of 29 questions divided into 6 scales, each measuring a patient need, were administered to 876 patients and a further CFA. A validation step was undertaken. To assess test-retest reliability, 200 respondents were sent a second copy of the MeIQ two weeks later (response rate of 90%).

**Results:** Four key independent areas of need were identified for patients starting a new medication: The need for quality information; the ability to participate in decision-making; coming to terms with their diagnosis and treatment; and the ability to self-manage. Statistical analyses revealed that some of the subheadings within the constructs worked best as separate scales: self-management as 3 scales measuring role & responsibility, capacity and support to self-manage. Decision-making as 2 scales: active communication and informed decision-making. All questions within the scales were strongly congruent with their underlying construct. No items had substantial associations with other constructs (cross-loadings), and CFA fit indices supported the hypothesized factor model. The refined MeIQ consisted of 29 questions across 6 scales.

**Conclusions:** The MeIQ was developed using advanced psychometric processes and found to be a robust, multidimensional questionnaire which incorporates the patient's perspective. The MeIQ is generic and can therefore be used to evaluate education about any medication. It is likely to fill an important gap in the evaluation of educational interventions about medications.

**Disclosure:** S. Ciciriello: None; R. Buchbinder: None; I. Wicks: None; R. H. Osborne: None.

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**1002**

Multispecialty Unit for Infusion Therapy: Patient, Nursing and Provider Satisfaction. Barbara E. Ostrov, Kristine Reynolds and Lisabeth V. Scalzi. Penn State Hershey, Hershey, PA.

**Background:** Current treatment of many complex diseases includes infusion therapy. In recent years, individuals with autoimmune diseases have been increasingly treated in infusion centers (Pat Pre Adherence 2009:3 335), second only to the long term tradition of infusion therapy for hematological-oncology (HO) patients. Patients with hematologic diseases may have reservations about being treated in a unit for “cancer” patients. Additionally, due to long term experience, infusion nurses may be more at ease caring for HO patients than individuals with RA, for example, Education about the different needs of non-HO patients is lacking for infusion nurses (J Infusion Nurs 2008;31:350). Therefore, in 2009, when building a new Cancer Institute, we considered moving non-hematology-oncology (non-HO) patients into a separate infusion unit. We assessed patient versus provider and staff satisfaction with the multispecialty combined unit to determine whether a separate infusion unit should be recommended.

**Methods:** A 7-question Likert scale survey about satisfaction with the infusion unit was collected over 2 weeks from 3 groups: infusion nurses, non-HO physicians and non-HO patients. The tool was designed to assess differences in patient satisfaction and perceived patient satisfaction by staff with our multispecialty infusion unit. Reliability of the tool was measured using Cronbach’s alpha. Mean sums for all questions were calculated for individuals within their groups and analyzed using a one-way ANOVA. A post-hoc analysis was examined to determine which groups were similar.

**Results:** Surveys were completed by 13 nurses, 52 non-HO patients and 18 non-HO physicians. Missing responses resulted in a total of 49 patients, 12 nurses, and 14 physicians. The tool was reliable, with good internal consistency (Cronbach’s alpha=0.92). The overall mean of the 7 items in the instrument was 28.1 ± 6.8. Patients had higher satisfaction than perceived by providers and nurses across all of the items, as evidenced by higher total mean score: patients 31.3 ± 4.8, nurses 22.1 ± 6.8, physicians 21.9 ± 4.8. These results demonstrated significant intergroup differences (p<0.001) shown in the figure.

**Conclusions:** Physicians and nurses were more concerned than were patients about non-HO infusion therapy in a multispecialty but primarily cancer infusion center. Based on this survey, a combined multispecialty infusion center is acceptable to patients. Improved understanding of patient preferences were demonstrated to providers and nurses by this assessment. A follow-up survey is planned.

**Disclosure:** B. E. Ostrov: None; K. Reynolds: None; L. V. Scalzi: None.

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**1003**

Rheumatoid Arthritis (RA) Disease Activity Assessment and Treatment Decisions in Rheumatology Practice. J. Timothy Harrington, Leslie R. Harroll, George Reed, Hong Chang, Joel M. Kremers and Jeffrey D. Greenberg. Millburn, NJ; The Center for Rheumatology, Albany, NY; Tufts Medical School, UMass Medical Schi, Worcester, MA; UMass Medical Schi, University of Wisconsin, Madison, WI.

**Background:** Disease Activity Scores (DASs) for RA include a variety of patient, physician, and laboratory derived data. DASs have been used in clinical trials, but seldom in rheumatology practice in the United States. Treatment is guided instead by a variably determined Physician Global Assessment (PtGA). We have studied the PhGA and other DASs using the CORRONA registry (the Consortium of Rheumatology Researchers of North America, Inc).

**Objectives:** 1. To compare the correlations between the PhGA and the Clinical Disease Activity Index (CDAI), Disease Activity Score 28 joint (DAS28), Global Assessment Score (GAS), and the Patient Global Assessment (PtGA). 2. To evaluate treatment changes in relation to the PhGA and PtGA.

**Methods:** RA patients enrolled from 6/2001 to 11/2008 were included in this study if they had 2 visit reports within 3–6 months indicating no treatment changes during that interval, and if all data required to calculate each DAS

**Results:** Surveys were completed by 13 nurses, 52 non-HO patients and 18 non-HO physicians. Missing responses resulted in a total of 49 patients, 12 nurses, and 14 physicians. The tool was reliable, with good internal consistency (Cronbach’s alpha=0.92). The overall mean of the 7 items in the instrument was 28.1 ± 6.8. Patients had higher satisfaction than perceived by providers and nurses across all of the items, as evidenced by higher total mean score: patients 31.3 ± 4.8, nurses 22.1 ± 6.8, physicians 21.9 ± 4.8. These results demonstrated significant intergroup differences (p<0.001) shown in the figure.

**Conclusions:** Physicians and nurses were more concerned than were patients about non-HO infusion therapy in a multispecialty but primarily cancer infusion center. Based on this survey, a combined multispecialty infusion center is acceptable to patients. Improved understanding of patient preferences were demonstrated to providers and nurses by this assessment. A follow-up survey is planned.

**Disclosure:** B. E. Ostrov: None; K. Reynolds: None; L. V. Scalzi: None.
were reported, including the 0–100 visual analogue PhGA, PtGA, and patient global pain scores, swollen and tender 28 joint counts, ESR, and mHAQ. Correlation coefficients were computed for the PhGA versus the PtGA and the 3 composite measures. Both the PhGA and PtGA were stratified by disease activity as controlled [0–10], mild [11–40], moderate [41–80], and high [81–100]. Agreement or disagreement between the PhGA and PtGA in terms of controlled to mild disease activity (<40) or moderate to high disease activity (>40) were determined, as were the proportions of patients in each group whose non-biologic or biologic DMARDs were changed at their second visit or during the following 6 months.

**Results:** The 2456 CORRONA-enrolled RA patients who met the study inclusion criteria had a mean age was 62 (SD = 13), and most were female (76%) with established disease (mean disease duration of 12.0 years). The majority had low to moderate disease activity (mean PhGA = 15.1, PtGA = 25.7, CDAI = 9.3, DAS28 = 3.1 and GAS = 10.5). After adjusting for clustering of physicians, the correlation coefficients versus the PhGA were, CDAI = 0.774, DAS28 = 0.629, GAS = 0.644, and PtGA = 0.445. There was slight correlation between the PhGA and PtGA (kappa = 0.20). Table 1 shows agreement between the PhGA and PtGA in 1859 patients (76%) of whom 125 (7%) had moderate to high disease activity. DMARD initiation or dose escalation occurred in only 32% of the latter patients.

**Conclusions:** 1. The variable correlations between the PhGA and other disease activity measures and the level of discordance between the PhGA and PtGA reflect the complexities of using DASs in clinical practice. 2. Their adoption will also require better understanding of the weak relationships observed between treatment changes and both the PhGA and PtGA, especially for those patients with moderate to high disease activity.

**Table 1. Agreement/Disagrrement Between the Physician and Patient Global Assessments and Treatment Changes Related to These Assessments**

<table>
<thead>
<tr>
<th>Agreement</th>
<th>Disagreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled to mild disease (N=1734)</td>
<td>Moderate to high disease (N=125)</td>
</tr>
<tr>
<td>MD &gt; Pt**</td>
<td>Pt &gt; MD**</td>
</tr>
<tr>
<td>DMARD initiation (N, %)</td>
<td>128 (7%) (28 (22%)</td>
</tr>
<tr>
<td>DMARD dose increases (N, %)</td>
<td>206 (12%)</td>
</tr>
</tbody>
</table>

*Physician states moderate to high disease activity but patient reports controlled or mild disease

**Disclosure:** J. T. Harrington: Corrona, 5; L. R. Harrold: Corrona, 5; G. Reed: Corrona, 5; H. Chang: Corrona, 5; J. M. Kremer: Corrona, 9; J. D. Greenberg: Corrona, 5.

### 1004

**Scleroderma QuERI: Reduced Utility of Echocardiography in Pulmonary Hypertension Screening in the Community.** James R. Seibold, Amparo Casanova1, Mary Tan1, Daniel E. Furst2, Nicholas Hill2, Vallerie V. McLaughlin3, Richard M. Silver4, Virginia D. Steen1 and Anatoly Langer5.

**Objective:** Strategies are needed for early recognition of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc, scleroderma). Current modalities include history and physical examination, pulmonary function testing, biomarkers of myocardial stress (NTproBNP) and echocardiography with Doppler for estimation of right ventricular systolic pressure. None are fully validated and few measures have been made of a potential ‘care gap’ between specialty centers and primary care settings.

**Methods:** Physicians (27 US rheumatologists including 22 community practice settings) enrolled 207 scleroderma patients (known or newly diagnosed) and provided data on a recommended panel of diagnostic tests. The QuERI methodology prompts by computerized feedback for completeness of testing and use of appropriate follow up testing, e.g. right heart catheterization (RHC). We report results on the use of echocardiography (echo).

**Results:** Data are reported as median, 25th and 75th percentile. Patients enrolled were 57 years old (49, 86); 90% female. There were a total of 193 patients (93%) that had at least one echo done during the study, however, only 86 (45%) of these had an RVSP value recorded and only 108 (56%) had the presence of TR jet mentioned. Estimated RVSP value was greater than the a priori threshold of 40 mmHg in 24 patients (12%) and of these 6 had RHC, 9 had only echo repeated and 9 had neither. During the follow up period mortality/hospitalization rate was 29% among those with RVSP >40 vs 5% in those with RVSP reported <40 vs 19% in those in whom RVSP was not reported (p = 0.008).

**Conclusions:** Echocardiography with Doppler is a robust tool for screening for pulmonary hypertension in a research setting and in specialized programs. However, these data derived from community practices suggest that RVSP and or tricuspid jet velocity measures are inconsistently reported. This is in spite of these tests being utilized as part of a funded research project focused on PAH. Interdisciplinary teamwork and education between rheumatologists and cardiologists continues to require attention Better understanding and stricter adherence to published guidelines could advance quality of care of these high-risk patients.

**Disclosure:** J. R. Seibold: Actelion Pharmaceuticals US, 2, 5, Gilead Sciences, Inc., 2, 5, Pfizer Inc, 2, 5, United Therapeutics, 2, 5; A. Casanova None; M. Tan None; D. E. Furst None; N. Hill None; V. V. McLaughlin: Actelion Pharmaceuticals US, 2, 5, 8, Bayer, 5, Gilead Sciences, Inc., 2, 5, 8, Novartis Pharmaceuticals Corporation, 2, United Therapeutics, 2, 5, 8; R. M. Silver None; V. D. Steen None; A. Langer: Actelion Pharmaceuticals US, 2.

### 1005

**Secondary Fracture Prevention in Home Health Care: Initial Results from a Group Randomized Trial.** Meredith L. Kilgore, Jeffrey R. Curtis, Ryan C. Outman5, Julie Locher6, Jeroan Allison7 and Kenneth G. Saag5.

**Statement of Purpose:** To develop and evaluate a multimodal intervention to increase rates of osteoporosis treatment in high risk patients receiving home health services.

**Methods:** We developed and tested an intervention to improve the rates of treatment, particularly use of prescription osteoporosis drugs, among patient with a history of fracture receiving home health services. The intervention included an educational component for nurses, a computerized care plan that prompted the nurse to initiate specific actions related to osteoporosis management, easy reference materials for physicians, prepared order sheets to facilitate osteoporosis drug prescription, and patient education materials focused on osteoporosis, fracture risks, fracture prevention, and medication adherence. Field offices (n = 24) of a home health agency operating throughout Alabama were randomized to receive the intervention or serve as controls. The primary outcome measure was the rate of osteoporosis medications prescribed among patients with a fracture history. A t-Test of proportions was used to assess difference between groups.

**Summary of Results:** We found an absolute difference of 3.9% (NS) between the treatment and control group in post-intervention osteoporosis care. The figure shows the monthly distribution of treatment rates by office before and after the intervention.

**Figure 1.** Pre- & post-intervention osteoporosis medication prescription rates in intervention and control groups.

While all but one of the treatment offices showed an improvement, overall rates were low, and the corresponding rates in the control arm improved as well.

A secondary analysis tested whether treatment rates increased when the nursing care plan was activated. In this case the difference was 15.3% (p < 0.0001).
Conclusions: Preliminary results do not demonstrate significant efficacy of the intervention overall, but suggest that improvements in processes of care could have significant effects on appropriate osteoporosis care delivery. Future studies should examine the impact of reinforcement of the nursing in-service training with audit and feedback to field offices on their relative performance rates, particularly with respect to activating the nursing care plan.

Disclosure: M. L. Kilgore: None; J. R. Curtis: Eli Lilly and Company, 2, 8, Merck Pharmaceuticals, 2, 5, Novartis Pharmaceuticals Corporation, 2, 8, Proctor and Gamble, 2, 5; R. C. Outman: None; J. Locker: None; J. Allison: None; K. G. Saag: Amgen Inc., 2, 5, Eli Lilly and Company, 2, 5, GlaxoSmithKline, 2, Merck Pharmaceuticals, 2, 5, Novartis Pharmaceuticals Corporation, 2, 5, 8, Proctor & Gamble Enterprises, 2, Roche, 2, 5, L. Morgan: None; E. Kitchin: None; J. R. Curtis: Eli Lilly and Company, 2, 8, Merck Pharmaceuticals, 2, Novartis Pharmaceuticals Corporation, 2, 5, 8, Proctor & Gamble Pharmaceuticals, 2, 5, 8.

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Purpose: U.S. guidelines recommend bone density screening with central dual energy x-ray absorptiometry (DXA) in all women 65 years or older. However, less than one-third of eligible U.S. women undergo DXA testing. The main barrier in achieving greater rates of osteoporosis screening is identifying a systematic, effective and generalizable way for healthcare providers and patients to schedule and receive DXA results.

Methods: We conducted a group randomized, controlled trial involving 39 primary care physicians at the University of Alabama at Birmingham. Women 65 years or older with no identifiable DXA scan in the past 4 years cared for by these physicians were identified using administrative billing data (n = 5122). Randomization was performed in two waves, each forming a cohort. In each of the two cohorts, 30 patients per physician were randomized to the intervention (sent mailed materials twice), the remainder of each physician’s patients comprised the control group (received no mailing). The intervention included a patient brochure regarding osteoporosis and fracture risk and a letter providing patients the opportunity to self-schedule a DXA. Results from the two cohorts were similar and pooled for analysis. Stratified results compared receipt of DXA among women receiving primary care proximate to the site where the DXA scanner was located (62% of study population) vs. a more distant DXA among women receiving primary care proximate to the site where the DXA scanner was located.

Results: Of 5122 identified women meeting inclusion criteria, 978 women were randomized to the intervention group and 4,144 to the control group. A total of 19.5% of women in the intervention group scheduled and received a DXA, compared to 6.3% women receiving DXA in the control group (Risk Difference for DXA receipt 13.2%, 95% CI 10.8 16.0).

Conclusions: DXA scan scheduling and receipt was improved significantly through the use of a simple mailed osteoporosis brochure and the availability for patients to self-schedule their own scans. This modality may be an effective component of a multi-faceted quality improvement program to increase rates of osteoporosis screening.

Disclosure: A. H. Warriner: NIH; 2, R. C. Outman: None; K. G. Saag: Amgen Inc., 2, 5, 8, Aventis Pharmaceuticals, 5, Eli Lilly and Company, 2, 5, GlaxoSmithKline, 2, Merck Pharmaceuticals, 2, 5, Novartis Pharmaceuticals Corporation, 2, 5, 8, Proctor & Gamble Enterprises, 2, Roche, 2, 5, L. Morgan: None; E. Kitchin: None; J. R. Curtis: Eli Lilly and Company, 2, 8, Merck Pharmaceuticals, 2, Novartis Pharmaceuticals Corporation, 2, 5, 8, Proctor & Gamble Pharmaceuticals, 2, 5, 8.

1007


Methods: Between December 2009 and April 2010 an anonymous, self-directed questionnaire was intermittently administered to all rheumatology outpatients attending our clinic. Included in this survey were questions concerning age, current opinions regarding the usefulness of appointment reminders, access to technology, and preferences regarding method and timing of appointment reminders. Patients were divided into generational age groups as follows: Generation Y (18–28 years), Generation X (29–49 years), Baby Boomers (50–67 years), Silent Generation (68–85 years), and GI Generation (≥ 86 years). Overall group preferences, as well as preferences by generational age, were analyzed.

Results: A total of 637 surveys were included in the final analysis. The patients surveyed ranged in age from 18 to 94 years, with a mean age of 58 years. Baby Boomers comprised the largest percentage of the patient population (46%), followed by Generation X (25%), and the Silent Generation (24%). Over 99% of patients viewed appointment reminders as a good idea. Overall, the preferred method of reminder was a phone call (52%), followed by standard mail (24%). SMS was the least preferred modality (4%).

Conclusions: Improved attendance rates in rheumatology clinics would be beneficial given the requirement for disease and medication monitoring. Patients value appointment reminders. Phone call reminders are preferred in all generational age groups except Generation Y. The preference of new modalities such as SMS varies with age and is limited to the younger patients of Generation Y.

Disclosure: C. Gauthier: None; W. E. Davis: None; R. J. Quinet: None.

1008


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1008


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Disclosure: C. Gauthier: None; W. E. Davis: None; R. J. Quinet: None.
Purpose: To assess teen transition needs, barriers and opportunities among pediatric rheumatology providers.

Methods: Using surveymonkey, we queried all Childhood Arthritis and Rheumatology Research Alliance (CARRA) members about teen transition care including needs, barriers and opportunities for transition program development. We compared our results to the American Academy of Pediatrics (AAP) 2008 survey on transitional care.

Results: 158/291 (54%) providers responded. Top two major stated barriers to transition are fragmented adult medical care and lack of sufficient time to provide services (Table 1).

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Major Barrier</th>
<th>Somewhat a barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric staff lack sufficient time to</td>
<td>40.3%</td>
<td>42.4%</td>
</tr>
<tr>
<td>provide transition services</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fragmentation of primary and specialty</td>
<td>39.2%</td>
<td>44.8%</td>
</tr>
<tr>
<td>care in adult care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents/parents/physicians have</td>
<td>32.6%</td>
<td>59.7%</td>
</tr>
<tr>
<td>developed an effective bond that is</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hard to break</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents’ lack of knowledge about</td>
<td>31.3%</td>
<td>61.8%</td>
</tr>
<tr>
<td>their own condition and/or skills to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>self-advocate at physician visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric staff lack skills in transition</td>
<td>28.7%</td>
<td>51.7%</td>
</tr>
<tr>
<td>planning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of knowledge about or linkages to</td>
<td>27.0%</td>
<td>61.0%</td>
</tr>
<tr>
<td>community resources that support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>older adolescents/young adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of available adult specialists to</td>
<td>26.4%</td>
<td>47.9%</td>
</tr>
<tr>
<td>care for older adolescents/young adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with special needs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of insurance reimbursement for</td>
<td>25.4%</td>
<td>38.7%</td>
</tr>
<tr>
<td>transition services</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of available family physicians and</td>
<td>24.5%</td>
<td>44.8%</td>
</tr>
<tr>
<td>internal medicine physicians to care for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>older adolescents/young adults with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>special needs</td>
<td></td>
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</tr>
</tbody>
</table>

As a part of routine transition care services, respondents help with finding an adult rheumatologist (70%), discuss confidentiality and consent before 18 (49%), assist with medical summary (51%), provide educational packets (42%), create an individualized transition plan (21%), utilize an assessment of transition readiness (30%), and 2/3 discuss patient’s educational and vocational plans. Compared with AAP survey participants, pediatric rheumatologists are similar or more proficient in many transition practices, except for creating a medical summary and referring to a primary care provider.

Useful resources for the transition process include brochures and pamphlets (91%); open ended discussions during visits (91%); and having a portable personal health/medical record (82%). 78% use open ended discussions already, but use of phone calls (56%) and emails (43%) directly with teens is less frequent. Providers do not want to communicate via texting (58%) or social networking (49%).

Outcomes ranked as very important in defining a successful transition are survival (76%), seeing an adult rheumatologist within 6 months of the final pediatric rheumatology visit (66%), and maintaining insurance coverage (57%).

Discussion: Pediatric rheumatologists report many barriers to transition care, revealing unmet needs in improving teen self-efficacy, and assuring adequate provider time, education and reimbursement for transition planning. Technology offers some potential solutions including portable personal health records and health information access via hospital/health insurance portals. From the provider perspective, assessment of long term transition outcome is focused on quantitative measures rather than qualitative items as provider/patient satisfaction or patient quality of life.

Conclusion: Pediatric rheumatologists report the same concerns about providing transition care as general pediatricians. Opportunities include creating a standardized transition protocol to be followed by CARRA members, incorporating technology to facilitate the process such as developing personal health records, educational programs, and tracking long term outcomes after transfer of care.

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1009

Testing Patient Knowledge about Methotrexate: Development and Validation of the Methotrexate in Rheumatoid Arthritis Knowledge Test (MiRAK). Sabina Ciciriello1, Ian Wicks2, Richard H. Osborne3 and Rachelle Buchbinder1. 1Cabrini Medical Center, Malvern, Australia, 2Deakin University, Melbourne, Australia, 3Royal Melbourne Hospital, Melbourne, Victoria, Australia, 4Royal Melbourne Hospital, Melbourne, Australia

Background: The study describes the development and validation of the MiRAK, a new tool designed to specifically measure patient knowledge about methotrexate (MTX) treatment for RA. MTX is an effective treatment for RA and is the cornerstone of modern RA treatment. However it is not without risks and patients need to understand complex information in order to make an informed decision about starting MTX and to take it safely. In planning a randomized controlled trial to assess the effectiveness of a new multimedia patient education program about MTX and RA we found no suitable outcome tool designed to measure patient knowledge about MTX.

Methods: The knowledge tested by the MiRAK was guided by a literature review and consultation with rheumatologists (N=15) as well as concept mapping workshops with RA patients (N=24) exploring their information needs when starting MTX. To ensure face validity, draft items of the MiRAK were tested with both patients and rheumatologists. The draft questionnaire was administered to 317 RA patients treated with MTX (response rate 53%). The data was analyzed using item response theory with a Rasch model. To assess test-retest reliability, 146 respondents were sent a second copy of the MiRAK two weeks later (response rate 90%).

Results: 60 candidate questions were generated, of which 32 were true/false, 22 yes/no, 5 multiple choice. The knowledge tested by the MiRAK was uni-dimensional allowing the questions to be summed into a single knowledge score. Scores ranged from 8–57 correct responses out of 60 (mean SD 35.78 (7.7)). Scale fit indices revealed that the observed responses fit well with the Rasch model indicating sound measurement properties. The MiRAK questions covered all levels of underlying knowledge in the sample population. The MiRAK had excellent internal consistency (Cronbach’s alpha 0.84) and test-retest reliability (ICC 0.89).

Conclusions: Advanced psychometric analyses were used to generate the MiRAK and provide strong evidence for its validity and reliability. Further work is underway to evaluate its sensitivity to change. The MiRAK may be useful as an outcome measure in both clinical trials of interventions designed to educate patients about MTX, and in routine care to assess patient knowledge of MTX prior to commencement of treatment.

Disclosure: S. Ciciriello: None; I. Wicks: None; R. H. Osborne: None; R. Buchbinder: None.

1010

The Impact of the ACR Treatment Recommendations on Physician Prescribing in a U.S. Cohort of Rheumatoid Arthritis Patients. Leslie R. Harroll1, Jeffrey D. Greenberg1, Jeffrey R. Curtis2, Daniel E. Furst3, Mary Jane Langlois4, Ying Shan4, George Reed4 and J. Timothy Harrington1. 1Millburn, NJ, 2george.reed@umassmed.edu, 3UMass Medical Schl, Worces- ter, MA, 4UMass Medical School, 5University of Alabama - Birmingham, Birmingham, AL, 6University of California Los Angeles Medical School, Los Angeles, CA, 7University of Wisconsin, Madison, WI

Purpose: To examine changes in prescribing patterns in relation to publication of the American College of Rheumatology (ACR) Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs) in Rheumatoid Arthritis (RA). Specifically we examined nonbiologic and biologic DMARD use based on disease activity in order to evaluate the impact of the ACR recommendations on medication patterns.

Methods: We identified biologic naïve RA patients cared for by US rheumatologists participating in the CORRONA registry with visits prior to and/or at least 6 months after publication of the ACR recommendations on 6/15/08 (time period: 2/02–6/08 vs. 12/08–12/09). Initiation or dose escalation of biologic and nonbiologic DMARDs in response to active disease and/or at least 6 months after publication of the ACR recommendations before and after publication was compared in the two cohorts stratified by disease activity using regression models adjusting for clustering of physician and geographic region.
Results: In MTX only users, 91–95% of those with low disease activity and 79–89% of those with moderate disease activity and good prognosis were receiving nonbiologic DMARDs, consistent with the recommendations. Among those with moderate disease activity and poor prognosis, 20–23% had their MTX dose increased and/or initiated another nonbiologic DMARD and 14–15% initiated a biologic, resulting in 34–38% of patients receiving care consistent with the recommendations. Similarly, among those with high disease activity, 24–26% had their MTX dose increased and/or were initiated on a nonbiologic DMARD and 18–19% initiated a biologic (43–44% receiving care consistent with the guidelines). In the multiple nonbiologic DMARD users with moderate activity, 44–53% received care consistent with the recommendations (30% had initiation and/or dose escalation of their nonbiologic DMARD therapy and 9–22% initiated on a biologic). In adjusted analyses there were no significant differences in prescribing practices after publication of the treatment recommendations.

Conclusions: Only approximately 40 to 50% of RA patients in the CORRONA US registry with high disease activity or moderate disease activity with a poor prognosis received care consistent with the current ACR treatment recommendations within 6 to 18 months after their release. In addition, publication of the recommendations did not appear to change treatment recommendations within 6 to 18 months after their release. In adjusted analyses there were no significant differences in prescribing practices after publication of the treatment recommendations.

Aim of the Study: Aim of the present study was to preliminary test the feasibility of this core set in routine clinical practice and to develop a computerized data base to collect patient’s data.

Methods: Seven centres (Austria, Italy, 2 Poland, Portugal, Switzerland, Thailand) participated to the study and were asked to collect data of at least 5 consecutive SLE patients during routine assessment.

Results: Sixty-five patients were enrolled (55 Caucasians and 10 Asians; F: 64; M: 1; mean age 41 years), on average 10 minutes were required to fill the chart of the core set, although the time required appeared related with the type of organ involvement.

Disease activity using validated indices was calculated in all patients in routine clinical practice (ECLAM (15 patients): mean 2, SLEDAI (50 patients): mean 5), while the SLIC/ACR damage index (mean value 1) and the quality of life were evaluated only in 49% of patients. With respect to the adherence to recommendations, interestingly, this preliminary analysis showed that 86% of patients treated with immunosuppressive drugs had been assessed for the presence of chronic HBV and HCV infections and only 38% for tuberculosis. In addition, 15% of patients had never been assessed for osteoporosis or for lipid profile.

Following this preliminary testing, and based on the participants comments and suggestions, a Web based data base has been developed to collect data on SLE patients using the core set chart and including the ECLAM and SLELENA-SLEDAI and the SLIC/ACR damage index. Recorded data can be downloaded and used for additional statistical analysis.

Conclusions: These preliminary data show that the use of a standardized core set in routine clinical practice is feasible and could represent a tool to reduce variability in data collection and to increase adherence to recommendations in clinical practice and therefore could lead to improvement of quality of care and of data travelling.

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1012

The Use of Electronic Health Record To Improve Tuberculosis Screening in Pediatric Rheumatology Patients Receiving Biologic Response Modifiers. David W. Moser1, Elaine Haddix2, Mary Beth Burns3, James Brown4, Anna Carmela P. Sagae-Gironella5, Thomas A. Griffin1, Hemine Brunner6 and Esi M. Morgan DeWitt7. 1Children’s Hospital Med Ctr, Cincinnati, OH, 2Cincinnati Child Hosp Med Ctr, Cincinnati, OH, 3Cincinnati Children’s Hospital, 4Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, 5Children’s Hospital, 6Children’s Hospital Medical Center, Cincinnati, OH, 7Children’s Hospital of Cincinnati, OH

Purpose: Activation of latent tuberculosis (TB) has been associated with tumor necrosis factor inhibitor (TNFi) use. As a result, screening with tuberculin skin testing (TST) is recommended prior to initiating treatment with biologic response modifiers (BRMs). However, compliance with this recommendation is imperfect. The electronic health record (EHR) can be leveraged to measure and improve compliance. We conducted a quality improvement (QI) project using the EHR and other interventions to increase the proportion of patients with Juvenile Idiopathic Arthritis (JIA) screened for TB prior to the start of BRMs.

Method: During January 2010 to May 2010 we conducted a QI initiative employing “Plan, Do, Study, Act” (PDSA) cycle improvement ramps. Baseline data from March 2008 to December 2009 was obtained by querying the EHR for all patients who initiated a BRM, the date of TST placement, and whether a result was reported. During the project’s first three months, we developed non-EHR based interventions which included: Introduction of a log to track patients who had a TST placed, development of a patient instruction sheet and TST results card, and initiation of reminder phone calls 40–48 hours after TST placement. Rheumatology providers completed a weekly survey of new BRM starts to ensure that no eligible patients were missed. At the end of the third project month, the intervention was modified to include an EHR based practice alert (BPA) instructing physicians to confirm the placement of a TST each time a BRM is ordered. An EHR BPA is a pop-up box programmed into the EHR with a reminder and an order that
satisfies the alert. The outcome measure was the proportion of patients who received a TST with documentation of results within 180 days of BRM start.

Results: Our baseline data spanned a period of 21 months. There were 247 eligible patients identified; of these, 65 (26.3%) had both a TST placed and resulted. During the 3 month period of non-EHR based interventions, 30 eligible patients were identified, 60.0% of which had both a TST placed and resulted. After the EHR BPA was activated 9 patients were identified in six weeks, 8 (88.9%) of which had TSTs ordered and resulted. A t-test comparing non-EHR based interventions to baseline and M-test comparing the EHR BPA phase to the non-EHR phase generated a p = 0.225.

Conclusion: We observed a statistically significant improvement in the proportion of patients with JIA screened for TB prior to the start of BRMs compared to baseline during the non-EHR portion of our QI project. Further improvements were seen once the EHR BPA was activated. Additional time and patients will be required to determine if the improvement with the EHR BPA intervention reaches clinically significant levels of statistical significance. We conclude that the use of EHR in conjunction with non-EHR based interventions may be an effective tool to improve the proportion of JIA patients screened for TB prior to the start of BRMs.

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1013 Treating Rheumatoid Arthritis to Target: Multinational Recommendations Assessment Questionnaire. Boulou Harauzi13, Josef S. Smolen18, Daniel Alehau12, Ferdinand C. Bredexd14, Maarten van der Wit15, Maxime Dougados14, Paul Emery14, Allan Gifford10, Desiree M. Van Der Heijde19, Gerd R. Burmester3, Mario Cardiel-Rios7, Catalin Codreanu1, Patrick Durez23, Joao Eurico Fonseca11, Tsutomu Takeuchi17 and the Treat to Target Taskforce.

Purpose: An international survey was conducted to measure the level of agreement and application of the 10 recommendations developed by the Treat to Target initiative (Smolen JS, et al. Ann Rheum Dis. 2010) aimed at defining therapeutic goals and achieving optimal outcomes for rheumatoid arthritis (RA).

Methods: A 10-point Likert items scale (1 = fully disagree, 10 = fully agree) measured the level of agreement with each of 10 recommendations. A 4-point Likert items scale (1 = never, 2 = not very often, 3 = very often, 4 = always) assessed the degree to which each recommendation was being applied in current daily practice. If respondents answered “never” or “not very often”, they were asked whether they would change their practice according to the particular recommendation.

Results: 1568 physicians, representing 33 countries, participated. Practitioners in University hospitals, general hospitals, and private clinics were well represented, with 37%, 31%, and 21% of respondents, respectively. Years in practice ranged from 0 to 52 years (mean 18.5 ± 10.72). Both agreement with and application of the recommendations were high. Recommendations #1 (“The primary target for treatment of RA should be a state of clinical remission”) and #10 (“The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist”) received the highest agreement scores of 9.156 and 9.272, respectively. Recommendations #5 (“Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently [such as every 3 to 6 months] for patients in sustained low disease activity or remission”) and #3 (“While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease”) received the lowest agreement scores, 8.445 and 8.515, respectively, although these are still very high. In regard to application of recommendations in daily practice, the majority of respondents were “always” and “very often”. However, recommendation #5 also received the highest number of “never” or “not very often” responses (12.43%). Of the participants who were currently not applying these recommendations in clinical practice, many (36.27% to 68.18% depending on the recommendation) were willing to change practice according to the recommendations. However, 38.92% of participants not applying recommendation #5 indicated they would not change their practice.

Conclusion: The results of this survey demonstrate support of “Treating RA to Target” recommendations amongst the international rheumatology community. Since these recommendations are based on evidence and consensus, additional efforts may be needed to encourage their application also amongst clinicians who are hesitant to change their practice.

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Disclosure: B. Harauzi: Abbott Laboratories, 2; J. S. Smolen: Abbott Laboratories, 2; D. Aletaha: Abbott Laboratories, 2; F. C. Bredexd: Abbott Laboratories, 2; M. de Wilt: Abbott Laboratories, 2; M. Dougados: Abbott Laboratories, 2; P. Emery: Abbott Laboratories, 2; A. Gifford: Abbott Laboratories, 2; D. van der Heijde: Abbott Laboratories, 2; G. R. Burmester: Abbott Laboratories, 2; C. Codreanu: Abbott Laboratories, 2; P. Durez: Abbott Laboratories, 2; J. E. Dougados: Abbott Laboratories, 2; B. G. Graninger: Abbott Laboratories, 2; V. Hamuryudan: Abbott Laboratories, 2; M. J. Jannant-Fena: Abbott Laboratories, 2; J. Kalender: Abbott Laboratories, 2; K. Krievi: Abbott Laboratories, 2; I. Lauruni: Abbott Laboratories, 2; C. Montecucco: Abbott Laboratories, 2; J. A. Pereira de Silva: Abbott Laboratories, 2; G. Poor: Abbott Laboratories, 2; P. I. Santos Moreno: Abbott Laboratories, 2; E. Stanislawski-Biernat: Abbott Laboratories, 2; T. Takeuchi: Abbott Laboratories, 2; T. Target Taskforce: Abbott Laboratories, 2.

1014 Using an Electronic Data Capture System To Measure Outcomes in Patients of Biologic DMARD Therapy: The Rheumatology Health Tracker (RHT). Sita A. Narayanan1, Jeffrey R. Lisse2, Alexis A. Alvarez2, Catherine Lo, Rafael G. Grai3, Eric P. Gail4 and Oscar Furet5. 1Univ of Arizona, Tucson, AZ, 2Univ of AZ Arthritis Ctr, Tucson, AZ, 3Univ of AZ Arthritis Ctr, Indianapolis, IN, 4Univ of AZ Arthritis Ctr

Background: Patient outcomes are increasingly important to track the response to disease modifying drugs (DMARD) over time. The Rheumatology Health Tracker (RHT) is an electronic capture system that tracks the outcomes in patients with rheumatoid arthritis on different biologic DMARDs over time in a real world setting, and can be important in detecting outcomes. This report evaluated outcome measures for a patient population undergoing biologic DMARD therapy after a second year of analyzing RHT use in European rheumatic pathology and academic institutions.

Methods: Patients with rheumatoid arthritis were already participating in an observational study using a web based electronic capture system. After informed consent, at each visit they were asked to record the following outcome parameters: Involved Joint Count (IJC), Short Form 12 (SF-12), Health Assessment Questionnaire (HAQ), and Visual Analog Scale of their overall disease activity (VAS), demographic information, and information on health care utilization. Participants then filled out a Tender Joint Count (TJC), SF12 score, and a visual analog scale. These outcomes were analyzed after a year and found to be statistically and clinically stable. A second annual analysis was performed on the same biologics with inclusion of newly consented patients resulting in a larger sample size.

Results: There were 155 patients enrolled in the study who were on biologic DMARDs: Overall HAQ was 0.824, SJC was 5.062, TJC was 6.662, SF-12 was 35.302, and VAS was 24.175. Initial baseline HAQ scores for the different biologics was 0.5547 for etanercept (n = 41), 0.9184 for infliximab (n = 39), 0.642 for adalimumab (n = 41), 0.99 for rituximab (n = 20), and 1.18 for abatacept (n = 14). The change in HAQ score between the initial visit and the first follow up visit was +0.175 for etanercept, −0.088 for rituximab, −0.218 for infliximab, +0.121 for adalimumab, and −0.151 for abatacept. SF12 scores all increased however infliximab, rituximab, and abatacept showed the most improvement in patient-perceived health status.

Conclusions: Electronic medical records offer a means to record outcome parameters in patients on biologic DMARDs in a clinic outpatient setting. This reflects the use of different biologics in our practice. This second
A critical analysis showed the utility of using this system over time to record patient and physician reported outcomes. This allows long-term monitoring of patients on biologic DMARDs with the RHT, and gives physicians the opportunity to adjust treatment accordingly. It is an accessible, reproducible electronic information source that can be accessed by multiple practitioners to assess and treat their patients over time.

Disclosure: S. A. Narayanan: None; J. R. Lisse: Centocor, Inc.; 2: A. A. Alvarez: None; C. Lou: None; R. G. Grau: None; E. P. Gall: None; O. Furet: None.

ACR Poster Session B
Rheumatoid Arthritis - Clinical Aspects: Clinical Features, Disease Risk Factors, Bone in RA, CVD II
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

1015
Anti-Cyclic Citrullinated Peptide Antibodies in Rheumatoid Arthritis Patients with Lymphoma. Eva Baecklund10, Karin Ekström Smedby1, Carin Backlin2, Johan Rönnelid2, Erik Ahlín2, Rene Toes6, Johan Asking3, Ephraim Hochberg3, Mandakolathur Murali1, Lars Klareksog1, Tom Huizinga4, Fred Hochberg1 and Jonathan Kay11. 1Cancer Center, Massachusetts General Hospital, Boston, 2Clinical Immunology, Uppsala University, 3Epidemiology Unit, Karolinska Institutet at Karolinska University Hospital, Stockholm, 4Epidemiology, Rheumatology, Karolinska Institutet at Karolinska University Hospital, Stockholm, 5Genetics and Pathology, Uppsala University, 6Immunology, Leiden University Medical Center, 7Immunology, Massachusetts General Hospital, Boston, 8Rheumatology, Leiden University Medical Center, 9Rheumatology, Medical Sciences, Uppsala University, Uppsala, Sweden, 10Rheumatology, Medical Sciences, Uppsala University, Uppsala, Sweden, 11UMass Memorial Medical Center, Worcester, MA

Background: The risk for lymphoma and, in particular, diffuse large B-cell lymphoma (DLBCL), is increased in patients with rheumatoid arthritis (RA). No biomarkers for the development of lymphoma in patients with RA have been identified.

Objective: To investigate if anti-CCP antibody levels and subclasses are associated with occurrence of lymphoma in patients with RA.

Methods: We identified 37 index patients with RA and subsequent lymphoma from two population-based Swedish case-control studies, one of lymphoma (the SCALE study, 1999–2002) and the other of RA (the EIRA study, 1986–2006). To each index RA-lymphoma case, three pairs of control subjects were matched based upon age at diagnosis of RA or lymphoma (+5 years) and lymphoma subtype. Controls consisted of 73 patients with RA (EIRA), 73 patients with lymphoma only (SCALE), and 74 individuals with neither disorder (EIRA). Blood samples were collected from all subjects at either diagnosis of lymphoma (SCALE) or of RA (EIRA). The self-reported RA diagnosis (SCALE) was validated in medical records. Blood samples from all 257 study subjects were analyzed for anti-CCP IgG (ELISA, Eurodiagnostica) and AC-CCP isotypes: anti-CCP IgGl-4, IgA, and IgM (Leiden). Anti-CCP IgG levels ≥25 U/ml were defined as positive. The chi2 and Wilcoxon rank sum tests were used for statistical analysis.

Results: Similar proportions of patients with RA only (65%) and of patients with RA-lymphoma (65%) had positive anti-CCP IgG levels, as did lymphoma cases (1.4%) and population controls (5%). Similar results were obtained for all anti-CCP subclasses. The median level of anti-CCP IgG in index patients with RA-lymphoma (306 U/ml; min 1-max 5033) was higher than in non-lymphoma RA patients (140 U/ml; min 0-max 5706), but the difference was not statistically significant (p=0.25).

The most common lymphoma subtype among the index cases was DLBCL (37%). The median anti-CCP IgG was numerically higher in RA patients with DLBCL (495 U/ml; min 1-max 5033) compared to patients with RA and other non-Hodgkin lymphoma subtypes (175 U/ml; min 1-max 3626), (p=0.87).

Conclusion: This population-based study with carefully matched controls does not support an association between IgG anti-CCP antibody positivity or levels or ACPA subclasses (IgG, IgGl-4, M or A) and lymphoma occurrence in RA. Further studies are needed to identify other potential biomarkers of lymphoma occurrence in RA.

Disclosure: E. Baecklund: None; E. Ekström Smedby: None; C. Backlin: None; J. Rönnelid: None; E. Ahlín: None; R. Toes: None; J. Asking: None; E. Hochberg: None; M. Murali: None; L. Klareksog: None; T. Huizinga: None; F. Hochberg: None; J. Kay: None.

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Introduction: Rheumatoid arthritis (RA) is a systemic inflammatory disease that is associated with an increased cardiovascular risk and a greater number of ischemic events than the general population.

Objectives: To evaluate the cardiovascular risk and frequency of ischemic events in a group of patients diagnosed with RA.

Material and Methods: We have included, consecutively, two hundred patients with rheumatoid arthritis diagnosed according to 1987 criteria of American College of Rheumatology (ACR), which are monitored regularly in the outpatient clinic of a tertiary care university hospital. We have reviewed retrospectively both the physical and the informatised medical record in the hospital and primary care and have gathered the following variables: a) age, sex, weight and height, b) duration of RA, c) parameters of activity of the disease, d) rheumatoid factor and anti-CCP, e) cardiovascular risk factors (smoking history, hypertension, hyperlipidemia, diabetes mellitus) and f) vascular ischemic events registered to date. From the age, sex, smoking history, arterial blood pressure levels and serum total cholesterol, we calculated the SCORE cardiovascular risk index (low-risk model). We calculated the SCORE cardiovascular risk index and we multiplied the result by 1.5 in patients who fulfilled the last EULAR recommendations (modified SCORE). The data were collected in an Access 2003 database and analyzed with the statistical software SPSS. Statistical significance was set at p <0.05.

Results: The mean age of patients was 60 ± 12 years. 76% were women. The mean duration of RA was 12 ± 10 years. 82% were rheumatoid factor positive and 77%, positive anti-CCP. According to the DAS28, 51% of patients had a low activity, 39% moderate and 10% high. With regard to cardiovascular risk factors: 30% of patients were smokers or former smokers, 41% were diagnosed with hypertension, 52% were dyslipidemic and 12% had diabetes (2%, treated with insulin). The medium SCORE index (modified according to EULAR criteria) was 2.7 ± 2.9%, the change was indicated in 59% of patients. The cardiovascular risk calculated by SCORE correlated with classical vascular risk factors (age, male gender, smoking, hypertension and diabetes) and C-reactive protein. The modified SCORE is correlated also with positive RF and positive anti-CCP.

With regard to ischemic events, nine patients had one or more: coronary (2 angina pectoris and 5 acute myocardial infarctions) or neurologic (two transient ischemic attacks and three strokes). Patients who had presented an ischemic event had higher age and higher modified SCORE than the other patients and they were more frequently male and smokers in a statistically significant way.

Conclusions: In patients with RA in our series, the incidence of cardiovascular risk factors and ischemic events is significant and is related to classical cardiovascular risk factors and C-reactive protein.

Disclosure: M. Robustillo: None; C. Gomez-Vaquero: None; J. Narvaez: None; J. Rodriguez-Moreno: None; P. Estrada: None; L. Lopez-Vives: None; J. M. Nolla: None.

1017
Association between Serum Osteoprotegerin Levels and Carotid Atherosclerotic Plaque in Patients with Rheumatoid Arthritis. Yu Asanuma, Yuki Shimada and Toshihide Mimura. Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University

Background: Osteoprotegerin (OPG), a regulator in bone resorption, is implicated in pathogenesis of rheumatoid arthritis (RA) and atherosclerosis. The expression of OPG is detected in human atherosclerotic
plaque. OPG concentrations are elevated in patients with coronary artery disease and associated with severity of disease and increased cardiovascular mortality in general population. The purpose of this study is to determine the relationship of serum OPG levels, traditional coronary risk factors and RA-related factors to carotid atherosclerotic plaque in patients with RA.

Methods: Ninety-six patients with RA were studied (84.4% female, age 60±10(SD) years). Serum OPG levels were measured by ELISA. All patients underwent carotid ultrasonography. The relationship between the patient's clinical characteristics and the presence or absence of carotid atherosclerotic plaque was examined. Spearman correlation analyses and Mann-Whitney tests were used to define the association between OPG levels and other variables. Logistic regression was used to assess association among OPG, cardiovascular risk factors, markers of inflammation and carotid plaque.

Results: OPG concentrations were significantly higher in patients with plaque than those without plaque (median: 1374 vs. 868 pg/ml, P<0.001). The presence of carotid plaque increased across OPG quartiles (p trend=0.005). Older age and higher levels of CRP or MMP-3 were more common in RA patients with plaque. Significant difference was not found in sex, disease duration, blood pressure, BMI, smoking, LDL cholesterol, DAS28, modified Sharp score and daily dose of prednisolone between RA patients with and without plaque. Serum OPG levels were correlated with CRP after adjusting for age and sex (P=0.009). After adjusting for age, sex and CRP, increased levels of OPG were associated with carotid plaque in patients with RA (P=0.024), however the association was not found between other risk factors for atherosclerosis, markers of inflammation or disease activity and presence of carotid plaque.

Conclusions: Patients with RA, a group that is known to have accelerated coronary atherosclerosis, also have increased concentrations of OPG, a mediator linked to coronary artery disease in other populations. OPG concentrations are independently associated with carotid plaque. Increased OPG levels would be a useful biomarker for atherosclerosis in patients with RA.

Disclosure: Y. Asanuma: None; Y. Shimada: None; T. Mimura: None.

1018
Body Composition Trends in Patients with Rheumatoid Arthritis: Associations with Disease Characteristics and Inflammatory Markers. Henry R. Kramer1, Joan M. Bathon1 and Jon T. Giles2. 1Division of Rheumatology, Johns Hopkins University, Baltimore, MD, 2Johns Hopkins Univ, Baltimore, MD

Background: Recent evidence suggests that patients with rheumatoid arthritis (RA) have altered body composition (BC) relative to non-RA patients. However, while it is hypothesized that systemic inflammation and the RA disease process play a major role in the development of these alterations, these associations have not been thoroughly evaluated.

Methods: Using a longitudinal study design, BC was evaluated by total body dual-energy x-ray absorptiometry (DXA) in 152 patients enrolled in the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis (ESCAPE-RA) study. DXA was performed at visits 1 and 3. DXA-derived measures included total body fat mass (TFM), fat mass index (FMI: kg/m2 of height), total body lean mass (TLM), and fat-free mass index (FFMI: kg/m2). Associations of RA characteristics with yearly rates of change in BC measures were explored using multivariate linear regression, adjusting for baseline BC and pertinent sociodemographic and lifestyle characteristics identified from univariate models.

Results: Of the 152 patients, mean age was 63 years, 64% were women, and 88% were Caucasian. Median RA disease duration at baseline was 12 years, 75% of patients were seropositive by RF or CCP, and median DAS28-CRP was 3.1. Median follow-up time was 3.2 years. As expected, significant gender differences in BC were detected, with men having significantly greater TLM than women and women having greater TFM than men. However, the rates of change were similar by gender, with a median gain of 0.31kg/year for TFM and a median loss 0.27kg/year for TLM. FMI increased at a median rate of 0.16kg/m2/year, and FFMI decreased at a median rate of 0.43kg/m2/year. Yearly change in FMI was negatively correlated with depression score (p=0.044) and cumulative CRP (p=0.038). Compared to seronegative patients, those with RF or CCP had a significantly lower adjusted yearly change in FMI (Figure 1A). Patients with higher baseline Sharp scores demonstrated a higher adjusted yearly change in FFMI compared to those with lower scores (Figure 1B).

Conclusions: In RA patients, yearly changes in BC were similar in both men and women, and patients with greater disease burden by radiograph experienced a higher rate of loss of lean mass. Interestingly, in our study population with a median of 12 years of disease, patients with RF or CCP did not experience the same yearly increases in fat mass compared to seronegative patients. These data suggest that factors associated with RA severity may promote low body mass, a state associated with all-cause and cardiovascular mortality, by both accelerating loss of lean mass and limiting the gain of fat associated with normal aging.

Disclosure: H. R. Kramer: None; J. M. Bathon: None; J. T. Giles: None.
Cardiovascular Risk Estimates in Rheumatoid Arthritis in the Netherlands. Inger L. Meek, Harald E. Vonkeman and Mart A. F. J. van de Laar. 1Enschede, The Netherlands, 2Enschede, The Netherlands, 3Rheumatology Centre Twente, University Twente & Medisch Spectrum Twente, Enschede, The Netherlands

Background: Over the past decades many reports have shown a relationship between rheumatic disease and cardiovascular morbidity and mortality. This relationship may be due to clustering of risk factors or a feature of the chronic inflammatory processes. In recent years both these factors have received special attention as part of general healthcare and development of potential anti-inflammatory agents and goal directed antirheumatic therapy, respectively. Therefore new data concerning cardiovascular risks in modern rheumatologic practice are needed.

Objective: To assess the prevalence of traditional cardiovascular risk factors in current daily clinical rheumatoid arthritis (RA) outpatient care compared to the general population.

Methods: A cohort containing all consecutive patients attending a large rheumatologic outpatient department in The Netherlands was cross-sectionally examined for prevalent cardiovascular risk factors. Data were collected between May and December 2009, and included demographics, lifestyle, body mass index (BMI), blood pressure, laboratory tests, rheumatologic diagnosis and disease activity, use of medication and medical history. Parameters of cardiovascular risk in RA patients were compared with data from the general population from the same region. Also, the SCORE 10-year risk estimate for the development of fatal cardiovascular events (developed for the use in daily clinical practice as described previously, a risk estimation above 10% or above 5% with one additional risk factor being regarded an indication for primary cardiovascular risk intervention) was calculated for each RA patient.

Results: Cardiovascular risk profiles were measured in 334 RA patients (mean age 60 years, 72% women, mean disease duration 88 months, 70% being in remission according to DAS28 or expert opinion, 8,7% having previously documented atherothrombotic cardiovascular disease). In RA patients we found significantly more hypertension (67 vs. 43% in men and 59 vs. 41% in women), higher mean BMI in women (27,7 vs. 26,4) and lower mean values of total cholesterol (5,0 vs. 5,79 mmol/L in men and 5,3 vs. 6,09 mmol/L in women) and total/HDL cholesterol ratio (4,2 vs. 5,1 mmol/L in men and 3,5 vs. 4,6 mmol/L in women) compared to the general population.

In RA patients the calculated mean SCORE 10-year risk for fatal cardiovascular events was 8,3% in men and 4,5% in women, 73% and 52% having a SCORE risk calculation above 5% and one additional risk factor, respectively.

Conclusions: When compared to the general population this cohort of RA patients, treated according to the current standard of goal directed therapy aiming at remission or low disease activity, shows reassuring results regarding traditional cardiovascular risk factors, with even surprisingly favourable serum cholesterol profiles. Possible advantageous effects of effective anti-rheumatic therapy on serum lipid profiles and the consequences of our findings on cardiovascular event rates need further investigation.

References:

Disclosure: I. L. Meek: None; H. E. Vonkeman: None; M. A. F. J. van de Laar: None.

1020 Circulating Immune Complexes in Patients with Severe Extra-Articular Rheumatoid Arthritis Induce Tumour Necrosis Factor Production by Peripheral Blood Mononuclear Cells. Carl Turesson, Linda Mathsson, Lennart Jacobsson, Gunnar Sturfelt and Johan Rönnelid. 1Skåne University Hospital, Malmö, Sweden, 2Skåne University Hospital, Lund, Sweden, 3Uppsala University Hospital, Uppsala, Sweden

Objective: A subset of patients with rheumatoid arthritis (RA) develop severe extra-articular disease manifestations. Autoantibodies and immune complexes (IC) have been implicated in the pathogenesis, but their role in systemic inflammation in RA remains to be defined. Our aim was to study circulating IC and their influence on cytokine production by peripheral blood mononuclear cells (PBMC) in patients with active, severe extra-articular RA (ExRA) compared to RA controls with no extra-articular manifestations.

Methods: Thirty-five consecutive patients with RA and severe ExRA manifestations according to predefined criteria (pericarditis, pleuritis, major cutaneous vasculitis, Felty’s syndrome, glomerulonephritis, vasculitis related neuropathy, scleritis, episcleritis, retinal vasculitis or major organ vasculitis involving other organs) were studied. Seventy controls with RA but no ExRA manifestations, individually matched for age, sex and disease duration, served as the comparison group. Blood was drawn directly after ExRA was diagnosed and before any new treatment was started, and samples were stored at –70°C until investigated. IC prepared as serum polyethylene glycol (PEG) precipitates were added to serum-free PBMC cultures and tumour necrosis factor (TNF) levels were measured after 20 hours using ELISA. Circulating C1q-binding IC and anti-CCP antibodies were determined using ELISA. RF was detected using nephelometry.

Results: Circulating IC levels were higher among patients with ExRA compared to RA controls [median 8.52 μgEq/mL; interquartile range (IQR) 3.63–24.27 vs median 4.51 μgEq/mL; IQR 1.81–10.45 (p = 0.005)]. TNF induction from PBMC was greater after adding serum PEG precipitates from ExRA patients [mean 17.7 pg/mL; standard deviation (SD) 12.1 vs mean 12.9; SD 7.6; for RA controls (p = 0.02)]. Levels of C1q-binding IC correlated with IC-induced levels of TNF among ExRA patients (r = 0.40; p = 0.02) as well as among RA controls (r = 0.35; p = 0.004). There was a strong association between circulating IC levels and RF among patients with ExRA (r = 0.62; p < 0.001), in particular in the subset with major cutaneous vasculitis (n = 9; r = 0.76; p = 0.03). Anti-CCP antibodies did not correlate with circulating IC levels in patients with ExRA.

Conclusion: Patients with severe ExRA manifestations were characterized by high levels of circulating IC, and IC from ExRA patients were stronger inducers of TNF production from PBMC compared to IC from RA controls. These results suggest that circulating IC enhance RF production and systemic inflammation in severe ExRA.

Disclosure: C. Turesson: None; L. Mathsson: None; L. Jacobsson: None; G. Sturfelt: None; J. Rönnelid: None.

1021 Clinical and Laboratory Risk Factors of Cardiovascular Disease (CVD) in a Cohort of Greek Patients with Early Rheumatoid Arthritis (RA). Nikolaos Papadopoulos, Georgios Tsiaousis, Marios Katsounaros, Dimitrios Baltzis and Vasiliki Galanopoulou. 1B Internal Medicine Clinic, Papanikolaou General Hospital, Thessaloniki, Greece, 2Cardiologist, Kastro- ria, Greece, 3Rheumatology Unit, Papageorgiou General Hospital, Thessaloniki, Thessaloniki, Greece

Background: Previous studies have shown that RA patients are at increased risk of developing cardiovascular disease.

Aim of the Study: To investigate the contribution of various clinical and laboratory risk factors to the development of CVD in a cohort of Greek patients with early RA.

Patients and Methods: From January 2000 until June 2009, one hundred and ninety seven patients with early RA and without a prior history of CVD, were first diagnosed and subsequently followed-up, every three months at the rheumatology unit of our hospital. Demographic, clinical, laboratory and therapeutic parameters were evaluated during every follow-up. At the end of the study, patients were divided, according to the development or not of CVD, which included acute myocardial infarction, diagnosis of a stable coronary artery disease, ischaemic cerebral vascular disease and thrombosis of a large vessel.

Results: At the end of the study 37 patients (18.27%) had suffered a CVD event. Univariate analysis revealed that late onset of RA (p < 0.005), male sex (p = 0.008), high mean CRP and ESR (p < 0.008 and 0.017 respectively), presence of extra-articular manifestations (p = 0.05) and positivity of anti-CCP autoantibodies and RF (p < 0.005 and 0.05 respectively), were in a statistically significant manner associated with the development of CVD. Concerning co-morbidities, the presence of hypertension (p < 0.005) and dyslipidaemia (p < 0.005) were also associated with CVD. A logistic regression model showed that anti-CCP positivity, age at RA onset, presence of extra-articular manifestations and history of hypertension and dyslipidaemia were independent risk factors of CVD. Cox regression analysis demonstrated that anti-CCP positivity significantly influenced the time of first CVD occurrence (Figure 1).
Conclusion: Patients with early RA, positive to anti-CCP autoantibodies, who display extra-articular manifestations and a history of hypertension and dyslipidaemia are at higher risk of developing CVD.

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1022
Computed Tomographic Densitometry (CTD) for the Evaluation of Interstitial Lung Fibrosis in Rheumatoid Arthritis (RA). Dimitrios A. Pappas3, Jon T. Giles4, Geoffrey Connors2, Noah Lechtzin2, Joan M. Bathon1 and Sonye Danoff1. 1Division of Pulmonary and Critical Care, Johns Hopkins University, Baltimore, MD, 2Division of Pulmonary and Critical Care, Johns Hopkins University, 3Division of Rheumatology, Johns Hopkins University, Baltimore, MD, 4Johns Hopkins Univ, Baltimore, MD.

Background: Pulmonary disease is a major source of morbidity and mortality in RA patients. Current diagnostic modalities lack sensitivity and are highly dependent on observer experience. We compared the reliability of expert visual CT scan evaluation (“Visual evaluation”) of interstitial lung fibrosis, with CT densitometry (CTD), an automated modality for determining the density of pulmonary parenchymal tissue, and the association of both methods with the presence of respiratory symptoms, pulmonary function test (PFT) abnormalities, impaired quality of life (QOL) and fatigue.

Methods: RA patients were evaluated with chest CT, PFT, respiratory questionnaires, fatigue (FACTIT-F) and QOL (SF-36) instruments. Fibrosis by CTD was measured as the percentage of attenuation below -940 and -250 Hounsfield units (HU). A single expert radiologist evaluated the same CT scans for the presence of fibrosis. A subset of scans was blindly read twice by the same reader who was not aware of any patient characteristics.

Intra-operator/observer reproducibility was evaluated by means of percent agreement. Univariate analyses were applied to evaluate the relationship of visual and CTD measurements with the presence of respiratory symptoms and PFT abnormalities.

For multivariable analysis, the SF36 physical function scale and the FACTIT-F subscale were used as outcomes and were handled as binary variables (lower quartile vs. upper quartiles). Independent variables were selected based on biologic plausibility. Final logistic regression models were built using forward and backward stepwise selection of variables. Concentrations of cystatin C were significantly higher in patients with RA (median (IQR): 1.16 (0.99–1.35) mg/L) than controls (1.01 (0.90–1.19) mg/L), (adjusted P < 0.001). Serum creatinine concentrations (P=0.62) and MDRD-eGFR (P=0.53) did not differ significantly among RA and control groups. In patients with RA, cystatin C concentrations were significantly positively correlated with creatinine (rho=0.43, P<0.001) and significantly inversely correlated with MDRD-eGFR (rho=-0.43, P<0.001). In RA cystatin C was positively correlated with ESR (rho=0.26, P<0.001), CRP (rho=0.20, P=0.01), FRS28 (rho=0.19, P=0.006), FRS (rho=0.44, P<0.001) and TNF-α (rho=0.20, P=0.01), but not with IL-6, or HOMA (both P>0.05). After adjustment for age, race and sex, only associations with ESR, CRP, FRS28 and FRS retained statistical significance. Cystatin C also correlated with CACS (P<0.001) in RA but this was not significant after adjustment for age, race, sex and FRS (P=0.67).

Conclusions: Cystatin C concentrations are higher in patients with RA than compared to subjects without RA; this may reflect undetected subclinical renal dysfunction and inflammation. Cystatin C provides information regarding the risk of atherosclerosis in RA, but this is not independent of the information provided by conventional cardiovascular risk factors.
Table. Relationship between Cystatin C and Cardiovascular Risk Factors, Inflammation and Coronary Calcium Score in RA

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cystatin C</th>
<th>Unadjusted p-value</th>
<th>Adjusted p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.44</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>0.49</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA index</td>
<td>0.09</td>
<td>0.26</td>
<td>0.15</td>
</tr>
<tr>
<td>Framingham score</td>
<td>0.44</td>
<td>&lt;0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>DAS28</td>
<td>0.19</td>
<td>0.013</td>
<td>0.006</td>
</tr>
<tr>
<td>ESR</td>
<td>0.26</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP</td>
<td>0.20</td>
<td>0.011</td>
<td>0.009</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.20</td>
<td>0.011</td>
<td>0.11</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.10</td>
<td>0.185</td>
<td>0.322</td>
</tr>
<tr>
<td>Coronary calcium score</td>
<td>0.32</td>
<td>&lt;0.001</td>
<td>0.067</td>
</tr>
</tbody>
</table>

*Adjusted p-values are all adjusted for age, race and sex, except for coronary calcium score that is additionally adjusted for Framingham risk score. Multivariable linear regression was used in Adjusted p-value.

**Univariate Spearman correlation coefficient (n=167)

HOMA Index=Homeostasis Model Assessment Index; DAS28= Disease Activity Score 28-joint assessment; ESR=Erythrocyte Sedimentation Rate; CRP=C-Reactive Protein; TNF-α=Tumor Necrosis Factor-α; IL-6=Interleukin-6

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Depressive Symptoms and Perceived Communication around Shared Decision Making among Patients with Rheumatoid Arthritis. Jennifer L. Barton1, Laura Trupin2, Mary E. Margaretten1, Laura J. Julian3, Jonathan D. Graff4, John Imboden5, Edward H. Yelin6 and Dean Schillinger1.


Background: Due to the high cost and potential toxicity of therapies for rheumatoid arthritis (RA), shared decision making is central to patient safety and quality of care. While depressive symptoms have been associated with poor clinician-patient communication in diabetes and coronary heart disease, this has not been studied in RA. We sought to examine whether depressive symptoms influence clinician-patient communication around shared decision making among RA patients.

Methods: Data were derived from a cohort of adults with diagnostically confirmed RA seen at two university-affiliated clinics. Subjects completed a structured telephone survey in English, Spanish, or Chinese, that included the Interpersonal Processes of Care Survey (IPC), a validated patient-reported measure. The IPC decision-making subscale is based on the mean score for two items, “How often did you and your doctors work out a treatment together?” and “If there were treatment choices, how often did doctors ask if you would like to help decide your treatment?” (range: 1 “never” to 5 “always”). Mean scores <4 (corresponding to never/rarely/sometimes) were categorized as poor communication. The Patient-Health Questionnaire-9 (PHQ-9) was administered in-person in the patient’s preferred language to determine depression symptom severity. PHQ-9 was categorized using three severity classifications: none-minimal (0–4), mild (5–9), and moderate to severe (≥10). Multivariate logistic regression was used to evaluate the independent association of depressive symptoms with poor communication, adjusted for demographic and disease characteristics, and trust in physician.

Results: The 227 subjects were 84% female with a mean age of 55 ± 14 years and mean disease duration of 11 ± 11 years; 143 (63%) spoke English, 52 (23%) Spanish, and 32 (14%) Cantonese. Fifty-five (24%) had moderate to severe depressive symptoms on the PHQ-9 and 70 (31%) reported poor communication on the decision-making subscale. Results from the multivariate model suggest that moderate to severe depressive symptoms were independently associated with poor communication (AOR = 3.8, 95% CI 1.4–10.7) (Table).

Table. Predictors of Poor Doctor-Patient Communication Around Shared Decision Making Among 227 Patients with RA

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease severity</td>
<td></td>
<td></td>
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<tr>
<td>Disease duration</td>
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<tr>
<td>Disease duration</td>
<td></td>
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<tr>
<td>Language</td>
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<tr>
<td>Spanish</td>
<td></td>
<td></td>
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<tr>
<td>Framingham score</td>
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<tr>
<td>HOMA index</td>
<td></td>
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<tr>
<td>ESR</td>
<td></td>
<td></td>
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<tr>
<td>CRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary calcium score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Depressive symptoms              |             |         |
|                                  |             |         |
| OR (95% CI)                      |             |         |
| Demonstrated                     |             |         |
| Adjusted                         |             |         |
| p-value                          |             |         |
| Suboptimal Trust in Physician    |             |         |

Disclosure: Among patients with RA, we found that moderate to severe depressive symptoms were independently associated with poor doctor-patient communication around shared decision making. While older age and suboptimal trust in physician have been associated with poorer communication in prior studies, depression status has not been observed as a correlate of shared decision making in RA. This study highlights the need for interventions to improve shared decision making in rheumatology practices, especially for those RA patients at greatest risk of poor communication.

Disclosure: J. L. Barton: None; L. Trupin: None; M. E. Margaretten: None; L. J. Julian: None; J. D. Graf: None; J. Imboden: None; E. H. Yelin: None; D. Schillinger: None.

1025

Differences in the Autonomic Reactivity Pattern upon Various Stresors in Patients with Rheumatoid Arthritis. Olga Malyshcheva1, Petra Baum2, Anke Voitzsch3 and Christoph G. O. Baerwald4.

1. University Hospital, Leipzig, Germany, 2. University Hospital, Leipzig, Germany

Background: Stress is recognized as an important risk factor in the pathogenesis of rheumatoid arthritis (RA). However, it is still incompletely understood how the autonomic nervous system and the immune system interact in patients with RA.

Methods: To characterize the stress pattern in 90 RA patients the autonomic response upon various stressors the heart rate variability (HRV) test (ProSciCard III, Version 2.2a, Medi-Syst GmbH, Germany) was performed and compared to 30 osteoarthritis (OA) patients exhibiting equal distribution of age and gender. Standardized stress tests included mental arithmetic tasks to induce mental stress (MST), Ewing test, deep breathing test (DBT) and Valsalva maneuver (VM). HRV measures including frequency domain parameters were calculated yielding measures of parasympathetic and sympathetic activity as well as the total power (TP) of autonomic nervous system influence on various parameters: high frequency (HF), low frequency (LF), and very low frequency (VLF) index of heart rate variability, variation coefficient (VC), and square root of the mean of the squares of successive R-R interval differences (RMSSD).

Results: At base line patients with RA were characterized by a combination of reduced TP as well as decreased parasympathetic activity compared to OA patients (TP: 4.79 ± 0.5 Hz vs. 10.5 ± 3.6 Hz; HF: 1.47 ± 0.18 Hz vs. 4.6 ± 1.5 Hz, respectively, p < 0.01). Stress tests revealed a disturbed sympathetic activity in RA patients compared to OA patients in the MST (LF HRV: 1.69 ± 0.21 Hz vs. 3.05 ± 1.0 Hz, and LF/HR HRV: 1.1 ± 0.09 vs. 3.4 ± 0.06, p < 0.05, respectively) as well as in the DBT (RMSSD: 34.7 ± 2.16 ms vs. 46.5 ± 4.2 ms, and VC: 7.02 ± 0.4 vs. 9.46 ± 0.43, p<0.005, respectively). Comparing low disease activity RA patients (DAS ≤ 2.3, LDA) to RA patients with high disease activity (DAS > 3.2, HDA) demonstrated a significant improvement in the sympathetic activity of LDA patients at base line (LF/HR HRV: 1.36 ± 0.1 Hz vs. 0.87 ± 0.02 Hz, p<0.01) as well as in various stress tests (MST, Ewing test, VM). Furthermore, in RA patients with HDA the DBT showed a disturbed sympathetic activity compared to LDA RA patients (VC: 6.2 ± 0.2 vs. 8.1 ± 0.3, p<0.01). Stratifing the patients for therapy revealed an increase of the parasympathetic tone at base line, as well in various stress tests (DBT, Ewing test), for RA patients under anti-TNF medication compared to methotrexate mono-
ECG positive i.e. EURO-Score

HLP family history of myocardial infarction, Hypert
DM Diabetes mellitus, pAVK peripheral artery disease, stroke = history of stroke, FamHX = family history of myocardial infarction, Hypert = Arterial Hypertension, HLP = Hyperlipoproteinemia, Smoker (ex) = current smoker, ESC = EURO-Score, ECG = Electrocardiogram, BNP = NT-proBNP > 200 g/ml, RISK+ = at least one risk factor positive i.e. EURO-Score ≥ 3% or NT-proBNP > 200 g/ml or pathological ECG pattern.

Results: Patients had rheumatoid arthritis (RA, n = 333), spondylarthropathies (SpA, n = 124), connective tissue diseases (CTD, n = 145) and no RD (Control, n = 73). For details of patients’ characteristics see table 1 and 2.

Introduction: The increased cardiovascular risk in patients with rheumatic diseases (RD) may be attributed to traditional cardiovascular (CV) as well as to RD-specific risk factors. We aimed to identify RD-specific correlates of CV risk in patients with RD.

Methods: 628 consecutive patients attending the rheumatology outpatient department of the University Hospital were assessed regarding CV risk factors by structured history taking, questionnaires, ECG and laboratory measurements including natriuretic peptides (NT-proBNP). Screening for increased risk of CV disease was regarded positive (RISK+) if any of the following was present: European CV Risk Score (EURO-Score) ≥ 3% or NT-proBNP ≥ 200 pg/ml or any pathological ECG pattern.

Results: Patients had rheumatoid arthritis (RA, n = 333), spondylarthropathies (SpA, n = 124), connective tissue diseases (CTD, n = 145) and no RD (Control, n = 73). For details of patients’ characteristics see table 1 and 2.

<table>
<thead>
<tr>
<th>DM</th>
<th>pAVK</th>
<th>Stroke</th>
<th>FamHX</th>
<th>Hypert</th>
<th>HLP</th>
<th>Smoker</th>
<th>ESC</th>
<th>≥ 3</th>
<th>ECG</th>
<th>BNP</th>
<th>RISK+</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>15%</td>
<td>12%</td>
<td>2%</td>
<td>42%</td>
<td>38%</td>
<td>47</td>
<td>19</td>
<td>32%</td>
<td>14%</td>
<td>18%</td>
<td>43%</td>
</tr>
<tr>
<td>SpA</td>
<td>10%</td>
<td>12%</td>
<td>1%</td>
<td>46%</td>
<td>24%</td>
<td>39</td>
<td>33%</td>
<td>17%</td>
<td>16%</td>
<td>5%</td>
<td>32%</td>
</tr>
<tr>
<td>CTD</td>
<td>6%</td>
<td>16%</td>
<td>3%</td>
<td>34%</td>
<td>42%</td>
<td>30</td>
<td>19%</td>
<td>21%</td>
<td>18%</td>
<td>14%</td>
<td>24%</td>
</tr>
<tr>
<td>Con</td>
<td>4%</td>
<td>12%</td>
<td>3%</td>
<td>61%</td>
<td>18%</td>
<td>32%</td>
<td>23%</td>
<td>22%</td>
<td>18%</td>
<td>14%</td>
<td>34%</td>
</tr>
</tbody>
</table>

DM = Diabetes mellitus, pAVK = peripheral artery disease, stroke = history of stroke, FamHX = family history of myocardial infarction, Hypert = Arterial Hypertension, HLP = Hyperlipoproteinemia, Smoker (ex) = current smoker, ESC = EURO-Score, ECG = Electrocardiogram, BNP = NT-proBNP > 200 pg/ml, RISK+ = at least one risk factor positive i.e. EURO-Score ≥ 3% or NT-proBNP > 200 pg/ml or pathological ECG pattern.

Logistic regression (dependent variable RISK+) was performed within the 4 groups using rheumatoid factor, disease duration, sex, haemoglobin, GFR, CRP, LDL-cholesterol, BSG, usage of NSAR, Steroids, DMARDs, or Biologicals, as well as DAS28 in RA. Odds ratio and 95% CI are reported. Positive correlates of RISK+ were in the RA group: use of DMARD 4.1 (1.49–11.30; p = 0.006), disease duration 1.05 per year (1.01–1.09, p = 0.011), LDL-cholesterol 1.01 per g/dl (1.00–1.03, p = 0.017), and CRP 1.27 per mg/dl (1.00–1.61; p = 0.048); negative correlates were: male sex 0.16 (0.07–0.39; p < 0.001) and renal function (GFR per ml/min/kg 0.98 (0.96–0.99; p = 0.007)).

In the SpA group a high CRP 2.25 per mg/dl (1.23–4.10, p = 0.008) and haemoglobin 2.20 per g/dl (1.16–4.17, p = 0.015) were associated with a worse risk profile.

Screening results in patients with connective tissue diseases were more likely to be positive in patients using DMARDs (3.73, 1.25–11.19, p = 0.019) and less likely if patients were male (0.18, 0.04–0.85, p = 0.031) and if renal function was good (GFR per ml/min/kg (0.96, 0.94–0.99, p = 0.002)). In the control group male sex (0.17, 0.001–0.25; p = 0.003) was associated with a reduced and ESR per mm (1.19, 1.003–1.42; p = 0.003) with an increased risk profile.

Conclusion: In different rheumatic conditions disease-specific risk factors indicating an increased cardiovascular risk could be identified, justifying further cardiology diagnostics and closer long-term follow-up.

Disclosure: O. Malysheva: None; P. Baum: None; A. Voititz: None; C. G. O. Baerwald: None.

1026

Disease Specific Cardiovascular Risk Factors in Patients with Rheumatic Diseases. Stefan Kleiner1, Margret Breunig1, Hans Peter T. Tomy3, Martin Feuchtenberger2, Stefanie Bouma1, Angermann E. Christiane1, Georg Ertl1 and Stefan Stoerk1. 1Department of Cardiology, Med. Klinik 1, University of Wuerzburg, 2Rheumatology / Clinical Immunology, Med. Klinik 2, University of Wuerzburg, Wuerzburg, Germany, 3Rheumatology / Clinical Immunology, Med. Klinik 2, University of Wuerzburg, Wuerzburg, Germany, 4Rheumatology/Clinical Immunology, Med. Klinik 2, University of Wuerzburg, Wuerzburg, Germany.

Background: COPD is recognized as an essential by RA patients(1). However, the knowledge of promising strategies to handle RA is still very limited and gender differences in COPD have only been scarcely investigated. We therefore checked the use of a previously introduced 18-item questionnaire(2) during the validation process of the RAID-questionnaire(1).

Objectives: First, to investigate the usage of coping strategies among men and women. Secondly, to find reasons for eventually occurring differences.

Methods: We analyzed the data of 433 RA patients from 12 countries stemming from the RAID study database(1) and providing complete information on all coping items. Before the start of the validation process, two numeric rating scales asking for the extent of coping effectiveness and perceived helplessness were added to the original coping questionnaire(2). First, we evaluated to which extent men and women are using cognitive reframing, pushing through the pain, emotional expression and active problem solving – the coping scales previously derived(2) from the questionnaire. We then addressed the question whether there are gender differences with respect to coping effectiveness and perceived helplessness. Finally, we set these results into relation to other common outcome variables measuring disease activity and health status.

Results & Conclusion: Men (N = 99) and women (N = 334) had long-standing (mean disease duration, men: 10.27 ± 9.77yrs; women: 13.47 ± 10.24yrs) and active (mean DAS28, men: 3.45 ± 1.72; women 4.3 ± 1.54) RA. Women made significantly more use of coping strategies when compared to men and showed a strong trend towards higher levels of perceived helplessness whereas coping effectiveness was not different.

Table 1. Descriptive data of coping scales and comparison of gender differences

<table>
<thead>
<tr>
<th>Coping Strategy</th>
<th>Mean ± SD (Sample)</th>
<th>Mean ± SD (Stratified for gender)</th>
<th>p Value</th>
<th>Significance test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pushing Through The Pain</td>
<td>1.90 ± 0.78</td>
<td>Male 1.79 ± 0.80</td>
<td>0.11</td>
<td>t-test</td>
</tr>
<tr>
<td>Female 1.93 ± 0.77</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Problem Solving</td>
<td>1.66 ± 0.87</td>
<td>Male 1.31 ± 0.86</td>
<td>0.04</td>
<td>t-test</td>
</tr>
<tr>
<td>Female 1.76 ± 0.87</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive Reframing</td>
<td>1.73 ± 0.79</td>
<td>Male 1.57 ± 0.79</td>
<td>0.03</td>
<td>t-test</td>
</tr>
<tr>
<td>Female 1.78 ± 0.78</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional Expression</td>
<td>1.43 ± 0.74</td>
<td>Male 1.30 ± 0.74</td>
<td>0.04</td>
<td>t-test</td>
</tr>
<tr>
<td>Female 1.47 ± 0.73</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helplessness†</td>
<td>4.00 ± 2.75</td>
<td>Male 3.54 ± 2.60</td>
<td>0.06</td>
<td>t-test</td>
</tr>
<tr>
<td>Female 4.13 ± 2.78</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coping Effectiveness†</td>
<td>5.65 ± 2.22</td>
<td>Male 5.64 ± 2.19</td>
<td>0.94</td>
<td>t-test</td>
</tr>
<tr>
<td>Female 5.66 ± 2.23</td>
<td></td>
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</tr>
</tbody>
</table>

*S Score ranging from 0-3 †Score ranging from 0-10

We set these results into relation to measures of disease activity and found significantly elevated levels of the patient’s and physicians evaluation of general health (VAS), the tender joint count 28, the HAQ-DI and accordingly
the DAS28 in female patients (all p ⬍ 0.01). Hence, female RA patients seem
to have both, a higher disease activity and worse physical functioning.
Therefore, they might be urged to cope more frequently with impact of
disease, while tending to feel more helpless at the same time.
References:

Pain, VAS 0–10

Tuesday, November 9

1028
Effects of HMG-CoA Reductase Inhibitor on Progression of Carotid
Intima-Media Thickness and Arterial Stiffness in Rheumatoid Arthritis
– A Randomized Controlled Trial. Lai-Shan Tam3, Edmund K. Li2, Qing
Shang3, Brian Tomlinson3, Vivian W. Lee3, Kenneth K. Lee3, Martin Li3,
Woon-Pang Kuan1, Tena K. Li3, Lorraine Tseung3, Gabriel Yip3, Ben
Freedman4 and Cheuk-Man Yu3. 1Hospital Selayang, Malaysia, 2The Chinese University of Hong Kong, Hong Kong, China, 3The Chinese University
of Hong Kong, 4University of Sydney
Objectives: To ascertain the efficacy and safety of rosuvastatin in the
prevention of subclinical atherosclerosis and arterial stiffness markers in
patients with rheumatoid arthritis (RA)
Methods: Fifty RA patients with stable disease activity (DAS⬍5.1 for at
least 3 months) were randomized in a double-blind placebo-controlled trial to
receive 10mg rosuvastatin (n⫽24) or placebo (n⫽26). Patients were prospectively followed every 3 monthly for 12 months. Intima-media thickness
(IMT), augmentation index (AIx) and subendocardial variabilty ratio (SEVR)
were measured at baseline, 6 and 12 months.
Results: Three out of 24 (12.5%) subjects in the rosuvastatin arm did not
complete the study because of adverse event (n⫽1) and major flare (DAS⬎
5.1) requiring escalation of DMARDs (n⫽2), while 5/26 (19.2%) subjects
had major flare requiring escalation of DMARDs in the placebo arm
(p⫽0.704). Rosuvastatin resulted in statistically significant reductions of total
cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), apolipoprotien B (Apo B) and urate levels vs placebo. After 1 year, rosuvastatin
treatment resulted in a mean (⫾SE) percent change of LDL-C: ⫺35.8 ⫾ 5.0
compared to placebo: 16.8 ⫾ 10.5 (p⬍0.001). Comparing the changes within
each group, significant reduction in the TC, HDL-C, LDL-C, Apo B,
fibrinogen and urate levels were observed at 6 and 12 months compared with
baseline in the rosuvastatin group.
Table 1. Changes in cardiovascular risk factors

HDL-C, mmol/L
LDL-C, mmol/L
TG, mmol/L
Apo A1, mg/dL
Apo B, mg/dL
Fibrinogen, g/L
Urate, mmol/L
Creatinine, ␮mol/L
BMI, kg/m2
SBP, mmHg
DBP, mmHg

Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo

Table 2. Changes in disease activity indexes and markers of inflammation.
EMS, mins

Disclosure: M. Englbrecht: None; L. Gossec: None; A. DeLongis: None; T. K.
Kvien: None; M. Scholte-Voshaar: None; T. Sokka: None; S. Georg: None.

TC, mmol/L

fibrinogen level (4.1 ⫾ 0.7g/L at baseline to 3.8 ⫾ 0.7g/L at 1 year, p⬍0.05)
was observed compared with baseline in the rosuvastatin group.

Baseline

6 months

12 months

p-value†

4.6 ⫾ 0.8
4.9 ⫾ 0.9
1.7 ⫾ 0.5
1.6 ⫾ 0.4
2.5 ⫾ 0.7
2.7 ⫾ 0.9
0.9 (0.7–1.1)
1.1 (0.8–1.7)
137 ⫾ 42
144 ⫾ 28
87 ⫾ 30
95 ⫾ 32
4.1 ⫾ 0.7
3.9 ⫾ 0.5
0.29 ⫾ 0.10
0.30 ⫾ 0.09
65.6 ⫾ 15.7
65.9 ⫾ 12.1
23.6 ⫾ 3.1
22.7 ⫾ 4.0
130 ⫾ 16
124 ⫾ 15
78 ⫾ 9
78 ⫾ 10

3.3 ⫾ 0.6*
4.9 ⫾ 1.0
1.5 ⫾ 0.4#
1.6 ⫾ 0.4
1.4 ⫾ 0.5*
2.8 ⫾ 1.0
0.9 (0.6–1.1)
1.2 (0.8–1.7)
149 ⫾ 30
153 ⫾ 35
63 ⫾ 21*
97 ⫾ 39
3.8 ⫾ 0.7#
3.8 ⫾ 0.7
0.26 ⫾ 0.09#
0.30 ⫾ 0.09
65.4 ⫾ 14.7
65.7 ⫾ 11.9
23.9 ⫾ 3.3
22.9 ⫾ 4.1
127 ⫾ 17
125 ⫾ 16
80 ⫾ 11
78 ⫾ 10

3.3 ⫾ 0.9*
5.1 ⫾ 1.0
1.6 ⫾ 0.4#
1.6 ⫾ 0.5
1.6 ⫾ 0.8*
3.0 ⫾ 1.0#
0.8 (0.6–1.2)
1.2 (0.9–1.6)
144 ⫾ 31
142 ⫾ 35
61 ⫾ 29*
98 ⫾ 28
3.8 ⫾ 0.7#
3.7 ⫾ 0.9
0.26 ⫾ 0.09#
0.31 ⫾ 0.09
64.4 ⫾ 13.5
66.8 ⫾ 13.4
23.9 ⫾ 3.4
22.9 ⫾ 4.0
130 ⫾ 18
126 ⫾ 17
79 ⫾ 11
78 ⫾ 11

⬍0.001
0.557
⬍0.001
0.353
0.804
⬍0.001
0.468

Patient global,
VAS 0–10
Physician global,
VAS 0–10
Tender joints
Swollen joints
HAQ
ESR, mm/hr
CRP, mg/L
DAS28-CRP
WCC,

⫻109/L

Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo

Baseline

6 months

12 months

p-value†

5 (0–30)
23 (0–60)
4.8 ⫾ 2.3
4.1 ⫾ 2.0
4.4 ⫾ 1.9
4.3 ⫾ 2.1
1.3 (1.0–2.9)
3.0 (1.3–4.0)
2.0 (1.0–5.0)
2.0 (0–7.0)
1.0 (0–2.0)
1.5 (0–4.0)
0.69 (0.50–1.13)
0.69 (0.13–1.28)
20 (14–45)
22 (11–40)
2.9 (1.4–11.0)
5.8 (2.6–14.2)
2.7 ⫾ 0.8
2.8 ⫾ 1.0
6.2 (5.1–7.3)
6.5 (5.4–7.8)

6 (0–60)
5 (0–38)
5.0 ⫾ 2.2
4.2 ⫾ 1.6
5.3 ⫾ 2.2*
4.5 ⫾ 2.1
1.5 (0.5–2.4)
2.0 (0.8–3.0)
2.0 (0–3.0)
2.5 (0–5.0)
1.0 (0–1.8)
1.0 (0–2.3)
0.94 (0.41–1.38)
1.0 (0.22–1.38)
18 (13–47)
22 (8–46)
3.0 (1.0–7.9)
3.7 (2.3–13.7)
2.5 ⫾ 0.9*
2.8 ⫾ 1.0
5.5 (4.7–7.1)
6.6 (4.9–7.7)

2 (0–30)
0 (0–30)⬁
4.7 ⫾ 2.3
4.1 ⫾ 2.4
5.0 ⫾ 2.5
4.5 ⫾ 2.3
1.0 (0–2.0)
1.8 (0.8–3.0)ˆ
1.5 (0–3.0)
2.0 (0–4.3)
0 (0–1.8)
0 (0–2.3)⬁
0.81 (0.50–1.47)
0.63 (0.13–1.38)
23 (13–49)
21 (6–45)
3.1 (0.9–13.3)
4.4 (1.2–12.3)
2.4 ⫾ 1.0*
2.6 ⫾ 1.0
6.7 (5.3–8.0)
6.8 (5.1–7.7)

0.229
0.453
0.684
0.843
0.586
0.676
0.739
0.525
0.705
0.459
0.140

Data are expressed as mean ⫾ SD or median (interquartile range) unless specified otherwise.
EMS⫽duration of early morning stiffness, VAS⫽visual analog scale, HAQ⫽health assessment
questionnaire, ESR⫽erythrocyte sedimentation rate, CRP⫽C-reactive protein, DAS28-CRP⫽28 joint
disease activity score, WCC⫽white cell count. † General linear model with repeated measures. *p⬍0.05,
#p⬍0.005 compared with baseline using paired-t tests. p̂⬍0.005, ⬁p⬍0.05 using Friedman test.

The treatment group had a significant increase in the changes of the
SEVR, but no significant effect was observed in the changes of IMT and AIx.
Table 3. Changes in intima-media thickness, augmentation index and subendocardial variability ratio.
Mean IMT, mm
Maximum IMT,
mm
AIx @ 75, %
SEVR, %

Baseline

6 months

12 months

p-value†

Rosuvastatin
Placebo
Rosuvastatin

0.90 ⫾ 0.14
0.92 ⫾ 0.18
1.08 ⫾ 0.20

0.94 ⫾ 0.14*
0.96 ⫾ 0.18*
1.08 ⫾ 0.21

0.91 ⫾ 0.14
0.93 ⫾ 0.16
1.06 ⫾ 0.20

0.877

Placebo
Rosuvastatin
Placebo
Rosuvastatin
Placebo

1.11 ⫾ 0.30
32.5 ⫾ 9.5
29.4 ⫾ 8.8
157 ⫾ 28
143 ⫾ 18

1.17 ⫾ 0.30*
28.9 ⫾ 10.0
30.6 ⫾ 10.5
148 ⫾ 26*
144 ⫾ 24

1.13 ⫾ 0.25
31.3 ⫾ 8.5
30.9 ⫾ 10.4
163 ⫾ 33
143 ⫾ 26

0.386

0.269
0.023

Data are expressed as mean ⫾ SD. IMT⫽intima-media thickness, AIx @ 75 ⫽
augmentation index standardized to a heart rate of 75 b.p.m.,
SEVR⫽subendocardial variability ratio. † General linear model with repeated
measures. *p⬍0.05 compared with baseline using paired-t tests.

Conclusions: Our data suggest that rosuvastatin has modest antiinflammatory effect in RA patients with low disease activity in terms of
reduction in DAS score and fibrinogen level. Rosuvastastin may also improve
subendocardial perfusion and lower urate level. Future large scale randomized
controlled trial will be required to ascertain whether statins can prevent
progression of atherosclerosis in RA.
Disclosure: L.-S. Tam: None; E. K. Li: None; Q. Shang: None; B. Tomlinson: None;
V. W. Lee: None; K. K. Lee: None; M. Li: None; W.-P. Kuan: None; T. K. Li: None;
L. Tseung: None; G. Yip: None; B. Freedman: None; C.-M. Yu: None.

0.01

1029

0.205

Elevated Prevalence of Hypothyroidism in Female Inflammatory Arthritis Patients in Primary Care Amplifies the Prevalence of Cardiovascular
Disease. Hennie G. Raterman2, Mark M. J. Nielen1, Mike J. L. Peters2,
Robert A. Verheij1, Francois G. Schellevis1 and Michael T. Nurmohamed2.
1
Netherlands Institute for Health Services Research (NIVEL), Utrecht, The
Netherlands, 2VU University Medical Center, Amsterdam, The Netherlands

0.952
0.656
0.671

Data are expressed as mean ⫾ SD or median (interquartile range) unless specified otherwise.
TC⫽total cholesterol, HDL-C⫽high density lipoprotein-cholesterol, LDL-C ⫽ low density
lipoprotein-cholesterol, Apo A1⫽apolipoprotein A1, Apo B ⫽ apolipoprotein B, BMI⫽body
mass index, SBP⫽systolic blood pressure, DBP ⫽ diastolic blood pressure. † General linear
model with repeated measures. *p⬍0.01, #p ⬍ 0.05 compared with baseline using paired-t test.

The treatment group did not have a significant effect on the changes of the
inflammatory markers. Nonetheless, a significant improvement in the DAS
(2.7 ⫾ 0.8 at baseline to 2.4 ⫾ 1.0 at 1 year, p⬍0.05) and reduction of

Objectives: Inflammatory arthritis is an emerging risk factor for cardiovascular disease (CVD). Hypothyroidism is another CVD risk factor and
appears related to inflammatory arthritis, best exemplified in secondary care
arthritis patients. The aim of this study was, first, to compare the prevalence
of hypothyroidism in inflammatory arthritis patients and a background
population and, second, to study the association of hypothyroidism and
cardiovascular disease (CVD) in subjects with and without inflammatory
arthritis registered in primary care.

S428


Methods: Data was used from the Netherlands Information Network of General Practice (LINH), which was retrieved from electronic medical records kept by a representative Dutch sample of 96 general practices with 360,000 registered patients in 2006. Prevalences of hypothyroidism were calculated for subjects with and without inflammatory arthritis. Logistic multilevel multivariate regression analyses were used to study associations of hypothyroidism and CVD in inflammatory arthritis.

Results: Overall, the prevalence of hypothyroidism was 5.0 per 100 patients with inflammatory arthritis and 2.4 per 100 patients in control subjects (p < 0.0005). The prevalence of hypothyroidism in female arthritis patients was 6.5% compared to 3.9% in female control subjects (p < 0.0005). In female subjects the prevalence of CVD (14.3%) was significantly higher in hypothyroid inflammatory arthritis patients when compared to inflammatory arthritis patients (5.9%), hypothyroids (4.3%) and control subjects (2.1%) (see table 1, model 1). These results attenuated, but remained significant after adjustment for age, hypertension, dyslipidemia and diabetes (see table 1, model 2).

Conclusion: In primary care the prevalence of hypothyroidism is elevated in female inflammatory arthritis patients and is associated with an amplified CVD prevalence independent of traditional cardiovascular risk factors. Therefore, clinicians must be more aware of coexistence of other autoimmune disease like hypothyroidism, as our results indicate a synergistic effect of hypothyroidism and inflammatory arthritis patients for cardiovascular disease.

Disclosure: H. G. Raterman; None; M. M. J. Nielen; None; M. J. L. Peters; None; R. A. Verheij; None; F. G. Schellevis; None; M. T. Nurmoohamed; None.

1030
Elevations in ApoC-III Containing Apolipoprotein Complexes Predict Coronary Atherosclerosis Progression in Rheumatoid Arthritis Patients. Joan M. Bathon1, Michael Centola4, Jon T. Giles2, Nicholas Knowlton1, Joshua Wages3, Adam J. Payne2, Guy Cavet1 and Petar Alaupovic1. 1Crescendo Biosciences, Inc., South San Francisco, CA, 2Johns Hopkins Univ, Baltimore, MD, 3Johns Hopkins Univ, Baltimore, MD, 4Oklahoma Med Research Foundation, Oklahoma City, OK, 5Oklahoma Medical Research Foundation, Oklahoma City, OK

Purpose: Higher rates of cardiovascular (CV) associated events and mortality in rheumatoid arthritis (RA) cannot be accounted for with conventional lipid measures. However, alterations in the equilibrium among apolipoprotein complexes that traffic plasma lipids may have atherogenic consequences in RA.

Method: Apolipoprotein complexes were measured at baseline in RA patients participating in the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis (ESCAPAE RA) study by precipitation and immunoturbidimetric analysis. Coronary artery calcification (CAC), a measure of coronary atherosclerosis, was assessed by cardiac computed tomography (CT) at two time points spanning approximately 3.5 years. Patients with a change in CAC ≥1 were designated as progressors, and patients with no change or improvement in CAC were designated as nonprogressors. Univariate comparisons were made using t-tests. To model all the ApoC-III containing complexes together, we combined them using a Principal Component Analysis (PCA). Multivariate analyses were performed using logistic regression.

Results: Baseline DAS 28 and ethnicity did not differ significantly between the groups (p=0.53 & p=0.419 respectively). However, gender and age distributions were significantly different between the groups, (p=0.011 & p=0.009, respectively). Of the 152 participants who had CAC measurements at two time points, 89 (59%) were progressors and 63 (41%) nonprogressors. Of the 12 apolipoprotein complexes measured, baseline mean values of 7 were statistically significantly higher in the progressors, compared to nonprogressors (see fig. 1). Interestingly, in contrast to the complexes not associated with progression, these 7 complexes all contain ApoC-III, which is predominantly a triglyceride carrier. All 7 complexes, when combined via PCA, were statistically associated with progression, both in crude analyses (OR 1.86; p=0.003) and after adjusting for Framingham Risk Score, age, and gender (OR 1.83; p=0.016).

Conclusion: Associations between ApoC-III plasma levels and CVD progression were more pronounced in RA patients than outcome associations of conventionally assessed lipoproteins (i.e. LDL-, HDL-cholesterol). Elevated plasma levels of apolipoprotein complexes containing ApoC-III particles were strongly predictive of progression of coronary atherosclerosis in RA. Elevation of these triglyceride rich particles is caused by defects in plasma triglyceride transport and metabolism, which may contribute to accelerated atherosclerosis in RA. These findings provide a means of developing a standardized assay to identify high risk CVD in RA patients and a potential therapeutic target for intervention.

Disclosure: J. M. Bathon: None; M. Centola: Crescendo Biosciences, 1, 5; J. T. Giles: None; N. Knowlton: Crescendo Biosciences, 1, 5; J. Wages: None; A. J. Payne: Crescendo Biosciences, 1, 5; G. Cavet: Crescendo Biosciences, 3; P. Alaupovic: None.

1031
Factors Associated with Upper and Lower Gastrointestinal Perforation in a Cohort of Patients with Rheumatoid Arthritis. Jeffrey R. Curtis5, Angel Lanasa6, Winifred Werther7, Ani John7, David A. Johnson1 and Kathy L. Schuman1. 1Eastern Virginia Medical School, Norfolk, VA, 2Genentech, A Member of the Roche Group, South San Francisco, CA, 3Outcomes Research Solutions, Inc. Bolton, MA, 4Universidad de Zaragoza, Zaragoza, Spain, 5University of Alabama at Birmingham, Birmingham, AL

Purpose: To evaluate the incidence of upper and lower gastrointestinal (GI) perforation and to identify associated risk factors in a cohort of patients (pts) with rheumatoid arthritis (RA).

Methods: In this retrospective, claims-based study (January 2001-June 2009), pts aged ≥18 were selected from the MarketScan® databases if they had at least 2 diagnoses of RA (ICD 9 CM 714.0, 714.3), between 30 and 365 days apart, and at least 1 year of continuous enrollment (defining "baseline period") prior to the beginning of follow-up time. Pts were excluded if they had at least 2 diagnoses of RA (ICD 9 CM 714.0, 714.3), between 30 and 365 days apart, and at least 1 year of continuous enrollment (defining "baseline period") prior to the beginning of follow-up time. Pts were excluded if they had a baseline history of hospitalized GI perforation or any GI malignancy. A validated algorithm for identifying hospitalized GI perforation in claims data was used to identify the first upper GI (UGI) and first lower GI (LGI) perforation. Pts were followed up until the date of GI perforation, database disenrollment, or study end. The GI perforation rate was reported in years of observed person time (PY). A Cox proportional hazards model was used to estimate the relative risk of GI perforation in the first 12 months of follow-up as a function of baseline demographics (age, gender, region, population density), comorbidities (Charlson Comorbidity Index), and use of RA and GI medications during the baseline period. These medications included NSAIDs, corticosteroids, biologic agents, methotrexate (MTX), and other DMARDs.

Results: The study population included 143,433 RA patients (mean age [SD], 57.7 [14.1]; 74.8% female) with mean (SD) follow-up of 2.9 (1.9) years. Hospitalization with GI perforation occurred in 0.5% of pts (n=696), with 6.6% of patients dying during admission. At baseline, pts with GI perforation were older (57.6 vs. 62.0 years; p<0.001) than without GI perforation and had lower RA severity scores (p=0.01) and higher Charlson Comorbidity scores (p<0.01). Overall, the GI perforation rate per 1000 PY was 1.73 (95% CI, 1.61–1.86), with the majority of events concentrated in the LGI: 1.44 (1.32–1.55) vs. UGI 0.30 (0.24–0.35). The unadjusted GI perforation rate per 1000 PY was higher in pts aged ≥65 years (2.3), with exposure Tuesday, November 9
to corticosteroids without accompanying NSAID (2,2), among pts with a pre-period history GI disturbance (3,4), specifically, diverticulitis (19.3), diverticulosis without diverticulitis (6,7), unspecified noninfectious gastroenteritis/collitis (4,9), esophageal or GI hemorrhage (4,2), ulcer (3,8), Crohn’s disease (3,7), and ulcerative colitis (2,1). The adjusted relative risk of GI perforation associated with demographic and RA-related medications during the first year of follow-up is presented in the Table.

**Conclusions:** GI perforation is a rare but serious condition impacting patients with RA, most frequently in the LGI tract. The short-term risk of GI perforation increases with age and is highest among patients with a history of diverticulitis, diverticulosis, and exposure to corticosteroids and NSAIDs.

### Table. Adjusted Relative Risk of GI Perforation by Significant (p<0.05) Risk Factor

<table>
<thead>
<tr>
<th>Baseline Parameter</th>
<th>Hazard Ratio</th>
<th>95% Confidence Limits</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;40</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 40 to 64</td>
<td>2.60</td>
<td>1.21</td>
<td>5.88</td>
<td></td>
</tr>
<tr>
<td>Age 65 and older</td>
<td>3.55</td>
<td>1.63</td>
<td>7.76</td>
<td></td>
</tr>
<tr>
<td>Exposure to NSAIDS &amp; corticosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure to either NSAIDS or corticosteroids</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to NSAID, no corticosteroid</td>
<td>1.77</td>
<td>1.13</td>
<td>2.79</td>
<td></td>
</tr>
<tr>
<td>Exposure to corticosteroid, no NSAID</td>
<td>2.23</td>
<td>1.45</td>
<td>3.45</td>
<td></td>
</tr>
<tr>
<td>Exposure to both NSAID &amp; corticosteroid</td>
<td>1.71</td>
<td>1.11</td>
<td>2.63</td>
<td></td>
</tr>
<tr>
<td>Exposure to MTX vs. no exposure to MTX</td>
<td>0.75</td>
<td>0.57</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Diverticulitis without diverticulitis</td>
<td>4.26</td>
<td>1.73</td>
<td>10.45</td>
<td></td>
</tr>
<tr>
<td>Diverticulosis</td>
<td>15.47</td>
<td>8.57</td>
<td>27.93</td>
<td></td>
</tr>
</tbody>
</table>

**Disclosure:** J. R. Curtis: Amgen Inc., 2, Centocor, Inc., 2, 5, Corrona, 2, 5, Roche, 2, 5, 8, UCB, Inc., 5, 8, A. Lanas: AstraZeneca, 5, EU Arthritis Council, 3, 5, Genentech, a member of the Roche group, 5, 9, Genentech, a member of the Roche group, 3, 9, A. A. Johnson: Genentech, a member of the Roche group, 9, K. L. Schuman: Genentech, a member of the Roche group, 5.

**1032**

Fatigue in Inflammatory Arthritis: Clinical Characteristics, and Contributor Factors Following 6-Months of Anti-TNF Therapy. Patricia Minnock, Barry Bresnihan, Gabrielle McKee, Oliver FitzGerald and Douglas Veale. Rheumatology Rehabilitation, Our Lady’s Hospice and Care Services, Dublin, Ireland, School of Nursing & Midwifery, Trinity College, Dublin, Ireland, St Vincent’s University Hospital, Dublin, Ireland

**Background:** The unique contribution of fatigue to the assessment of patients with inflammatory arthritis has been demonstrated. The aim of this study was to elucidate the clinical characteristics of, and contributor factors to, fatigue in patients with inflammatory arthritis prescribed anti-TNF therapy.

**Methods:** Patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) commencing anti-TNF therapy underwent standard clinical assessment of disease activity and fatigue at baseline, 3-months and 6-months. Fatigue was measured using the multidimensional assessment of fatigue scales (MAF), validated for use in RA. The MAF comprises 16 questions concerning the quality, degree, distress, impact and timing of fatigue, compiled to give a final score of 1–50; a low score corresponds to a low level of fatigue. The clinical characteristics of, and the relationship between fatigue and core outcome measures was evaluated.

**Results:** One-hundred thirty seven patients were evaluated (RA, 93; PsA, 44). Mean age (SD) years, and disease duration at inclusion were 52 (13), 12 (11), respectively. Both fatigue and the core outcome measures demonstrated a significant improvement over the 3-timepoints. Mean (SD) MAF levels were 27.5 (11.1) at baseline, 18.07 (12.1) at 3-months and 19.04 (11.8) at 6-months (p<0.001). Mean (SD) SJC were 7.6 (6.2) at baseline, 2.2 (3.1) at 3-months, and 1.6 (2.6) at 6-months (p<0.001). Mean (SD) TJC were 9.4 (7.8) at baseline, 2.9 (4.5) at 3-months and 2.6 (5.1) at 6-months (p<0.000). Mean (SD) Pain were 5.4 (2.1) at baseline, 3.5 (3.2) at 3-months and 3.5 (2.0) at 6-months (p<0.000). Mean (SD) GH were 5.9 (2.2) at baseline, 3.7 (2.4) at 3-months and 3.8 (2.1) at 6-months (p<0.000). Mean (SD) HAQ were 2.5 (1.0) at baseline, 0.78 (0.80) at 3-months and 0.75 (0.66) at 6-months (p<0.000). Mean (SD) CRP were 20.6 (25.4) at baseline, 71.0 (7.8) at 3-months and 8.8 (15.3) at 6-months (p<0.000). All correlations were significant at the 0.01 level.

**Conclusion:** Fatigue provides unique information in the assessment of outcome for patients with inflammatory arthritis which warrants further in-depth examination.

**Disclosure:** P. Minnock: None; B. Bresnihan: None; G. McKee: None; O. FitzGerald: None; D. Veale: None.

**1033**

Favorable Changes in the Lipid Profile in the First Year of Early Arthritis. Karin Britsømen, Dirkjan van Schaardenburg, Willem F. Lems and Michael T. Nurmohamed, Jan van Breemen Institute Amsterdam, 2VU University Medical Center Amsterdam

**Background:** Several studies provided evidence for excess cardiovascular (CV) mortality and morbidity in rheumatoid arthritis (RA). The inflammatory process and traditional CV risk factors, e.g. dyslipidemia, are considered as the two major contributors to this excess CV disease. Recent studies suggested that abnormal levels of apolipoprotein A (Apo-A1) and apolipoprotein B (ApoB), and particularly the ApoB:ApoA ratio, is at least comparable with the total cholesterol:HDL-cholesterol ratio as predictor of CV morbidity. In this study we investigated the conventional lipid profile and levels of Apo-A1 and ApoB in untreated patients with early arthritis and the effects of anti-rheumatic treatment on these levels after six and 12 months.

**Methods:** Patients from the Amsterdam Early Arthritis Cohort (EAC) with a disease duration of <2 years, at least 2 swollen joint and no prior DMARD treatment were studied. Patients with osteoarthritis, crystal arthropathy, connective tissue diseases and infectious arthritis were excluded. Lipid levels, inflammation markers and disease activity score (DAS28) were evaluated at baseline and after six and 12 months.

**Summary of Results:** The study population comprised 155 patients (mean age 53 [14], 72% female, median symptom duration 1.8 [IQR 1.1–3.7] months, median swollen and tender joint count 5 [3–10] and 7 [5–10], respectively, mean DAS28 4.9 [1.4]). DMARDS were prescribed in 100% and 96% at 6 and 12 months, respectively. Biologic treatment was given in 2% and 32% at 6 and 12 months, respectively. Table 1 summarizes the mean lipid levels, disease activity markers and acute phase reactants at baseline and after 6 and 12 months. Total cholesterol, Apo-A1 levels, LDL- and HDL- cholesterol increased significantly after 6 and 12 months of treatment. Since the changes were larger in HDL cholesterol and ApoA-I, this resulted in a decreased and more favorable total cholesterol:HDL ratio and ApoB:ApoA-I ratio. During the 12 months follow-up decreasing levels of CRP and DAS-28 were significantly associated with increasing levels of total cholesterol, ApoA-I and HDL-cholesterol and decreasing total cholesterol:HDL ratio and ApoB:ApoA-I ratio’s.

**Table 1.** Lipid profile of 155 patients at baseline and after 6 and 12 months

<table>
<thead>
<tr>
<th>Disease activity markers</th>
<th>Baseline 6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/L</td>
<td>8 (IQR 2–20)</td>
<td>2 (IQR 1–5)</td>
</tr>
<tr>
<td>Total cholesterol, mmoles/L</td>
<td>5.07 ± 1.06</td>
<td>5.56 ± 1.07</td>
</tr>
<tr>
<td>Apo A-1, g/mL</td>
<td>1.53 ± 0.31</td>
<td>1.70 ± 0.31</td>
</tr>
<tr>
<td>Apo B, g/mL</td>
<td>0.84 ± 0.22</td>
<td>0.84 ± 0.21</td>
</tr>
<tr>
<td>LDL, mmoles/L</td>
<td>3.06 ± 0.91</td>
<td>3.30 ± 0.93</td>
</tr>
<tr>
<td>HDL, mmoles/L</td>
<td>1.27 (IQR 1.05–1.63)</td>
<td>1.49 (IQR 1.29–1.85)</td>
</tr>
<tr>
<td>Total Cholesterol: HDL ratio</td>
<td>4.02 ± 1.32</td>
<td>3.66 ± 1.03</td>
</tr>
<tr>
<td>Apo B:Apo A-1 ratio</td>
<td>0.55 ± 0.17</td>
<td>0.50 ± 0.15</td>
</tr>
</tbody>
</table>

**Conclusion:** This is one of the first studies demonstrating that patients with early arthritis have favorable changes in the lipid profile after six and 12 months of treatment that ultimately may lower their CV risk. These changes in lipid profile, including the total cholesterol:HDL and ApoB:ApoA ratio, are significantly associated with decreasing levels of CRP and DAS-28.

**Disclosure:** K. Britsømen: None; D. van Schaardenburg: None; W. F. Lems: None; M. T. Nurmohamed: None.
Free Fatty Acids Are Associated with Insulin Resistance but Not Coronary Artery Atherosclerosis in Rheumatoid Arthritis. Michelle J. Ormseth1, Larry Swift2, Sergio Fazio3, MacRae F. Linton3, Cecilia P. Chung4, Paolo Raggi1, Young-Hee Rho4, Joseph Solus4, Annette M. Oeser5, Emyry University, 1Emory University, 2Vanderbilt University, Nashville, TN, 3University of Texas HSC, San Antonio, TX, 4Vanderbilt University, Nashville, TN, 5VUMC 23rd Ave South Pierce, Nashville, TN.

Background: Free fatty acids (FFA) affect insulin signaling and are implicated in the pathogenesis of insulin resistance and atherosclerosis. Inflammatory cytokines such as interleukin-6 (IL-6) increase lipolysis and thus FFA concentrations. Patients with rheumatoid arthritis (RA) have increased atherosclerosis that is associated with insulin resistance and higher IL-6 concentrations. Thus, a unifying mechanism underlying accelerated atherosclerosis in RA may be that increased IL-6 concentrations are associated with increased FFA concentrations resulting in insulin resistance and atherosclerosis.

Methods: Clinical variables, concentrations of non-esterified FFA and inflammatory cytokines, homeostasis model assessment for insulin resistance (HOMA), and coronary artery calcium (CAC) were measured in 166 patients with RA and 92 controls. We compared FFA concentrations in RA and controls using Wilcoxon rank sum tests and a multivariable linear regression analysis.

Results: Patients with RA and controls were of similar age, race, sex and BMI. HOMA was significantly higher in RA (median [IQR]: 3.24 units [1.16–4.27]) than controls (0.83 units [0.54–1.79], p < 0.001), as was CAC score (2.7 units [0.9–15.0] and 0.0 units [0.0–8.7], p < 0.016). Triglyceride concentrations were similar (p = 0.18), but LDL cholesterol was lower in RA than controls (111 mg/dL [88.0–135.0] and 122 mg/dL [104.0–145.0], p = 0.016). FFA concentrations did not differ significantly in RA and controls (0.56 mmol/L [0.38–0.75] and 0.56 mmol/L [0.45–0.70], p = 0.75). In RA, FFA concentration was positively correlated with CRP (rho = 0.25, p = 0.001), BMI (rho = 0.16, p = 0.046), HOMA (rho = 0.20, p = 0.011), triglycerides (rho = 0.15, p = 0.048), insulin (rho = 0.18, p = 0.024) and Framingham risk score (FRS) (rho = 0.22, p = 0.005); FFA were not correlated with IL-6 (rho = 0.48), TNF-α (rho = 0.29) or CAC score (p = 0.62). After adjustment for age, race, sex and BMI, FFA remained associated with HOMA (rho = 0.011); insulin (p = 0.023), CRP (p = 0.009), triglycerides (p = 0.004) and FRS (p = 0.048).

Conclusions: FFA concentrations do not differ significantly in patients with RA and controls. In patients with RA, FFA concentrations are correlated with obesity, insulin resistance, CRP concentrations and FRS, but not with IL-6, TNF-α and CAC score. FFA may contribute to insulin resistance, but do not provide a mechanistic link between inflammation, insulin resistance and coronary atherosclerosis in RA.

Disclosure: M. J. Ormseth: None; L. Swift: None; S. Fazio: None; M. F. Linton: None; C. P. Chung: None; P. Raggi: None; Y.-H. Rho: None; J. Solus: None; A. M. Oeser: None; A. Blanc: None; T. Gebretsadik: None; A. Shintani: None; C. M. Stein: None.

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Gene-Environment Interaction Determines Intersitial Lung Disease in Rheumatoid Arthritis. Jose Felix Restrepo1, Inmaculada del Rincon1, Ricardo Zuniga1, Samvel Pogosian2 and Agustin Escalante1. 1Univ of Texas HSC San Antonio, San Antonio, TX, 2Univ of Texas HSC, San Antonio, San Antonio, TX, 3University of Texas HSC, San Antonio, TX, 4UTHSCSA, San Antonio, TX.

Background: Intersitial lung disease (ILD) is a progressive fibrotic process of unknown cause that may affect rheumatoid arthritis (RA) patients. We examined the role of gene-environment interaction as a determinant of the presence of ILD in RA patients.

Method: We performed a cross sectional study of prevalence and factors associated with ILD in a cohort of RA patients. ILD was diagnosed using chest X-ray, CT scan, MRI, or lung biopsy. Patients with ILD were compared to RA patients without ILD or other pulmonary diseases. We used the following independent variables: age, gender, rheumatoid factor (RF), disease duration, DAS 28, ESR, smoking status, SF36 general health, global assessment of disease severity and activity, Steinbrocker functional class, modified HAQ, current or past use of methotrexate and current use of prednisone. HLA-DRB1 shared epitope (SE) was assessed using sequence-specific DNA primers. We used t-test for continuous variables; chi square and odds ratio (OR) for categorical variables and logistic regression for multivariable analyses, adjusting for confounders.

Results: The sample included 779 RA patients. Sixty nine of them (8.8%) had ILD. We compared them to the 563 patients without pulmonary disease. We included 147 patients who had other pulmonary conditions. Significant differences between the two groups included (mean in ILD compared to non-ILD patients): age 60.2 vs 52.9 (p < 0.0001), age of RA onset: 47.5 vs 42.7 (p < 0.004), SF36 general health: 68 vs 62 (p < 0.01), ESR: 58 vs 39 (p < 0.0001), DAS28: 5.96 vs 5.37 (p < 0.002), modified HAQ 2.04 vs 1.87 (p < 0.05), diseases severity: 3.76 vs 2.77 (p < 0.0004) and Steimbrocker functional capacity 2.40 vs 2.06 (p < 0.001). For categorical variables, ILD was associated with nodules, OR (95% CI) = 1.85 (1.05, 3.2; p < 0.001); rheumatoid factor, OR = 3.15 (1.29, 10, p = 0.006); male gender, OR = 3.33 (1.93, 5.7, p < 0.00001), current prednisone, OR = 2.02 (95% CI, 1.17–3.5), smoking OR = 2.19 (1.23, 4.04, and the SE, OR = 1.98 (0.99, 4.32). In multivariate analysis, male gender, OR = 3.08 (1.74, 5.44), RF, OR = 2.58 (1.04, 6.39), prednisone, OR = 1.77 (1.007–3.13); DAS28, OR = 1.42 (1.17, 1.73) showed significant, independent association with ILD.

We tested the SE for interaction with smoking using product terms in logistic regression. Smoking was strongly associated with ILD in the presence, but not in the absence of the SE. (Table)

<table>
<thead>
<tr>
<th>Shared Epitope</th>
<th>Smoking OR for ILD (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0.54 (0.15–1.99)</td>
<td>0.152</td>
</tr>
<tr>
<td>Positive</td>
<td>2.19 (1.14–4.5)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Conclusion: ILD is frequent in RA, and is associated with aging, male gender, nodules, active disease, positive RF and current use of prednisone. The SE was necessary for smoking to be associated with ILD, providing an example of gene-environment interaction. Further research should focus on the use of variables associated with ILD for early identification of patients at risk for ILD. Mechanistic research into the SE x smoking interaction would be of great interest.

Disclosure: J. F. Restrepo: None; J. del Rincon: None; R. Zuniga: None; S. Pogosian: None; A. Escalante: None.

1036

Glucocorticoid Use Is Not Associated With an Increased Risk of Cerebrovascular Accidents in Patients with Rheumatoid Arthritis. A Population-Based Study. Antonio Avina-zubieta1, Michal Abrahamowicz2,3, Hyon K. Choi4, M. Mushfigir Rahman5, Marie-Pierre Sylvestre6, John Esdaile7 and Diane V. Lacaille8. 1Arthritis Res Centre of Canada, Vancouver, BC, Canada, 2Department of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada, 3Samuel Lunenfeld Research Institute, 4Univ of British Columbia, Vancouver, BC, Canada.

Purpose: While it has been shown that RA patients treated with glucocorticoids (GC) have an increased risk of coronary artery disease, the data available for cerebrovascular accidents (CVA) are scarce and controversial. We examined the effect of GC on risk of CVA in patients with rheumatoid arthritis (RA).

Methods: Using population-based administrative health data we assembled a cohort of 7,051 incident RA cases with disease onset between 1997 and 2001 with no history of CVA and no GC use prior to RA onset. Follow-up was until 2006. GC exposure was evaluated using four time dependent variables updated monthly: GC use, mean daily dose, total cumulative dose and total cumulative duration of use. CVA outcomes included acute thrombotic and hemorrhagic strokes, but not transient ischemic attacks, and were ascertained using ICD-9 codes (431, 434 and 436) from hospitalization and vital statistics data. To control for confounding by indication, wherein GC would be given to cases with more severe disease and/or less adverse cardiovascular profiles, we calculated propensity scores to control for the observed differences between GC users and non-users. We performed Cox-regression models to estimate the relative risk (RR) for CVA, adjusting for demographics, cardiovascular risk factors, RA characteristics, propensity scores and time-dependent prescription medications (methotrexate, Cox-2 inhibitors and other non-steroidal anti-inflammatory drugs).

Results: The mean age of the cohort was 56 yrs (57 and 54 for GC users and non users respectively) and 66% were females (70% and 64% for GC users and non-users respectively). Over a mean of 6 years of follow-up...
Heptavalent Conjugate Pneumococcal Vaccine (Prevenar) Elicits Similar Antibody Responses as 23-Valent Polysaccharide Vaccine (PPV) in Adult Patients with Established Arthritis. Melia C. Kapetanovic1, Carmen Roseman2, Göran Jönsson1, Lennart Truedsson3, Tore Saxne1 and Pierre Geborek.1 Dept of Clinical Sciences Lund, Section of Rheumatology, Lund University, Lund, Sweden,2Dept of Laboratory Medicine, School of Medicine, KyungHee University, Seoul, Korea, Republic of,3Division of Rheumatology, Department of Internal Medicine, School of Medicine, KyungHee University, Seoul, Korea, Republic of,4Division of Rheumatology, Department of Internal Medicine, School of Medicine, KyungHee University

Background: The immunogenicity of 23-valent polysaccharide vaccine (PPV) is debated. Heptavalent conjugate pneumococcal vaccine (Prevenar) has been shown to elicit better immune responses compared to PPV in children and healthy adults. Corresponding data in patients with inflammatory rheumatic diseases receiving immunosuppressive treatments is lacking.

Aim: To study immune response after vaccination with A) Prevenar in immunosuppressed patients with rheumatoid arthritis (RA) and patients with spondylarthropathy including psoriatic arthritis (SpA) not receiving immunosuppressive treatment compared to B) immunosuppressed RA patients and healthy controls vaccinated with PPV.

Patients and Methods: In total, 254 patients with RA on methotrexate alone, TNF-blockers as monotherapy or methotrexate + TNF-blockers and 86 patients with SpA not treated with immunosuppressive drugs received a single dose (0.5 ml) of Prevenar. Altogether, 149 patients with RA receiving corresponding immunosuppressive treatments and 47 healthy controls were vaccinated with 0.5 ml of a single lot of PPV, as previously reported (ref). Levels of serotype specific IgG to 23 F and 6B were measured prior to vaccination and 4–6 weeks after vaccination using standard ELISA. Pre- and postvaccination antibody levels for each serotype and immune response (IR), defined as ratio between post- and prevaccination antibody levels, were compared between the groups. Differences in IR were analysed using univariate analysis of variance (ANOVA) adjusted for age, gender, prevacccination antibody levels, and concomitant methotrexate /prednisolone treatment when appropriate.

Results: Pneumococcal vaccination resulted in significant increase in post-vaccination antibody levels in all groups compared to baseline levels for both serotypes. RA patients vaccinated with Prevenar gained in general similar postvaccination antibody levels and IR as those receiving PPV (Table). SpA patients had better IR for serotype 23F compared to healthy controls who received PPV vaccine. Among Prevenar vaccinated RA patients, IR was similar in the respective treatment modalities as those receiving PPV.

Conclusion: Pneumococcal vaccination using conjugate vaccine elicits similar immune response as 23-valent polysaccharide vaccine in patients with established RA receiving immunosuppressive treatments. Pneumococcal conjugate vaccine did not give better immune response in general but may be better for some serotype.

Background: The association of rheumatoid arthritis with increased atherosclerotic burden has led some to equate the cardiovascular risk of rheumatoid arthritis (RA) with that of diabetes mellitus (DM). We compared the risk of perioperative cardiovascular outcomes among patients with RA, DM, both conditions, and neither.

Methods: This is a cross-sectional analysis of the National Inpatient Sample of the HealthCare Utilization Projects using data from years 1998 to 2002. We abstracted the diagnoses of RA, DM, potential confounding comorbidities and the principal surgical procedure using International Classification of Diseases, ninth revision codes. The principal surgical procedure was categorized into Low, Intermediate, and High risk according to established guidelines. The study endpoint was a composite cardiovascular outcome including an acute myocardial infarction, acute stroke, non-ST elevation MI, and/or congestive heart failure with pulmonary edema. Logistic regression accounting for survey design provided the adjusted magnitude of association between the covariates and the study endpoint.

Results: The total weighted frequency of hospitalizations with Low, Intermediate, and High risk principal procedures was 1,003,904, 6,011,950, and 277,010, respectively. The weighted frequency for individuals with RA without DM was 7,831, 92,005, and 1,767 for Low, Intermediate, and High risk surgical procedures, respectively. The weighted frequency of composite cardiovascular events in Low, Intermediate, and High surgical risk levels were 9,542, 38,542, and 31,772, respectively. The proportion of composite cardiovascular events was higher in DM as compared to RA patients for Low (1.63% vs. 0.81%), Intermediate (1.03% vs. 0.44%), and High (18.53% vs. 6.61%) risk surgical procedures. Relative to individuals without RA or DM, the adjusted odds of composite cardiovascular event in patients with RA without DM was 0.73 (95% confidence interval [CI]: 0.41, 1.30), 0.68 (95% CI: 0.54, 0.85), and 0.76 (95% CI: 0.47, 1.22) for Low, Intermediate, and High risk surgical procedures, respectively. Relative to individuals without RA or DM, diabetes without RA undergoing a Low, Intermediate, and High risk surgical procedures had an adjusted odds of composite cardiovascular endpoint of 1.30 (95% CI: 1.16,1.45), 1.23(95% CI: 1.15,1.32), and 1.67(95% CI: 1.53,1.83), respectively.

Table. Odds of In-Hospital Composite Cardiovascular Event by Risk Category of Principal Procedure

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Low OR (95% CI)</th>
<th>Surgical Risk Category</th>
<th>Intermediate OR (95% CI)</th>
<th>High OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-RA, Non-DM</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>RA, Non-DM</td>
<td>0.73 (0.41,1.30)</td>
<td>0.68 (0.54,0.85)</td>
<td>0.76 (0.47,1.22)</td>
<td></td>
</tr>
<tr>
<td>Non-RA, DM</td>
<td>1.30 (1.61,1.45)</td>
<td>1.23 (1.15,1.32)</td>
<td>1.67 (1.53,1.83)</td>
<td></td>
</tr>
<tr>
<td>RA, DM</td>
<td>1.48 (0.59,3.70)</td>
<td>0.91 (0.50,1.64)</td>
<td>0.84 (0.34,2.05)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–50</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>50–75</td>
<td>2.61 (2.11,3.24)</td>
<td>12.53 (20.13,15.36)</td>
<td>3.10 (2.69,3.57)</td>
<td></td>
</tr>
<tr>
<td>&gt;75</td>
<td>4.41 (3.45,5.63)</td>
<td>33.46 (27.54,40.66)</td>
<td>4.34 (3.74,5.03)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.74 (0.66,0.82)</td>
<td>0.88 (0.84,0.92)</td>
<td>0.65 (0.61,0.70)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>1.08 (0.97,1.19)</td>
<td>0.65 (0.61,0.69)</td>
<td>0.55 (0.50,0.61)</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>2.49 (2.20,2.83)</td>
<td>5.49 (5.16,5.85)</td>
<td>2.17 (2.02,2.35)</td>
<td></td>
</tr>
<tr>
<td>VHD</td>
<td>2.79 (2.16,3.59)</td>
<td>2.55 (2.22,2.94)</td>
<td>0.47 (0.41,0.54)</td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>1.66 (1.21,2.28)</td>
<td>1.67 (1.36,2.06)</td>
<td>0.69 (0.53,0.89)</td>
<td></td>
</tr>
<tr>
<td>Admission Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>0.24 (0.20,0.30)</td>
<td>0.45 (0.42,0.48)</td>
<td>0.15 (0.14,0.17)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Rheumatoid arthritis was not an independent predictor of perioperative cardiovascular events. In contrast, diabetes mellitus was associated with increased odds of cardiovascular outcomes across all surgical risk levels.

Disclosure: A. Yazdanyar: None; M. C. Wasko: None; K. L. Kraemer: None; M. M. Ward: None.

Hypogonadism in Males with Rheumatoid Arthritis. Danette S. Johnson and Robert W. McMurray. G.V. (Sonny) Montgomery VA and University of Mississippi Medical Center, Jackson, MS

Background: The pituitary-gonadal axis has significant immunoregulatory effects on autoimmune diseases and a role in the pathogenesis or modulation of rheumatoid arthritis (RA) has been suggested. We investigated the role of sex hormones on disease activity of male RA patients.

Methods: Levels of testosterone (T) and prolactin (PRL) were examined in male patients with a diagnosis of RA (n=67) from a Jackson subpopulation of the Veterans Affairs Rheumatoid Arthritis (VARA) registry. Serum T and PRL were determined by RIA in a blinded fashion and the correlation with disease activity and severity calculated.

Results: Patients had the following demographics (age=68.3 yrs (range 40–91 yrs), disease duration =14.5 yrs (range 1.7–32.5 yrs), RF positive =79%, CCP positive = 70%, mean DAS 28 = 3.2 ± 1.4). Although mean PRL levels were within normal limits with 5 patients being hypoprolactinemic and 3 with high PRL, hypogonadal patients had significantly higher prolactin levels (mean=8.02 ng/ml vs. 5.55 ng/ml, p=0.39) than patients with normal T. Mean T levels were 302 ± 121 ng/dl and there was no relationship to age or DAS28. A surprisingly high number (n=24; 36%) of male RA patients in this study were hypogonadal (T < 250 ng/dl) which was associated with higher BMI (p=0.001). There was no statistical relationship between low serum total testosterone and age, disease activity and severity, and corticosteroid or narcotic use. However, patients with hypogonadism had a trend toward higher CRP (mg/l) (mean= 14.96) that was >40% higher than those patients with normal T levels (CRP 8.95; p=0.08).

Table. Characteristics of male patients with RA.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Low Testosterone (T &lt; 250 ng/dl)</th>
<th>Normal Testosterone (T ≥ 250 ng/dl)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (ng/dl)</td>
<td>183.5 ± 50</td>
<td>368.7 ± 94</td>
<td>0.039</td>
</tr>
<tr>
<td>Prolactin (ng/ml)</td>
<td>8.02 ± 8</td>
<td>5.55 ± 2</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>69.8 ± 10</td>
<td>67.5 ± 9</td>
<td>0.17</td>
</tr>
<tr>
<td>BMI</td>
<td>30.4 ± 2</td>
<td>26.1 ± 5</td>
<td>0.003</td>
</tr>
<tr>
<td>RF (+)</td>
<td>79%</td>
<td>79%</td>
<td>0.76</td>
</tr>
<tr>
<td>ACCU (+)</td>
<td>71%</td>
<td>70%</td>
<td>0.85</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>14.96 ± 24</td>
<td>8.95 ± 11</td>
<td>0.08</td>
</tr>
<tr>
<td>DAS28</td>
<td>3.3 ± 1.3</td>
<td>3.1 ± 1.4</td>
<td>0.28</td>
</tr>
<tr>
<td>Erosion on hand X-ray</td>
<td>58.3%</td>
<td>56.7%</td>
<td>0.95</td>
</tr>
<tr>
<td>Nodules</td>
<td>58.3%</td>
<td>44.2%</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Conclusion: There was a high prevalence of hypogonadism in our male RA population. Hypogonadal men had higher prolactin levels and BMI and a trend toward higher CRP levels. These findings suggest hypogonadal men may fare worse overall and consideration should be given to screening testosterone in older men with RA.

Disclosure: D. S. Johnson: None; R. W. McMurray: None.

II-17 as a Novel Predictor of Vascular Damage in Rheumatoid Arthritis. Wendy Marder, Shokoufeh Khalatbari, James D. Myles, Rita P. Hench, Susan Lustig, Robert D. Brook and Mariana J. Kaplan. Division of Cardiology, University of Michigan, Division of Rheumatology, University of Michigan, Ann Arbor, MI, Michigan Institute for Clinical and Health Research, Ann Arbor, MI
Background: The enhanced risk of premature cardiovascular risk is well recognized in patients with inflammatory diseases such as rheumatoid arthritis (RA). In addition to overt atherosclerosis, a significant proportion of RA patients have subclinical vascular disease, manifested as impaired endothelial function and increased arterial stiffness. While pro-inflammatory cytokines, particularly TNF-α, have been linked to the development of atherosclerosis and endothelial dysfunction in RA, the roles of other proinflammatory mediators such as IL-17 have not been systematically assessed. We analyzed candidate variables that could potentially influence microvascular endothelial function and arterial compliance in RA patients with low Framingham risk factors and overall low disease activity.

Methods: RA patients with stable disease and stable therapy for at least 3 months underwent flow-mediated dilatation (FMD) of the brachial artery, assessment of arterial compliance with SphygmoCor, and endothelium-dependent microvascular function with the Endo-PAT2000 device. Circulating biomarkers of CV damage were quantified by ELISA (ICAM-1, VCAM-1, MCP-1 and IL-17). Insulin resistance was quantified by HOMA2-IR. Analysis was performed on 57 patients who were stratified into 2 subsets: 31 patients were on biologic therapy (with or without DMARDS) at the start of the study, and 26 patients were not on biologic therapy (with or without DMARD) at the start of the study. The RA group as a whole was also analyzed.

Results: Microvascular function for the overall group of RA patients negatively correlated with ESR (−0.40, p = 0.003) and VCAM-1 (−0.40, p = 0.003). In the group of patients on biologics, IL-17 was the factor that most strongly showed a negative association with microvascular endothelial function. Indeed, there was a significant negative correlation of serum IL-17 with reactive hyperemia pulse amplitude tonometry (−0.39, p < 0.03), which persisted in multivariate regression analysis adjusting for known confounders. In contrast, arterial stiffness, which was assessed by aortic pulse wave velocity (PWV), was associated primarily with traditional CV risk factors. PWV significantly correlated with age and systolic blood pressure in the biologic-treated patients, the non-biologic treated patients, and the group as a whole (age: 0.53, p = 0.004, 0.63, p = 0.001, 0.61, p < 0.001; SBP: 0.47, p = 0.01, 0.53, p = 0.01, 0.54, p < 0.001 respectively). Higher levels of rheumatoid factor negatively correlated with microvascular and conduit endothelial function among patients on biologics (−0.40, p = 0.03, −0.43, p = 0.03 respectively), and conduit function among the group as a whole (−0.29, p = 0.04).

Conclusion: The factors that are associated with alterations in microvascular function in RA patients differ from those that are associated with large vessel arterial stiffness, and are primarily related to the inflammatory milieu rather than to traditional risk factors. This study suggests that IL-17 may play a significant role in the development of microvascular dysfunction in RA, potentially leading to premature vascular damage.

Disclosure: W. Marder: None; S. Khalatbari: None; J. D. Myles: None; R. P. Hench: None; S. Lustig: None; R. D. Brook: None; M. J. Kaplan: None.

1043 Incidence of Progressive Interstitial Pneumonia in Patients with Rheumatoid Arthritis. Yoko Takahashi, Hiroyuki Yamashita, Yo Ueda, Yuji Yoshida, Hiroshi Kaneko and Akio Mimori. Division of Rheumatic Diseases, National Center for Global Health and Medicine, Shinjyuku-ku, Tokyo, Japan

Objective: Rheumatoid arthritis (RA) often involves interstitial pneumonia (IP), and chronic IP is common in RA patients in the course of their disease. However, few reports have examined the incidence of progressive RA-IP Needing steroid therapy. This study estimated the incidence based on our hospital records.

Methods: We used our complete database containing all 550 RA patients registered from 1990 to 2010; we obtained the number of inpatients that received steroid therapy for RA-IP during this period and the total observation years for each outpatient during the same period. As most registered RA patients are followed in our hospital, and not by family physicians, and they are almost always admitted to our hospital when they need hospitalization including treatment for pulmonary complications, the method met our purpose. Patients with IP that developed outside our observation of the RA, i.e., patients referred because of IP, were excluded from the study.

Results and Discussion: During the 21-year study period, 127 cases of RA were treated for pulmonary complications accompanied by an interstitial shadow on a chest x-ray. Of these, 113 cases were excluded from the study for the following reasons: 59 cases of pulmonary infection and existing chronic IP or exacerbation of chronic IP due to infection; 10 cases of drug-induced pneumonia, including four of methotrexate-induced pneumonia; and 44 patients referred because of pulmonary complications, including infection, drug-induced pneumonia, and RA-IP. Of these last 44 cases, nine had progressive IP, which was a clue to diagnosing their RA. After excluding these 113 cases, the remaining 14 cases (14 patients) had progressive RA-IP during our observation and were treated successfully with steroid therapy. Of these, diagnoses based mainly on radiological findings indicated that four had progressive non-specific interstitial pneumonia (NSIP) and organizing pneumonia (OP, formerly called bronchiolitis obliterans with organizing pneumonia (BOOP)). From the total observation period of 3833 person-years, the calculated incidence of progressive RA-IP was 0.37%/year (14/3833).

Before this study, we estimated the incidence as 0.30–0.39%/year (8/2031–2635) based on our hospital records up to 2005, which included some ambiguity because of dropped-out patients. This study gave a similar incidence using additional patients enrolled up to 2010 and more precise information on the observation periods of the outpatients. Our RA patients had rarely been treated with biologics before 2005, whereas 38% of the patients had received at least one biologics therapy up until the present. Therefore, the incidence of progressive RA-IP may not be influenced by differences in antirheumatic therapy.

Conclusion: The incidence of progressive interstitial pneumonia caused by rheumatoid arthritis was calculated as 0.37%/year (14/3833).

Disclosure: Y. Takahashi: None; H. Yamashita: None; Y. Ueda: None; Y. Yoshida: None; H. Kaneko: None; A. Mimori: None.

1043 Infertility in Women with RA and Pregnancy Loss in Women with SLE Contribute to Smaller Than Desired Family Size. Megan E. B. Clowse1, Eliza F. Chakravarty1, Karen H. Costenbader2, Christine D. Chambers3 and Kaleb D. Michaud4. 1Mountain View, CA, 2Brigham & Women, Boston, MA, 3Duke Univ Med, Durham, NC, 4Univ of Nebraska Med Ctr, Omaha, NE, 5University of California, San Diego

Purpose: Past studies have suggested that women with RA and SLE have diminished fecundity. We sought to understand the role of underlying RA or SLE upon family size.

Methods: A comprehensive reproductive history questionnaire was mailed to women diagnosed by a physician with RA (n=870) or SLE (n=237) participating in a US longitudinal observational study of rheumatic diseases. By disease, participants were divided into 2 main groups: those who had finished having children prior to diagnosis and those still interested in further children at the time of diagnosis. This second group was divided into 2 subgroups: those who had the same number of children that they wanted and those who had fewer children than they originally wanted. Comparisons were made by disease between the finished and not finished groups, as well as the women who had the same or fewer children than they wanted. Statistical analyses were performed using t tests and Fisher's exact tests in STATA.

Results: The response cohort consisted of 578 RA patients (66% response rate) and 114 SLE patients (48% response rate). Over 60% of women had finished childbearing at the time of diagnosis; these women were approximately 20 years older than women still interested in childbearing (see Tables 1 & 2). More than half of the women who had the same or fewer children than they desired had, on average, 1 less child than either women who had their children despite disease or had completed their family prior to diagnosis. For women with RA, those with fewer than desired children had significantly fewer pregnancies (2.2 vs. 3.2, p < 0.01) and a 1.5-fold higher rate of reported infertility compared to women with all of the children they desired. In contrast, women with SLE who had fewer children had a similar number of pregnancies but a 3-fold higher rate of miscarriage than those who completed their family despite SLE.

Conclusion: Young women diagnosed with RA and SLE are likely to have fewer biologic children than they wanted. Patient choice to avoid pregnancy may play a part, but much of this difference appears to be due to infertility in women with RA and pregnancy loss in women with SLE.
Table 1. Results from women with Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Number of women (%)</th>
<th>Fewer than desired children of diagnosis</th>
<th>Number of children of diagnosis</th>
<th>Finished having children at time of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29 (25%)</td>
<td>16 (14%)</td>
<td>69 (61%)</td>
</tr>
<tr>
<td>Mean age at diagnosis (SD)</td>
<td>25.4 (12)</td>
<td>28.7 (13)</td>
<td>41.9 (11)**</td>
</tr>
<tr>
<td>Mean current age (SD)</td>
<td>52.0 (11)</td>
<td>50.4 (15)</td>
<td>55.4 (10)</td>
</tr>
<tr>
<td>Number of pregnancies (SD)</td>
<td>2.9 (1.8)</td>
<td>3.1 (1.0)</td>
<td>3.3 (1.7)</td>
</tr>
<tr>
<td>Number of children (SD)</td>
<td>0.9 (1.6)</td>
<td>0.3 (0.5)</td>
<td>0.7 (1.2)</td>
</tr>
<tr>
<td>Number reporting Infertility (%)</td>
<td>5 (17%)</td>
<td>4 (25%)</td>
<td>9 (13%)</td>
</tr>
</tbody>
</table>

*p < 0.01 for comparison between women who had fewer and the same number of children as they wanted. **p < 0.01 for comparison between women who had and had not finished having children at time of diagnosis.

Table 2. Results from women with Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Number of women (%)</th>
<th>Fewer than desired children of diagnosis</th>
<th>Number of children of diagnosis</th>
<th>Finished having children at time of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 (42%)</td>
<td>27 (28%)*</td>
<td>65 (18%)**</td>
</tr>
</tbody>
</table>

*p < 0.01 for comparison between women who had fewer and the same number of children as they wanted. **p < 0.01 for comparison between women who had and had not finished having children at time of diagnosis.

Conclusion: We have provided detailed estimates of the influence of ILD on multiple aspects of RA outcome. ILD had a significant, independent negative impact on the physical function, disability and survival of patients with RA, but not on measures of mental health. A better understanding of the causes and pathogenesis of ILD in RA is needed to find ways to prevent and treat this complication.

Disclosure: I. Del Rincon: None; J. F. Restrepo: None; M. Sahai: None; D. F. Battafarano: None; L. R. Zuniga-Montes: None; A. Escalante: None.

1045

Lower Extremity Ulcers in Rheumatoid Arthritis. David M. DeMaria², Christopher E. Attinger³ and Victoria K. Shannumagum. ³Center for Wound Healing, Georgetown University Medical Center, Washington, DC, ²Division of Rheumatology, Immunology and Allergy, Georgetown University Medical Center, Washington, DC

Lower extremity ulcers are a known complication of rheumatoid arthritis (RA). They are associated with longstanding uncontrolled RA. However, their prevalence has not been assessed since the advent of more effective biologic and non-biologic disease modifying anti- rheumatic therapies (DMARDs). The purpose of this study was to establish the prevalence of lower extremity ulcers in a modern day consecutive cohort of RA patients, and to report the features associated with ulcer development.

Methods: Consecutive patients evaluated in the Georgetown University Hospital Division of Rheumatology between June 2007 and June 2010 and fulfilling the ACR criteria for rheumatoid arthritis were identified using an ICD-9 diagnosis code search of the electronic medical record (Centricity, GE). Charts were reviewed for the presence of lower extremity ulcers during the study period. Demographic characteristics, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) positivity, presence of comorbidities including venous and arterial disease, presence of other vasculitis manifestations of RA such as neuropathy and nodulosis, complement levels, inflammatory markers, biopsy findings and prothrombotic screen were noted.

Results: In the three years of this study 366 RA patients were evaluated, and 16 had active leg ulcers, giving a prevalence of 4.37%. Patients with ulcers were predominantly female (81.25%) and 56.25% were African American. All patients had erosive disease, and 62.5% were RF or CCP positive. Ulcers were bilateral in 43.75%. The mean age at first ulcer was 64.81 ± 3.533 years. In 3 patients RA had previously been undiagnosed. In the remaining 13 patients the mean duration of RA at the time of ulcer development was 25.92 ± 4.944 years. In 37.5% of patients, the joint disease was in remission at the time of ulcer development. However at the initial visit the mean ESR was elevated at 56.63 ± 7.591 mm/hr, mean CRP was 5.928 ± 1.561 mg/dL and DAS-28 score was 3.836 ± 0.5460 suggesting ongoing inflammation. All patients had normal complement levels and negative SSA and SSB antibodies. Biopsy specimens were available in 12 cases. Only 3 had clear evidence of vasculitis, the biopsy was inconclusive in 5, 3 patients had gangrene and one had cholesterol emboli. Size of the initial ulcer ranged from 0.01 to 800 cm². None of the patients in this study had significant titers of antiphospholipid antibodies, and the frequency of genetic prothrombotic states was similar to that reported in the general population. The mean duration of follow-up was 22.6 months but only 31.25% of ulcers were healed at the last follow-up visit. Due to the small sample size we were unable to...
show a significant association between ulcer healing and use of biologic or non-biologic DMARDs.

**Conclusions:** Even in the era of biologic and non-biologic DMARD therapy, the prevalence of lower extremity ulcers in RA is 4.37%. We found healing rates of only 31.25% in 22.6 months of follow-up. Larger studies are warranted to evaluate the role of small vessel vasculitis in chronic wounds and to investigate the role of aggressive immune suppression even when the joint disease is in remission.

Disclosure: D. M. DeMaria: None; C. E. Attinger: None; V. K. Shannugam: Dr. Shannugam is supported by the American College of Rheumatology, Research and Education Foundation, Physician Scientist Development Award, 2.

1046

**Lower Prevalence and Severity of “Vulnerable” Coronary Plaque in a-TNF-Exposed Asymptomatic Patients with Rheumatoid Arthritis (RA).**

George A. Karpouzas1, Nasar Ahmad2, Tae-Young Choi2, Fereshteh Hajsadeghi2, Silvia Munoz3 and Mathew Budoff4. 1-Harbor-UCLA, Long Beach, CA, 2-Harbor-UCLA

**Background:** Tumor necrosis factor-alpha inhibitors (TNFi) have been recently reported to decrease the risk of myocardial infarction (MI) in patients (pts) with RA. The exact mechanisms, however, as well as the effects on coronary plaque quantity and composition are largely unknown. We prospectively evaluated the presence, total burden, and differences in the quality of coronary plaque in asymptomatic RA pts treated with TNFi vs. DMARDs alone.

**Methods:** We report on the first 74 of 150 recruited pts from a single center. Pt characteristics, including traditional risk factors and treatments are shown in table 1. Pts underwent 64-slice cardiac Computed Tomography Angiography (CTA); this non-invasive modality includes an initial non-contrast phase assessing coronary calcium, followed by a contrast scan that detects plaque with equal accuracy to conventional angiography, and is superior in the assessment of non-calcified, lipid-rich, non-obstructive or "vulnerable" plaque. Individual coronary trees were evaluated for plaque volume and composition by standard methods (American Heart Association). Non-parametric tests were used for data analysis; regression models for plaque prevalence ratios (PR) and relative risk for plaque burden in TNFi vs. DMARD treated pts, adjusted for conventional risk factors were constructed.

**Results:** TNFi treated individuals had significantly longer disease duration (table 1). Despite that, they had significantly lower extent and severity of total plaque compared to DMARD treated pts; they exhibited lower numbers of affected coronary segments (p=0.009) and less total plaque burden score (p=0.03). More importantly, they displayed lower prevalence and severity of "vulnerable" plaque. TNFi exposed pts had significantly fewer segments harboring NC/mixed plaque (p=0.01) and significantly lower NC/mixed plaque burden score (p=0.04). TNFi treated pts had 76% less risk for the presence of "vulnerable" plaque (p=0.006) and 16% lower burden of NC/mixed plaque risk vs. DMARD treated pts, adjusted for age, sex and Framingham RF (p=0.03).

**Conclusions:** TNFi-exposed asymptomatic RA pts have significantly lower prevalence and severity of total, but more importantly, "vulnerable" coronary plaque compared to DMARD treated pts, despite significantly longer disease duration. These findings insinuate additional favorable effects of TNFi on plaque homeostasis and stabilization and may reflect less future cardiovascular morbidity.

Disclosure: G. A. Karpouzas: None; N. Ahmad: None; T.-Y. Choi: None; F. Hajsadeghi: None; S. Munoz: None; M. Budoff: None.

1047

**Measuring Therapeutic Adherence in Rheumatoid Arthritis (RA) Using a Medication Event Monitoring System (MEMS®).**

Christian A. Waimann, Maria F. Marengo, Sofia de Achaval, Vanessa L. Cox, Araceli Garcia Gonzalez, Marsha N. Richardson and Maria E. Suarez-Almazor. The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Treatment adherence is an important aspect in RA. Multiple methods of measuring adherence have been proposed, with electronic monitoring considered one of the most accurate measures. The objective of our study was to electronically quantify adherence to oral disease modifying anti-rheumatic drugs (DMARDs) and prednisone in patients with RA.

**Methods:** This study was part of a 2–year prospective cohort of 201 patients from 2 publicly-funded county hospitals, in which 110 patients agreed to have their RA therapy electronically monitored with MEMS® caps (AARDLEX). These are medication bottle caps with a microchip that records the time and date of bottle openings. Adherence to daily medications was determined as the percentage of days with correct number of doses taken. Adherence to weekly methotrexate (MTX) was determined as the percentage of doses taken within an interval of 7 ± 1.7 days. We also estimated percentage of prescribed doses taken (not considering dosing interval). MEMS® data was downloaded with each refill. Patient outcomes were assessed at baseline, 3, 6, 12, 18 and 24 months including functional status, Disease Activity Index 28 (DAS28), SF-12, Medical Outcome Study social support (MOS), Center for Epidemiologic Studies Depression Scale 10 items (CES-D-10) and sociodemographic variables. 91% of the patients completed 2 years follow-up; for the remainder we used the last observation for analysis. The statistical analysis was carried out using SAS.

**Summary of Results:** 86% were female, 67% Hispanic, and 21% African-American; mean age was 49±5.11, disease duration 7±5.5, DAS28 4.1±1.4, MHAQ 1.8±0.5. 47% received monotherapy, 39% two DMARDs, 12% three DMARDs and 56% biologics (not oral, therefore not electronically monitored). Adherence of 5 drugs was electronically monitored (table). Adherence for doses taken on schedule (day/wk) was 59% for DMARDs and 61% all drugs. Only 21(20%) of patients had an average adherence ≥ 80%. At 2 years, these patients showed better patient self-reported disease activity and pain by VAS (p<0.029; p<0.008). No differences were observed for DAS28. Percent prescribed doses taken was greater than % days or weeks with correct doses taken, especially for MTX, suggesting lack of adherence with appropriate prescribed intervals. Patients with self-reported worse global status by visual analogue scale (VAS), and those with better mental health by SF12 MCS were statistically more likely to be adherent (p<0.03; p<0.003). Patients living alone, and those separated or widowed were less adherent (p<0.008; p<0.003). Social support (MOS) showed a borderline positive correlation (r=0.18, p<0.06).

**Conclusion:** On average, RA patients showed 61% correct medication intake, with only 1 in 5 taking oral therapies as prescribed at least 80% of the times. Long-term cohort studies should evaluate the impact of non-adherence on RA outcomes.

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Polyautoimmunity and Autoimmune Aggregation in Rheumatoid Arthritis, Adriana Rojas-Villarraga\(^1\), Ricardo A. Cifuentes\(^1\), Diana Botello-Corzo\(^2\), Antonio Iglesias-Gamarra\(^3\), Ruben D. Mantilla\(^1\) and Juan-Manuel Anaya\(^1\). \(^1\)Center for Autoimmune Diseases Research (CREA), Universidad del Rosario, Bogota, Colombia; \(^2\)CREA, Universidad del Rosario, \(^3\)Rheumatology Unit, Universidad Nacional, \(^4\)Riesgo de Fractura-CAYRE IPS

Objectives: Characterization of the extent to which particular combinations of autoimmune diseases occur in excess of what could be expected as a result of chance may offer new insights into possible common pathophysiological mechanisms. The goal of this study was to investigate the spectrum of polyautoimmunity [i.e. autoimmune diseases (Ads) co-occurring within families] and aggregation in patients with rheumatoid arthritis (RA).

Methods: This was a cross-sectional study in which 304 consecutive patients with RA (ACR criteria) and their nuclear families were included. The history of 23 Ads was investigated. A multivariate logistic regression analysis was performed in a search for risk factors that were significantly associated with the presence of polyautoimmunity. Aggregation (\(\lambda_p\)) was obtained by the ratio between the prevalence of Ads in relatives and the current prevalence of Ads in the general population.

Results: There were 98 (32.3%) patients presenting with at least one other AD. A total of 116 Ads were observed in patients of which the most frequent were autoimmune thyroid disease (AITD), Sjögren’s syndrome (SS) and antiphospholipid syndrome (APS), registered in 64 (21.1%), 36 (11.8%) and 8 (2.6%) cases respectively. Of the patients with polyautoimmunity, 16 (16.3%) presented with multiple autoimmune syndrome (i.e., two or more Ads in addition to RA). Female gender (AOR: 2.8, 95%CI:1.22–6.31), cardiovascular disease (AOR: 2.2, 95%CI:1.17–3.94) and the presence of antimicrobial antibodies (AOR: 2.0, 95%CI: 1.08–3.84) were risk factors for polyautoimmunity. Seventy-three families (24%) had at least one first degree relative (FDR) with an AD. Of the 571 FDR in these 73 families, 145 (25%) had one or more AD. The most frequent Ads registered in FDR were AITD (9.5%), RA (4%) and systemic lupus erythematosus (1.4%), with a \(\lambda_p\) of 3.5, 8 and 7 respectively.

Conclusion: Polyautoimmunity and familial autoimmunity are frequent in RA and influenced by clinical and immunological features. These findings support the hypothesis that clinically different autoimmune phenotypes might share common susceptibility variants.

Disclosure: A. Rojas-Villarraga: None; R. A. Cifuentes: None; D. Botello-Corzo: None; A. Iglesias-Gamarra: None; R. D. Mantilla: None; J.-M. Anaya: None.

1049 Prediction of 10-Year Cardiovascular and All-Cause Mortality in Rheumatoid Arthritis Using the Ankle-Brachial Index, Carlos Ramirez\(^1\), Agustin Escalante\(^2\), Mrisa Sahai\(^2\), Daniel F. Battafarano\(^3\), Samvel Pogosian\(^1\) and Inmaculada Del Rincon\(^2\). \(^1\)Brooke Army Medical Ctr, San Antonio, TX, \(^2\)UTHSCSA, San Antonio, TX, \(^3\)UTHSCSA

Introduction: The ankle-brachial index (ABI) is a non-invasive test of lower limb arterial function that can be readily performed at the bedside. It provides information about arterial flow obstruction and also about arterial wall rigidity. The ABI is frequently abnormal in rheumatoid arthritis (RA). It has clinical significance is underappreciated. We examined the association between the ABI and 10-year cardiovascular (CV) and all-cause mortality in RA patients.

Methods: We measured the ABI in 644 RA patients, among whom it was normal in 489 (76%), obstructed in 83 (13%) and incompressible in 72 (11%). Observation time from enrollment until death or last follow-up was 6,498 patient years (a median of 10.4 years per patient). During this time, 160 deaths occurred, for a mortality rate of 2.5 per 100 patient-years (95% CI 2.1, 2.9). Of these deaths, 90 were due to CV causes, for a CV mortality rate of 1.5 per 100 patient-years (1.2, 1.9). CV mortality rates per 100 patient years among patients with a normal ABI was 1.1 (0.8, 1.4); among patients with obstructed ABI mortality was 2.1 (1.3, 3.5), hazard ratio (HR) 2.0 (1.1. 3.6); and in patients with incompressible ABI CV mortality was 5.5 (3.1, 6.7), HR 4.4 (2.7, 7.2). Multivariable adjustment for demographic variables, measures of RA activity and damage and CV risk factors, attenuated the association with mortality with arterial obstruction, but did not efface that with incompressible lower limb arteries. The Figure shows a Kaplan-Meier plot of the all-cause survival function according to ABI.

Conclusion: Incompressibility of the peripheral arteries in RA patients is associated with increased CV and all-cause mortality. The ABI, a non-invasive test performed at the bedside with readily available equipment, is a potentially useful method to stratify mortality risk in RA.

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1050 Prevalence and Predictors of Pain in Rheumatoid Arthritis Patients in DAS28 Remission, Yvonne C. Lee\(^1\), Jing Cui\(^2\), Bing Lu\(^3\), Michelle Fris\(^4\), Crisitine K. Iannaccone\(^1\), Nancy A. Shadick\(^1\), Michael E. Weinblatt\(^4\) and Daniel Hal Solomon\(^4\). \(^1\)Brigham & Womens Hospital, Boston, MA, \(^2\)Brigham and Women’s Hospital, Foxboro, MA, \(^3\)Brigham and Women’s Hospital, Boston, MA, \(^4\)Brigham and Womens Hospital, Boston, MA

Background: Physicians often presume that inflammation is the stimulus for pain in rheumatoid arthritis (RA), but many patients have pain despite well-controlled disease. We assessed the prevalence of pain in RA patients in remission according to Disease Activity Score (DAS28) and examined the associations between baseline characteristics and ongoing pain despite remission.

Methods: One hundred and sixty-four RA patients in DAS28 remission (DAS28 < 2.6) completed questionnaires and underwent physical examination, blood work and hand radiographs at baseline and one year. Pain severity was assessed using the pain score from the Multi-Dimensional Health Assessment Questionnaire (MDHAQ). The association between baseline clinical predictors and clinical pain severity at one-year was assessed using multivariable linear regression.

Results: Twenty-eight patients (18.7%) in DAS28 remission had an MDHAQ pain score \(\geq 40\) at baseline. Thirty-five (22.0%) had an MDHAQ pain score \(\geq 40\) at one year. In unadjusted analyses, baseline MDHAQ pain score, MDHAQ sleep score, MDHAQ fatigue score, Arthritis Self Efficacy score and smoking were significantly associated with MDHAQ pain score at one year. Baseline Sharp score, C-reactive protein level (CRP) and DAS28 were not significantly associated with MDHAQ pain score at one year. In multivariable linear regression analyses adjusted for age and gender, baseline MDHAQ pain (\(P < 0.0001\)) and MDHAQ fatigue (\(P = 0.002\)) remained significantly associated with one-year MDHAQ pain score (see table).
**Table.** Association between baseline MDHAQ pain severity and baseline MDHAQ fatigue levels and MDHAQ pain at one year among rheumatoid arthritis patients in DAS28 remission (N = 164).

<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>Mean One-Year MDHAQ Pain Score (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>27.8 (21.8, 33.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>50–59</td>
<td>30.8 (24.3, 37.2)</td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>21.7 (16.2, 27.3)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23.9 (20.7, 27.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>Male</td>
<td>29.6 (21.8, 37.4)</td>
<td></td>
</tr>
<tr>
<td>Baseline MDHAQ pain (0–100)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>16.6 (10.7, 22.6)</td>
<td></td>
</tr>
<tr>
<td>19–29</td>
<td>22.4 (16.7, 28.2)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>41.2 (33.7, 48.7)</td>
<td></td>
</tr>
<tr>
<td>Fatigue (0–100)</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>19.0 (12.4, 25.5)</td>
<td></td>
</tr>
<tr>
<td>20–49</td>
<td>26.3 (19.7, 32.9)</td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td>35.0 (29.1, 40.9)</td>
<td></td>
</tr>
</tbody>
</table>

*P*-values from multiple linear regression, adjusted for age and gender.

**Conclusion:** Despite being in DAS28 remission, many RA patients still experience pain. In this cohort, RA-associated factors (e.g., Sharp scores, CRP, DAS28) were not significantly associated with pain severity at one year, but baseline pain severity and fatigue were strongly associated with pain severity at one year. These findings suggest that physicians should consider non-inflammatory etiologies of pain, such as a central sensitivity/symptom intensification syndrome, when evaluating pain in RA patients in remission.

**Introduction:** As discussed, patients in DAS28 remission have persistent inflammation on histological analysis of affected joints, often related to disease activity. Synovial collapse can be seen, but with inflammation typically present, with synovitis, effusion, and erosion. The biopsy specimens were scored by a pathologist and the total scores were classified as minimal (0–5), mild (6–10), moderate (11–15) or severe (16–20) disease activity. Nine of 13 joints also revealed synovitis, erosion and Doppler signal. MRI studies have shown that patients in DAS28 remission have persistent synovitis on ultrasound (US) and Magnetic Resonance Imaging (MRI). A central question is whether abnormal imaging findings in remission represent active joint inflammation.

**Methods:** We performed a structured medical chart review of RA patients and matched controls who had been admitted with acute MI to one of three hospitals in Victoria, Australia between 1995 and 2005. The administration and timing of acute reperfusion therapy and in-hospital treatment with secondary prevention medications after acute MI in RA patients and controls were reviewed. Demographic details, cardiovascular risk factors and other co-morbidities of the RA and control patients are shown in Table 1.

<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>RA (n = 90)</th>
<th>Controls (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>55 (61)</td>
<td>55 (61)</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>71 (10)</td>
<td>71 (10)</td>
</tr>
<tr>
<td>RA disease duration in years, mean (SD)</td>
<td>20 (13)</td>
<td>–</td>
</tr>
<tr>
<td>No. of DMARDS, mean (SD)</td>
<td>1.4 (1.1)</td>
<td>–</td>
</tr>
<tr>
<td>Taking NSAI at time of MI, n (%)</td>
<td>21 (23)</td>
<td>6 (7)*</td>
</tr>
</tbody>
</table>

*Pre-existing co-morbidities:

<table>
<thead>
<tr>
<th>Disease, n (%)</th>
<th>RA (n = 90)</th>
<th>Controls (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>31 (34)</td>
<td>33 (37)</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>10 (11)</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Non-cardiac vascular disease, n (%)</td>
<td>26 (29)</td>
<td>14 (15)*</td>
</tr>
<tr>
<td>IDDMM, n (%)</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>NIDDM, n (%)</td>
<td>22 (24)</td>
<td>27 (30)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>52 (58)</td>
<td>56 (62)</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>22 (24)</td>
<td>38 (42)*</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>14 (15)</td>
<td>16 (18)</td>
</tr>
<tr>
<td>Congestive cardiac failure, n (%)</td>
<td>15 (17)</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Chronic lung disease, n (%)</td>
<td>22 (31)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Chronic renal impairment, n (%)</td>
<td>15 (17)</td>
<td>8 (9)</td>
</tr>
</tbody>
</table>

*p < 0.05

Table 2 shows the treatment received by the RA and control patients after acute MI. The RA patients were significantly less likely to receive acute reperfusion compared with the controls (16% vs 37%; OR 0.27 (95% CI
reperfusion and secondary prevention medications less frequently than vs 83%: OR 0.42 (95% CI 0.18–0.96)) and lipid-lowering agents (40% vs

Table 2. Treatment received by RA and control patients following MI

<table>
<thead>
<tr>
<th>RA (n = 90)</th>
<th>Controls (n = 90)</th>
<th>Unadjusted OR§ (95% CI)</th>
<th>Adjusted OR§ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute reperfusion*</td>
<td>14 16</td>
<td>33 37</td>
<td>0.27 (0.10–0.74)</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>8 9</td>
<td>22 24</td>
<td>0.30 (0.10–0.86)</td>
</tr>
<tr>
<td>PCI</td>
<td>10 11</td>
<td>30 33</td>
<td>0.20 (0.06–0.55)</td>
</tr>
<tr>
<td>RCA</td>
<td>39 43</td>
<td>52 58</td>
<td>0.41 (0.16–0.92)</td>
</tr>
<tr>
<td>CABGS</td>
<td>11 12</td>
<td>17 19</td>
<td>0.57 (0.21–1.46)</td>
</tr>
</tbody>
</table>

Urgent reperfusion is not necessarily indicated in all cases of MI, however in the event of STEMI early thrombolysis or PCI is considered the standard of care. Of the total study cohort, 29 of the RA patients and 39 of the controls were diagnosed with STEMI. Acute reperfusion was administered in 48% of the RA-STEMI patients versus 74% of the control-STEMI patients (p=0.027).

Table 3 shows the number of RA and control patients who received treatment with selected secondary prevention medications after MI. The RA patients received less frequent in-hospital treatment with beta blockers (71% vs 83%; OR 0.42 (95% CI 0.18–0.96)) and lipid-lowering agents (40% vs 70%; OR 0.21 (95% CI 0.09–0.46)).

Table 3. In-hospital treatment with secondary prevention medications received by RA and control patients following myocardial infarction

<table>
<thead>
<tr>
<th>RA (n = 90)</th>
<th>Controls (n = 90)</th>
<th>OR§ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>85 94</td>
<td>0.20 (0.02–1.71)</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>64 71</td>
<td>0.42 (0.18–0.96)</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>61 68</td>
<td>1.18 (0.67–2.08)</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>36 40</td>
<td>0.21 (0.09–0.46)</td>
</tr>
</tbody>
</table>

Conclusions: RA patients who experience acute MI receive acute reperfusion and secondary prevention medications less frequently than controls. This may contribute to higher case fatality rates after MI in RA patients.

Disclosure: S. Van Doornum: None; C. Brand: None; V. Sundararajan: None; A. Ajani: None; I. Wicks: None.

1. 1053

Discordance of Cardiovascular Risk Factors in Japanese Patients with Rheumatoid Arthritis: From a Large Observational Study, IORRA. Eiichi Tanaka1, Eiuke Inoue2, Toru Yamada3, Ayako Nakajima4, Atsuo Taniguchi5, Shigeki Momohara6 and Hisashi Yamanaka2. 1Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan, 2Institute of Rheumatology, Tokyo Women’s Medical University, Shinjuku-ku, Tokyo, Japan, 3Institute of Rheumatology, Tokyo Women’s Medical University Background: The incidence and mortality of coronary heart diseases (CHD) are lower among Japanese in comparison to individuals in Western countries based on population-based cohort study. However, we reported that the incidence of CHD was higher in Japanese RA patients compared to Japanese population, as previously indicated in Western countries.

Objectives: To investigate the risk factors of CHD in Japanese patients with RA, using a large cohort of RA patients.

Methods: Among 8,699 RA patients enrolled in an observational cohort study in our institute, IORRA (Institute of Rheumatology Rheumatoid Arthritis) study from October 2000 to October 2008, 8,387 RA patients without a history of CHD were selected as this study cohort (Female 82.5%, mean age 55.3 years, mean RA duration 7.5 years). All patients were of Japanese origin. The occurrence of first-ever CHD (myocardial infarction or angina pectoris) events were collected by the biannual patient self-reports and all cases were confirmed by their medical records. BMI and smoking status, and factors in relation to RA including disease activity (DAS28) and Japanese HAQ (J-HAQ) were collected. The multivariate adjusted hazard ratio (HR) for CHD events was calculated according to these factors using Cox proportional hazards model in order to identify the risks associated with CHD events in Japanese RA patients.

Results: During the observation period (38,297 person-years, the mean follow-up period 4.6 years), 34 first-ever CHD events (myocardial infarction: 16, angina pectoris: 18) in men, and 52 first-ever CHD events (myocardial infarction: 18, angina pectoris: 34) in women were observed. The age-adjusted incidence rates (per 100,000 person-years) of all CHD events were 238.5 and 92.1, and those of myocardial infarction were 134.8 and 35.5, and those of angina pectoris were 103.7 and 56.7 in men and women, respectively. DAS28 and Japanese HAQ (J-HAQ) scores at study entry were 4.3 and 0.96 in the CHD group, 4.0 and 0.77 in the non-CHD group, respectively. Cox proportional hazards after adjusting for age, gender and RA disease duration, confirmed that hypertension (HR: 2.7 [95%CI: 1.7–4.4]), hypercholesterolemia (HR: 2.6 [1.7–4.1]), current smoking (HR: 2.4 [1.3–4.4]) and DAS28 (HR: 1.2 [1.0–1.4]) were significant factors associated with CVD events.

Conclusion: Disease activity assessed by DAS28 is a risk for the excess incidence of CHD in Japanese RA patients, however traditional risk factors for CHD such as hypertension, hypercholesterolemia and smoking were more significant risk factors for CHD. These data suggest that not only controlling the RA disease activity but also managing the co-morbid diseases is important for the improvement of long-term prognosis of RA patients.

Disclosure: E. Tanaka: None; E. Inoue: None; T. Yamada: None; A. Nakajima: None; A. Taniguchi: None; S. Momohara: None; H. Yamanaka: Abbott Japan Co., Ltd, 2, 5, Astellas Pharma Inc., 2, 5, Banyu Pharmaceutical Co., Ltd, 2, Chugai, 2, 5, Daiichi Sankyo, 2, Eisai, 2, 5, Hoffmann-La Roche, Inc., 5, Janssen Pharmaceutical K.K., 2, 5, Kissei Pharm.

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moderate) at 3 and 6 months after initiation of anti-TNF therapy was achieved in 51% (cases 65%, controls 47%, n.s.) and 67% (cases 79%, controls 64%, n.s.), of the patients respectively. Comparing cases to controls, a good or moderate EULAR response at 3 or 6 months was not associated with risk of ACS, OR 1.65 (0.54–5.05) and 1.48 (0.32–6.88) respectively, adjusted for disease activity before treatment start. Furthermore, no significant associations between response and risk of ACS were observed after adjustment for previous CVD.

Conclusion: In this study of patients with early RA, treatment with, or response to, anti-TNF could not be linked to any decrease in the risk of acute coronary events. Whether this is due to factors specific for this cohort or if TNF-inhibition have limited protective abilities is not possible to conclude.

Disclosure: L. Ljung: None; J. F. Simard: None; L. T. H. Jacobsson: None; S. M. Rantapaa-Dahlqvist: None; J. Asking: None.

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Objective: The present randomized controlled study addressed whether sonographic needle guidance affected the outcomes of intraarticular injection of the rheumatoid joint.

Methods: 400 rheumatoid joints were randomized to injection by conventional palpation-guided anatomic injection, sonographic image-guided injection enhanced with a one-handed RPD (the reciprocating procedure device) syringe, or the RPD alone. A one needle, two-syringe technique was used. After intraarticular placement and synovial space dilation were confirmed by sonography, a syringe exchange was performed, and triamcinolone acetonide was injected with the second syringe through the indwelling intraarticular needle. Baseline pain, procedural pain, pain at outcome (2 weeks and 6 months), responders, therapeutic duration, reinjection rates, total cost, and cost per responder were determined.

Results: Relative to conventional palpation-guided methods, sonographic guidance for injection of the rheumatoid joint resulted in 45% reduction in procedural pain (p<0.001), a 19% reduction in pain scores at outcome, a 20% increase in therapeutic duration, and a 23% increase in time to next injection. The RPD syringe alone was also beneficial with results midway between the conventional syringe and tsongraphic guidance using the RPD syringe.

Conclusions: Sonographic needle guidance can improve the performance, clinical outcomes, and cost-effectiveness of intraarticular injections of the rheumatoid joint.

Disclosure: C. R. Johnson: None; N. Chavez Chiang: None; S. Delea: None; H. Norton: None; W. L. Sibbitt: Avasca, 1, Becton Dickinson, 5, NIH, 2; A. D. Bankhurst: None.

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Statin Discontinuation and Risk of Acute Myocardial Infarction in Rheumatoid Arthritis: A Population-Based Study. Mary A. De Vera, Hyon K. Choi, Michal Abrahamowicz, Jacek Kopeć, Maria Victoria Goycochea-Robles and Diane V. Lacaille. Arthritis Research Centre of Canada, Vancouver, BC, Canada, 2Arthritis Research Ctr Canada, Vancouver, BC, Canada, 3McGill University, Montreal, QC, Canada, 4Research Unit of Clinical Epidemiology, Hospital Regional 1 IMSS, Mexico City, Mexico, 5Univ of British Columbia, Vancouver, BC, Canada

Purpose: Screening for cardiovascular risk factors and treating hyperlipidemia with statins are recommended to reduce the significantly increased cardiovascular risk in individuals with rheumatoid arthritis (RA). However, poor compliance with statins may limit their therapeutic benefit. Our objective was to evaluate the impact of statin discontinuation on risk of acute myocardial infarction (AMI) among RA patients.

Methods: We conducted a retrospective longitudinal study of a population-based cohort of RA patients with incident statin use followed from May 1996 to March 2006 with administrative health data. Primary exposure was statin discontinuation for ≥3 months at any time during follow-up; primary outcome was combined hospitalized AMI and fatal AMI events occurring outside of hospitals. To evaluate the impact of statin discontinuation on AMI risk, we used Cox’s proportional hazards analysis and modeled statin discontinuation as a time-varying exposure variable, updated monthly. Covariates included: age, gender, comorbidities (prior AMI, cerebrovascular accident, angina, use of diabetes, hypertension, and congestive heart failure medications), and use of medications known to influence cardiac risk (hormone replacement therapy, anticoagulants), assessed at baseline. As well, proxy measures of RA severity (use of RA medications [DMARDs, glucocorticosteroids, NSAIDs, methotrexate] and rate of RA-related medical visits) were included as time-dependent covariates.

Results: The cohort of incident statin users with RA comprised 4,102 individuals with mean age of 66 years and 60% female. Atorvastatin was the most commonly initiated statin in 48% of patients, followed by simvastatin and pravastatin, initiated in 22% and 12% of patients, respectively. Overall, 1,833 (45%) individuals in the cohort met the study definition for statin discontinuation. Over 15,669 person-years of follow-up, we identified 264 AMI events. Statin discontinuation was associated with a 67% increased risk of AMI (adjusted hazard ratio: 1.67; 95% CI: 1.24–2.25). Other significant predictors of increased AMI risk included older age, male sex, prior AMI, use of diabetes, hypertension and congestive heart failure medications, as well as current glucocorticosteroid use, and cumulative rate of RA-related medical visits measured as time-dependent covariates. In subgroup analyses, the association between statin discontinuation and AMI was not modified by timing of first statin prescription, prior AMI status, sex, and age (p-values for interactions: >0.17).

Conclusion: These population-based data indicate that RA patients who discontinue statins have an increased risk of AMI. To our knowledge, this is the first study to document the impact of statin discontinuation on cardiovascular outcomes in individuals with RA. Given the recent emphasis on the management of cardiovascular risk factors in RA, our findings have implications for the care of people with RA. Not only is it important to assess cardiovascular risk and initiate recommended statin therapy in patients, it is also essential to monitor and ensure patient compliance to the prescribed therapy regimen.

Disclosure: M. A. De Vera: None; H. K. Choi: None; M. Abrahamowicz: None; J. Kopeć: None; M. V. Goycochea-Robles: None; D. V. Lacaille: None.

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Stroke in Rheumatoid Arthritis: (When) Is There an Increased Risk? Marie E. Holmqvist, Lennart T. H. Jacobsson, Lars Alfredsson and Johan Asling. Karolinska Institutet, Karolinska University Hospital, Malmö University Hospital

We recently showed that the risk of ischemic heart disease, known to be elevated in established RA, increases rapidly after RA onset (1). Data on risk of cerebrovascular disease are conflicting and risks in relation to RA disease duration are lacking. Few have assessed the risk of ischemic and hemorrhagic stroke separately or stratified on serostatus.

Objective: To assess the risk of stroke in patients recently diagnosed with RA with short symptom duration at diagnosis, as a function of time since diagnosis, and stratified on serostatus.

Methods: From the Swedish RA register, ongoing since 1995, we
identified 7,176 patients with recently diagnosed RA (<18 months of symptoms at inclusion). As a comparator cohort, 5 individuals from the general population were selected for each RA patient, matched on age, sex, calendar year, residential area and marital status (n=35,171). Information on all hospitalizations listing stroke was retrieved from the nationwide Swedish Hospital Discharge Register (through 2006). We assessed stroke overall, as well as ischemic and hemorrhagic stroke separately. One individual could contribute first events to both subgroup outcomes, as well as to the overall outcome. Start of follow-up was date of RA diagnosis in RA patients. Comparators were given the same start date as their matched RA patient.

Incidence rates were calculated. Relative risks (RR) and 95% confidence intervals (CI) of stroke after RA-diagnosis were estimated using Cox proportional hazards regression.

Results: Mean age at start of follow-up was 57 years. 70% were women. Follow-up amounted to 31,318 person-years in the RA cohort and 153,180 person-years in the general population cohort. Median follow-up was 3.9 years (range 12 years) in both cohorts. 2.6% of all patients with RA and of all comparators had any cerebrovascular event during follow up (incidence rate 6/1000 person-years in both cohorts) which corresponded to an overall RR of 1.0 (95% CI 0.9, 1.2). The incidence rates of ischemic (4.8/1000 person-years in RA and 4.1 in comparators) and hemorrhagic stroke (0.9/1000 person-years in RA and 1.2 in comparators) were similar in both cohorts, corresponding to RRs of 1.1 (95% CI 0.9, 1.3) and 0.7 (95% CI 0.5, 1.1) respectively. During this time-frame, no increased risk of stroke was observed, neither overall nor by stroke subtype nor time since RA-diagnosis. When stratified by serostatus no heterogeneities were detected (data not shown).

Conclusion: In contrast to the rapid increase in IHD risk, the risk of stroke, ischemic or hemorrhagic, is not elevated in RA within 12 years of RA diagnosis. Stratification by serostatus did not alter these results. This does, however, not preclude an increased risk of stroke in RA patients with longer disease duration but may point to distinct aetiologies behind IHD and stroke in early RA.

References:
2. L. T. H. Jacobsson: None; L. Alfredsson: None; J. Asking: None.

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Subclinical Atherosclerosis in Patients with Rheumatoid Arthritis Is Associated with Decreased Activity of Lecithin Cholesterol Acyl-Transferase, a High Density Lipoprotein (HDL)-Associated Protein Involved in Reverse Cholesterol Transport. Christina Charles-Schoeman1, Yuen Yin Lee2, Sogol Amjadi3, John D. FitzGerald4, Veena K. Ranganath2, Michael Gottwald1, Denio Ridjab2, Stephanie Gloecke1, Kathrin Behring1, Robert Lange3, Christian Butter1 and Michael Zaenker1. EFKH and Heart Center Brandenburg, Bernau, Germany, 2Amgen Inc., 3Hospitalverbund and Rheumatologischen Zentrum Brandenburg.

Background: Incidence of HF is 2-fold higher for patients with RA compared to general population. Independent association of RA with diastolic dysfunction and increased NT-proBNP levels has been demonstrated. The chronic elaboration of inflammatory cytokines like TNFa is likely substantial contributor to myocardial dysfunction. However, there still are conflicting results of clinical trials whether TNFa inhibition does promote or prevent heart failure in RA patients.

Objective: To determine the rate of symptomatic heart failure, increased NT-proBNP and diastolic dysfunction among RA-patients with and without TNFa-inhibition.

Methods: In this prospective study all RA-patients were consecutively included, who showed up in a 3 months period for follow up. Inclusion criteria were written consent, and diagnosis of RA, fulfilling ACR-criteria. All patients were interviewed using a standardized questionnaire to assess cardiovascular (cv) risk factors, cv disease, and symptoms of heart failure. Clinical signs were evaluated based upon Framingham criteria. Laboratory tests included chest x-ray, ECG, spirometry, and echocardiography.

Results: 133 patients with RA, 68% female, mean (SD) age 60.3 (±13.6) years, median disease duration 8.0 years, median DAS28 2.7, median HAQ 1.25 were included. 57% reported any dyspnoea, 42% dyspnoea according to NYHA-class II, 9% NYHA-III, 4% NYHA-IV, 50% reported any edema, whereas raised NT-proBNP levels >220 ng/ml were found in only 29% of patients. Diastolic dysfunction was found in 13.7 %, systolic dysfunction in 1.9%. Cardiovascular risk factors were hypertension in 52%, hypercholesterolemia in 24%, current smoker in 23%, diabetes in 17% of patients. Previous diseases included TIA/stroke in 4%, peripheral arterial disease in 9%, CAD in 22%, MI in 8%. N=48 (36%) had anti-TNFa therapy, 64% other treatment with DMARDS, abatacept, or rituximab. Comparing the subgroups with and without anti-TNFa therapy no significant differences were found for mean age, DAS28, HAQ, ESR, CRP, rate of increased NT-proBNP (68.7 vs. 70.6%), mean NT-proBNP (244 vs. 263 ng/ml, rate of dyspnoea (54.2 vs. 58.8%), rate of NYHA II (41.6 vs. 42.3%), NYHA III (10.4 vs. 8.2 %), NYHA IV (2.0 vs. 4.7%), diastolic dysfunction (14.6 vs. 12.5%). The patients with anti-TNFa therapy had longer disease duration (14.5 vs. 6.0 years, p<0.001), worse HAQ (1.5 vs. 1.0, p=0.044), higher rate of hypercholesterolemia (33.3 vs. 16.2% in the groups without anti-TNFa therapy).

LCAT activity was measured in patient plasma as the change in ratio of the intact to hydrolyzed LCAT monomer substrate (470/390 nm of emission intensity) over time. Lipoprotein cholesterol levels were measured by standard methods and traditional cardiovascular risk factors, medication use, and RA disease characteristics were assessed for all patients.

Results: Carotid plaque was identified in 49% of the RA patients studied. LCAT activity was significantly lower in patients with plaque compared to patients without plaque (See table). After multivariable analysis, LCAT activity (OR 0.002, p=0.009), age (OR 1.1, p=0.001), and gender (OR 9.0, p=0.005) were significantly associated with plaque in RA patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>Activity (yrs)</th>
<th>F</th>
<th>HSCRP</th>
<th>HDL-C</th>
<th>LDL-C</th>
<th>HSCRP</th>
<th>HDL-C</th>
<th>HTN</th>
<th>BMI</th>
<th>HAQ-DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque</td>
<td>0.29±0.038*</td>
<td>61±9</td>
<td>78±4</td>
<td>4.4±1.9</td>
<td>42±10</td>
<td>32*</td>
<td>29</td>
<td>27±4</td>
<td>6.0 ±0.77</td>
<td></td>
</tr>
<tr>
<td>No Plaque</td>
<td>0.237±0.043</td>
<td>49</td>
<td>11</td>
<td>71</td>
<td>41.7</td>
<td>17.9</td>
<td>15</td>
<td>104±37</td>
<td>23</td>
<td>7.7±1.86</td>
</tr>
</tbody>
</table>

Yuen Yin Lee3, Sogol Amjadi3, John D. FitzGerald4, Veena K. Ranganath2, Michael Gottwald1, Denio Ridjab2, Stephanie Gloecke1, Kathrin Behring1, Robert Lange3, Christian Butter1 and Michael Zaenker1. EFKH and Heart Center Brandenburg, Bernau, Germany, 2Amgen Inc., 3Hospitalverbund and Rheumatologischen Zentrum Brandenburg.
The Clinical Implication of Anti-Cyclic Citrullinated Peptide Antibody in Late Onset Rheumatoid Arthritis. Se Jin Jung1, Yoon Kang2, You-Jung Ha3, Kwang-Hoon Lee4, Sang Won Lee5, Min-Chan Park6, Soo Kon Lee7 and Yong-Beom Park. Gangnam Severance Hospital, Seoul, Korea, Republic of; 2Yonsei Univ College of Med, Seoul, Korea, Republic of; 3Yonsei Univ College of Med

Background: Late onset rheumatoid arthritis (LORA), onset of which is over 60 years old, has clinical features that are different from those of younger onset rheumatoid arthritis (YORA). While anti-cyclic citrullinated peptide antibody (anti-CCP) is known to be more disease-specific in RA, clinical implications of anti-CCP in LORA have not been reported to date.

Purpose: To investigate the association of anti-CCP and its titer with markers reflecting disease Activity of RA.

Methods: We retrospectively investigated medical records of 238 patients with RA, who visited Severance Hospital between January 2005 and May 2009. All patients were divided into two groups according to the age of 60 when they were diagnosed with RA (LORA (N=61) and YORA (N=177)). Rheumatic factor (RF) and anti-CCP were analyzed, and disease activity score (DAS) 28 at diagnosis was assessed at their first visit. Initial as well as accumulated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were measured. Accumulated levels were obtained using the area under curve (AUC) during the first year after diagnosis. Patients having anti-CCP were evenly distributed in three groups according to the range of the titer of anti-CCP (low (>5), moderate (5–135) and high (>270) titer groups).

Results: The mean ages of patients with LORA and YORA were 67.1 ± 6.0 and 43.7 ± 10.5 years old, respectively. There were no significant differences in joint involvement, symptom duration, clinical manifestations, positivity of RF or anti-CCP, and medications between the two groups. However, patients with LORA had higher ESR, anti-CCP titer and CRP levels than those with YORA. The titer of anti-CCP was well correlated with initial and accumulated levels of ESR in patients with LORA (r=0.416 and r=0.432, p<0.05), but not with patients with YORA.

Conclusions: In patients with LORA, but not with YORA, the titer of anti-CCP was significantly correlated with initial and accumulated levels of ESR, suggesting that initial titer of anti-CCP might be used as a value to predict the extent of inflammation during the first year after diagnosis in LORA patients.

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The Effect of Calcium and Vitamin D Supplementation on the Incidence of Rheumatoid Arthritis in the Women’s Health Initiative Randomized Study. Marcus Racovcn10, Brian Walitb10, Christopher Collins10, Mary Pettinger2, Christine Parks4, James Shikany6, Jean Wactawski-Wende8, JoAnn E. Manson1, Larry Moreland8, Nicole Wright5, Rebecca Jackson5 and Barbara V. Howard1. Brigham and Women’s Hospital, Harvard Medical School, 2Frd Hutchinson Cancer Research Center, 3MedStar Research Institute, 4National Institute of Environmental Health Sciences, 5Ohio State University, 6University of Alabama, 7University of Arizona, 8University of Buffalo, 9University of Pittsburgh, 10Washington Hospital Center

Objective: To determine if calcium and vitamin D supplementation reduces the incidence of rheumatoid arthritis (RA).

Methods: 32,435 postmenopausal women enrolled in the WHI calcium plus vitamin D (CaD) randomized controlled trial were included in a study with primary endpoints of hip fracture or colorectal cancer. The participants were assigned in a randomized, double-blind manner to either daily 1000 mg of calcium carbonate plus 400 IU of vitamin D3 or placebo. In a post-hoc analysis, a previously validated method was used to identify RA cases using participant self-report plus concomitant use of disease modifying anti-rheumatic drugs (DMARDs). Cox proportional hazards ratios and Kaplan-Meier curves were used to compare the incidence of RA in the treatment versus the placebo groups. Covariates, such as age, hormone therapy, smoking, duration of breastfeeding and geographic location, were considered in the model.

Disclosure: None; W. F. N. Chan: None; D. Naismith: None; N. van der Westhuizen: None; J. Woo: None; V. Cortez: None; J. L. Nelson: None.
Results: 163 new RA cases were identified over 6 years. No significant differences were observed between the two groups in terms of demographics or non-experimental vitamin D intake (total vitamin D supplementation \( p = 0.96 \), multivitamin intake \( p = 0.07 \) and sun exposure \( p = 0.85 \)). There was no difference between the two groups in RA incidence \( p = 0.82 \), Figure 1). Stratification of the results by age, regional solar irradiance and total vitamin D intake and adjustments for covariates such as smoking, hormone therapy, longer duration of breastfeeding did not alter the results.

Conclusions: Calcium and vitamin D intake as a dietary supplement did not have a statistically significant effect on the incidence of RA in the WHI randomized CaD trial. These results suggest that calcium and low dose vitamin D replacement had no effect on the development of RA in post-menopausal women. Further research is needed to assess the effect of supplementation with higher doses of vitamin D on the incidence of RA.

Figure 1. Cumulative hazard of incident RA.

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The Impact of Rheumatoid Arthritis (RA) on Women: Focus on Pain, Productivity and Relationships. Vibeke Strand\(^4\), Paul Emery\(^1\), Scott Fleming\(^4\) and Catherine Griffin\(^3\). \(^1\)Chapel Allerton Hospital, Leeds, United Kingdom, \(^2\)Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, CA, \(^3\)Echo Research, London, UK, \(^4\)UCB, Slough, UK.

Background: It is widely recognized that daily life-burdens associated with RA, including functional impairment, pain, inability to participate in desired family, social and leisure activities and reduced productivity at work and within the home, have a profound impact on the overall health-related quality of life (HRQoL) of RA patients. However, this impact on daily life in women, as well as on relationships and overall well-being, has not been well characterized.

Objective: To explore the impact of RA on women’s daily lives and relationships.

Methods: Women with RA from 7 countries (USA, Canada, UK, France, Germany, Italy, and Spain) were recruited by an online research panel to complete an internet survey regarding how their lifestyle has been affected by RA. Eligible women were aged 25–65 years with a formal diagnosis ≥6 months; screening criteria were established to exclude those without a diagnosis of RA and/or who did not satisfy the age criteria. Respondents were queried regarding the physical, emotional and social impacts of RA on their lives. Mean responses to each question were computed for the overall patient population.

Results: 27,459 women were recruited via an online research panel. Of these, a total of 1958 women with RA (USA, UK, Germany, and Spain 300 patients each; Canada, 155; France, 301; Italy, 302) completed the survey between July 30 and August 31, 2009. No major regional differences were observed in any outcome measured. Mean age was 46 years, 75% had RA diagnosed ≥1 year and 69% self-reported moderate to severe disease. Among the 75% of respondents who were currently taking pain-relief medications, a high proportion still reported experiencing daily pain (72%). The majority of respondents felt they had to conceal pain (68%). Furthermore, 67% of respondents agreed/strongly agreed that they constantly look for new ideas to address pain, and nearly 9 out of 10 mentioned pain in discussions with their physicians. Another key finding of the survey was the negative impact of RA on productivity at work. Of those employed (n=1108), 71% reported they were less productive at work because of RA, 23% had to stop work altogether, and 17% had to switch to part-time employment. Respondents reported that the emotional impact of RA is high: many have feelings of detachment and isolation from their friends and family due to their condition; 26% felt isolated, and 32% that RA had affected their closest relationships for the worse. RA was also reported to negatively affect the most intimate aspects of patients’ lifestyles, with 4 of 10 single women agreeing that RA makes it more challenging to find a partner, and 22% divorced/separated respondents indicating that RA had at least some role in their decision to separate.

Conclusions: Pain is a paramount issue for women with RA; the majority experience pain despite taking pain relief medication. In all countries evaluated, respondents indicated that RA had a negative impact on employment and caused them to feel isolated, negatively affecting intimate relationships. Optimization of treatment strategies to reduce pain, increase productivity, and manage the social aspects of the disease is thus needed.


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There Are No Differences in Lipids between RA Patients and Their Siblings, Despite Higher Incidence of CHD in RA. Namita Kumar, Nicola J. Marshall, David J. Walker and Philip N. Platt. University Hospital of North Durham

Introduction: The interest in coronary heart disease (CHD) and cardiovascular risk remains high in our patients with inflammatory arthritis and especially Rheumatoid Arthritis (RA). The exact cause of the increased risk is still unclear with contradictory data regards the role of lipids and their response to treatment.

We looked at a cohort of RA patients and their siblings to assess this further.

Method: A population of RA patients and their same sex siblings were studied in Newcastle-upon-Tyne, UK. This population were matched for age and sex. Diagnosis of CHD and a number of risk factors were assessed and compared. Diabetics were excluded.

Results: Data from 79 pairs were available. Female:male ratio was 67:12. There was a twofold increase in the amount of diagnosed CHD in the index cases compared to the siblings (Mann-Whitney test, \( p < 0.0001 \)). There was a significant increase in CRP and ESR \( p < 0.0004 \) in the index cases and increased BMI in the siblings. Current and previous smoking status between the 2 groups was similar. There was no difference in the use of statins and other lipid lowering drugs between the 2 groups.
Linear regression showed no association between CRP, cholesterol: HDL, LDL, apolipoprotein A or B and the incidence of CHD in our patients with RA. There was also no correlation with CRP and any of the lipids shown in Table 1.

In those pairs who had no CHD there was still no difference in cholesterol, triglycerides, cholesterol: HDL and apolipoprotein A and B levels, all of which were in the normal range.

**Conclusion:** RA patients have higher CHD than same sex siblings when matched for age, sex, diabetes and smoking status. They have lower BMIs and higher inflammatory markers. This data suggest that lipids within this RA population were not a major component of risk.

**Disclosure:** N. Kumar: None; N. J. Marshall: None; D. J. Walker: None; P. N. Platt: None.

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### Table 1.

<table>
<thead>
<tr>
<th>N = 79 pairs</th>
<th>RA</th>
<th>Sibling</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.9 (9.2)</td>
<td>59.4 (10.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Diagnosed CHD</td>
<td>36 (20%)</td>
<td>9 (11%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/l median (range))</td>
<td>11 (3.232)</td>
<td>3 (0.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²) (mean SD)</td>
<td>25.7 (5.6)</td>
<td>27.3 (5.1)</td>
<td>x0.016</td>
</tr>
<tr>
<td>Cholesterol mmol/l (mean, SD)</td>
<td>3.8 (1.0)</td>
<td>3.9 (1.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Triglycerides mmol/l</td>
<td>1.5 (0.6, 3.8)</td>
<td>1.3 (0.4, 4.1)</td>
<td>ns</td>
</tr>
<tr>
<td>HDL-Cholesterol mmol/l</td>
<td>1.5 (0.4)</td>
<td>1.6 (0.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Cholesterol: HDL mmol/l</td>
<td>3.8 (1.0)</td>
<td>3.9 (1.0)</td>
<td>ns</td>
</tr>
<tr>
<td>LDL mmol/l (mean, SD)</td>
<td>3.3 (1.0)</td>
<td>3.6 (1.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Apolipoprotein A1 (mean, SD)</td>
<td>1.45 (0.3)</td>
<td>1.5 (0.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Apolipoprotein B (mean, SD)</td>
<td>0.99 (0.25)</td>
<td>1.01 (0.3)</td>
<td>ns</td>
</tr>
</tbody>
</table>

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**Thigh Fat and Muscle in Rheumatoid Arthritis: Associations with Disease Features and Physical Functioning.**

**Background:** Body fat is increased and lean mass decreased, on average, in rheumatoid arthritis (RA) patients. However, no studies have explored longitudinal predictors of thigh fat and muscle composition, an important anatomic site for physical functioning.

**Methods:** Participants in ESCAPE RA, a prospective cohort study of cardiovascular disease in RA, underwent mid-femur computed tomography (CT) scanning at study visit 3, occurring 3.2 ± 0.3 years from baseline. The associations of baseline and cumulative demographic, lifestyle, and RA disease and treatment characteristics with thigh fat area (TFA), thigh muscle area (TMA), and thigh muscle density (TMD) were explored using multivariate linear regression (MVLR). MVLR was also used to model associations of TFA, TMA, and TMD with disability, assessed using HAQ and with the components and summary score of the Short Physical Performance Battery (SPPB).

**Results:** A total of 152 RA patients (64% female; 88% Caucasian; mean age=63 years; median baseline RA duration=12 years, median DAS28 at visit 3=3.1) were scanned. Among RA characteristics, longer RA duration, higher tender joint count, higher cumulative IL-6, and current prednisone use were significantly associated with lower TMA, even after adjusting for demographics, smoking, physical activity, depression, and thyroid disease. RA characteristics accounted for 24% of the explainable variability in TMA. These same RA characteristics were also significantly associated with TMD, and accounted for 45% of the explainable variability. For TFA, longer RA duration and higher FACIT fatigue scores were significantly associated with higher TFA, and current prednisone use was associated with 28cm² lower TFA compared to non-use (p=0.001); however, cumulative prednisone dose was not associated with TFA. RA characteristics accounted for 28% of the explainable variability in TFA. Biologic and non-biologic DMARD treatment was not significantly associated with thigh composition. Lower TMD and higher TFA (but not TMA) were significantly associated with higher HAQ scores, after adjusting for exercise, DAS28, Sharp score, and FACIT score. These six characteristics accounted for 59% of the explainable variability. RA patients with the lowest SPPB scores had significantly lower TMA and TMD compared to those with the highest scores (Figure). TFA was not significantly associated with SPPB score.

**Conclusions:** These findings suggest that: 1) the origins of altered muscle bulk and quality, and changes in fat distribution, are likely multifactorial in RA patients, with contributions from inflammation, joint damage, fatigue, and treatments (i.e. glucocorticoids) and 2) abnormal fat and muscle composition, in particular muscle quality, contribute substantially to physical functioning.

**Disclosure:** H. R. Kramer: None; K. R. Fontaine: None; J. M. Bathon: None; J. T. Giles: None.

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**Figure.** Thigh muscle area and density according to short physical performance battery summary score.

**TNF Inhibitors and the Risk of Fracture in Rheumatoid Arthritis.**

**Background:** Prior studies suggest an increased risk of fracture with RA. Potential causes include the underlying inflammation of RA as well as use of glucocorticoids. Several prior investigations demonstrate an improvement in bone mineral density associated with use of TNF inhibitors (TNFi). However, there are no studies comparing the risk of fracture related to different DMARDs in patients diagnosed with RA.

**Methods:** Our study cohort was drawn from two data sources—a population-based cohort from a Canadian province and a large US commercial insurance plan. Patients with at least 2 diagnoses of RA were eligible for the study cohort at the time of a DMARD addition or switch. DMARD additions or switches were categorized into three mutually exclusive groups: 1) TNFi, with or without other DMARDs; 2) methotrexate (MTX), without a TNFi; or 3) other DMARDs, without a TNFi or MTX. Group 3 (other DMARD) was considered the reference group. Subjects were followed until they experienced a hip, humerus, wrist, or pelvis fracture based on diagnosis and procedure codes identified in the health care utilization data. The composite of any of these fracture types was considered the primary outcome. Incidence rates for fractures were compared across exposure groups. In addition, adjusted hazard ratios were calculated in Cox regression with covariates including age, gender, Charlson comorbidity index, prior fractures, oral glucocorticoids, other fracture risk factors, and health services utilization. Secondary analyses focused on groups with oral glucocorticoid use and prior fractures.

**Results:** The study cohort consisted of 25,988 subjects with RA starting one of the three groups: 5,856 TNFi, 12,554 MTX, and 7,578 other DMARDs. Mean follow-up was 6 months. The three groups' characteristics were similar with respect to age, gender, and comorbidities, but differed with respect to oral glucocorticoid and opioid use, with higher rates for TNFi users. The incidence rates per 1,000 person-years for the composite fracture outcome were 5.11 (95% CI 3.50–7.45) for TNFi, 5.35 (95% CI 4.08–7.02) for MTX, and...
6.38 (95% CI 3.78–10.77) for other DMARDs. Adjusted hazard ratios for the primary outcome and secondary analyses are shown in the Table. The risk of fracture was similar across DMARD exposure groups.

Table. Adjusted hazard ratio (95% CI) for fracture among subjects with RA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.11 (1.07, 1.16)</td>
</tr>
<tr>
<td>Smoker (Y/N)</td>
<td>2.91 (1.28, 6.64)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.02 (1.00, 1.04)</td>
</tr>
<tr>
<td>Apo B (g/l)</td>
<td>7.63 (2.28,25.51)</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>0.76 (1.01, 1.07)</td>
</tr>
<tr>
<td>Adiponectin (mg/l)</td>
<td>1.19 (1.05, 1.36)</td>
</tr>
</tbody>
</table>

Conclusions: Among subjects diagnosed with RA, the adjusted risk of fracture was similar across persons starting a TNFi, MTX, or other DMARDs. This result was robust across secondary analyses.


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Purpose: Patients with inflammatory polyarthritis (IP) have an excess risk of cardiovascular (CV) mortality due to accelerated atherosclerosis. Markers identifying individuals with subclinical atheromatous plaque may allow for attenuation of CV risk. The objective of this study was to identify risk markers associated with atheromatous plaque in an incident cohort of patients with early IP.

Methods: Consecutive patients with early IP (> or equal to 2 joints swollen for > or equal to 4 weeks) aged 18–65 years, who were within 24 months of symptom onset were recruited as part of a primary-care based inception cohort between 2004–2008. Patients underwent assessment of classic risk factors, completion of a health assessment questionnaire (HAQ) and a 28 joint count for calculation of disease activity score (DAS28). Blood was taken for rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA), C-reactive protein (CRP), high sensitivity CRP (hs-CRP), fasting glucose, novel and traditional lipid levels (LDL, HDL, triglycerides, paroxonase 1 (PON1) apolipoprotein (Apo) A1 and B), markers of vascular damage (E-selectin, vascular adhesion molecule (VCAM)) and adipokine (leptin and adiponectin). All patients underwent B mode Doppler ultrasound examination of the carotid arteries to assess for the presence of plaque. In univariate analyses we identified factors that were associated with plaque presence after age and gender adjustment. An additive stepwise multivariable logistic regression model investigated the independence of any associations.

Results: Of the 316 patients studied 93 (29%) patients were male. The median (IQR) age and symptom duration at study entry was 51 (42–58) years and 6.6 (4.2–11.2) months respectively. The patients had a mean (SD) blood pressure of 134/82 (17/10) mmHg, 71 (23%) were smokers and 149 (47%) had detectable plaque. From the univariate analysis; age, smoking, total cholesterol, triglycerides, Apo B, hs-CRP, adiponectin and E-selectin were significantly associated with plaque presence. There was no significant association found between HAQ score, DAS28, exposure to steroid therapy and DMARDs, RF and ACPA status and plaque presence at baseline (OR (95% CI); 0.97 (0.68, 1.40), 1.06 (0.85, 1.32), 0.77 (0.39, 1.51), 0.98 (0.58, 1.64), 1.54 (0.92, 2.57), 1.39 (0.81, 2.39)). In an additive stepwise multivariable logistic regression model age, smoking, systolic blood pressure, Apo B, hs-CRP and adiponectin remained significant independent predictors of plaque (Table).

Conclusion: Markers known to be associated with atherosclerosis in the general population including smoking, higher systolic blood pressure and Apo B are associated with early atherosclerosis in this population. The association with hs-CRP and adiponectin suggests that low-grade inflammation, even in early disease, may contribute to atherogenesis in early IP.

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Purpose: We have previously shown that in a North American Native (NAN) population in Central Canada, the prevalence of RA is 2–3 times higher than that seen in most other populations, with a particularly high frequency of familial disease. We have also demonstrated a high prevalence of anti-citrullinated protein antibodies (ACPA), rheumatoid factor (RF), and of RA-like joint symptoms in the first-degree relatives (FDR) of RA probands from this population. We sought to get a better understanding of the relationship between joint symptoms and RA autoantibodies in disease-free NAN individuals who may be at risk for developing future RA.

Methods: The prevalence of joint symptoms was compared in three distinct groups: 1) FDR of NAN RA patients (n=306), 2) NAN controls (NC, n=330), and 3) Caucasian controls (CC, n=293). The two control groups had no family history of RA or related autoimmune diseases, and NC were from the same geographic areas as FDR. All study subjects completed a questionnaire which included demographic data, health related habits, family health history, and six questions probing into whether they experience pain, swelling, or stiffness of the hands or of other joints. Anti-CCP2 antibodies were tested by ELISA and RF and ACPA by nephelometry in FDR (n=287), NC (n=198), CC (n=100).

Results: The mean age of FDR was 35±13, NC was 33±11, CC was 42±13, p<0.0001. The percentage of females was FDR=69%, NC=63%, and CC=63%, p=ns. In all groups, females reported more joint pain, swelling, and stiffness, and overall had an OR=1.6, p<0.01 for having any joint symptom. Compared to both control groups, FDR were more likely to report joint symptoms in the hands: pain (54%, 35%, 18%), swelling (36%, 16%, 7%), stiffness (40%, 23%, 14%); and in other joints: pain (57%, 34%, 32%); swelling (30%, 17%, 11%); stiffness (39%, 24%, 25%) for FDR, NC, CC, respectively; all comparisons p<0.0001. The high prevalence of joint symptoms in FDR was confirmed after matching FDR to NC by age and sex. Compared to CC, NC had more joint symptoms (p<0.01 for all hand joint symptoms). There was a higher prevalence of joint symptoms in FDR living in urban vs. rural locations (79% vs. 60%, p<0.0001). The prevalence of anti-CCP2 was: FDR = 8.3%, NC = 1%, and CC = 1%, p<0.0001, and RF was: FDR = 4.5%, NC = 1%, and CC= 1%, p<0.05. Logistic regression modeling demonstrated that age and FDR status were strong independent predictors of having any joint symptoms (p<0.0001 for both), while gender, RF, and ACPA status were not significant predictors in the model. Similar results were obtained when modeling the individual joint symptoms, although gender was found to be a predictor of hand symptoms.

Conclusion: RA-like joint symptoms are more common in FDR of NAN RA patients than in either NAN or Caucasian individuals having no...
family history of RA, a finding that is not explained by the higher prevalence of ACPA and RF in FDR. This finding, combined with the overall higher frequency of joint symptoms seen in NAN compared to Caucasian controls, and in urban compared to rural FDR raises the possibility that pre-clinical joint symptoms based on biological and psychosocial factors may be part of the risk profile for developing future disease in high risk individuals and populations.

Disclosures: I. Smolik: None; Q. Tan: None; X. Wang: None; D. Hart: None; M. Newkirk: None; C. N. Bernstein: None; D. B. Robinson: None; H. S. El-Gabalawy: None.

ACR Poster Session B
Rheumatoid Arthritis - Human Etiology and Pathogenesis II
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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'Shared' T-Cell Clones Identified in Lymph Nodes and Synovial Tissue of Early Rheumatoid Arthritis Patients Using a Novel High Throughput Sequencing Technology. Paul L. Klarenbeek, Marjoelijn J. de Hair, Stefano Alivernini, Marleen G. van de Sande, Marieke E. Doorenspleet, Barbera D. van Schaik, Ferco H. Berger, Rebecca E. Esvedt, Antoine H. van Kampen, Danielle M. Gerlag, Frank Baas, Paul P. Tak and Niek de Vries. Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, Dept of Radiology, Academic Medical Center-University of Amsterdam, Dept of Clin. Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center-University of Amsterdam, Div of Clin Immunology & Rheumatology, Academic Medical Center-University of Amsterdam, Amsterdam, The Netherlands, Lab. For Genome Analysis, Academic Medical Center-University of Amsterdam

Background: T-cells are likely to play important roles in the pathogenesis of rheumatoid arthritis (RA), but the role of T-cell clones remains to be elucidated. Although the synovial tissue (ST) is the primary target tissue in RA, previous observations from our group suggested that other sites might also be involved in the early phases. As a primary site for adaptive immune responses the lymph node (LN) is a likely candidate. Previously, we demonstrated, using newly developed High Throughput Sequencing (HTS) technology, that T-cell clones are present in the ST of RA-patients, and that the T-cell repertoire in the ST is markedly different from that in the peripheral blood (PB). Here, for the first time, we analyzed paired samples from LN, ST and PB to study T-cell clones in early RA.

Objectives: Investigate paired LN, ST, and PB samples of early RA patients for presence of T-cell clones to analyze the relation between these compartments with regard to adaptive immune responses.

Methods: mRNA was isolated from paired LN, ST and PB samples of 2 DMARD-naive anti-CCP+ RA-patients (pt) (fulfilling ACR-criteria at inclusion; disease duration ≤ 1 year) after arthroscopic ST sampling of an arthritic ankle and ultrasound guided needle biopsy sampling of a regional lymph node. A linear amplification with primers for all V(variable)-genes of the T-cell receptor β-chain was performed. The amplified products contain the Complemmentarity Determining Region 3 (CDR3), which can be used as ‘fingerprint’ for each clone. The samples were processed using a Genome Sequencer (454/Roche) analyzing up to 1 million receptors at once. The frequency of each clone was determined by the CDR3 using bioinformatics algorithms. Clones with a frequency of ≥1% were arbitrarily considered as highly expanded.

Results: The LN samples showed only few highly expanded clones when compared to the ST (2 vs. 25 clones (pt1) and 1 vs 24 (pt2) in LN and ST respectively). Few expanded clones were detected in PB as well (0 (pt1) and 2 (pt2)). Evidence of circulation between the compartments was seen in both patients. E.g. of the 24 highly expanded clones in pt2 9 clones were found in the PB and 8 were found in the LN. Of these, 4 were found both in the LN and the PB. Whereas these shared clones were highly expanded in the ST, they were of low frequency in the PB and LN (0.01–0.09% in LN and 0.01–0.52% in PB). Little overlap was seen in the T-cell repertoire between ST and PB/LN. In pt1 only 6% and 8% of the ST clones were shared with the LN and PB respectively. In pt2 this was 9% for both LN and PB.

Conclusions: This is the first analysis of T-cell clones in LN samples compared to ST and PB, using the HTS technology. In these patients we found T-cell clones in both the regional LN and the ST. Only few highly expanded clones were found in the LN while multiple highly expanded clones were found in the ST, perhaps due to epitope spreading in the ST. Many of the highly expanded ST clones could be found back in LN and/or PB. The frequencies of these clones in LN/PB were very low suggesting local retention and/or proliferation of these clones in the inflamed ST. Additional studies are underway to further characterize the roles of T- and B-cell clones in early RA and to investigate the role of the LN in RA.

Disclosures: P. L. Klarenbeek: None; M. J. de Hair: None; S. Alivernini: None; M. G. van de Sande: None; M. E. Doorenspleet: None; B. D. van Schaik: None; F. H. Berger: None; R. E. Esvedt: None; A. H. van Kampen: None; D. M. Gerlag: None; F. Baas: None; P. P. Tak: None; N. de Vries: None.

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Anti-citrullinated Peptide Antibodies (ACPAs) in the Sera of Heavy Smokers without Arthritis. A Differential Role of Associated Pulmonary Disease? Virginia Ruiz-Esquide, Maria Jose Gomara, Victor Peinado, Jose Alfredo Gomez Puerta, Maria Victoria Hernandez, Joan A. Barbera, Julio Ramirez, Juan de Dios Canete, Isabel Haro and Raimon Sannmarti. Pneumology Service, Hospital Clinic of Barcelona, Barcelona, Spain, Rheumatology Service, Hospital Clinic of Barcelona, Barcelona, Spain, Rheumatology Service, Hospital Clinic of Barcelona, Barcelona, Spain, Unit of Synthesis and Biomedical Applications of Peptides, IQAC-CSIC, Barcelona, Spain

Background: Anti-citrullinated peptide antibodies (ACPAs) are the most specific serological markers of rheumatoid arthritis (RA). An increased risk of RA has been described in smokers, but only in ACPA-positive RA patients. The frequency of ACPAs in serum of heavy smokers is not known.

Objectives: To analyze the frequency and levels of ACPAs in the serum of heavy smokers subjects, with and without lung disease, and to compare them with a healthy control group.

Methods: Serum samples of 110 heavy smokers (39% women, mean age 56.9 ± 10 years) were obtained. Subjects were selected, from a Pneumology service data base and from hospital health workers, regardless of whether they had chronic obstructive lung disease (COPD) or not. Study subjects were compared with a healthy control group who had never smoked (51% women, 41.8 ± 12 years) (n=209). Both groups were tested for two different antibodies against citrullinated proteins, a commercial CCP2 test and a home-made chimeric fibrin/filagrin citrullinated synthetic peptide (anti-CFFCP). The frequency of positive results and autoantibody levels were compared between groups.

Results: Of the 110 heavy smokers, 54 had COPD and 56 were healthy smokers. None had RA. Mean pack-years were 44.3 ± 36 (53 ± 28 in COPD disease and 36 ± 16 in healthy smokers, p<0.01). The percentage of positive results together with the mean serum levels of the two citrullinated autoantibodies in all the study groups are shown in Table 1.

The prevalence of positive anti-CFFCP was higher in the heavy smoker group than in non-smokers, although the difference was not significant. The highest prevalence of positive anti-CFFCP was seen in patients with COPD (7.4%); the difference was at the limit of statistical significance compared with the control group (2.4%) (OR 3.26 95% CI 0.85–12.6 p=0.07). There was no significant difference in the frequency of positive anti-CCP antibodies between groups.

The differences in the mean serum levels of anti-CFFCP and anti-CCP antibodies in heavy smokers compared with never smokers were not statistically significant. Heavy smokers with COPD had significantly higher levels of both autoantibodies than those without pulmonary disease, although almost all patients had serum levels below the cut-off values.

Table 1. Frequency (%) of patients with positive autoantibodies and mean serum levels of antibodies in the study groups.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>NON COPD</th>
<th>COPD</th>
<th>NON COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACPA</td>
<td>0.0%</td>
<td>1.9%</td>
<td>0.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>CFFCP</td>
<td>4.5%</td>
<td>7.4%</td>
<td>1.9%</td>
<td>2.4%</td>
</tr>
<tr>
<td>CFFCP mean ± SD</td>
<td>0.09 ± 0.5</td>
<td>0.10 ± 0.12</td>
<td>0.09 ± 0.5</td>
<td>0.10 ± 0.12</td>
</tr>
</tbody>
</table>

Conclusion: ACPAs are rarely seen in the sera of non-arthritic heavy smokers. However the production of these autoantibodies seems to be higher in heavy smokers patients with associated COPD disease. Larger series...
studies are necessary to confirm these findings and to ascertain the relationship between ACPAs and inflammatory lung disease.

Disclosure: V. Ruiz-Esquide: None; M. J. Gómez: None; V. Peinado: None; J. A. Gómez Puerta: None; M. V. Hernández: None; J. A. Barbera: None; J. Ramírez: None; J. Caiceto: None; I. Haro: None; R. Sannotti: None.

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Anti-Citrullinated Protein Antibodies (ACPAs) in Unaffected Siblings of ACPA-Positive Rheumatoid Arthritis Patients. Lillian Barra1, Elizabeth Wilson1, Matthias Scinocca1, Kelly Summers1, Ewa Cairns2 and David A. Bell.1,2The University of Western Ontario, 1The University of Western Ontario, London, ON, Canada

Background: We have previously reported that ACPA purified from RA patients injected intra-peritoneally (ip) into FcgRIIIB-deficient mice induced inflammatory arthritis; whereas, ip injections of IgG devoid of ACPA from the same RA patients did not. ACPA has been shown to be positive in some unaffected first degree relatives of patients with RA (approximately 2% prevalence in a predominantly Caucasian population and 17% in a North American Native population) and its prevalence increases with the presence of the shared epitope (SE).

Objective: To determine whether unaffected siblings of ACPA positive RA probands have RA features and whether their ACPA can induce inflammatory arthritis experimentally.

Methods: Patients were included if they met ACR criteria for RA, had IgG anti-CCP2>50 and had unaffected siblings (confirmed after assessment by a physician). A questionnaire detailing medical history and risk factors for RA was completed. ACPA was affinity purified using a proprietary synthetic citrullinated peptide (JED) and administered ip to pre-autoimmune FcγRIIB deficient mice. IgG and IgM anti-JED and anti-CCP2 were measured by ELISA. All subjects were tested for the presence of the SE; levels of 27 cytokines were determined by Luminex®.

Results: Twelve families were recruited for a total of 33 siblings (32 were unaffected with RA); there were two monozygotic twins discordant for RA. All subjects were Caucasian. Mean age of RA probands was 60, mean age of disease onset was 44, 10/12 (83%) were smokers, and 10/12 (83%) were in complete remission. Mean age of siblings was 51 and 10/12 (83%) were smokers, which was significantly less than RA probands (p=0.024). 9/12 probands were also IgG anti-JED positive and 7/12 were IgM anti-JED positive. One sibling was IgG anti-JED and anti-CCP2 positive. 10/31 siblings were IgM anti-JED positive; whereas, all normals (n=9) were negative. The monozygotic twins were also discordant for the presence of anti-JED and anti-CCP2. The results of HLA-typing and ip ACPA transfers are pending. Pro-inflammatory cytokines were elevated in RA patients compared to siblings and normals (p<0.05). Siblings did not have higher levels of pro-inflammatory cytokines than normals; however, the levels in smokers were higher than non-smokers (p<0.05).

Conclusions: Siblings of IgG anti-CCP2 positive RA probands had an increase in IgM anti-JED, but barely had IgG anti-JED and IgG anti-CCP2 and also lacked elevation of pro-inflammatory cytokines characteristic of RA. Interestingly, monozygotic twins discordant for RA were also discordant for the presence of anti-CCP2 and anti-JED antibodies. Future work aims to determine whether IgM and IgG anti-JED isolated from these unaffected siblings is pathogenic in a mouse model of inflammatory arthritis.

Disclosure: L. Barra: None; E. Wilson: None; M. Scinocca: None; K. Summers: None; E. Cairns: None; D. A. Bell: None.

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Atherogenic Properties of Rheumatoid Arthritis Plasma: Effect on Cholesteral Transport Genes. Allison B. Reiss1, Iryna Voloshyna1, Michael Littlefield2, Elise Bellilos1, Kristina Belostocki2, Lois A. Bonetti1, Gary C. Rosenblum1 and Steven E. Carsons.1Winthrop University Hospital, Mineola, NY, 2Winthrop University Hospital, Jamaica, NY

Purpose: The risk of cardiovascular (CV) morbidity and mortality is profoundly increased in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). We have reported that SLE patients manifest a pattern of disturbance in expression of genes involved in lipid transport that is atheroma-promoting. When THP-1 human monocytes/macrophages are exposed to lupus plasma, the cholesterol efflux proteins 27-hydroxylase (27-OHase) and ATP binding cassette transporter (ABC)A1 are suppressed while the scavenger receptor CD36 that facilitates cholesterol uptake is augmented, leading to cholesterol overload and foam cell formation (FCF). This study examines whether RA patients exhibit comparably atherogenic plasma. In addition to the genes already mentioned, we look at the nuclear hormone receptor liver X receptor (LXR), which stimulates cholesterol efflux and induces expression of ABC transporters.

Methods: CD36, ABCA1, 27-OHase and LXR expression were evaluated in THP-1 human monocytes and human aortic endothelial cells (HAEC), cell types relevant to atherogenesis. Cells were incubated for 18h and 24h in medium containing 0, 10 or 25% of either RA patient plasma or normal human plasma (NHP). Following the 18h incubation, mRNA was isolated and reverse transcribed. The resulting cDNA was subjected to quantitative PCR using specific primers for each gene. Cellular extracts were prepared for Western immunoblotting after 24h.

Results: Pooled plasma from RA patients in this study population was compared to NHP. The presence of 10% RA plasma upregulated CD36 message by 270.8 ± 88.0% in HAEC (n=3, P<0.001) above NHP (Figure 1).

Conclusion: Traditional CV risk assessment is inadequate in RA. This study demonstrates pro-atherogenic properties of RA plasma that may promote atherosclerosis by increasing vulnerability to cholesterol overload. Demonstration of disrupted cholesterol homeostasis in this select group of patients provides further evidence of the involvement of the immune system in atherogenesis. Our findings may lead to the use of a cholesterol transport gene profile for evaluation of CV risk in this susceptible population.

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Circulating Cytokines Influence the Fetal Growth in Pregnant Women with Rheumatoid Arthritis. Florentien D. O. de Steenwinkel, Johanna M. W. Hazes, Yael A. de Man, Anita C. S. Hokken, Yolanda B. de Rijke and Radboud J. E. M. Dolhain, 1Erasmus Medical Center, Rotterdam, The Netherlands, 2Radboud University Nijmegen Medical Centre, the Netherlands.

Background: High RA disease activity during pregnancy is associated with lower birth weight. Lower birth weight, even within the normal range, has been linked with cardiovascular diseases and metabolic syndromes later in life. Outside pregnancy, active RA is associated with high levels of circulating cytokines.

Purpose: To assess the levels of IL-10, IL-6 and TNFα in pregnant women with RA and to evaluate correlations between these levels, disease activity, and birth weight.

Methods: Current study is embedded in the PARA-study, a prospective study on RA and pregnancy. 134 pregnant RA patients are enrolled in first and second trimester. 33 healthy pregnant women served as control. We analyse data using birth weight standard deviation scores (bwsds), a measure for birth weight adjusting for gestational age and sex of the child. Maternal disease activity is based on DAS28. 1IL-6, 2IL-6 and TNFα are determined by Immulite 1000.

Results: Levels of IL-10, IL-6 and TNFα decrease during pregnancy. Strong correlations are found between these cytokines in first and third trimester and between DAS28 and IL-6, IL-10. First trimester patients with detectable IL-10 (n=12) show a higher disease activity than the IL-10 negative patients, a median DAS28 4.4 (SD 1.2) and 3.6 (SD 1.1) respectively. To diminish the influence of disease activity on birth weight we match the IL-10 positive to an IL-10 negative group. Matching is on disease activity, parity and prednisone use. Mean bwsds is significantly higher (p=0.02) in the IL-10 positive group 0.92 (SD 0.7), than in the IL-10 negative match, 0.15 (SD 0.7). No such association is found in third trimester.

To determine the additional effect of IL-6 to disease activity on bwsds stratification is done. In first trimester we stratify IL-6 and DAS28 in high and low group based on their median, resulting in 4 groups. In the two high DAS28 groups (defined median over 3.8), bwsds is significantly lower in high IL-6 than in low IL-6 (p<0.05). In the high IL-6 group bwsds is −0.19 (SD 1.12) in the low IL-6 group bwsds is 0.36 (SD 0.93). No such association is found in third trimester.

TNNα is stratified the same way. In third trimester, only in patients with low disease activity, bwsds is lower in the low TNNα group than in the high TNNα group, bwsds of 0.05 (SD 0.97) and 0.52 (SD 0.96) respectively (p<0.05). Same trend is seen in the healthy cohort group, although not significant. No such association is found in first trimester or in patients with high RA disease activity.

Conclusion: Circulating cytokines influence fetal growth in pregnant women with RA. In first trimester elevated IL-10 seems to protect against the negative influence of RA disease activity on birth weight, IL-6 seems to amplify this negative influence. Both cytokines create a seesawing effect on birth weight, even within the normal range. Lower birth weight, even within the normal range, has been linked with cardiovascular diseases and metabolic syndromes later in life. Outside pregnancy, active RA is associated with high levels of circulating cytokines.


Background: Evidence is beginning to emerge that there may be susceptibility loci for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) that are common to both diseases.

The aim of this study was to investigate single nucleotide polymorphisms (SNP) that have been reported to be associated with SLE in a UK cohort of RA cases and controls.

Methods: 3,962 RA patients and 9,275 controls were included in the study. Of the SLE loci identified to date (1), eleven SNPs mapping to confirmed SLE loci were investigated. These mapped to the TNFSF4, BANK1, TNIP1, PTTG1, UHRF1BP1, ATG5, JAZF1, BLK, KIAA1542, ITGAM and UBE2L3 loci. Genotyping was undertaken using a Sequenom platform with iPLEX chemistry. Genotype frequencies were compared between RA cases and controls using the trend test implemented in PLINK software. P-values < 0.0045 were regarded as significant after correcting for multiple testing.

Summary of Results: The SNPs mapping to the BLK and UBE2L3 loci showed significant evidence for association with RA (rs2736340, P = 3.0 × 10−4, OR 1.11 95% CI 1.05–1.17; rs5754217, P = 2.4 × 10−3, OR 1.11 95% CI 1.04–1.19). Two other SNPs, mapping to ATG5 and KIAA1542, showed nominal evidence for association with RA (P = 0.02 and P = 0.02, respectively) but these were not significant after applying a Bonferroni correction. Additionally, we found a significant global enrichment in carriage of SLE alleles in RA patients compared to controls (P =
9.1 \times 10^{-7}). Meta-analysis of this and previous studies confirm the association of the BLK and UBE2L3 gene with RA at genome-wide significance levels ($P<5 \times 10^{-8}$). Together, we estimate that, after excluding HLA-DRB1 alleles, the overlapping loci identified so far explain \(\sim 5.8\%\) of the genetic susceptibility to RA as a whole.

**Conclusions:** The findings confirm the association of the BLK and UBE2L3 loci with RA thus adding to the list of loci showing overlap between RA and SLE, which currently include HLA-DRB1, PTPN22, STAT4, TNFAIP3, FCGR2A, PRDM1, IRF5 and PXK.

**References:**

**Disclosure:** G. Orozco: None; S. Eyre: None; A. Hinks: None; W. Thomson: None; J. Worthington: None; A. Barton: None.

**1076**

**Confirmation of the Especial Interaction of Autoimmunity Against Citrullinated α-Enolase with Genotypes Predisposing to Rheumatoid Arthritis.** Antonio Gonzalez1, Ariana Montes2, Rebeca Dieguez-Gonzalez2, Manuel Calaza2, Eva Perez-Pampin2, Antonio Mera2 and Juan J. Gomez-Reino2. 1Hospital Clinico Universitario de Santiago, Santiago de Compostela, A Coruña, Spain, 2Hospital Clinico Universitario de Santiago

**Background:** Autoimmunity against citrullinated α-enolase has been proposed as a major component of the anti-citrullinated proteins response characterizing rheumatoid arthritis (RA) patients with worse spontaneous disease evolution. This claim was based on the extraordinary interaction between the presence of antibodies against the immunodominant peptide of α-enolase (CEP-1) and genetic and environmental susceptibility factors for RA.

**Methods:** DNA and serum samples from 451 patients with RA and 277 healthy controls of Spanish ancestry were obtained. Antibodies to CCP-2 and CEP-1 were measured by ELISA. HLA-DRB1 was genotyped by the sequencing-based-typing method (SBT) and the R620W SNP of PTPN22 by a Taqman genotyping assay. Interactions between factors were evaluated as departures from additivity of the individual effects.

**Results:** Anti-CEP-1 antibodies were detected in 26.8 % of the RA patients whereas 71.2 % were anti-CCP positive. Most of the patients with anti-CEP-1 antibodies, 86.6 %, were also positive in the anti-CCP2 test. This group of patients with RA positive for the two antibodies were disproportionately associated with the SE (Fig. 1), especially with the DRB1*04 allele (not shown), and with the 620W risk allele of PTPN22 (Fig. 2).

**Conclusions:** We have confirmed that autoimmunity against citrullinated α-enolase accounts for a disproportionately large part of the effect of the genetic susceptibility alleles of HLA-DRB1 and PTPN22 among patients positive for anti-CCP antibodies. However, other citrullinated proteins seem to be also important targets in RA pathogenesis. In contrast with a previous report, we did not find any evidence of association with the smoking habit, but we have a small percentage of smokers among our patients.

**Disclosure:** A. Gonzalez: None; A. Montes: None; R. Dieguez-Gonzalez: None; M. Calaza: None; E. Perez-Pampin: None; A. Mera: None; J. J. Gomez-Reino: None.

There was significant evidence of epistasis between the two genetic factors only when considering the patients that were positive for the two antibodies ($p = 0.002$, Fig. 3).

The patients that were anti-CCP+ but anti-CEP-1- showed also association with these susceptibility genetic factors although of a lower magnitude and without significant interaction.

There was not association of any of the subgroups of patients with the smoking habit, probably in relation with the much lower prevalence of this habit among our patients (18.7 %) than in other published series.

**Conclusions:** We have confirmed that autoimmunity against citrullinated α-enolase accounts for a disproportionately large part of the effect of the genetic susceptibility alleles of HLA-DRB1 and PTPN22 among patients positive for anti-CCP antibodies. However, other citrullinated proteins seem to be also important targets in RA pathogenesis. In contrast with a previous report, we did not find any evidence of association with the smoking habit, but we have a small percentage of smokers among our patients.

**Disclosure:** A. Gonzalez: None; A. Montes: None; R. Dieguez-Gonzalez: None; M. Calaza: None; E. Perez-Pampin: None; A. Mera: None; J. J. Gomez-Reino: None.
Background: Plasma CRP levels are associated with disease activity in RA and influence clinical management. CRP SNPs correlate with plasma CRP levels and cardiovascular events. There are large differences in minor allele frequencies (MAF) of some clinically relevant CRP SNPs between Caucasians and AAs.

Objective: To test the hypotheses that, after accounting for other variables, CRP SNPs are associated with radiographic severity or plasma CRP levels in AAs with early RA (< 2 years disease duration).

Methods: Genotyping of CRP SNPs (rs3093058, rs3093059, rs2794521, rs3093061, rs3093062, rs3091244, rs1417938, rs1800947, rs3093066 rs1205, rs2808630), baseline plasma CRP level measurement and baseline radiographs of hands/feet scoring (Sharp/van der Heijde score) were performed on 357 AA RA patients and 150 AA controls enrolled in the CLEAR study. Differences in MAF were analyzed using chi square analysis. Univariable and multivariable negative binomial regression was used to evaluate the association of CRP SNPs with baseline radiographic erosions scores and CRP levels. Other relevant variables examined in univariable analyses were: HLA-DRB1 shared epitope, RF, anti-CCP antibody, age, gender, disease duration, body mass index (BMI), use of DMARDs, biologic agents, and corticosteroids. Those obtaining a p value < 0.1 in the univariable analyses were included as covariates in the multivariable analyses.

Results: 40% of RA subjects had radiographic erosions at baseline. Mean age of RA onset was 49 years, median disease duration was 1.5 years, 82.4% were female, mean BMI was 31.2; DMARD use (77.7%), biologic use (4.0%), and mean baseline plasma CRP was 17.9 mg/L.

There were no significant differences in the distribution of the CRP SNPs between RA cases and controls. In the multivariable analysis, significant associations were found between 5 CRP SNPs and plasma CRP levels: rs3093058 (p = 0.0002), rs3093061 (p = 0.0042), rs3093062 (p = 0.002), rs3091244 (p = 0.0212), rs1205 (p = 0.0425) after adjusting for BMI, age at RA onset, and biologic use (Table 1a). The majority of the observed effect was due to the rs3093064 T and rs1205 T alleles (Table 1a). In the multivariable analysis of radiographic erosions, 5 CRP SNPs demonstrated significance: rs3093059 (p = 0.0096), rs2794521 (p = 0.0238), rs3091244 (p = 0.0026), rs3093066 (p = 0.0090), rs2808630 (p = 0.0081) after adjusting for disease duration and biologic use (Table 1b). The majority of the observed effect was due to the rs2794521 G allele (Table 1b). There was no association between baseline plasma CRP levels and radiographic erosions.

Table 1a. Multivariate analysis of CRP SNPs and CRP levels, adjusted for factors found to be significant in the univariate analysis: BMI, age at RA onset, and biologic use.

Table 1b. Multivariate analysis of CRP SNPs and erosions, adjusted for factors found to be significant in the univariate analysis: disease duration and biologic use.

Conclusions: In AAs with early RA, CRP variants are associated with CRP levels and baseline radiographic erosions independent of other clinical factors. These findings have important implications for assessment of disease activity and risk of erosive disease in AAs with early RA.

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Background: Several polymorphisms in the interleukin-23 receptor gene (IL23R) have shown strong association to autoimmune diseases including ankylosing spondylitis, Crohn’s disease and psoriasis. There have also been some less convincing reports of association with rheumatoid arthritis (RA). These associations are interpreted as highlighting a significant involvement of the IL23/IL17 pathway in disease pathogenesis and, therefore, are of great interest for the understanding of disease pathogenesis.

Methods: We have examined 5 SNPs in the IL23R gene (rs11209026, rs1343151, rs7530511, rs2201841, rs11209032) that were strongly associated with RA and healthy controls revealed no differences in the distribution of some less convincing reports of association with rheumatoid arthritis (RA).

These associations are interpreted as highlighting a significant involvement of the IL23/IL17 pathway in disease pathogenesis and, therefore, are of great interest for the understanding of disease pathogenesis.

Results: One of the SNPs was rejected due to lack of Hardy-Weinberg equilibrium. Comparison of allele frequencies of the other 4 SNPs in patients with RA and healthy controls revealed no differences in the distribution of IL23R allele frequencies. However, there were differences between anti-CCP+ and anti-CCP− patients and between the two subgroups of patients and the controls (Table 1).
RA. The effect was of an increased risk for the anti-CCP positive phenotype in the patients bearing the minor allele of rs1343151, and of an opposed trend for the anti-CCP negative phenotype. These contrasting associations may explain previous results of genetic studies of this locus in RA that have shown a predominant effect of the rs1343151 SNP but some variation between patient cohorts. They also arise the intriguing possibility of their contribution to the differentiation of these two major subgroups of RA patients. This possibility together with the evidence of multiple independent associations in other diseases interest the interest in the dissection of the mechanisms affected by the IL23R polymorphisms.

Disclosure: A. Gonzalez: None; A. Ferreiro: None; E. Perez-Pampin: None; M. Calaza: None; F. J. Lopez-Longo: None; J. L. Marenco: None; J. F. Blanco: None; R. Culla: None; J. Narvaez: None; F. Navarro: None; J. Caute: None; A. R. de la Serna: None; I. Gonzalez-Alvarez: None; G. Herrero-Beaumont: None; J. L. Pablos: None; A. Balsa: None; B. Fernandez-Gutierrez: None; J. J. Gomez-Reino: None.

DNA Damage, T Cell Lymphopenia and Immunosenescence in Rheumatoid Arthritis. Lan Shao1, Hiroshi Fuji2, Jorg J. Gronyen3 and Cornelio M. Weyand4. 1Stanford University School of Medicine, Stanford, CA, 2Tohoku University School of Medicine, Sendai, Japan

Background/Purpose: In RA, immune aging is accelerated by 25-30 years. The immune system is homeostatically controlled; lymphocyte regeneration/proliferation compensates for cell attrition. Lymphocytes age prematurely if they proliferate excessively; imposed by too much loss or too little cell input. We have examined whether RA patients have higher T cell loss than age-matched controls by focusing on naive CD4 T cells which have not yet been recruited into any immune response. Specifically, we have examined signals and molecular mechanisms regulating survival of naive T cells that build the immune reserve.

Methods: Naive CD4 T cells from sero-positive RA patients and demographically matched controls were tested ex vivo for their susceptibility to apoptosis by cytometric analysis of 7AAD and Annexin V with and without T cell receptor stimulation. The load of damaged DNA was quantified by Comet assay and telomeric length was measured by modified qPCR. Repair mechanisms for telomeric and non-telomeric DNA were assessed through the analysis of three enzymatic systems involved in DNA repair/ telomeric maintenance: telomerase and the phosphatase and protein kinases Ataxia-telangiectasia mutated (ATM) and DNA-dependent protein kinase catalytic subunit (DNA-PKcs). DNA damage sensing enzymes were knocked down by si-RNA technology or forcefully overexpressed by transfection.

Summary of Results: Naive human CD4 T cells, both resting and triggered with anti-CD3/CD28, died through the intrinsic death pathways, regulated by pro-apoptotic Bcl-2 family members. RA CD4 T cells, freshly isolated from patients or kept without stimulation ex vivo were highly susceptible to apoptosis with doubling of death rates (28.2% RA T cells vs. 15.1% control T cells; p = 0.01). Increased apoptotic susceptibility coincided with accumulation of DNA double strand breaks (p = 0.0001), suggesting that unrepaird DNA and telomeres shorten survival of naive T cells. Induction of the telomere repair enzyme telomerase was impaired in RA T cells (p = 0.0001). Also, RA T cells insufficiently upregulated the damage-sensing enzyme ATM (p = 0.008) but expressed high levels of DNA-PKcs transcripts and protein (p = 0.03). Forced overexpression of telomerase or ATM and blockade of DNA-PKcs rescued RA T cells from apoptosis (p = 0.008, 0.001 and 0.005, respectively). The shift in apoptotic threshold setting was not a consequence of therapy but was equally present in untreated RA patients (p = N.S., Tx vs. non-Tx).

Conclusions: Naive CD4 T cells in RA patients are under genotoxic stress. Telomeres are shortened and insufficiently repaired and DNA doubles strand breaks accumulate. Repair pathways involving the enzyme ATM are suppressed. Chronic repair activity signaled by the DNA-PKcs pathway sustains cell-intrisn stress signals that harm the cell and lead to apoptosis. Excessive T cell loss strains homeostatic mechanisms and, by depleting the proliferative reserve of long-lived T cells, leads to premature immune aging. Mechanisms regulating intactness of telomeric and non-telomeric DNA should be considered in attempts to reset the dysfunctional immune system of RA patients.

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a marker for macrophages, in the tissues were semi-quantitatively determined by immunohistochemistry using a digital image analyzer.

2) Arthritis was induced by cocktails of anti-type II collagen antibody in CB57/B6 mice (CAIA). Mice were pretreated with an HO-1 inducer, hemin or PBS, followed by induction of arthritis. Macrophoic arthritis score (0–3) and thickness of foot pad were evaluated.

Results: 1) HO-1 expressing cells were significantly more abundant in synovial tissues from RA than those from OA.

Figure 1. Expression of HO-1 proteins in synovial tissue.

While HO-1 expression was localized in the lining layer of OA synovium, analysis of serial sections revealed that HO-1 expression was detected in CD68+ synovial sublining macrophages and CD31+ vascular endothelial cells of RA synovium. Number of HO-1 expressing cells was correlated with those of CD68+ cells (r = 0.81) and those of CD31+ cells (r = 0.78), respectively.

2) Arthritis score and thickness of foot pad were significantly higher in CAIA mice pretreated with hemin than controls. In concordant with the clinical score, more abundant HO-1 expressing cells and angiogenesis were found in synovial tissues of hemin-treated group than controls.

Conclusions: The present study demonstrates HO-1 is associated with angiogenesis which potentially promotes development of arthritis in both human RA and arthritis in animal models, whereas HO-1 suppresses inflammatory responses by the innate immune systems including RA synoviocytes. Both features of HO-1 should be considered in the clinical application for inflammatory arthritis.

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Expanded Cytokine/Chemokine Testing Improves Prediction of Time to Future Diagnosis of Seropositive Rheumatoid Arthritis (RA) in an Age-Dependent Manner. Kevin D. Deane1, Colin I. O’Donnell2, Lezlie A. Derber3, Jess D. Edison1, William R. Gilliland1, Wolfgang Hueber4, Jeremy Sokolove5, Pyanka E. Chandra1, Jill Norris1, William Robinson1 and V. Michael Holers1. 1Department of Medicine, Rheumatology Section, Walter Reed Army Medical Center, Washington, DC, 2Department of Preventive Medicine and Biometrics, University of Colorado Denver, Denver, CO, 3Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, 4Novartis Institutes for Biomedical Research, Basel, Switzerland, 5Stanford Univ School of Med, Stanford, CA, 6Stanford University School of Medicine, Palo Alto, Mountain View, CA, 7Stanford University School of Medicine, Palo Alto, Palo Alto, CA, 8Univ of Colorado School of Med, Aurora, CO, 9University of Colorado Denver, Aurora, CO, 10Walter Reed Army Med Ctr, Washington, DC

Purpose: We have previously shown using testing for 14 cytokines/chemokines that the number of elevated cytokines/chemokines predicted time to diagnosis of future RA in an age-dependent manner. However, with this limited number of cytokines/chemokines, accurate prediction was limited to <5 years prior to RA diagnosis. Herein we examine the effect of testing for increased numbers of cytokines/chemokines (N=48 current versus 14 prior) on the prediction of time to diagnosis of future RA.

Methods: For this analysis we selected 101 stored pre-RA diagnosis serum samples from 51 military cases (69% male, mean age at RA diagnosis 39) that would develop future rheumatoid factor (RF) and/or CCP positive RA. These pre-diagnosis samples were selected based on positivity for anti-CCP and/or 2 or more RF isoforms, an autoantibody profile shown prior to have 74% sensitivity and >96% specificity for future RA. Each of these pre-diagnosis samples was tested for 48 cytokines/chemokines using a magnetic bead-based assay. Cytokine/chemokine positivity was established using additional military post-RA diagnosis case versus matched control samples (N=43 each group), with cutoff levels selected for positivity >90% specific for RA. The time from pre-diagnosis sample collection to RA diagnosis was analysed using mixed-model regression analysis, with predictor variables age-at-diagnosis (stratified by decade) and cytokine/chemokine counts.

Results: The number of elevated cytokines/chemokines (cytokine/chemokine counts) increased as the time of diagnosis of RA approached, with the highest cytokine/chemokine counts present <2 years prior to RA diagnosis. Increasing cytokine/chemokine counts predicted time to diagnosis in an age-dependent manner (Figure). The regression coefficients for age-at-diagnosis (by decade) and cytokine/chemokine counts were respectively betal = -0.975 (p<0.01) and betad = 0.147 (p<0.01). In contrast to prior analysis with 14 markers, testing for 48 markers allowed for accurate prediction of time of onset of future RA more than 6 years prior to diagnosis as well as allowing for finer prediction of time to diagnosis in times <3 yrs prior to diagnosis.

Table 1. Risk of RA associated with EBV Serologies

<table>
<thead>
<tr>
<th>IgG Serology</th>
<th>Unadjusted OR* (95% CI)</th>
<th>Multivariate OR** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCA</td>
<td>1.01 (0.87, 1.18)</td>
<td>1.02 (0.87, 1.18)</td>
</tr>
<tr>
<td>EBNA-1</td>
<td>1.02 (0.87, 1.20)</td>
<td>1.03 (0.88, 1.21)</td>
</tr>
<tr>
<td>EBNA-2</td>
<td>1.03 (0.89, 1.19)</td>
<td>1.02 (0.89, 1.18)</td>
</tr>
<tr>
<td>EA-D</td>
<td>2.68 (0.73, 9.81)</td>
<td>2.88 (0.75, 10.99)</td>
</tr>
<tr>
<td>EA-R-D</td>
<td>0.98 (0.82, 1.16)</td>
<td>0.98 (0.82, 1.18)</td>
</tr>
<tr>
<td>BZLF-1 (+)</td>
<td>0.75 (0.36, 1.59)</td>
<td>0.72 (0.34, 1.55)</td>
</tr>
</tbody>
</table>


*Odds ratio of a 2-fold elevation in the IgG geometric mean titer, or presence of IgG antibody to BZLF-1.

**Multivariate conditional logistic regression model controlling for age and smoking.

Conclusions: Two-fold elevated anti-EBV GMTs, and BZLF-1 positivity, were not associated with future risk of RA, diagnosed a mean of 5.2 years later, in these women.

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Increasing Cytokine/Chemokine Counts Predict Time to Future Diagnosis of Seropositive Rheumatoid Arthritis. All subject samples (N=101 from 51 RA cases) included in this analysis were positive for anti-CCP and/or 2 or more RF isotypes, a autoantibody profile >90% specific for future RA. In regression analysis, time to diagnosis for future RA was the outcome, and cytokine/chemokine counts and age (by decade) were predictor variables. For example, in a subject 45 years-old at assessment, a cytokine/chemokine count of 30 positive predicts a time to diagnosis of future RA of ~2 years.

Conclusions: In pre-clinical case samples positive for autoantibodies highly specific for future RA, increasing cytokine/chemokine counts from a panel of 48 cytokines/chemokines predicts time-to-diagnosis in an age-dependent manner, improving a prior model using 14 cytokines/chemokines. These findings provide insight into the biology of pre-clinical RA as well as provide a methodology for identification of currently arthritis-free subjects at risk for imminent RA who may be candidates for intervention studies.

Disclosure: K. D. Deane: Patent application, 9. The views expressed in this presentation are those of the authors and do not reflect the official policy or the Department of the Army, Department of Defense, or U.S. Government, 9; C. I. O’Donnell: None; L. A. Derber: None; J. D. Edison: None; W. R. Gilliland: None; W. Hueber: Patent application, 9; J. Sokolove: None; P. E. Chandra: None; J. Norris: None; W. Robinson: Patent application, 9; V. Holers: Patent application, 9.

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1 VU University Medical Center, Amsterdam, The Netherlands, 2 VU University Medical Center

Background: Targeting of B cells using rituximab, a monoclonal antibody directed against the B cell marker CD20, is one of the options for treatment of rheumatoid arthritis (RA). Despite the fact that rituximab depletes the B cells in all the patients treated, the fact that not all patients show a favorable clinical response raised questions about the mechanism of action. In order to provide insight in the biological basis of the clinical response to rituximab we evaluated the pharmacological effects of rituximab using genome-wide gene expression technology on whole blood of RA patients.

Methods: RNA was isolated from peripheral blood (PB) samples collected from 13 RA patients before, three and six months after start of treatment with rituximab. Gene-expression profiling was performed using Illumina HumanHT 12-v2 bead chips. Clinical responder status was determined after three and six months using ΔDAS28 (7 responders and 6 non-responders) and EULAR (4 responders, 5 moderate responders and 4 non-responders) response criteria. Hierarchical cluster analysis, Significance Analysis of Microarrays and MetaCore pathway level analysis were used for data analysis and interpretation. Differences in type I IFN response gene expression levels between responders and non-responders were analyzed using Student’s unpaired t-test.

Results: Pharmacogenomic analyses demonstrated that despite the overall decrease in the expression of B cell markers RA patients exhibited interindividual differences in their pharmacological responses towards rituximab therapy. Genes that were differentially regulated between patients after rituximab treatment represented the following biological processes: humoral immunity, cytokotoxic T and NK cell mediated immunity, type I Interferon (IFN) response, IL17 signalling, granulocyte development, chemotaxis and adhesion, and genes related to the ubiquitin proteasomal pathway and Activin A signaling.

When we investigated the pharmacological differences between patients in relation to clinical response we observed that only the cluster of IFN type I genes were correlated with the treatment response to rituximab as defined by ΔDAS28 and EULAR response measurements. Good responders exhibited a selective induction of the expression of type I IFN response genes after three months of treatment, whereas non-responders showed no induction under the influence of rituximab (p=0.0397 and p=0.0478 for ΔDAS28 and EULAR respectively). The increase in IFN type I activity in the good responders correlated with a low baseline level IFN type I activity and returned to baseline values at 6 months after the start of therapy. These results indicate that the pharmacological induced change in type I IFN gene activity correlates with the clinical response of rituximab treatment in RA.

Conclusions: An increase in IFN-response activity during rituximab treatment is associated with a favorable response and may provide insight in the biological mechanism underlying the therapeutic response. Moreover, this information could be used to develop surrogate markers to monitor efficacy of rituximab.

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Heterogeneity in the Bone Marrow B Cell Compartment: Implications for Pathogenesis of Human RA, Arumugam Palanichamy, Chris Cistrone, Jennifer Hossier, Chungwen Wei, James Kobie, Inaki Sanz and Jennifer Anolik. University of Rochester Medical Center

Purpose: Recent studies suggest that the bone marrow (BM) may be an active compartment in the development of autoimmune responses in RA. However the precise phenotype, function and regulation of mature B cells in BM remain largely unexplored in humans. Investigation of BM compartment may provide critical insights into the role of B cells in the pathogenesis of RA.

Methods: B cells in BM and matched peripheral blood (PB) samples from 10 subjects (5 RA and 5 normal controls (NC)) were analyzed by 11 color flow cytometry. For analysis DAPI+, CD3+ T and CD24hi CD38hi early B cells were negatively gated and CD19+ mature B cells were divided into memory subsets (switched (SM): IgD-, CD27+; unswitched (USM): IgD+, CD27+; double negative (DN): IgD-, CD27-) and true naive (N: IgD-, CD27-) population and expression of markers associated with activation and differentiation including FcRHa and B220 were examined. In 2 NC, single B cells from memory subsets were sorted, reverse transcribed, Ig-VH3 genes amplified by nested PCR, sequenced and mutational imprints compared between BM (n=58) and PB (n=57).

Results: Frequency of CD27+ memory B cells in RA BM remained lower compared to matched PB or normal BM (BM: 2.9 v 29.04±13.2 or 25.16+13.0; RA BM v RA PB or normal BM) which reflected in a reduction of SM B cells (7.87±3.0 v 16.86±13.6; RA BM V NC BM). Examination of expanded markers, such as B220 (which is previously shown to be expressed on a majority of CD27+ and a subset of CD27+ B cells) revealed an increased number of B220 expressing BM mature naive and USM cells in RA as opposed to NC (P<0.05). Furthermore elevated levels of B220 expressing cells were noticed in naive and memory subsets in RA PB compared to BM suggesting tissue specific differential expression. Analysis of the FcRHa (an inhibitory FcR homolog) showed a slightly higher number of USM and naive B cells from RA PBL that was FcRHa+ compared to the BM. On the molecular level, Ig gene analysis of memory subsets between BM and PB of normal controls showed no differences in the overall mutational frequencies between BM and PB. However significant changes were noted in the pattern of mutational targeting in Ig-VH framework (FR1-3) and hypervariable regions (CDR1 and 2). Of note, SM B cells from BM exhibited a 2 fold higher mutations in FR2 compared to PB, whereas in USM B cells, a 2 fold increased mutations were seen in CDR1 compared to PB. Both SM and USM had higher numbers of G mutations in hotspot motifs in PB. Mutational analyses of RA BM and PB memory subsets are underway.

Conclusion: Molecular analysis of BM and matched PB hints increased AICDA enzymatic activity in PB revealed by G mutations and tissue specific generation/selection of distinctly targeted B cell subsets. Distinct mature B cells with consistent heterogeneity in RA BM suggest that these cells may...
play a role in the mounting autoimmune responses. Further analyses are needed to elucidate the functionality of these cells.

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**1086**

**High Level of Serum Matrix Metalloproteinase-3 Could Be Implicated in the Pathogenesis of Rheumatoid Intertstitial Lung Disease.** Yoshinobu Koyama1, Kosuke Tsuruno1, Toshiyuki Ota2 and Kenji Fujii1. 1Center for Rheumatic Diseases, Iizuka Hospital, 2Department of Laboratory and Transfusion Medicine, University of Occupational and Environmental Health, Iizuka Hospital, Iizuka, Japan

**Background:** Pulmonary complications such as interstitial lung disease (ILD) are common in patients with rheumatoid arthritis (RA) even in the absence of symptoms. Presentation of ILD has been reported to associate with seropositive and erosive joint disease. Although the etiology of ILD in RA is still unclear, matrix metalloproteinases (MMPs) are believed to play important roles in the pathogenesis of idiopathic pulmonary fibrosis recently. Among them, MMP-3 is known to be one of the most established markers indicating RA activity. However, the correlation between ILD and level of serum MMP-3 in RA has not been well discussed.

**Objectives:** To identify whether serum MMP-3 level has implication for the pathogenesis of ILD in RA.

**Methods:** Newly diagnosed RA patients (n = 86) were enrolled in this study. As a loss of carbon monoxide diffusing capacity (DLCO) is quantitative and one of the most sensitive marker for ILD, correlations between a loss of DLCO and serum indices for diagnosis of RA were evaluated. Before the patients were exposed to medication, the activity of RA (DAS-28) and the level of laboratory data such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), serum amyloid A protein (SAA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibody and %DLCO were evaluated. RA patients were classified in three groups by the %DLCO based on the criteria of the American Thoracic Society (group A: DLCO >70%; normal to slight decrease, group B: 50%<DLCO<70%; moderate decrease, group C: DLCO<50%; severe decrease). Statistical analysis was performed to identify the characteristic pattern of serum markers in the three groups.

**Results:** At the time of diagnosis for RA, the titer of RF and anti-CCP antibody seemed to be no significant influence on a loss of DLCO. Although DAS28, CRP or SAA seemed to be no direct impact on %DLCO, a weak association between high ESR and the loss of DLCO was found (P <0.05). The serum level of MMP-3 was the most significant index correlating with a loss of DLCO (P <0.01). The significant negative correlation between MMP-3 and %DLCO was also detected (P <0.05). If the level of MMP-3>450ng/ml, the relative risk of severe decrease of DLCO (DLCO<50%) was 6.1.

**Conclusion:** Although the elevation of inflammatory markers such as ESR or CRP is known to be associated with the elevation of serum MMP-3, we found the MMP-3 was the most significant index correlating with a loss of DLCO. In our study, titer of RF or CCP antibody seems no significant association with rheumatoid ILD at the time of diagnosis for RA. As MMPs are believed to play important roles in the pathogenesis of idiopathic pulmonary fibrosis recently, our finding suggests that MMP-3 is possible to play an important role in the developing of ILD associated with RA. The novel approach such as the correction of inappropriate expression of MMP-3 would be worth to discuss for preventing progression of ILD in RA patients.

Disclosure: A. Kadi: None; R. Izae: None; J.-P. Jais: None; T. Lequerre: None; O. Vittecoq: None; X. Le Loet: None; P. Dieude: None; G. Chiocchia: None.

**1088**

**In Early RA, Serum Increase of IL-21 Is Associated with Serum Level of IL-6, Autoantibody Secretion, Markers of B-Cell Activation, and Radiographic Progression.** Jacques-Eric Gottenberg3, Pascale Roux-Lombard2, Alain Cantagrel1, Alain Saraux1, Cédric Lukás1, Jean-Michel Dayer2, and Xavier Mariette. 1Brest Hospital, 2Geneva Hospital, 3Montpellier Hospital, 4Strasbourg Hospital, 5Toulouse Hospital

**Objectives:** IL-21, a cytokine mainly expressed by CD4 T cells, was recently suspected to play a pathogenic role in rheumatoid arthritis (RA). However, levels of serum IL-21 have never been assessed in a prospective cohort of early RA. We recently reported that IL-6 and serum markers of B-cell activation were correlated and increased in early RA. IL-6 is a strong inducer of IL-21. We therefore investigated serum IL-21 level in early RA.

**Patients and Methods:** In the ESPRIO early arthritis cohort (at least 2 swollen joints for more than 6 weeks but less than 6 months), serum IL-21 and diagnosis of RA using the new 2010 ACR/EULAR criteria were assessed at enrollment in 723 patients with early arthritis, naïve to corticosteroid and DMARD treatment. Results for serum levels of IL-beta, IL-1Ra, IL-2, IL-4, IL-6, IL-10, IL-17, TNF-alpha, IFN-gamma, MCP-1, BAEFF and markers of B-cell activation (beta2-microglobulin, total IgG, IgA, IgM and free light chains) were previously reported. Radiographic progression was defined as an increase of total Sharp/van der Heijde score (SHS) greater or equal to 1 between inclusion and 1 year.

**Results:**

Higher levels of IL-21 in patients with early RA compared to other early arthritides

There was a trend in favor a higher frequency of detection (21.5% vs 15.3%, p = 0.07) and a higher level of serum IL-21 (391.3 pg/ml [181.9–593.9] versus 191.6 pg/ml [142.5–543.4], p = 0.08) in the 523 patients with early RA versus the other patients with undifferentiated arthritis.

**Conclusion:** Serum baseline IL-21 and autoantibody secretion, markers of B-cell activation and IL-6 in patients with early RA

IL-21 was significantly more frequently detected in RF-positive patients (30.2% vs 7.5% in RF-negative patients, P < 0.0001) and in anti-CCP-positive patients (28.5% vs 13.5%, P < 0.0001). Serum IL-21 could be detected in 33.3% of patients with detectable IL-6 levels compared to 14.6%
in patients without detectable IL-6 (P = 0.02). No association was observed between IL-21 and BAFF, or the other 9 assessed cytokines.

Patients with detectable IL-21 had significantly higher levels of serum beta-2 microglobulin, IgG, kappa and lambda free light chains (P = 0.003, 0.02, 0.0003, 0.0003, respectively).

- Association between baseline IL-21, early RA erosions and radiographic progression

Patients with early RA and erosions at enrollment had significantly more frequently detectable IL-21 (29.6% of patients with detectable IL21 compared to 19.6% in patients without erosions, P = 0.05).

Radiographic progression after 1 year of follow-up was significantly higher in patients with detectable IL-21 at enrollment (mean increase in SHS of 2.9 ± 0.6 compared to 1.3 ±0.2 in patients without detectable IL-21, P = 0.005).

Conclusion: In early RA, increase in serum IL-21 is strongly correlated with autoantibody secretion, B-cell biomarkers levels, IL-6 increase and radiographic progression. This suggests that IL-21 could be the intermediate between IL-6 overexpression and B-cell activation. This study suggests that targeting IL-21 might be a useful therapeutic strategy in early RA.

Disclosure: J.-E. Gottenberg: None; P. Roux-Lombard: None; A. Cantagrel: None; A. Saraux: None; C. Lukas: None; J.-M. Dayer: None; X. Mariette: None.

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Strong Activation of Dopamine Pathway in Synovial Tissue from Rheumatoid Arthritis Patients: New Target of Pathology? Silvia Capellino1, Christine Wolff2, Franca Marino3, Alessandra Luiini1, Marco Cosentino1 and Rainer H. Straub1

1University Hospital Regensburg, Dept. of Internal Medicine I, Regensburg, Germany, 2University Hospital Regensburg, Dept. of Internal Medicine I, Regensburg, Germany, 3University of Insubria, Varese, Italy

Introduction: Synovial cells produce catecholamines in osteoarthritis (OA) and rheumatoid arthritis (RA) patients. Dopamine (DA) is the most abundant catecholamine locally produced during arthritis. However, expression of DA receptors in synovial tissue and role of DA on synovial inflammation are still unknown. Aim of this study is to investigate the presence of DA receptors and DA transporter (DAT) on synovial cells in OA and RA and to study their role on immune response.

Material & Methods: Synovial tissue was collected from 10 OA and 10 RA patients. Control synovial tissue samples were obtained by 5 joint trauma patients. For immunofluorescence analysis D1, D3, D4, D5 and DAT were analyzed alone or in combination with CD45 (lymphocyte marker), CD163 (macrophages) or prolyl-4-hydroxylase (fibroblasts). For real-time PCR, isolated synovial fibroblasts were used. Expression of all dopamine receptors (D1 to D5) was evaluated. For cell culture, mixed synovial cells were treated with SCH23390, a D1-like antagonist. After 24hrs treatment, supernatants were collected and IL-6, IL-8, TNF and IL-10 were measured.

Results: In RA patients a large amount of synovial cells are positive for D1, D3, D4, D5 and DAT compared to OA patients. No positive cells are found in control synovial tissue. Doublelabeling immunofluorescence reveals that mostly fibroblasts are positive for D5 receptor. Quantitative PCR analysis shows a very strong expression of all DA receptors in synovial fibroblasts compared to OA patients. Treatment with SCH23390 inhibits IL-8 both in OA and RA, and IL-6 in RA patients.

Conclusions: These results show strong upregulation of dopamine pathway in RA synovial cells, especially in fibroblasts. The initiation of dopamine pathway is related to chronic inflammation, as neither dopamine receptor-positive cells nor dopamine-producing cells are present in normal synovial tissue. Functional experiments demonstrate that the blockade of D1-like receptors influence cytokines production during arthritis. Taken together, these results suggest that peripheral upregulation of DA pathway in rheumatoid arthritis patients influence the immune response.

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1Chapel Allerton Hospital, Leeds, United Kingdom, 2University of Leeds

Background: We reported that T-cell subset dys-regulation can predict response to treatment in early RA independently of the treatment received as well as relapse in patients who achieved clinical remission. Naive cells frequency were the most significant circulating T-cells in early disease although, a subset of regulatory T-cell expressing CD62L showed significance. Cytokine activated T-cells (IRC) were less informative as systemic inflammation was low. The aim of the current study is to determine whether T-cell subset analysis done within 4 hours of blood collection can predict future diagnostic in early inflammatory arthritis.

Methods: 60 patients with < 12 months inflammatory arthritis (IA) were enrolled; age, sex, CRP, symptom duration, RA, ACPA and shared epitope status were included in the analysis. 6 colour flow cytometry was performed using standard protocols. 36 healthy controls were used to build the age relationship with naive cell frequency. ELISA were used to measure cytokines and chemokines.

Results: Of the 60 IA patients, 25 satisfied the ACR criteria for RA at baseline, the 35 remained classified as undifferentiated (UA). There was no difference at baseline between groups for age and CRP however DAS was higher in the RA group (P = 0.04). There were also no difference between RA and UA for T-cell subsets with the exception of a trend for lower naive T-cell frequency in RA (P = 0.075). In relation with higher CRP, IRC frequency was also higher in RA and the relationship between CRP and IRC was confirmed using both groups (R=0.460, P=0.040). CD25+FoxP3+ Treg were reduced in both groups with no difference in CD62L+Treg. Using ACPA positivity as criteria, ACPA+ disease was associated with a trend for higher CRP (n=42, P=0.099) and lower naive T-cell (P=0.150). In contrast naive cell in ACPA-negative disease were close to healthy controls. IRC were only increased in ACPA-positive disease with normal frequency in ACPA- patients. Similarly, both Treg and CD62L+ Treg were lower and higher respectively in ACPA-negative disease and close to normal in ACPA-negative disease. The levels of all tested cytokines differed in patients compared to healthy controls using both ACR and ACPA as criteria. IL-12 and IL-7 were reduced in both RA (P<0.001) and UA (P<0.001) and MIP-1alpha increased (P=0.02 and P=0.0001). There was no difference between ACPA-positive and negative disease for levels of MIP-1alpha and IL-7 however, IL-12 reduction was more marked in ACPA-negative disease (both P<0.001). The added value of IL-7 and MIP-1alpha for the diagnostic of ACPA-negative RA needs to be further analysed.

Conclusion: The development of RA appears clearly associated with profoundly abnormal immunological parameters at baseline however more closely associated with ACPA-positive disease. Associated with differences in genetic background between ACPA-positive and negative diseases, these data support two divergent pathogenesis, one involving T-cell in ACPA-positive disease. Providing novel diagnostic criteria by transferring flow cytometry protocols and ELISA from research lab to routine hospital services appears promising.

Disclosure: R. Cuthbert: None; R. Parmar: None; J. Nam: None; E. Villeneuve: None; D. Corscadden: None; K. Henshaw: None; P. Emery: None; F. Ponchel: None.

1091

The Development of the ACPA Repertoire Prior to the Onset of Clinical RA. Lotte A. van de Stadt1, Margret de Koning2, Rob J. van de Stadt1, Gertjan Wolbink4, B. A. C. Dijkmans5, Dirkjan van Schaardenburg2, Jan van Breeumen Institute, 2Jan van Breeumen Institute, 3Sanquin Diagnostics, 4Sanquin Research, 5VU Medical Centre, Amsterdam, The Netherlands

Background: Rheumatoid Arthritis is an auto-immune disease in which anti-citrullinated protein antibodies (ACPAs) probably play a pathogenic role. The ACPA response is already expanded before the first symptoms of RA and remains stable thereafter [1].

Objectives: To explore the degree of epitope spreading prior to onset of clinical RA and the pattern of auto-antigen reactivity at the start of the immune response.

Methods: Multiple serial serum samples of 79 RA patients who donated blood before disease onset were available for analysis. 47 patients tested aCCP positive prior to onset of clinical RA. Of these patients a median of 5 (IQR 3–7) sequential pre-RA sera spaced one to two years apart were tested for reactivity to 5 distinct citrullinated peptides in an ELISA. Two fibronogen, 1 vimentin, 1 alpha-enolase and 1 cyclic citrullinated peptide (CCP1) were tested. Reactivity to the 5 corresponding arginine peptides was also tested.

Results: Four anti-CCP positive patients (9%) did not show reactivity to any peptide. In the selected patient samples seroconversion to ACPA was detected in 24 patients (51%). In 14 of these patients (58%) the immune response started with reactivity to one peptide. In four patients (17%) it started with two peptides, in four (17%) it started with three peptides and in two (8%) it started with four peptides. The number of recognised peptides increased
over time (figure 1). Median antibody titers directed to all peptides also increased over time. The ACPA response did not start with reactivity to one particular peptide (figure 2).

Conclusion: ACPA epitope spreading occurs over several years prior to onset of clinical RA. None of the tested auto-antigens is solely responsible for the initial auto-immune response.


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Table 1. Risk for developing RA according to HLA-DRB1 susceptible alleles and smoking†

<table>
<thead>
<tr>
<th>HLA-DRB1/Smoking</th>
<th>No. of cases/controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shared Epitope</td>
<td></td>
<td></td>
</tr>
<tr>
<td>allele</td>
<td></td>
<td></td>
</tr>
<tr>
<td>−/−</td>
<td>218/503</td>
<td>reference</td>
</tr>
<tr>
<td>−/+</td>
<td>45/63</td>
<td>3.28 (1.80–6.00)</td>
</tr>
<tr>
<td>+/+</td>
<td>803/327</td>
<td>6.28 (4.91–8.02)</td>
</tr>
<tr>
<td>+/−</td>
<td>162/46</td>
<td>15.68 (9.04–27.18)</td>
</tr>
<tr>
<td>*0901 allele</td>
<td></td>
<td></td>
</tr>
<tr>
<td>−/−</td>
<td>218/503</td>
<td>reference</td>
</tr>
<tr>
<td>−/+</td>
<td>45/3</td>
<td>3.29 (1.77–6.10)</td>
</tr>
<tr>
<td>+/+</td>
<td>318/162</td>
<td>4.43 (3.34–5.89)</td>
</tr>
<tr>
<td>+/−</td>
<td>59/33</td>
<td>7.73 (3.97–15.06)</td>
</tr>
</tbody>
</table>
†All odds ratio (OR) and 95% confidence intervals (95% CI) were calculated by comparing each group with reference [individuals without HLA-DRB1 risk alleles (*0101, *0404, *0405, *0410, *0901, *0101)] and were adjusted for age and sex. The attributable proportions (AP) was 0.45 (0.19–0.72) for smoking and SE alleles, and 0.17 (0.44–0.79) for smoking and *0901 allele.

Conclusions: Gene-environment interaction of HLA-DRB1 *0901 allele is differ from SE alleles. The DRB1*0405/*0901 heterozygote enhances the susceptibility to both anti-CCP-positive and anti-CCP-negative RA.

Disclosure: S.-Y. Bang: None; H.-S. Lee: None; J.-S. Lee: None; E.-M. Kim: None; K. W. Lee: None; S.-C. Bae: None.

1093

The Smoking-Induced Heat Shock Protein DNAjC6 Is Downregulated in Rheumatoid Arthritis, Caroline Ospelt1, Joanna Stanczyk2, Christoph Kolling3, Renate E. Gay1 and Steffen Gay4. 1Center of Experimental Rheumatology and Center of Integrative Human Physiology, Zurich, Switzerland, 2Center of Experimental Rheumatology and Center of Integrative Human Physiology, Zurich, Switzerland, 3Schulthess Clinic Zurich, Switzerland, 4University Hospital Zurich, Zurich, Switzerland

Background: Previously we had found that the heat shock protein DNAjC6 is upregulated in joints of mice after exposure to cigarette smoke as well as in the synovium of human smokers compared to non-smokers. Smoking has repeatedly been shown to be a risk factor for the development of rheumatoid arthritis (RA) in susceptible individuals. On the other hand nicotine has also been found to have anti-inflammatory properties and smoke exposure delays the onset of collagen-induced arthritis in mice. Also heat shock proteins have been described to protect cells from environmental damage and act as tumor suppressors, as well as to elicit aberrant immune responses. In the current work we aimed at elucidating the effect of increased levels DNAjC6 in joints of smokers and its possible role in pathogenesis of RA.

Material and Methods: Expression of DNAJs, MMPs, IL-6, IL-8 and microRNAs (miRs) in synovial fibroblasts (SFs) and tissues was measured by Real-time PCR. Relative quantification with 18S or EF-1 alpha as reference genes was used to quantify levels of gene expression. Synovial fibroblasts were transfected with siRNA targeting DNAjC6 or siRNA control by nucleoporation.
from a cohort of ~1600 subjects. Kappa testing was performed to assess agreement of CCP tests.

Results: See Table 1: The SENS of CCP for RA by any kit was higher in NAN RA cases compared to SERA cases, and the SENS of CCP+ in RA cases was highest using combined kit testing, although SPEC was lower. In NAN and SERA FDRs, CCP3 and 3.1 kits had higher prevalence of positivity compared to CCP2, with differences most pronounced in SERA FDRS: CCP2+ (2%), CCP3+ (4%) CCP3.1+ (9%). Median levels of CCP were lowest in SERA FDRs.

Table 1. Anti-CCP Kit Test Results (Sensitivity/Specificity, Prevalence, and Titers) in Established RA and Healthy First-Degree Relative (FDR) Cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>CCP2 (kappa*)</th>
<th>CCP3 (kappa*)</th>
<th>CCP3.1 (kappa*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NANRA (N=112)</td>
<td>71%</td>
<td>67%</td>
<td>69%</td>
</tr>
<tr>
<td>SERA Controls (N=100)</td>
<td>99%</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>Seras</td>
<td>99%</td>
<td>95%</td>
<td>91%</td>
</tr>
</tbody>
</table>

NANRA (N=31) Prevalence of CCP positivity: 13/31 (42%) 13/31 (45%) 16/31 (52%) SPEC 97% 98% 96% 95%

Median level (range) [levels calculated only in those positive]

NAN RA 104 (7–134) 315 (38–401) 366 (38–401) N/A
SERA FDR 107 (47–127) 280 (25–401) 327 (30–401)
SERA RA 78 (5–201) 296 (21–420) 286 (23–406)
SERA FDR 22 (5–113) 43 (21–401) 28 (21–401)

Abbreviations: NAN = North American Native cohorts; SERA = Studies of the Etiologies of Rheumatoid Arthritis cohorts; SENS = sensitivity; SPEC = specificity

See Table 2: Test agreement (kappa) was lowest in SERA FDRs, although kappa improved when anti-CCP cutoffs for positivity were set at 3-times established kit cut-offs.

Table 2. Anti-CCP Kit Agreement, By Cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>CCP2 and 3 (kappa*)</th>
<th>CCP2 and 3.1 (kappa*)</th>
<th>CCP3 and 3.1 (kappa*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAN RA</td>
<td>0.81</td>
<td>0.77</td>
<td>0.96</td>
</tr>
<tr>
<td>SERA RA</td>
<td>0.72</td>
<td>0.71</td>
<td>0.93</td>
</tr>
<tr>
<td>NAN FDRs</td>
<td>Standard cut-off**</td>
<td>0.74</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>Cut-off &gt;3x normal**</td>
<td>0.87</td>
<td>0.87</td>
</tr>
<tr>
<td>SERAFDRs</td>
<td>Standard cut-off**</td>
<td>0.19</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Cut-off &gt;3x normal**</td>
<td>0.44</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*Cohen's kappa
**For CCP2 standard kit cut-off >5 units, x3 >15 units, for CCP3, 3.1 standard cut-off >20 units, x3 >60 units

Abbreviations: NAN = North American Native cohorts; SERA = Studies of the Etiologies of Rheumatoid Arthritis Cohorts

Conclusion: In this study CCP kits differ in SENS/SPEC for RA, prevalence in FDRs and cohort-related kit agreement. In particular, in SERA FDRs the differential prevalence of CCP+ by kit and decreased kit agreement may indicate that CCP reactivity in these currently healthy individuals, who have perhaps early RA-specific autoimmunity, is fundamentally different than in established disease, possibly due to differences in autoantigen specificity or autoantibody isotypes. Further study is needed to understand the biologic factors behind these CCP results and the role of these CCP tests for identification of pre-clinical RA-specific autoimmunity.

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Variability of Anti-CCP Kit Testing in Cohorts with and without RA.

Kevin D. Deane1, Kristen Demourelle10, Mark Parish4, Whitney Hilton5, Lauren Harrington4, Lezlie Derber2, Jason R. Koffenbach12, Jan M. Hughes-Austin1, Michael H. Weisman3, Ted R. Mikuls14, James R. O’Dell8, Richard M. Keating1, Peter K. Gregersen2, Jane Buckner3, Irene Smolik9, Donna Hart10, Charles N. Bernstein5, David B. Robinson2, Jill Norris5, V. Michael Holers1 and Hani S. El-Gabalawy11,12. Oak Park, IL, 1Benaroya Research Institute at Virginia Mason, Seattle, WA, 2Department of Medicine, University of Colorado School of Medicine, Aurora, CO, 3North Shore Univ Hosp, Manhasset, NY, 4Univ of CO Schl Med, Aurora, CO, 5Univ of Colorado School of Med, Aurora, CO, 6Univ of Nebraska Medical Center, Omaha, NE, 7University of Colorado Denver, Aurora, CO, 8University of Colorado School of Medicine, 9University of Ottawa, Winnipeg, MB, Canada, 10University of Manitoba, Winnipeg, MB, Canada, 11University of North American Native; SERA = Studies of the Etiologies of Rheumatoid Arthritis Cohorts; SENS = sensitivity; SPEC = specificity

Purpose: Anti-CCP positive (CCP+) subjects without current symptoms of RA are important to identify in order to investigate the biology and evolution of RA development. However, it is unknown how clinically-available CCP tests identify CCP+ in individuals who do not currently have RA. Here we examine the sensitivity (SENS) and specificity (SPEC), prevalence and test agreement of 3 CCP kits in RA cases and currently healthy first-degree relatives (FDRs) of probands with RA.

Methods: CCP testing was performed in a single laboratory using standard protocols for 3 ELISA kits: CCP2 (IgG) (Axis-Shield), CCP3 (IgG) and CCP3.1 (IgG, IgA) (INOVA). Sera from 2 established RA cohorts were tested with each kit: a Cree/Ojibway North American Native (NAN) population from Central Canada, and the RA population from the U.S.-based Studies of the Etiologies of RA [SERA] (Caucasian 85%). The SENS/SPEC of kits for RA were calculated compared to non-RA controls (NAN, N=100; SERA random blood donor controls, N=200). Sera from 2 FDR cohorts (NAN and SERA) were also tested with each kit. The NAN FDRs were selected on the basis of CCP2+ at least once during the course of their longitudinal follow-up in the study. SERA FDRs were randomly selected regardless of CCP+
ACR Poster Session B
Rheumatoid Arthritis Treatment - Small Molecules, Biologies and Gene Therapy: Predicting and Measuring Outcomes, Novel Compounds II
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Clinical Study of Apilimod Mesylate, an Oral IL-12/IL-23 Inhibitor, in Patients with Active Rheumatoid Arthritis. Sarah Krause1, Maartje J.H. Boumans1, Danielle M. Gerlag2, Joelle Lufkin3, Amo W. R. van Kuijk1, Alian A. B. Bakker1, Maarten de Boer4, Beatrijs M. Lodde5, Kris A. Reedquist2, Eric W. Jacobson6, Michael O’Meara7 and Paul P. Tak1; 1Academ Med Ctr/Univ of Amsterdam, Amsterdam, Amsterdam, The Netherlands, 2Academic Medical Center/ University of Amsterdam, 3Academic Medical Center/University of Amsterdam, 4Synta Pharmaceuticals

Objective: Apilimod mesylate (STA-5326) is an oral small-molecule compound. It selectively inhibits production of interleukin (IL)-12 and IL-23, which play an important role in regulating the immune response, and has demonstrated safety and efficacy in a phase I/IIa trial for Crohn’s disease. We investigated the efficacy, safety and tolerability of STA-5326 in patients with active rheumatoid arthritis (RA).

Methods: We performed a phase IIa, single-center, randomized, double-blind, placebo-controlled, proof-of-principle study of STA-5326 in combination with methotrexate (MTX) in 29 patients with active RA (3:1, STA-5326 to placebo). In stage I, 9 patients were treated with STA-5326 100 mg QD and 2 with placebo for 4 weeks. In stage II, 8 patients received STA-5326 100mg QD and 3 placebo for 8 weeks. In stage III, 5 patients received STA-5326 100 mg BID and 2 placebo for 8 weeks, with an optional extension of 4 weeks. Clinical response was assessed according to DAS28 and ACR response criteria. Synovial tissue samples were obtained at baseline and day 29 (stage I/II) or day 57 (stage III), and stained for CD3, CD22, CD55, CD68 and IL-1β by immunohistochemistry, and evaluated by digital image analysis.

Results: STA-5326-treated patients (100mg QD) showed a modest, but statistically significant reduction in DAS28 compared to baseline at day 29 and day 57, but an ACR20 response was reached in only 6% of patients at day 29 and 25% at day 57 (Table). This was similar to the response in placebo treated patients. The increased dosage (100mg BID) did not improve clinical efficacy. Consistent with the clinical results, there were no clear cut changes in expression of synovial biomarkers between baseline and day 29 in stages I/II or day 57 in stage III. While only mild adverse events (mainly gastro-intestinal and dizziness) were observed in stages I/II, in stage III all patients experienced debilitating side-effects (nausea and headache) causing 2 of 5 STA-5326-treated patients to withdraw prior to day 57 and only 1 patient to extend the study until day 85.

Table. Changes in DAS28 and ACR responses in RA patients treated with STA-5326 100mg QD, 100mg BID or placebo

<table>
<thead>
<tr>
<th>Stage I/II, 100mg QD</th>
<th>Day 29 (n = 17)</th>
<th>Day 57 (n = 8, stage II only)</th>
<th>ΔDAS28</th>
<th>ACR20</th>
<th>ACR50</th>
<th>ACR70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(p = 0.004)</td>
<td></td>
<td>-0.41</td>
<td>1 (6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(p = 0.004)</td>
<td></td>
<td>-0.61</td>
<td>2 (25%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(p = 0.004)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(p = 0.004)</td>
<td></td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>(p = 0.004)</td>
<td></td>
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</tbody>
</table>

Conclusion: The results presented here do not support the notion that STA-5326 treatment is able to induce robust clinical improvement of RA.

Disclosure: S. Krause: None; M. J. H. Boumans: None; D. M. Gerlag: None; J. Lufkin: Synta Pharmaceuticals, 1, 3; A. W. R. van Kuijk: None; A. A. B. Bakker: None; M. de Boer: None; B. M. Lodde: None; K. A. Reedquist: None; E. W. Jacobson: None; M. O’Meara: Synta Pharmaceuticals, 1, 3; P. P. Tak: None.

1096

ALD518 (BMS945429), a High-Affinity Anti-Interleukin-6 Monoclonal Antibody, Provides Improvements in Health-Related Quality of Life (HRQoL) in Patients with Rheumatoid Arthritis (RA) and an Inadequate Response to Methotrexate. Vibeke Strand1, Levan Shalamberiya1, Aleksandar Dzanic1,2, Jeffrey Smith3, Robin Mukherjee1, and Philip Mease4; 1Alder Biopharmaceuticals Inc., Bothell, WA, 2Bristol-Myers Squibb, Princeton, NJ, 3Division of Immunology/Rheumatology, Stanford University, Palo Alto, CA, 4Institute of Rehabilitation and Treatment, Niska Banja, Serbia, 5Swedish Medical Center and University of Washington, Seattle, WA, 6Tsitlanadze Scientific Practical Centre of Rheumatology, Tbilisi, Georgia

Background: ALD518 (BMS945429) is a monoclonal antibody directed against IL-6. Rapid and significant ACR responses have previously been demonstrated with ALD518 in patients with RA through 16 weeks1. Here, the authors report HRQoL outcomes from a Phase II randomized controlled trial of intravenous ALD518 in patients with active RA and inadequate responses to methotrexate (MTX).

Methods: This was a 16-week, double-blind, placebo (PL)-controlled study in which patients with active RA were randomized 1:1:1 to ALD518 80, 160 or 320 mg or PL. Two infusions were given (at Day 1 and Week 8), and patients were maintained on stable doses of MTX (≥10 mg/week) throughout. HRQoL was evaluated by the Medical Outcomes Survey Short Form-36 (SF-36). Analyses were performed on the modified intent-to-treat population for patients with data available at the visit of interest (as observed). Minimum clinically important differences (MCID) were 2.5–5.0 for physical and mental component summary scores (PCS and MCS, respectively); 5.0–10.0 for domain scores and MID for SF-6D=0.0412.3.

Results: 127 patients were randomized and treated, and 116 completed the trial (80, 39; 160 mg, 33; 320 mg, 25; PL, 29/33); mean age was 52.3 years; mean RA duration was 6.8 years; and mean tender and swollen joint counts were 26.1 and 16.7, respectively. Mean baseline PCS and MCS were 31.0 and 35.0, 2 and 1.5 standard deviations less than normative values of 50, respectively. At Week 12, improvements in PCS and MCS were 7.1 and 12.3 in the 80 mg group, 6.1 and 7.6 in the 160 mg group and 8.5 and 13.5 in the 320 mg group versus 4.2 and 1.8 in the PL group. At Week 16, in the ALD518 80, 160 and 320 mg groups, respectively, improvements in PCS were 6.7, 6.6 and 8.3 versus 4.7 with PL; improvements in MCS were 10.8, 9.4 and 11.0, respectively, versus 5.0 for PL. Improvements at Week 16 in MCS scores were observed to be greater in the ALD518 80 and 320 mg groups (p=0.05 each) when compared with PL, and ≥MCID. Observed mean changes in BL in bodily pain, general health and social functioning in the ALD518 80, 160 and 320 mg groups exceeded those with PL; and in vitality in the 160 and 360 mg groups and mental health in 360 mg group. Changes ≥MCID were observed in all domains, including SF-6D (Table).

Table: Changes in physical and mental component summary scores from baseline to week 16, stage I only

<table>
<thead>
<tr>
<th>Domain</th>
<th>Physical component summary score</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>31.0 (26.1 – 36.3)</td>
<td>4.7</td>
<td>6.6</td>
<td>9.4</td>
</tr>
<tr>
<td>Role</td>
<td>31.0 (26.1 – 36.3)</td>
<td>6.7</td>
<td>6.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Bodily</td>
<td>31.0 (26.1 – 36.3)</td>
<td>10.8</td>
<td>9.4</td>
<td>11.0</td>
</tr>
<tr>
<td>General</td>
<td>31.0 (26.1 – 36.3)</td>
<td>7.1</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>31.0 (26.1 – 36.3)</td>
<td>4.7</td>
<td>6.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Social</td>
<td>31.0 (26.1 – 36.3)</td>
<td>10.8</td>
<td>9.4</td>
<td>11.0</td>
</tr>
<tr>
<td>Mental</td>
<td>31.0 (26.1 – 36.3)</td>
<td>7.1</td>
<td>12.3</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: ALD518 improves HRQoL in patients with active RA compared to baseline, with improvements in all domains, including SF-6D at Week 16. Results were similar across all treatment groups. Limitations include the small sample size and the short duration of follow-up.

Disclosure: J. Krause: None; J. H. Boumans: None; D. M. Gerlag: None; J. Lufkin: Synta Pharmaceuticals, 1, 3; A. W. R. van Kuijk: None; A. A. B. Bakker: None; M. de Boer: None; B. M. Lodde: None; K. A. Reedquist: None; E. W. Jacobson: None; M. O’Meara: Synta Pharmaceuticals, 1, 3; P. P. Tak: None.

*0–100 scores are presented for each domain to enable interpretation within the context of the MCIDs; shading indicates changes ≥MCID in domain scores and ≥MID in SF-6D; tp ≤ 0.05.
Conclusions: Treatment over 16 weeks with the IL-6 inhibitor ALD518 resulted in improvements in physical, mental and emotional aspects of HRQoL that were clinically meaningful. These improvements were statistically significant in some but not all SF-36 domains, which may be due to large changes in the placebo group. These data support continued evaluation of ALD518 for treatment of patients with active RA and inadequate responses to MTX.

References:

Disclosure: V. Strand: Abbott Laboratories, 5; Alder, 5; AstraZeneca, 5; Biogen Idec, 5; Bristol-Myers Squibb, 5; CanFite, 5; BCBio, 5; Centocor, Inc., 5; Chiesa, 5; Crescendo, 5; Cyprus Biosciences, Inc., 5; Eli Lilly and Company, 5; Eurl; L. Sharrard: Alder Biopharmaceuticals Inc., 2; A. Dimic: Alder Biopharmaceuticals Inc., 2; J. Smith: Alder Biopharmaceuticals Inc., 1; L. Klareskog: Centocor Biopharmaceuticals Inc., 3, 1; R. Mukherjee: Bristol-Myers Squibb, 1; P. Mease: Alder Pharmaceuticals, 5; Biogen Idec, 2, 5; 8; Genentech and Biogen IDEC Inc, 2, 5; 8.

1097

Assessment of Inflammation and Damage by MRI in Established RA Patients with Methotrexate Inadequate Response Receiving Golimumab: Results of the GO-FORWARD Trial. Philip G. Conaghan1, Paul Emery2, Mikkel Østergaard3, Ed C. Keystone4, Mark C. Genovese5, Lars Klareskog6, Wen-Chuan Xu7, Elizabeth C. Hei8, Elizabeth C. Hei8, Fabiola Atzeni6, Giusy Peluso3, G. Biasi1, Mariangela Manfredi5, Piercarlo Sarzi Puttini6, Bruno Lagana2 and Carlomaurizio Montecucco4. 1Department of Clinical and Experimental Medicine, Section of Rheumatology & Internal Medicine, University of Verona, Verona, Italy, 2Division of Clinical Immunology and Rheumatology, S. Andrea University Hospital, “Sapienza” University of Rome, II School of Medicine, Rome, Italy, 3Department of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, 4Division of Rheumatology, University of Pavia, IRCCS S. Matteo Foundation, Pavia, Italy, 5Centocor Research and Development, Inc., 6Karolinska University Hospital, Stockholm, Sweden, 7Stanford University, Sunnyvale, CA, 8University of Toronto, Toronto, ON, Canada.

Background: Previously reported results of the GO-FORWARD trial have shown the beneficial effects of adding the human monoclonal antibody golimumab (GLM) on signs and symptoms and physical function in an established RA cohort with methotrexate (MTX) inadequate response. Magnetic resonance imaging (MRI) provides a sensitive tool for the objective assessment of both inflammation and damage.

Objective: To evaluate the effect of GLM on the inflammation and structural damage detected by MRI in pts with active RA despite MTX.

Methods: Patients (n=444) were randomly assigned to receive placebo (PBO) + MTX, GLM 100mg + PBO, GLM 50mg + MTX, or GLM 100mg + MTX. A subset of study sites capable and willing participated in the GO-FORWARD substudy. All pts from each substudy site were eligible for the substudy (n=240). GLM and PBO were administered via subcutaneous injection q4 wks. At wk16, pts in the PBO + MTX, GLM 100mg + PBO, and GLM 50mg + MTX groups with <20% improvement in both tender and swollen joint counts entered early escape to receive GLM 50mg + MTX, GLM 100mg + MTX, and GLM 100mg + MTX, respectively. The main comparison was between the combined GLM + MTX and PBO + MTX groups. MRI results were adjusted for baseline and within-group differences using the RAMRIS index.

Results: Significant improvements in synovitis and bone edema (ostitis), which are known prognosticators of future structural damage, were observed in the combined GLM + MTX groups versus the PBO + MTX group. The minimal changes in bone erosions observed in all treatment groups (Table), indicated this population would have minimal changes in bone erosion.

Conclusion: Results of MRI assessments showed that GLM + MTX significantly improved synovitis and bone edema (ostitis) relative to PBO plus MTX as early as wk12 and also at wk24. The effect of GLM on bone erosions could not be determined by semi-quantitative scoring in this population of RA pts who had minimal changes in bone erosion during this study.

Table. RAMRIS scores including at baseline and changes from baseline to weeks 12 and 24

<table>
<thead>
<tr>
<th>RAMRIS scores</th>
<th>values are mean–median (interquartile range)</th>
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<tbody>
<tr>
<td>Placebo + MTX</td>
<td>GLM 100mg + PBO</td>
</tr>
<tr>
<td>GLM 50mg + MTX</td>
<td>GLM 100mg + MTX</td>
</tr>
<tr>
<td>Combined GLM + MTX</td>
<td>(n = 72)</td>
</tr>
</tbody>
</table>

Synovitis

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLM 100mg + MTX</td>
<td>7.7 1.5</td>
</tr>
<tr>
<td>PBO + MTX</td>
<td>7.7 1.5</td>
</tr>
<tr>
<td>p value</td>
<td>0.299</td>
</tr>
</tbody>
</table>

Bone erosion (Ostesitis)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLM 100mg + MTX</td>
<td>7.1 2.3</td>
</tr>
<tr>
<td>PBO + MTX</td>
<td>7.1 2.3</td>
</tr>
<tr>
<td>p value</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Given that several sites did not have the capacity to obtain post gadolinium images, synovitis evaluations of the wrist and MCP joints were obtained in 56, 53, 38, and 39 patients in the PBO + MTX, 100 mg + PBO, 50 mg + MTX, and 100 mg + MTX groups, respectively.


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Biomarkers Predictors of Good EULAR Response to B Cell Depletion Therapy (BCDT) in Seropositive Rheumatoid Arthritis Patients. Gianfranco Ferraccioli1, Barbara Tolusso2, Francesca Bobbio Pallavicini3, Elisa Grengese1, Viviana Ravagnani1, Maurizio Bencucci1, Edoardo Podesta2, Fabiola Atzeni6, Giusy Peluso3, G. Biasi1, Mariangela Manfredi4, Piercarlo Sarzi Puttini6, Bruno Lagana2 and Carlomaurizio Montecucco4. 1Department of Clinical and Experimental Medicine, Section of Rheumatology & Internal Medicine, University of Verona, Verona, Italy, 2Division of Clinical Immunology and Rheumatology, S. Andrea University Hospital, “Sapienza” University of Rome, II School of Medicine, Rome, Italy, 3Department of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, 4Division of Rheumatology, University of Pavia, IRCCS S. Matteo Foundation, Pavia, Italy, 5Centocor Research and Development, Inc., 6Karolinska University Hospital L. Sacco, Milan, Italy.

Background: The best predictor of a good response to BCDT in Rheumatoid Arthritis (RA) is IgM rheumatoid factor (RF) positivity. No data are available on which biomarkers can identify the best profile of a good responder to BCDT in strictly seropositive RA patients.

Objective: To define possible biomarkers of a 6th months good EULAR response in RA patients strictly seropositive for one or more autoantibodies.

Methods: One hundred and forty eight RA patients (122 female; disease duration: 13.0±10.6 years) who did not respond to previous DMARDs and/or TNF-α blockers were enrolled in a multicentric Italian study to evaluate the efficacy of BCDT. All the RA patients were seropositive to at least one of the Autoantibodies (AAB) tested: RF IgG, RF IgM, RF IgA, anti-CCP2 and anti-MCV (Axis-Shield and Ortho Diagnostica GmbH). At baseline and every 3 months, demographic, clinical, previous TNF blocker therapies and current therapy with glucocorticoids (GC), immunological and laboratory data, HAQ, DAS score were recorded. Plasma levels of IL6 and BAFF were determined at baseline with ELISA methods. A logistic regression models
was evaluated to determine the influence of the independent variables that reached the value of \( p < 0.05 \) at the univariate analysis, considering the optimal cut-off value resulted by the analysis with receiver operating characteristic (ROC) curves on the dependent variable “good EULAR response at 6th month”. A p value at the 0.05 level was accepted as statistically significant.

**Results:** 74.7% of RA patients were positive for anti-CCP2 antibodies, 79.5% for RF IgG, 63.0% for RF IgM, 53.7% for RF IgA, 88.4% for anti-MCV; 10.1%, 12.2%, 18.2%, 23.0% and 36.5% of RA patients were positive for 1, 2, 3, 4, 5 AAB, respectively. 73.7% of the patients had been treated with one or more TNFa-blockers and 78.9% were on steroid therapy. A EULAR good response was obtained in 23.9% of subjects at the 6th month FU visit.

On multivariate analysis, “EULAR good response to BCDT after 6th months FU” was closely correlated with baseline lymphocytes count \(< 187 \times 10^9/\text{L}(95\% \text{ CI}: 0.78(1.56–21.45))\), RF IgG levels \( > 52.1 \text{ IU/mL} \) (OR \( 95\% \text{ CI): } 4.48 (1.05–19.24) \)), plasma BAFF levels \( < 1011 \text{ pg/mL} \) (OR \( 95\% \text{ CI): } 6.27 (1.13–34.79) \)) and no current steroid therapy (OR \( 95\% \text{ CI): } 0.12 (0.03–0.51) \)).

**Discussion:** Two easy markers (no current steroids and a low lymphocyte count) and two immunological parameters (high RF IgG and low plasma BAFF levels) identify the best responder to BCDT. Data support the original theory that IgG RF could be the main driver of the AAB mediated rheumatoid inflammation.

**Disclosure:** E. Gremese: None; R. K. Wolff: None; J. Ying: None; C. L. Hayden: None; B. C. Sauer: None; R. Curtis: None; D. S. Johnson: None; G. S. Kerr: None; J. S. Richards: None; L. Caplan: None; A. Reimold: None; T. R. Mikuls: None.

### 1100

**CCRI Antagonist CCX354-C in Phase 2 Clinical Development for Rheumatoid Arthritis**


***Purpose***

CCX354-C is an oral drug targeting the chemokine receptor CRCC1, which is instrumental in monocyte/macrophage infiltration into the joints of RA patients. The purpose of the preclinical and clinical studies conducted to date was to determine the safety, pharmacokinetic (PK) and pharmacodynamic (PD) properties of CCX354-C. This paved the way for a Phase 2 clinical trial in patients with RA.

**Methods**

PK/PD requirements for complete inhibition of CCRI-mediated leukocyte infiltration were defined in rabbits (LPS injection into the knee joint) and rats (thioglycollate-induced sterile peritonitis), following oral dosing of CCX354-C. In the Phase 1 program, 84 male or female healthy volunteers (HVs) received either placebo or CCX354-C orally at doses ranging from 1 to 300 mg in the single-dose study and from 3 to 300 mg/day in the multiple-dose study. In total, 70 HVs received CCX354-C. Blood was collected at pre-specified time points for PK and PD analyses. In the 10, 30, and 100 mg dose cohorts, blood was collected for ex vivo analysis of CCRI receptor coverage on blood monocytes using a flow-cytometric assay with Alexa487-CCL3. Based on this information, 24 patients with stable RA were randomized to receive either placebo or daily doses of 100 to 200 mg CCX354-C for 14 days. In total, 18 RA patients received CCX354-C. Safety, PK and potential effects on concomitant methotrexate administration were assessed in this study.

**Results**

CCX354-C blocked chemotaxis of human mononuclear cells towards 17 separate RA synovial fluids. In the preclinical models, leukocyte infiltration into inflamed rabbit knee or rat peritoneum was effectively blocked if plasma levels of CCX354 were maintained sufficiently high to produce 90% CCRI blockade on circulating leukocytes. CCX354-C was well tolerated, displayed excellent oral bioavailability and dose-proportional increases in exposure in all 3 clinical trials conducted in HVs and RA subjects. No serious adverse events or withdrawals due to adverse events have been observed. Plasma levels as high as 5,000 ng/mL and 3,700 ng/mL were reached in the single and multiple-dose studies, respectively. These levels of CCX354 far exceed those required for CCRI blockade (e.g., 90% inhibition (IC\(_{90}\)) of CRCC1-mediated chemotaxis of human monocytes in 100% human plasma required 110 ng/mL). The plasma half-life of the drug approached 7 hours at the 300 mg dose. In the RA study, co-administration of CCX354-C with methotrexate had no influence on the plasma levels of either drug. In the clinical ex vivo PD assay, high levels of receptor coverage (> 90%) at the 12-hour time point were achieved in blood after a single dose of 100 mg CCX354-C.

**Conclusions**

The oral CCRI-specific antagonist CCX354-C showed an excellent safety and tolerability profile in Phase 1 studies in 70 HVs and 18 RA patients. PK and PD data indicate that daily doses of 200 mg CCX354-C produce greater than 90% receptor coverage in blood at all times. No drug-drug interactions were noted between CCX354-C and methotrexate. Based on results from these clinical trials and supportive preclinical studies,
a Phase 2 clinical trial has been initiated in 150 patients with active RA with an inadequate response to methotrexate.


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Change in CRP at 12 Weeks Predicts the Risk of Rapid Radiographic Progression at 2 Years in Methotrexate-Treated Patients with Early Rheumatoid Arthritis. Boulou Harauoui1, Paul Emery2, Neelufar Mossaffarian3, Benoit Guerre4, Hartmut Kupper5, Kashik Patra6 and Arthur Kavanaugh7. 1Abbott Laboratories, Abbott Park, IL, 2Abbott Laboratories, France, 3Abbott Laboratories, Bedford, MA, 4Institut de Rhumatologie, Montreal, QC, Canada, 5University of California-San Diego, La Jolla, CA, 6University of Toronto, Toronto, ON, Canada

Background: In patients with rheumatoid arthritis (RA), radiographic progression is an important contributor to long-term disability. Hence, identifying patients at risk of rapid radiographic progression (RRP) early in the course of disease is an important goal of medical management, as it affects therapeutic decision-making.

Objective: To determine whether change in CRP after 12 weeks of treatment can indicate risk of RRP in patients with early RA.

Methods: We examined data from methotrexate (MTX)-naïve patients with early RA in the PREMIER study, a 104-week, phase III, placebo-controlled trial in which patients were randomized 1:1:1:1 to weekly MTX, adalimumab (ADA) 40 mg every other week, or ADA + MTX. This post hoc analysis evaluated patients from the intention to treat population who had CRP measures at baseline and at week 12, as well as radiographs at baseline and week 104. RRP was defined as an increase of ≥3 units/year in the modified total Sharp score (mTSS) at 52 wks. Patients were categorized on the basis of clinical response (LDAS) at wk 12 and maintained the response at wk 24; “delayed responders” did not meet the clinical target until wk 24. The percentages of patients at 52 wks with LDAS (ΔmTSS < 3.2), clinical remission (ΔmTSS < 2.6), and RRP (ΔmTSS > 3 units/year) in each group were determined.

Results: In both treatment groups, early clinical responses were associated with better long-term outcomes than delayed responses (Table). Achieving early or delayed ACR70 responses did not result in treatment group differences in the proportion of patients achieving LDAS or clinical remission at wk 52. Importantly, delayed responses to MTX resulted in a high proportion of patients with RRP. Indeed, delayed ACR70 responses were associated with an RRP prevalence of 40%. In addition, an early improvement in ΔmTSS > 2 with MTX was associated with low radiographic progression (41% RRP). In contrast, early or delayed clinical responses to ADA + MTX resulted in low proportions of RRP at 52 wks, even for patients with a delayed ACR20 response (11% RRP). Of note, ADA + MTX-treated delayed responders had less RRP than MTX-treated early responders.

Composite Remission Using Clinical, Structural, and Functional Criteria in Patients with Rheumatoid Arthritis (RA) Treated with Etanercept. 


Background: Remission of treatment for patients with RA, can be defined in terms of signs and symptoms (clinical remission), radiographic progression (structural remission), and function (functional remission). The purpose of this analysis was to examine the incidence of "composite remission" using clinical, structural, and functional criteria in patients receiving etanercept (ETN).

Methods: Data from a clinical trial of patients with early RA (ERA) and established RA (TEempo) were retrospectively analyzed for 2-year outcomes. Patients in ERA received ETN 10 mg or 25 mg twice weekly (BIW) or methotrexate (MTX). Patients in TEMPO received ETN 25 mg BIW, MTX, or both. Composite remission was defined as: Disease Activity Score based on 28 or 44 joints with erythrocyte sedimentation rate as the indicator of inflammation (DAS28ESR) < 2.6 or DAS44ESR < 1.6 (clinical remission). Total modified Sharp Score annualized progression rate (TSSRate) < 0 (structural remission), and Health Assessment Questionnaire Disability Index (HAQ-DI) score ≤ 0.5 (functional remission).

Results: Patients had similar baseline clinical characteristics across treatment groups within each study. In the ERA study, mean baseline DAS28ESR scores were 6.3 and mean DAS44ESR scores ranged from 5.2 to 5.3; mean baseline HAQ-DI scores ranged from 1.4 to 1.5. In TEMPO, mean baseline DAS28ESR scores ranged from 6.7 to 6.9, and mean DAS44ESR scores ranged from 5.5 to 5.7; mean baseline HAQ-DI scores ranged from 1.7 to 1.8. Patients achieving composite remission are shown in the table.

Rates of Clinical, Structural, and Functional Remission

<table>
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<tr>
<th></th>
<th>ETN 10 mg (N = 208)</th>
<th>ETN 25 mg (N = 207)</th>
<th>MTX (N = 217)</th>
<th>ETN + MTX (N = 223)</th>
<th>TEMPO (N = 231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTyr 1</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>16/208 (7.8)</td>
<td>20/207 (9.8)</td>
<td>162/217 (74)</td>
<td>18/223 (8.1)</td>
<td>17/231 (7.4)</td>
</tr>
<tr>
<td></td>
<td>1 yr 10/189 (5.3)</td>
<td>17/190 (8.9)</td>
<td>17/197 (8.6)</td>
<td>22/182 (12.1)</td>
<td>18/182 (9.9)</td>
</tr>
<tr>
<td></td>
<td>2 yr 10/187 (5.3)</td>
<td>17/190 (8.9)</td>
<td>17/197 (8.6)</td>
<td>22/182 (12.1)</td>
<td>18/182 (9.9)</td>
</tr>
<tr>
<td></td>
<td>2 yr 14/149 (9.7)</td>
<td>20/170 (11.8)</td>
<td>13/159 (8.2)</td>
<td>19/167 (11.4)</td>
<td>17/163 (10.4)</td>
</tr>
<tr>
<td></td>
<td>2 yr 12/149 (8.1)</td>
<td>18/180 (9.7)</td>
<td>17/159 (7.5)</td>
<td>19/167 (11.4)</td>
<td>17/162 (10.5)</td>
</tr>
</tbody>
</table>

Conclusions: In both trials the rates of composite remission were similar whether using DAS28ESR or DAS44ESR. Similar remission rates were observed in monotherapy arms across all trials, including ETN 10 mg BIW. These data reinforce the value of monotherapy with ETN or combination therapy with ETN and MTX in early and established RA, and demonstrate that up to a third of patients receiving combination therapy with ETN and MTX are able to attain a composite remission using stringent criteria.

Disclosure: M. C. Genovese: None; C. Lukas: None; J. Sibilia: None; B. Fautrel: None; L. Gossec: None; S. Patternotte: None; M. Dougados: None.

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Differential Serum Glycosylation Changes in Rheumatoid and Psoriatic Arthritis—In Response to Anti-TNF Therapy. 

Azita Alavi, Oliver M. FitzGerald, Emily S. Collins, Fraser Edmond, Tarelli Chén, and Teck Ng. Barrens, Douglass J. Veale and John S. Axford. St. Georges University of London, United Kingdom, St. Georges University of London, St. Vincent’s University Hospital, Dublin, Ireland.

Background: Our earlier research into IgG glycosylation changes associated with rheumatoid arthritis (RA) and other rheumatic diseases has indicated the presence of disease specific glycosylation profiles, which in the case of RA have been shown to correlate with disease activity and to revert to normal in pregnancy induced remission. We have since extended these studies using whole serum to assess the direct diagnostic and prognostic potential of serum sugar biomarkers.

Objectives: Evaluate the influence of anti-TNFα therapy on the serum N-glycosylation profile of RA and psoriatic arthritis (PsA) patients and to assess the potential of these sugar biomarkers as a measure of disease response.

Methods: Serum N-glycan profile of a cohort of RA (n=24) and PsA (n=18) patients on anti-TNFα therapy, at baseline and 1 year after starting treatment, were investigated. Enzyme released N-glycans were analysed by MALDI-TOF mass spectrometry. Direct comparisons of the sugar profiles (mass / charge ratio) indicated significant changes in the profile of several biantennary N-glycan structures; distinguished by the presence / absence of galactose (G), fucose (F), bisecting GlcNAc (bis) and sialic acid (A) attached to the core biantennary heptasaccharide [GlcNAcβ1→2Manα1→6] [GlcNAcβ1→2Manα1→3]-Manβ1→4GlcNAcβ1→4GlcNAc. The glycans comprised of G0 (non-galactosylated), G2 (fucosylated-di-
galactosylated), A1G2F (mono-sialylated G2F), A2 (di-sialylated G2) and A2BiHF (fucosylated di-sialylated G2 with a bisecting N-acetylglucosamine).

**Results:** RA and PsA were found to have distinct serum glycan profiles, which underwent significant changes in response to treatment with anti-TNFα (Figure). Levels of G0 decreased significantly in both RA (p = 0.012) and PsA (p = 0.028). This was accompanied by a moderate, but significant, increase in A1G2F (RA; p = 0.018 and PsA; p = 0.010).

Anti-TNFα treatment also resulted in significant increase (19–20%; p < 0.05) in the levels of other glycan structures; G2F and A2G2 in RA, and A2G2BiHF in PsA. The G2F glycan values were found to significantly correlate with changes in diseases activity (DAS-28) in RA patients (n = 24) after one year of anti-TNFα therapy (Pearson; r (22) = 0.421 > p > 0.04).

Interestingly, there were also marked differences between Etanercept and Adalimumab, with the RA Adalimumab treated group showing significantly more pronounced changes in G0 and A2 (PsA cohort too small for analysis).

**Conclusion:** RA and PsA have distinct serum N-glycan profiles which undergo significant changes in response to anti-TNFα therapy. These differential changes which include galactosylation as well as sialylation could be a useful marker of disease response, and may provide a better insight into the different mechanistic action of TNF antagonists currently used for treatment of inflammatory arthritis.

**Disclosure:** A. Alavi: None; O. M. FitzGerald: None; E. S. Collins: None; O. Fraser: None; E. Tarelli: None; C. T. Ng: None; B. Bresnihan: None; D. J. Veale: None; J. S. Axford: None.

**1106**

Double-Blind, Randomized, Controlled, Placebo-Included, Pilot Study Comparing Classical Ayurvedic Medicine, Methotrexate, and Their Combination in RA. Daniel E. Furst1, Manorama M. Venkatraman2, Mary McGann3, P. Ram Manohar4, Cathryn Booth-LaForce4, Dinesh Khanna2, K. G. Raveendran5, Reshmi Sarin1, Anita Mahapatra1, Jidesh Gopinath1 and Yu Cai1. 1Hutchison MediPharma Ltd, Shanghai, China, 2Hutchison MediPharma Ltd, Shanghai, China, 3Hutchison MediPharma Ltd, Shanghai, China, 4University of California Los Angeles Medical School, Los Angeles, CA, 5University of Washington

**Background:** Classical Ayurveda is a 3000 year old complete system of natural medicine, which is used by millions in India and elsewhere. It is a holistic, multifaceted treatment system which includes complex herbal-mineral formulations, dietary and lifestyle modification, and detoxification routines. Its description of rheumatic diseases is similar to modern descriptions of RA features. Classical Ayurveda for RA has hitherto never been tested in an RCT. The aim of this study was to compare classical Ayurveda, methotrexate (MTX), and their combination in a randomized, double-blind, double dummy pilot trial of RA over 36 weeks.

**Methods:** In a pilot study, 43 seropositive RA patients by ACR criteria with disease duration ≤7 years were assigned to the following treatment groups: MTX plus Ayurvedic placebo (n = 14), Ayurveda plus MTX placebo (n = 12), Ayurveda plus MTX (n = 17). DAS28-CRP, ACR20/50/70, and HAQ-DI were obtained every 12 weeks for 36 weeks. Analyses included descriptive statistics, ANOVA, Chi-Square or Student’s t-test. The unique Ayurvedic pharmacological dosage forms and individualization of Ayurvedic therapy. Neither medications nor placebos contained any heavy metals or foreign substances (e.g., steroids) as shown by HPLC.

**Results:** All patient groups and physicians were shown to remain blinded throughout. All 3 groups were comparable (p = ns) at baseline (means): age: 45–47.9 years; RA duration: 1.1–2.7 years; RF+: 71–78%; CCP+: 8–29%; % erosions: 61–69%; DAS28-CRP: 6.5 (high disease activity); CRP: 27–42 mg/dl; female: 83–88%. No statistical differences in response were found except in patient pain VAS (see Table 1 & Figure 1). There were no statistically significant differences in the occurrence of Adverse Events (AE) among groups although the groups using MTX had more frequent AE (MTX: 174; Ayurveda: 112; Combination: 176). No deaths occurred.

**Conclusion:** In this first ever, double dummy, double-blind, randomized, controlled pilot study comparing Ayurveda, MTX, and their combination, MTX and Ayurvedic treatments were approximately equivalent although the trial size and pilot nature of the trial precludes definitive conclusions. AE were numerically but not statistically fewer in the Ayurveda group. These results also show that double-blind, placebo-included, randomized controlled studies are possible when testing classical Ayurvedic versus allopathic treatment in ways acceptable to western standards and to Ayurvedic physicians.

**Table 1. Mean Differences (+/- SD) from Baseline to 36 weeks**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>MTX + Ayurvedic placebo (n = 14)</th>
<th>Ayurveda + MTX placebo (n = 12)</th>
<th>MTX + Ayurveda (n = 17)</th>
<th>p value by ANOVA-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28-CRP (0–10 units)</td>
<td>2.4 (1.5)</td>
<td>1.7 (1.4)</td>
<td>2.4 (1.5)</td>
<td>.379</td>
</tr>
<tr>
<td>Tender Joint Count (max = 28)</td>
<td>13.7 (7.0)</td>
<td>11.3 (8.2)</td>
<td>13.8 (5.2)</td>
<td>.581</td>
</tr>
<tr>
<td>Swollen Joint Count (max = 28)</td>
<td>11.3 (7.7)</td>
<td>8.2 (8.8)</td>
<td>11.6 (7.4)</td>
<td>.492</td>
</tr>
<tr>
<td>Patient’s assessment of pain (100 mm VAS)</td>
<td>44.9 (25.4)</td>
<td>44.9 (14.4)</td>
<td>23.2 (27.9)</td>
<td>.026</td>
</tr>
<tr>
<td>Patient’s global assessment of disease activity (100 mm VAS)</td>
<td>43.8 (23.8)</td>
<td>45.2 (18.7)</td>
<td>25.4 (31.1)</td>
<td>.073</td>
</tr>
<tr>
<td>Ayurvedic physician’s global assessment of disease activity (100 mm VAS)</td>
<td>22.8 (8.6)</td>
<td>15.7 (7.4)</td>
<td>17.8 (13.9)</td>
<td>.223</td>
</tr>
<tr>
<td>Allopathic physician’s global assessment of disease activity (100 mm VAS)</td>
<td>45.1 (13.0)</td>
<td>44.6 (19.4)</td>
<td>46.3 (18.1)</td>
<td>.959</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>12.9 (37.4)</td>
<td>2.8 (41.0)</td>
<td>26.2 (44.8)</td>
<td>.327</td>
</tr>
<tr>
<td>HAQ-DI SCORE</td>
<td>87.1 (72)</td>
<td>86.5 (58)</td>
<td>64.5 (55)</td>
<td>.508</td>
</tr>
</tbody>
</table>

*Includes Intent to Treat Population (ITT) with Last Observation Carried Forward (LOCF)

**Disclosure:** D. E. Furst: Abbott Laboratories, 2, Actelion Pharmaceuticals US, 2, Amgen Inc., 2, BMS, 2, Genentech and Biogen IDEC Inc, 2, Gilead Sciences, Inc., 2, GSK, 2, Nitec, 2, Novartis Pharmaceuticals Corporation, 2, Roche, 2, UCB, Inc., 2, Wyeth, M. M. Venkatraman: None; Mary McGann: None; P. Ram Manohar: None; C. Booth-LaForce: None; D. Khanna: Actelion Pharmaceuticals US, 2, 8, Gilead Sciences, Inc., 2, 8, NIAMS-NIH, 2; K. G. Raveendran: None; R. Sarin: None; A. Mahapatra: None; J. Gopinath: None; P. R. Krishna Kumar: None.
(RA), multiple sclerosis (MS), and respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). The central role that IκB kinase β (IKKβ) plays in regulating NF-κB signaling in response to inflammatory stimuli has made this enzyme as an attractive target for therapeutic intervention. Here we report the identification and preclinical characterization of HM-A42, a potent, selective, and orally bioavailable inhibitor of IKKβ kinase.

**Methods and Results:** HM-A42 is a potent and highly selective inhibitor of IKKβ kinase (IC50 = 0.006–0.058μM) and demonstrated 127-fold selectivity against IKKα kinase. In OVA-induced asthma model in BN rat, HM-A42 treatment led to reduced inflammatory cell number in the BAL fluid with an EDSO of 0.49 mg/kg. In an acute PLP139–151 peptide-induced EAE mouse model of MS, HM-A42 treatment resulted in rapid and substantial regression of EAE relapses. It also significantly reduced EAE clinical score in a dose dependent manner over a 6 week period with an EDSO of 3.7 mg/kg. Histopathological examination of the spinal cords showed that disease scores for inflammation and the area of demyelination were all significantly lower in HM-A42 treated animals versus vehicle control group. HM-A42 was also tested in a murine collagen-induced arthritis model of RA in a prophylactic setting. Oral administration of HM-A42 resulted in significant reduction of disease symptom that continued through the course of treatment with an EDSO of 4.3 mg/kg. In addition, HM-A42 exhibited favorable pharmacokinetic profile including good oral absorption and bioavailability in various species and low potential for CYP450 inhibition. Moreover, from safety point of view, HM-A42 had low affinity for hERG and was negative in Ames test. Its no adverse effect level (NOAEL) was 500 mg/kg in rat, showing a big safety window over efficacy doses in multiple disease models.

**Conclusion:** The administration of HM-A42, a potent and highly selective IKKβ kinase inhibitor, resulted in substantial efficacy in aggressive models of asthma, rheumatoid arthritis (RA) and multiple sclerosis (MS). These studies support further development of HM-A42 in clinical studies.


**1108**

**Impact of Genetic Interactions on Response to Adalimumab Plus Methotrexate Versus Methotrexate Alone: Six Month Results of the OPTIMA Trial.** Alla Skapenko1, Kauschik Patra2, Hartmut Kupper1 and Hendrik Schulze-Koops3. 1Abbott GmbH & Co. KG, Ludwigshafen, Germany, 2Abbott Laboratories, Abbott Park, IL, 3University of Munich, Munich, Germany.

**Background:** Identification of genetic factors that affect rheumatoid arthritis (RA) disease severity and response to treatment can guide personalized therapeutic approaches.

**Objective:** To explore the impact of candidate genetic factors on changes in disease activity following treatment with adalimumab (ADA) plus methotrexate (MTX) or MTX alone.

**Methods:** OPTIMA is an ongoing 78-week study with 26- and 52-week periods. Eligible patients had RA <1 year, DAS28 >3.2, ≥2 SJC, ≥8 TJC. ESR ≥28 mm/h or CRP ≥1.5 mg/dL, and ≥1 of the following: >1 erosion, RF+, or anti-CCP+. MTX-naive patients were randomized to ADA 40 mg every other week + MTX or placebo (PBO) + MTX. Patients were genotyped by allele-specific polymerase chain reaction (PCR) and direct sequencing as needed for the presence of the HLA-DRB1 shared epitope (SE), the FcγRIIb I232T single nucleotide polymorphism (SNP), and the IL4R 150V SNP. Clinical responses to 26 weeks of treatment were examined by genetic background for each allele independently, and in the allele combinations of SE and IL4R.

**Results:** Subjects in the treatment groups demonstrated a comparable distribution of 0, 1, or 2 copies of the HLA-DRB1 SE (PBO + MTX: 37%, 48%, 15%; ADA + MTX: 33%, 49%, 19%; P = 0.28). Likewise, the IL4R alleles, AA, AG, and GG, were distributed similarly between treatment groups (PBO + MTX: 29%, 52%, 20%; ADA + MTX: 33%, 47%, 20%, P = 0.38). The FcγRIIb alleles, however, were dissimilarly appropriated between treatment groups, and no further analysis was conducted on this SNP. Presence of the SE did not affect treatment response to MTX alone (e.g., ACR50 of 40%, 33%, and 29% for 0, 1, or 2 copies, P = 0.23). Conversely, treatment response rates were correspondingly enhanced with increasing copies of the SE in subjects receiving ADA + MTX (ACR50 of 42%, 53%, and 65% for 0, 1, 2 SE, P = 0.004). Thus, presence of 1 copy of the SE afforded a 20% increase in ACR50 for ADA + MTX subjects relative to the PBO + MTX group (P < 0.001), and 2 copies of SE increased ACR50 in ADA + MTX by 36% over PBO + MTX (P < 0.001). Similarly, clinical responses to MTX were not affected by IL4R alleles, while treatment with ADA + MTX was enhanced in subjects with AA or AG IL4R alleles. Examination of treatment responses for the SE and IL4R allele combinations in the PBO + MTX group shows no alteration in responses by genotype, supporting results from analysis of the individual alleles. In the absence of the SE, IL4R genotype affects treatment response to ADA + MTX, while presence of the SE masks effects of the IL4R alleles (table).

**Conclusion:** Clinical responses to adalimumab plus methotrexate are independently affected by both the HLA-DRB1 shared epitope and IL4R alleles, while there was no impact of genotype on the response to methotrexate monotherapy. There appears to be an interaction between the HLA-DRB1 shared epitope and IL4R alleles in response to treatment with adalimumab plus methotrexate.

**Disclosure:** A. Skapenko: None; K. Patra: Abbott Laboratories, 1, 3; H. Kupper: Abbott Laboratories, 1, 3; H. Schulze-Koops: Abbott Laboratories, 5.

**1109**

**Improved Disease Control in Response to Tocilizumab Therapy Is Accompanied by Decreased Platelet Reactivity in Patients with Rheumatoid Arthritis.** Paul A. MacMullan1, Anne M. Madigan1, Paola Bagaglia2, Dermot Kenny3 and Geraldine M. McCarthy1. 1Mater Misericordiae Univ. Hosp. Dublin, Ireland, 2Mater Misericordiae Univ. Hosp, Dublin, Dublin, Ireland, 3RCSCI, Dublin, Ireland.

**Background:** Patients with rheumatoid arthritis (RA) die prematurely of cardiovascular disease (CVD). Platelets play a crucial role in the pathogenesis of CVD. Our previous work demonstrates increased platelet reactivity in patients with active inflammatory arthritis, mediated by the adenosine diphosphate (ADP) pathway [1]. Interleukin 6 (IL-6) plays a key pathogenic role in both inflammation and CVD.

**Objective:** To prospectively evaluate the impact of IL-6 receptor inhibition on platelet function in patients with RA.

**Methods:** This work was conducted alongside a PHASE IV study evaluating IL-6 receptor inhibition with tocilizumab in patients with RA. Patients with seropositive RA who had failed conventional and biologic treatment were recruited. Those receiving anti-platelet therapy or with a history of CVD were excluded. All were treated with intravenous infusions of tocilizumab (8mg/kg) at 4-weekly intervals for a minimum of 6 months. 2 patients discontinued treatment due to dermatitis and raised transaminases, respectively. Pre and post-treatment platelet function analyses were performed using a modification of light transmission aggregometry. The ex vivo aggregation responses to arachidonic acid, collagen, ADP, epinephrine and thrombin receptor activating peptide (TRAP) were tested. Disease activity was measured using standard inflammatory biomarkers (ESR, CRP, fibrinogen) and the internationally validated DAS-28 Score (<2.6=remission, >5.1=severe disease). The direct effect of elevated IL-6 on platelet ADP responsiveness was examined in vitro in samples obtained from 6 healthy volunteers. Platelet-rich plasma (PRP) was incubated with 10mg/ml of IL-6 or vehicle control and the aggregation responses to increasing concentrations of ADP were tested.

**Results:** Pre and post-treatment data from n=6 female patients were analysed. Disease activity improved significantly in the entire cohort (Mean DAS-28 Scores: 5.1+/−0.37 at baseline, and 2.9+/−0.47 at 6 months, p<0.01). Platelet reactivity decreased across a range of agonists in most
benefit in a cohort of patients at high risk of CVD. This is a novel demonstration of a potential cardioprotective effect accompanied by significantly decreased platelet reactivity in patients with refractory RA. The analysis was based on RA patients enrolled in the German biologics register RABBIT at start of an anti-TNF treatment. Remission rates (DAS28 < 2.6) after three years of follow-up were compared between patients enrolled from 2001 to 2003 (n = 841) and those recruited from 2004 to 2006 (n = 1,290). Logistic regression was applied to compare both groups after adjustment for prognostic factors.

**Results:** Crude remission rates at 36 months were significantly higher in patients enrolled between 2004–2006 than in those enrolled between 2001–2003 (26% vs. 19%). Higher rates were observed especially in patients with highly active disease (DAS28 > 6) at baseline (19.7% vs. 12.4% in remission). The increase could not be explained by differences in baseline status.

Although not significant, there was a trend towards an association between worse disease activity at inclusion and the need to start a biologic. Furthermore, patients who failed their first DMARD due to inefficacy, within six months of starting, were more likely to need a biological later on.

**Conclusion:** In this cohort of patients with early IP, ACPA positive patients and those who failed their first DMARD due to inefficacy were more likely to need a biologic during follow-up. These data would support the earlier use of biologics in patients with primary non-response to their first DMARD.

**Disclosure:** S. M. M. Verstappen: None; M. Lunt: None; D. K. Bunn: None; D. G. I. Scott: None; D. P. M. Symmons: None.

1111

**Increasing Chance of Remission in Patients with Rheumatoid Arthritis**

Anja Strangfeld1, Maria Eveslage3, Martin Aringer1, Rainer Dockhorn1, Matthias Schneider6, Joachim Listing1 and Angela Zink2. 1German Rheumatism Research Center, Berlin, Germany, 2German Rheumatism Research Center and Charité University Medicine Berlin, 3German Rheumatism Research Center, Berlin, 4Rheumatologist, Dresden, Germany, 5Rheumatologist, Weener, Weener, Germany, 6Scientific Advisory Board, Düsseldorf

**Background:** During the last years treatment aims in patients with rheumatoid arthritis (RA) have changed. Nowadays, achieving remission is a major goal. We therefore analyzed if the proportion of patients who achieved remission in DAS28 after several years of treatment with biologic agents changed during the last years.

**Methods:** The analysis was based on RA patients enrolled in the German biologics register RABBIT at start of an anti-TNF treatment. Remission rates (DAS28 < 2.6) after three years of follow-up were compared between patients enrolled from 2001 to 2003 (n = 841) and those recruited from 2004 to 2006 (n = 1,290). Logistic regression was applied to compare both groups after adjustment for prognostic factors.

**Results:** Crude remission rates at 36 months were significantly higher in patients enrolled between 2004–2006 than in those enrolled between 2001–2003 (26% vs. 19%). Higher rates were observed especially in patients with highly active disease (DAS28 > 6) at baseline (19.7% vs. 12.4% in remission). The increase could not be explained by differences in baseline status.

The short term treatment response (DAS28 after 6 months) was the most distinct predictor for being in remission after 3 years. Additionally, male patients, younger patients, patients with better functional capacity and patients with a low disease activity at baseline had a higher chance of remission. When adjusting for these factors by multiple logistic regression the beneficial effect for patients enrolled between 2004–2006 was associated with the activity of the RA 6 months after start of treatment (Table).
Patients with an active disease 6 months after start of treatment had a higher chance of remission when they were enrolled in the later period (table). This was not due to more treatment changes in patients registered later (37% vs. 37% patients who started another biologic) but was possibly caused by more frequent use of novel biologics with different mechanisms of action (14% vs. 3%).

### Table 1. Probability of remission after 3 years estimated by multiple logistic regression stratified by enrollment period and level of disease activity after 6 months of the initial treatment.

<table>
<thead>
<tr>
<th>DAS28 after 6 months</th>
<th>2001–2003 remission (%)</th>
<th>2004–2006 remission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3.2</td>
<td>217</td>
<td>427</td>
</tr>
<tr>
<td>&gt; 3.2 &amp; ≤ 4.1</td>
<td>180</td>
<td>308</td>
</tr>
<tr>
<td>&gt; 4.1 &amp; ≤ 5.1</td>
<td>200</td>
<td>271</td>
</tr>
<tr>
<td>&gt; 5.1</td>
<td>244</td>
<td>284</td>
</tr>
<tr>
<td>total</td>
<td>841</td>
<td>1,290</td>
</tr>
</tbody>
</table>

Conclusion: The availability of more treatment options accompanied with changes in treatment strategies increases the chance for RA patients to achieve remission.

Disclosure: A. Strangfeld: None; M. Eveslage: None; M. Aringer: None; R. Dockhorn: None; M. Schneider: None; J. Listing: None; A. Zink: None.

1112

**Influence of ESR on EULAR Response Rates in Patients Treated with Tocilizumab. Results from the German Biologics Register RABBIT.**

Anja Strangfeld,1 Maria Eveslage,1 Joachim Listing,1 Peter Herzer,1 Anke Liehbaber2, Brigitte Krummel-Lorenz2 and Angela Zink3.1 German Rheumatism Research Center, Berlin, Germany. 2German Rheumatism Research Center and Charité Berlin, Berlin, Germany. 3Rheumatologist Frankfurt/M, Frankfurt, Germany. 4Rheumatologist Halle/S, Halle/Saale, Germany. 5Scientific Advisory Board, Munich, Munich, Germany

**Background:** Tocilizumab, a biologic agent newly approved for the treatment of rheumatoid arthritis (RA), is a human anti-interleukin (IL)-6 receptor antibody. Clinical studies reported high response and remission rates in patients treated with this agent. Blocking the IL-6 receptor directly inhibits the production of acute-phase reactant proteins (including CRP) in hepatocytes. CRP or ESR are important components of the disease activity score (DAS) used to measure the effectiveness of a treatment.

We therefore investigated the contribution of the single components of the DAS28 to treatment response in tocilizumab treated patients in daily rheumatologic care.

**Methods:** The German biologics register RABBIT is a prospective cohort study observing all licensed biologic agents applied in RA patients since 2001. In January 2009, tocilizumab was approved in Germany and patients starting this treatment were enrolled in the register. All patients included in the register will be followed up for at least 5 years with regular assessments including clinical status as well as therapy. Disease activity is measured with the DAS28 using the ESR.

**Results:** A total of 6,861 patients were enrolled in the register, 243 patients were treated with tocilizumab. Their mean age at start of tocilizumab was 57 years and the median disease duration 10 years.

Of 119 patients with a three months follow-up, 36% achieved a good and additional 29% a moderate EULAR response. 27% of the patients were in remission (DAS28 < 2.6). After 6 months (n = 55) the proportion of patients reaching a good EULAR response was 49%, a moderate response was reached by additional 29%. 40% of the patients were in remission.

Separating the DAS28 into its components, significant changes in swollen and tender joint counts and patient global assessment were observed in patients treated with tocilizumab. Compared to patients receiving other biologics the decrease in ESR levels was significantly higher (figures).

**Conclusion:** Treatment with tocilizumab improves RA in a substantial proportion of patients, response and remission rates are high. However, when considering EULAR response rates, changes in DAS28 scores or DAS28 remission rates the high impact of ESR changes on these measures has to be taken into account.

**Disclosures:** A. Strangfeld: None; M. Eveslage: None; J. Listing: None; P. Herzer: None; A. Liehbaber: None; B. Krummel-Lorenz: None; A. Zink: None.

1113

**Joint Space Narrowing Has a Stronger Impact on Physical Function Than Joint Erosion: Results from 8-Year Longitudinal Analyses.**

Desiree M. Van Der Heijde1, Robert Landewe2, Benoit Guerette3, Sanjoy Roy4, Kaushik Patra4, and Ed C. Keystone4. 1Abbott Laboratories, 2Leiden University Medical Center, Maastricht, The Netherlands, 3University of Toronto, Toronto, ON, Canada

**Background:** Structural damage, assessed by the modified Total Sharp Score (mTSS), has been shown to be related to physical function. Thus far, it remains unclear to what extent the individual components of the mTSS contribute to long-term physical function.

**Objective:** To characterize the longitudinal relationship between physical function and mTSS in patients with advanced RA.

**Methods:** DE019 was a 52-week, randomized, placebo-controlled trial for the treatment of moderate to severe advanced RA, in which patients with an inadequate response to methotrexate (MTX) were randomized to MTX, adalimumab (ADA) 20 mg every other week (eow) + MTX, or ADA 40 mg eow + MTX. Patients completing the double-blind study were eligible to receive open-label ADA 40 mg eow + MTX for an additional 7 years. This post hoc analysis evaluated the 8-year completers cohort with radiographs at baseline and years 5, 6, and 8. 28-joint Disease Activity Score (DAS28) was used to assess clinical levels of disease activity. Physical function was assessed through the Health Assessment Questionnaire (HAQ). Radiographic damage was assessed using the modified Total Sharp Score (mTSS). Longitudinal generalized linear modeling was used to characterize the dependence of the HAQ on concurrent DAS28, total mTSS, JSN, and JE.
values, following adjustment for baseline age and gender and for concurrent CRP.

Results: Over time, DAS28 was linearly associated with the HAQ (P < 0.001). Similarly, the mTSS was significantly associated with the HAQ throughout treatment duration (P < 0.001). A 1 unit increase in DAS28 and a 20 unit increase in mTSS were associated with 0.22 and 0.044 increases in the HAQ, respectively. A breakdown of mTSS into the individual components revealed that JSN more strongly impacted the HAQ over time than JE, although the significant determinant (P < 0.001 for both) a 20 unit increase in JSN and JE were associated with 0.1 and 0.06 increases in the HAQ, respectively. Interestingly, negative changes in mTSS trended towards lower HAQ values over time.

Conclusions: For patients with advanced disease, long-term physical functioning is associated with both the level of disease activity (DAS28) and the extent of radiographic damage (mTSS). Of the contributors to the mTSS, JSN had a greater impact on the HAQ over time than JE, suggesting that therapies with high potency for inhibiting both the progression of JSN and JE should be considered.


1114


Objective: To evaluate the relationship between changes in inflammation and structural damage detected by MRI and clinical and radiographic outcomes.

Methods: Data from 2 large study populations were evaluated: 1) GO-BEFORE evaluated (MTX)-naïve pts with active RA and 2) GO-FORWARD evaluated pts with active RA despite MTX. In both studies, pts were randomly assigned to receive placebo(PBO)+MTX, GLM100mg+PBO, GLM50mg+MTX, or GLM100mg+MTX. GLM and PBO were administered SC q4wks. A subset of study sites capable and willing participated in MRI substudies. All pts from each site were eligible to participate in the substudies (n=318 GO-BEFORE; n=240 GO-FORWARD). MRIs of pt’s dominant wrist and metacarpophalangeal joints were obtained at baseline and wks12,24,52&104. Results through wk24 are presented here. Images were scored by 2 independent expert readers blinded to image time point or sequence, pt identity, or treatment group. Readers scored synovitis(0–21), bone erosions(0–230), and bone edema(0–69) using Rheumatoid Arthritis MRI Scoring (RAMRIS) system. Preliminary assessments of relationships between RAMRIS system scores and clinical and radiographic measures were done using Spearman correlation coefficients. Disease activity was measured using 28-joint count Disease Activity Score calculated using CRP (DAS28-CRP). Structural damage was measured using the van der Heijde modification of the Sharp (vDHS)-S score.

Results: Analysis results are summarized in the Table. In both studies, statistically significant correlations were observed between baseline synovitis, bone edema, and bone erosion scores and baseline vDHS-S scores; strongest correlations were between baseline RAMRIS bone erosion and baseline vDHS-S scores. Changes in DAS28-CRP scores at wks12&24 correlated with changes in vDHS-S scores. Changes in RAMRIS synovitis, RAMRIS bone edema scores among MTX-adequate responders in GO-FORWARD correlations were generally weak or moderate. Percent changes from baseline in CRP levels correlated with changes in

<table>
<thead>
<tr>
<th>Highest CRP % vs</th>
<th>DAS28 to wks 12</th>
<th>DAS28 to wks 24</th>
<th>vDHS-S to wks 24/28</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP % to wks 12</td>
<td>0.23</td>
<td>0.18</td>
<td>0.14</td>
</tr>
<tr>
<td>CRP % to wks 24</td>
<td>0.02</td>
<td>0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>RAMRIS Δ to wk 12</td>
<td>0.10</td>
<td>0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>RAMRIS Δ to wk 24</td>
<td>0.14</td>
<td>0.09</td>
<td>0.12</td>
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</tbody>
</table>


1115

Optimal Dose Prediction by Pharmacokinetic and Biomarker Response of Subcutaneous Tocilizumab Treatment – A Phase II Study Evaluating the Safety, Pharmacokinetics and Clinical Response in Patients with Rheumatoid Arthritis. Shuji Ohta1, Tomomi Tsuru2, Kimio Terao2, Seiji Mogi3, Midori Suzuki3, Hitoshi Nakashima3, Eiisuke Shono4, Eriko Tarumi4 and Masato Imai5. 1Chugai Clinical Research Center Co., Ltd, 2Chugai Pharmaceutical Co., Ltd, Tokyo, Japan, 3Fukuoka University, 4Med Co LTA PS Clinic, 5Med Co LTA PS Clinic, Fukuoka, Japan, 6Shono Rheumatism Clinic, 7Taga General Hospital, Hitachi, Ltd, Japan 8Taga General Hospital, Hitachi, Ltd, Japan

Background: Interleukin-6 (IL-6) plays pathologic roles in immune-inflammatory disease as rheumatoid arthritis. Tocilizumab is a humanized monoclonal antibody which inhibits IL-6 signal transduction by binding with both soluble and membranous IL-6 receptor. It has been shown IL-6 inhibition therapy by tocilizumab is effective in RA, JIA and Castleman’s disease. Previous data is established by tocilizumab by one hour infusion. Regarding with ease of use, we evaluated the safety, pharmacokinetics, biomarker response and clinical response in patients with rheumatoid arthritis using a tocilizumab new formulation for subcutaneous injection.

Objective: To evaluate the safety, pharmacokinetics and efficacy of tocilizumab subcutaneous injection.

Method: This is an open label, multicenter, dose escalation, combined single dose (Step1) and multiple dose study (3 doses: Step2) with a 6 month extension (Step3) for two of the three treatment arms. Last treatment arm entered into study for 6 month multiple dose study followed by three times repeated administration. Eight, 12 and 12 patients eligible enrolled in cohort 1, 2 and 3, respectively. And they received tocilizumab at 81 mg Q2W treatment in cohort1, 162mg Q2W in cohort2, and 162mg QW in cohort3. Total duration of treatment is 33 weeks for cohort 1and 2, and 27 weeks for cohort 3.
**Result:** No treatment related serious adverse event were observed, and there are also no serious injection site reaction.

Cmax and AUC was 4.9 μg/mL and 444 μg hr/mL at 81mg, and 10.9 μg/mL and 2300 μg hr/mL at 162mg after 1st administration.

CRP is decreased after single dose within first week for all three dose groups. However, the CRP returned to baseline for 81 mg Q2W dose group from Week 2, 3, 5, 7 and 9 at just before the injection. After week 9, dose was switch to 81 mg QW, then mean CRP decreased slowly. At 162 mg Q2W dose level, CRP returned to baseline at the end of week 3. Repeated administration (Step2,3) mean CRP decreased progressively going below ULN and remained over the period of this study. In the 162 mg QW group, the CRP decreased below ULN at the end of Week 1 and remained.

Eight out of 12 patients(66%) serum tocilizumab levels in 162mg Q2W group was maintained above 1 μg/mL at week2, CRP was completely normalized in these patients. The normalization of CRP indicated that tocilizumab administration, which is capable binding of IL-6R, is sufficient to inhibit IL-6 signal.

At week 9, ACR20/50/70 response are 12.5%, 0% and 0% at 81mg Q2W, 75.0%, 16.7% and 16.7% at 162mg Q2W. At the week25, ACR20/50/70 response are 37.5%, 37.5% and 37.5% at 81mg Q2W, 83.3%, 83.3% and 58.3% at 162mg Q2W, 91.7%, 83.3% and 66.7% at 162mg QW, respectively. CDAI at the end of this study is 11.21(18.19 at baseline), 3.76(25.55 at baseline), 2.73(13 at baseline) at 81mg QW, 162mg Q2W and 162 mg QW respectively.

**Conclusion:** Tocilizumab subcutaneous injection is well tolerated upto 162mg QW and is associated with good clinical response both 162 mg QW and QW.

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### 1116

**Preclinical Development of Autologous, Autoantigen-Loaded Dendritic Cells Modified with Bay11–7082 for Tolerizing Immunotherapy in Anti-Citrullinated Peptide Antibody Positive Rheumatoid Arthritis Patients Bearing the HLA-DR Shared Epitope.**

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**Background:** Effective antigen-specific suppression of pathogenic T cells in rheumatoid arthritis (RA) patients might be anticipated to provide durable remission with low toxicity, suitable for suppression of early disease or prevention in individuals at risk. We showed previously that bone marrow derived dendritic cells modified with the irreversible short-acting NF-kB inhibitor, Bay11–7082 (Bay-DC), exposed to arthriogenic antigen, express low levels of MHC class II and costimulatory molecules and transfer antigen-specific suppression of established antigen-induced arthritis in mice, through induction of regulatory T cells. We undertook preclinical development of human autologous peripheral blood (PB) monocyte-derived Bay-DC pulsed with four SE-restricted citrullinated peptides, to establish feasibility and potential toxicity prior to a phase I trial in anti-citrullinated peptide antibody (ACPA+) RA patients.

**Methods:** Under good laboratory practice conditions, we elutriated monocytes from 250 ml PB from RA patients, then generated DC in the presence of 10% human serum, GM-CSF, IL-4, and varying concentrations of Bay11–7082. We compared Bay DC and DC for surface markers and intracellular indoleamine 2,3-dioxogenase (IDO) expression by flow cytometry, the capacity to stimulate T cells in mixed lymphocyte responses, and the ratio of tryptophan to kynurenine in culture medium by HPLC. We tested DC proliferation in vitro and in vivo, as well as standard cytotoxicity, mutagenesis and clastogenesis assays. In vivo toxicity was tested by s.c. adoptive transfer of peptide-loaded human Bay-DC into SCID mouse recipients followed by hematolgy, biochemistry and organ patholagy.

**Results:** From 9 RA patients, we elutriated an average of 10 ± 2.5 × 10⁶ (mean ± SEM) monocytes and generated 3 ± 1.3 × 10⁵ Bay-DC from 250 ml PB. Addition of Bay11–7082 dose dependently reduced expression of DC surface HLA-DR and CD86 and their capacity to stimulate allogeneic T cells. IDO expression and catabolism of tryptophan to kynurenine increased in Bay-DC after lipopolysaccharide exposure. SCID mice recipient of peptide-loaded Bay-DC showed no hematological effects or organ pathology relative to saline-treated mice after 1 week or 1 month, except a reduction in blood glucose from 7.5 to 5 umol/L.

**Conclusions:** Bay-DC with poor T cell costimulatory capacity and activity of the immunosuppressive enzyme IDO in response inflammation, can be feasible generated from PB monocytes of RA patients. Transfer studies suggest Bay-DC loaded with SE-restricted citrullinated peptides have innate immune effects on glucose metabolism. A phase I trial of citrullinated antigen-specific immunotherapy using autologous Bay DC in ACPA+ RA patients is in progress to test safety, and effects on innate and adaptive immunity.

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### 1117

**Prediction of One-Year Response to Etanercept and Methotrexate in Rheumatoid Arthritis Patients in TEMPO.**

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**Background:** The ability to predict which rheumatoid arthritis (RA) patients (pts) will respond to biologic therapy is a challenging but important endeavor. TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) data were used to evaluate moderate to severe RA pts initiating etanercept (ETN) with or without methotrexate (MTX) to derive and validate a decision tree that would predict which pts would have a good response after 1 year of therapy, determine which pts could have a treatment decision made at week (wk) 12, and identify pts who needed additional time on therapy.

**Methods:** Pts were included if they had disease activity scores (DAS28) at 52 (or 48) wks of therapy with either ETN 25 mg twice weekly with MTX (n = 193) or ETN alone (n = 172). Pts were classified as responders if they had low disease activity (DLA) at wk 52, i.e., DAS28 ≤ 3.2. Pts who dropped out for safety reasons were excluded. Classification and Regression Trees (CART) software [Salford Systems], which identifies variables affecting the outcome and partitions data accordingly, was used to develop and validate decision trees on clinical and demographic variables, stratified by TEMPO treatment arm. Tenfold cross-validation was used to guard against overfitting.

**Results:** Sixty percent (115/193) of pts in the ETN + MTX arm (Figure 1) and 39% (67/172) of pts in the ETN arm (Figure 2) achieved LDA response at wk 52. As shown in Figure 1, LDA was predicted by DAS28 at wk 12 and 53% (92/172) of pts were able to be classified as responders, 25% (49/193) of pts with 88% (43/49) accuracy; and 3) uncertain likelihood of response at wk 52. As shown in Figure 1, LDA was predicted by DAS28 at wk 52 and 10.9% (11/106) of pts with 100% (11/11) accuracy (98/121 correctly classified as responders); 2) non-responders, 25% (49/193) of pts with 88% (43/49) accuracy; and 3) uncertain likelihood of response for the remaining 12% (23/193) of pts.

In the ETN only arm, results were similar (Figure 2). Response to therapy in this cohort was predicted by DAS28 at wk 12 and tender joint count at wk 8. By wk 12, 53% (92/172) of pts were able to be classified as responders, 39% of pts as non-responders (67/172), and the remaining 8% were not able to be classified well.
Conclusion: Most TEMPO pts initiating ETN with or without MTX could be classified within 12 wks of starting therapy as likely to have a good response or not at wk 52. However, approximately 10–15% of pts needed additional time on therapy to decide whether to continue ETN. This preliminarily validated decision tree needs replication and may help physicians in deciding whether to continue or change anti-TNF therapy at 12 wks.


1118
Predictors of Response to Rituuximab in Patients with Active Rheumatoid Arthritis and Inadequate Response to Anti-TNF Agents or Traditional DMARD.

Objective: Identifying early predictors of response to biological agents is important for both the individual patient and health economics. The aim here was to identify clinical variables that are easily assessed in clinical practice associated with a major response to rituximab (moderate-to-good EULAR response, according to DAS28 values) in patients with active rheumatoid arthritis (RA) and inadequate response to anti-TNF agents or traditional DMARD.

Methods: Rituuximab (2 X 1 g, two weeks apart) was administered to 108 patients in four different Spanish centres. The primary efficacy endpoint was the percentage of patients who achieved a major response at six months. Potential predictors of a major response were identified using multivariate binary logistic regression models.

Results: Ninety-eight patients (91%) received RTX after the failure of ≥1 anti-TNF agent (number of previous anti-TNF agents used: 1.4 ± 0.8). Primary or secondary inefficacy, rather than development of side effects, was the reason for the anti-TNF failure in the majority of cases (70.2%). Seven of these patients had also failed to respond to other biological agents (abatacept or tocilizumab). In ten patients (9%), RTX was administered as a first-line biological therapy due to contraindications for anti-TNF therapy. The mean age of patients (86 women) was 58.4 ± 12.2 years and the median disease duration was 9.8 ± 9.4 years (range: 1–36). Rheumatoid factor (RF) and/or anti-CCP antibodies were positive in 84.3% of cases; only 15.7% of patients were seronegative for both antibodies. The mean number of previous DMARDs used was 2.9 ± 1.4. RTX was administered alone in 31 (28.7%) patients and in combination with one DMARD (mainly methotrexate or leflunomide) in the other 77 (71.3%) cases. The mean DAS28 score at baseline was 5.8 ± 1.1 and the mean HAQ value was 1.500 ± 0.67. At six months of treatment 75.9% of patients achieved a major response (good: 24.1%; moderate: 51.8%). Comparing the clinical features at baseline between patients who did or did not achieve a major response, significant differences were found in RF and anti-CCP positivity, as well as in the number of failed anti-TNF agents prior to RTX.

While RTX delivers clinical benefit in seronegative patients, the presence of RF and/or anti-CCP consistently enriches clinical responses. In the multivariate analysis the only predictors of a major response were anti-CCP antibodies (p = 0.045) and the number of previous anti-TNF agents used (p = 0.028). Thus, patients with an anti-CCP titre > 300 were 3–4 times more likely to achieve a major EULAR response (OR: 3.38, 95% CI: 1.025 – 11.17). By contrast, those patients who had failed to respond to more than one anti-TNF agent had a 72.5% lower probability of achieving a moderate-to-good EULAR response (OR: 0.275; 95% CI: 0.087 – 0.871) than did patients who had only failed to respond to one such agent.

Conclusion: Anti-CCP titre and a lower number of previously-failed TNF blockers can help select the best candidates for RTX therapy in patients with RA.

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1119
Proof of Concept Study for a Potent p38 MAPK Dual Action Inhibitor BMS-582949 in Subjects with RA Receiving Concomitant Metrotrexate.

Background/Purpose: BMS-582949 is a potent and selective dual action inhibitor of p38 MAPK. It inhibits both p38 kinase activity and activation in cells. Previous studies showed BMS-582949 to be well tolerated in both healthy and RA subjects for up to 28 days.

Methods: This 16 week, randomized, double-blind, placebo-controlled study consisted of a 12-week treatment, and a 4-week follow-up period. One hundred and twenty one (121) subjects with active RA, with an inadequate response to MTX, were randomly assigned in a 1:1 ratio to once daily oral treatment with placebo or BMS-582949 300 mg. Efficacy, safety, PK and PD endpoints were monitored throughout the study. The ACR20 response at Day 85 was defined as the primary endpoint. Secondary endpoints were ACR50/70, ACR-N, HAQ-DI and changes in DAS28 on Day 85.

Results: Sixty and 61 subjects with RA, treated concomitantly with MTX, received BMS-582949 300 mg and placebo once daily. The proportion of BMS-582949 300 mg treated subjects (53.3%) who achieved an ACR20 response at Day 85 (Week 12) was significantly higher than the placebo group (32.8%) (p = 0.036). At Day 85, the mean treatment group difference for DAS28, favoring active arm, was –0.83 (95% CI: –1.29, –0.36). The study also met its secondary endpoints in changes in DAS28, ACR-N and HAQ-DI scores.

<table>
<thead>
<tr>
<th>Endpoints at Week 12</th>
<th>ACR20 (%)</th>
<th>ACR50 (%)</th>
<th>ACR70 (%)</th>
<th>Mean Change from Baseline in DAS28</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-582949 (N=60)</td>
<td>53</td>
<td>15</td>
<td>2</td>
<td>–1.81</td>
</tr>
<tr>
<td>Placebo (N=61)</td>
<td>33</td>
<td>10</td>
<td>7</td>
<td>–0.98</td>
</tr>
</tbody>
</table>

BMS-582949 led to a decrease in CRP, with the active treatment group having a larger median decrease in hs-CRP compared with placebo at week 12. Additional post-hoc analyses revealed that efficacy appeared to be related to exposure (Cmin) and that higher responses were observed in patients with baseline CRP levels >10 mg/L.

There were 5 discontinuations due to an AE; 2 subjects treated with BMS-582949 (diarrhea, and fatigue) and 3 subjects treated with placebo (ALT elevation, presyncope and panniculitis). No deaths were reported, and only 1 serious adverse event (SAE) of polyarthritis deterioration (placebo) was reported. Most AEs were mild to moderate in intensity. No significant increase in the frequency of subjects developing abnormal liver function tests, elevated CPK, dizziness and skin rashes was seen compared to placebo.

Conclusions: BMS-582949 300 mg significantly increased the proportion of ACR20, DAS28, and HAQ-DI responders in patients with active RA who had an inadequate response to MTX compared to placebo. BMS-582949 was safe and well tolerated in subjects with RA who were receiving concomitant therapy with MTX. The effect on biomarker (CRP) and clinical efficacy observed with this dual action p38 inhibitor indicate that this approach to...
targeting the p38 MAPK pathway may be possible for the treatment of inflammatory diseases.

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1120

Radiographic Progression Correlates Well with Patient-Reported RAPID3 Disease Activity Levels in Methotrexate (MTX)-Naive Patients with Early Rheumatoid Arthritis (RA): Insights from the AGREE Study.

Background: Structural damage early in (RA) can translate into long-term disability; however, assessment of radiographic progression is not routinely performed in clinical practice. Consequently, a patient-derived instrument that correlates with radiographic progression would be helpful in therapeutic decision making. Here we investigate the relationship between X-ray progression and patient-derived RAPID3 disease activity, as well as therapeutic decision making. Here we investigate the relationship between instrument that correlates with radiographic progression would be helpful in
terms disability; however, assessment of radiographic progression is not

Methods: With early (<2 years) RA and poor prognostic factors were randomized (1:1) to ABA plus MTX or placebo plus MTX (MTX alone)
in the double-blind Phase III AGREE study1. X-ray progression at Year 1 assessed by change in Genant-modified Sharp total score (TS) was a
corresponding endpoint. In this post-hoc analysis, mean change in TS from baseline to Year 1 was analyzed by RAPID3-assessed disease activity (high
>12; moderate 12–6; low <6–3; near-remission <3) and HAQ-DI score (high >1.5; moderate 0.8–1.5; low 0.5–0.8; remission <0.5) at Year 1. Data are for patients who had data available at the visits of interest (as-observed).

Results: Patients had high baseline disease activity (mean DAS28 [CRP] 6.3) and short disease duration (6.5 months); TS was 7.1. HAQ-DI was 1.7 and
86.1% of patients were seropositive for RF and anti-CCP2. In the ABA
plus MTX and MTX alone groups, respectively, 215 and 217 patients had data available for the X-ray+RAPID3 analysis, and 215 and 218 had data available for the X-ray+HAQ-DI analysis. In the MTX alone group, greater
X-ray progression was seen with RAPID3-assessed high/moderate disease activity at Year 1 compared with patients in low activity or near-remission; for the ABA plus MTX arm, greater progression was seen for patients in high disease activity compared with moderate/low disease activity states (Figure). Regardless of RAPID3 state, smaller changes from baseline in TS were seen for patients treated with ABA plus MTX versus MTX alone. Similar trends were seen for HAQ-DI scores: mean TS changes for patients with high, moderate, low HAQ-DI and remission, respectively, were 0.53 (n=33) vs
1.64 (n=46), 0.69 (n=55) vs 0.92 (n=71), 0.39 (n=29) vs 0.77 (n=28), and
0.59 (n=98) vs 0.97 (n=73) for ABA plus MTX versus MTX alone.

Conclusions: Radiographic progression in patients with early RA receiving
MTX showed good agreement with RAPID3 assessed disease activity state. The association between RAPID3 and radiographic progression with
ABA plus MTX was not seen to the same degree, as TS change was consistently low regardless of RAPID3 driven disease activity state. Similar
results were observed with HAQ-DI. The agreement observed between
RAPID3 and X-ray progression in MTX patients supports the use of the
RAPID3, based on patient-reported outcomes, as a guide to management of
RA in routine care.


1121

REGN88/SAR153191, a Fully-Human Interleukin-6 Receptor Monoclonal Antibody, Reduces Acute Phase Reactants in Patients with Rheumatoid Arthritis: Preliminary Observations from Phase I Studies.

Background: Targeting the p38 MAPK pathway may be possible for the treatment of inflammatory diseases.

Methods: Three phase 1, randomized, double-blind, placebo-controlled trials were conducted; RA patients received REGN88 or placebo (PBO) with concomitant methotrexate. Study 801 evaluated single ascending doses of 50, 100, or 200 mg REGN88 or PBO (n=15). In study 803, patients with active RA were administered parallel single doses of 50, 100, or 200 mg REGN88 or PBO (n=32). Study 802 evaluated patients with RA receiving 5 weekly or 3 biweekly doses of 50, 100, 150, 200 mg REGN88 or PBO (n=60). High-sensitivity C-reactive protein (hsCRP), serum amyloid A (SAA), erythrocyte sedimentation rate (ESR), hepcidin and interleukin-6 (IL-6) were measured to assess pharmacodynamic response. Safety and tolerability were evaluated by combining data from all 3 studies (REGN88 n=83; PBO n=24).

Results: Suppression of hsCRP, SAA, hepcidin and ESR was observed in a dose-dependent manner in REGN88 groups; at day 8, a single 200 mg dose of REGN88 was associated with median reductions of 91.7% in hsCRP, 92.5% in SAA, 66.2% in hepcidin and 33.8% in ESR. For hsCRP, reductions were observed through day 15 (p<0.005 vs PBO). Reductions in inflammatory markers were paralleled by increases in serum IL-6 levels that peaked at day 8 after the 200 mg dose (median increase 647%) before returning to baseline by day 22. Four patients withdrew due to adverse events; 3 on
REGN88 and 1 on PBO. The most commonly reported adverse events were upper respiratory infection, increase in alanine aminotransferase (ALT) levels, and RA flare. One patient on REGN88 50 mg in Study 803 reported a serious adverse event of RA flare requiring hospitalization, as per Russian standard of care. During a maximum 16-week exposure/follow-up period, 1 patient on REGN88 and PBO groups had a transient elevation of ALT
3–5 times upper limit of normal (ULN), and 1 patient who received REGN88 had ALT >5x ULN. Also during this period, 5 patients on REGN88 and 0 on PBO had a transient decrease in neutrophil count (0.5–1.0 ×10^9/L), no patients had neutrophils <0.5 ×10^9/L. No changes in neutrophils or liver enzymes were associated with adverse clinical outcomes.

Conclusion: IL-6Ra inhibition with SC REGN88 in active RA patients resulted in dose-related reductions in hsCRP, SAA, ESR and serum hepcidin with concomitant increases in IL-6. The clinical significance of these changes has not been evaluated. SC REGN88 was well-tolerated in these patients, with no dose-limiting toxicities observed. REGN88 is being investigated in a Phase 2 program in RA and ankylosing spondylitis.

Results from a Phase I Study of MLTA3698A, a Novel Anti-Lymphotoxin-a Monoclonal Antibody: Safety, Tolerability and Biologic Activity in Patients with Active Rheumatoid Arthritis. Brandi Emu1, Diana Luca1, Carolyn Offutt1, June Grogan1, John Davis2, Bernadette Rojkovich1, Marma Williams1, Memia Tang1 and June Lee1. 1Budai Igualmasrendi, 2Genentech, Inc., South San Francisco, CA, 3Genentech, Inc.

Background: Lymphotoxin (LT)-α is a cytokine transiently expressed by subsets of activated lymphocytes that are implicated in the pathogenesis of RA/autoimmunity including T-helper cells (Th1, Th17) and B cells. The biologic agent MLTA3698A is a humanized monoclonal antibody directed against the LTα cytokine. LTα, and has several distinct mechanisms of action, including blocking soluble and membrane-bound LTα from interacting with its receptors and selectively depleting subsets of activated immune cells. We report a randomized, double-blind, placebo-controlled trial designed to assess safety, tolerability, pharmacokinetics, impact on biomarkers, and preliminary evidence of biologic activity after single and multiple doses of either intravenous or subcutaneous administration of MLTA3698A in RA patients.

Methods: The CAPRA-1 study compared the novel formulation (3–10 mg/day, average of 6.8 mg/day) in 288 patients to conventional immediate release prednisone over 12 weeks, the CAPRA-2 study compared 5 mg/day MR prednisone + DMDAR in 350 patients to placebo + DMDAR over 12 weeks. An open-label extension of CAPRA-1 provided safety data for up to 12 months. In addition, the effect of MR prednisone on the Hypothalamus-Pituitary-Adrenal (HPA) axis was investigated in a CRH test subgroup study, as part of CAPRA-1 (62 tests in 28 patients under treatment with MR prednisone or IR prednisone). All Adverse Events (AEs) from these studies were collected by neutral questioning in a standardized manner.

Results: The incidence of serious adverse events (SAEs) and adverse events (AEs) in all treatments was low and comparable between MR prednisone and IR prednisone and comparable to the placebo arm, with more AEs related to RA signs and symptoms (arthralgia and RA flare) in the PBO arm than in the MR prednisone arm. In all studies MR prednisone was shown to be safe and well tolerated. The most frequent AEs are shown in Table 1. CRH tests in patients on treatment with MR prednisone or IR prednisone showed no evidence for a different effect on the HPA axis.

Conclusions: The biologic profile of LTα is a promising dose escalation of MLTA3698A or placebo to doses (0.3, 1.0, 2.0, 3.0, 5.0 mg/kg; n=30) in patients with stable RA. The second stage of the study consisted of a multiple dose escalation phase in which patients with active RA (on stable regimen for RA, with ≤5 swollen joints, >5 tender joints and CRP ≥1.0) received 3 doses of MLTA3698A or placebo every 2 weeks (1.0, 3.0, 5.0 mg/kg; n=35). Safety and tolerability were assessed in patients in both single and multiple dose escalation stages. CXCL-13, a downstream chemokine in LTα signaling pathway, was measured prior to and after dosing. Clinical activity endpoints were measured at multiple time points in patients in the multiple dose escalation stage.

Results: Baseline characteristics of patients who received MLTA3698A or placebo were similar with respect to demographics and RA disease status (median age of 57 years, median CRP of 1.21, and median DAS28-CRP of 4.21). The majority of adverse events were mild to moderate. There were no serious adverse events or dose-limiting toxicities in the trial. There were no serious infections or notable changes in peripheral lymphocyte subsets. Pharmacokinetic profiles were linear and clearance was independent of dose. Substantial reductions in levels of serum CXCL-13 were observed. Preliminary evidence of clinical activity was seen in the multiple dose stage as evidenced by ACR20, ACR50, and ACR70 response rates as well as reduction in DAS28CRP scores and C-reactive protein (CRP) levels. We report a randomized, double-blind, placebo-controlled trial designed to assess safety, tolerability, pharmacokinetics, impact on biomarkers, and preliminary evidence of biologic activity after single and multiple doses of either intravenous or subcutaneous administration of MLTA3698A in RA patients.

Safety of a Novel Modified-Release (MR) Prednisone Formulation: Results of the “Circadian Administration of Prednisone in Rheumatoid Arthritis” (CAPRA) Studies. Frank Buttgereit1, Jacek Szechiński2, Gisela Döring3, 4, Christine Knauer2, 3, Michael Graf4, 5 Saag6, Greg Rieke7. 1Charité University Med-Berlin, Berlin, Germany, 2Horizon Pharma GmbH, Mannheim, Germany, 3Horizon Pharma GmbH, Mannheim, Germany, 4Horizon Pharma Inc., Northbrook, IL, 5Med. Uni. Department of Rheumatology, Wroclaw, Poland, 6Merck KGaA, Schlosspark-Klinik, Unimed, Berlin, Germany, 7University of Alabama-Birmingham, Birmingham, AL

Conclusion: Two large phase 3 clinical trials established a favorable safety profile of low-dose chronotherapy with MR prednisone. MR Prednisone has been shown to reduce duration of morning stiffness and to be more effective than placebo with regard to standard RA outcome parameters.

Safety, Pharmacokinetics and Pharmacodynamics of ALD518 (BMS-945429), a High-Affinity Monoclonal Antibody Directed Against IL-6R (IL-6) Administered by Subcutaneous Injection: A Phase I Trial. Sepehr Shakib2, Barbara Francis3 and Jeffrey Smith1. 1Alder Biopharmaceuticals Inc., Bothell, WA, 2Royal Adelaide Hospital, Adelaide, Australia

Background: ALD518 (BMS-945429) is an asialo, humanized anti-IL-6 monoclonal antibody with a half-life of ~30 days. ALD518 binds to IL-6 with high affinity, preventing interaction and signalling mediated via IL-6R. Rapid and significant treatment responses have been demonstrated with intravenous (IV) ALD518 in patients with RA1; here we report the pharmacokinetics and pharmacodynamics of subcutaneous (SC) ALD518 in healthy subjects.

Methods: In this Phase I, double-blind, placebo-controlled study, 27 subjects were randomized 2:1 to receive a single dose of ALD518 or placebo in the following groups: ALD518 50 mg SC, ALD518 100 mg SC or
ALD518 100 mg IV (n=6 active and n=3 placebo per group). The primary objective was to assess safety of SC ALD518 versus placebo over 12 weeks. Plasma concentrations of ALD518 and serum concentrations of C-reactive protein (CRP) were assessed as secondary objectives. Assessments were performed daily in Week 1 and then on Day 10, Week 2, 4, 6 and 8, and then monthly to Week 12. The study was unblinded at Week 12, and ALD518 subjects were monitored to Week 24.

Results: Over 24 weeks, there were no deaths or serious AEs, and no withdrawals due to AEs. Nearly all subjects (89%) experienced AEs, which were mild or moderate except one event of severe gastroenteritis in the ALD518 SC 50 mg group. Injection site reactions occurred in 5/12 ALD518 SC subjects, 1/6 placebo SC subjects and 1/3 placebo IV subjects (none were reported in ALD518 IV subjects). These were mild except one case of moderate erythema and pruritis in the ALD518 100 mg SC group. Increases in direct bilirubin and neutrophil counts below the limit of normal were more common in subjects receiving ALD518 than placebo; all were CTC Grade 1 or 2. The half life of ALD518 was similar across all groups (mean range: 30.7–33.6 days). The median T_max of ALD518 was longer after SC (~1 week) than after IV administration (~end of infusion). The PK of SC ALD518 was dose-proportional in terms of AUC and C_max at doses of 50 mg and 100 mg. Based on AUC_0-28 (day*µg/mL) of 237, 452 and 764 for the ALD518 50 mg SC, 100 mg SC and 100 mg IV groups, respectively, the bioavailability of ALD518 was ~60% for the SC versus IV groups. Subjects receiving ALD518 experienced rapid and sustained reductions in serum CRP (Figure).

Conclusions: In this Phase I study, the anti-IL-6 antibody ALD518 was well tolerated when administered in a single SC dose; injection site reactions were generally mild. The bioavailability of SC ALD518 was ~60% of IV ALD518, and the half life was ~30 days. Rapid and significant reductions in CRP were observed, which were sustained over 24 weeks of assessment.

Reference:

Disclosure: S. Shakib: IDT Pharmaceuticals, 5; B. Francis: CPR Pharma Services Pty Ltd, 1, 3, IDT Australia Ltd, 1, 3; J. Smith: Alder Biopharmaceuticals Inc, 1, 3.

1125

Selective Activation of Naturally Occurring Regulatory T Cells (Tregs) by the Monoclonal Antibody (mAb) BT-061. Markers of Clinical Activity and Early Phase II Results in Patients with Rheumatoid Arthritis (RA). Anatoly Rudnev1, Sukanya Ragavan2, Christina Trollmo2, Vivianne Malmstroem2, Christian Becker2, Helmut Jonuleit2, Vibeka Strand3, Silke Aigner4, Niklas Czeloth5, Benjamin Daelken2, Andre Engling2, Helga Koch2, Gabriele Niemann1, Frank Osterroth1, Christoph Uhreke1, Andrea Wartenberg-Demand1, Olga Ershova4, Tatiana Sotnikova2 and Alexander Orlov-Morozov1.

Biotest AG, 2; B. Daelken: Biotest AG, 1; Andre Engling: Biotest AG, 1; H. Koch: Biotest AG, 1; G. Niemann: Biotest AG, 3; F. Osterroth: Biotest AG, 3; A. Uherek: Biotest AG, 5; A. Wartenberg-Demand: Biotest AG, 3; O. Ershova: Biotest AG, 2; T. Sotnikova: Biotest AG, 2; A. Orlov-Morozov: Biotest AG, 2.

Background: Response to B-cell depletion with rituximab in rheumatoid arthritis is variable. Several factors have been shown to have predictive value at baseline, such as circulating memory B cell numbers, synovial expression of CD79a, as well as persistence of circulating plasma blasts and synovial plasma cells after treatment. These data suggest it may be possible to select patients for therapy based on parameters indicating greater active B-cell involvement. However, parameters identified to date are not accurate and many are not suitable for routine clinical practice. We therefore studied a new serum cytokine that has a hypothetical role in B-cell function in RA to better understand the determinants of response, and as convenient biomarkers.

Patients and Methods: 85 patients were treated with rituximab and clinical response was evaluated at 6 months by EULAR criteria. Relapse was determined by rise in DAS28 ≥ 0.6. Serum was tested for BAFF (n=85 at baseline, 29 serial samples), IL6 (n=46) and IL10 (n=26) by ELISA (R&D Systems). B cell subsets were measured by 6-parameter flow cytometry using CD19, CD20, CD3, CD14, CD27 and CD38. The strength of correlations was tested by Spearman’s rank test and relationships between cytokine titres and categorical variables by either Mann Whitney U test or log transformation and Student’s t test, as appropriate.

Results: Baseline Cytokines and disease activity: IL6 was correlated with CRP at baseline as expected (R = 0.591, p < 0.001) but there was no relationship of BAFF or IL10 with DAS28 or CRP, nor any interrelationship between cytokines.

Cytokine changes after therapy: 6 months after B cell depletion, BAFF significantly increased (p<0.001) and IL-6 significantly reduced (p=0.001) but there was no substantive or significant change in IL10. As expected, IL-6 naturally occurring Tregs are essential for maintaining normal immune homeostasis in healthy individuals. In patients with autoimmune diseases reduced numbers or functional impairment of Tregs has been observed. A humanized agonistic mAb, BT-061 selectively activates Tregs. It binds to a unique epitope of the CD4 molecule, leading to induction of Treg specific signaling events. While freshly isolated and resting Tregs do not inhibit T cell proliferation, pre-treatment of Tregs with BT-061 leads to suppression of CD4 and CD8 T effector cell proliferation, reduction of pro-inflammatory cytokines and a moderate increase in the anti-inflammatory cytokine TGF-beta.

To further assess the potential of BT-061 to modulate immune responses, in vitro studies with synovial fluid derived mononuclear cells from patients with active RA were performed. Addition of BT-061 at concentrations between 0.01 and 50 micro g/mL to isolated CD4-positive cells derived from the highly inflammatory milieu of RA synovial fluid suppressed proliferation as well as IFN-gamma production following antigen-specific stimulation.

In a Phase I/IIa trial in patients with psoriasis, a single dose of BT-061 resulted in PASI 50/75 responses for up to 90 days at doses of 0.5, 2.5, 10, 20, 125 mg iv and 12.5, 25 mg sc. A Phase Ila, multicenter, randomized placebo-controlled trial with BT-061 monotherapy was performed in 96 patients with active RA and inadequate responses to one or more traditional DMARD despite 3 months or more of treatment. Patients were randomized to 12 treatment groups: from 1.25, 25 mg sc 0.5, 2.5 mg iv, once weekly for 6 weeks: 6 patients received BT-061 and 2 received placebo in each group. Initial data analysis confirmed the clinical activity of BT-061 by ACR20/50/70 responses in a meaningful proportion of patients despite the short duration of therapy. No major safety signals were identified. Final analyses of safety and efficacy data are ongoing and will be presented.

Phase II multiple dose trials with BT-061 are underway to further evaluate the clinical benefit of BT-061 in patients with RA and psoriasis.


1126


1 Leeds, West Yorkshire, United Kingdom, 2 Chapel Allerton Hospital, Leeds, United Kingdom, 3 Leeds Teaching Hospitals NHS Trust, Leeds, West Yorkshire, United Kingdom, 4 University of Leeds, Leeds, West Yorkshire, United Kingdom

Background: Response to B-cell depletion with rituximab in rheumatoid arthritis is variable. Several factors have been shown to have predictive value at baseline, such as circulating memory B cell numbers, synovial expression of CD79a, as well as persistence of circulating plasma blasts and synovial plasma cells after treatment. These data suggest it may be possible to select patients for therapy based on parameters indicating greater active B-cell involvement. However, parameters identified to date are not accurate and many are not suitable for routine clinical practice. We therefore studied a new serum cytokine that has a hypothetical role in B-cell function in RA to better understand the determinants of response, and as convenient biomarkers.

Conclusions: In this Phase I study, the anti-IL-6 antibody ALD518 was well tolerated when administered in a single SC dose; injection site reactions were generally mild. The bioavailability of SC ALD518 was ~60% of IV ALD518, and the half life was ~30 days. Rapid and significant reductions in CRP were observed, which were sustained over 24 weeks of assessment.

Reference:

Disclosure: S. Shakib: IDT Pharmaceuticals, 5; B. Francis: CPR Pharma Services Pty Ltd, 1, 3, IDT Australia Ltd, 1, 3; J. Smith: Alder Biopharmaceuticals Inc, 1, 3.
was higher in non-responders at 6 months ($p<0.001$). Levels of each cytokine correlated between baseline and 6 months after therapy (BAFF, $R = 0.735$, $p<0.001$; IL-6, $R = 0.541$, $p<0.001$; IL-10, $R = 0.675$, $p = 0.008$).

**Predictive value of baseline cytokines:** Baseline DAS28, its components, and CRP/ESR did not differ between responders and non-responders. Most importantly, levels of IL-6 and BAFF were predictive of response at baseline; in responders BAFF was higher ($p = 0.03$) and IL-6 was lower ($p = 0.014$).

**No relationship of serum cytokines with B cell depletion or repopulation:** No relationship was identified between IL6, IL10 or BAFF levels at baseline or follow up and baseline B-cell number, degree of depletion at 2 or 6 weeks or rate of repopulation of any subset.

**Conclusions:** Serum BAFF and IL-6 titres are predictive of response to rituximab in rheumatoid arthritis and may have utility as biomarkers. However, this effect appears to be independent of B cell depletion, and the hypotheses that BAFF inhibits B cell depletion, as suggested by animal models, is not supported by these results. These relationships may differ in the synovium or other tissues.

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### 1127

**Serum Markers Associated with Structural Damage in Methotrexate Naive Rheumatoid Arthritis Patients Treated with MTX in Combination with Placebo or Glumumab, a Human Anti-TNFa Monoclonal Antibody.** Carrie Wagner2, Dion Chen1, Hsiao Kwan Fan1, Sudha Viswanathan1, Elizabeth C. Hsaia1, Paul Emery3, Roy M. Fleischmann4, Michael Mack1 and Mahboob U. Rahman1.

**Methods:** In the GO-BEFORE study, 637 patients were randomly assigned in a 1:1:1:1 ratio to receive placebo (PBO) + methotrexate (MTX), GLM 100 mg + PBO, GLM 50 mg + MTX, or GLM 100 mg + MTX. Sera were collected at wks 0, 4 and 24 from a subset of approximately 100 patients for testing select markers of inflammation and bone/cartilage metabolism and protein profiling using multi-analyte profiles (Rules Based Medicine). The baseline, absolute change and percent change from baseline to wk 4 in these markers were compared between the PBO+MTX and the combined GLM group [GLM+MTX (50 mg + 100 mg) and GLM+PBO groups] against changes in van der Heijde modified Sharp (vdh-S) score, erosion score and joint space narrowing score at wks 28 and 52. Significant biomarker correlations with efficacy in the GLM group relative to the PBO treatment group were evaluated using Fisher Z-transformation test.

**Results:** Biomarker correlations with structural damage endpoints were predominantly observed for only the PBO+MTX treatment group and very few correlations were observed with GLM treatment. With PBO+MTX treatment, only IL-1ra was observed to be repeatedly correlated with the structural damage endpoints at wks 28 and 52. However, there were a number of more consistently observed structural damage correlations in the PBO+MTX treatment group using either absolute change from baseline or percent change from baseline in biomarker levels. Absolute change or percent change from baseline markers that were repeatedly correlated with changes in structural damage endpoints at wks 28 and/or 52 included CD-40 ligand (CD40-L) and epidermal growth factor (EGF). There were repeated, but less frequent structural damage correlations with change or percent change in matrix metalloproteinase 3, MMP-18 and Col 2-3/4C long neoepitope. The only biomarker that was repeatedly correlated with structural damage endpoints in the GLM treatment group was IL-1ra.

**Conclusions:** Biomarker correlations with structural damage endpoints were predominantly observed in the PBO+MTX treatment group, but rarely in the GLM+MTX treatment group, likely reflecting the reduced structural damage observed following anti-TNF treatment. Change and percent change from baseline to wk 4 in levels of certain markers were repeatedly associated with structural damage endpoints at wks 28 or 52 in the PBO+MTX treatment. Markers that were repeatedly associated with structural damage measures at wks 28 and/or 52 included EGF and CD40-L. CD40-L has been reported to regulate osteoclastogenesis and EGF has been implicated in bone remodeling. Additional studies are needed to confirm whether these markers would be similarly correlated with structural damage measures in MTX-refractory patients.

**Disclosure:** C. Wagner; Centocor Research and Development, Inc., 3; D. Chen; Centocor Research and Development, Inc., 3; H. Fan; Centocor Research and Development, Inc., 3; S. Visvanathan; Hoffman La Roche, 3; E. C. Hsia; Centocor Research and Development, Inc., 3; P. Emery; Centocor Research and Development, Inc., 2, 9; R. M. Fleischmann; Centocor Research and Development, Inc., 2, 9; M. Mack; Centocor Research and Development, Inc., 3; M. U. Rahman; Centocor Research and Development, Inc., 3.

### 1128

**Targeting Potassium Channels for the Treatment of Rheumatoid Arthritis.** Xueyou Hu, Teresina Laragione1, Liang Sun, Shyshy Koshy2, Karlie R. Jones3, Frank T. Horrigan4, Percio S. Gulko3 and Christine Beeon5.

1.Baylor College of Medicine, Houston, TX, 2.Baylor College of Medicine, 3.Feinstein Institute for Medical Research, Manhasset, NY, 4.Feinstein Institute for Medical Research

**Background:** Activated fibroblast-like synoviocytes (FLS) in the rheumatoid arthritis (RA) synovium (RA-FLS) are major players in inflammation, synovium and bone destruction, angiogenesis, and hyperplasia. However, no currently-approved therapies specifically target these cells. Potassium channels regulate cell signaling and thus a large number of functions of non-excitable cells such as fibroblasts, lymphocytes, or astrocytes. We therefore hypothesized that targeting the potassium channels expressed by RA-FLS may represent an attractive target for the treatment of RA.

**Methods:** We have used four complementary methods (RT-PCR, western blot, immunocytochemistry, and patch-clamp electrophysiology) to identify the potassium channels expressed by RA-FLS isolated from 5 different patients. We next used selective blockers of KCa1.1 channels (paxilline andiberiotoxin) to probe their roles on RA-FLS proliferation, invasion, and production of cytokines, chemokines, angiogenic factors, and matrix metalloproteinases (MMPs).

**Results:** We have identified KCa1.1 channels (BK, Maxi-K, Slo-1) as the major potassium channels expressed by RA-FLS. Blocking KCa1.1 channels inhibited the proliferation of RA-FLS and their ability to produce vascular endothelial growth factor (VEGF), IL-8, and MMP-2 without inducing cytotoxicity or affecting the production of IL-6. In keeping with these data, blocking KCa1.1 channels also inhibited the invasion of RA-FLS in matrigel assays.

**Conclusions:** KCa1.1 channels play a major role in the pathogenic functions of RA-FLS. These channels are therefore attractive targets for the treatment of RA.

**Disclosure:** X. Hu; None; T. Laragione; None; L. Sun; None; S. Koshy; None; K. R. Jones; None; F. T. Horrigan; None; P. S. Gulko; None; C. Beeon; Armmd, Inc., 4, 5, Johnson & Johnson, 5, Kineta Onc, 4, 5.

### 1129


**Background:** Tasocitinib (CP-690,550) is an orally available, small molecule Janus kinase inhibitor that has previously demonstrated efficacy and acceptable safety in patients with active rheumatoid arthritis (RA) in randomized studies of up to 24 weeks of treatment. Here we report the safety and tolerability of tasocitinib and the durability of response beyond 24 weeks in patients with RA.

**Methods:** In this Phase 2/3, open label study of 1070 patients who had participated in a prior randomized study of tasocitinib (PRST), treatment was initiated with either 5 or 10 mg tasocitinib twice daily. The baseline is that of the PRST for patients who enrolled within 14 days of PRST participation; if initiated with either 5 or 10 mg tasocitinib twice daily. The baseline is that of the PRST for patients who enrolled within 14 days after PRST participation, baseline was the start of this study. The primary endpoints were laboratory safety and adverse event (AE) reports. Secondary endpoints included ACR20, ACR50 and ACR70 response rates, Disease Activity Score using the erythrocyte sedimentation rate (DAS28-4 (ESR)), and the Health Assessment Questionnaire-Disability Index (HAQ-DI).

Results are reported for all patients (ALL) and stratified according to those who completed Month 12 (M12) and Month 24 (M24) visits.

**Results:** 1070 patients were treated for a total duration of 1295.7
The Bacterial Effector Protein YopM Reduces Bone Destruction in Rheumatoid Arthritis (RA).

**Background:** Bone marrow macrophages (BMM) are precursors of osteoclasts, which mediate the degradation of bone during rheumatoid arthritis (RA). The yersinia outer protein M (YopM) is an effector protein of Yersinia species that is able to enter host cells by membrane penetration. In the cell YopM mediates down-regulation of inflammatory responses. We investigated whether YopM has the potential to act as a “self-delivering” immune therapeutic agent by reducing the inflammation and joint destruction linked to RA.

**Methods:** We analysed the penetration of recombinant YopM into BMMs by confocal laserscanning microscopy and studied the effects of YopM on osteoclastogenesis using an in vitro osteoclast formation assay. To unravel the signaling pathways involved in the effects of YopM, we investigated the activation of MAP-kinases (ERK, AKT and p-38) and NF-KB signaling by Western Blot analysis. With respect to a potential in vivo application of YopM, we injected YopM intra-articular and intravenous of wildtype and hTNFtg mice and monitored its distribution by fluorescence reflection imaging (FRI). Additionally, we treated hTNFtg mice, as animal model for RA, with YopM and recorded clinical parameters (weight, grip strength and paw swelling). Finally, we analysed the destruction of bone and cartilage histologically compared to untreated hTNFtg mice and wildtype mice.

**Results:** As seen in confocal scanning microscopy, YopM penetrated the cell membrane of BMGs and accumulated near the nucleus. Studying the signaling pathways affected by YopM, we found that YopM reduced the TNF alpha induced activation of NF-KB by reducing the phosphorylation of IkB alpha. TNF alpha mediated phosphorylation of MAP kinases were not altered by YopM. Most interestingly, we found a strong reduction of osteoclast formation by YopM. Incubation of BMMs with YopM led to a 90% reduction in osteoclasts precursors and osteoclasts. YopM-Cys injected intra-articular into the knee joints of a mouse was detectable without a systemic distribution of YopM during a time period of 72 hours. Analysing the clinical parameters of RA in hTNFtg mice, we observed a delay of onset of paw swelling. At histological analysis of the hind paws, we found reduced bone destruction and inflammation in YopM treated hTNFtg mice in comparison to untreated hTNFtg mice.

**Conclusion:** These results suggest that YopM has the potential to reduce inflammation and bone destruction in vivo. Therefore YopM may constitute a novel therapeutic principle for the treatment of RA.

**Disclosure:** J. Bertrand: None; C. Rüter: None; J. Scharnert: None; A. Schmidt: None; T. Pap: None.

1131

The Effects of Manzamine A on Rheumatoid Arthritis Synovocyte Cytokine Secretion.

**Purpose:** Manzamine A (MZA) is a marine alkaloid isolated from sponges on the ocean floor known to have anti-inflammatory properties on activated macrophages. The complete synthesis of this complex molecule has recently been reported. Rheumatoid Arthritis (RA) is characterized by increased production of pro-inflammatory cytokines by a variety of synovial cells found in the synovial tissue (ST) including fibroblast-like synoviocytes (FLS). We hypothesized that MZA would decrease the levels of pro-inflammatory cytokines secreted by RA cell types.

**Methods:** RA FLS and RA synovial tissue (ST) explants collected from patients with IRB approval were treated with MZA (10 μM, 1 μM, 0.1 μM, 0.05 μM, and 0.01 μM MZA) or vehicle control, to observe for alterations in pro-inflammatory cytokine production and to observe any cytotoxic effects. Condition media (CM), with or without IL-1β stimulation was collected at various time points. Toxicity was determined using trypan blue exclusion while cytokine levels were analyzed using antibody microarrays and ELISAs.

**Results:** Toxicity studies on RA FLS suggest that concentrations of 10 μM, 1.0 μM and 0.1 μM MZA had no toxic effects after 24 hours of incubation. However, after 48 and 72 hours, the 10 μM and 1.0 μM MZA concentrations appear to significantly decrease FLS viability. Using an antibody microarray, 24 hour CM with 10 μM MZA appeared to decrease the production of several pro-inflammatory mediators in both RA FLS and RA ST. Proteins decreased include monocyte chemoattractant protein (MCP)-1 (CCL2), interleukin (IL)-8 (CXCL8), growth related oncogene (Gro)-α (CXCL1), regulated on activation of normal T cell expressed and secreted (ENA)-78 (CXCL5). To confirm data obtained from the cytokine microarray analysis, the level of protein expression was further examined by ELISA. At 24 hours, 10 μM, 1.0 μM and 0.1 μM MZA significantly decreased the production of MCP-1 by 57%, 37% and 44% respectively (n=5; p<0.05). Additionally 0.1 μM MZA decreased MCP-1 by 43% at 48 hours (n=5; p<0.05). MCP-1 production, when stimulated with IL-1β, was significantly decrease with 10 μM, 1.0 μM, 0.1 μM, 0.05 μM and 0.01 μM MZA by 87%, 84%, 57%, 62% and 67%, respectively, at 24 hours (n=5; p<0.05). MCP-1 production, when stimulated with IL-1β, was significantly decrease with 10 μM and 1.0 μM MZA by 79% and 69%, respectively, at 24 hours, and also by 54% with 0.1 μM MZA at 72 hours (n=5; p<0.05). IL-1β stimulated Gro-α production was significantly decreased with 10 μM and 1.0 μM MZA by 86% and 75%, respectively, at 24 hours, and also by 59% with 0.1 μM MZA after 72 hours (n=5; p<0.05). Also, IL-1β stimulated Gro-α production was significantly decreased by 0.01 μM MZA by 26% after 24 hours (n=5; p<0.05).

**Conclusions:** While some concentrations of MZA applied appeared toxic to RA FLS, we identified a number of significant effects of MZA at non-toxic swelling levels and times with YopM. At histological analysis MZA decreases RA-associated inflammation by reducing pro-inflammatory cytokines and appears to have solid pharmacological potential to serve as a novel therapeutic in RA therapy.

**Disclosure:** K. Chong: None; K. Klosowska: None; J. M. Woods: None.


1National Data Bank for Rheumatic Diseases, Wichita, KS, 2Univ of Nebraska Med Ctr, Omaha, NE.

Objective: Improvement in rheumatoid arthritis (RA) clinical trials is often greater than improvement seen in the clinic. But follow-up clinical trial studies by sponsors almost invariably show sustained improvement (durability of response). We investigated whether sponsored trial participation influenced study results to determine if the result of clinical trials are upwardly biased by the Hawthorne effect.

Methods: We studied 264 RA patients who completed a commercially sponsored 3-month, open label, phase 4 trial of a Food and Drug Administration approved RA treatment. We evaluated changes in the Health Assessment Questionnaire disability index (HAQ) and VAS scales for pain, patient global, and fatigue during three periods: Pretreatment in the trial, on treatment at the close of the trial, and by a trial-unrelated survey 8 months after the close of the trial, but while the patients were receiving the same treatment. The study forms were the same for the trial and post-trial assessments.

Results: The HAQ score (0–3) improved by 41.3% during the trial, but only by 16.5% when the end point was the post-trial result. Similar results for the other variables were patient global (0–10): 51.9% and 34.6%; pain (0–10) 51.7% and 39.7%; fatigue (0–10) 45.6% and 24.6%. Worsening between the trial end and the first survey assessment was: HAQ 0.29 units, pain 0.8 units, global 0.8 units, and fatigue 1.1 units. These values are documented in Table 1 and Figure 1.

Changes in Study Variables According to Study Time and Setting.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trial Start</th>
<th>Trial end</th>
<th>Post-trial follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Positive ES (95% CI)</td>
<td>Mean (SD)</td>
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<td>63.1</td>
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<td>20.2</td>
</tr>
<tr>
<td>HAQ (0–3)</td>
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<td>0.71 (0.61)</td>
</tr>
<tr>
<td>Global (0–10)</td>
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<td>2.5 (2.1)</td>
</tr>
<tr>
<td>Pain (0–10)</td>
<td>5.8 (2.3)</td>
<td>0.001</td>
<td>2.8 (2.4)</td>
</tr>
<tr>
<td>Fatigue (0–10)</td>
<td>5.7 (2.7)</td>
<td>0.001</td>
<td>3.1 (2.7)</td>
</tr>
</tbody>
</table>

Trial start: pre-treatment; trial end (6 months later); Post-trial follow-up (0.8 years later). Differences between trial end and trial follow-up are significant at p < 0.001. Positive = clinical improvement, negative = clinical worsening. ES = Effect Size.

Conclusions: Almost half of the improvement noted in the clinical trial HAQ score disappeared on entry to a non-sponsored follow-up study, and from 23%-44% of improvements in pain, patient global, and fatigue also disappeared. These changes can be attributed to the Hawthorne effect. The difference between the clinical trial HAQ and the community (clinic) HAQ is important because HAQ values are commonly used to map to utility scores and then in the calculation of cost effectiveness. If clinical trial results overstate HAQ scores, then the true effectiveness—the real functional status — is overstated. Based on our data, we hypothesize that the absolute values of RA outcome variables in clinical trials are upwardly biased, and that that treatment effect is less than observed. Our results suggest that 3rd party (non-sponsored) follow-up studies, removed from the trial assessment, can and should be used to estimate actual clinical improvement.

Disclosure: F. Wolfe: None; K. D. Michaud: None.

The Relationship of Serum Cytokine Levels with Disease Activity Parameters and Ultrasonographic Findings in RA Patients before and after Treatment with TNF Antagonists. Nevsun Inanc1, Atilla Bulur2, Meryem Can1, Onder Ergonul1, Pamir Atagunduz2, Sule Yavuz3 and Haner Direskeneli2. 1Marmara University Medical School, Department of Infectious Diseases, 2Marina University Medical School, Division of Rheumatology.

Background: Although effective in most patients, response to TNF antagonists is heterogeneous and unpredictable in rheumatoid arthritis (RA). Bio-markers like serum cytokine levels or imaging methods like ultrasonography (US) might be helpful in predicting response to treatment with TNF-antagonists.

Methods: Levels of IL1, IL1Ra, IL6, MCP, TNF, VEGF, IFN gamma, IL10, IL12. IL13 were measured by a Luminex multiplex technology, VEGF-R1 and ANG-1 by quantitative sandwich ELISA in 26 RA patients (72 samples) before and after TNF antagonist therapy at 3 and 6 months. Tender and swollen joint counts, ESR, CRP, DAS28, patient and physician’s global assessment were recorded at each visit. US evaluation included GrayScale (0–3)(GS) and PowerDoppler (0–3)(PD) semiquantitative examination with a My Lab 70 XVG (Esaote Biomedica, Italy) equipped with 6–18 and 3–9 broad band linear transducer in 28 joints to calculate total GS and PD scores.

Results: Mean (SD) age was 49±11 and disease duration 9.7±6.2 years. Mean DAS28(SD) score was 5.3±0.6 at baseline and 3.3±1.3 at 6 months’ follow-up. The number of patients in remission was 2(8%) at 3 months and 9(35%) at 6 months’ visit, respectively. Although levels of all selected cytokines decreased at 6 months’ visit, only the changes at levels of MCP (p=0.009), IL10 (p=0.005) and IFNgamma (p=0.005) reached statistical significance. IL6 levels correlated with DAS28 at all visits (r=0.334, p=0.003). The baseline levels of VEGF, TNFalpha, IL6 and IL12 were found to be predictors of remission at 6 months according to DAS28 with an AUROC of 0.64 (95% confidence interval (CI) 0.4–0.9), 0.58 (95% CI: 0.4–0.8), 0.59 (95% CI: 0.4–0.8), 0.58 (95% CI: 0.3–0.8) respectively. Total GS score decreased significantly at both 3 (12.3±2.7)(p<0.001) and 6 months’ visits (9.9±6.6)(p<0.001) compared to the baseline visit (21.2±15.3). Similarly total PD score changes at both 3 (7.5±4.4)(p=0.001) and 6 months’ visits (5.9±2.41)(p=0.001) differed significantly from the baseline (16.7±13.5). Total GS (r=0.402, p<0.001) and PD (r=0.455, p<0.001) scores correlated with DAS28 in all visits. However, only the levels of IL6 correlated with total GS (r=0.544, p=0.009) and total PD scores (r=0.523, p=0.006) among the selected biomarkers.

Conclusion: US findings and DAS28 correlated in all visits in our study, suggesting that both clinical and imaging follow-up is useful in monitoring RA patients before and after taking TNF antagonists. Although MCP, IFNgamma and IL10 serum levels decreased significantly at 6 months, IL6 seem to be the best cytokine for follow-up, correlating both with DAS28 and US findings. Baseline levels of VEGF, TNFalpha, IL6 and IL12 might also be appropriate for the prediction of remission during TNF antagonists.

Disclosure: N. Inanc: None; A. Bulur: None; M. Can: None; O. Ergonul: None; P. Atagunduz: None; S. Yavuz: None; H. Direskeneli: None.

The Therapeutic Potential of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Rheumatoid Arthritis. Yanying Liu, Rong Mu, Shiyao Wang and Zhanguo Li. Peking University People’s Hospital.

Introduction: Rheumatoid arthritis (RA) is a T-cell-mediated systemic autoimmune disease, characterized by synovium inflammation and articular destruction. Bone marrow mesenchymal stem cells could be effective in the treatment of several autoimmune diseases. However, there has been thus far no report on umbilical cord (UC)-MSCs in the treatment of RA. Here, potent immunosuppressive effects of human UC-MSCs in RA were evaluated.
Methods: The effects of UC-MSCs on responses of FLSs and T cells in RA patients were explored. The possible molecular mechanism mediating this immunosuppressive effect of UC-MSCs was explored by addition of inhibitors to indoleamine 2,3-dioxygenase (IDO), Nitric oxide (NO), prostaglandin E2 (PGE2), transforming growth factorβ1 (TGF-β1) and interleukin 10 (IL-10). The therapeutic effects of systemic infusion of human UC-MSCs in collagen-induced arthritis (CIA) in mice model were explored.

Results: In vitro, UC-MSCs were capable of inhibiting proliferation of FLSs from RA patients, via IL-10, IDO and TGF-β1. Furthermore, the invasive behavior and IL-6 secretion of FLSs were also significantly suppressed. Albeit inducing hyposponsiveness of T cells mediated by PGE2, TGF-β1 and NO, UC-MSCs could promote the expansion of CD4+ Foxp3+ regulatory T cells from RA patients. More importantly, systemic infusion of human UC-MSCs reduced the severity of CIA in mice model. Consistently, there were reduced levels of proinflammatory cytokines and chemokines (TNF-α, IL-6 and MCP-1) and increased levels of the anti-inflammatory/regulatory cytokine (IL-10) in sera of UC-MSCs treated mice. Moreover, such treatment shifted Th1/Th2 type responses and induced Tregs in CIA.

Conclusions: In conclusion, human UC-MSCs suppressed the various inflammatory effects of FLSs and T cells of RA in vitro, and attenuated the development of CIA in vivo, strongly suggesting that UC-MSCs might be a therapeutic strategy in RA.

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TRA-8 (CS-1008), a Novel Anti-Arthritic Biologic Agent That Targets Macrophages with Low Toxicity. Jun Li1, Hui-Chen Hsu2, Ping Ar Yang2, Qi Wu2 and John D. Mountz2. 1Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, 2Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL.

Background: Macrophages contribute to joint inflammation and destruction in both the acute and chronic phases of rheumatoid arthritis (RA). However, biologic agents that can selectively eliminate pathogenic macrophages in RA have not been identified. Death receptor 5 (DR5) is a pro-apoptotic protein, which mediates apoptosis upon binding to a novel anti-human DR5 antibody, TRA-8 (humanized, CS-1008). We have found that macrophages isolated from both synovium and peripheral blood of RA patients express DR5 and are susceptible to TRA-8 mediated killing. The purpose of this study is to use a humanized DR5 transgenic mouse to evaluate the therapeutic efficacy of TRA-8 by eliminating pathogenic macrophages in a chicken collagen II (CII)-induced arthritis (CIA) model.

Methods: A chimeric human/mouse DR5 transgenic mouse was generated using a 3 kb mouse promoter/Floxed STOP/humanized mouse DR5 construct in which the extracellular domain of mouse DR5 was replaced by the human counterpart. Macrophages specific expression of chimeric DR5 is achieved by crossing the DR5 mice with lysozyme M-Cre mice. Arthritis was induced by AdIL-17 at day −2 plus intradermal injection of CII in CFA/IFA on day 0 and day 30. TRA-8 (0.2 mg per mouse) was administered i.v. every 3−7 days starting on day 0 (early treatment) or on day 30 (late treatment) until mice were sacrificed 3 months after the primary CIA injection. Enumeration of macrophages before and after CIA injection was determined by FACS analysis. In vivo joint macrophage activity was quantitated using an infrared cathespin B in vivo imaging analysis. Clinical scoring and histologic assessments were performed to evaluate the severity of arthritis.

Results: There was a higher percentage of CD11b+ macrophages in the spleen of CIA immunized mice (12.08%) compared to naïve mice (2.5%). Chimeric DR5 is highly expressed on CD11b+ macrophage. TRA-8 treatment resulted in 60% and 48% reduction of CD11b+ activated macrophages isolated from the spleen for early and late TRA-8 treatment, respectively. For both early and late TRA-8 treatments, joint histopathology showed a significantly decreased severity of inflammatory cell infiltration, synovial hyperplasia, cartilage damage, and bone erosion. Immunohistochemistry staining further demonstrated a dramatically reduced Mac-3+ macrophages in the synovium after TRA-8 treatment. In vivo live imaging of joints revealed that there was a significantly decreased macrophage activation-induced cathespin B activity in chimeric DR5 Tg mice that received TRA-8 treatment. The arthritis clinical scores were highly correlated with the abundance of macrophages in synovium and spleen. Neither systemic toxicities nor increased incidences of infections and malignancies were found in TRA-8 treated DR5 Tg mice.

Summary: This study demonstrated that TRA-8 (CS-1008) is a novel anti-arthritic biologic agent with high safety. Importantly, since the DR5 molecule is expressed on macrophages, our results suggest that TRA-8 can be developed into a novel therapy to either prevent the onset or suppress established arthritis via elimination of macrophages.

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Treat-To-Target for the Management of Rheumatoid Arthritis: A Validation Using Patient Reported Outcomes Data from Two Phase III Clinical Trials of Golimumab. Ed C. Keystone6, Roy M. Fleischmann2, Chenglong Han3, Paul Emery2, Mark C. Genovese5, Timothy Gathany3, Elizabeth C. Hsia1 and Mahboob U. Rahman3. 1Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, 2Chapel Allerton Hospital, Leeds, United Kingdom, 3Johnson and Johnson Pharmaceutical Services, LLC, 4Rheumatology Associates, Dallas, TX, 5Stanford University, Sunnyvale, CA, 6University of Toronto, Toronto, ON, Canada.

Objectives: To assess the impact of disease remission, a treatment target in the management of rheumatoid arthritis (RA) recommended by the International Task Force, on patient reported outcomes 1.

Methods: The efficacy and safety of golimumab (GLM) were assessed in metabolically active, MTX-naïve RA patients (GO-BEFORE, N=637), and RA patients with inadequate response to MTX (GO-FORWARD, N=444). In both trials, patients with active RA were randomly assigned to placebo (PBO) + MTX, GLM 100mg + PBO, or GLM (50 or 100mg) + MTX, q 4 weeks. Clinical remission was defined as DAS28 (ESR) <2.6. Patient reported outcomes included physical function, quality of life, fatigue, pain and work productivity as measured using instruments of Health Assessment Questionnaire (HAQ), 36-item short-form health survey (SF36 PCS and MCS), Assessment of Chronic Illness Therapy-Fatigue (FACT-F), Pain Severity Score of Brief Pain Inventory (BPI-Pain) and a visual analogue scale of daily work productivity. An ANOVA on van der Waerden normal scores or Chi-square test were performed for between-group comparisons.

Results: At week 24, a greater proportion of patients treated with GLM + MTX achieved DAS28 <2.6 compared to patients treated with PBO + MTX (22.3% vs. 11.3% in GO-BEFORE, and 21.4% vs. 6.0% in GO-FORWARD, all p<0.01). GLM + MTX treated-patients had a greater improvement in patient reported outcomes than patients treated with PBO + MTX. The overall distribution of SF36-PCS shifted significantly towards a distribution observed in the normal population at week 24 through 104. Compared to patients without remission, more patients in remission at week 24 achieved a normal physical function (HAQ=0.5) (75.3% vs. 27.3%), a SF-36 PCS=50 (median value of general population) (48.3%, vs. 7.6%) and a SF-36 MCS=50 (median value of general population) (66.3% vs. 40.3%), regained employability (43.5% vs. 27.6%) and achieved significant improvement in work productivity (80% vs. 28.3%) from baseline (all p-values<0.01). Greater improvements (median) in FACIT-Fatigue (week 24: 12.0 vs. 4.0) and in BPI-Pain score (week 14: 2.1 vs. 0.8) were observed among patients in remission than patients without remission.

Conclusion: This analysis indicates that controlling disease activity in patients with RA is crucial to regaining a normal life. Thus DAS28 remission may be a reasonable target in the management of RA.


Validation of an Algorithm Using Genome-Wide SNP Analysis for Prediction of Responders, Non-Responders, and Adverse Events of Tocilizumab-Treated RA Patients Using Two Population Samples from Multiple Medical Cohorts. Tsukasa Matsubara, Satoru Koyano, Keiko Funahashi, Takafumi Hagiwara, Takako Miura, Kosuke Okuda, Akira Sagawa, Takeo Sakurai, Hiroaki Matsumoto, Tomomaro Izumiha, Eisuke Shono, Kou Katayama, Toyotomi Tsuchida, Mitsuhiro Iwahashi, Tomomi Tsuru, and Motohiro Oriibe. 1Higashi-hiroshima Memorial Hospital, Higashihiroshima, Japan, 2Research Institute of Joint Diseases, Kobe, Japan, 3Sagawa Akira Rheumatology Clinic, Sapporo, Japan, 4Sakura Clinic, Fukuoka, Japan, 5Matsubara Mayflower Hospital, Kato, Japan, 6Matsubara Mayflower Hospital, Kato, Japan, 7Matsumo Clinic for Rheumatic Diseases, Toyama, Japan, 8Oribe Rheumatism and Internal Medicine Clinic, Oita, Japan, 9PS Clinic, Fukuoka, Japan, 10Research Institute of Joint Diseases, Kobe, Japan, 11Sagawa Akira Rheumatology Clinic, Sapporo, Japan, 12Shono Rheumatology Clinic, Fukuoka, Japan, 13Tsuchida Clinic, Chiba, Japan

Purpose: Tocilizumab, a human anti-IL-6 receptor antibody, is an effective biological agent for inflammatory diseases such as RA. However, there is no method for prediction of responders, non-responders, and adverse events which can occur during the treatment. We established and validated an SNP algorithm for prediction of responders or non-responders, and adverse events among tocilizumab-treated RA patients by using multiple medical cohorts.

Patients and Methods: Samples were obtained from RA patients who failed to the treatment with DMARDS including MTX. The first population sample included 106 RA patients and the second included 93 patients: a total of 199 patients from 11 hospitals in different regions of Japan. The efficacy was determined by Clinical Disease Activity Index (CDAI) within 24–30 weeks after the initial treatment. The efficacies of tocilizumab was judged by the scores of CDAI (remission and low disease activity group—‘responders’, moderate and high disease activity group—‘non-responders’). Adverse events such as leukopenia, high total cholesterol, fever, and skin manifestations were documented. Genome-wide SNP genotyping was performed by Illumina HumanHap300K chip technology. Case-control analyses between 277,141 SNPs and responsiveness or occurrence of adverse events were examined by Fisher’s exact tests. We selected 10 SNPs associated with tocilizumab-responsiveness, or adverse events which were common in analyses of both the first and second population (p < 0.02). We then scored the relationship between each SNP and responsiveness, the estimated total score of 10 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in responders: +1 point, hetero allele: 0 point, and homo allele in the majority of non-responders: −1 point), and examined relationships between responders and non-responders, or occurrence of adverse events plus or minus, and the total score.

Results: Accuracy ((true positive + true negative)/total), specificity (true negative/false positive + true negative)) and sensitivity (true positive/(true positive + false negative)) of the algorithm for responsiveness of tocilizumab ranged from 87–92%. For adverse events, accuracy, specificity and sensitivity of the algorithm ranged from 85–91%. It is therefore suggested that the SNP algorithm can predict responders and adverse events prior to the initiation of treatment with tocilizumab.

Conclusion: This highly accurate algorithm using SNP analysis may be useful in the prediction of responsiveness and adverse events before treatment with tocilizumab, and in this way can contribute to future tailor-made treatment with biologic agents.

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ACR Poster Session B
Systemic Lupus Erythematosus - Clinical Aspects and Treatment II
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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1α,25-Dihydroxyvitamin D3 Suppresses Differentiation, Maturation and Activation of Dendritic Cells from Patients with Systemic Lupus Erythematosus. Hai Jing Wu, Chak Sing Lau and M Yin Mok. The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Dendritic cells (DC), professional antigen presenting cells, are believed to play a crucial role in the pathogenesis of systemic lupus erythematosus (SLE). 1α,25-Dihydroxyvitamin D3 (VitD3), in addition to its effect on bone metabolism, has been increasingly recognized to have immunomodulatory action.

Objective: To examine the effect of VitD3 on the differentiation, maturation and activation of DCs in SLE patients.

Method: CD14+ monocyte-derived DCs from SLE patients and age- and sex-matched controls were derived from growth medium cultured with IL-4 and GM-CSF. Mature DCs were induced by addition of lipopolysaccharide (LPS) and tumour necrosis factor-α (TNF-α) in the presence or absence of VitD3 (1×10−10 M) and/or dexamethasone (1×10−6 M). The expression of CD1a and co-stimulatory molecules was examined by flow cytometry. After stimulation of DCs with CD40L transfected cell line for 24h, the production of pro-inflammatory cytokines including IL-12 and IL-6, were measured by ELISA kits.

Results: 50 SLE patients and 32 normal controls were studied. VitD3 was found to suppress differentiation of monocytes into DCs with lower level of expression of CD1a for both controls (p<0.05) and SLE patients (p<0.01) compared to untreated condition. With or without dexamethasone, VitD3 inhibited up-regulation of maturation markers, including CD86, CD40 and CD83 (p<0.05), but not CD80 and HLA-DR (Table 1&2). In terms of pro-inflammatory cytokine production, stimulated and unstimulated DCs produced less IL-12p70 and IL-6 in SLE patients as well as controls under the effect of VitD3 with or without dexamethasone compared to pre-treatment DCs.

Conclusion: VitD3 is found to inhibit differentiation, maturation and activation of DCs in vitro in both SLE patients and controls and may be considered as immunomodulatory agent in the treatment of SLE.

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30-Year Follow-Up of Lupus Nephritis in a Single Clinic—Outcome, Serology and Ethnicity. Sara C. Croca, Teresa Rodrigues, and David A. Isenberg. 1Faculdade de Medicina de Lisboa, Laboratory of Biomatics, Lisboa, Portugal, 2Hospital de Santa Maria, Department of Medicine 1, Lisboa, Portugal, 3UCL Div of Medicine, London, United Kingdom

Objectives: Although lupus nephritis (LN) represents one of the most common and potentially severe complications of systemic lupus erythematosus (SLE), there are few data on the very long-term follow-up of these patients. Our aim was to characterize a LN cohort followed at a single centre for 30 years and assess its evolution over time.

Methods: Between 1975 and 2005, 156 patients were diagnosed as having LN at University College Hospital London (UCHL). We divided the cohort into 3 groups (1975–1985, 1986–1995 and 1996–2005), allowing for a minimum 5-year follow-up. The 3 groups were compared in terms of their clinical, demographic and serological characteristics, as well as disease outcome. Outcomes were defined as the 5-year mortality rate or end-stage renal disease (ESRD) development.
Results: Clinical characteristics were comparable between groups; however, the proportion of Afrocaribbean (AC)-origin patients rose significantly over time accompanied by an increased prevalence of anti-ENA antibodies (ENAab). No other clinical association was found between the ENAab subgroups and ethnicity. In terms of outcome, AC-origin was associated with a poorer overall prognosis whereas no significant influence was linked to the other factors considered. The 5-year mortality rate decreased by 60% between the first and second decades and stabilised throughout the third. Disappointingly, the 5-year ESRD rate remained constant during time. An increasing number of renal transplants (RTx) was performed (n=16, in table) with encouraging results, particularly when a living-related donor graft was used. The prognosis for the ESRD group was poorest for AC patients, with no other factors showing any influence.

Conclusions: LN is associated is a common complication of SLE associated with increased mortality and morbidity, particularly among AC-origin patients. Despite encouraging results for RTx, once ESRD is established the prognosis is relatively poor and no improvement was achieved in preventing its development. Moreover, although a significant decrease in mortality was noted over the 3 decades, it has remained stable for 10 years. This result suggests that we have maximised the benefits of conventional therapies and, if further improvement is to be achieved, novel drug regimens must be considered.

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A Flow Cytometric Receptor Occupancy Assay Demonstrates Dose-Dependent Blockade of B7RP-1 by AMG 557 on Circulating B Cells from SLE Subjects. Barbara A. Sullivan1, Cherie L. Green2, Ming Zhang1, Christina Abbott1, Shelley Belouski1, John Thomas1, Kevin Gorski1, Gerald Siu2, John B. Chung1, 1Amgen, Thousand Oaks, CA, 2Amgen Inc., Thousand Oaks, CA, 3GlaxoSmithKline, Stevenage, United Kingdom

Background: Assessment of RO (receptor occupancy) is useful in drug development to confirm physical target coverage and support dose selection when combined with PK modeling. We describe a B7-related protein-1 (B7RP-1, B7th, ICOSL) FACS RO assay from initial experiments in SLE mouse models to validation and application to whole blood samples from subjects treated with a fully human IgG2 anti-B7RP-1 clinical candidate (AMG 557). B7RP-1 blockade in SLE is supported by the role of ICOS: B7RP-1 engagement in germinal center formation, B cell class switch recombination and antibody affinity maturation. Establishment of a correlation of B7RP-1 occupancy and efficacy with in vivo studies, including a murine lupus model, provided a rationale for incorporation of RO in an AMG 557 clinical trial.

Methods: Preclinical: NZB/W F1 mice were injected with 8, 1.5, or 0.3 mg/kg of B17-V2, 8 mg/kg mouse IgG1 isotype control or PBS once weekly for 23 weeks. RO was measured 3 months after starting treatment and just prior to the next dose; serum anti-dsDNA antibody levels were measured by ELISA as one measure of disease at 6 months. Clinical: Whole blood was collected from subjects in a Phase 1a single dose-escalating study of AMG 557. A four-color flow cytometric whole blood assay was constructed and validated to measure B7RP-1 on human circulating B cells. Antibody reagents directed against B7RP-1 were generated in-house according to standard procedures in mice and rats; all other antibodies were commercially available (Becton Dickinson, Inc., Immunotech S.A.).

Results: B7RP-1 RO on circulating B cells correlated with efficacy in the NZB/NZW F1 mouse model of lupus. For the clinical assay, two monoclonal antibodies from two immunization campaigns (mouse and rat) were chosen: one that competed with AMG 557 for B7RP-1 (Ab 1.64.1) and one that did not (Ab 3.7.1). These antibodies were fluorescently labeled for use in a 4-color FACS assay. The assay was validated by initially demonstrating selective inhibition of 1.64.1 binding to B cells in vitro (by AMG 557), followed by analysis of specimen stability and biological variability from ten healthy volunteers across three sequential visits. The RO assay was next implemented in the Phase 1a single dose-escalating study of AMG 557. The RO data from the clinical trial showed a reversible, dose-dependent coverage of B7RP-1 by AMG 557 in this single dose study. Moreover, measurement of receptor levels with antibody 3.7.1 indicated a dose-dependent transient rise in total B7RP-1 on circulating B cells in the treated subjects.

Conclusions: The RO assay demonstrated coverage of B7RP-1 on circulating B cells from SLE subjects after single dose administration of AMG 557 in a dose-dependent and reversible manner. Total receptor levels on the B cells increased in association with increasing occupancy in a dose dependent manner in keeping with preclinical observations in mouse studies. The relationship of receptor occupancy and pharmacodynamic effects in mouse models provides an important consideration for interpreting the RO results from the Phase 1 study and for guiding dose selection in future clinical trials of AMG 557.

with QTc prolongation could receive appropriate counseling to avoid drugs that may put them at risk for life-threatening arrhythmias.

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Allogeneic Mesenchymal Stem Cells Transplantation in Severe and Refractory Systemic Lupus Erythematosus. Lingyun Sun1, Dandan Wang1, Huayong Zhang1, Jun Liang1, Xuebing Feng1 and Yayi Hou2.

Objective: To assess the long-term efficacy and safety of allogeneic bone marrow (BM) or umbilical cord (UC) mesenchymal stem cells transplantation (MSCCT) for patients with severe and refractory systemic lupus erythematosus (SLE).

Methods: A single-arm trial involved 82 SLE patients, aged from 12 to 56 years old, average disease duration was 44 months. 24 patients were infused once with BM MSC, 50 patients received once UC MSC, while the other 8 patients received both MSC twice. Allogeneic MSC were administered ≥1.0×10^{10}/kg intravenously. BM MSC were aspirated from related healthy donors and expanded in vitro, and UC MSC were obtained from Stem Cell Center of Jiangsu Province of China. The clinical manifestations and laboratory parameters were compared pre- and post-MSCCT, with a mean follow-up of 16.5 months (range, 3 to 36 months). Side effects were monitored all the time during and post-MSCCT.

Results: Complete remission (CR) of disease activity (SLEDAI less than 3 and prednisone dose≤10mg/d) was seen in 9/41 (22%) patients 1 year post-MSCCT and up to 9/16 (56%) and 3/6 (50%) at 2 and 3 years point respectively. Probability of disease relapse (DR) or unresponsive to MSCCT (SLEDAI increased ≥3 and an increase in prednisone or immunosuppressive drug) was 8/41 (20%) at 1 year and 4/16 (25%) at 2 years visit. Of 5 patients completed 3 years visit, 2 of which with DR, and both were unresponsive to a second MSCCT. The other 6 patients, who received second MSCCT, reached to complete or partial remission. Significant improvements in SLEDAI score were examined 3 months (9.4±0.5) post-MSCCT (n=82, p<0.01 vs pre-MSCCT 14.0±0.6), and further decline in 1 and 2 years visit (4.9±0.4 vs 14.1±0.6, n=41 in 1 year, 3.6±0.6 vs 18.4±1.5, n=16 in 2 years, p<0.01). SLEDAI score <3 in 3 patients at 3 years visit. Amelioration of lupus nephritis was identified by the obvious decline of 24-hour proteinuria in 3 (1771±157mg vs 2799±152mg, n=64, p<0.05) and 6 months (1353±153mg vs 2584±179mg, n=31, p<0.05) visit, with further decline at 1 year visit (945±177mg vs 2045±112mg, n=20, p<0.05), and for 11 patients completed 2 years visit (989±289mg, p<0.05). Serology index showed albumin and complement C3 increased combined with decline of serum autoantibodies. In addition, of 22 patients with moderate to severe hematological disorders, haemoglobin and or/platelet count reached to almost normal levels post-MSCCT. Furthermore, 4 patients had central nervous system involvement (seizures, cerebritis) with improvement and no relapsed post-MSCCT. Significant improvements of glomerular filtration rate were found for 3 patients 12, 12, 20 months after MSCCT respectively (from 65.23, 71.86, 23.45 ml/min to 94.45, 100.07, 69.82 ml/min). There was no difference in efficacy between BM and UC MSCCT. Four patients died 5, 6, 6, 65.23, 71.86, 23.45 ml/min to 94.45, 100.07, 69.82 ml/min). There was no

Conclusion: Allogeneic MSCCT is safe and results in amelioration of disease activity. These data provide a foundation for conducting BM or UC MSCCT for severe and treatment-refractory SLE.

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Analysis of the Use of Rituximab in the Treatment of Lupus Nephritis. Sara C. Croca and David A. Isenberg.

Background: Lupus nephritis (LN) represents one of the most common and potentially severe complications of systemic lupus erythematosus (SLE). Classical serological markers of disease activity include the erythrocyte sedimentation rate (ESR) and the levels of anti-dsDNA antibodies and C3. Other serological markers with potential prognostic value such as the anti-ENA antibodies (ENAab) have also been studied. As traditional therapies show their limitations in achieving rapid disease control and damage prevention, novel treatment approaches have emerged. Rituximab (RTX) is an anti-CD20 monoclonal antibody that has been widely reported to be effective in treating renal disease flares. Our published data (Lu et al, Arthritis Rheum 2018) indicates that clinical benefit is related to the period of B-cell depletion. In this study we have analysed this period in detail, trying to determine if there are correlations to standard lupus tests and ethnicity.

Methods: Between July 2001 and December 2009, 40 LN patients were treated with RTX at the University College Hospital London (UCHL). A minimum follow-up of 12 months was required for this study (n=38).

Patients were assessed at baseline and at 6 months after RTX in terms of serological and renal profile. Response to treatment was defined as an absolute reduction ≥15% in CD19 count < 0.005 and values above this were considered evidence of repopulation.

Results: Following the first RTX cycle, 89.47% (n=34) were successfully depleted (CD19< 0.005). After 6 months, only 32.35% (n=11) of these remained depleted. When comparing the depleted vs. the repopulated group, no differences were found in terms of the classical disease activity markers (ESR, anti-dsDNA and C3). Other serological markers such as the anti-C1q antibodies, ENAab and anti-cardiolipin antibodies also showed no association with depletions. However, the ENAab subgroup showed that anti-Sm negative patients tend to remain depleted at 6 months. The baseline proteinuria and serum creatinine level also failed to influence response. In terms of ethnicity, Afro-caribbean origin patients were more likely to have repopulated at 6 months.

Conclusions: In the last 10 years, RTX has progressively shown its potential as an effective drug in the treatment of SLE flares. However, its use in the context of LN is not as well documented. Despite the limitations imposed by the small size of our sample, a few interesting results have emerged. Renal disease background and classical disease activity markers did not predict response to treatment. Other serological markers such anti-C1q antibodies, antiphospholipid antibodies and ENAab status are also irrelevant. However, anti-Sm positive patients seem to be more likely to repopulate. In addition, AC patients tend to have higher rates of repopulation. Thus, classical disease activity markers are of no use in predicting response to RTX, apart from anti-Sm antibodies which may be associated with earlier repopulation. Finding predictors of response is important in order to select the patients more likely to respond and identify those with a probable shorter term response allowing for closer monitoring.

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Introduction: Systemic lupus erythematosus (SLE) usually manifests in women during their childbearing age. Women with SLE have a lower number of births compared to healthy controls although fertility is considered not to be reduced. Anti-Mullerian hormone is expressed in granulosa cells of growing follicles, reflects the size of the primordial follicle pool and therefore is used to assess fertility potential.

Method: Serum samples of 40 patients with SLE without previous cytotoxic – especially cyclophosphamide – treatment and 40 age matched, healthy controls were collected. All patients gave written informed consent and filled out a questionnaire on menstrual irregularities, lifestyle, pregnancy outcomes and contraception. AMH was quantified using a standard ELISA with standard value 1–5μg/l, values <1μg/l defined as reduced, <0.4μg/l as severely reduced fertility. Systemic lupus erythematosus disease activity index (SLEDAI) and European Consensus Lupus Activity Measurement (ECLAM) were used for clinical disease activity assessment.

Results: Median age was 29.5 (20–39) years. Disease activity was low to moderate with a median SLEDAI of 2 (0–17) and ECLAM of 1,75 (0–5). The median AMH level was 1,7 (0,01 – 15μg/l) and thus lower compared to historic control groups with 2,1 and 2,3 (1). In 30% (12 patients) AMH level
was below 1 µg/L and in 6 even < 0.4 µg/L. 8 patients were pregnant at the time of sample acquisition and patients had an average of 0.55 children.

Discussion: This is the first study to examine AMH levels in women with SLE. Lupus patients seem to have a reduced ovarian reserve and a reduced period of reproduction. As cytotoxic therapy is still standard for some SLE manifestations this data has an impact on fertility preservation strategies. Ovary protection during cytotoxic treatment is even more important in SLE patients.

Literature:

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Purpose: To assess the effects of belimumab on biomarkers, and B- and T-cell populations in patients with seropositive SLE.

Methods: In 2 randomized, double-blind, placebo-controlled phase 3 studies (BLISS-52, NCT00424476; and BLISS-76, NCT00410384), 1684 seropositive (ANA ≥1:80 and/or anti-dsDNA ≥30 GPL/mL) SLE patients with SELENA-SLEDAI ≥6 on stable standard-of-care (SOC) therapy ≥30 d received belimumab 1 or 10 mg/kg, or placebo, plus SOC, on 0, 14, and 28, then q28d for 48 wk in BLISS-52 and 72 wk in BLISS-76. Immunoglobulin (Ig), complement (C), and autoantibodies (anti-dsDNA, ANA, anti-Sm, anti-CL, anti-ribosomal P) were evaluated. In addition, B- and T-cell subsets were evaluated in BLISS-76.

Results: Overall, belimumab treatment reduced autoimmune antibody titers and promoted conversion from antibody seropositive to seronegative status (table). More patients treated with belimumab converted from positive to negative for anti-dsDNA, anti-Sm, anti-ribosomal P, and aCL-IgG compared with placebo. Belimumab-treated patients had significantly greater increases in C3 and C4 levels with a dose response; patients receiving 10 mg/kg had significantly greater increases at every visit through wk 52 and a greater % achieved normalized levels (table). Normalization of hypergammaglobulinemia (≥16.2 g/L) occurred in significantly more patients in the 2 belimumab groups vs placebo (49.2% vs 19.7%; table). Belimumab significantly reduced various circulating B-cell subsets, but not T-cell subsets. Reductions in naïve B-cells and short-lived plasma cells (CD20+/CD27+ naïve), as well as the SLE B-cell subset (CD19+/CD3+ B cells), were observed as early as wk 8 with the 10-mg/kg dose. Memory B-cells increased ≥100% by wk 8 and gradually decreased toward baseline levels through wk 52. A significant expansion of T-cell subsets was observed at wk 52, but this is considered to be a secondary effect of the B-cell reductions.

Conclusions: In these phase 3 studies, belimumab treatment led to rapid, significant, and sustained reductions in autoantibodies, and normalization of C3, C4, and hypergammaglobulinemia compared with placebo. These findings, and the selective reduction of B-cell and short-lived plasma cell subsets, are all consistent with the mechanism of action of belimumab.

Table: Biomarker Data at Wk 52

<table>
<thead>
<tr>
<th>SOC</th>
<th>Placebo</th>
<th>Belimumab</th>
<th>SOC + Belimumab</th>
<th>Belimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>562</td>
<td>559</td>
<td>563</td>
<td>563</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive, patients median % change</td>
<td>10.2</td>
<td>36.6</td>
<td>36.6*</td>
<td>40.8*</td>
</tr>
<tr>
<td>Median % change</td>
<td>2.2%</td>
<td>14.7%*</td>
<td>49.2%</td>
<td>49.2%</td>
</tr>
<tr>
<td>% normalized</td>
<td>38/193 (19.7%)</td>
<td>91/185 (49.2%)*</td>
<td>97/197 (49.2%)*</td>
<td>97/197 (49.2%)*</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive, patients median % change</td>
<td>22.7</td>
<td>30.8</td>
<td>31.2*</td>
<td>30.8</td>
</tr>
<tr>
<td>Median % change</td>
<td>2.2%</td>
<td>17.6%</td>
<td>30.8%</td>
<td>31.2%</td>
</tr>
<tr>
<td>% normalized</td>
<td>30/176 (17.0%)</td>
<td>51/193 (26.4%)*</td>
<td>77/202 (38.1%)*</td>
<td>77/202 (38.1%)*</td>
</tr>
<tr>
<td>Anti-CL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive, patients median % change</td>
<td>1.2%</td>
<td>11.3%</td>
<td>34.9%</td>
<td>34.9%</td>
</tr>
<tr>
<td>Median % change</td>
<td>2.2%</td>
<td>13.6%</td>
<td>34.9%</td>
<td>34.9%</td>
</tr>
<tr>
<td>% normalized</td>
<td>38/193 (19.7%)</td>
<td>89/185 (49.2%)*</td>
<td>97/197 (49.2%)*</td>
<td>97/197 (49.2%)*</td>
</tr>
<tr>
<td>Anti-ribosomal P</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive, patients median % change</td>
<td>1.2%</td>
<td>34.9%</td>
<td>64.4%</td>
<td>64.4%</td>
</tr>
<tr>
<td>Median % change</td>
<td>2.2%</td>
<td>34.9%</td>
<td>64.4%</td>
<td>64.4%</td>
</tr>
<tr>
<td>% normalized</td>
<td>40/218 (18.3%)</td>
<td>86/246 (35.0%)*</td>
<td>115/295 (44.4%)*</td>
<td>115/295 (44.4%)*</td>
</tr>
</tbody>
</table>


1147
Comparison of Serum Free Light Chains, Interferon and Interleukins as Biomarkers of Disease Activity in Systemic Lupus Erythematosus (SLE). S. Francis4, Rohit Aggarwal6, Rachel Mikolaitis3, Timothy B. Niewold2, Susanna Chubinskaya3, Joel A. Block3, Winston Sequeira5, and Meenakshi Jolly3.

1 Rush University Medical Center, Chicago, IL, 2 Rush University Medical Center, Chicago, IL, 3 Rush University Medical Center, Chicago, IL, 4 Rush University Medical Center, Chicago, IL, 5 Rush University Medical Center, Section of Rheumatology, Chicago, IL, 6 Rush University Medical Center, Section of Rheumatology, Chicago, IL, 7 University of Chicago, Section of Rheumatology, Chicago, IL, 8 University of Pittsburgh Medical Center, Pittsburgh, PA.

Background: SLE may affect any organ and is associated with significant morbidity and mortality. Other than DNA damage in the context of Lupus nephritis, studies thus far exploring a biomarker for disease flare have been equivocal. We previously reported superior utility of serum free light chains (FLC) compared to DNAx and IgG as biomarkers for disease activity in SLE. We also reported that Total FLC (TFLC) elevation was greater in SLE as compared to rheumatoid arthritis, and that its association with disease
activity was stronger in SLE than rheumatoid arthritis. There have been studies by other authors showing association of Interleukin-6 (IL-6), Interleukin-10 (IL-10) and Interferon (IFN-α) with SLE disease activity. Herein, we compare the utility of total FLC with IL-6, IL-10 and IFN-α for disease activity in SLE.

**Aims:** To determine the association of (1) serum TFLC with IL-6, IL-10 and IFN-α (2) to compare their association of disease activity, demographic variables (age, gender and ethnicity), immunosuppressive agents and ACR criteria.

**Methods:** This is a cross-sectional study of 134 SLE patients (ACR criteria) recruited from a University Center from 2008–2010. PGA and SLEDAI were assessed by the same physician. Adjusted SLEDAI was calculated by deleting DNA and complement items from the SLEDAI. Serum was tested for TFLC (The Binding Site U.K.), IL-6, IL-10 and IFN-α. Chart review was done for demographics, clinical and serological characteristics and treatment. Statistical analysis performed included correlation analysis, Mann Whitney test.

**Results:** Mean age of the patients was 43±12 yrs; females composed 91% of the study group; African American 50%, Caucasians 24%, Hispanic 16%. PGA (Mean±SD, Median) was 0.5±0.6, 0, while SLEDAI was 4±2, 2. Forty eight percent patients were on prednisone. The (Mean±SD, median) values were: TLC (58±264, 43), IL-6 (6±7, 4), IL-10 (16±20, 13) and IFN-α (21±39, 4). TFLC was correlated with IFN-α (r =0.37, p<0.0001) and IL-6 (r=0.25, p=0.009). IFN-α correlated with IL-6 (r=0.20, p=0.05). TFLC showed a moderate correlation with PGA (r =0.39, p=0.002), SLEDAI (r=0.35, p=0.001) and adjusted SLEDAI (r=0.34, p=0.005). IL-10 was moderately associated with adjusted SLEDAI (r=0.32, p=0.02). IL-6 weakly correlated with SLEDAI (r=0.23, p=0.04) but not adjusted SLEDAI. IFN-α was not associated with either of them.

**Conclusion:** Serum TFLC is moderately correlated with PGA and adjusted SLEDAI. Strength of TFLC association with adjusted SLEDAI is greater than observed with IL-10. Longitudinal studies to determine if changes in disease activity result in changes in TFLC are now indicated.

**Disclosure:** S. Francis: The Binding Site, UK. 2. R. Aggarwal: The Binding Site, UK. 2; R. Nikolaitis: None; T. B. Niewold: None; S. Chubinskaya: None; J. A. Block: None; W. Sequeira: None; M. Jolly: The Binding Site, 2.

### Table 1. Proportion (%) with coronary artery calcium (>0), by study group and age

<table>
<thead>
<tr>
<th>Variable</th>
<th>SLE Patients (n=88)</th>
<th>MESA Controls (n=583)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>33/57 (58%)</td>
<td>31/144 (22%)</td>
</tr>
<tr>
<td>55–64</td>
<td>13/22 (59%)</td>
<td>52/144 (36%)</td>
</tr>
<tr>
<td>65–74</td>
<td>5/7 (71%)</td>
<td>120/211 (57%)</td>
</tr>
<tr>
<td>75+</td>
<td>2/2 (100%)</td>
<td>70/84 (83%)</td>
</tr>
</tbody>
</table>

After controlling for age, ethnicity, diabetes, hypertension, hyperlipidemia, smoking, education, and BMI, SLE patients had a significantly higher prevalence of CAC than controls (Prevalence Ratio 1.8 (1.5, 2.3)) (Table 2).

**Table 2.** Association between predictors and presence of coronary calcification based on a multivariable prevalence-ratio regression model.
a rise in C3 levels, while only 17% had a decline. Decreasing C3 levels during pregnancy were predictive of a higher rate of pre-eclampsia, compared to stable or rising C3 levels. The risk of pre-eclampsia is higher in SLE pregnancies, occurring in 22–30% of pregnancies, compared to 5–7% of normal pregnancies. Earlier studies have suggested renal disease, thrombocytopenia and anti-phospholipid antibodies to be the predictors of pre-eclampsia in SLE. Our study suggests that a declining trend of C3 level is another risk factor for pre-eclampsia.

**Disclosure:** A. Lateef: None; L. S. Magder: None; M. A. Petri: None.

### 1150

**Dendritic Cells and Regulatory T CD4$$^+$$CD25$$^{bright}$$ in Pregnant Patients with Systemic Lupus Erythematosus.** Luis J. Jara1, Griselda Teresa Romero-Sánchez1, Laura A. Montiel-Cervantes1, Gabriela Medina1, Polita Cruz-Cruz2, Jorge Vela-Ojeda1, Rafael Arias-Flores1, Olga Vera-Lastra1 and Miguel A. Saavedra Salinas1. 1Hospital de Especialidades Centro Medico La Raza, IMSS, Mexico City, DF, Mexico, 2Hospital de Gineco-Obstetricia No.3, Centro Medico La Medica Raza, IMSS, Mexico City, DF, Mexico

**Introduction:** During pregnancy, dendritic cells (DC) participate in the shift from T-helper 1 (Th1) to T-helper 2 (Th2) activity. Myeloid DC induce Th1 cell differentiation, and plasmacytoid DC induce Th2 cell differentiation. On the other hand, CD4$$^+$$CD25$$^{bright}$$+ FOXP3 + regulatory cells (Treg cells) are CD4$$^+$$ T cells with suppressive properties. An inadequate expression of Treg cells is associated with obstetric complications. Therefore, Treg/DC maintain maternal-fetal tolerance. However, their role in systemic lupus erythematosus (SLE) and pregnancy remains unknown.

**Objective:** To analyze the changes of DC and Treg cells in the peripheral blood of pregnant SLE patients in comparison with normal pregnancy. To correlate these alterations with clinical activity and maternal-fetal complications of SLE patients.

**Material and Methods:** Fifty pregnant, 25 with SLE (mean age 26.6±6 years), and 25 pregnant healthy as controls (mean age 27.8±5 years) were enrolled in the study. The majority of SLE patients were treated with low doses of prednisone (96%) and chloroquine (68%). Mononuclear cells of peripheral blood were obtained during pregnancy (each trimester) and postpartum. The subtypes of DC and Treg cells from whole blood samples were analyzed as previously described. A total of 100 microlitres of whole blood was incubated with 20 microlitres of monoclonal specific antibodies: For DC Lin+FITC, CD123-PE, HILADR-PE/C, CD11C-APC for determination of CD14(Myeloid DC), and CD2 (plasmacytoid DC). For Treg: FoxP3, CD4 PerPC, CD25 APC. The antibodies and cells were incubated for 25 min at room temperature in a dark room. Labeled cells were analyzed with the program Cell Quest pro, using FACSCalibur BD flow cytometer. We used SLAM-M modified to measured SLE activity during pregnancy. Statistical analysis: Mann-Whitney U test, Spearman correlation, and logistic regression.

**Results:** Fetal loss (2), pre-eclampsia (2), and abortion (2) were observed in SLE patients. No maternal-fetal complications were observed in controls. During pregnancy, decrease tendencies of percentages of CD1, and Treg were observed in SLE patients vs controls: CD1, 35.2±42 vs 58.3±44 (p<0.006), and Treg, 53.9±56 vs 89.8±113 (p<0.02), with a significant decrease of CD2, 9.9±8 vs 26.6±25 (p<0.003), respectively. In postpartum, a significant decrease of CD1 was observed in SLE patients: pregnancy SLE, 40.2±35 vs postpartum SLE, 17.7±17 (p<0.05) without significant differences in CD2 and Treg. A direct correlation between CD1 and CD2 (r=0.58, p<0.001), CD1 and Treg (r=0.65, p<0.0001), and CD2 and Treg (r=0.27, p<0.05) was found in SLE patients. In normal controls we did not observe a correlation among subpopulations of CD, and Treg. We did not observe a direct correlation among CD1, CD2, and Treg with SLAM-M in SLE patients.

**Conclusions:** The significant decrease of CD2 during pregnancy, and CD1 in postpartum of SLE patients, with positive correlation among CD1, CD2, and Treg without correlations with SLE activity may reflect the immunological and subclinical activity of SLE. These alterations may be associated with maternal-fetal complications observed in these patients despite of treatment.

**Disclosure:** L. J. Jara: None; G. T. Romero-Sánchez: None; L. A. Montiel-Cervantes: None; G. Medina: None; P. Cruz-Cruz: None; J. Vela-Ojeda: None; R. Arias-Flores: None; O. Vera-Lastra: None; M. A. Saavedra Salinas: None.

### 1151

**Distinctions in the ISN/RPS 2003 Subclasses of Class IV Lupus Nephritis.** Suhail Hameed1, Kun Chen2, Surya Seshan3 and Michael D. Lockshin1. 1Hosp for Spec Surgery, Cornell, New York, NY, 2Hospital for Special Surgery, Cornell, New York, NY, 3Weill Cornell Medical Center

**Purpose:** We hypothesized that the ISN/RPS 2003 classification subclasses of Class IV Lupus Nephritis (LN) better correlate with respect to clinical, immunological and prognostic distinctions. The distinction between the subclass IV-Segmental (IV-S) and IV-Global (IV-G) has been the subject of a few prior studies without a consensus in conclusions. Whether this distinction between IV-S and IV-G will be retained in future iterations of ISN/RPS classification will depend on how distinct these subclasses prove to be.

**Methods:** This is a single institution retrospective study comparing the ISN/RPS 2003 Class IV LN subclasses, 95 SLE patients who had biopsy diagnosed Class IV LN from 1990 to 2007 and had clinical follow-up at our institutions were included.

All renal biopsies were reclassified according to the ISN/RPS 2003 LN classification by a single renal pathologist. Relevant clinical data was collected from the medical records of the subjects. The investigators were blinded to the histopathologic and clinical data of the subjects until all data collection was complete. A comparison of IV-S and IV-G with respect to clinical, morphological and pre-defined outcome measures was made. Independent samples t-test for means, Fischer’s exact test and Kaplan-Meier survival curves were performed for statistical analysis.

**Results:** Out of the 95 Class IV LN patients, there were 58 G (61%) and 37 S (39%). Overall, there were 82.8% females and 17.2% males with 16.7% Caucasians, 30.8% African Americans, 34.6% Hispanics and 17.9% Asians. 53.7% had Medicaid and 46.3% had private medical insurance.

The mean duration of follow-up since renal biopsy was 93.79 months and mean duration of SLE at diagnosis of lupus nephritis was 50.30 months. The mean age at diagnosis of SLE was 22.13 years and mean age at diagnosis of LN was 26.42 years. Significant clinical and histopathologic distinctions in ISN/RPS 2003 subclasses of Class IV LN were noted as shown in figure 1.

**Figure 1.** Shows significant clinical and histopathologic distinctions in ISN/RPS 2003 Subclasses of Class IV LN.

**Table: Mean baseline clinical characteristics**

<table>
<thead>
<tr>
<th>Mean baseline clinical characteristics</th>
<th>Segmental</th>
<th>Global</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>31.90</td>
<td>29.59</td>
<td>0.057</td>
</tr>
<tr>
<td>Lymphocyte (%)</td>
<td>13.12</td>
<td>20.59</td>
<td>0.001</td>
</tr>
<tr>
<td>Neutrophil (%)</td>
<td>79.93</td>
<td>71.20</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum albumin (G/dl)</td>
<td>2.72</td>
<td>2.49</td>
<td>0.034</td>
</tr>
<tr>
<td>Urate protein (gm/24hr)</td>
<td>3.44</td>
<td>4.78</td>
<td>0.055</td>
</tr>
</tbody>
</table>

**Table: Histopathologic characteristics**

<table>
<thead>
<tr>
<th>Histopathologic characteristics (% Present)</th>
<th>Segmental</th>
<th>Global</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segmental Cellular Proliferation</td>
<td>9.19</td>
<td>6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global Cellular Proliferation</td>
<td>2.7</td>
<td>94.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Segmental Glomerulonecrosis</td>
<td>45.9</td>
<td>13.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Global Glomerulonecrosis</td>
<td>45.9</td>
<td>29.3</td>
<td>0.099</td>
</tr>
<tr>
<td>Fibrinous Crescents</td>
<td>43.2</td>
<td>22.4</td>
<td>0.032</td>
</tr>
<tr>
<td>Interstitial Fibrosis</td>
<td>64.9</td>
<td>43.1</td>
<td>0.038</td>
</tr>
<tr>
<td>Tubular Atrophy</td>
<td>67.6</td>
<td>50.0</td>
<td>0.092</td>
</tr>
<tr>
<td>Wire Loops</td>
<td>27.0</td>
<td>81.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyaline Thrombi</td>
<td>2.7</td>
<td>41.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Subclass G had hypocomplementemia, hypoalbuminemia, increased proteinuria, hyaline thrombi, wire loops and higher activity index, implying an immune complex etiopathogenesis. Subclass S had higher hematocrit, relative lymphopenia and neutrophilia, higher chronicity, glomerulonecrosis and fibrosis suggesting more of a pauci-immune and relapsing process. Subclasses S and G had similar outcomes and there was no statistically significant difference in any of the pre-defined outcome measures including remission, relapse, doubling of serum creatinine, ESRD and death.
Conclusion: S and G are clinically and morphologically distinct subclasses of Class IV LN suggesting different underlying pathogenetic mechanisms. Currently the 2003 ISN/RPS classification does not distinguish the prognosis of subclass S from G. Therapeutic advances targeting the different pathogenetic mechanisms for these subclasses, might yield a change in their prognosis.

Disclosure: S. Hameed: None; K. Chen: None; S. Seshan: None; M. D. Lockshin: None.

1152
Does Smoking Influence Disease Manifestations and Disease Severity in Systemic Lupus Erythematosus? Nayeef Al Ghanim1, Aqeel Ghanem2, Ebrahim Nahar3, John M. Esdaile4 and Diane Lacaille5. 1Mubarak Al Kabeer Hospital, 2Vancouver, BC, Canada, 3University of British Columbia, Vancouver, BC, Canada

Objective: Several studies have established that smoking is a risk factor for Systemic Lupus Erythematosus (SLE). However, few studies have evaluated whether smoking influences disease manifestations or disease activity and severity.

The objective of our study was to evaluate whether smoking is associated with differences in pattern of organ involvement and with greater disease severity, as measured by the SLICC.

Method: A retrospective medical chart review was conducted between 2002 and 2005 of all SLE patients seen since 1990 from eight rheumatology practices. All patients included met the 1982 ACR criteria for SLE. Data were extracted on: demographics, SLE duration, SLE treatment, SLICC, and organ involvement using predefined criteria derived from the SLAM, and current smoking status at baseline (ie time of first rheumatologist visit). Smokers and non-smokers were compared using Chi-square for categorical variables and Student t-test for continuous variables. To take into account the multiple comparisons tested, we considered p < 0.01 as statistically significant. SLICC score, because of its skewed distribution, was analyzed as a binary variable with a cut off of 2 (i.e. values of 0 or 1 vs. values of 2 or greater). Multivariable binary logistic regression analysis was performed with SLICC score as the dependent variable, controlling for SLE duration, age, gender, and ethnicity.

Results: Our sample included 306 patients, 52 were smokers and 254 non-smokers (92% women, mean (SD) age 43.3 (12.9) years, disease duration 12.2 (8.8) years). No significant differences were observed in the pattern of organ involvement between smokers and non-smokers (Table 1). A trend was observed with smokers having increased frequency of antiphospholipid syndrome (APLS) compared to non-smokers (31.4% vs 17%, respectively, p = 0.03). However, it did not reach statistical significance at the preselected level of p < 0.01. No difference was observed in the medications received for SLE, such as glucocorticosteroids or immunosuppressant medications (data not shown). After adjusting for age, gender, disease duration and ethnicity, the likelihood of severe disease, as measured by SLICC >= 2, was not increased in smokers compared to non-smokers (OR: 1.18, 95% CI: 0.56–2.46).

Conclusion: In our sample of SLE patients, there was no association between smoking and the pattern of organ involvement or disease severity measured by SLICC.

Disclosure: N. Al Ghanim: None; A. Ghanem: None; E. Nahar: None; J. M. Esdaile: None; D. Lacaille: None.

1153
Early Treatment with Rituximab (RTX) in Newly Diagnosed Systemic Lupus Erythematosus (SLE) Patients: A Steroid Sparing Regimen. Amara N. Ezeonyeji1 and David A. Isenberg2. 1UCL Div of Medicine, Room 331, 3rd Floor, London, United Kingdom, 2University College London Hospital NHS Trust, London, United Kingdom

Introduction: The efficacy of a RTX as induction therapy enabling long-term steroid therapy reduction or withdrawal has recently been reported in patients with lupus nephritis by Pepper et al.1 We describe a RTX/Azathioprine (AZA) based steroid sparing regimen given in 9 newly diagnosed mostly non-renal patients with SLE.

Patients and Methods: Nine female patients fulfilling at least 4 of the revised ACR criteria for the diagnosis of SLE were treated. Mean age at time of B cell depletion therapy was 39 years, Mean duration of symptoms prior to treatment was 16.5 months (range 4–96). Eight were treated with two intra-venous (iv) infusions of RTX (1000mg) and methylprednisolone (2 x 100mg) and one iv 750mg infusion of cyclophosphamide (Cyc). One patient received 375mg/m² equivalence RTX over 3 weeks with CYC. Post treatment all patients received AZA and any steroid treatment rapidly weaned [table 1]. The British Isles Lupus Assessment Group (BILAG) disease activity index was used for both individual organ system assessment and as a global index. The patients full blood count, serum creatinine (Cr), serum C3, immunoglobulin G (IgG), erythrocyte sedimentation rate (ESR), anti-dsDNA and circulating B lymphocytes (CD19+) count were tested at baseline, 1, 3, 6 and 12 months post treatment.

Table 1. Patient characteristics: prednisolone; pred; weeks; wks

<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease manifestation at baseline</th>
<th>Therapy pre-RTX</th>
<th>Therapy post-RTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Headache, rash, pleurisy, proteinuria</td>
<td>Pred 30 mg d over 8 weeks for flare</td>
<td>Pred 40 mg d over 4 wks</td>
</tr>
<tr>
<td>2</td>
<td>Rash, lymphadenopathy, angioedema, fevers, anti-dsDNA, lymphopenia</td>
<td>Dexamethasone 120mg d.i.m.</td>
<td>Pred 20mg d over 8 wks at 2 months for flare</td>
</tr>
<tr>
<td>3</td>
<td>Rash, headache, alopecia, sicca symptoms, C3, C4, lymphopenia</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Rash, headache, thrombocytopenia, anaemia, proteinuria</td>
<td>AZA (stopped) &amp; Pred 2.5 mg Pred 30mg d over 2 wks for thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Rash, livedo racemosa, serositis, oral ulcers, proteinuria, anti-dsDNA, lymphopenia</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Polyarthritis, anti-dsDNA, lymphopenia</td>
<td>Pred 7.5mg d over 2 wks</td>
<td>AZA</td>
</tr>
<tr>
<td>7</td>
<td>Skin rash, raiynads, alopecia, pleurisy, anti-dsDNA, lymphopenia</td>
<td>None</td>
<td>AZA</td>
</tr>
<tr>
<td>8</td>
<td>Rash, alopecia, raiynads, arthralgia, C3</td>
<td>None</td>
<td>AZA</td>
</tr>
<tr>
<td>9</td>
<td>Polyarthritis, anti-dsDNA, lymphopenia</td>
<td>AZA for colitis</td>
<td>AZA</td>
</tr>
</tbody>
</table>

Results: All patients achieved B cell depletion (CD 19 < 0.005 x 10⁹/μL) at 1 month). Patient 3 re-populated at 6 months but did not flare. The mean BILAG global score fell from 12.1 (SD 8.6) (n=9) at baseline to 7.4 (SD 4.7) (n=7) at 1 month, 3.9 (SD 2.3) (n=7) at 3 months, 3.5(SD 1.3) (n=4) at 6 months, and 1.5 (SD 0.7) (n=2) at 1 year. Patients 7 achieved improvement of BILAG grades A→D for mucocutaneous manifestations by 3 months and patient 2 and 8 by one year although patient 2 had a musculoskeletal flare at 2 months requiring steroid treatment. No patient developed any major sustained deterioration i.e. new A or D→B scores. Manifestations such as rash, arthritis, fever, thrombocytopenia and pleurisy responded well. Mean ESR fell from 76 to 32.9 at 3 months for flare and patient 2 had a musculoskeletal flare at 2 months requiring steroid treatment. Mean total serum IgG fell modestly from 15 mg/mmol by 1 month in patient 4. Mean total serum IgG fell modestly from 20.3 to 13.8 g/l.

Abbreviations: MSK: Musculoskeletal; CNS: Central Nervous System; APLS: Antiphospholipid syndrome; GI: Gastrointestinal System

Disclosure: None.

15 mg/mmol by 1 month in patient 4. Mean total serum IgG fell modestly from 20.3 to 13.8 g/l.

1 Headache, rash, pleurisy, proteinuria
2 Rash, lymphadenopathy, angioedema, fevers, anti-dsDNA, lymphopenia
3 Rash, headache, alopecia, sicca symptoms, C3, C4, lymphopenia
4 Rash, headache, thrombocytopenia, anaemia, proteinuria
5 Rash, livedo racemosa, serositis, oral ulcers, proteinuria, anti-dsDNA, lymphopenia
6 Polyarthritis, anti-dsDNA, lymphopenia
7 Skin rash, raiynads, alopecia, pleurisy, anti-dsDNA, lymphopenia
8 Rash, alopecia, raiynads, arthralgia, C3
9 Polyarthritis, anti-dsDNA, lymphopenia

AZA for colitis

AZA
Adverse Events: Treatment was safe and well tolerated. There were no adverse events on follow up.

Conclusions: A RTX/AZA protocol as a steroid sparing regimen is safe and effective in newly diagnosed patients with SLE.

References:

Disclosure: A. N. Ezeonyeji: None; D. A. Isenberg: Roche, 9.

1154

Evidence of Peripheral B Cell Depletion in Subjects with Controlled Systemic Lupus Erythematosus (SLE) Following Subcutaneous Administration of SBI-087. Roy M. Fleischmann1, Stanley B. Cohen2, Patricia Pardo3, Marianne L. Shaw4, Megan E. B. Clowse2, Kyri Denuassi-Joannopoulos5, Indranil Bhattacharya6, Sudhakar T. Sridharan7, Annette Diehl7 and Ian Gourley8. 1Altoona Center for Clinical Research, Duncansville, PA; 2Duke University, Durham, NC; 3Metroplex Clinical Research Center, Dallas, TX; 4Miami Research Associates, 5Pfizer Inc, Collegeville, PA; 6Rheumatology Associates, Dallas, TX

Background: Preclinical data have shown a critical role of B cells in murine SLE models. Positive results from several open-label trials with CD20+ depleting agents and other B cell directed therapies support targeting B cells in human SLE. There have been two negative controlled studies of rituximab in SLE; however methodologic issues may have contributed to these results. SMIP™ biologics are disulfide bonded single chain polypeptide comprising binding, hinge, and constant domains designed to meet preclinical and pharmacological specifications for diseases such as SLE. SBI-087 is a humanized SMIP biologic directed against the CD20 antigen located on B cells. SBI-087 is structurally different from rituximab, and has shown B cell depletion to the lower limit of quantitation (0.3 cells/uL) between wks 2 and 4. The 75 mg dose depleted peripheral blood B cell levels in all subjects below 20 cells/uL, by wk 4. SBI-087 has been generally well tolerated. Treatment-emergent adverse events (AEs) in more than 1 subject were upper respiratory tract infection, back pain, diarrhea, headache, fatigue, anxiety, chills, flushing, muscle spasms, nasopharyngitis, pain in extremities, and somnolence. Serious AEs included pregnancy, ankle fracture, spinal stenosis, diverticular perforation, and urinary tract infection. Chills occurred in 2 subjects after administration of 25 mg SC, and were abrogated in the 75 mg SC cohort with a day-of-treatment oral steroid regimen. 2 subjects in the 200 mg SC cohort had moderate flushing on the day of injection that was self-limiting. Injection site reactions have not been seen in any subject. Immunoglobulin levels have remained within normal limits in all subjects.

Conclusions: SBI-087 given as a single SC dose with a day-of-treatment oral steroid regimen appears to be generally well tolerated with an acceptable safety profile. B cell depletion has been observed in all SC cohorts dosed to date. Data from later timepoints for the 200 mg SC cohort will be necessary to fully explore the exposure/B cell response relationship and to select doses for future studies in SLE.

<50. For those >40, the 10 year probabilities of a major OP event (FRAX Major) and hip fracture (FRAX Hip) were calculated using age, sex, BMI, past fractures, family history, smoking, alcohol, presence of rheumatoid arthritis, steroid use and femoral neck BMD. Risks high enough to warrant pharmacological treatments are >20% for FRAX Major and >3% for FRAX Hip.

**Results:** Subjects had a mean (SD) age of 43.8 (13.1) years, SLE duration of 11.6 (10.4) years, BMI (kg/m²) of 26.3 (6.3), 57% were smokers, 44% were non-drinkers, 38% were postmenopausal, 28% had a prior fracture, 24% were on steroids >7.5 mg, and 41% were on steroids for at least 3 months. Calcium and vitamin D were used by 48% and 39% respectively. There was a significant correlation between BMD of the femoral neck (r = -0.26, p = 0.001) and hip (r = -0.35, p < 0.01) with the duration of steroid use.

In females <50 years (32%), the mean t-scores of the spine, hip, and femoral neck were -0.73, -0.52, -0.78 respectively. OP was diagnosed overall in 48%, and in 11.5%, 4.2%, and 5.7% in spine, hip, and femoral neck respectively.

In females <50 (67.2%), the mean z-scores of the spine, hip, and femoral neck were -0.22, 0.11, and -0.19 respectively. Low bone mass was at the spine, hip, and femoral neck in 52.7%, 39%, and 2.8% of the participants.

Overall, there was no difference in BMDs based on calcium and vitamin D intake. However, spine BMD was significantly lower in those who took calcium and vitamin D compared with those who did not. We found a significant correlation between low spine BMD and low vitamin D intake. However, spine BMD was significantly lower in those who took calcium and vitamin D compared with those who did not.

**Conclusion:** Immunosuppression in addition to PAH-specific therapies may improve functional and exercise capacity in patients with SLE-PAH.

**Disclosure:** J. Ashour: None; Y. Sung: None; R. Zamanian: Actelion Pharmaceuticals US, 2, Gilead Sciences, Inc., 5, United Therapeutics, 5; L. Chung: Actelion Pharmaceuticals US, 8, Gilead Sciences, Inc., 2, United Therapeutics, 2.

1157

**Immunosuppression in the Treatment of Systemic Lupus Erythematosus Associated Pulmonary Arterial Hypertension: Improvement in Functional and Exercise Capacity.** Judith Ashouri1, Yon Sung2, Roham Zamanian2 and Lorinda Chung1. 1Stanford Univ Medical Center, Palo Alto, CA, 2Stanford University School of Medicine

**Purpose:** Accumulating evidence suggests that autoimmunity and inflammation are important in the pathogenesis of systemic lupus erythematosus associated pulmonary arterial hypertension (SLE-PAH). Several case reports and series have described improvement in dyspnea, exercise capacity, and hemodynamics with aggressive immunosuppression (IMM), both alone and in combination with PAH-specific therapies. We aimed to assess the effects of IMM in combination with PAH-specific therapies on the clinical outcomes of SLE-PAH patients followed at our center.

**Methods:** We identified 13 patients from Stanford’s PAH database diagnosed with PAH by right heart catheterization between 1999–2009. All patients fulfilled ACR criteria for a diagnosis of SLE based on medical record review, and patients who fulfilled ACR criteria for another connective tissue disease were excluded. All patients received PAH-specific therapies according to standard of care. Patients who underwent aggressive IMM for a minimum of 8 months between the baseline and follow-up evaluations were compared with those receiving PAH-specific therapies alone. Cumulative probability of freedom from worsening New York Heart Association functional class (FC) was calculated using the Kaplan-Meier estimator, and compared using the log-rank test. Follow-up time was calculated from the time of the baseline evaluation. The mean changes in clinical parameters were compared between the IMM and non-immunosuppression (non-IMM) groups using Student’s t-test.

**Results:** All patients were female, 69% Asian, 15% white, with a mean age of 38±9 years and mean SLE disease duration at PAH diagnosis of 5.6±1 years. 46% had a history of renal disease, 46% had Raynaud’s, and 38% a history of serositis. 100% were ANA+, 85% anti-dsDNA+, 71% anti-RNP+, 40% anti-Smith+, and 29% antiphospholipid antibody+. 4 (30%) patients were treated with aggressive IMM (with high dose steroids and mycophenolate mofetil, 1 with hematopoietic stem cell transplant) during a mean follow-up time of 14.2±4.3 months. At baseline, there were no significant differences in demographics, SLE clinical features or autoantibodies in patients treated with or without IMM, except for increased prevalence of oral ulcers in the IMM group (23% vs. 8%, p = 0.02). Baseline PAH disease duration (9±15 vs. 35±21 months), hemodynamics (mean right atrial pressure 13.1±6.1 vs. 7.5±4.9 mmHg, mean pulmonary arterial pressure 46±12.7 vs. 51±16.1 mmHg, cardiac index 2.6±0.7 vs. 2.3±0.6, peripheral vascular resistance 101.5±2 vs. 124±6.1 WU), FC (3.3±0.5 vs. 2.7±0.9), 6 minute walk distance (6MWD, 276±168 vs. 397±177 m), and PAH-specific therapies did not differ significantly between the IMM and non-IMM groups. At follow-up, hemodynamics and PAH-specific therapies did not differ between the groups. No patients in the IMM group had worsening FC (p = 0.45) compared with 1 out of 4 in the non-IMM group (p = 0.2). Mean improvements in FC (−2.2±1 vs. 0±1, p = 0.01) and 6MWD (+26±46 vs. +52±200 m, p = 0.054) were higher in the IMM group.

**Conclusion:** Imunosuppression in addition to PAH-specific therapies may improve functional and exercise capacity in patients with SLE-PAH.

**Disclosure:** J. Ashour: None; Y. Sung: None; R. Zamanian: Actelion Pharmaceuticals US, 2, Gilead Sciences, Inc., 5, United Therapeutics, 5; L. Chung: Actelion Pharmaceuticals US, 8, Gilead Sciences, Inc., 2, United Therapeutics, 2.

**Methods:** An extensive retrospective chart review was conducted on the records of 764 patients, including 91 men and 673 women, enrolled in the Michigan Lupus Cohort (MLC) from 2000 – present, to determine the frequency of administration of immunosuppressive drugs. The evaluation included all University of Michigan electronic records spanning 1992 – present, in addition to any available outside records. Chart review confirmed that patients satisfied ≥4 ACR criteria for SLE. An electronic medical search engine (EMERSE) was used to scan patient records for use of immunosuppressive drugs; all records were then carefully assessed to confirm that the immunosuppressive was prescribed to treat SLE. The use of CYC, MMF, azathioprine (AZA), and/or methotrexate (MTX) was then recorded if the drug was prescribed to treat SLE and the patient began treatment.

**Results:** Of the 764 patients enrolled, the majority of patients received treatment with at least one immunosuppressive drug including 81.3% of men and 72.1% of women. CYC was used by 52.7% men vs. 37.7% women (p = 0.006). MMF was used by 62.9% of men vs. 51.1% of women (p = 0.001). In contrast, AZA was used by 36.3% of men vs. 41.8% of women, and MTX was used by 16.5% of men vs. 26.6% of women (p = 0.0375). Approximately 75% of men in the MLC received at least one first line drug as treatment for their SLE.

**IMS Medications**

<table>
<thead>
<tr>
<th>Female</th>
<th>Male</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYC</td>
<td>254</td>
<td>48</td>
</tr>
<tr>
<td>MMF</td>
<td>344</td>
<td>63</td>
</tr>
<tr>
<td>CYC or MMF</td>
<td>388</td>
<td>68</td>
</tr>
<tr>
<td>AZA</td>
<td>281</td>
<td>33</td>
</tr>
<tr>
<td>MTX</td>
<td>179</td>
<td>15</td>
</tr>
<tr>
<td>None</td>
<td>188</td>
<td>17</td>
</tr>
</tbody>
</table>

(%) percent

**Conclusions:** There is a highly significant increase in the proportions of men who receive first line drugs for severe lupus, cyclophosphamide and...
myophenolone meftolin, compared with women. These data highlight the importance of fully characterizing pathogenic mechanisms contributing to the increased severity of lupus in men vs. women.

Disclosure: E. E. Lewis: None; E. Crooks: None; Z. Sun: None; P. C. Cagnoli: None; T. Gonzalez-Rivera: None; M. J. Kaplan: None; W. Marder: None; P. Raus: None; E. C. Somers: None; W. J. McCune: None.

1159

Increased Recruitment of Brain Activation within the Hippocampus in SLE Patients as Shown by Functional MRI May Be a Compensatory Mechanism To Cope with Memory Impairment. Daphna Paran1, Itai Glikmann-Johnston2, Talma Hendler2, Irena Litinsky3, Eli Vakil2, Dan Caspi3 and Irit Shapira-Lichter2. 1Department of Psychology and Gonda School at Houston, Houston, TX

Objectives: The hippocampus has been shown to have a major role in memory processes. Atrophy of the hippocampus has been correlated to cognitive impairment in SLE and other diseases. This study aimed to assess neural correlates of memory impairment within the hippocampus in SLE patients by functional MRI.

Methods: Twelve female SLE patients (mean age: 50±5.9 years; mean education: 14.6±1.7 years; disease duration 9.5±3.4 yrs; SLE disease activity index: 7.9±1.0) were recruited. SLE patients with overt NPSLE and 11 female healthy controls (mean age: 29.8±6.8 years; mean education: 15.1±1.3 years) underwent fMRI testing using an auditory verbal memory test. The paradigm consisted of three blocks of verbal encoding and repeated free recall steps followed by a recognition test. During retrieval blocks subjects indicated by pressing a key when a word was recalled or recognized. Brain activation patterns were evaluated within the hippocampus in both groups using this paradigm. Hippocampal volume was measured using Brain Voyager QX.

Results: Free recall was impaired in SLE patients as compared with healthy subjects (p<0.05). Among SLE patients, learning was correlated with hippocampal responsiveness to the encoding task, reflected in the percent signal change in activation from baseline to each of the encoding blocks (EB) (left hippocampus: EB1: r=−0.38, p<0.05; EB2: r=−0.39, p<0.05; EB3: r=−0.4, p<0.05; right hippocampus: EB1: r=0.4, p<0.05; EB2: r=0.36, p<0.05; EB3: r=0.37, p<0.05). No such correlation was seen in the healthy controls. Furthermore, greater activations were evident within both the right and left hippocampus in SLE patients compared to controls during the encoding, free recall and recognition tests. The left hippocampus was significantly smaller in SLE patients as compared to controls (p<0.05), however there was no correlation between hippocampal volume and learning abilities (i.e. number of learned words).

Conclusions: SLE patients demonstrated memory difficulties along with greater activity in the hippocampus as compared to healthy controls. This increased activity correlated with learning performance. These findings suggest that increased brain activation within the hippocampus during learning in SLE patients may reflect compensatory mechanisms required to overcome impaired memory and learning abilities and cope with memory tasks.

Disclosure: D. Paran: None; I. Glikmann-Johnston: None; T. Hendler: None; I. Litinsky: None; E. Vakil: None; D. Caspi: None; L. Shapira-Lichter: None.

1160

Inhibition of Complement Activation by Heparins but Not Fondaparinux on Alternative, Mannose/Mannan Binding Lectin (MBL) and Classical Pathways in Active SLE with Low C3/C4. Andrea A. Ramirez1, Ankur A. Kamdar2 and Barry L. Myones1. 1Baylor College of Medicine/ Texas Children’s Hospital, Houston, TX; 2University of Texas Medical School at Houston, Houston, TX

Background: Activation of 1 or more of the complement cascades has been implicated in disease pathogenesis in several autoimmune disease processes including SLE and antiphospholipid antibody syndrome (APS). Low molecular weight heparins (LMWH) have been used to treat thrombosis, microangiopathic processes and anecdotally in the therapy of giant coronary aneurysms in Kawasaki Disease. Unfractionated heparin (UHF) and LMWH have also been implicated in classical pathway complement inhibition in APS.

We have previously demonstrated complement inhibition only at suprapharmacologic levels of heparin (5 to 10x the accepted therapeutic cutoff).

Purpose: Evaluate the effect of UHF, LMWH, and a factor Xa inhibitor (fondoparinux) on cell membrane-associated classical (CP), MBL, and alternative pathway (AP) activation in vitro utilizing serum with normal and very low C3/C4 (simulating active SLE).

Methods: AP hemolytic assay was modified to 100% lysis. Unsensitized rabbit erythrocytes (Rae) (direct activator of human AP) (±1.25 ×106 in GVB/MgEGTA (blocks CP activation by calcium chelation) were utilized per tube. Sheep erythrocytes (ShE) were sensitized with mannan by CrC3 incubation in MBL assay (GVB/Ca+++/Mg++). ShE were sensitized with hemolysin (anti-ShE IgM) in CP hemolytic assay. Varying doses of UHF or enoxaparin (0.5–10 I.u/ml final concentration) or fondoparinux (1.25 – 6.25 mg/ml) were added to normal human serum (C3 120–140 mg/dL; C4 >15 mg/dL) and non-active/inactive SLE (C3 25–50 mg/dL; C4 0–10 mg/dL) as complement sources. (C3/C4 ascertained by Mancini immunodiffusion; C4 allotyping performed on test sera). Mixtures were incubated up to 30 minutes @37°C. Supernatants were assessed at OD541 and expressed as % lysis against controls.

Results: Escalating doses of enoxaparin or UHF (up to 20 I.u/ml) resulted in increased % inhibition of complement-mediated Rae or ShE lysis (1mg enoxaparin ~100 IU anti-Factor-Xa activity) whereas fondoparinux had no appreciable inhibition of lysis in control or patient serum. A small % inhibition (~20%) of membrane-associated complement activation was noted at anti-factor-Xa activity levels achievable with standard therapeutic anticoagulant regimens of UHF or LMWH, but LMWH > UHF achieved inhibition at higher (~2 I.u/ml) dosing levels for CP > AP components for both controls and SLE patients (only ~50–70% inhibition at 5 I.u/ml). Sera with higher C3/C4 (>140 mg/dL; >20 mg/dL) were much harder to inhibit. Sera with limited C3/C4 levels (~<30 mg/dL; <5 mg/dL) resulted in significantly more inhibition of complement-mediated Rae or ShE lysis at lower dosing levels of UHF or LMWH (1 to 2 IU/ml).

Conclusions: UHF and LMWH inhibit membrane-associated complement activation via all 3 pathways in vitro while fondaparinux, a factor Xa inhibitor, had no effect. Anticoagulation effects were again discordant from complement inhibitory effects in controls and SLE patients with normal C3/C4 levels. Active SLE sera with very low C3/C4 levels resulted in inhibition by heparins at 1.5 to 2 IU/ml dosing levels (lower bleeding risk). These data suggest heparins as an additional therapeutic modality in very active SLE patients with limited complement supply.

Disclosure: A. A. Ramirez: None; A. A. Kamdar: None; B. L. Myones: None.

1161


1Baylor College of Medicine/ Texas Children’s Hospital, Houston, TX; 2National Institute of Neurological Disorders and Stroke, Bethesda, MD, 3National Institute of Arthritis, Musculoskeletal and Skin Diseases, 4National Institute of Diabetes, Digestive and Kidney Diseases, 5National Institute of Neurological Diseases and Stroke, 6National Institute of Arthritis, Musculoskeletal and Skin Diseases, 7National Institute of Diabetes, Digestive and Kidney Diseases, 8National Institute of Arthritis, Musculoskeletal and Skin Diseases, 9National Institute of Diabetes, Digestive and Kidney Diseases, 10National Institute of Neurological Disorders and Stroke, 11NIDCR, NIH #10 1N114, Bethesda, MD

Background: Despite improvements in the outcomes of SLE patients with major organ involvement, treatment failure and relapse continue to affect significant proportion of patients. In this pilot study we tested if intensive lymphoablation followed by autoH SCT can lead to sustained, complete, treatment-free remission in severe, recalcitrant SLE and whether this approach fundamentally changes abnormal immune response.

Methods: Patients were enrolled with active SLE despite prior treatment with IV cyclophosphamide (CYC). Of the 8 patients treated, 2 had transverse myelitis, 1 retinal vasculitis and 5 WHO Class IV nephritis. Stem cell mobilization regimen consisted of 2,000 mg/m2 RTX, 750 mg/m2 rituximab (RTX) and G-CSF. Conditioning regimen consisted of 750 mg/m2 RTX, 4.8 ± 1.9 mg/m2 cyclophosphamide (CYC) and 120 mg/m2 fludarabine, followed by CD34+ selected stem cell infusion and G-CSF.

All immunosuppressive medications and hydroxychloroquine (HCQ)
Microembolic Signals Detected by Transcranial Doppler Ultrasound Corresponds to Persistence of Foramen Ovale in Neuropsychiatric Lupus with Brain MRI Abnormalities. Melissa Padovan1, Alessandra Bortoluzzi2, Cristiano Azzini3, Alessandro De Vito4, Maria Rosaria Tola4, Francesco Trotta3 and Marcello Govoni4. 1Neurology Unit, Department of Neurosciences, Azienda Ospedaliero-Universitaria Sant’Anna, Ferrara, Italy, 2Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Ferrara and Azienda Ospedaliero-Universitaria Sant’Anna - Ferrara, Ferrara, FE, Italy, 3Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Ferrara and Azienda Ospedaliero-Universitaria Sant’Anna - Ferrara (Italy)

Background: Magnetic resonance imaging (MRI) abnormalities, as small punctuate hypointense lesions in subcortical and periventricular brain white matter areas (WMHL) are a frequent but not specific finding in systemic lupus erythematosus (SLE) patients with and without neuropsychiatric (NP) involvement. Their pathogenesis is not fully understood yet, being recurrent cerebral ischemia - detectable through transcranial Doppler ultrasound (TCD) - one of the hypothesized mechanism. In general population microembolic signals (MES) may be detected with a reported frequency of about 15 % often due to the persistence of foramen ovale.

Aim: To assess the frequency of microembolic signals (MES) by using transcranial Doppler (TCD) ultrasound in SLE patients with and without brain MRI abnormalities.

Methods: A TCD registration to detect MES from the middle cerebral artery was carried out according to a local standardized protocol in 21 SLE patients (mean age of 42.2 years, range 32–55) with and without NP involvement lupus, after exclusion of aortic and/or carotid atheromatous disease. In all patients brain magnetic resonance imaging (MRI) and transesophageal echocardiography were performed. Patients were stratified in two groups, with and without MRI WMHL and compared. Antiphospholipids antibodies (APL) and lupus anticoagulant (LA) status were checked too.

Results: MES were detected in a total of 11 patients (52.3%), 4 APL/LA+ and 7 APL/LA-, 9 out of 15 patients (60 %) with abnormal MRI and history of NP SLE had MES compared with 2 out of 6 patients (33.3 %) with normal MRI (1 NPSLE and 5 without NP involvement). No correlations between MES and APL or LA were found. The persistence of foramen ovale was confirmed in almost all case of MES detection. However with abnormal MRI only one case did not show persistence of foramen ovale.

Conclusion: Compared with what has been reported in general population, MES is a frequent finding in SLE patients irrespective of their previous history of NP involvement and more prevalent in patients with MRI abnormalities compared with patients with normal MRI. These finding either suggest caution in the interpretation of MRI pictures and a careful evaluation of MES in patients with MRI abnormalities which should be included in the work-up of SLE patients prompting further investigations for micro-embolic sources (i.e. carotid plaques and/or right-left shunt due to the persistence of foramen ovale).

Disclosure: M. Padovan: None; A. Bortoluzzi: None; C. Azzini: None; A. De Vito: None; M. R. Tola: None; F. Trotta: None; M. Govoni: None.

1163

Multivariate Analysis of Vitamin D Insufficiency and Deficiency in SLE: The SOLD (Systemic Lupus Associates of Low Vitamin D) Project. Caroline D’Souza, Kayode Jibril Bello, Hong Fang, Laurence Magder and Michelle A. Petri. 1Timonium, MD, 2Johns Hopkins University, 3University of Maryland

Purpose: Vitamin D is an important immunomodulator in animal models of autoimmune diseases. In humans, in addition to its role in bone health, it may be important in the prevention of diabetes, cardiovascular disease, and certain cancers. We explored clinical and laboratory associates of Vitamin D insufficiency (<32 ng/mL) and deficiency (<15 ng/mL) in SLE.

Methods: 810 SLE patients (mean age 44.94, 49.54% Caucasian, 40.36% African-American, 92.07% female) were included. 25 OH Vitamin D was measured from July 2009 to April 22, 2010.

Results: Univariate analyses suggested that age, ethnicity, hypertension, diabetes, physician global assessment of SLE activity (PGA), urine protein/creatinine ratio (>0.5), systolic blood pressure, cholesterol, and obesity were associated with both Vitamin D insufficiency and Vitamin D deficiency.

Table 1. Association between various factors and deficiency/insufficiency of Vit D in patients with SLE based on a multivariable logistic regression model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI) with Vit D Deficiency</th>
<th>P-Value</th>
<th>Odds Ratio (95% CI) with Vit D Insufficiency</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>31–49</td>
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<td>0.524</td>
<td>1.20 (0.77; 1.85)</td>
<td>0.419</td>
</tr>
<tr>
<td>50+</td>
<td>0.40 (0.21; 0.78)</td>
<td>0.007</td>
<td>0.63 (0.39; 0.99)</td>
<td>0.048</td>
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<td>Race</td>
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<td>1.00 (reference)</td>
<td></td>
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<tr>
<td>White</td>
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<td></td>
<td>1.00 (reference)</td>
<td></td>
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<tr>
<td>Black</td>
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<td>0.001</td>
<td>2.18 (1.57; 3.04)</td>
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</tr>
<tr>
<td>Other</td>
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<td>1.22 (0.68; 2.18)</td>
<td>0.501</td>
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<tr>
<td>Urine Pr/Cr Ratio</td>
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<td>1.00 (reference)</td>
<td></td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>&gt;0.5</td>
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<td>0.967</td>
<td>1.71 (0.90; 3.24)</td>
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</tr>
<tr>
<td>BMI</td>
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<td>0.003</td>
<td>2.51 (1.79; 3.33)</td>
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<tr>
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<tr>
<td>&gt;200</td>
<td>1.43 (0.93; 2.21)</td>
<td>0.102</td>
<td>1.79 (1.26; 2.55)</td>
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<td></td>
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<tr>
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<td>1.49 (0.85; 2.61)</td>
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</tbody>
</table>

However, in the best multivariate logistical regression model (see table 1), age, ethnicity, and obesity remained statistically significant, but urine protein/creatinine ratio did not. In the best multivariate linear regression model (see table 2), urine protein/creatinine ratio was significantly associated with Vitamin D levels.

Table 2. Association between various factors and Vit D levels in patients with SLE based on a multivariable linear regression model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect on Mean Vit D</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>0.04</td>
<td>0.005</td>
</tr>
<tr>
<td>Race (Black vs White)</td>
<td>1.37 (1.02; 1.84)</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic BP (per mmHg)</td>
<td>-7.54 (2.31; 12.87)</td>
<td>0.156</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.04</td>
<td>0.044</td>
</tr>
<tr>
<td>Urine Pr/Cr Ratio</td>
<td>1.55</td>
<td>0.78</td>
</tr>
<tr>
<td>BMI</td>
<td>0.29</td>
<td>0.07</td>
</tr>
<tr>
<td>Cholesterol (per mg/dL)</td>
<td>-0.04 (0.01; 0.08)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Conclusion: Younger age, African-American ethnicity and obesity are associated with both Vitamin D insufficiency and deficiency, after adjustment for other variables, in multiple variable models. The association with urine protein/creatinine ratio, however, did remain in the multivariate linear regression model. This suggests that Vitamin D deficiency may play a role in renal lupus.

Disclosure: C. D’Souza: None; K. J. Bello: None; H. Fang: None; L. Magder: None; M. A. Petri: None.

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Network Analysis of Associations between Serum Interferon Alpha, Serology, and Clinical Features in Systemic Lupus Erythematosus in a Large Multi-Ancestral Cohort.

Corinna E. Weckerle1, Beverly S. Franek2, Jennifer Kelly2, Marissa Kumabe2, Rachel Mikolaitis3, Stephanie Green4, Gail R. Bruner5, Tammy O. Utset6, Meenakshi Jolly7, Judith A. James1, John B. Harley8 and Timothy B. Niewold9. 1Oklahoma Med Research Foundation, Oklahoma City, OK, 2Oklahoma Medical Research Foundation, Oklahoma City, OK, 3Rush University Med Ctr, 4Univ of Chicago Med Ctr, Chicago, IL, 5Rush University Med Ctr, 6Univ of Chicago Med Ctr, Chicago, IL, 7Univ of Chicago Med Ctr, 8Univ of OK Hlth Sci Ctr, Oklahoma City, OK, 9University of Chicago, Chicago, IL

Background: Interferon-alpha (IFN-α) is a primary pathogenic factor in systemic lupus erythematosus (SLE), and high IFN-α levels may be associated with particular clinical manifestations. The prevalence of individual clinical and serological features differs significantly by ancestry. We used logistic regression modeling to establish the network of associations between clinical and serologic manifestations and serum IFN-α in SLE patients from multiple ancestral backgrounds.

Methods: We analyzed the presence or absence of ACR clinical criteria for SLE, autoantibodies, and high serum IFN-α in 1089 SLE patients (387 African-American, 186 Hispanic-American, and 516 European-American). Iterative multivariate logistic regression was performed in each background separately to establish associations between variables, and network diagrams were constructed illustrating associations that were significant following Bonferroni correction.

Results: We found 14 unique associations forming network maps of relatively sparse density in each background. Of those, only 7 associations were shared by more than one ancestral background. Network maps of the interactions between clinical criteria were different in different ancestral backgrounds. In contrast, associations between autoantibodies and IFN-α were very similar in different backgrounds. In all backgrounds, high IFN-α was associated with presence of anti-Ro and anti-dsDNA antibodies (p-values 4.6×10−18 and 2.9×10−18 respectively). IFN-α and serology were not associated with ACR clinical features in these multivariate models.

Conclusions: Serum IFN-α was strongly and consistently associated with serology, and not independently associated with clinical features in SLE. Our study suggests that IFN-α may be more relevant to humoral tolerance and initial disease pathogenesis than ongoing late clinical disease manifestations.

Disclosure: C. E. Weckerle: None; B. S. Franek: None; J. Kelly: NIH, 2; M. Kumabe: None; R. Mikolaitis: None; S. Green: None; G. R. Bruner: None; T. O. Utset: Genentech and Biogen IDEC Inc, 5; M. Jolly: None; J. A. James: NIH, 2; J. B. Harley: NIH, 2, Rheumatinions, Inc., 2; T. B. Niewold: NIH, 2.

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Peripheral Neuropathy in Patients with Systemic Lupus Erythematosus.

Brandusa Florica2, Jiandong Su1, Ellie Aghdassi1, Dafna D. Gladman1, Murray B. Urowitz1 and Paul R. Fortin1. 1University Health Network, 2University of Toronto, Toronto, ON, Canada

Background: Peripheral neuropathy (PN) is a common feature of neuropsychiatric syndromes in Systemic Lupus Erythematosus (SLE) that can affect the quality of life of these patients. Currently the studies describing the clinical features of SLE patients with PN are scarce.

Objective: To determine in SLE patients: 1) the prevalence, the clinical course of PN and the impact on quality of life, 2) the clinical features and sub-classes of PN, and 3) whether there is an association between PN and any other clinical feature.

Methods: Patients who met at least 4 of the ACR classification criteria and met the ACR case definition criteria for peripheral neurological SLE were selected from the database registry of the University of Toronto Lupus Clinic. Chart review was performed to confirm clinical findings, determine the contributing factors and outcome of PN. PN found to be due to non-SLE causes were analyzed but kept in a separate group than SLE-related PN. Demographic data including age, gender and SLE duration, as well as SLE related clinical and investigational data at the time of the first appearance of PN were extracted by chart review. Disease activity and damage were assessed by SLEDAAcitivity Index (SLEDAI-2K) and SLICC Damage Index (SDI) at the time of the first appearance of PN. Quality of life was determined using the SF-36 questionnaire and scored for the physical (PCS) and mental (MCS) component summary scores. Data were analyzed using SAS statistical program.

Results: Out of 1520 patients in the database, 210 (14%) with a mean (SD) ACR criteria of 5.7 (2.0) met the inclusion criteria. Subjects had mean (SD) for age of (44.14) years and SLE duration of 9.2 years (10.2); median (IQR) for SLEDAAcitivity Index of 6.0 (IQR: 20.0, 12.0) and SDI of 1.0 (IQR: 0.0, 2.0); and 86.6% were female. Among patients, 66.9% had at least one SLE-related or possible SLE-related PN including mononeuropathies multiplex (14.2%), sensory PN (27%) and mononeuropathy (25.8% including cranial neuropathy in 7.4%). Asymmetric presentation was most common (62.8%), and distal weakness occurred in 31.8% of patients. Peroneal nerve (61.4%), sural nerve (51.8%) and median nerve (40.9%) were frequently involved. Associated SLE features were: 85% arthritis, 69.3% rash, 47.8% CNS involvement. ANAs of 1:320 or higher was significantly more prevalent in patients with SLE-related PN than non-SLE related PN (43.5% vs. 21.4%; p=0.028). EMG/NCS was performed in 67.7% of patients and indicated axonal neuropathy in 76.8% and demyelination in 18.3% of patients. Treatment included oral steroid in 85.4%, cyclophosphamide in 19.3% and pulse steroids in 7.9% of patients. Chart review completed in 130 of the patients, showed that 67.7% of patients improved and 28.4% had no response to treatment, within a mean (SD) follow up period of 5.4 (7.6) years. SF-36 PCS was low in those with PN with a mean (SD) of 35.8 (10.7).

Conclusion: PN is relatively prevalent in SLE, may occur at any time after SLE diagnosis and with different presentations. This manifestation of SLE has a big impact on patient’s quality of life.

Disclosure: B. Florica: None; J. Su: None; E. Aghdassi: None; D. D. Gladman: None; M. B. Urowitz: None; P. R. Fortin: None.

1166

Predictors of Mortality in Diffuse Alveolar Haemorrhage (DAH) Associated with Systemic Lupus Erythematosus.

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Objectives: Evaluation of clinical, demographic and treatment-associated mortality factors in patients with DAH associated with SLE.

Methods: Clinical, laboratory test, SLEDAI-2K, predictors of mortality (APACHE II) and different treatments including cyclophosphamide, methyl-prednisolone and rituximab were evaluated in SLE patients who were diagnosed with DAH, to determine potential association with factors that could be predictive of mortality.

Results: Twenty nine episodes of DAH in 22 SLE patients were included (one patient with 4 episodes, 4 patients with 2 episodes (7 recurrences)), 15 died. Mean age was 25.1 years and 1.5 years of SLE evolution with haemoglobin drop 3.4 g/dl. In 4 of 22 patients, the DAH diagnosis was confirmed by autopsy. Six episodes were in patients under 18 years of age (2 patients with recurrence). DAH was the initial manifestation of SLE in 10 patients. Of the 22 patients, 17 were women and 22/29 DAH episodes. Treatment evaluation of all included factors, only thromboctopenia, renal failure, requirement for mechanical ventilation and high APACHE II were associated with higher mortality. In 3 patients mycoses were diagnosed, all died. There is benefit using cyclophosphamide in selected patients (not statistically differences). Table 1 show the main characteristics evaluated in the 29 episodes.

Disclosure: C. E. Weckerle: None; B. S. Franek: None; J. Kelly: NIH, 2; M. Kumabe: None; R. Mikolaitis: None; S. Green: None; G. R. Bruner: None; T. O. Utset: Genentech and Biogen IDEC Inc, 5; M. Jolly: None; J. A. James: NIH, 2; J. B. Harley: NIH, 2, Rheumatinions, Inc., 2; T. B. Niewold: NIH, 2.
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Prefrontal Lobe Volume Could Reveal Memory Function in Patients with System Lupus Erythematosus. Yongfei Fang1, Hailuo Li1, Qinghua Zou1 and Yun Lin1. 1Department of Radiology, Southwest Hospital, Chongqing, China, 2Department of Rheumatology, Southwest Hospital, Third Military Medical University, Chongqing, China, 3Department of Rheumatology, Southwest Hospital, Third Military Medical University, Chongqing, China

Background: As a disease found with multiple organ involvement, cerebral atrophy in systemic lupus erythematosus has been reported by recent studies. The aim of the current study is i) to localize cerebral areas affected by SLE, and ii) to find any clinical index significantly correlated with cerebral atrophy.

Methods: 45 patients with SLE and 30 age, gender and education matched healthy controls were included, patients first underwent a working memory task named Paced Visual Serial Adding Test (PVSAT) and then scanned in a 3.0 Tesla MRI scanner for whole brain by 3D MP-RAGE sequence. Images were process by Statistical Parametric Mapping (SPM8) software using a voxel based morphometry (VBM) through a newly improved Diffuseomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) approach, which mainly included segmenting brain images into grey matter, white matter and cerebral spinal fluid; estimating the deformations that best align the images together by iteratively registering the segmented images with their average, and generating spatially normalised and smoothed Jacobian scaled grey matter images, by using the deformations estimated in the previous step; and finally a two sample t test to depict cerebral atrophy of SLE patients with significant atrophy compared with controls.

Results: diffuse grey matter atrophy was found in patients with SLE, mainly involved with prefrontal, temporal lobe, and cerebellum. By extracting individual volume of these cerebral areas, prefrontal lobe volume was positively correlated with test score of working memory task, and whole brain volume was negatively correlated with disease duration. No other clinical indexes were found to be in significant correlation with cerebral atrophy of SLE.

Conclusion: in consistence with previous researches, diffuse grey matter atrophy was found in patients with SLE. Further more, correlation between cognitive impairment and prefrontal lobe atrophy was discovered, indicating that i) cognitive impairment in SLE could be reflected by individual prefrontal lobe volume; ii) prefrontal lobe volume may be served as an marker of cognitive function in SLE. Nevertheless, negative correlation between disease duration and whole brain volume demonstrated a significant and chronic impact of SLE on human brain. However, as such results were generated based on a limited number of subjects, further research is required to depict the insights of the profile in the future.

Disclosure: Y. Fang: None; H. Li: None; Q. Zou: None; Y. Lin: None.

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Preliminary Results: Baseline Nutritional Vitamin D Level Does Not Predict Progression of Subclinical Atherosclerosis in Women with SLE. Apinya Lertratanakul1, Peggy Wu1, Alan R. Dyer2, Craig Langman3, William Pearce4, Kim Sutton-Tyrrell5, George Kondos2, Daniel Edmundowicz6, James Carr7 and Rosalind Ramsey-Goldman8. 1Childrens Memorial Hospital, Chicago, IL, 2Northwestern University, Chicago, IL, 3University of Illinois, Chicago, IL, 4University of Pittsburgh, Pittsburgh, PA

Background: CV events and subclinical atherosclerosis are increased in women with SLE. Low levels of 25(OH)D have been associated with disease activity and cardiovascular (CV) risk factors in SLE. CV events and subclinical atherosclerosis are increased in women with SLE.

Objective: Determine if baseline 25(OH)D level predicts progression of subclinical atherosclerosis in women with SLE.

Methods: Demographic, traditional CV risk factors, disease activity (SLEDAI) and severity (ACR/SLICC-DI), medications and imaging to assess subclinical atherosclerosis by carotid B-mode ultrasound to measure carotid plaque index (PI), intima-media thickness (IMT) and electron beam or multidimensional computed tomography to measure coronary artery calcification (CAC), and aortic calcium (AC) were measured at baseline and 3 yrs later in the Study of Lupus Vascular and Bone Long-Term Endpoints (SOLVABLE). Abnormal PI, CAC, and AC were defined as PI=1, CAC>10 and AC>100. Progression at 3y was defined as abnormal and an increase in PI, CAC>10 and AC>100 with an increase of >10% in CAC and AC. Hypertension (HTN) was defined as SBP≥140 or DBP≥90 or on treatment. Regression models investigated the relationship between PI, CAC, AC, and IMT and traditional CV risk factors, SLEDAI and ACR/SLICC-DI as well as baseline 25(OH)D (adjusted for age, race, sex, season) and progression of each imaging modality.

Results: In 118 women, mean ±SD age, disease duration, SLEDAI, ACR/ SLICC-DI, and 25(OH)D levels at baseline were 44.3 ±9.6 yrs, 12.6 ±8.8, 3.6 ±3.2, 1.7 ±1.7 and 28.2 ±11.6 mg/mL, respectively. Preliminary imaging data at baseline and 3y followup were available on 118 women for IMT and PI, 91 with CAC, and 56 with AC. The frequency at baseline (%) of abnormal PI, CAC, and AC was 35 (38%), 21 (23%), and 26 (29%), respectively. The frequency at baseline (%) of abnormal PI, CAC, and AC was 35 (38%), 21 (23%), and 26 (29%), respectively. The frequency at baseline (%) of abnormal PI, CAC, and AC was 35 (38%), 21 (23%), and 26 (29%), respectively. The frequency at baseline (%) of abnormal PI, CAC, and AC was 35 (38%), 21 (23%), and 26 (29%), respectively. 13, 5, and 9 patients progressed from normal to abnormal at 3y followup visit for PI, CAC, and AC, respectively. The mean (SD) for IMT at baseline and 3y followup was 0.61 (0.12) and 0.64 (0.15), respectively. IMT change was associated with triglycerides (p=0.035, β=0.019,95% CI 0.001–0.037). PI, CAC, and AC progression were associated with HTN (p=0.045, OR=3.96,95% CI 1.14–18.41), (p=0.038, OR=2.91,95% CI 1.09–8.30), (p=0.017, OR=3.59,95% CI 1.32–10.98), respectively. AC and CAC progression were associated with ACR/SLICC-DI (p=0.003, OR=1.61,95% CI 1.20–2.26), (p=0.002, OR=1.63,95% CI 1.22–2.25), CAC progression was also associated with fibrinogen (p=0.039, OR=1.64,95% CI 1.03–2.70).

Vitamin D and Progression of PI, CAC, AC, and IMT

<table>
<thead>
<tr>
<th>Imaging Type</th>
<th>β</th>
<th>Adjusted vitamin D model</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>0.73</td>
<td>0.33,1.48</td>
<td>0.40</td>
</tr>
<tr>
<td>CAC</td>
<td>0.95</td>
<td>0.51,1.74</td>
<td>0.88</td>
</tr>
<tr>
<td>AC</td>
<td>1.18</td>
<td>0.62,2.26</td>
<td>0.62</td>
</tr>
<tr>
<td>IMT</td>
<td>−0.02</td>
<td>−0.04,0.002</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Conclusion: These preliminary results suggest that baseline 25(OH)D levels did not predict progression of PI, CAC, AC, or IMT over 3 yrs in women with SLE. However, traditional CV risk factors and SLE-related markers may be important in predicting progression of vascular bed abnormalities.

Disclosure: A. Lertratanakul: None; P. Wu: None; A. R. Dyer: None; C. Langman: None; W. Pearce: None; K. Sutton-Tyrrell: None; G. Kondos: None; D. Edmundowicz: None; J. Carr: None; R. Ramsey-Goldman: None.

Objective: to determine the rate and risk factors of carotid atherosclerosis progression in patients with Systemic Lupus Erythematosus (SLE).

Patients and Methods: carotid intima-media thickness (IMT) and plaque were obtained by ultrasound at an interval of 39(37–42) months in 157 lupus patients out of 181 patients initially included in a prospective study. Progression of atherosclerosis was defined by either an increase of common carotid IMT>0.15mm or a larger plaque score. Traditional risk factors for coronary heart disease (CHD) and SLE-related factors were assessed longitudinally. Poisson regression was used to assess the predictors of atherosclerosis progression, given robust relative risk (IRR) for each independent variable.

Results: The cohort was 96.2% female, 75.8% non-white, with a median (IR) age at baseline of 38(29–46) years. Median (IR) age at lupus diagnosis and disease duration was 27.3(21.5–34.7) years and 7.72 (4.31–11.44) years, respectively. A common carotid IMT increase of 0.06(–0.01–0.14)mm was detected, with a mean annual increase of 0.018(–0.003–0.015)mm. Forty three patients (27.4%) had progressive atherosclerosis: nine(5.7%) had higher plaque progression rate. Multivariate determinants of atherosclerosis progression were duration of SLE (p=0.007; RR=1.06 CI95%=1.03–1.10) and nephrotic proteinuria (p=0.021; RR=4.22 CI95%=2.18–8.15). Traditional risk factors for CHD were not independently related to atherosclerosis progression.

Conclusion: Atherosclerosis progresses in a substantial number of young SLE patients during short-term follow up. SLE-related risk factors were associated with IMT and plaque progression after controlling for the traditional risk factors for CHD.

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Regional Brain Diffusion Abnormalities in Systemic Lupus Erythematosus. Šimone Appenzeller1, Leticia Ritter2, Gabriel Leonardi3, Martin Vieilles3, Bruno Pike1 and Ann Clarke1. 1McGill University, Canada 2State University of Campinas, Brazil 3State University of Campinas, Brazil.

Objective: To determine regional brain diffusion abnormalities and to evaluate the relationship between diffusion parameters [fraction anisotropy (FA) and mean diffusivity (MDI)] and cognitive impairment and mood disorders in systemic lupus erythematosus (SLE).

Method: We screened consecutive female SLE patients followed in a longitudinal cohort between 2007/2008. We excluded patients with any factors associated with cerebral atrophy or vasculopathy [i.e., age ≥ 50 years, hypertension, renal insufficiency, transient ischemic attack or stroke, scleroderma features, diabetes, drug abuse, or malignancy] or not educated primarily in English or French. Healthy age-matched women were selected as controls. All underwent a standardized neuropsychological evaluation assessing the following: simple attention, complex attention, memory, visuospatial processing, language, reasoning/problem solving, psychomotor speed, and executive functions. Individual results were converted into standard scores and compared to normative data. Subjects with a total score in any of the 8 domains =2 SD below the normative value were considered impaired. Mood disorders were determined by Becks Depression and Becks Anxiety Inventory (BDI and BAI). Magnetic resonance imaging (MRI) was performed on a Siemens 3 Tesla scanner and volumetric TI, T2 and PD weighted images were used for automatic segmentation of the brain. Diffusion images were acquired in 63 directions (b=1000s/mm2; TR=10900ms; TE=105ms; FOV=256mm). Brain regions of interest (ROI) were overlaid to the diffusion images acquired and FA and MD were calculated for each structure. The FA and MD values were compared between groups using the t-test. Correlation between cognitive impairment, mood disorders and FA and MD was assessed through the Pearson correlation.

Results: Twenty-seven patients (mean age 34.08, SD 8.85) and ten controls (mean age 33, SD 8.3) were included. We observed significantly lower FA and higher MD in SLE when compared to controls in the following white matter structures: bilateral frontal lobe (p=0.011), right temporal lobe (p=0.031), bilateral parietal lobe (p=0.02), in addition to bilateral amigdala (p=0.005) and the thalamus (p=0.01). No difference between diffusion parameters were observed in the hippocampus, left frontal lobe, occipital lobes, cerebellum, corpus callosum, caudate, putamen and parahippocampal region. FA and MD of the amigdalacorrelated with the severity of anxiety (r=0.7, p=0.001) and FA and MD of the frontal lobe with cognitive impairment (r=0.56, p=0.03).

Conclusion: Diffusion abnormalities are not uniform in SLE patients. Increased MD and reduced FA, indicating reduction in myelin and axonal damage were observed in frontal, temporal, parietal white matter and in the amigdala. The severity of anxiety and the presence of cognitive impairment correlated with axonal damage in the amigdala and in the frontal lobe white matter. Diffusion parameters can be used to evaluate SLE patients with central nervous system manifestations and visually normal MRIs.

Disclosure: S. Appenzeller: None; L. Ritter: None; G. Leonardi: None; M. Vieilles: None; B. Pike: None; A. Clarke: None.

Renal Biopsy in Systemic Lupus Erythematosus Patients with Low Levels of Proteinuria. Esther Rodriguez, Julio Sánchez, Eva Salgado, Isabel Mateo, Maria Galindo and Patricia E. Carreira. Rheumatology Department, Hospital 12 de Octubre, Madrid, Spain.

Objective: To evaluate the need of performing renal biopsy in SLE patients with low levels of proteinuria.

Patients and Methods: From 443 patients included in our SLE data base (1974–2009), 150 with biopsy proven lupus nephritis were selected. Demographic (sex, age at onset and diagnosis, death), clinical (type of nephritis, proteinuria, urinary casts, creatinine, aDNA, complement, high blood pressure –HBP–, treatment and outcome (renal failure, relapse, death) data, had been previously included in the data base, or were obtained from the charts. In patients with proteinuria <1 g/d, relationship between clinical data and renal histology, and risk factors for relapse and renal failure were analyzed. Clinical and outcome data were compared between patients with proteinuria lower and higher than 1 g/d. Chi square, Student t test and binary logistic regression were used for statistics.

Results: Out of 150 patients, 42 (29%; 39 f, 3 m; age 30±14 a) had proteinuria <1g/d. Ten patients (24%) did not have renal symptoms, 15 (37%) presented HBP, 8 (19%), all with HBP creatinine elevation, 9 (21%) glomerulonephritis, 26 (62%) aDNA and 36 (86%) low complement levels. Renal biopsies showed: minimal changes 1 (2%), mesangial GN 18 (43%), focal proliferative GN 7 (17%), diffuse proliferative GN 12 (29%) and membranous GN 4 (9%). No correlation between clinical characteristics and histological findings were found. One patient did not receive any treatment, 19 received only glucocorticoids, 15 cyclophosphamide, 6 azathioprine and 1 mophetil mycophenolate. Thirty seven (97%) responded well to therapy (28 complete and 9 partial response). After 14±8 years of follow up, 8 patients relapsed, 6 developed renal failure and 6 died. Presence of proliferative/membranous GN was a risk factor for relapse in this group (p<0.0001). Renal failure in patients with low levels of proteinuria was related to the presence of HBP (p<0.001) and creatinine elevation (p=0.006). Compared to 107 patients with higher proteinuria levels, these had more frequently diffuse proliferative GN (p=0.007) and more relapses (p=0.03). Both groups developed renal failure with similar frequency.

Conclusions: More than half SLE patients with low proteinuria levels present severe disease on renal biopsy. Although they present less diffuse proliferative GN and renal relapses than patients with higher proteinuria, may develop renal failure with the same frequency. Our results support the convenience of performing renal biopsy and careful follow-up to patients with low proteinuria levels, especially if HBP and/or creatinine elevation are present.

Disclosure: E. Rodriguez: None; J. Sánchez: None; E. Salgado: None; I. Mateo: None; M. Galindo: None; P. E. Carreira: None.
Purpose: To provide phase 2 and 3 clinical trial safety data on belimumab in SLE patients.

Methods: Safety data were evaluated in 2133 patients with seropositive SLE from 11 phase 2 (LBSL02; N=449; NCT00471487) and 2 phase 3 (BLISS-52; N=865; NCT00442446; and BLISS-76; N=819; NCT00413084), multicenter, double-blind, placebo-controlled studies of belimumab (1 and 10 mg/kg in all studies, plus 4 mg/kg in phase 2 only). Belimumab or placebo was infused over 1–2 h on d 0, 14, and 28, and q2q8d thereafter, for 48 or 72 wk. All patients received SLE standard of care (SOC), including various combinations of corticosteroids, antimalarials, and immunosuppressants. Clinical and laboratory findings were monitored at every scheduled visit and adverse events (AEs) were reported as they occurred. All 3 studies had a 52-wk placebo-controlled phase; only BLISS-76 had a controlled phase to wk 76. Pooled data of belimumab 1 and 10 mg/kg were included in the table.

Results: There were no remarkable differences between the belimumab 1- and 10-mg/kg, and placebo groups when AEs were categorized by severity, seriousness, or whether they resulted in discontinuation of study agent. Rates of different AEs are shown in table. Rates of infections were numerically slightly higher in the belimumab groups, while rates of serious and/or severe infections were comparable across all groups. Rates of infections of special interest (using a composite definition for each, such as sepsis, cellulitis, herpes, fungal, and respiratory infections, were comparable among all treatment groups. Rates of infusion reactions were numerically slightly higher in the belimumab groups. There were no reports of malignancy, death, or serious hypersensitivity/infusion reactions with the 4-mg/kg dose during the double-blind period. The rate of malignancy, excluding nonmelanoma skin cancers, per 100 patient-y in patients exposed to belimumab was similar to the rate in SLE patients reported by Bernard et al (2005). The safety profile of the 4-mg/kg dose was comparable to those of the 1- and 10-mg/kg doses, and placebo in LBSL02.

Conclusions: Overall, belimumab plus SOC therapy was generally well tolerated, with a safety profile comparable to placebo plus SOC.

Table. Integrated Safety Data of 52-Wk Double-Blind Phase

<table>
<thead>
<tr>
<th>% patients with ( \geq 1 ):</th>
<th>SOC + Placebo (n=675)</th>
<th>SOC + Belimumab 1 mg/kg (n=673)</th>
<th>SOC + Belimumab 10 mg/kg (n=674)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE in general</td>
<td>92.4</td>
<td>93.0</td>
<td>92.7</td>
</tr>
<tr>
<td>AE resulting in discontinuation</td>
<td>7.1</td>
<td>6.2</td>
<td>6.7</td>
</tr>
<tr>
<td>Serious and/or severe AE</td>
<td>21.5</td>
<td>23.0</td>
<td>22.6</td>
</tr>
<tr>
<td>AE infections in general</td>
<td>66.7</td>
<td>71.0</td>
<td>69.9</td>
</tr>
<tr>
<td>AE infection resulting in discontinuation</td>
<td>1.0</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Serious and/or severe AE infection</td>
<td>6.7</td>
<td>7.3</td>
<td>5.9</td>
</tr>
<tr>
<td>AE infections of special interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>6.4</td>
<td>8.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.4</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Fungal</td>
<td>3.3</td>
<td>3.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Herpes viral</td>
<td>8.0</td>
<td>7.6</td>
<td>6.5</td>
</tr>
<tr>
<td>All respiratory</td>
<td>48.4</td>
<td>50.8</td>
<td>51.9</td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>8.6</td>
<td>11.3</td>
<td>12.0</td>
</tr>
<tr>
<td>Possible opportunistic</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All Infusion/hypersensitivity reactions, %</td>
<td>14.7</td>
<td>16.6</td>
<td>16.8</td>
</tr>
</tbody>
</table>

Rates of infections were generally similar to the rates in SLE patients reported by Bernard et al (2005). The safety profile of the 4-mg/kg dose was comparable to those of the 1- and 10-mg/kg doses, and placebo in LBSL02.

1173

Second Renal Biopsy in Proliferative Lupus Nephritis. Alberto Allièri, Ana Malvar Perrin, Bruno Lococo, Mariac Cristina Basta, Paola Pirruccio, Sebastien Andres Muñoz, Alejandro Quevedo, Bernarda Fazzini, Valeria Alberton and Alejandro Iotti. 1Hospital Britanico, Ciudad Autónoma de Buenos Aires, Argentina, 2Hospital Juan A Fernandez, Ciudad Autonoma de Buenos Aires, Argentina

Background: Renal biopsy is one of the main diagnostic tools in lupus nephritis. Disease activity and prognosis can be established through a systematic light microscopic and indirect immunofluorescence analysis of renal tissue. Ultrasoundographic guided biopsy has made the collection of renal tissue a common and safe procedure in clinical nephrology. Frequently only clinical parameters are used to evaluate therapeutic response. Correlation between clinical response and histopathology is not always present.

Purpose: To compare the predictive value of clinical and histopathological criteria after six month of induction therapy in diffuse proliferative lupus nephritis at two years.

Methods: thirty three SLE patients with diffuse proliferative lupus nephritis were evaluated prospectively between august 2002 and september 2007. A second renal biopsy was performed after induction treatment with six pulses of cyclophosphamide in 29 patients and sodium mycophenolate in four patients. All patients completed 2 years of maintenance treatment. Responders were treated with azathioprine. We compared between clinical parameters and second renal biopsy findings as predictors of clinical outcome after 24 months. Renal biopsies were evaluated by two experienced renal pathologists blinded to clinical data. The ISN/RPS 2003 classification was used. Serum creatinine levels and 24 hr proteinuria were compared with the second biopsy findings as predictors of clinical outcome after 24 months. Patients were categorized according to their response to treatment. Those patients with complete or partial response were defined as responders. Clinical response was based on increase or decrease of 24 hr proteinuria and creatinine. Histological response was assessed according to the activity and chronicity index. The increase of both parameters was considered no response, the disparity of both was partial response and the improvement of both parameters was considered response.

Results: Thirty three patients were assessed according to the protocol.
have biopsy results for all of them and they have been followed for 2 years. Seven patients presented membranous glomerulopathy in the second biopsy; 6/7 had good clinical evolution two years later. 19/26 patients with good clinical response after induction treatment were in low concordance with clinical evolution two years after (46.15%; Spearman's: 0.1785, Kappa: 0.13). Second renal biopsy performed after induction treatment revealed information more accurate about two years clinical evolution with concordance of 73.08 % (Spearman's: 0.57, Kappa: 0.50, p<0.001).

**Conclusions:** In our experience, membranous nephropathy in the second renal biopsy was coincidental with good clinical evolution. Second renal biopsy revealed more accurate information than clinical evolution.

**Disclosure: A. Allevi:** None; A. Malvar Perrin:** None; B. Lococo:** None; M. C. Basta:** None; P. Pirruncio:** None; S. A. Muñoz:** None; A. Quevedo:** None; B. Fazinni:** None; V. Alberton:** None; A. Iotti:** None.

**1174**

**Seroprevalence of NMO-IgG (Anti-Aquaporin 4 Antibodies) in Patients with Neuropsychiatric Systemic Lupus Erythematosus.** Jakub Zavada1, Petra Nytrova1, Klaus-Peter Wandinger2, Svobodova Radka4, Ivana Putova4, Peschken1, Carol A. Hitchon3, Hani S. El-Gabalawy2 and Shikha Mittoo1. 1Univ of Manitoba, Winnipeg, MB, Canada, 2University of Manitoba, Winnipeg, MB, Canada, 3University of Manitoba, Winnipeg, MB, Canada, 4University of Pittsburgh Medical Center, Pittsburgh, PA

**Background:** Neuropsychiatric manifestations are present in up to 60% of patients with systemic lupus erythematosus (SLE) with psychosis, seizures, headaches and cerebrovascular accidents being most common. However, transverse myelitis has also been described in approximately 1–2% of SLE patients. Neurymeliotis optica (NMO) is an inflammatory demyelinating disease (syndrome) of the central nervous system (CNS), characterized by sequential or concomitant attacks of transverse myelitis (TM) and optic neuritis (ON), and has occasionally been reported in conjunction with SLE. The distinction between myelitis associated with NMO-IgG and myelitis of another etiology may be difficult but crucial for further treatment and prognosis of the involved patients. The serum autoantibody NMO-IgG (anti-aquaporin 4 antibody) is considered to be a sensitive and specific marker for NMO. The antigenic target of these antibodies is aquaporin-4 (AQP4), the most abundant water channel in the CNS. Although the prevalence of NMO-IgG antibodies was examined in minor cohorts of patients with established SLE, only one very recent study reported data on SLE patients with established neuropsychiatric involvement. That is why we decided to evaluate the NMO-IgG seroprevalence in another larger cohort of patients with diagnosed neuropsychiatric lupus (NPSLE).

**Patients and Methods:** We have retrospectively studied NMO-IgG (anti-AQP4 Ab) in sera of 50 patients with NPSLE. All of the patients fulfilled the American College of Rheumatology (ACR) criteria for SLE and suffered from neuropsychiatric involvement as defined by the ACR nomenclature for NPSLE. Only one of them was treated for TM. ON was not documented in this strictly defined cohort. NMO-IgG (anti-AQP4 Ab) has been tested by indirect immunofluorescence on AQP-4 transfected HEK cells.

**Summary of the Results:** Only one of the examined sera (in the patient with TM who has not fulfilled the criteria for NMO) has been positive for NMO-IgG (anti-AQP4 Ab). None of the remaining 49 NPSLE patients without documented concomitant ON or TM has been found to be seropositive for NMO-IgG (anti-AQP4 Ab) antibodies.

**Conclusion:** These findings support the notion that NMO-IgG (anti-AQP4 Ab) could play a role in the pathogenesis of some cases of TM and/or ON. NMO-IgG (anti-AQP4 Ab) are not detectable in NPSLE patients without TM and/or ON. However, in patients with SLE and concomitant ON/TM, it is very useful to assess the NMO-IgG (anti-AQP4 Ab) in serum due to selection of a suitable treatment regimen.

**Acknowledgements:** The study was supported from Grant Agency of Charles University (grant GAUK 132010) and MZO 00023728

**Disclosure: J. Zavada:** None; P. Nytrova:** None; K.-P. Wandinger:** None; R. Radka:** None; I. Putova:** None; D. Tegzova:** None; J. Vencovsky:** None.

**1175**

**Serum Free Light Chains and Disease Activity in Systemic Lupus Erythematosus.** Meenakshi Jolly1, Rohit Aggarwal2, Rachel Mikolaïtis2, Joel A. Block3 and Winston Sequeira4. 1Rush University Medical Center, Chicago, IL, 2Rush University Medical Center, Chicago, IL, 3Rush University Medical Center, Chicago, IL, Rush University Medical Center, 4University of Pittsburgh Medical Center, Pittsburgh, PA

**Purpose:** We previously reported the superiority of using Total Free Light Chains (TFLC) as a biomarker of disease activity as compared to high sensitivity DsDNA and IgG in 75 patients with Systemic Lupus Erythematosus (SLE). Herein we report our experience with the use of TFLC in 205 SLE patients as a biomarker for disease activity.

**Methods:** 211 consecutive consenting SLE patients attending an outpatient Rheumatology clinic at a University Hospital were enrolled. Disease activity was assessed using physician global assessments (PGA) and Selenas-SLEDAI. Adjusted SLEDAI (adjSLEDAI= SLEDAI – [C3C4 and Ds-DNA score]) was obtained. Serum FLC (Kappa (k), Lambda (λ) and total FLC (k + λ)) was measured using nephelometry (Binding site, UK). Additional data on DsDNA (positivity (n= 182) and titres (n=171)) and complement C3 and C4 abnormality (n= 171) and titres (n=109)) were available from the same blood sample. Spearman correlation was used to correlate total FLC, DsDNA positivity, titre, Complement abnormality and titre with PGA, SLEDAI and adjusted SLEDAI. Mann-Whitney or Kruskall Wallis test was used to compare continuous data.

**Results:** The mean age was 42 ± 13 yrs. African American 45%, Caucasian 30%, Hispanic 12%, Asian 10% and Others 3%. PGA and SLEDAI were (mean± SD, median) 0.7± 0.8, 0.5 and 4.2 ±4.3, 2 respectively. Fifty six percent were taking prednisone. The TFLC values (mean± SD, median) were 62.5 ± 69.8, 44.3. Correlations are tabulated below.

**Table 1. Correlation between markers and disease activity.**

<table>
<thead>
<tr>
<th>TFLC</th>
<th>DsDNA</th>
<th>DsDNA</th>
<th>Complement</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>titre</td>
<td>C4</td>
<td>titre</td>
</tr>
<tr>
<td>PGA</td>
<td>0.39</td>
<td>0.39</td>
<td>0.34</td>
</tr>
<tr>
<td>(P=0.0001)</td>
<td>(P=0.0001)</td>
<td>(P=0.0001)</td>
<td>(P=0.07)</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>0.44</td>
<td>0.49</td>
<td>0.47</td>
</tr>
<tr>
<td>(P=0.0001)</td>
<td>(P=0.0001)</td>
<td>(P=0.0001)</td>
<td>(P=0.16)</td>
</tr>
<tr>
<td>Adj-SLEDAI</td>
<td>0.39</td>
<td>0.23</td>
<td>0.211</td>
</tr>
<tr>
<td>(P=0.0001)</td>
<td>(P=0.03)</td>
<td>(P=0.05)</td>
<td>(P=0.45)</td>
</tr>
</tbody>
</table>

**Conclusions:** TFLC is correlated with disease activity, even after removing DsDNA and complement information from the disease activity score. Its correlation with adjusted SLEDAI is the strongest as compared to DsDNA positivity, titres, complement abnormality or complement titres. These data suggest that TFLC may serve as a potential biomarker for SLE, especially in the patients who lack DsDNA antibodies. Longitudinal studies are now indicated.

**Disclosure: M. Jolly:** The Binding Site, 2; R. Aggarwal:** The Binding Site, 2; R. Mikolaïtis:** None; J. A. Block:** The Binding Site, 2; W. Sequeira:** The Binding Site, 2.

**1176**

**Shrinking Lung Syndrome Is Associated with Pleuritis.** David Allen3, Zohir Bhoyt1, Melissa Moyen1, David B. Robinson3, Christine A. Peschken1, Carol A. Hitchon1, Hanif El-Gabalawy2 and Shikha Mittoo1. 1Univ of Manitoba, Winnipeg, MB, Canada, 2University of Manitoba, Winnipeg, MB, Canada, 3University of Manitoba, Winnipeg, MB, Canada

**Background:** Shrinking lung syndrome (SLS) is a form of pulmonary damage in systemic lupus erythematosus (SLE) characterized by unexplained dyspnea, small lung volumes and restrictive lung physiology with or without diaphragmatic elevation. The pathophysiology of SLS is incompletely understood but is associated with significant morbidity and may require escalation of therapy to avoid fulminant respiratory failure. Pleuritis has been reported in 30–60% of patients with SLS. We set out to determine the frequency of SLS in patients with SLE and if pleuritis is associated with SLS.

**Methods:** Consecutive patients ≥ 18 years of age who met American College of Rheumatology (ACR) criteria for SLE were enrolled. Demographic, disease duration, smoking status, body-mass index (BMI), self-reported dyspnea, pleuritic chest pain (CP), autoantibodies and measures of disease activity; SLE Activity Measure (SLAM), cumulative organ damage (Systemic Lupus International Collaborating Clinics damage index (SDI), ACR criteria modified to exclude pulmonary variables (mACR)) were recorded. All
patients underwent pulmonary function testing (PFTs) and chest imaging (X-ray or CT scan).

Pleuritis was defined as serositis by ACR criteria, relying on the presence of CP, a rub or a history of pleural effusion on chest X-ray. At enrollment, SLS was defined as a forced vital capacity (FVC) or total lung capacity (TLC) <80% predicted without evidence of interstitial/pleural disease on imaging or myositis/myalgia causing impairment.

Univariate and multivariate logistic regression was used to determine factors associated with SLS and the relationship between pleuritis and SLS. Results are reported as mean ± SD unless stated otherwise.

**Results:** One hundred patients (94% women, 81% Caucasian) with an age at diagnosis of 33.8 ± 13.8 years, disease duration of 13.2 ± 9.2 years, had a mACR of 5.5 ± 1.2, total SLD of 1.2 ± 1.2, and total SLAM of 7.1 ± 3.6. Fifty-four of 99 reported ≥1 respiratory symptom; 52/99 had dyspnea and 26/99 had CP. Thirty-four had SLS; 23/33 had dyspnea and 13/33 had CP. Dyspnea and CP were more common in those with SLS [n = 25/34 (71%) vs. n = 27/65 (42%)], p = 0.006 and [n = 15/34 (43%) vs. n = 11/64 (17%), p = 0.007].

Thirty-five patients had pleuritis. SLS was more common among those with pleuritis compared to those without, [26/34 (75%) vs. 14/65 (22%), (p < 0.0001)]. As well, disease duration (p = 0.05), self-reported dyspnea (p = 0.02), anti-RNP (p = 0.001), anti-Sm (p = 0.002), and mACR (p = 0.02) were significantly associated with SLS. However, age at diagnosis, BMI, pCP, ethnicity, smoking status, SDI, SLAM and anti-dsDNA, anti-Ro, and anti-La, were not associated with SLS.

In multivariate analysis controlling for pleuritis, disease duration, self-reported dyspnea, mACR, presence of anti-RNP and Sm antibodies, only pleuritis remained associated with SLS [OR = 3.6, 95% CI of 1.3–10.1, p = 0.02].

**Conclusions:** SLS was a frequent finding in this unselected cohort, occurring in 57% of patients and pleuritis was significantly associated with SLS. This suggests that pleural disease may be important in the etiology of SLS. Further, the presence of pleural disease in patients with SLE should result in an assessment for SLS.

**Disclosure:** D. Allen: None; Z. Bhoutry: None; M. Moyen: None; D. B. Robinson: None; C. A. Peschken: None; C. A. Hitchon: None; H. S. El-Gabalyawy: None; S. Mittoo: None.

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**The Metabolic Syndrome in Systemic Lupus Erythematosus: More Than the Sum of Its Parts?** Ben Parker1, Yasmine Ahmad2, Joanna Shelmerdine1, Sahena Haque1, and Ian N. Bruce. 1Manchester, United Kingdom, 2Manchester, United Kingdom, 3Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, 4Manchester Royal Infirmary, Manchester, United Kingdom

**Purpose:** The metabolic syndrome (MetS) is a clustering of metabolic abnormalities in individuals with increased adiposity and is associated with an increased risk of developing diabetes and coronary heart disease (CHD). The prevalence of the MetS is increased in SLE although rates of obesity are not.

Therefore lupus-specific factors and inflammatory disease may be an important contributor to the metabolic derangements observed in those SLE patients with the MetS. The aim of this study is to determine those disease characteristics associated with the presence of the MetS and to investigate whether the MetS is associated with the presence of carotid plaque in patients with SLE.

**Methods:** Caucasian women with SLE were assessed in a cross-sectional observational study. Disease activity (SLEDAI), disease damage (SLICC-DI) and clinical characteristics were determined. The MetS was defined according to the 2009 Consensus Statement from the IDF and partners. All patients underwent B-mode ultrasound of the common carotid and proximal internal and external carotid arteries to detect plaque. Multivariate logistic regression was performed to determine the association between disease characteristics and the MetS, and the presence of carotid plaque and the MetS.

**Results:** 200 women with SLE were assessed of whom 30% fulfilled the criteria for the MetS. Those meeting the MetS definition were older (median (IQR) age 53 (46, 59) years vs. 46.5 (41, 53) years, p = 0.001) and had a longer disease duration (median (IQR) 14 (6–22) years vs. 7 (4–16) years, p = 0.002) than those who did not. In a multivariate model the presence of the MetS was associated with age, disease duration and low C3 but not with average steroid dose.

**Table 1. Lupus Features associated with the MetS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age-Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low C3</td>
<td>8.46 (1.25, 57.0)</td>
</tr>
<tr>
<td>Age</td>
<td>1.06 (1.01, 1.10)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>1.05 (1.01, 1.09)</td>
</tr>
<tr>
<td>Steroids Ever</td>
<td>2.46 (0.69, 8.72)</td>
</tr>
<tr>
<td>Azathioprine Ever</td>
<td>2.06 (0.89, 4.75)</td>
</tr>
<tr>
<td>SLAM</td>
<td>0.91 (0.99, 1.85)</td>
</tr>
<tr>
<td>Renal Disease Ever</td>
<td>1.89 (0.63, 5.66)</td>
</tr>
<tr>
<td>Average Steroid Dose (6 months)</td>
<td>1.03 (0.97, 1.11)</td>
</tr>
</tbody>
</table>

Carotid plaque was present in 42% of SLE patients with the MetS compared to 23.5% of patients without (p = 0.01). Overall, the MetS was not independently associated with the presence of carotid plaque (OR 1.7 (95% CI 0.8, 3.4). However, fulfilling IDF criteria for high blood pressure and hyperglycemiaemia (OR 2.9 (1.3, 6.3) and 2.2 (1.1, 4.4) respectively) were both associated with the presence of carotid plaque.

**Conclusions:** The MetS is more prevalent with increasing age in SLE. Low complement and disease duration were independently associated with the presence of the MetS in SLE suggesting a role for inflammatory activity in contributing to the syndrome. The MetS was not associated with the presence of carotid plaque overall, although individual criteria were. Therefore a CHD risk assessment strategy attending to these individual risk factors would appear to be more important to modify CHD risk in patients with SLE.

**Disclosure:** B. Parker: None; Y. Ahmad: None; J. Shelmerdine: None; S. Haque: None; I. N. Bruce: None.

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**The Prevalence of Liver Abnormalities in Patients with Systemic Lupus Erythematosus:** Darryl Huang1, Ellie Aghdassi2, Jiandong Su3 and Paul R. Fortin1. 1Toronto Western Hospital, Toronto, ON, Canada, 2University Health Network, Division of Rheumatology, Toronto, ON, Canada

Studies reporting on liver involvement in Systemic Lupus Erythematosus (SLE) are limited, often focused on liver transaminases and without inclusion of imaging procedures and/or liver biopsies. Furthermore, the etiology for the abnormal transaminases has not been investigated.

This study determined in SLE patients: 1) the prevalence of abnormal liver function tests (LFTs) and whether further investigations were done; 2) the differences in SLE-related and/or metabolic factors in patients with and without abnormal LFTs. Patients who met at least 4 of the ACR classification criteria for SLE and had 1.5 times the upper limit for AST or ALT on two visits within a 2-year period were selected from the database registry of the University of Toronto Lupus Clinic. Demographic, and laboratory data at the time of the first appearance of LFTs abnormality were extracted from these patients as well as the age, gender and SLE duration matched controls who had normal LFTs. Disease activity and damage were assessed by SLE-Disease Activity Index (SLEDAI) and SLICC Damage Index (SDI). Chart review was performed to determine the contributing factors to these liver abnormalities. Data analysis were evaluated using SPSS statistical program. Out of 1533 patients in the database, 135 (8.8%) with a mean (SD) ACR of 3.6 (1.5) met the inclusion criteria. The subjects had mean (SD): age of 40.1 (13.7) years, BMI of 25.9 (5.8) kg/m2, SLEDAI of 6.4 (5.4), SDI of 1.5 (1.8) and 83% were female. Among patients, 65% were Caucasian; 23% smoked; 30% consumed alcohol, 61% had hypertension, 7% had previous cardiovascular involvement and 68% had other autoimmune disorders. Medication profile of the two year period preceding the first abnormal LFT included: prednisone (67%) of patients with a mean (SD) dose of 12.1 (15.3) mg; antimalarial (63%), immunosuppressants (61%), statins (16%), hormone replacement therapy (13%) and anticoagulants (13%). Laboratory findings were normal for CBC, blood glucose and lipid profile except for serum triglycerides that was elevated (2.10 ± 2.04 mg/dl). The mean (SD) levels for AST and ALT were 73 (67) and 88 (79) respectively. Chart review completed in 60 of the patients, showed that only 12 patients were further evaluated by a Hepatologist, 30 had an abdominal ultrasound (US) (15 fatty liver, 3 fibrosis, 11 with suspected drug-induced hepatitis), and only 3 had a liver biopsy. However, only 15 of the US were done specifically for liver investigation. In the nested case control study of 134 matched subjects, cases had higher prevalence of: hypertension (60% VS. 46%, p = 0.02); antiphospholipid syndrome (9% VS. 2%, p = 0.02); and immunosuppressants use (60% VS. 37%, p < 0.001), especially azathioprine (39% VS. 22%, p < 0.001) and methotrexate (22% VS. 10%, p < 0.01) compared to controls. Although, BMI, SLEDAI and SDI were similar, blood biochemistry showed a significantly lower IgM (1.2 (0.7) vs 1.5 (1.0), p = 0.03) and higher triglycerides (2.1 (2.1) vs 1.7 (1.2), p = 0.05) among cases compared to the controls. Factors associated with the metabolic syndrome, such as obesity, insulin resistance, and hypertension, as well as side-effects of the drugs used in the treatment of SLE may contribute to liver abnormalities in SLE.

**Disclosure:** D. Huang: None; E. Aghdassi: None; J. Su: None; P. R. Fortin: None.
Undertreatment of Active Disease May Increase Mortality in Lupus Patients with End Stage Renal Disease. Anna R. Broder and Chaim Putterman. Albert Einstein College of Med, Bronx, NY, Montefiore Medical Ctr, Bronx, NY

Background: Earlier studies have concluded that SLE becomes quiescent once end stage renal disease (ESRD) develops. However, more recent publications and our clinical experience suggest that SLE can remain active even in patients undergoing dialysis. SLE patients with ESRD receiving chronic dialysis may not be followed as closely by the rheumatologists, and, therefore, active SLE is underdiagnosed and undertreated.

Methods: We identified all patients over 18 years old with SLE who started dialysis between 2000 and 2010 at a large urban tertiary care center. Mortality data was obtained using in-hospital records and Social Security Death Index database.

Results: We identified 92 ESRD/SLE on dialysis, 79 women and 13 men, mean age 48 (±16) years. The median duration between first dialysis and last follow-up was 1.6 years IQR (0.5, 2.5). Twenty of these patients (22%) died during follow-up from various causes including infections, GI or CNS hemorrhage, status epilepticus, and heart failure. ESRD/SLE patients seen frequently by rheumatologists were younger compared with patients followed infrequently (35 years old (28, 43) vs. 51 years old (41, 58)). The 2 groups were similar in terms of race/ethnicity and duration of follow-up.

The results of survival analysis are shown in Figures 1 and 2.

ESRD/SLE patients followed frequently in rheumatology clinics at our center had significantly lower mortality rates compared with patients followed infrequently, 3/25 (12%) vs. 22/67 (33%), log rank p-value =0.039; HR 0.24, 95% CI (0.07, 0.83), p=0.041 adjusted for age and the number of rheumatology visits before they began dialysis. Moreover, ESRD/SLE patients treated with prednisone alone had higher mortality rates compared with prednisone in combination with hydroxychloroquine, mycophenolate mofetil, or azathioprine, 16/36 (44%) vs. 5/35 (14%), log rank p = 0.036; adjusted HR 0.36, 95% CI (0.13, 1.0), p=0.05. We did did account for medication doses. Differential selection, misclassification, and medication compliance may have affected the results in this retrospective analysis.

Conclusions: Treatment with prednisone alone in ESRD/SLE patients may be associated with higher mortality rates compared to prednisone in combination with other DMARDs. Active disease in SLE patients on dialysis may be unrecognized and undertreated leading to increased mortality.

Disclosure: A. R. Broder: None; C. Putterman: None.

1180 Vitamin D Levels Are Positively Associated with Complement among Patients with SLE. Michelle A. Petri1, Kayode Jibril Bello2, Hong Fang3 and Laurence Magder4. Timonium, MD, Johns Hopkins University School of Medicine, University of Maryland School of Medicine

Purpose: Vitamin D deficiency is common in SLE. Vitamin D deficiency has been associated with diabetes mellitus, cardiovascular disease, and certain forms of cancer; all represent outcomes increased in SLE patients. In murine SLE models, Vitamin D is an immunomodulator. We investigated whether Vitamin D levels were associated with disease activity in patients who took Vitamin D supplements for vitamin D deficiency.

Methods: As part of routine clinical care, 478 SLE patients were determined to have low levels of 25 OH Vitamin D (<32 ng/mL). 50,000 units Vitamin D was then given weekly for 12 weeks, with Ca/D 200 units twice daily. One physician measured the patient's global assessment (PGA) and SLEDAI at all visits. Linear regression models were used to estimate the association between change in vitamin D and change in various measures of disease activity. The dependent variables analyzed in the models were change in PGA, change in SLEDAI, change in Urine Protein/Creatinine Ratio, change in C3, change in C4, and change in anti-dsDNA. The independent variable was change in Vit D. Generalized estimating equations were used to account for the repeated observations from the same patients.

Results: The SLE patients were 91.7% female, mean age 44.9, 53.9% Caucasian, 38.3% African-American, 7.8% other ethnicity. At baseline, the mean 25 OH Vit D was 29.3 ± 14.9. The mean 25 OH Vit D at baseline was 29.3 ± 14.9 and at 3 months was 35.9 ± 14.9.

Table 1. Effect of change in Vit D on disease activity by univariate analysis

<table>
<thead>
<tr>
<th>Estimated change in variable per 10 units increase in Vit D</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA 0.002 ± 0.012</td>
<td>0.9004</td>
</tr>
<tr>
<td>SLEDAI 0.029 ± 0.051</td>
<td>0.5680</td>
</tr>
<tr>
<td>Urine Protein/Creatinine Ratio −0.009 ± 0.011</td>
<td>0.4124</td>
</tr>
<tr>
<td>C3 1.739 ± 0.542</td>
<td>0.0013</td>
</tr>
<tr>
<td>C4 0.315 ± 0.118</td>
<td>0.0076</td>
</tr>
<tr>
<td>Anti-dsDNA 2.281 ± 1.978</td>
<td>0.2487</td>
</tr>
</tbody>
</table>

Vit D levels were not associated with PGA, SLEDAI, urine protein/Creatinine ratio, but were associated with an improvement in C3 and C4.

Conclusion: Change of Vitamin D levels in this outpatient SLE population were neutral in terms of clinical disease activity. Further followup of this population will allow us to determine if there are delayed clinical effects. However, there was a statistically significant effect on both C3 and C4. The effect on C3 might have clinical implications in that low C3 is known to be associated with SLE renal disease and increases the risk of flare. This analysis cannot address the effects of "super" supplementation, since no attempt was made to achieve 25 OH Vit D levels higher than 40 ng/mL. However, the data suggest that clinical trials to achieve higher levels of 25 OH Vit D are indicated.

Disclosure: M. A. Petri: None; K. J. Bello: None; H. Fang: None; L. Magder: None.
Acute Flares of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) Are Sometimes Associated with Spikes of Interferon-alpha Activity in the CSF.

Elisabet Svenungsson1, Clio P. Mavragani2, Liisa Hopia3, Mohsen Khademi4, Anna Laveskog5, Mary K. Crow7 and Magnus Andersson2. 1Hospital for Special Surgery, New York, NY, 2Karolinska Institutet, Stockholm, Sweden, 3Karolinska Institutet, Sweden

Background: Neuropsychiatric involvement in Systemic Lupus Erythematosus (NPSLE) is a serious complication affecting a large proportion of systemic lupus erythematosus (SLE) patients. Diagnosis and treatment is a challenge as no specific biomarker/investigation for NPSLE is available. Enhanced interferon-alpha (IFN-α) activity has been identified as an important ethiopathogenic factor in SLE, and a previous study reported that IFN-α contributes to NPSLE. We investigated IFN-α activity in the systemic and intrathecal compartments of patients with acute and chronic symptoms of NPSLE.

Methods: 59 NPSLE patients, who fulfilled the ACR 1982 revised criteria for SLE, were evaluated clinically. Lumbar puncture and magnetic resonance imaging (MRI, n=56) was performed. All presented with one or several NPSLE manifestations as defined by the ACR NPSLE criteria.

Results: The majority (n=49) had chronic NPSLE symptoms but 10 were investigated during acute NPSLE flares. Paired blood and cerebrospinal fluid (CSF) samples were collected from patients and controls (15 Multiple Sclerosis (MS) patients, 22 patients with other neurological diseases (OND)). IFN-α activity was measured as a score with a functional cell reporter assay. mRNA expression of IFN-α was determined in peripheral blood and CSF mononuclear cells (PBMCs; CSF-MCs) in 39 patients and in a different set of controls (MS=34, OND=24).

Conclusion: Our results indicate that IFN-α activity in the CSF is high in some patients with NPSLE and is often associated with acute NPSLE symptoms. As a group, patients with chronic NPSLE had similar IFN-α activity in CSF and blood to controls. IFN-α activity may be of diagnostic potential in patients with SLE who present with acute neurological symptoms.

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1182

Allogeneic Mesenchymal Stem Cells Inhibited OAZ Expression in Patients with Systemic Lupus Erythematosus (SLE). Xuebing Feng1, Ronghong Li1, Jing Huang2, Dandan Wang3, Xiaolei Ma4, Betty P. Tsao5 and Lingyun Sun2. 1Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, 2Affiliated Drum Tower Hospital of Nanjing University Medical School, 3UCLA School of Medicine, Los Angeles, CA

Objective: Allogeneic mesenchymal stem cell transplantation (MSCT) has been applied to successfully treat patients with refractory systemic lupus erythematosus (SLE) (Sun et al A&R, 2010). However, the underlying mechanism is still unclear. Recently we have shown Olf/EBF associated zinc finger protein (OAZ), a novel lupus susceptibility gene, involves in the production of antineuronal antibody (ANA) that is partly through the regulation of ID genes. This study is to explore whether allogeneic MSCT helps down-regulate elevated OAZ expression in SLE patients.

Methods: Study protocol was approved by the hospital’s Ethics Committee. MSCs were isolated and expanded from bone marrow of 5 SLE patients and 6 healthy subjects. After culturing for 3 passages, MSCs were harvested and mRNA levels of OAZ and ID1, ID3, two downstream genes of OAZ, were measured by qRT-PCR. MSCs expanded from umbilical cord (9 cases) or bone marrow cells (1 case) of healthy donors were infused once to 10 refractory SLE patients at 10^6 cells/kg of body weight. Peripheral blood cells (PBMCs) were collected before and one week as well as four weeks after MSCT, and transcript levels of OAZ and ID genes were measured. Concurrently, serum levels of IL-10, IL-12, IL-21, CCL2 and ANA were tested by ELISA. Relationships between gene expressions and cytokine levels as well as ANA levels were analyzed.

Results: Compared to PBMCs, MSC expression of OAZ transcripts was 150 and 110 times higher in SLE patients and normal controls, respectively. OAZ expressions of MSCs in SLE patients were elevated compared to those in normal subjects (p = 0.03), but expressions of ID1 and ID3 were not different. Ten SLE patients (9 female and 1 male, 32.2 ± 3.7 years old) who accepted MSCT had decreased OAZ expressions in PBMCs by 42.6% ± 17.1% one week after MSCT compared to those before MSCT (p < 0.05) with concomitant reduction in disease activity (SLEDAI score was 14.9 ± 6 before MSCT, 13.0 ± 0.5 one week later) which continued to drop further four weeks after the transplant (a reduction of 37.6% ± 12.4% compared to those at one week, p < 0.05). Peripheral gene expressions of ID1 and ID3 were also significantly down-regulated after MSCT (p < 0.05). Four weeks after MSCT, serum levels of IL-10, IL-21 and ANA were significantly decreased (p < 0.05 in all), while CCL2 levels was elevated (p < 0.05) compared to the baseline levels. Compared to the value before MSCT, increased peripheral OAZ expression four weeks after MSCT was inversely correlated with reduced IL-21 levels (r = −0.88, p < 0.05) and ANA values (r = −0.91, p < 0.01) but positively correlated with increased CCL2 levels (r = 0.92, p < 0.01).

Conclusion: OAZ is highly expressed in MSCs from SLE patients. Allogeneic MSCT helps down-regulate OAZ expression and its downstream components, which may account for the ameliorated SLE disease activity. The differential expressions of ID1 and ID3 in peripheral blood cells but not MSCs support that MSCs could exert their roles through the regulation of other cell types.

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Analysis of Vascular Endothelium from Female Systemic Lupus Erythematosus (SLE) Patients Identifies an Interferon Signature That Correlates with Disease Activity. Diana Goldenberg3, Mikhail Olferiev3, Duygu Ousat1, Danieli Andrade3, Mary K. Crow3, Paolo C. Colombo1 and Jane E. Salmon1. 1Columbia University College of Physicians and Surgeons, New York, NY, 2Hospital for Special Surgery, New York, NY, 3Hospital for Special Surgery, New York, NY

Background: Accelerated atherosclerosis has emerged as a significant threat to the health of patients with systemic lupus erythematosus (SLE). Endothelial dysfunction represents an important precursor to the development of atherosclerosis. The type 1 interferons likely influence the relationship between endothelial dysfunction and vascular health in lupus patients. To study the pathogenesis of endothelial dysfunction in SLE, we utilized a novel, minimally-invasive approach to sample venous endothelial cells (ECs) and perform gene expression profiling.

Methods: Venous endothelial cells were sampled from 11 adult SLE patients and 10 healthy controls. ECs were collected from arm veins using endovascular wires. ECs were purified; amplified RNA was hybridized with Affymetrix HG-U133 2.0. Samples were normalized to the baseline median level according to the RMA algorithm. Data was analyzed using GeneSpring GX 11 software. Student T test analysis for multiple samples was performed. Differentially expressed genes with |log fold expression| ≥ 2.0 and p<0.05 were selected. SLE disease activity was assessed by SLEDAI at the time of endothelial sampling. The interferon score was determined using the mean of the normalized expression values for IFIT1, IFIT3, MX2 and OAS2. To simulate our in vivo findings and to determine whether SLE serum could directly alter A & R cell gene profiles, we cultured HUVECs with sera from SLE patients and healthy controls and assessed their capacity to induce interferon-inducible genes, IFIT1, IFIT4 and MX1 using Real-time quantitative polymerase chain reaction.

Results: Eleven (8 females, 3 males) adult SLE patients meeting American College of Rheumatology criteria for SLE and 10 age-matched controls...
were studied. Their mean age was 32.2 ± 10.2 yrs, mean SLEDAI score was 6.82; range 0–20. Ten age-matched healthy subjects were studied. A total of 2013 known genes were differentially expressed (FC ≥2, p<0.05) between all SLE patients and controls while 183 known genes were differentially expressed (FC ≥2, p<0.05) between female SLE patients and matched controls. IFIT1 and IFIT3 were upregulated in the 11 SLE patients compared with controls. In female SLE patients the interferon signature was particularly robust: IFIT1, IFIT3, MX2 and OAS2 were upregulated. The interferon score correlated significantly with SLEDAI in female patients (R = 0.75, p = 0.04). Similar to the results of our in vivo venous endothelial samples, HUVECs cultured with sera from SLE patients showed increased expression of the interferon inducible genes compared with those exposed to sera from control patients (109.1 ± 41.42 vs 0.04 ± 0.01).

**Conclusions:** Microarray analysis of primary venous endothelial cells distinguished SLE patients from healthy controls based on the expression of interferon-inducible genes. In the 8 female SLE patients, SLE disease activity correlated with the interferon score. These results support the possibility that interferon contributes to the pathogenesis of endothelial dysfunction in SLE patients.

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**1184**

**Anti-C1q Antibodies Are Associated with Global Activity of Systemic Lupus Erythematosus, but Not Specifically with Nephritis.** Yuko Okamoto1, Yasuhiro Katsumata1, Yasushi Kawaguchi2, Kohsei Miyake1, Manabu Kawamoto1, Kae Takagi1, Takahisa Gono1, Sayumi Baba2, Yuko Ota1, Masako Hara3 and Hisashi Yamazaki4. 1Tokyo Women’s Medical University, Tokyo, Japan; 2Tokyo Women’s Medical University, Tokyo, Japan; 3Tokyo Women’s Medical University, Shinjuku-ku, Tokyo, Japan; 4Tokyo Women’s Medical University, Kamakura Kanagawa, Japan; 5Tokyo Women’s Medical University.

**Purpose:** Antibodies against complement C1q (anti-C1q Abs) are frequently found in patients with autoimmune diseases such as systemic lupus erythematosus (SLE). It has been reported that they correlate with the occurrence and activity of nephritis and cutaneous vasculitis in SLE. Additionally, their pathogenic role in SLE, such as direct link with apoptosis, has been suggested. However, the significance of anti-C1q Abs in SLE has not been fully characterized. This study was conducted to investigate associations between anti-C1q Abs and clinical and serological parameters of SLE.

**Methods:** Anti-C1q Abs were measured using ELISA kit (BUHLMANN Laboratories AG, Schönenbuch, Switzerland) in sera of 126 consecutive active SLE patients who were admitted to our university hospital from 2007 through 2009. Sera of patients with high-titer anti-C1q Abs at initial evaluation were re-evaluated when their disease ameliorated (n = 20). Sera of patients with other autoimmune diseases and normal healthy controls were also assessed (n = 20 in each control group). Associations between anti-C1q Abs and clinical and serological parameters of SLE were statistically analyzed.

**Results:** The titers and the positivity rate of anti-C1q Abs were significantly higher in patients with active SLE than in patients with rheumatoid arthritis, systemic sclerosis, or normal healthy controls (p < 0.0001 in all comparisons).

**Conclusions:** These findings indicate that anti-C1q Abs are associated with global activity of SLE, but not specifically with active lupus nephritis. Moreover, anti-C1q Ab might be useful as a surrogate marker of SLE in cases with this antibody.

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**1185**

**Biomarkers of Oxidative Stress, mTOR Activation, and Treg Depletion Correlate with Disease Activity in Patients with Systemic Lupus Erythematosus.** Zhiwei Liu1, Adam Bartos1, Tiffany Yekiarico2, Robert Hanczko1, Gabriella Miklossy1, Brandon Clair1, John Jimah1, Lisa Francis1, Hajra Tily1, Ricardo Garcia1, Maha Dawood1, David R. Fernandez1, Paul E. Phillips2, Joana Coman3 and Andras Perl1. 1SUNY, SUNY-Upstate Medical Univ, Syracuse, NY; 2Upstate Medical Univ, Syracuse, NY

**Purpose:** Systemic lupus erythematosus (SLE) patients’ T cells exhibit persistent elevation of the mitochondrial transmembrane potential (∆Ψm) or mitochondrial hyperpolarization (MHP) which predisposes to pro-inflammatory death via necrosis. Persistent MHP has been attributed to the depletion of reduced glutathione (GSH) and increased production of nitric oxide (NO) and reactive oxygen intermediates (ROI). Here, we evaluated metabolic checkpoints of mitochondrial dysfunction as biomarkers of disease activity in patients with SLE.

**Patients and Methods:** 34 female SLE patients and 34 female healthy controls were studied. 24 patients with stable disease were enrolled in double-blind placebo-controlled treatment trial with N-acetylcysteine (NAC; ClinicalTrials.gov identifier: NCT00775476). 10 patients with uncontrolled disease due to lack of efficacy or tolerance to current medications were enrolled in prospective treatment trial with rapamycin (RAPA; NCT00775194). SLE disease activity was assessed by using the British Isles Lupus Assessment Group (BILAG) and SLE Disease Activity Index (SLEDAI). Peripheral blood lymphocytes (PBL) and untouched T cells (using Dynal negative T-cell isolation kit) were freshly isolated on the same morning from patients and controls matched for ethnicity and age within 10 years and investigated in parallel for ∆Ψm, mitochondrial mass, glutathione, NO and...
ROI production, cytosolic [Ca2+]c and mitochondrial calcium levels ([Ca2+]m), and T and B cell subset distribution by flow cytometry after 24 h with or without CD3/CD28 co-stimulation. mTOR activity was assessed through the phosphorylation of its substrates by western blot. Spearman’s correlation coefficients rho and the two-tailed significance levels were estimated in SPSS version 17.

Results: SLEDAI (8.6 +/− 1.2) and BILAG (24.6 +/− 1.8) of 24 patients enrolled in the NAC trial were exceeded by the SLEDAI (16.5 +/− 2.9; p = 0.004) and BILAG (33.0 +/− 4.4; p = 0.04) scores of 10 patients enrolled in the RAPA trial. Mich, increased mitochondrial mass, increased [Ca2+]c, and increased NO production were detected in all T cell subsets irrespective of disease activity. mTOR activity was increased in negatively isolated T cells. Foxp3 expression was reduced in CD4+ T cells. [Ca2+]c was also increased in CD19+ B cells. Across all patients, individual total SLEDAI scores best correlated with glutatione depletion (p = 0.002) and ROI elevation in T cells (p = 0.008). Within SLEDAI components, anti-DNA titers were correlated with increased [Ca2+]m in CD3+/CD4+, CD3+/CD4–/CD8– (p < 0.008) but not in CD3+/CD8+ T cells. Leukopenia was correlated with diminished CD4+/CD25+ T cells (p = 0.003).

Conclusion: While mitochondrial dysfunction is detectable in lupus T cells irrespective of disease activity, oxidative stress characterized by the depletion of GSH and increased ROI production as well as activation of mTOR and Treg depletion may represent biomarkers of disease activity in patients with SLE.

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CD138 RNA Can Be Detected in the Circulation of Patients with Systemic Lupus Erythematosus and Correlated to Other Factors Suggestive of Plasma Cell Activation. Ming Chen1, Joy G. Hutcheson2, Stan Kamp3, Danny Walker2 and Joan T. Merrill1. 1Oklahoma Med Research Foundation, Oklahoma City, OK, 2OMRF, Oklahoma City, OK, 3OMRF, Allen, TX

Background: Plasma cells are key components in models of SLE pathogenesis, but are sequestered from easy analysis in humans, being rare and difficult to detect in peripheral blood. We hypothesized that quantification of CD138 RNA by real time PCR of peripheral blood leukocytes (BAFF) RNA and protein by RTPCR and ELISA, and immune complexes (anti-dsDNA antibodies and complement consumption) could provide a sensitive marker for activation of the plasma cell compartment.

Methods: The following measurements were performed on blood samples from 102 patients with SLE: CD138 RNA by RTPCR, BlyS (BAFF) RNA and protein by RTPCR and ELISA, and immune complexes (CIC/C1Q) by ELISA. Routine blood testing and clinical information were also recorded.

Results: CD138 RNA was detectable in most patient samples. Samples were divided into two groups: Group A was comprised of 39 patients with higher levels of CD138 (5–28 copies/ng). Group B included 61 patients with CD138 < 5 copies/ng. There were no differences in age (median 46 vs 47), gender (% female 89.5 vs 91.3) or ethnicity (% CAUC/AFR/ASIAN 63/26/11 Group A and 61/21/18 Group B). Compared to group B, Group A had greater prevalence of anti-dsDNA (28% vs 6.5%, p = 0.008), and C3 below normal (25.6% vs 5.0%, p = 0.007). Group A trended to higher levels of immune complexes (median 417 ng/ml vs 189, p = ns) as well as increased BlyS protein (median 3333 ng/ml vs 2805, p = ns) and BlyS RNA (median 529 copies/ng vs 421, p = ns). Levels of CD138 did not impact on disease activity by SLEDAI or BILAG, although CIC were increased in patients with SLEDAI >25 vs those with lower scores (median 1580.7ng/ml vs 1326.2, p = 0.009) as were levels of BlyS protein (median 3927ng/ml vs 2742, p = 0.042). An exploratory multivariate analysis was performed, considering the possibility that circulating CD138 reflects increased global plasma cell activity, which might contribute to autoantibody formation and complement consumption systemically. C3 levels were chosen as the dependent variable by virtue of being the furthest downstream of the elements studied. After adjusting for several potentially confounding factors, CD138 maintained a strong, independent effect on C3 levels (see table).

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Univariate p value</th>
<th>Multivariate p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-dsDNA</td>
<td>&lt;0.001</td>
<td>0.008</td>
</tr>
<tr>
<td>CIC/C1Q</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>CD138 RNA</td>
<td>&lt;0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>BlyS protein</td>
<td>0.014</td>
<td>0.059</td>
</tr>
<tr>
<td>BlyS RNA</td>
<td>0.022</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Conclusions: CD138 can be measured in peripheral blood from lupus patients and may be related to meaningful upstream B cell stimuli (such as BLYS) as well as downstream effects of plasma cell activation, anti-dsDNA antibodies and complement consumption. Since some biologic agents in development are expected to have more impact on plasma cells than others, studies of the few that enter the circulation could provide predictive biomarkers for treatment selection.

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Characterisation of Lipid Order in Lymphocyte Subsets from Patients with Systemic Lupus Erythematosus (SLE). Laura Miguel1, Chrissie Lim2, David A. Isenberg1 and Elizabeth C. Jury2. 1UCL Div of Medicine, London, United Kingdom, 2University College London, London, United Kingdom

Membrane lipid microdomains (lipid rafts) enriched with cholesterol and glycosphingolipids are thought to play an important role in lymphocyte function by forming areas of high lipid order that facilitate the activation process. Patients with SLE have defects in T and B cell receptor-mediated activation pathways involving altered expression and membrane localisation of key intracellular signalling molecules. However, the precise role that lipid rafts play in these abnormalities is not fully understood.

Here, using a new probe, di-4-ANEPPDHQ, to define lipid microdomains, we were able to distinguish areas of high lipid order (lipid rafts) and disorder (non-rafts) in the membrane of T and B lymphocytes from patients with SLE (n = 79) compared with healthy volunteers (n = 44), and patients with Sjogren Syndrome (SS) (9) or rheumatoid arthritis (RA) (n = 15) as controls. Lipid order was quantified by calculating a generalized polarization (GP) value from mean fluorescence intensity emissions at 570nm and 630nm using a LSRII flow cytometer. Plasma membrane lipid order was related to naive, memory, regulatory and activated phenotypes using a range of T and B cell surface markers and flow cytometry. In addition membrane lipid order was related to levels of membrane and serum cholesterol, triglycerides, HDL and LDL.

The results revealed that lymphocytes from healthy controls had three distinct populations with relative High, Intermediate and Low membrane lipid order. The majority of T cells had high membrane order, whereas B lymphocytes had an expanded Intermediate order population. Patients with SLE and RA had significantly reduced lipid microdomain membrane order compared with healthy controls (p < 0.001), except for patients with inactive SLE on prednisolone therapy who had lymphocytes of higher overall order than healthy controls (p = 0.01). No significant differences were observed in patients with SS compared with healthy volunteers.

Phenotyping showed that in both healthy and patient samples T cells with high lipid order were predominantly naive and responder cells whilst Low order T cells were associated with activated, regulatory and effector memory phenotypes. Immature B cells tended to be associated with Low membrane order. These results correspond with the increased frequency of activated, regulatory and memory T cells in patients with autoimmune disease. Interestingly, in healthy volunteers, the serum cholesterol:HDL ratio showed a positive correlation with plasma membrane lipid order (p = 0.05). However, this relationship was lost in patients with SLE, regardless of therapy, who had increased serum LDL and reduced serum HDL resulting in high cholesterol:HDL ratios.

In conclusion, the correlation between immune phenotype and membrane lipid order supports an important role for lipid microdomains in modulating adaptive immune responses and the contribution of dyslipidaemia to immunopathology. The results support the need for further investigation to define the relationship between serum cholesterol and plasma membrane microdomains in lymphocytes from healthy volunteers compared to patients with autoimmune rheumatic disease.

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Correlates of ANA Positivity in Healthy Individuals. David R. Karp1,2,3, Quan-Zhen Li4,5, Valerie K. Branch2, Jiecia Quan5 and Nancy J. Olsen6.1Univ of TX Southwestern Med Ctr, Dallas, TX, 2UT Southwestern Med Ctr, Dallas, TX, 3UT Southwestern Med Ctr, Dallas, TX.

The significance of ANA positivity that is observed in up to 25% of the population is unknown. We sought to determine demographic, immunologic and gene expression correlates of elevated ANA values in healthy controls (HC) to provide insights into when this might signal elevated risk for development of autoimmune disease. ANA was measured by ELISA in serum samples from 1159 individuals in the Dallas Regional Autoimmune Disease Registry (DRADR) and autoantibodies in the ENA panel were quantitated by a LumineX-based assay. CCP measurements utilized ELISA. More detailed studies were carried out on a subset of HC with high ANA (N = 18) or low ANA (N = 18) and SL patients (N = 14) matched for gender and age. A slide-based array was used to measure approximately 100 autoantibodies in IgG and IgM classes. Gene expression profiles were measured in these individuals using RNA isolated from whole blood and analyzed on the Illumina Human-6 V3 Bead Chip. Elevated ANA levels in the HCs were strongly correlated with female gender (P = 0.033) but not with age (R² = 0.01). CCP autoantibodies did not show gender dimorphism in HC or autoimmune individuals, indicating that female gender is not a risk factor for all autoantibodies. Autoantigen arrays identified 12 autoantibodies with SLE-comparable levels in ANA high but not ANA low HC. Of these, 6 (50%) were directed against antigens associated with autoimmune skin disorders (MMP-1, nidogen-1, laminin 5, α6β4 integrin, desmoglein-4, plectin-1) or other autoimmune diseases (dsDNA, aggrecan, thyroglobulin, liver cytosol type-1). A total of 95 genes were significantly (P < 0.01) dysregulated in ANA high vs ANA low HC, and the vast majority (90%) were upregulated in the ANA high group. The highest upregulated gene in ANA high HC was TGM2 which encodes transglutaminase2, a celiac disease autoantigen. Some gene components of the Type I IFN signature were elevated in the ANA high group (MX1, IFITM3, IFITM1, IFIT3) while others, notably IFI27, were only elevated in SLE (Figure).

The findings suggest that early lupus-like autoimmunity might begin in the skin and that some ANA positivity may herald development of other autoimmune diseases. Identification of gene and protein patterns along with ANA and demographic features has potential to predict risk of lupus and other autoimmune diseases in normal individuals.

Disclosure: D. R. Karp: None; Q.-Z. Li: None; V. K. Branch: None; J. Quan: None; N. J. Olsen: None.

Dysregulation of the Microvascular as Assessed by Expression of Protective and Injury Associated Markers Is Reflected in the Non-Lesional Non-Sunexposed Skin of Patients with Lupus Nephritis. Peter M. Izmirly1, Shane Meehan2, Sherry X. Xu3, Anca D. Askaslan2, Joan T. Merrill1, Jill P. Buon3 and Robert M. Clancy4.1NYU School of Medicine, New York, NY, 2NYU School of Medicine, 3Oklahoma Med Research Foundation, Oklahoma City, OK, 4Tisch Hospital 4–407, New York, NY.

Purpose: Coagulation is one of the first pathways to be elicited by vascular injury, and its activation is followed by proinflammatory phenomena, in part due to loss of the anti-inflammatory activity of both the Protein C pathway and membrane Endothelial Protein C receptor (mEPCR). It has been recently demonstrated that mEPCR is highly expressed in the cortical peritubular capillaries of kidneys from patients (pts) with active lupus nephritis compared to normal human kidney. Profound upregulation of mEPCR levels and increased chemotactic responses were both reduced to normal after apol-mimetic peptide or imatinib treatment.

Conclusions: Dysfunctional pHDL has profound pro-inflammatory effects on human monocytes. These effects can be neutralized by blocking the PDGFRβ receptor. Therefore, pHDL directly influences monocyte biology and could promote accelerated atherosclerosis in SLE patients imatinib or an apol-mimetic peptide could be used as targeted therapy in pHDL+SLE subjects at risk of atherosclerosis as determined by the presence of plasma pHDL.

Disclosure: B. J. Skaggs: None; B. H. Hahn: None; L. Sahakian: None; J. M. Grossman: None; M. A. McMahon: None.
and five healthy controls (4 females, 1 male). The paraffin skin sections were individually stained with specific antibodies against mEPCR and adiponectin (protective markers), ICAM-1 (proinflammatory) and CD31 (pan endothelial marker). Immunohistochemistry (IHC) was scored by counting peroxidase-
denaturing conditions.

Results: The 28 renal biopsies comprised the following ISN/RPS classifications: 4 Class III, 7 Class IV, 8 Class V, 1 Class VI, 3 Class III/V, 3 Class IV/V. Nineteen percent of the pts had a GFR <60 (mean GFR, 82 ml/min). Abnormal laboratory values for complement and anti-dsDNA antibodies were reported in 72% and 75% of pts, respectively. Nephrotic range proteinuria was present in 37%. For IHC skin assessments of the controls, the mean score for mEPCR was 1 (highest 2), ICAM-1 was 4 (highest 7) and adiponectin was 1 (highest 2). In 17/25 (68%) of the SLE non-lesional non-sun exposed skin sections, mEPCR was expressed above the highest control. In 16/30 (53%) ICAM-1 staining exceeded 7. In contrast, only 6/25 (19%) expressed adiponectin above 2. For each specific stain there were no apparent differences between biopsy class, degree of proteinuria, presence of anti-dsDNA or low complement levels. However, pts with mEPCR staining above 2 had higher GFR measurements than those with staining <2 (88 ml/min ± 31 versus 53 ± 32, p = 0.0168). In contrast, GFR was unrelated to ICAM-1 and adiponectin expression.

Conclusion: These data are consistent with the notion that there is widespread activation of the microvasculature. The capacity of endothelial cells to utilize anticoagulation pathways is not restricted to the kidney and expression of mEPCR in the microcirculation likely represents an attempt to limit microvascular inflammation in kidney and skin.

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Evidence of N-methyl-D-aspartate Receptor (NMDAR) Expression on Primary Human Endothelial Cells. Cagri Yildirim-Torun1, Paola Mina-Osario2 and Betty Diamond1. 1Feinstein Institute for Medical Research, Manhasset, NY, 2Feinstein Institute for Medical Research, 3Morgan Stanley Children’s Hospital of NewYork- Presbyterian Columbia University Medical Center, Feinstein Institute for Medical Research, New York, NY

Background: A subset of anti-DNA antibodies has been implicated in neuropsychiatric lupus. These antibodies bind NMDARs and mediate excitotoxic neuronal death, but cause no appreciable neuronal damage when present in the circulation unless there is a breakdown in the blood-brain barrier (BBB). Thus, the BBB is the limiting step for the onset of neurotoxicity. Identifying the mechanisms of antibody transfer through the BBB has important prophylactic and therapeutic implications. It has recently been proposed that anti-NMDAR antibodies modify the permeability of BBB, but presence of NMDARs on BBB is controversial. In order to address this controversy, we studied two different human endothelial cells (EC) considered as in-vitro models of human BBB, Human Umbilical Vein Endothelial cells (HUVEC) and human brain microvascular endothelial cells (HBMEC), to determine the presence of the NMDAR in EC.

Methods: After HUVEC cells were grown to confluency, total RNA was isolated with the RNeasy RNA isolation kit (Qiagen) and reverse-transcribed by using the iScript RT-PCR System (BioRad). Resulting cDNA was amplified with NR1 and NR2B primers. PCR amplicons were visualized in a 1% agarose gel.

For immunoprecipitation, cells were trypsinized, lysed with and then centrifuged at 14,000 rpm. The supernatants were incubated overnight with 2 µg/ml of a polyclonal anti-NR2B antibody. The lysates were then incubated for 1h at 4°C with protein-A agarose. The beads were pelleted by a short centrifugation, washed several times and resuspended in Laemmli sample buffer. Then immunoprecipitates were separated by PAGE under denaturing conditions. HUVEC were grown to confluency on gelatin-coated culture dishes. After trypsinization, cells were fixed in 1% PFA, permeabilized in Triton-X100 0.1%/PBS for 10 min, washed and incubated with the indicated antibodies or an isotype control for 1 hour at 4°C followed by a PE-conjugated secondary antibody for 30 min at 4°C. Cells were subsequently analyzed in a FACs-Calibur flow cytometer.

Results: Human endothelial cells express NMDAR and bind anti-DNA/ NMDAR cross-reactive antibodies. RT-PCR experiments demonstrate the expression of NMDAR subunits, NR1 and NR2B, are expressed in HUVEC (Fig1A). We were also able to immunoprecipitate the NR2B subunit of NMDAR from total cell lysates of HUVEC (Fig1B). Finally, the anti-NMDAR antibody R4A and two human anti-NMDAR antibodies (clone E2 and G11) bound to HUVEC and HBMEC as determined by flow cytometry (Fig1C).

Conclusion: NMDARs are expressed in in-vitro models of human BBB. The demonstrated physical interaction of these anti-NMDAR antibodies with NMDAR raises the possibility of a role for the antibodies in modulating the permeability of BBB through antibody-receptor interaction in the pathogenesis neuropyschiatric lupus. Functional and expression assays are ongoing to elucidate the role of anti-NMDAR antibodies on BBB.

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Expression of B Cell Subsets in SLE Pregnancy: Correlation with Preterm Birth. Megan E. B. Clowse1, Sara Sparks2, Sallie Allgood3, Mark Lanasa4 and David S. Piesky1. 1Duke Univ Med, Durham, NC, 2Duke University, Durham, NC, 3Duke University Medical Ctr, Durham, NC

Background: Pregnancy demands significant shifts in immunologic function to maintain tolerance to the fetus. Women with systemic lupus erythematosus (SLE), particularly active SLE, have a several-fold higher rate of preterm birth and miscarriage compared to healthy women, suggesting that immune systems changes in SLE affect maternal-fetal tolerance and thereby promote pregnancy complications. To investigate this possibility, we tested whether alterations in the B cell compartment associated with SLE (increased plasmablasts and plasma cells and decrease naïve B cells) are associated with SLE activity and pregnancy outcomes.

Methods: Pregnant women with rheumatologic disease were consecutively enrolled in a prospective cohort. Disease activity using the SLE pregnancy disease activity index (SLEPDAI), and blood for autoantibody levels and peripheral blood mononuclear cells were collected in the first trimester, at a mid-pregnancy visit (between 20–26 weeks gestation) and at least 6 weeks post-partum. Flow cytometry was performed and data analyzed using Flowjo. Plasmablasts were identified as CD27+ +, CD38 + +, and IgD− cells. Plasma cells, memory B cells, and naive B cells were delineated based on the degree of CD27 positivity. T tests and Fisher’s exact test were used to determine statistical significance.

Results: The cohort included 25 pregnant women: 19 with SLE and 6 with rheumatoid arthritis (RA). Extractable nuclear antigens were identified in 68% and anti-dsDNA antibody was positive in 42% of the women with SLE. Five women had active disease, determined by a SLEPDAI ≥8. Three of the SLE pregnancies resulted in a pregnancy loss. Of the live births, 37% of SLE pregnancies were delivered preterm (<37 weeks gestation). All of the RA pregnancies resulted in a live birth at term.

Pregnant women with RA had a higher percentage of naive B cells than women with SLE both at mid-pregnancy (RA 88% vs SLE 80%, p = 0.07) and post-partum (RA 88% vs SLE 80%, p = 0.007). Women with a positive anti-dsDNA antibody had a higher percentage of plasmablasts (p = 0.03), plasma cells (p = 0.07), and memory B cells (p = 0.08), but fewer naive B cells (p = 0.09) than other women with SLE. Compared to values post-partum, in the 1st trimester women with SLE had a trend toward fewer lymphocytes, a higher percentage of B cells, fewer memory B cells and more naive B cells (see Table).
Phages. According to our hypothesis, an immune deficient state – low levels of anti-PC – predispose to chronic inflammatory diseases. We here study atherosclerosis as determined by carotid ultrasound in systemic lupus erythematosus (SLE) and the role of traditional and non-traditional risk factors for atherosclerosis and CVD.

Methods: One hundred fourteen patient with SLE were compared with one hundred twenty two age- and sex matched population-based controls. Common carotid intima-media thickness (IMT), calculated intima-media area (cIMa) and plaque occurrence were determined by B-mode ultrasound as a surrogate measure of atherosclerosis. Plaques were graded according to echogenicity and grouped as I–IV, with I being echoluscent, and considered most vulnerable. Osteoporosis was studied by DXA and anti-PC by ELISA.

Results: IMT and cIMa did not differ significantly between groups. However, plaques were more often found in SLE patients (p = 0.029). Age, LDL and IgM anti-PC (lowest tertile) were independently associated with plaque occurrence in SLE. Further, the left carotid arteries echoluscent plaques (grade 1) were more prevalent in SLE as compared to controls (p = 0.016).

Triglycerides, insulin resistance (determined by homeostasis model assessment of insulin resistance) hypertension, and C-reactive protein (CRP) were increased in SLE (p < 0.01) while smoking, LDL and HDL did not differ between groups. Low levels of anti-PC IgM (lowest tertile) were more common in SLE patients than in controls (p = 0.002). Osteoporosis was more prevalent in the hip in SLE-patients as compared to controls (p < 0.05) but not otherwise. 18.4% of SLE patients and 1.6% of controls (p < 0.01) exhibited a history of CVD (myocardial infarction, angina, heart valve disease, stroke or claudication).

Conclusion: Plaque occurrence and the frequency of vulnerable plaques in the carotid arteries are increased in SLE. Anti-PC could be a novel risk marker also with a therapeutic potential in SLE.

Disclosure: C. Anania: None; T. Gustafsson: None; X. Hua: None; J. Su: None; M. Heimbürger: Abbott Immunology Pharmaceuticals, 3; T. Jøgestrand: None; J. Frostegård: Athera Biotechnologies AB, 1, 4, 5, 8, Co-founder and minor shareholder of Athera Biotechnologies AB, 1, 4, 5, 8.

Increased Male Fetal Loss and Fewer Male Siblings in a Cohort of Systemic Lupus Erythematosus Families.

Purpose: A sex bias has been found absent in sibships of non-female predominant diseases like diabetes. We undertook this study to enhance our understanding of sex ratios in live sibships and lost fetuses in a large cohort of Systemic lupus erythematosus (SLE).

Methods: Families were collected through the Lupus Family Registry and Repository. All patients met at least four of the 1982 ACR classification criteria for SLE. All families had at least one member with SLE. Collective sibling gender data were obtained for the SLE cohort studied. Spontaneous miscarriage and abortion information was assessed, when self-reported, on a standard questionnaire filled by the patient. Male to female sex ratios were calculated.

Results: Collectively, 282 SLE affected male patients had 314 male siblings and 415 female siblings. The 2296 SLE affected female patients had 3113 male siblings and 3772 female siblings. Thus the ratio of male to female siblings = (314 + 3113) / (3772 + 415) = 0.82. SLE affected females reported 36 events of male fetal loss and 20 events of female fetal loss. Thus, ratio of male to female fetal loss was found to be 1.81.

Conclusions: There is a trivial explanation for too few male siblings in this cohort. Sibships with lots of girls are more likely to have SLE because of the excess girls with SLE and, therefore, are more likely to be included in the study. So, to correct for the ascertainment bias, we left out the SLE patients. Even when this is done, the male/female ratio is 0.8 and live births and fetal loss is nearly twice more common in males. The most parsimonious and perhaps the only explanation is a gene on X where a mutation or allele is lethal for males in utero and gives girls risk for SLE as we have discussed. This means this gene should be on the maternal X chromosome of patients in families where the sibship containing the SLE patient has excess girls and/or there are reports of male fetal loss.

Disclosure: R. Aggarwal: None; R. H. Sosfiedl: None.

Low Levels of Atheroprotective Natural IgM Antibodies Against Phosphocholine and Increased Prevalence of Vulnerable Atherosclerotic Plaques in Patients with SLE.

Background: We recently reported that natural antibodies against phosphocholine (anti-PC) are negatively associated with atherosclerosis and cardiovascular disease (CVD) in the general population: low IgM anti-PC levels predict increased risk of CVD and high levels protect against increase in atherosclerosis over time. We have determined two potential mechanisms: anti-inflammatory effects of anti-PC (inhibiting inflammatory phospholipids which are implicated in both atherosclerosis and RA) and decreased uptake of oxidized lipids in macrophages. According to our hypothesis, an immune deficient state – low levels of anti-PC – predispose to chronic inflammatory diseases. We here study atherosclerosis as determined by carotid ultrasound in systemic lupus erythematosus (SLE) and the role of traditional and non-traditional risk factors for atherosclerosis and CVD.

Methods: One hundred fourteen patient with SLE were compared with one hundred twenty two age- and sex matched population-based controls. Common carotid intima-media thickness (IMT), calculated intima-media area (cIMa) and plaque occurrence were determined by B-mode ultrasound as a surrogate measure of atherosclerosis. Plaques were graded according to echogenicity and grouped as I–IV, with I being echoluscent, and considered most vulnerable. Osteoporosis was studied by DXA and anti-PC by ELISA.

Results: IMT and cIMa did not differ significantly between groups. However, plaques were more often found in SLE patients (p = 0.029). Age, LDL and IgM anti-PC (lowest tertile) were independently associated with plaque occurrence in SLE. Further, the left carotid arteries echoluscent plaques (grade 1) were more prevalent in SLE as compared to controls (p = 0.016).

Triglycerides, insulin resistance (determined by homeostasis model assessment of insulin resistance) hypertension, and C-reactive protein (CRP) were increased in SLE (p < 0.01) while smoking, LDL and HDL did not differ between groups. Low levels of anti-PC IgM (lowest tertile) were more common in SLE patients than in controls (p = 0.002). Osteoporosis was more prevalent in the hip in SLE-patients as compared to controls (p < 0.05) but not otherwise. 18.4% of SLE patients and 1.6% of controls (p < 0.01) exhibited a history of CVD (myocardial infarction, angina, heart valve disease, stroke or claudication).

Conclusion: Plaque occurrence and the frequency of vulnerable plaques in the carotid arteries are increased in SLE. Anti-PC could be a novel risk marker also with a therapeutic potential in SLE.

Disclosure: C. Anania: None; T. Gustafsson: None; X. Hua: None; J. Su: None; M. Heimbürger: Abbott Immunology Pharmaceuticals, 3; T. Jøgestrand: None; J. Frostegård: Athera Biotechnologies AB, 1, 4, 5, 8, Co-founder and minor shareholder of Athera Biotechnologies AB, 1, 4, 5, 8.

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Presence of HMGB1 (High Mobility Group Box 1) and Antibodies to HMGB1 in Systemic Lupus Erythematosus (SLE).

Background: Apoptotic cells accumulate in SLE and are considered to play an important role in the pathogenesis. High mobility Group box 1 is a non-histone nuclear protein, that can be secreted actively by inflammatory cells, and is released passively from apoptotic and necrotic cells where it may act as an autoantigen and as a pro-inflammatory mediator. There is increasing evidence that HMGB1 contributes to the pathogenesis of chronic inflammatory and auto-immune diseases. Indeed, presence of HMGB1 in serum of mice with SLE has been reported in the serum of lupus mice.

Objectives: In this study we determined levels of HMGB1 and anti-HMGB1 in SLE patients compared to healthy controls (HC). Also their relation with clinical and biochemical parameters was assessed.

Methods: The study population consisted of 69 SLE patients and 35 age and sex matched HC. Of the 69 SLE patients 35 were visiting the outpatient clinic and randomly chosen. The other 34 patients were selected for active disease and paired samples of these patients were selected during inactive phase of the disease. Eighteen of 34 patients had renal involvement and remaining 16 patients had other organ involvement. HMGB1 levels were measured with a Western blot and anti-HMGB1 levels were measured with an in-house developed ELISA using recombinant HMGB1 as antigen. Clinical and biochemical parameters of all patients were assessed routinely.

Results: HMGB1 levels in all SLE patients were significantly increased compared to HC. HMGB1 levels were relatively more increased in patients with renal involvement compared to non renal patients. HMGB1 levels were correlated with disease activity, as determined by SLEDAI. HMGB1 levels were correlated with anti-dsDNA levels and showed a negative correlation with C3. Anti-HMGB1 levels were significantly increased in all SLE patients compared to HC and were correlated to HMGB1 levels in all SLE patients.

Conclusions: In SLE patients serum HMGB1 levels are significantly increased, in particular in patients with renal involvement, and are related to disease activity. Furthermore, in SLE patients increased levels of anti-HMGB1 antibodies were detected. Whether HMGB1, and HMGB1-antibody immune complexes play a role in the pathogenesis of SLE, in particular in patients with renal involvement needs to be established.

Disclosure: D. Abdulahad: None; J. Westra: None; P. Limburg: None; C. Kallenberg: None; M. Bijl: None.

Table. Comparison of B cell subsets for pregnant women with SLE.

<table>
<thead>
<tr>
<th>1st trimester</th>
<th>Post-partum</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total white blood cell count</td>
<td>6.7 × 10⁹ cells/mm²</td>
<td>6.3 × 10⁹ cells/mm²</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>1.5 × 10⁹ cells/mm²</td>
<td>2.2 × 10⁹ cells/mm²</td>
</tr>
<tr>
<td>B cells (% of lymphocytes)</td>
<td>5.3%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Memory B cells (% of B cells)</td>
<td>9.5%</td>
<td>12%</td>
</tr>
<tr>
<td>Naïve B cells (% of B cells)</td>
<td>85%</td>
<td>80%</td>
</tr>
<tr>
<td>Plasma cells (% of B cells)</td>
<td>0.56%</td>
<td>0.69%</td>
</tr>
<tr>
<td>Plasmablasts (% of B cells)</td>
<td>0.55%</td>
<td>0.53%</td>
</tr>
</tbody>
</table>

The week of delivery correlated negatively with the percentage of plasmablasts in the 1st trimester (r = 0.7, p = 0.02) and trended towards a negative correlation with plasma cells (r = 0.5, p = 0.07). SLE activity and pregnancy loss were not correlated with any B cell subset.

Conclusion: Women with SLE have altered B cell homeostasis in the 1st trimester which may reflect the immunologic changes of pregnancy that allow fetal tolerance. In women with SLE, increased numbers of plasmablasts in the first trimester were associated with preterm delivery.
Tily: mitochondrial hyperpolarization (MHP) and ATP depletion which predispose populations, viral DNA association, increased viral loads in the peripheral environment. Agents, the ubiquitous Epstein Barr virus (EBV) has been development of SLE among susceptible individuals. Among potential viral factors, these mechanisms may contribute to the pathogenesis of SLE. Specifically, viral DNA association with T cell subsets and the presence of EBV in the peripheral blood may predispose individuals to SLE development. T cell subsets such as CD4+ and CD8+ T cells, and EBV-specific T cell responses have been implicated in the pathogenesis of SLE. EBV-specific T cell responses have been shown to be increased in patients with SLE compared to healthy controls. These responses may contribute to the pathogenesis of SLE through mechanisms such as immune activation and inflammation. In conclusion, EBV and its association with T cell subsets and viral DNA may play a role in the development of SLE among susceptible individuals. Further research is needed to elucidate the mechanisms by which EBV contributes to SLE development.
pregnancy that is accompanied by a high Type I IFN score is suggestive of SLE flare rather than PE. Elevated type I IFN may help distinguish SLE from PE in pregnant patients.

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Vitamin D and Vascular Stiffness in Patients with Systemic Lupus Erythematosus.

John A. Reynolds1, Sahena Haque,2 Jacqueline L. Berry,3 Lee-Suan Teh2, Pauline Ho1, Rachel Gorodkin1 and Ian N. Bruce4. 1Central Manchester University Hospitals NHS Foundation Trust, 2East Lancashire Hospitals NHS Trust, 3University of Manchester, Manchester, United Kingdom, 4University of Manchester

Background: Vitamin D deficiency is highly prevalent amongst patients with systemic lupus erythematosus (SLE) and is associated with increased disease activity. Low vitamin D levels are associated with increased cardiovascular events in the general population. We hypothesised that in patients with SLE, lower vitamin D levels would be associated with increased vascular stiffness (measured by aortic pulse-wave velocity, aPWV), and subclinical atherosclerosis (carotid intima-media thickness (cIMT) and plaque presence).

Methods: Patients with SLE who fulfilled 4 or more ACR 1997 criteria were recruited from regional outpatient clinics. Clinical assessment and serum collection occurred between Jan 2007 and Jan 2009. Serum 25-hydroxyvitamin D (25(OH)D) was measured by ELISA and 25(OH)D deficiency was defined as <20ng/ml. Aortic pulse-wave velocity was measured (Micro Medical PWV) and cIMT and plaque measured using B-mode Doppler ultrasound.

Results: We studied 75 female patients with SLE with a median (IQR) age and disease duration of 53 (46, 60) and 16 (8, 27) years respectively. Thirty three (53%) of patients had inactive disease (SLEDAI score=0). The median (IQR) serum 25(OH)D was 19.7 (15.1, 29.6) ng/ml, and 39 (52%) of subjects were vitamin D deficient.

Vitamin D levels were significantly lower (median [IQR] 12.88 [12.0, 16.2] ng/ml) in patients with the most active disease (SLEDASS score≥75th centile) compared to less active disease (20.5 [16.5, 30.8] ng/ml) (p=0.0187).

Serum 25(OH)D was significantly associated with increased aPWV (p=0.010), but not carotid plaque presence (p=0.205) or cIMT (p=0.571). The association with aPWV remained significant after adjustment for traditional CVD risk factors (age, systolic blood pressure, smoking, body mass index (BMI) and season sample taken) (p=0.04), but this association did not remain following adjustment for lupus disease activity (p=0.16).

Table. Serum 25(OH)D and subclinical markers of cardiovascular disease

<table>
<thead>
<tr>
<th>Marker</th>
<th>Unadjusted 25(OH)D Model</th>
<th>Adjusted 25(OH)D Model1</th>
<th>Adjusted 25(OH)D Model2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marker</td>
<td>OR 95% CI p</td>
<td>OR 95% CI p</td>
<td>OR 95% CI p</td>
</tr>
<tr>
<td>Aortic pulse wave velocity*</td>
<td>0.022 0.04, 0.01</td>
<td>0.028 0.00, 0.05</td>
<td>0.05 0.91, 1.75</td>
</tr>
<tr>
<td>Carotid plaque presence*</td>
<td>1.03 0.96, 1.09</td>
<td>0.99 0.91, 1.00</td>
<td>0.99 0.91, 1.00</td>
</tr>
<tr>
<td>Carotid intima-media thickness*</td>
<td>1.02 1.01, 1.03</td>
<td>0.99 0.92, 1.00</td>
<td>0.99 0.92, 1.00</td>
</tr>
</tbody>
</table>

β = β coefficient, CR=odds ratio, 95% CI=95% confidence interval, p=95% value
1 Linear regression model of log(aPWV)
2 Logistic regression model
3 Logistic regression model, cIMT above upper quartile
4 Adjusted for age, season (summer or winter), body mass index (BMI), systolic blood pressure, pack-years smoking, disease duration
5 An 0.1 model plus disease activity score (SLEDAI)

Discussion: Vitamin D deficiency was highly prevalent within our study population. Lower levels of 25(OH)D were associated with increased vascular stiffness, but not cIMT or plaque presence. This association may be mediated by increased disease activity, and prospective studies are now required to determine whether treatment of vitamin D deficiency can modify CVD risk in patients with SLE.

Disclosure: J. A. Reynolds: None; S. Haque: None; J. L. Berry: None; L. S. Teh: None; P. Ho: None; R. Gorodkin: None; I. N. Bruce: None.
A Pilot Study To Evaluate Digital Perfusion in Scleroderma Patients Treated with Oral Treprostinil. Ami A. Shah, Laurn K. Hummers, Kristan D. Rollins, Susan Walker, Mike Wade, Cynthia Anderson, Robert Wise, Francesco Boin and Frederick M. Wigley. 1Johns Hopkins University, Baltimore, MD, 2Johns Hopkins University, Baltimore, MD, 3Johns Hopkins University, 4United Therapeutics

Background: Raynaud’s phenomenon and a small vessel oblitative vasculopathy in scleroderma frequently lead to ischemic digital ulcers (DU). Previous studies have demonstrated a therapeutic effect of intravenous prostacyclin analogs for ischemic DU, but oral prostacyclin analogs have had limited success. During the first 6-8 weeks of serial measures of digital perfusion and drug concentration were obtained at each of the 2 study visits. Repeated measures analysis using random effects models were performed using perfusion and skin temperature as dependent variables of interest and perfusion obtained at drug trough, log-transformed drug concentration, visit number, individual timepoints of Doppler assessment at each PK visit, and left/right hand as potential explanatory variables. Covariates with p-values <0.15 were retained in the statistical model.

Results: Ten subjects with scleroderma and a history of recent or active ischemic DU were enrolled into the study. All subjects received oral treprostinil and titrated the dose up to 4mg twice daily (BID) as tolerated over 6–8 weeks. Assessments were performed when subjects achieved the 2mg and 4mg (or maximally tolerated) doses. Subjects who did not reach a dose of 2 mg BID during the study had assessments performed only at the end of study visit. Eight serial measures of digital perfusion and drug concentration were obtained at each of the 2 study visits. Repeated measures analyses using random effects models were performed using perfusion and skin temperature as dependent variables of interest and perfusion obtained at drug trough, log-transformed drug concentration, visit number, individual timepoints of Doppler assessment at each PK visit and left/right hand as potential explanatory variables. Covariates with p-values <0.15 were retained in the statistical model.

Conclusions: An increase in digital perfusion was observed with increased treprostinil blood concentrations, suggesting a dose-response relationship. Further investigation with a larger sample size and a control population is needed to confirm this association, to correct for individual subjects’ natural perfusion variations, and to evaluate for dose effects.

Disclosure: A. A. Shah: United Therapeutics; 2, L. K. Hummers: United Therapeutics; 2, K. D. Rollins: United Therapeutics; 1, 3; S. Walker: United Therapeutics; 1, 3; M. Wade: United Therapeutics; 1, 3; C. Anderson: None; R. Wise: None; F. Boin: None; F. M. Wigley: United Therapeutics, 2.

### Table: EULAR guideline

<table>
<thead>
<tr>
<th>EULAR guideline</th>
<th>Medication</th>
<th>% of CSRG patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Calcium channel blockers should be considered for first-line therapy for SSc-related RP.</td>
<td>Calcium channel blockers</td>
<td>47.3</td>
</tr>
<tr>
<td>2. Intravenous prostacyclin or iloprost. Should be considered for severe SSc-related RP.</td>
<td>Iloprost</td>
<td>3.1</td>
</tr>
<tr>
<td>3. Bosentan should be considered in treatment of diffuse SSc patients with multiple DU, after failure of PPIs and, usually, prostanoid therapy.</td>
<td>Bosentan</td>
<td>9.2</td>
</tr>
<tr>
<td>4. Bosentan should be strongly considered in the treatment of SSc-related PAH.</td>
<td>Bosentan</td>
<td>19.0</td>
</tr>
<tr>
<td>5. Sitaxentan may be considered in treatment of SSc-related PAH.</td>
<td>Sitaxentan</td>
<td>11.9</td>
</tr>
<tr>
<td>6. Silodenal should be considered in treatment of SSc-related PAH.</td>
<td>PDE5 inhibitors</td>
<td>14.3</td>
</tr>
<tr>
<td>7. Intravenous epoprostenol should be considered for the treatment of SSc-related PAH.</td>
<td>Epoprostenol</td>
<td>6.1</td>
</tr>
<tr>
<td>8. Methotrexate may be considered in the treatment of skin involvement in early diffuse SSc.</td>
<td>Methotrexate</td>
<td>18.8</td>
</tr>
<tr>
<td>9. Cyclophosphamide should be considered in the treatment of SSc-related ILD.</td>
<td>Cyclophosphamide</td>
<td>16.2</td>
</tr>
<tr>
<td>10. ACE inhibitors should be used in the treatment of scleroderma renal crisis.</td>
<td>ACE inhibitors</td>
<td>77.1</td>
</tr>
<tr>
<td>11. Prokinetic agents should be used for prevention of SSc-related GERD, esophageal ulcer and strictures.</td>
<td>PPIs (GERD)</td>
<td>85.5</td>
</tr>
<tr>
<td>12. Prokinetic agents should be used for prevention of SSc-related GERD, esophageal ulcer and strictures.</td>
<td>Promotility agents (GERD)</td>
<td>24.6</td>
</tr>
<tr>
<td>13. Prokinetic agents should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, delayed gastric emptying, bloating, pseudoobstruction, etc.)</td>
<td>Promotility agents (delayed gastric emptying)</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Perfusion was positively associated with log-transformed plasma concentration at the 4mg visit (but not the 2mg visit), after adjusting for the individual time points of Doppler assessment at each PK visit (p=0.015). Digital skin temperature was positively associated with log-transformed plasma concentration at the 4mg visit (but not the 2mg visit), after adjusting for the individual time points of Doppler assessment at each PK visit (p=0.013).
Conclusions: Although the guidelines were not published until after our site analysis, there were differences in use of D-penicillamine (although infrequent) for MRSS ≥10 (p = 0.004), Between site performing of chest X-rays (>72–98%, p = 0.000), HRCTs (11–41%, p = 0.000) and ECGs (75–98%, p = 0.000) were different. Annual echo- cardiograms (91–100%, p = 0.2) and PFTs (85–97%, p = 0.17) were usually performed annually and did not vary among sites.

Treatment and investigation practice frequency and variation among centers with n >50

Conclusion: There is site variation in SSc with respect to investigations and management among CSSRG centers suggesting a need for a standardized approach to the investigation and treatment of SSc. One would speculate that more variability would occur between rheumatologists who did not have a critical mass of SSc and were not given reminders of annual tests to be performed (e. cherocheodiagrams) as we looked only at practices within a database.

Disclosure: S. Harding; None; S. Khimdias; None; A. Bonner; None; M. Baron: The CSSRG: None.

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Are SSc Experts Doing What They Should Do? An Analysis of Practice Variability in Large SSc Centers within the Canadian Scleroderma Research Group (CSRG) Shows Practice Differences. Sarah Harding, Sarit Khimdias, A. Bonner, Murray Baron and Janet E. Pope, Jewish General Hospital, Montreal, QC, Canada, McMaster University, St. Joseph Health Care London, London, ON, Canada, University of Western Ontario

Objective: There is currently no consensus on best practice in SSc. To determine if variability in treatment and investigations exists, practices among Canadian Scleroderma Research Group (CSRG) centers were compared.

Methods: Prospective clinical and demographic data from adult SSc patients are collected annually from 15 CSRG treatment centers. Laboratory parameters, self-reported socio-demographic questionnaires, current and past medications and disease outcome measures are recorded. For centers with >50 patients enrolled, treatment practices were analyzed to determine practice variability.

Results: Data from 640 of 938 patients within the CSSRG database met inclusion criteria, where 87% were female, the mean ± SEM age was 55.3 ± 0.5; 49% had limited SSc and 48% had diffuse SSc (3% uncharacterized). Several investigation and treatment practices were inconsistent among 6 centers including proportion receiving PDE5 inhibitors for Raynaud’s phenomenon (p = 0.036); cyclophosphamide (p = 0.037) and azathioprine (p = 0.037) for treatment of ILD; hydroxychloroquine (p = 0.023), D-penicillamine (p = 0.008), and steroids (p = 0.039) for inflammatory arthritis; hyaluronic alginates (p = 0.000) and esophageal dilations (p = 0.000) among centers analyzed. Where negative trials exists, there were differences in use of D-penicillamine (although infrequent) for MRSS ≥10 (p = 0.004).

Treatment and investigation practice frequency and variation among centers with n >50

Disclosure: J. E. Pope: None; S. Harding: None; S. Khimdias: None; A. Bonner: None; M. Baron: The CSSRG: None.

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Assessing Health Status in Patients with Systemic Sclerosis: Construct Validity of the Karnofsky Performance Status Score. Christelle Nguyen, Alice Bérezné, François Rannou, Caroline Mestre-Stanislas, Sandrine Morell-Dubois, Loïc Guillevin, Serge Poiraud and Luc Mouton, Université Lille 2, Service de Medecine Interne; Centre de Reference Pour la Sclerodermie Systemique, Hopital Claude Huriez; Lille, France; Universite Paris Descartes; Faculte de Medecine Paris Descartes; Pole de Medecine Interne, Centre de Reference Pour les Vasculartes Necrosantes et la Sclerodermie Systemique, Hopital Cochin; Assistance Publique-Hopitaux de Paris (AP-HP); Universite Paris Descartes; Faculte de Medecine Paris Descartes; Service de Medecine Physique et Readaptation; Hopital Cochin AP-HP, Inserm, Institut Federatif de Recherche sur le Handicap, Paris
**Purpose:** Systemic sclerosis (SSc) is a connective-tissue disease, responsible for skin, tendon, joint, and vessel damage, which can ultimately lead to disability, compromised health-related quality of life and poor health status. However, available instruments assessing global, patient’s perceived and location-specific disabilities do not specifically survey patient global health status. An example of a score that surveys global health status is the Karnofsky Performance Status (KPS) score. Previous data support the use of the KPS score to predict outcome in SSc. Nevertheless, before considering the KPS score as a suitable outcome measure in SSc, its relevance should be definitely established. Therefore, we aimed to assess the construct validity of the KPS score in the assessment of health status in patients with SSc, by determining its convergent and divergent validity.

**Methods:** Three-hundred-and-sixty-two SSc patients fulfilling the American College of Rheumatology and/or the Leroy and Medsger criteria were assessed for visceral involvement, handicap and health-related quality of life (HRQoL). Global health status was evaluated by the KPS score. KPS score convergent and divergent validities were assessed using the Spearman’s rank correlation coefficient.

**Results:** Mean age and disease duration at the time of evaluation were 55.7 (13.3) and 9.6 (7.9) years, respectively. Thirty-three (9.3%) patients had limited SSc, 179 (50.7%) limited cutaneous SSc, and 141 (39.8%) diffuse cutaneous SSc. Mean total score of the KPS score was 77.6 (11.7). The KPS score had fair convergent validity with disease duration (r = -0.361), dyspnea (NYHA classification, r = -0.308), perceived handicap as assessed by McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (r = -0.479) and global disability as assessed by the Health-Assessment Questionnaire (HAQ, r = -0.337), and no correlation with hand-located disability as assessed by the Coffin Hand Functional Scale (r = -0.278), mouth-located disability as assessed by the Mouth Handicap In Systemic Sclerosis Scale (r = -0.003), anxiety and depression symptoms as assessed by the Hospital Anxiety and Depression Scale (r = -0.553), aesthetic impairment assessed on an 11-point scale (r = -0.071), and HRQoL as assessed by SF-36 mental and physical component scores (r = 0.064 and r = 0.168, respectively).

**Conclusion:** For assessing global health status in patients with SSc, the KPS score has acceptable construct validity. The weak correlation between KPS score and previously validated outcome measures in SSc suggests that the KPS score adds useful information for assessing the global health status in patients with SSc and that it may be a suitable instrument for daily practice or clinical trials in SSc.

**Disclosure:** C. Nguyen: None; A. Bézézé: None; F. Rannou: None; C. Mestre-Stanislas: None; S. Morell-Dubois: None; L. Guillevin: None; S. Poiraudreau: None; L. Mouton: None.

**1206**


**Background:** Systemic sclerosis-associated gastrointestinal tract involvement (SSc-GIT) is an important predictor of depressive symptoms. UCLA Scleroderma Clinical trial Consortium Gastrointestinal tract 2.0 (UCLA SCTC GIT 2.0) is a 34 item instrument that captures GIT symptom severity and impact on quality of life. This instrument is feasible, reliable and valid. It has seven scales—reflux, distension/bloating, diarrhea, fecal soilage, constipation, emotional well-being and social functioning and a total GIT score.

**Objective:** To assess 1) whether there is an association between depressed mood with GI symptoms as assessed by the UCLA SCTC GIT 2.0 instrument, and 2) to explore which GI specific symptom scales are associated with depressed mood in patients with SSc.

**Methods:** Consecutive patients who fulfilled the ACR criteria for SSc were invited for this cross-sectional study on BMD and body composition (BC) in a group of Southern Chinese patients with SSc.

**Conclusion:** Whether bone mineral density (BMD) is lower in patients with systemic sclerosis (SSc) than age-matched population is controversial. We conducted a case-control study on BMD and body composition (BC) in a group of Southern Chinese patients with SSc.

**Disclosure:** C. C. Mok: None; L. Y. Ho: None; C. H. To: None; K. M. Ma: None.
Clinical Significance of Defined ANCA Positivity in Systemic Sclerosis.

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Purpose: While an atypical ANCA is reported in 20–30% of patients who have systemic sclerosis (SSc), this is not usually clinically significant. Conversely, patients with systemic sclerosis who have confirmed ANCA positivity with either myeloperoxidase (MPO) or proteinase-3 (PR3) antibodies on ELISA and clinical vasculitis are rarely reported in the literature. We have interrogated our database of patients with SSc who also have listed a clear clinical or histological diagnosis of vasculitis to look for the prevalence of overlap disease with ANCA-associated vasculitis (AAV) and whether these patients have altered disease features.

Methods: We examined a clinical database of 2200 patients with either limited or diffuse cutaneous SSc. Patients who had a clear clinical or histological diagnosis of vasculitis of any description had their serology investigations reviewed and repeated if possible to look for ANCA positivity with either MPO or PR3 reactivity. The clinical features, serology, and histology of those patients who had both SSc and AAV were examined in detail.

Results: From our SSc cohort, 35 patients (1.6%) had a current or previous history of vasculitis, in whom the distribution of antibodies characteristically associated with the SSc features of their disease was comparable to those previously published from our cohort. For example, 20% were anti-centromere positive, 20% anti-topoisomerase-1 positive and 6% anti-fibrillarin antibody positive. Of these 35 patients, 8 (24%) had either anti-MPO or anti-PR3 antibody positive. Both patients from the 35 who carried anti-fibrillarin antibodies, usually associated with overlap disease and increased incidence of renal and cardiac complications, were ANCA positive. No patients with vasculitis and anti-centromere antibodies were ANCA positive. Of the 8 ANCA positive patients, 7 had limited cutaneous SSc and anti-MPO antibodies and one had diffuse disease with anti-PR3 antibodies. The latter patient had clinical features of microscopic polyangiitis with renal, neurological and skin involvement. None of the MPO positive patients had granulomatous disease. All but one had glomerulonephritis, and 6 had pulmonary fibrosis.

Conclusions: SSc in overlap with ANCA-associated vasculitis is rare, and clinical features are more mixed than when either of these two conditions occurs separately. From our database, anti-fibrillarin antibodies may be more associated with overlap AAV than the other sclerodermaspecific antibodies.

Disclosure: E. C. Derrett-Smith: None; S. Niftyanaova: None; J. Parker: None; C. Bunn: None; A. Burns: None; M. A. Little: None; C. P. Denton: None.

1209
Coronary Artery Calcification in Systemic Sclerosis: There Was No Difference between SSc and Healthy Control Groups.


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Background: Several systemic autoimmune diseases are associated with an increased prevalence of coronary artery disease. In systemic sclerosis (SSc), microvascular abnormality is well recognized, but previous studies about macrovascular disease including coronary artery disease showed conflicting results. Measurement of coronary calcification score (CCS) by a multi-detector computed tomography (MDCT) is an accurate and non-invasive method to detect coronary atherosclerosis, and the high level of CCS can predict coronary events.

Objective: To investigate the CCS in patients with SSc by using MDCT and to evaluate the risk of coronary artery disease.

Methods: We investigated the clinical and laboratory characteristics in patients with SSc (41 patients, all were women, mean 50 years, 22 with limited and 19 with diffuse type). The CCS was measured by MDCT and the risk of coronary events were evaluated by CCS and Framingham risk score (FRS). We selected sex and age-matching controls (123 controls) among the historical healty control group in South Korea, who were scanned by same CT scanner with our group, and analysed data statistically between SSc and control groups. We also assessed whether disease specific factors of SSc were correlated with CCS.

Results: The mean CCS of SSc was not significantly increased compared with healthy control (7.0±26.3 vs 5.5±41.2, p=0.829). The frequency of CCS>0 was not significantly different between SSc and control groups (17% vs 13%, p=0.339) (figure 1). There was also no difference in coronary
calcification between SSc and control groups after correction for the confounders high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting glucose, body mass index and waist measurement. The CCS had no significant correlations with disease specific factors. The FRS was evaluated in 36 patients, all patients were categorized into low-risk group (FRS<10%).

<table>
<thead>
<tr>
<th>Control (n=123)</th>
<th>SSc-total (n=41)</th>
<th>p-value</th>
<th>SSc-limited (n=22)</th>
<th>SSc-diffuse (n=19)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5 ± 41.2</td>
<td>7.0 ± 26.3</td>
<td>0.829</td>
<td>12.0 ± 35.3</td>
<td>1.1 ± 3.2</td>
<td>0.161</td>
</tr>
<tr>
<td>16 (13.0)</td>
<td>7 (17.1)</td>
<td></td>
<td>5 (22.7)</td>
<td>2 (11.2)</td>
<td></td>
</tr>
<tr>
<td>CCS=0, no. (%)</td>
<td></td>
<td></td>
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</tbody>
</table>

Conclusion: These results imply that the risk of coronary events due to coronary atherosclerosis might not be high in patients with SSc.

Disclosure: Y.-E. Park: None; S.-H. Park: None; S.-H. Bae: None; J.-H. Lee: None; J.-W. Lee: None; G.-T. Kim: None; Y.-J. Joong: None; S.-Y. Choi: None; W.-H. You: None; S.-I. Kim: None.

1210

CXCL4, a Novel Marker for Systemic Sclerosis That Clearly Correlates with the Clinical Hallmarks and Pathological Events. Timothy Ruben Radstake, Lenny van Bon1, Jasper Broen1, Romy Beatrix-Christmann1, Alysa Affandi1, Madelen Vonk1, Mike York1, Cindy Collins1, Mark Wenink2, Roger Hesselstrand3, Dirk Wutte4, Sandeep Agarwal5, John Reveille3, Joost Drenth4, Jaqueline de Graaf4, Martin Den Heijer2, Cees Kalenberg5, Marc Bijl6, Wim van den Berg5, Joost Leo6, Waander van Heerde5, Piet van Riel7 and Robert Lafyatis8.

1. Boston Medical Center, 2. Radboud University Nijmegen Medical Center, 3. Radboud University Nijmegen Medical Center/Boston Medical Center, Nijmegen, The Netherlands, 4. University Hospital Groningen, 5. University Hospital Groningen, 6. University Hospital Houston, TX, 7. University Hospital Lund, Sweden

Background: Despite recent advances in our understanding of systemic sclerosis (SSc) many patients still suffer from progressive disease leading to severe complications and premature death. Currently predictors for disease phenotype and prognosis are lacking.

Methods: We exploited proteome-wide analysis (SELDI-TOF) of secreted proteome from plasmacytoid dendritic cells (pDCs) from clinically well-defined groups of SSc patients (n = 214) to study the differential expression of proteins between SSc subsets. We confirmed the presence of the most predominant protein CXCL4 by ELISA in the supernatant and plasma of SSc patients in comparison with healthy individuals (n=129) and other autoimmune (SLE, n = 109), auto-inflammatory (AS, n = 93) and fibrosing (liver fibrosis, n = 129) clinical conditions. Using SSc phenotypic data including the presence of autoantibodies, skin- and lung fibrosis and pulmonary arterial hypertension (PAH) we examined the potential correlation between these clinical hallmarks and circulating CXCL4 levels. Finally, we studied the direct effects of CXCL4 on skin fibroblasts and HUVEC by investigating COMP expression and secretion of endothelin-1, respectively.

Results: Circulating pDCs were found at higher frequencies in SSc patients but did not spontaneously produce higher levels of IFNα compared to controls. Proteome-wide analysis of SSc pDC supernatants revealed the chemokine CXCL4 as the most abundant protein detected, seen predominantly in patients having early diffuse disease. Validation using ELISA confirmed this observation and also showed that circulating CXCL4 levels were significantly higher in SSc patients compared to controls and other conditions such as SLE, AS and liver fibrosis. CXCL4 levels were higher in diffuse SSc compared with limited SSc but showed by far the highest levels in those patients having early diffuse SSc. CXCL4 levels correlated well with the extent of skin fibrosis and the presence of lung fibrosis and PAH. These correlations could be explained by the ability of CXCL4 to induce myofibroblast transformation of skin fibroblasts and the secretion of endothelin-1 by human endothelial cells (HUVEC).

Conclusion: The anti-angiogenic chemokine CXCL4 is highly expressed in SSc patients and correlates well with the clinical hallmarks of SSc skin- and lung fibrosis and PAH and therefore provides a novel biomarker for SSc phenotype but also other fibrosing diseases.

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1211

Determinants of Work Disability in Patients with Systemic Sclerosis: A Longitudinal Study of the GENISOS Cohort. Rozoebeh Shariati6, Maureen D. Mayes7, Ferry M. Nicassio1, Emilio B. Gonzalez2, Hilda T. Draeger2, Terry A. McNearney2, Deepthi K. Nair3, John D. Reveille4, Frank C. Arnett2 and Shervin Assassi5. 1. Department of Psychiatry, University of California, Los Angeles, CA, 2. Division of Rheumatology and Immunogenetics, University of Texas Health Science Center at Houston, Houston, TX, 3. Division of Rheumatology and Immunogenetics, University of Texas Health Science Center at Houston, Houston, TX, 4. University of Texas Health Science Center at San Antonio, San Antonio, TX, 5. University of Texas Medical Branch at Galveston, Galveston, TX, 6. University of Texas Medical Branch at Galveston, TX, 7. University of Texas-Houston, Houston, TX, 8. UT Medical School, Houston, TX

Background: Systemic sclerosis (SSc) is associated with substantial morbidity and mortality. SSc can have profoundly detrimental impact on the patients’ personal and professional life. There are no published data on the prevalence of the work disability (WD) in patients with SSc in the United States, nor longitudinal studies examining long-term predictors of WD in general. The goal of this study was to determine the prevalence and correlates of WD at enrollment and to investigate the longitudinal determinants of WD in the patients enrolled in the Genetic versus Environment in Scleroderma Outcome Study (GENISOS) cohort.

Methods: Patients were subdivided into three groups based on their employment status at enrollment: work disabled, working, and retired or homemakers. The latter group was excluded from further analysis. Utilizing logistic regression analysis with a forward hierarchical variable selection strategy, we evaluated the independent socio-demographic, clinical, and quality of life measure correlates of WD at enrollment. Furthermore, patients working at enrollment were included in the longitudinal study. We used a Cox regression proportional Hazard’s model with a similar variable selection strategy to determine the predictors of WD on follow up visits. All quality of life measures demonstrated adequate internal consistency reliability in the current study.

Results: At the time of analysis, 284 patients with mean age of 48.7 (±13.2) years were enrolled in the GENISOS cohort. There were 237 (83.5%) female; 133 (46.8%) Caucasian, 83 (28.9%) Hispanic, 58 (20.4%) African American, and 10 (3.5%) from other ethnic groups. Overall, 162 (57.0%) patients had diffuse cutaneous involvement; the disease duration at enrollment was 2.5 (±1.6) years. Patients were followed for 3.9 (±3.6) years; in 1438 consecutive visits. At entry; 124 patients (43.7%) were WD, 131 (46.1%) working, and 29 (10.2%) retired or homemakers. In a multivariate regression model, older age (p=0.012), educational level below associate degree (p<0.001), higher Fatigue Severity Score (p=0.045), lower SF-36 physical component scores (p<0.001) and lower % predicted FVC (p=0.009) were independently associated with WD at the cross sectional level.

At mean follow-up of 4.4 (±3.8) years (range up to 12 years) of those working at baseline, 96 (73.3%) were still working while 35 (26.7%) became disabled. Using multivariate Cox regression analysis, lower coping skills as measured by higher IBQ scores (p=0.004), lower % predicted DLCO (p=0.047), and the presence of joint contractures in small joints (p=0.004) were the independent predictors of WD on follow up visits.

Conclusion: Socio-demographic, lung involvement, fatigue severity, and SF-36 physical component scores were the strongest independent correlates of WD in patients with SSc at early stages of the disease. Whereas joint contracture, lung involvement, and higher IBQ scores, reflecting lower coping skills are the main predictors of the WD at the later stages of the disease.

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Developing a Disease Activity and Therapeutic Response Index in Connective Tissue Disease Related Interstitial Lung Disease (CTD-ILD): Rationale, Aims, Design and Results from Tier 0, the Pre-Delphi Exercise.

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Background: There are currently no licensed therapies for interstitial lung disease (ILD). There is no consensus on measures of disease activity or therapeutic responsiveness, thus hampering effective drug development and regulatory evaluation of candidate therapies. We present the first phase of a multi-tiered investigation to identify consensus on provisional criteria to measure disease activity and therapeutic response in CTD-ILD and Idiopathic Pulmonary Fibrosis (IPF).

Methods: A multi-disciplinary steering committee (authors) engaged in extensive literature review and agreed upon the following methodology: Pulmonary, rheumatology and cardiology specialists with ILD expertise were identified by literature review, task force membership in international societies and peer recommendation. Each was invited to participate in a 3-Tier Delphi project with a preceding ‘Tier 0’ exercise. The goal of ‘Tier 0’ was to engage the participants in a brainstorming exercise to identify qualities that are important to measure (‘domains’) in CTD-ILD and IPF and ‘instruments’ to measure these domains. The goal of contrasting CTD-ILD and IPF is to distinguish similarities and differences between these entities. Additionally, suggestions of positive and negative instruments were collected for specific CTD-ILD disease groups. Data was collected via a custom designed secure web-site. Participants typed their additions into a ‘sparse’ framework of 12 sample ‘domains’ with 12 sample ‘instruments’. The steering committee initially participated in a series of individual exercises followed by a group effort to limit redundancy and identify the broadest spectrum of reasonable domains that would appropriately accommodate the diversity of ‘instruments’ or ‘outcome measures’ suggested by the participants.

Results: 98% of invited experts participated. 137 pulmonary, 102 rheumatology and 4 cardiology specialists participated from 32 countries representing 6 continents. 74% and 69% of participants considered ‘ILD’ and ‘rheumatologic lung disease’ respectively to be their primary fields of investigation. 133 domains were suggested and after review resulted in the 23 domains listed below. More than 6700 instruments were proposed and later reduced to 616.

**Table 1. Final 23 Preliminary Domains From Tier 0 of the Delphi Process**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Definition</th>
<th>Code</th>
</tr>
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<tbody>
<tr>
<td>Survival</td>
<td>Mental Health</td>
<td></td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Sleep</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>Global Assessment</td>
<td></td>
</tr>
<tr>
<td>Lung Physiology/Function</td>
<td>Health Related Quality of Life</td>
<td></td>
</tr>
<tr>
<td>Lung Parenchyma</td>
<td>Functionality</td>
<td></td>
</tr>
<tr>
<td>Lung Vascular</td>
<td>Participation</td>
<td></td>
</tr>
<tr>
<td>Cardiac Function</td>
<td>Employment</td>
<td></td>
</tr>
<tr>
<td>Composite Scores</td>
<td>Extra-Pulmonary/CTD Features</td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal Reflux</td>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>Co-Morbidities</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Barriers to Care</td>
<td></td>
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<tr>
<td>Fatigue</td>
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</table>

Discussion: This is the first known multi-disciplinary effort to assess domains and instruments in the study of CTD-ILD – which is essential in a field devoid of meaningful outcome measures and with many candidate therapies on the horizon. The high response rate of this comprehensive, multi-disciplinary, international effort reflects both the need for a systematic approach to ILD and the collective interest in establishing criteria for this group of diseases. The overall results are very promising and reflect the innate complexities of the spectrum of ILD, thus creating a robust platform for next phases of this consensus study.


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Development of a Limited Scleroderma Cutaneous Activity and Damage Index.

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1 Stanford Univ Medical Center, Palo Alto, CA, 2 Stanford Univ Medical Center, 3 UCLA Medical School, 4 University of California Los Angeles, Los Angeles, CA, 5 University of California Los Angeles Medical School, Los Angeles, CA, 6 University of Pennsylvania, Philadelphia, PA.

Purpose: Most clinical trials for skin disease in systemic sclerosis patients have excluded patients with the limited cutaneous subtype (lcSSc) due to the lack of a robust measure of cutaneous disease in these patients. We sought to develop and partially validate a novel cutaneous index for patients with lcSSc.

Methods: We developed the Limited Scleroderma Cutaneous Activity and Damage Index (L-SCADI) based on an extensive literature review and input from 11 SSc experts (6 rheumatologists and 5 dermatologists) providing face and content validity. Following a 30 minute training session, 6 physicians (2 rheumatologists and 4 dermatologists) used the L-SCADI to score the severity of skin disease in 12 lcSSc patients. To assess construct validity, physicians completed visual analogue scales (VAS) to score global assessment of cutaneous activity and damage (PGA-a and PGA-d), and patients completed a VAS global assessment of skin disease (PGAa), the Health Assessment Questionnaire Disability Index, the Dermatology Life Quality Index, and the Short-Form-36 (SF-36). Inter-rater reliability was assessed using intra-class correlation coefficient (ICC) in a 2-way random model. After scoring every patient once, each physician scored at least one patient a second time to assess intra-rater reliability.

Results: All 12 patients were female, 83% Caucasian, with mean disease duration from first non-Raynaud’s symptom of 11.9±9.6 years (5 with ≤ 5 years; 7 with > 5 years; mean age was 63±0.6; median was 62.9±1.3 years). Mean time to complete the L-SCADI was 6.9±5.1 min. Mean activity (0–63), damage (0–53), and total (0–116) scores were moderately correlated with PGA-a and PGA-d (rho=0.77, p=0.004) for activity, 0.8 (p=0.002) for damage). L-SCADI activity and damage scores were highly correlated with PGA-a and PGA-d (rho=0.77, p=0.004) for activity, 0.8 (p=0.002) for damage). L-SCADI activity was moderately correlated with PGA (rho=0.6, p=0.04), while L-SCADI damage was highly negatively correlated with the SF-36 Physical Component Summary score (rho=−0.92, p=0.0001). The inter-rater reliability for PGA-a and PGA-d was 0.77 (ICC 0.86, p=0.004). The inter-rater reliability for the L-SCADI activity score is moderate, but better than the PGA-a, with much greater intra-rater agreement for the assessment of disease damage. The variability in physician assessments suggests that more extensive training prior to use of the L-SCADI is essential, and further development of the scale is necessary.

Conclusion: The L-SCADI is easy to perform and has reasonable construct validity. Inter- and intra-rater reliability for the L-SCADI activity score is moderate, but better than the PGA-a, with much greater intra-rater agreement for the assessment of disease damage. The variability in physician assessments suggests that more extensive training prior to use of the L-SCADI is essential, and further development of the scale is necessary.

Disclosure: L. Chung: None; D. E. Furst: None; P. Maranian: None; K. Arefiev: None; J. Zwerner: None; D. Khanna: None; V. P. Werth: None; D. Fiorentino: None.
Effect of Selective and Dual Endothelin Receptor Antagonists (ERAs) on SSc and Control Endothelial Cells Apoptosis.

Yongying Wang, Omar R. Kahaly and Bashar Kahaleh. University of Toledo, Toledo, OH.

Objectives: microvascular endothelial cells (MVEC) apoptosis is a critical event in the pathogenesis of SSc vascular disease. Endothelin 1 (ET) signaling in MVEC favors cell survival and antagonizes apoptotic signals. In this study we examined the effects of selective and non-selective ERAs on ET mediated resistance to apoptosis.

Methods: MVEC apoptosis was induced by oxidative stress or by growth factor withdrawal (GFW) and was assessed by flow cytometry, caspase-3 activity and cell viability. We tested the selective and non-selective ERAs: PD145065 a dual ERA, BQ 788 a selective B, and the selective type A ERAs FR139317 and Ambriresentan. We also investigated the effects of si-RNA knockdown of EDNRA, B or A&B mRNAs on MVEC apoptosis. Finally, a focused apoptosis gene expression microarray was utilized to investigate the effect of ET and ERAs on MVEC apoptotic gene expression profile.

Results: significant upregulation of both type A and B-ET receptors in SSc- MVEC was noted, particularly the A receptors. SSc- MVEC apoptotic responses to oxidation or GFW were significantly higher in SSc than in control cells. The addition of ET resulted in a significant, albeit incomplete, reversal of MVEC apoptosis, particularly in control cells. The addition of ERAs alone did not alter the level of apoptotic responses. Selective type A-ERAs maintained ET anti-apoptotic effects, while selective type B-ERA and dual-ERAs completely blocked the anti-apoptotic effect of ET. ET effects were also blocked when selective A-ERAs concentrations were increased beyond the concentrations associated with selectivity of the tested agent. To confirm the conclusion that signaling through type B receptor mediates ET protective effects, we performed si-RNA knock down experiments. Type A receptor mRNA knock down had no effect on ET protective effect, while type B receptor knock down and the combined A&B mRNAs knock down completely abolished ET anti-apoptotic effects. Next, we performed focused apoptosis microarray gene expression profiling of MVEC after GFW and the effects of ET and ERAs on gene expression were examined. GFW induced an upregulation of the pro-apoptotic gene BAX expression and the addition of ET inhibited BAX expression. Selective type A-ERA maintained ET induced downregulation of BAX while the nonselective ERAs and selective type B-ERA prevented ET effect on BAX expression.

Conclusions: - Oxidation and growth factor withdrawal induced MVEC apoptosis is prevented by ET.
- ET anti-apoptotic effects are mediated by inhibition of BAX gene expression.
- Selective A-ERAs preserve ET anti-apoptotic effects, while the dual and selective B-ERAs negate ET protective effect.
- Therapeutic strategies utilizing selective A-ERAs may be superior to the non-selective approaches from a vascular perspective.

Disclosure: Y. Wang: None; O. R. Kahaly: None; B. Kahaleh: None.

1215 Findings in Ocular Examination of Patients with Systemic Sclerosis.

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Background: Systemic sclerosis (SSc) is characterized by vascular dysfunction (Raynaud’s phenomenon, pulmonary hypertension), while patients often complain for dry symptoms. Eye examination provides information on both exocrine function and vascular integrity.

Objectives: To seek for evidence of vascular dysfunction and sicca syndrome in a cohort of SSc patients.

Methods: Patients with SSc, underwent ophthalmologic screening for dry eyes [Schirmer’s test (ST), Break-up time (BUT), Rose Bengal stain (RBS)]. For comparison age and sex-matched healthy controls underwent similar testing. A patient or control was considered to have xerophthalmia, if at least 2 out of 3 tests were positive (ST<5 mm after 5 min, BUT<10 sec, RBS suggestive of dry keratopathy grade >3+). Patients were also surveyed for symptoms of xerostomia by means of a questionnaire and screened for antinuclear antibody (ANA) positivity and type. Those with strong evidence of Sjögren’s syndrome (SS) underwent minor salivary gland biopsy. Finally, a random subset of patients underwent full ophthalmologic examination, including fundoscopy and fluorangiography.

Results: Seventy-two SSc patients (65 females, 7 males, mean age 53.4±14.8 years) and 72 matched controls were screened for dry eyes. Twenty-four SSc patients were positive for xerophthalmia (33.3%), compared to only 11 controls (15.3%) (p<0.05). Further, 38 (52.3%) SSc patients reported xerostomia, while 21 (29.2%) complained for both dry eyes and mouth. Only 31 (43%) of SSc patients were completely free of dry symptoms and signs. Among patients with xerophthalmia 87.5% reported dry mouth, 95.5% were ANA-positive, 45.8% had anti-Scl-70, 33.3% had anticientromere-mer, 8.3% anti-U1-RNP, 25% anti-Ro and 12.5% anti-La antibodies. The corresponding values for SSc patients without dry eyes were 35.4% for dry mouth, 97.9% for ANA and 45.8, 18.8, 16.7, 35.4 and 2.1% for the ANA subtypes. Minor salivary gland biopsy was undertaken in 14 patients and was suggestive of SS in 9. Overall 9 (12.5%) patients had SS based on sicca symptoms, positive ophthalmologic tests and positive anti-Ro/La antibodies or biopsy, fulfilling the American-European consensus criteria for SS. Finally, 29 patients underwent anterior segment examination, fundoscopy and fluorangiography. Blepharitis was the most common clinical abnormality in 11 (37.9%) patients, followed by pinguecula in 6 (20.7%). In fundoscopy and fluorangiography retina was normal in 19 (65.5%) patients. The most common abnormality was maculopathy and pigmented epithelium impairment in 6 (20.7%) patients suggestive of vascular damage of the choroidal layer. Other findings were drusen in 3 (10.3%) patients, a peripheral aneurysm in one patient and a nevus in another. While all patients had Raynaud’s phenomenon, no major retinal arterial abnormalities were detected.

Conclusion: Objective signs of xerophthalmia are encountered in 1/3 of SSc patients, and are usually associated with symptoms of dry mouth. Full-blown SSj may be found in 1 every 8 SSc patients. There seems to be a sparing of retinal arteries in contrast to choroidal vessels in SSc.

Disclosure: N. Tsifedaki: None; C. Papagoras: None; C. A. Paschides: None; A. A. Drosos: None.

1216 Genetic and Clinical Correlates of Anti-Fibrillarin (U3-RNP) Auto-Antibodies in African Americans with Systemic Sclerosis.

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Background: Previous studies have suggested that anti-fibrillarin (U3-RNP) autoantibodies (AFA) are specific for systemic sclerosis (SSc) and occur more frequently in African Americans (AA) and men. A better prognosis in AAs with AFA also has been reported. The aim of this study was to investigate the associations of clinical features and human leukocyte antigen (HLA) class II alleles among AA patients with AFA and compare it with the AFA negative AA patients and unaffected AA controls.

Methods: Between 1990 and 2010, 74 AA patients were enrolled in the ongoing observational cohort studies of AA patients, at our institution. Genetic characteristics, autoantibody profile, and clinical manifestations were examined. AFA were determined by immunoprecipitation of the full length radiolabelled recombinant protein. HLA class-II (DRB1, DQA1, and DQB1) alleles were genotyped or sequenced in AA patients (n=74) and AA controls (n=263). We used chi-square, Fisher’s exact test, and student’s t-test for comparative studies. We compared allelic frequencies between AFA positive AAs with SSc and compare it with the AFA negative AA patients and unaffected AA controls.

Results: The mean age of AA patients with SSc was 47.7 ±13.4 years. Sixty one (61; 82.4%) were female and 52 (70.2%) had diffuse disease. There were no significant differences in gastrointestinal, cardiac, renal or limited SSc). There were no significant differences in gastrointestinal, cardiac, renal or limited SSc). There were no significant differences in gastrointestinal, cardiac, renal or limited SSc. There were no significant differences in gastrointestinal, cardiac, renal or limited SSc.

Conclusions: These findings imply a strong association between HLA-DRB1*08, DRB1*0804, DRB1*0804, DRB1*0801, DQB1*0601 and having two of three DQB1 alleles HLA-DQB1*0601, 0602, and DQB1*0601 in AA patients with SSc. This subset of SSc patients had less musculoskeletal involvement and secondary Sjögren’s disease.
<table>
<thead>
<tr>
<th>Comparison between AFA positive (n=30) and AFA negative patients (n=44)</th>
<th>Comparison between AFA positive and unaffected AA controls (n=263)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P-value</strong></td>
<td><strong>OR (CI)</strong></td>
</tr>
<tr>
<td>DRB1*0108</td>
<td>0.031</td>
</tr>
<tr>
<td>DRB1*0804</td>
<td>NS*</td>
</tr>
<tr>
<td>DRB1*1302</td>
<td>NS*</td>
</tr>
<tr>
<td>DQA1*0101</td>
<td>NS*</td>
</tr>
<tr>
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<td>NS*</td>
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<tr>
<td>DQB1*0301/0602/0604f</td>
<td>0.008</td>
</tr>
<tr>
<td>Arthritis</td>
<td>0.005</td>
</tr>
<tr>
<td>Joint contractures</td>
<td>0.036</td>
</tr>
<tr>
<td>Myositis</td>
<td>0.044</td>
</tr>
<tr>
<td>Loss of digital pulp</td>
<td>0.011</td>
</tr>
<tr>
<td>Sclerodactyly</td>
<td>0.032</td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>0.024</td>
</tr>
</tbody>
</table>

* NS: not significant; two or more of these alleles

**Disclosure:** R. Sharif: None; M. J. Fritzler: None; J. D. Reveille: None; S. Assassi: None; M. D. Mayes: None; F. C. Arnett: None.

### 1218

**Is Surfactant D or CC-Chemokine Ligand 18 Biomarkers for Interstitial Lung Disease in Systemic Sclerosis?**


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**Objective:** Previous studies have indicated that surfactant D (SP-D) levels correlate with the presence of interstitial lung disease (ILD) in patients with systemic sclerosis (SSc).

CC-chemokine ligand 18 (CCL18) is a chemokine produced by activated macrophages that upregulates collagen production in lung fibroblasts. Previous studies have suggested that CCL18 predicts the change in forced vital capacity (FVC) in patients with idiopathic pulmonary fibrosis.

Our goal was to investigate the predictive significance of SP-D and CCL18 for the decline rate in FVC over time in a large prospective cohort of SSc patients.

**Methods:** SP-D and CCL18 levels were determined in 266 SSc patients and 100 age, ethnicity and gender matched unaffected controls using commercially available ELISA kits. The SSc plasma samples were collected at the initial visit of the Genetics versus Environment in Scleroderma Outcome Study (GENIOS), an observational cohort of patients with early SSc. Pulmonary function tests (PFT) were obtained at the initial visit and annually thereafter. The primary outcome was FVC expressed as a percentage of predicted value. First, the protein levels between patients and controls were compared by t-test. Subsequently, the correlation of protein levels with the FVC at the enrollment visit was investigated by linear regression. Finally, a generalized linear mixed model with the sequentially obtained FVCs as the outcome variable was utilized for the longitudinal analysis. The predictive value of SP-D and CCL18 for the decline rate in FVC was investigated by the interaction term between the protein levels and follow up time. The protein levels were examined as continuous variable as well as a dichotomized variable according to the 95th percentile level in controls.

**Results:** The average disease duration at enrollment was 2.5 years. 156 patients (59%) had diffuse cutaneous involvement. The mean follow up time in the study was 3.8 years. 926 FVC measurements belonging to 244 patients fulfilled the American Thoracic Society criteria and were included in the analysis.

SP-D levels were significantly higher in SSc patients than controls (p=0.001, mean difference=643.9, CI=256–1031.8). Furthermore, the SP-D level correlated with the FVC levels at enrollment (p=0.008, R2=0.033). However, the SP-D did not predict the decline rate in FVC over time (p=0.649). Similarly, the dichotomized value of SP-D (based on 95th percentile in controls) did not predict the rate of decline in FVC (p=0.195).

CCL18 levels did not differ significantly between patients and controls (p=0.212, mean difference=7.4, CI=−4.3–19.1). The CCL18 did not correlate with the FVC at enrollment (p=0.211). Furthermore, CCL18 did not predict the decline rate in FVC over time as a continuous or dichotomized variable (p=0.439 and p=0.212, respectively).

A repeat analysis after adjustment for smoking status showed similar results for both proteins.

**Conclusion:** Although SP-D correlates with the concomitantly obtained FVC levels, it is not useful as a predictive biomarker for the decline rate in FVC. On the other hand, CCL18 correlates neither with the concomitantly obtained FVC nor with its progression over time in SSc.

**Disclosure:** S. Assassi: None; J. Charles: None; F. C. Arnett: None; R. Sharif: None; R. E. Lasky: None; E. B. Gonzalez: None; H. T. Draeger: None; T. A. McNearney: None; S. K. Agarwal: None; R. V. Gutala: None; R. M. Estrada-Y-Martin: None; M. D. Mayes: None.
Longitudinal Fatigue Severity Scale Scores Correlate with Modifiable Psychosocial Variables in Early Systemic Sclerosis. Astrid Lorraine Leyva1, Shervin Assassi1, Maureen D. Mayes2, Deepthi K. Nair3, Michael Fischbach4, Rozbeh Sharif5, John D. Reveille5, Emilio B. Gonzalez3 and Terry A. McNearney6. 1Univ of Texas Health Science Center Houston, TX, 2Univ of Texas Medical Branch, Galveston, TX, 3Univ of Texas Medical Branch; Currently at Eli Lilly and Co, Indianapolis, IN, 4Univ Texas Health Sci Ctr, Houston, TX, 5University of Texas-Houston, TX

Purpose: Fatigue is a major complication of Systemic Sclerosis (SSc). Longitudinal studies examining the baseline predictors of fatigue in SSc have not been reported previously. We analyzed the association of the baseline demographic, clinical and self-reported psychometric variables with longitudinally obtained Fatigue Severity Scale (FSS) scores to identify potentially modifiable factors to improve fatigue severity in SSc.

Methods: FSS scores in 266 patients enrolled in the Genetics versus Environment in Scleroderma Outcomes Study (GENISOS) were examined. GENISOS is a large multi-center, prospective observational cohort of patients with early SSc (disease duration ≤ 5 years at enrollment). The association of baseline variables with sequentially obtained FSS was investigated in a generalized linear mixed model. A comprehensive list of baseline variables including demographic characteristics, disease type, autoantibody status, pulmonary function test parameters and psychometric measures were examined. Initially a univariate analysis was conducted, followed by a multivariate analysis utilizing a hierarchical forward variable selection strategy. Internal consistency of the psychometric variables including the FSS was assessed and validated with Cronbach’s alpha computation.

Results: The mean age was 48.6 years, 83% of patients were female and 47% of patients were Caucasian. Fifty-nine percent had diffuse cutaneous involvement. The mean follow up time was 3.8 years, ranging up to 11.4 years. The average baseline FSS score was 4.7 ± 0.96, comparable to scores reported in other systemic lupus erythematosus and multiple sclerosis patients. A total of 1090 FSS measurements obtained during the enrollment time were studied for the longitudinal analysis. The FSS did not show a consistent trend for change over time (p=0.221). Although a number of baseline variables were associated with longitudinally obtained FSS, only coping skills as measured by the Illness Behavior Questionnaire (p<0.001), Short Form-36 physical component summary (p<0.001), shortness of breath-visual analogue scale (p=0.011) and Gastrointestinal Medsger Severity Index (p=0.025) were independent predictors of FSS in the multivariable model.

Conclusions: Longitudinal FSS scores were strongly associated with perceived physical functioning and coping patterns of illness behavior. Our results emphasize the importance of potentially modifiable psychosocial factors in treatment of fatigue. For example, an interventional strategy targeting coping mechanisms in SSc patients may directly improve fatigue severity. Consideration of specific psychosocial and behavioral support may have more impact in managing fatigue severity than currently available traditional or pharmacologic interventions.

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Loss of Microvascular Response to Central Nervous Impulses to Finger Pulp in Systemic Sclerosis. Tone Kristin Bergersen1,2, Anna-Maria Hoffmann-Vold3,4, Oivind Midtvet4, Jan Tore Gran2, Cato Mork4 and Karin Toska4. 1Oslo University Hospital, Oslo, Nydalen, Norway, 2Oslo University Hospital, Oslo, Norway, 3University of Oslo, Blindern, Norway

Thickening and fibrosis of digital skin with recurrent digital ulcers are major problems in systemic sclerosis (SSc). Probably, digital ulcers are caused by damage of the microvascular bed (1). Typically, the fingers are more severely affected than the proximal parts of the palm. Blood flow in skin of fingers and thenar region is mainly controlled by the arteriovenous anastomoses (AVAs) located in the palm and nailbeds (2). The vasomotion of the AVAs is controlled by the CNS and is synchronous in all skin areas. We have studied the vasomotor activity in skin of fingers and thenar region in SSc.

Laser Doppler flux (Moor instruments, England) from finger pulp and thenar region were simultaneously recorded together with ipsilateral radial artery blood velocities (ultrasound Doppler, SD100, Vingmed, Norway) and mean arterial blood pressure (Finapres) in 11 patients and in 11 aged matched healthy subjects. The subjects were resting on a bench in thermoneutral condition for 30 min before a 15 min continuous recording was obtained.

The mean duration of SSc was 7.3 yrs (range 2–15 yrs), mean age 55 yrs (range 45–67 yrs). Eight of the patients had previous history of digital ulcers, but none had ongoing ulcers. All patients had Raynaud’s phenomenon and disturbed microvascular architecture visualized by nailfold capillaroscopy. The blood velocity in the radial artery in both groups showed the typical large fluctuations caused by synchronous opening and closing of the AVAs (2) (Fig. 1A). In the control group, fluctuations in thenar flux and finger pulp flux were closely correlated to the velocity fluctuations in the radial artery (Table 1). In the SSc group, there was also a close correlation between the thenar flux and the velocity fluctuations in the radial artery (Fig 1A and B, Table 1). However, the simultaneous finger pulp flux was statistically significantly less correlated to the velocity in radial artery than the thenar flux (Table 1). Furthermore, in some patients, a positive correlation was seen between finger pulp flux and short-time variability in MAP (Fig. 1 C and D).

Figure 1. Simultaneous blood velocity, flux and MAP in a patient with SSc.

Table 1. Simultaneous blood velocity, flux and MAP in a patient with SSc.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SSc Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>finger pulp flux - radial artery</td>
<td>0.27 -0.15, 0.67</td>
</tr>
<tr>
<td>thaner flux - radial artery</td>
<td>0.77 0.65, 0.86</td>
</tr>
<tr>
<td>Wilcoxon sign test, p</td>
<td>0.016 0.81</td>
</tr>
</tbody>
</table>

r = correlation coefficient, CI = Confidence Interval, significance level p<0.05

In conclusion, the pattern of bursts of efferent sympathetic impulses to skin AVAs is probably unchanged in SSc. However, the AVAs in the SSc finger do have an attenuated response to impulses from the CNS. A positive correlation between perfusion of finger tip and short-time variability in MAP suggest a passive vascular bed where blood flow variations is a result of variations in MAP.

References:

Disclosure: T. K. Bergersen: None; A.-M. Hoffmann-Vold: None; O. Midtvet: None; J. T. Gran: None; C. Mork: None; K. Toska: None.

Lower Education as a Proxy for Socioeconomic Status Is?Not Associated with Poor Outcomes in Systemic Sclerosis (SSc): Data from a Large SSc Cohort (Canadian Scleroderma Research Group). Samah Mansour, Ashley Bonner, Murray Baron, Janet E. Pope and The CSRG. 1Jewish General Hospital, Montreal, QC, Canada, 2McMaster University, 3St Joseph Health Care London, London, ON, Canada, 4University of Western Ontario

Background: In SLE, socioeconomic status (SES) has a large effect on outcomes such as renal failure. It is unknown what the effect of SES is on outcomes in SSc. SES is often measured by income and education. In SSc, in general, highest education would be attained often decades prior to disease onset whereas current income could be low due to SSc and thus would confound interpretation of effect of SES on SSc. SES can modify outcomes

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by altering timing of access to care, access to medications, and adherence.
Lower SES may be a surrogate for other health related behaviors that can impact outcome.

Methods: The Canadian Scleroderma Research Group (CSRG) collects detailed data annually on more than 1000 SSc patients including income, education level, antibodies, organ involvement, medications and survival. For measuring SES we used education: did not complete high school (<HS) or completed high school (HS). We could not use income for SES as poor outcome was associated with lower income if it caused work disability. Linear regressions were used to adjust the education effect on disease outcome as measured by severity score, global physician scores and survival (time from onset of scleroderma till death). Logistic regressions were done to detect any effect of education on mortality, presence of Class III pulmonary artery hypertension (PAH), interstitial lung disease (ILD) [total lung capacity (TLC) less or more than 70%], renal failure [serum creatinine level less or more than 150 umol/L]. Data were subdivided into limited and diffuse cutaneous SSc and by disease duration.

Results: The study included 1145 patients. Eighty six percent of the patients were females (986 females) and 14 % were males (159 males). Their mean age was 55.4 years. About 27.6% of them did not complete high school while 72.4% completed high school. In table (1), linear regressions did not show any statistically significant association between education level and severity score, global physician severity score, global physician activity score, global physician damage score and survival (p = 0.94, 0.63, 0.89, 0.78, and 0.60 respectively). Moreover in table (2), logistic regressions did not show any statistically significant association between education level and ILD, PAH, renal failure and mortality. The odds ratio and its confidence intervals were 1.87 (95% CI 0.87 - 4.09), 2.72 (1.22 - 5.96), 0.66 (0.32 - 1.36) and 0.61 (0.37, 1.02) respectively. Education was not predictive of worse outcomes of scleroderma containing usual risk factors (Gender, age, ESR, Hb, ANA and SCL70).

Conclusions: Unlike SLE which has younger onset, in SSc education is not associated with worse outcomes when adjusting for usual risk factors.

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1222
Open Label Trial of Oral Treprostinil in Patients with Systemic Sclerosis and History of Digital Ulcers: Multiple Dose Pharmacokinetics and Tolerability. Elena Schiopu1, Laura K. Hummers2, Ami A. Shah3, Susan Walker3, Kristine Phillips4, James R. Seibold5, Fredrick M. Wigley1 and Kristan Rollins1. Johns Hopkins University, Baltimore, MD, 2Johns Hopkins University, Baltimore, MD, 3University of Michigan, Ann Arbor, MI

Purpose: Fibrotic vasculopathy leading to endothelial dysfunction is the hallmark of scleroderma (SSc) and is the underlying cause of clinical complications including Raynaud’s phenomenon, digital ulcers, pulmonary hypertension and renal crisis. Treprostinil diethanolamine (TDE) is an innovative salt form of the prostacyclin analog treprostinil for oral delivery as a sustained-release (SR) osmotic tablet for twice-daily dosing. Prior studies of sustained plasma concentrations, particularly with immediate release oral prostacyclin analogs, may have limited the ability of prostanoiids to produce sustained benefits in earlier studies. The objective of this study was to evaluate the disposition of TDE SR in patients with systemic sclerosis with peripheral vascular complications.

Methods: Patients with SSc and evidence of peripheral vaso-occlusive disease (defined as presence or history of an active digital ulcer within the past 6 months) participated in this study. Subjects with PAH were excluded. All subjects received oral treprostinil and the dose was titrated, based on tolerability, up to a target dose of 4 mg BID (or maximum dose tolerated by patients), in 0.25 mg increments approximately every 48 hours over eight weeks. Pharmacokinetic assessments were performed when subjects achieved a 2 mg and 4 mg BID (or maximally tolerated at end of study) dose. Eight blood samples were obtained over 12 hrs following dose administration and plasma concentrations of treprostinil quantified by liquid chromatography/mass spectrometry. Pharmacokinetic (PK) parameters were calculated using non-compartmental analysis.

Results: Twenty subjects (17 F/3 M), mean age of 47.9 yrs (SD 9.7) and mean scleroderma disease duration of 11.5 yrs were enrolled. Fifty-five percent of subjects had limited cutaneous scleroderma. Seventeen subjects reached a dose of 2 mg BID and twelve subjects completed the study at the target dose of 4 mg BID. Headache, gastrointestinal complaints (nausea, diarrhea, vomiting), body aches, and flushing were the most commonly reported adverse events. Manipulation of the study drug titration was a successful strategy for managing adverse events. Summary of pharmacokinetic parameters are shown as mean (CV%).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2 (hr)</td>
<td>3.9 (0.94)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>4.0 (0.63)</td>
</tr>
<tr>
<td>Cmax (pg/mL)</td>
<td>2107 (46%)</td>
</tr>
<tr>
<td>AUC0-12hr (hr*pg/mL)</td>
<td>12688 (43%)</td>
</tr>
</tbody>
</table>

Conclusions: TDE SR is absorbed and sustained concentrations over the 12 hr dosing interval. Total plasma exposure and peak concentration appeared roughly proportional to dose at these two doses. There were no unexpected adverse effects following escalation up to a dose of 4 mg in SSc patients with digital ulceration. Selection of individual tolerable dosing regimens may be required in SSc patients, a finding also reported in previous clinical trials of prostacyclins in patients with PAH or Raynăud’s phenomenon.

Disclosure: E. Schiopu: United Therapeutics, 2, 8; L. K. Hummers: United Therapeutics, 2; A. A. Shah: United Therapeutics, 2; S. Walker: United Therapeutics, 1, 3; K. Phillips: United Therapeutics, 2, 8; J. R. Seibold: United Therapeutics, 5, 8; F. M. Wigley: United Therapeutics, 2, 9; K. Rollins: United Therapeutics, 1, 3.

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Outcomes in a Newly Diagnosed Population of Connective Tissue Disease-Associated Pulmonary Arterial Hypertension Patients from the REVEAL Registry. Lorinda Chung1, Lori Parsons1, Paul M. Hassoun2, Michael McGoon3, David Badesch4, Dave P. Miller5, Mark R. Nicholls6 and Roham T. Zamanian7. ICON Clinical Research, 8United Hospitals of King County, 5Stanford Hospitals, 9Mayo Clinic, 4Stanford Univ Medical Center, Palo Alto, CA, 3Stanford University, 6University of Colorado

Purpose: We previously examined a large cohort of prevalent and newly diagnosed cases of connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) patients from the REVEAL Registry. We found that patients with systemic sclerosis (SSc), the most common form of CTD-PAH, had significantly worse outcomes than patients with systemic lupus erythematosus (SLE)- and rheumatoid arthritis (RA)-PAH. The objective of this study was to examine outcomes in a newly diagnosed population of CTD-PAH patients followed for 3 years.

Methods: The Registry to Evaluate Early and Long Term PAH Management (REVEAL) is a prospective registry of >3,500 patients with WHO Group I pulmonary hypertension from 55 US centers. For this analysis, we included patients with CTD-PAH diagnosed by right heart catheterization (mean pulmonary artery pressure > 25mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15mmHg) within 90 days of enrollment into the registry. Patients with significant interstitial lung disease (chest imaging with severe fibrosis OR moderate fibrosis AND total lung capacity < 60% predicted) were excluded. SSc-PAH was used as the reference group. Comparisons of baseline characteristics were evaluated with Student’s t-test and chi-square analyses. Kaplan-Meier curves were estimated for survival and freedom from hospitalization from the time of enrollment. Differences in outcomes between the groups were assessed by the log-rank test.

Results: Patients with SSc (N=166, 30 diffuse, 88 limited, 48 classified) were older than patients with MCTD (N=22) and SLE (N=30), with a mean age of 61 ± 11 vs. 50 ± 17 years (p<0.001), but similar in age to patients with RA (N=17, age 59 ± 18). The majority of patients were female and Caucasian in all groups, except there was a higher proportion of non-Caucasians in the SLE group. The SSc group did not differ from the other CTD groups with regards to functional class, hemodynamics, pulmonary function tests, echocardiographic findings, or brain natriuretic peptide (BNP) levels, except that SLE patients had a lower PCWP (8.4 ± 3.4 vs. 9.1 ± 3.5 mmHg, p=0.04), higher FEV1 (79 ± 25 vs. 68 ± 19 %predicted, p=0.04), and lower BNP (255 ± 369 vs. 676 ± 999 pg/ml, p=0.03) than patients with SSc. 6 minute walk distance was lowest in the SSc group (288 ± 114 vs. 364 ± 138 in MCTD (p<0.001), 372 ± 106 in SLE (p<0.001), and 336 ± 129 m in RA (p=0.07)). PAH-specific therapies did not differ between the groups. Survival was poorest in the SSc and RA groups, with 1- and 3-year survival estimates of 78% and 54% in the SSc group, and 88% and 61% in the RA group (p=0.4 vs. SSc), compared with 84% and 84% in the MCTD group (p=1 vs. SSc), and 92% and 87% in the SLE group (p=0.01 vs. SSc). Similarly, the SSc and
RA patients were less likely to remain free from hospitalization at 3-years (39% in SSc; 35% in RA (p = .98); 60% in MCTD (p = .38); 66% in SLE (p = .03)).

Conclusions: The poorer outcome of patients with SSc reinforces the need for compliance with recommendations for routine screening for PAH in these patients in order to permit early detection and treatment. Patients with RA also have poor outcomes after the initial diagnosis of PAH.

Disclosure: L. Chung: Actelion Pharmaceuticals US, 5, Gilead Sciences, Inc., 2, United Therapeutics, 2; L. Parsons: Actelion Pharmaceuticals US, 5; P. M. Hassoun: Actelion Pharmaceuticals US, 2, Novartis Pharmaceuticals Corporation, 6; M. McGoon: Actelion Pharmaceuticals US, 5, Gilead Sciences, Inc., 2, 5, LungRx, 5; M. Medrano, 2, 5, Medtronics, 2, 5; D. Badescu: Actelion/CoTherix, 2, 5; BioGen Idec, 5; Eli Lilly & Co/ICOS, 2, 5, Encyvec Pharmaceuticals, 2, 5, Gilead/Myxogen, 2, 5, GlaxoSmithKline, 5, Lung Rx, 2, 5, mandoBiOTech, 2, 5, NIH/NHLBI, 2, 5; Pfizer Inc., 2, 5, United Therapeutics, 2; D. P. Miller: ICON Clinical Research, 3; M. R. Nizzoli: None; R. T. Zamanian: Actelion Pharmaceuticals US, 2, Gilead Sciences, Inc., 2, United Therapeutics, 5.

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Patients with Systemic Sclerosis and Anti-Centromere Antibodies Are Affected with Accelerated Atherosclerosis. Annica Nordlin1, Lena Björnådal3, Kerstin Jensen-Urstad1 and Elisabet Svenungsson4. 1Dept. of Clinical Physiology, Södersjukhuset, Karolinska Institutet, Sweden, 2Dept. of Medicine, Rheumatology Unit, Karolinska Institutet, Sweden, 3Dept. of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, 4Dept. of Medicine, Rheumatology Unit, Karolinska Institutet, Sweden.

Purpose: If patients with Systemic Sclerosis (SSc) are affected with accelerated atherosclerosis is an unresolved question as previous studies report divergent results. We know that patients with Anti-centromere antibodies often have a limited disease and have a higher risk for vasculopathy such as pulmonary arterial hypertension (PAH), but we don't know if this subgroup of patients also have more atherosclerosis. We investigated surrogate measures of atherosclerosis in a cohort of well-characterized SSc patients and in populationbased matched controls.

Methods: 110 consecutive patients who fulfilled the American College of Rheumatology criteria for SSc and 105 controls matched for age, gender and region of living participated. All underwent a thorough medical examination. Traditional risk factors for cardiovascular disease (CVD), biomarkers of systemic inflammation and autoantibody patterns were investigated. As surrogate measures of atherosclerosis ankle-brachial index (ABI) and carotid ultrasound was performed.

Results: Mean age was 61.8 ± 12.4 years versus 61.4 ± 12.3 years among patients and controls respectively. There was no difference between patients and controls concerning carotid plaque occurrence, intima media thickness (IMT) or ABI on a group level but Sedimentation Rate (p = 0.007) and Triglycerides (p = 0.03) were higher and BMI (p = 0.03) lower in patients than in controls. In the patient group, 35 (32%) were Anti-centromere Antibody positive (ACA+) and 75 (68%) were Anti-centromere antibody negative (ACA-). Of the 75 ACA+ patients 23 (31%) had antibodies to Sc170, 22 (29%) to SSA and/or SSB, 22 (29%) had antinuclear antibodies (ANA) of unknown specificities and 8 (11%) were ANA negative. Plaque occurred in 65.7% of the ACA+ patients and in 38.7% of the ACA- patients (p = 0.008). ABI was 1.09 ± 0.15 in the ACA+ patients and 1.13 ± 0.09 in the ACA- patients (p = 0.05). IMT did not differ between the patient groups. After adjusting for age, ACA+, blood pressure and ever smoked still remained associated with plaque occurrence and ACA+, ever smoked and waist hip ratio remained associated with a low ABI. Waist hip ratio was lower in ACA+ patients 0.80 ± 0.07 vs. 0.85 ± 0.10 (p = 0.008). Lipid levels, blood-pressure, blood glucose, ever smoked, Body Mass Index or markers of systemic inflammation did not differ between ACA+ and ACA- patients.

We included the variables, which remained associated after age adjustment in multivariable-adjusted logistic regression models. Independent predictors of plaque were age (p = 0.0001), systolic blood pressure (p = 0.02), ever smoked (p = 0.02) and ACA+ (p = 0.02) and for ABI age (p = 0.02), ever smoked (p = 0.008) and waist-hip ratio (p = 0.01).

Conclusion: Atherosclerosis was more prevalent in SSc patients with Anti-centromere antibodies than in SSc patients without these antibodies. ACA+ patients already has a higher risk for vasculopathy such as PAH and this subgroup of SSc patients also seems to have more atherosclerosis and may thus be at higher risk for CVD.

Disclosure: A. Nordlin: None; L. Björnådal: None; K. Jensen-Urstad: None; E. Svenungsson: None.

1225

Physician Opinion of Variables That Differentiate Disease Activity and Damage in Systemic Sclerosis. Genevieve Gyger, Ernest Lo, Marie Hudson. Canadian Scleroderma Research Group and Murray Baron, McGill, Canada.

Background: An important barrier to the study of systemic sclerosis (SSc) is difficulty in measuring disease activity and damage. We undertook this study to 1) identify the variables that physicians think indicate activity and damage, and 2) identify the variables that, according to physicians, best differentiate activity from damage in SSc.

Methods: We surveyed 18 rheumatologists with a specific interest in SSc. The participants were given a list of 148 variables that represent the spectrum of SSc manifestations. The participants rated the importance of each variable separately for activity and for damage, using a scale of 0 (not relevant) to 20 (absolutely important). The scores of each participant were used to rank the variables from 1 (highest importance) to 148 and the median rank for each variable across all raters was determined. We then compared the median damage rank versus median activity rank for each variable using a Mann-Whitney U test. We considered variables that differentiated between activity and damage to be those with the largest statistically significant difference between median ranks (P-values < 0.05, after adjustment for multiple testing) AND were in the top 15% of the ranks for either activity or damage but not both.

Results: The variables with the highest median ranks for disease activity were: recent renal crisis, digital necrosis/gangrene, extent of change in DLCO in past year, presence of active myositis, and substantial increase in pulmonary systolic pressure in last year. The variables with the highest median ranks for damage were: uses home oxygen, needs total parenteral nutrition, worse New York Heart Association class, pulmonary arterial hypertension (PAH), and digital necrosis/gangrene. After excluding the variables that did not differentiate between activity and damage, the most important variables indicative of disease activity included extent decline in DLCO in the last year, presence of active myositis, and substantial increase in pulmonary systolic pressure in last year. The variables indicative of disease damage included uses home O2, needs TPN, has PAH, pulmonary fibrosis on Xray or CT scan, and pacemaker (see Table).

Table. Variables that differentiate between activity and damage according to physician opinion with p < 0.05, are in top 15% of ranks AND are not in top 15% for both activity and damage

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Median Damage Rank</th>
<th>Median Activity Rank</th>
<th>p-value: Damage vs. Activity Ranks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables more important for activity than damage</td>
<td>extent of change in past year of DLCO % predicted</td>
<td>52</td>
<td>21</td>
</tr>
<tr>
<td>presence of active myositis</td>
<td>116.5</td>
<td>21.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>recent microangiopathy by your own assessment</td>
<td>85.5</td>
<td>24.75</td>
<td>0.02</td>
</tr>
<tr>
<td>active volar digital ulcers</td>
<td>65</td>
<td>27.25</td>
<td>0.02</td>
</tr>
<tr>
<td>higher joint count swollen joints</td>
<td>109</td>
<td>28.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>friction rubs anywhere</td>
<td>95.25</td>
<td>29</td>
<td>0.003</td>
</tr>
<tr>
<td>CRP</td>
<td>115</td>
<td>31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pleurisy</td>
<td>90.5</td>
<td>32.75</td>
<td>0.02</td>
</tr>
<tr>
<td>change in skin thickening last month</td>
<td>108.5</td>
<td>34.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESR</td>
<td>116.75</td>
<td>35.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Variables more important for damage than activity</td>
<td>uses home O2</td>
<td>16.25</td>
<td>76.25</td>
</tr>
<tr>
<td>needs TPN</td>
<td>17.5</td>
<td>64.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>has pulmonary arterial hypertension (PAH)</td>
<td>19.75</td>
<td>69.5</td>
<td>0.04</td>
</tr>
<tr>
<td>degree of fibrosis on xray or CT scan</td>
<td>24</td>
<td>99.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pacemaker</td>
<td>25.75</td>
<td>100.25</td>
<td>0.007</td>
</tr>
<tr>
<td>malabsorption</td>
<td>30.5</td>
<td>67.5</td>
<td>0.003</td>
</tr>
<tr>
<td>recently needed esophageal dilation</td>
<td>32</td>
<td>54.75</td>
<td>0.02</td>
</tr>
<tr>
<td>ECG conduction abnormalities or arrhythmias</td>
<td>32</td>
<td>94.5</td>
<td>0.02</td>
</tr>
<tr>
<td>decreased LVEF</td>
<td>34.5</td>
<td>90.75</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Conclusion: While experts felt that many variables were highly relevant to both disease activity and damage in SSc, a subset of variables that differentiates between the two states was identified. The results of this study will help to inform ongoing efforts aimed at developing measures of disease activity and damage in SSc.

Disclosure: G. Gyger: None; E. Lo: None; M. Hudson: None; Canadian Scleroderma Research Group: None; M. Baron: None.
Plasma Endogenous Met- and Leu-Enkephalin Levels Are Decreased and Associated with Clinical and Laboratory Parameters in Early Systemic Sclerosis. Terry A. McNearney2, Kathleen A. Sluka1, Chul W. Ahn2, John D. Reveille8, Michael Fischbach7 and Maureen D. Mayes1.

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Objective: Met-and leu-enkephalins are endogenous opioid neuropeptides with potent analgesic, vasoactive, immunomodulatory and anti-inflammatory properties. Endogenous enkephalin levels demonstrate modest effects on vascular patency under normal physiologic conditions in the brain, but have appreciable influence under periods of traumatic or anoxic stress. We hypothesized that clinical or immunological variables of early systemic sclerosis (SSc) might be correlated to plasma enkephalin levels.

Methods: Plasma samples were collected at study entry of the Genetics versus Environment in Scleroderma Outcomes Study (GENISOS) cohort (early SSc, N=136). Plasma met-enkephalin and leu-enkephalin levels (ug/ml) were measured by high performance liquid chromatography (HPLC) and correlated to clinical and laboratory parameters in the GENISOS database. Statistical analyses were performed by nonparametric Wilcoxon rank sum tests and Pearson correlation coefficients.

Results: 1. SSc patient vs matched normal controls study: SSc patients had significantly lower plasma levels (0.16±0.10 vs. 0.28±0.14 mg/ml, p=0.05) and lower plasma leu-enkephalin levels (1.04±0.90 vs 2.45±0.10 mg/ml, p=0.03). 2. Significantly lower plasma met-enkephalin levels were associated with anti-topoisomerase-I seropositivity (6±3 vs 14.9±22.8 ug/ml, p=0.02). 3. Plasma leu-enkephalin levels were significantly higher in SSc patients with digital pulp loss (95.6±130 vs 64.9±101 ug/ml, p=0.03). Lower plasma met-enkephalin and inversely higher leu-enkephalin levels were noted in SSc patients with Raynaud’s phenomena (p=NS). Plasma endogenous enkephalin levels were independent of seasonal temperatures, when analyzed by month or season (p=NS).

Conclusion: Lower plasma levels of endogenous enkephalins in small SSc vs matched control groups may reflect depressed synthesis or increased degradation related to ongoing neurogenic, vasogenic or fibrogenic processes. The associations of plasma enkephalin levels to immunologic or clinical pathologies in early SSc may underscore their vasogenic or fibrogenic significance and potential as therapeutic targets.

Disclosure: T. A. McNearney: None; K. A. Sluka: None; C. W. Ahn: None; J. D. Reveille: None; M. Fischbach: None; M. D. Mayes: None.

Predictors of Interstitial Lung Disease in Early Systemic Sclerosis: A Prospective Longitudinal Study. Shervin Assassi1, Roxoheb Sharif1, Robert E. Lasky5, Terry A. McNearney1, Rosa Estrada Y Martin8, Hilda T. Dreager6, Deepthi K. Nair2, Marvin J. Fritzler3, John D. Reveille8, Frank C. Arnett5 and Maureen D. Mayes1.

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Background: Pulmonary involvement is the primary systemic sclerosis (SSc) - related cause of death. Forced vital capacity (FVC, expressed as a percentage of predicted value) has been validated as an outcome measure of interstitial lung disease (ILD) in SSc. Large prospective observational studies examining progression of ILD and the predictive significance of clinical and demographic variables have not been reported. The purpose of this study was to examine the association of baseline demographic and clinical characteristics with sequentially obtained measurements of FVC and to identify predictors of decline rate in FVC over time.

Methods: At the time of analysis, 206 patients were enrolled in Genetics versus Environment in Scleroderma Outcome Study (GENISOS), a prospective, observational cohort of patients with early SSc. In addition to pulmonary function tests (PFT), clinical and laboratory data were obtained from each patient. PFTs were performed at the baseline visit and annually thereafter. The predicted PFT values were calculated according to consistent reference values. The association of baseline parameters with sequentially obtained FVC was investigated in a generalized linear mixed model. Using a similar model, the predictors of decline rate in FVC were examined by the interaction term between the baseline variable and follow up time.

Results: The cohort consisted of 125 white, 54 African American, and 77 Hispanic patients with average disease duration of 2.5 years at enrollment. The mean follow up time was 3.8 years, ranging up to 11.4 years; 59% of patients had diffuse cutaneous involvement. Only 22 patients (8.3%) had received cyclophosphamide before enrollment or during the follow up period. Upon review by a pulmonologist, 926 FVC measurements belonging to 244 patients fulfilled the American Thoracic Society criteria and were included in the analysis.

A number of baseline variables including African American ethnicity (p=0.002), diffuse disease type (p=0.012), baseline PFT values (p<0.001), modified Rodnan Skin Score (p=0.001), fibrosis on chest radiograph (p<0.001), subjective dyspnea (p<0.001), anti-topoisomerase antibodies (p<0.001), lung and skin subscores of Severity Index (p<0.001 and p=0.037, respectively) were associated with sequentially obtained FVC levels. Similar results were seen after adjustment for smoking status.

As expected, the follow up time in the study was associated with a decline in FVC (p<0.001). However, none of the baseline variables predicted the rate of decline in FVC over time. Specifically, ethnicity, disease type, baseline PFT values, Skin Score, chest radiographs, subjective dyspnea, autoantibody status, Medsger Severity Index subscores and smoking status did not predict the rate of decline in FVC. Moreover, an accelerated rate of decline in FVC was associated with poor survival (p=0.001).

Conclusion: Baseline clinical variables, associated with differential FVC levels did not predict the rate of decline in FVC. The association of faster decline in FVC with poor survival emphasizes the need for identification of predictive biomarkers by collection of genetic information and serial blood samples in cohort studies.

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Prevalence and Correlates of Sleep Disturbance in Systemic Sclerosis — Results from the UCLA Scleroderma Quality of Life Study. Tracy M. Frech3, Ron D. Hays1, Paul Maranian2, Philip J. Clements5, Daniel E. Furst1 and Dinesh Khanna1. 1Department of Internal Medicine, University of Utah, Salt Lake City, UT, 2Division of General Internal Medicine, David Geffen School of Medicine, Los Angeles, CA, 3Division of Rheumatology, David Geffen School of Medicine, Los Angeles, CA, 4University of California Los Angeles Medical School, Los Angeles, CA, 5University of California Los Angeles School of Medicine, Los Angeles, CA

Objective: Chronic arthritides are associated with sleep disturbances. This study examines the prevalence of sleep disorder and explores its correlates in patients with systemic sclerosis (SSc).

Methods: Participants are 180 SSc patients in the UCLA Scleroderma Quality of Life Study. At baseline, patients completed the Medical Outcomes Study Sleep measure (MOS-sleep scale). In addition, patients completed other patient-reported outcome (PRO) measures (SF-36, HAQ-DI, Functional Assessment of Chronic Illness therapy-Fatigue (FACT-Fatigue), Center for Epidemiologic Studies Depression scale (CESD), and University of California Los Angeles Scleroderma Clinical Trials Consortium Systemic Sclerosis Gastrointestinal Questionnaire (UCLA SCTC GIT 2.0). Descriptive statistics were assessed for 6 scales of MOS-Sleep and sleep problem index (SLP-9). We computed Spearman rank-order correlations between the MOS-sleep scale domains and the HAQ-DI, FACT-Fatigue, CESD, SLP-9, and SF-36 scales. In addition, we regressed SLP-9 scores on sociodemographic variables, disease severity, and PRO measures outlined above.

Results: Patients SSc patients reported a mean (SD) of 7.1 (1.73) hours slept a night (range 0–11 hours). Patients reported worse scores on 4 of 6 scales (except for snoring and sleep quantity) compared to US General population. SLP9 had “moderate” correlates with the CESD and FACT-Fatigue (rho's of 0.56 and 50), and “low” correlations with the HAQ-DI and UCLA SCTC 2.0 total score (rho's of 0.32 for both). In the multivariate regression model with sociodemographic variables, duration of SSc, patient assessment of disease severity, skin score, and PROs (HAQ-DI, FACT-Fatigue, UCLA SCTC GIT 2.0 total score, and CESD), the CESD and GIT total scores had significant association with SLP9 index.
Background: Systemic sclerosis (SSc) is a connective tissue disease that can occur in isolation or associated with other inflammatory diseases of autoimmune aetiology, modifying their phenotypic expression and/or progression. It has been suggested that subtypes of SSc may have an uneven trend towards those associations.

Aims: 1. To determine the prevalence of associated systemic autoimmune diseases in a Spanish population with SSc treated at our centre. 2. To evaluate the existence of differential patterns of association according to the subtype of SSc.

Methods: We performed a cross-sectional study that included a hospital in-patient and out-patient sample of all SSc patients who were assessed at our centre during 2009. Demographic, clinical and laboratory (antinuclear [ANA], anticientromere [ACA] and antitopoisomerase [ScI-70] antibodies) variables were collected. The definition of the associated autoimmune diseases (AAID) followed the international classification criteria. Statistical analysis: continuous variables are expressed as mean±SD and categorical variables as number of cases (%). The association between the presence of AAID and the manifestations and subtypes of SSc was analysed with the Student’s t test for the continuous variables and the χ² test for the categorical ones. Statistical significance was set at p<0.05 (Stata v.10).

Results: Sixty one SSc patients were included (93.4% female), 45 (73.8%) with limited cutaneous subset (lcSSc) and 16 (26.2%) with diffuse cutaneous subset (dcSSc). Mean age was 59.9±18.4 yrs and duration of disease was 9.7±9.5 yrs. The distribution of auto-antibodies was as follows: 91.5% were ANA positive (90.9% of lcSSc and 93.3% of dcSSc), 63.8% had ACA (only lcSSc) and 29.5% had ScI-70 (6.9% of lcSSc and 73.3% of dcSSc). At least one AAID was present in 29 (47.5%) patients. Sjögren’s syndrome [SS] (36.1%), primary biliary cirrhosis [PBC] (9.8%), systemic lupus erythematosus [SLE] (3.3%), autoimmune hepatitis [AH] (3.3%), thyroiditis [AT] (3.3%), rheumatoid arthritis [RA] (1.6%) and polyniomyitis (1.6%). Seven (11.5%) patients combined 2 AAID, being SS and PBC the most frequent association (6.5%). Other combinations were SS and RA (1.6%), SS and PBC (1.6%) and SS and AT (1.6%). The prevalence of SS and PBC was similar in both SSc subsets: 37.8% and 2.2% for lcSSc and 31.2% and 6.2% for dcSSc, respectively. However, the rest of AAID were found only in lcSSc patients, although differences did not reach statistical significance, probably due to the small population size. Neither clinical nor laboratory manifestations of the disease showed significant association with the existence of AAID.

Conclusions: Nearly half of our SSc patients had AAID, being Sjögren’s syndrome and primary biliary cirrhosis the most frequent associations. The prevalence of Sjögren’s syndrome and autoimmune thyroiditis was similar in both subtypes of SSc. However, our results suggest that lcSSc could exhibit a higher tendency to be associated with other autoimmune diseases.

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**Results:** There were 372 patients with a POL 3 and 657 DNoPol3 pts who had PFTs. POL 3 patients were older at onset of disease and had a higher skin score, although they had a lower sedimentation rate and a lower symptom score for lung. Twenty-five percent had an episode of renal crisis (compared to 15% in the DNoPol3 pts, p<0.001). The disease duration at last follow up for both groups was more than 12 years. The first recorded forced vital capacity (FVC) in the POL 3 and DNoPol3 was 82% and 69% (p<0.001) and the smallest recorded values were 78% and 65% respectively (p<0.001). Only 11.3% of the POL 3 patients ever developed a FVC less than 60% predicted, compared to 24.8% in DNoPol3 pts (p<0.001). There were 102 POL 3 and 191 DNoPol3 pts who had more than onset of PFTs recorded. Table 1 shows the baseline and last FVC and diffusing capacity (DLco) for these patients. Comparisons between 1st and last studies and between groups were all highly significant (p<0.0001). Only 29% of the POL 3 pts ever had some fibrosis on radiographic imaging compared to 51% in the DNoPol3 (p<0.0001). Only 6% of POL 3 pts were ever treated with cyclophosphamide for their lung disease compared to 18% of the DNoPol3 (p<0.001).

The 5 and 10 year survivals were 86% and 76% for the POL 3 and 83% and 69% for the DNoPol3 pts, (p<0.0001). Only 2% of the POL3 pts have died from pulmonary fibrosis compared to 13% of the DNoPol3 pts, (p<0.0001). Fewer 30% of the POL 3 pts died from scleroderma related causes (43% compared to 56% (p<0.001) and pulmonary fibrosis was the scleroderma related death in 15% of these patients compared to 25% (p<0.05) in the DNoPol3.

**Conclusions:** POL 3 antibodies are available commercially and are helpful prognostically. While POL 3 patients have severe cutaneous disease and a high frequency of renal crisis, they infrequently get severe lung disease. Premature treatment for pulmonary fibrosis in these patients who rarely get severe fibrosis should be used cautiously.

**Antibody 1** FVC Last FVC Delta Time 1st DLCO Last DLCO POL 3 87% 83% 3.3 76% 79% TOPO 73% 70% 3.5 61% 58%

**Disclosure:** V. D. Steen: None; R. T. Domsic: None; T. Medsger: None.

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**Survival in Pulmonary Hypertension Associated with Scleroderma-Spectrum Disease: A Single Center Experience.** Dinesh Khanna, Rajeev Saggar, Daniel Furst, Paul Maranian, Philip Clements and Rajan Saggar. UCLA

**Introduction:** SSc-PAH is leading cause of mortality in SSc. The impact of SSc-ILD associated PH is not well characterized, however, portends a very poor prognosis. The objective of this study is to investigate the survival and characteristics among SSc-spectrum associated PH.

**Methods:** SSc patients with PH (defined as mPAP> 25 mmHg and FVC< 60%) or ILD associated PH (defined as mPAP> 25 mmHg and FVC< 60%) confirmed by right heart catheterization (performed at a tertiary center) were included in the study. Kaplan-Meier and Cox proportional hazard models were used to compare the survival between SSc-PAH and SSc-ILD associated PH and to identify predictors of survival.

**Results:** Ninety-three SSc patients (48 with isolated PH and 45 with ILD-PH) were identified. 1-, 2- and 3-year survival for the entire cohort was 80%, 76%, and 73%. Survival was similar for those with isolated SSc-PH and those with ILD associated SSc-PH (1-, 2-, 3-year survival rates 86%, 83%, 82% versus 71%, 65%, 59%), p<0.05.

In univariate analysis, gender, FVC%, DLco%, resting oxygen, cardiac output (CO) and pulmonary vasculature resistance (PVR) were associated with increase mortality. Using multivariate co-proportional hazard model, only PVR (HR 1.11) and CO (HR 0.39) were independent predictors of mortality in the overall cohort. Also, younger age had a greater risk of death (HR 0.95) in the CO model.

Baseline lung function and type of therapy did not predict mortality in our model.

**Conclusions:** Survival in SSc-spectrum associated PH remains poor, however, improved compared to historical cohorts. The prognosis of patients with SSc-ILD associated PH is similar compared to isolated SSc-PAH. This suggests PAH therapies, including parenteral prostanoids, are safe and efficacious in those individuals with significant ILD. Earlier diagnosis and potentially aggressive treatment may improve outcome as worse hemodynamic parameters (PVR) predict increased mortality.

**Baseline Characteristics**

| Age (years) | 54.9 (12.7) | 52 (14.3) | 92 | 50 (54.3) |
| Diffuse | 23 (25) | 18 (19.5) |
| Overlap | 59.3 (20.5) |
| FVC % predicted | 41.2 (19.1) |
| DLco% predicted | 1.7 (0.69) |
| Heart Rate | 81.3 (13.6) |
| Rest O2 sat (%) | 92.8 (5.7) |
| Hemodynamics (mmHg) | |
| Right Atrial Pressure | 9.6 (5.7) |
| Mean Pulmonary Pressure | 40.3 (13.7) |
| Pulmonary Wedge Pressure | 12.8 (6.5) |
| Cardiac Output (L/min) | 4.8 (1.4) |
| Cardiac Index (L/min/m2) | 2.7 (0.70) |
| PVR dyn*sec/cm-5 | 494.8 (209.3) |
| PAH Therapy n (%) | |
| ERA | 55 (59.7) |
| PDE-5 | 34 (36.9) |
| Tretoprostil (IV/SQ) | 26 (28.2) |

**Disclosure:** D. Khanna: Actelion Pharmaceuticals US, 2, 8, Gilead Sciences, Inc., 2, 8, NIAMS-NIH, 2; R. Saggar: None; D. Furst: Actelion Pharmaceuticals US, 2, 8, Gilead Sciences, Inc., 2, 8; P. Maranian: None; P. Clements: Gilead Sciences, Inc., 2; R. Saggar: None.
p=0.001) after correction to conventional cardiovascular risk factors. SSc patients who had coronary calcification were older (<0.001), had higher mean arterial pressure (p<0.001), longer disease duration (p=0.006) compared to those with normal coronary arteries. Only age and disease duration were identified by logistic regression analysis as predictive factors for coronary calcification in SSc patients.

**Conclusion:** SSc was an independent predictive factor for coronary atherosclerosis.

**Disclosure:** M. Y. Mok: None; C. S. Lau: None; S. Chiu: None; A. Tso: None; K. F. Mak: None; W. S. Wong: None; P. L. Khong: None; K. S. L. Lam: None.

### 1234

**The Psychological Impact of Systemic Sclerosis-Related Telangiectases.**

Holly Ennis1, Helen L. Richards1, Claire Cassidy1 and Ariane L. Herrick2.

1Mercy University Hospital, Cork, Co. Cork, Ireland, 2Rheumatic Diseases Centre, Trust Salford, United Kingdom, 3University of Manchester, Manchester, United Kingdom

**Background:** Systemic sclerosis (SSc)-related telangiectases commonly occur on the face and hands and, although often disfiguring, little is known about their psychological impact. Our objectives were to (a) determine the extent of body image dissatisfaction (BID) in patients with SSc-related telangiectases (b) identify disease-related correlates with telangiectases (c) examine the subjective experiences of patients with telangiectases through qualitative analysis.

**Methods:** 227 patients aged over 18 years with SSc were invited to participate in a questionnaire survey. Clinical and demographic data was obtained for all participants from a clinical database. Each participant completed the Adjusted Satisfaction with Appearance Scale (ASWAP), the Hospital Anxiety and Depression Scale (HADS) and an open-ended telangiectases questionnaire. Thematic analysis was utilised to describe the qualitative data.

**Summary of Results:** 141 patients (62%) with SSc responded to the survey (83% female, 70% limited cutaneous SSc, median age 62 years). Telangiectases was reported by 113 (80%). All ASWAP scores (Table 1) were higher in those reporting telangiectases, and this was significant for the ‘dissatisfaction with appearance’ subscore (p=0.02). Anxiety and depression scores were similar in those with and without telangiectases. Those reporting telangiectases were more likely to be anticientromere positive (40% versus 18%, p=0.02) and to have a history of severe digital ischaemia (38% versus 18%, p=0.04) than those not. Qualitative analysis revealed four themes: changes in behaviour as a result of telangiectases (e.g. social avoidance), public and private self-image (e.g. feeling self-conscious), negative emotional impact of telangiectases (e.g. feelings of sadness or anger) and gaining new perspectives on life (e.g. focusing on positives such as the ability to walk).

**Conclusions:** BID, as measured by the ASWAP, was higher in patients with telangiectases, especially within the ‘dissatisfaction with appearance’ subscale. Telangiectases were associated with anticientromere positivity and digital ischaemia, lending further support for telangiectases as a potential marker for vascular involvement. Qualitative analysis provided new insights into the thoughts and feelings of patients with telangiectases, highlighting concerns and also methods of coping with telangiectases. Our findings highlight the impact of telangiectases and the need to address and manage related concerns.

<table>
<thead>
<tr>
<th>All participants</th>
<th>Telangiectases</th>
<th>No telangiectases</th>
<th>p value (Mann-Whitney U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=141</td>
<td>n=113</td>
<td>n=28</td>
<td></td>
</tr>
<tr>
<td>ASWAP Social impact, median (IQR)</td>
<td>14 (8–22)</td>
<td>14 (8–22)</td>
<td>12 (8–20)</td>
</tr>
<tr>
<td>ASWAP Dissatisfaction with appearance, median (IQR)</td>
<td>20 (14–26)</td>
<td>21 (15–27)</td>
<td>15 (12–23)</td>
</tr>
<tr>
<td>ASWAP Total score median (IQR)*</td>
<td>30 (25–36)</td>
<td>37 (27–47)</td>
<td>26 (20–41)</td>
</tr>
<tr>
<td>HADS Anxiety, median (IQR)**</td>
<td>7 (4–10)</td>
<td>7 (4–10)</td>
<td>8 (5–12)</td>
</tr>
<tr>
<td>HADS Depression, median (IQR)**</td>
<td>6 (3–9)</td>
<td>6 (3–9)</td>
<td>6 (3–8)</td>
</tr>
</tbody>
</table>

* 125 subjects.
** 281 subjects.

**Disclosure:** H. Ennis: None; H. L. Richards: None; C. Cassidy: None; A. L. Herrick: None.

### 1235

**The Use of Calcium-Channel Blockers May Prevent the Development of Scleroderma Renal Crisis.**

Gaia Montanelli, Lorenzo Beretta, Alessandro Santaniello and Raffaella Scorza. Referral Center for Systemic Autoimmune Diseases

**Background:** Scleroderma renal crisis (SRC) is one of the most severe complications of systemic sclerosis (SSc), with high mortality and morbidity rates. Past studies were conducted to determine which factors may precipitate or protect from the development of SRC. The use of corticosteroids, the diffuse cutaneous subset (dcSSc), the presence of friction tendon rubs, the presence of certain autoantibodies and an aggravating skin score were shown to be risk-factors for SRC. Apart from corticosteroids, which were associated with the onset of SRC, the role of other therapies, including vasodilators or loprost, in the progression of or in the protection from SRC is not clear.

**Methods:** A retrospective study was conducted in all the patients referred to our outpatient clinic between 1990 and 2010, with a disease duration < 5 years at referral. The development of SRC, defined as either hypertensive renal crisis or nonhypertensive renal crisis, up to 5 years (20 trimesters) from referral was sought. Medical records were reviewed to determine whether the patients had been treated with calcium-channel blockers (CCB), loprost or steroids. The dose of steroids (expressed as the medium dose Prednisone/day/trimester) was also reviewed.

Univariate Cox regression analysis with or without time-dependent covariates was used to assess the individual risk for SRC for baseline demographic and clinical characteristics and for therapies. Meaningful variables were inserted in a multivariate Cox regression model.

**Results:** Two-hundred-ninety-one patients (females = 89.7%; dcSSc = 25.8%) with a disease duration of 13 months at referral (interquartile range [IQR]: 4 – 29), were considered. Fifteen SSc (5.2%; 12 hypertensive, 3 normotensive) were observed, the median time-to-onset of SRC was 6 months (IQR: 3 – 12 months). Overall, 165 patients were treated with steroids with a median maximum dose of 25 mg/day/trimester (IQR: 14 – 50 mg); 260 subjects (89.3%) received CCB and 100 (34.4%) loprost, prior or concurrently to corticosteroids. On univariate analysis, gender, disease subset and the use of steroids were associated with a positive risk of SRC, whilst FVC, disease duration prior to referral and the use of CCB were negatively associated with SRC. On multivariate analysis the use of CCB was negatively associated with SRC (HR = 0.118, CI95 = 0.038–0.362, p<0.001), whilst steroids (HR = 1.014, CI95 = 1.002–1.026, p<0.035) and dcSSc (HR = 6.75, CI95 = 1.988–22.195, p<0.003) increased the risk for SRC.

**Discussion:** SRC is a relatively rare event in Italian patients. We confirmed that the use of steroids increases the risk for SRC, albeit this risk is relatively low (1.4% for every milligram of Prednisone used in the trimester prior to SRC). Conversely, the use of CCB is highly protective against the development of SRC. In our centre, the vast majority of patients is prescribed first-second generation dihydroypridine agents (Nifedipine or Nicardipine), that acting on L-type calcium channels may favour afferent renal arterioles vasodilatation, and counteract angiotensin II vasoconstrictive effects thus increasing or stabilising the glomerular filtration rate and glomerular filtration fraction.

**Disclosure:** G. Montanelli: None; L. Beretta: None; A. Santaniello: None; R. Scorza: None.

### 1236

**Time of Transition through Different Patterns of Nailfold Microangiopathy in Systemic Sclerosis.**

Alberto Sulli1, Carmen Pizzorni2, Francesca Ravera2, Elisa Alessandri2, Giuseppe Zampogna3, Bruno Seriolo3 and Maurizio Cutolo1.

1Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy; 2Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy

**Background:** Nailfold microangiopathy is an early aspect of systemic sclerosis (SSc), and its features may be detected by nailfold videocapillaroscopy (NVC). The evolution from “early”, to “active”, and to “late” patterns of microvascular damage was described by several studies.

**Objectives:** To investigate the time of transition through the different patterns of microangiopathy, in SSc patients with the “early” NVC pattern at baseline.

**Methods:** Thirty-eight SSc patients (mean age 48±12sd years; mean disease duration from Raynaud’s phenomenon onset 10±10 years, from the onset of the first SSc symptom different from RP 1 year) with the “early”
pattern of nailfold microangiopathy at baseline were followed-up by NVC for a mean time of 90 ± 18 months, every nine months by the same operator. The proper pattern of NVC microangiopathy ("early", "active", "late") was recorded at each visit, as previously reported[1,2]. "Early" NVC pattern: few (<33%) giant capillaries, few capillary haemorrhages, relatively well-preserved capillary distribution, no evident loss of capillaries; "active" NVC pattern: frequent (>66%) giant capillaries, frequent capillary haemorrhages, moderate (<33%) loss of capillaries, mild (<33%) disorganisation of the capillary architecture, absent or mild ramified capillaries; "late" NVC pattern: irregular enlargement of the capillaries, few or absent giant capillaries and haemorrhages, severe (>66%) loss of capillaries with avascular areas, disorganisation of the normal capillary array, and ramified/bushy capillaries.

**Results:** At the end of the follow-up, 17 patients (43%) were still showing the "early" scleroderma-pattern, while the NVC pattern of microangiopathy was changed in 57% of the patients. The NVC pattern was found "active" in 14 patients (38%), "late" in 5 patients (14%), and normal in 2 patients (5%). The mean time of progression from the "early" to the "active" pattern was of 28 ± 20 months, and from the "early" to the "late" pattern it was of 36 ± 29 months. Interestingly, in the subgroup of patients whose microangiopathy progressed from the "early" to the "late" NVC pattern through the "active" pattern, the mean time of progression from the "early" to the "active" pattern was only 8 ± 1 months, discovering a subset of SSc patients (14%) with fast progression of SSc microangiopathy.

**Conclusions:** The results of this longitudinal study confirm the transition of the SSc microvascular damage through different NVC patterns of microangiopathy. Forty % of SSc patients progressed quickly to "late" from "early" NVC pattern of microangiopathy. Patients showing a fast progression from the "early" to the "active" NVC pattern of microangiopathy should be strictly monitored as at risk of rapid progression to the "late" NVC pattern of microvascular damage, characterized by capillary desorganisation and disorganization.

**References:**

**Disclosure:** A. Sulli: None; C. Pizzorni: None; F. Ravera: None; E. Alessandrini: None; G. Zampogna: None; B. Seriolo: None; M. Cutolo: None.

### 1238

**Ultrasonographic Assessment of Hand Joint and Tendon Involvement in 30 Patients with Systemic Sclerosis.** Emmanuel Chatelus, Helène Chiffot, Virgine Clavert, Christelle Sordet, Jacques-Eric Gottenberg and Jean Sibilia.

**Hospital of Hautepierre, Strasbourg, France**

**Objective:** To evaluate joint and tendon involvement in the hands of patients with systemic sclerosis (SSc) using ultrasonography (US) and their correlation with clinical and X-ray examinations.

**Methods:** 30 patients with SSc according to ACR criteria (21 diffuse SSc and 9 limited SSc, median (25th-75th) age 55 (44–63) years, median (25th-75th) disease duration 5 (3–11) years, all negative for anti-CCP), were consecutively included in this study and underwent clinical, X-ray and US examinations. Synovial proliferation, joint effusion, bone erosion, tenosynovitis and the Power Doppler signal were evaluated using a Toshiba EUB-5500 with a 14 MHz linear-array transducer.

**Results:** US detected synovial proliferation in 11 patients (37%), and joint effusion in 10 (33%). US detected synovitis in 47% of patients, higher than that found by clinical examination (27%; p=0.01), which was not associated with the radiological presence of erosion and joint space narrowing. Synovial proliferation and joint effusion were more frequent in diffuse SSc (43% for both) than in limited SSc (22%, 11%, respectively). Lastly, tenosynovitis (24%), bone erosion and Power Doppler (19%) were observed only in diffuse SSc.

**Conclusion:** US provides relevant information on the hands of patients with SSc that complements that obtained by clinical and X-ray examination. Also, diffuse SSc is a subgroup at greater risk of tendon and joint involvement. US examination may therefore be particularly helpful in detecting synovitis and bone erosion early in patients with diffuse SSc, and designing therapy.

**Disclosure:** E. Chatelus: None; H. Chiffot: None; V. Clavert: None; C. Sordet: None; J.-E. Gottenberg: None; J. Sibilia: None.
Objective: To evaluate cellular and soluble factors’ profile of WF of SSc skin ulcers.

Patients and Methods: SSc patients with skin ulcers attending the Wound Care Outpatient Clinic of Rheumatology division of the Catholic University (Rome) were enrolled in the study. MMP-9, VEGF and IL-6 levels were detected through ELISA and MCP-1, IL-1β, IL-8 and TNFα levels through Flow Cytomix™ technology in plasma and WF, whereas the WF percentages of CD16, CD14, CD3 and CD19 were evaluated through Flow cytometry at baseline. Each patient underwent skin lesion’s evaluation, microbiological analysis and treatment with Suprasorb® or Suprasorb A® ± Ag® twice a week. WF collection was done through transparent dressing (OpSite, Smith & Nephew, UK).

Results: 11 SSc patients with skin ulcers (18% in fingertips) were enrolled in the study. A higher healing rate after 3 months of follow-up with the standard protocol was found in SSc compared to DM patients with chronic ulcers treated with the same protocol (8 patients (73%) vs 1/20%, p<0.001). Compared to healthy controls, SSc patients had higher plasma levels of IL-6 (2.4 ± 1.5 pg/ml vs 6.9 ± 1.8 pg/ml, p=0.011), VEGF (17.2 ± 15.4 pg/ml vs 43.11 ± 36.03 pg/ml, p=0.01), MCP-1 (255 ± 59.2 pg/ml vs 528 ± 270.78 pg/ml, p=0.001) and IL-8 (1.66 ± 3.62 pg/ml vs 3.55 ± 3.59 pg/ml, p=0.02). SSc patients with fingertip ulcers had lower levels of VEGF in WF compared to patients with major lesions (5157.3 ± 3767.3 pg/ml/lg albumin vs 21632.0 ± 515864.0 pg/ml/lg albumin, p=0.05).

Direct correlations in WF were found between IL-8 and MMP-9 (r=0.64, p=0.04), MPP-9 and IL-8 (r=0.82, p=0.004) and between percentages of CD3 and CD19 (r=0.76, p=0.03). Moreover there were direct correlations between the extension and border scores of ulcers and MCP-1 (r=0.62, p=0.05 for extension and r=0.63, p=0.03 for border score) and TNFα (r=0.65, p=0.03 for extension and r=0.65, p=0.02 for border score) in WF of SSc patients.

SSc patients who healed after 3 months of follow-up had lower WF levels of MCP-1 (50129 ± 3600.1 pg/ml/lg albumin vs 505173.1 ± 576739.8 pg/ml/lg albumin, p=0.03), TNFα (284 ± 372.8 pg/ml/lg albumin vs 36789 ± 79499.5 pg/ml/lg albumin, p=0.02) and VEGF (21140 ± 3825.7 pg/ml/lg albumin vs 111381.1 ± 212464.0 pg/ml/lg albumin, p=0.03) compared to non healers. All the inflammatory soluble factors (IL-6, IL-1β, TNFα and IL-8) were higher in WF compared to plasma in SSc patients (p<0.05).

Conclusions: A standard treatment seems to enhance healing rate in SSc skin ulcers. The plasma-WF polarization of factors such as IL-6, IL-1β, TNFα and IL-8 suggests that ulcers in SSc could be considered an acute phenomenon in a chronic inflammatory background. A stronger control of local inflammation should be looked for in the most inflamed lesions.

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ACR Poster Session B
T Cell Biology and Targets in Autoimmune Disease
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

1240
A Novel Role for the Jak-Stat Pathway in Rheumatoid Arthritis: Inhibition of TNF-Induced T Cell Attracting Chemokine Synthesis in Fibroblast-Like Synoviocytes (ELS) by Tascotininib, Sanna Rosengren1, Hendrik Schulze-Koops2 and Alla Skapenko2. 1Division of Rheumatology, University of Munich, Munich, Bavaria, Germany, 2Division of Rheumatology, University of Munich, Munich, Germany

Interleukin 9 (IL-9) is a pluripotent cytokine produced primarily by T cells in response to transforming growth factor (TGF)-β. Little is known about the role of IL-9 and of the IL-9-producing T cell subset. Herein, we investigated IL-9 production by different mature T helper (Th) cell subsets, and analyzed the effect of IL-9 on T cell differentiation.

The pan-Janus kinase (Jak) inhibitor, tascotininib (CP690,550) is currently in Phase III clinical trials for rheumatoid arthritis. Whereas the Jak-Stat signaling in lymphoid and myeloid lineage cells is well understood, less is known about its involvement in FLS signaling in the context of synovitis. Therefore, we measured the effect of tascotininib on expression and secretion of inflammatory mediators by cytokine stimulated FLS.

Results: Staining of FLS with IL-6, but not TNF, induced phosphorylation of Stat1 and Stat3, downstream indicators of Jak activation. Stat activation was inhibited by tascotininib with IC50 values of approximately 21 and 72 nM, respectively. IL-6 also induced expression of MCP1 mRNA and protein secretion but not other markers of FLS activation such as MMP3. MCP-1 expression was also completely prevented by tascotininib (200 nM-1 μM). Unexpectedly, tascotininib also inhibited TNF-induced gene expression and production of several other pro-inflammatory proteins. Time-course studies showed induction of IP-10, RANTES, and MCP1 mRNA expression and protein secretion after 7h but no inhibition by tascotininib. However, tascotininib significantly decreased IP-10, RANTES, and MCP1 mRNA expression after 16 hours of TNF stimulation (96%, 67%, and 55% inhibition, respectively; p<0.001 for all). TNF-induced secretion of RANTES and MCP1 protein at 18h was inhibited by 53% and 38%, respectively (p<0.005 for both). A smaller effect was observed on TNF-induced IL-6 and MMP1 expression, whereas other TNF-induced genes like IL-8 and MMP3 were unaffected by tascotininib. mRNA stability studies showed that the effect of the Jak inhibitor was independent of mRNA half life. However, blocking de novo protein synthesis with cycloheximide abolished the inhibitory effect of tascotininib on TNF induced IP-10 and RANTES mRNA expression.

Conclusions: TNF induces FLS expression of several chemokines involved in T cell recruitment in a manner that indirectly depends on Jak-Stat activation. TNF-induced FLS expression of these chemokines requires de novo protein synthesis and could involve disrupting late autocrine cytokine networks mediated by Jak-Stat signaling. These findings illuminate a potential novel mechanism of tascotininib in rheumatoid arthritis: not only does the compound directly inhibit cytokine signaling in T cells, but it also diminishes the production of chemokines by synovial fibroblasts and could limit recruitment of T cells and other infiltrating leukocytes to the synovium.

Disclosure: S. Rosengren: None; G. S. Firestein: Pfizer Inc, 5; D. L. Boyle: Pfizer Inc, 2.

1241
A Th17 Immune Response Can Be Amplified by Human Th9 Cells. Andreas Ramming1, Hendrik Schulze-Koops2 and Alla Skapenko2. 1Division of Rheumatology, University of Munich, Munich, Bavaria, Germany, 2Division of Rheumatology, University of Munich, Munich, Germany

Interleukin-9 (IL-9) is a pleiotropic cytokine produced primarily by T cells in response to transforming growth factor (TGF)-β. Little is known about the role of IL-9 and of the IL-9-producing T cell subset. Herein, we investigated IL-9 production by different mature T helper (Th) cell subsets, and analyzed the effect of IL-9 on T cell differentiation.

CD4+ CD45RA+ naive and CD45RO+ memory, and CD4+ CD25+ T cells were isolated from peripheral blood of healthy individuals, stimulated under different conditions, and analyzed for their cytokine profile by intracellular flow cytometry and Luminex.

TGF-β was identified as the master cytokine for the induction of human IL-9-producing T cells. CD45RA+ naive T cells required TGF-β together with IL-4 to convert into IL-9-producing cells. In CD45RO+ memory T cells, TGF-β alone was sufficient to induce IL-9 production. Mature T cell subsets, Th1, Th2, Th17 cells, and CD25+Foxp3+ regulatory T cells (Tregs) did not produce IL-9 together with the respective signature cytokine or transcription factor. Th9 cells itself demonstrated a highly specific cytokine secretion profile different from other effector cell subsets. Their signature cytokine, IL-9, enhances Th17 differentiation. Therefore, human Th9 cells are likely to exert a pro-inflammatory function.

Disclosure: A. Ramming: None; H. Schulze-Koops: None; A. Skapenko: None.

1242
Addition of Retinoic Acid and TGF-beta Accelerate the Maturation Naive CD8+ Cells into CD8+CD25+FOXP3+ Regulatory Cells. J. Dixon Gray1, Stephanie Q. Pan2 and David A. Horwitz2. 1University of Southern California, Los Angeles, CA, 2University of Southern California

Purpose: Regulatory T cells (Tregs) maintain immunologic homeostasis and prevent autoimmunity. Defects in the numbers and function of CD4+ Tregs in SLE and other immune-mediated rheumatic diseases are well described. Besides their well described cytotoxic activities, several populations of CD8+ regulatory cells (Treg) have been described that occur
naturally or can be induced ex-vivo and some of these subsets express Foxp3. The conditions required to induce mature functionally competent Foxp3+ Tregs are not well understood. We have reported that human naïve CD4+ T cells polyclonally stimulated with IL-2, TGF-β and all-trans retinoic acid (aTRA) rapidly become CD25+CD127- Foxp3+ T cells with marked suppressive activity both in vitro and in vivo. Here the objective was to learn whether CD8+ T cells could become Treg cells with a similar phenotype and function.

Methods: CD28+CD4+CD8+CD103+CD62L+CD25- cells from healthy subjects were stimulated with suboptimal numbers of anti-CD3/CD28 coated beads + IL-2 ± TGF-β or aTRA for 5 to 7 days. Since all anti-CD3 activated CD8+ T cells inhibit T cell proliferation in vitro, we investigated their ability to protect into immunodeficient NOD SCID IL-2R common gamma chain−/− (NOG) mice from a human anti-mouse GVHD.

Results: Activation of naïve CD8+ T cells with TGF-β doubled Foxp3 expression and induced CD8+ T cells became CD103+CD62L+, but the cells retained a naïve phenotype and remained CD127+. When the addition of aTRA to TGF-β, Foxp3 expression was consistently >50%. They remained predominantly CD25-CD62L hi, but became CD45RO+ and CD127-, consistent with a regulatory phenotype. The transfer of 2x10^6 human CD25- PBMC to NOG mice results in the rapid demise of these animals. The addition of aTRA/TGF-β CD8reg in a ratio of 1:reg to 4 PBMC doubled the survival of the mice. Studies with other epigenetic agents and comparing the effects of CD4 and CD8reg separately and together will be reported.

Conclusions: Although to date, attention has been focused on CD4reg, studies in both mouse and human SLE have documented an important, if not essential, role of CD8reg. The ability to rapidly generate both CD4 and CD8reg T cells could become a novel approach to treat patients with SLE and other chronic inflammatory immune-mediated rheumatic diseases.
of these entities on the primary and secondary anti-PT responses was monitored.

**Results:** In the HuSCID model, CDP7657 demonstrated a dose-dependent inhibition of the anti-PT antibody response with equivalent efficacy to that of aglycosyl hu5c8. Although all three entities were able to completely block the anti-PT immune response, the IgG1 version of hu5c8 was the most potent in this model system.

In the Cynomolgus macaque, all of the anti-CD40L molecules were capable of inhibiting the primary IgM and IgG anti-PT antibody responses, with a comparable degree of efficacy observed between CDP7657, the diFab PEG and the aglycosyl IgG antibody constructs. CDP7657 demonstrated a dose related effect on both primary and secondary (after re-challenge with PT) immune responses and also was able to effectively suppress secondary responses.

**Conclusions:** CDP7657 dose-dependently inhibited the immune response to PT in both HuSCID mice and Cynomolgus macaques. The inactive Fc formats tested had decreased efficacy in both models relative to hu5c8 which may reflect the potential deleterious capacity of this active isotype. Demonstration of the effective inhibition of CD40L-dependent immune responses by CDP7657 supports the therapeutic potential of this molecule for the treatment of human immune-mediated diseases such as SLE.


**1246**

**Characterization of Human Follicular Helper T Cells.** Sang Taek Kim1, Jinyoung Choi4, Begona Lainez4, Leah DiPlacido1, Vivian E. Vlamakis2 and Joseph E. Craft4. 1Department of Immunobiology, Yale University School of Medicine, New Haven, CT, 2Division of Rheumatology, University of Washington School of Medicine, Bothell, WA, 3Section of Bone Marrow Transplantation, Department of Internal Medicine, Yale University School of Medicine, Orange, CT, 4Section of Rheumatology, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT

Follicular helper T (T<sub>FH</sub>) cells are specialized CD4<sup>+</sup> T cells that are localized in B cell follicles and help B cells produce antigen-specific antibodies via contact and secretion of IL-21 and IL-4. In mouse studies, a spontaneous increase in T<sub>FH</sub> cells is associated with pathologic germinal center formation and autoantibody secretion, which leads to autoimmune diseases and end-organ damage. In mice, T<sub>FH</sub> cells are characterized by high expression of CXCR5, PD-1, ICOS, and Bcl-6, and as we have found, low expression of P-selectin glycoprotein ligand-1 (PSGL-1); however, study of T<sub>FH</sub> cells in human is more limited. Here we characterized T<sub>FH</sub> cells in human tonsils using flow cytometry and immunofluorescence staining and compared them using surface markers and cytokine production to traditional Th effector subsets. Samples were obtained from routine tonsilectomy at Yale New Haven Hospital. Both surface and intracellular staining were done with flow cytometry. T cells in human tonsil were sorted into populations of CD4<sup>+</sup> CD45RA<sup>-</sup> cells (Naive T cells), CD4<sup>+</sup> CD45RA<sup>-</sup> PSGL<sup>-</sup>PD-1<sup>-</sup>CXCR5<sup>-</sup> cells, CD4<sup>+</sup> CD45RA<sup>-</sup> PSGL<sup>-</sup>PD-1<sup>-</sup>CXCR5<sup>-</sup>Th1<sup>-</sup> cells, CD4<sup>+</sup> CD45RA<sup>-</sup> PSGL<sup>-</sup>PD-1<sup>-</sup>CXCR5<sup>-</sup>Th2<sup>-</sup> cells and CD4<sup>+</sup> CD45RA<sup>-</sup> PSGL<sup>-</sup>PD-1<sup>-</sup>CXCR5<sup>-</sup>Th17<sup>-</sup> cells. Subsequently sorted populations were stimulated with PMA/Ionomycin for 6 hours. Stimulated cells were used for qPCR/intra-cytometric staining and culture supernatants were used for ELISA. Tissue immunofluorescence staining was done using confocal microscopy to confirm the localization of T<sub>FH</sub> cells. We find that human T<sub>FH</sub> cells are ICOS<sup>+</sup>IL-7R<sup>-</sup>CD200<sup>-</sup>CD27<sup>-</sup>CXCR4<sup>+</sup> and IL21R<sup>-</sup>IL-7R<sup>-</sup>PSGL<sup>-</sup>CD62L<sup>-</sup>CCR7<sup>-</sup> and they produce both IL-4 and IL-21. Downregulation of PSGL-1 can be used as an additional surface marker for T<sub>FH</sub> cells as well as an anatomical marker of the B cell follicle by microscopy.

**Disclosure:** S. T. Kim: None; J.-Y. Choi: None; B. Lainez: None; L. DiPlacido: None; V. E. Vlamakis: None; J. E. Craft: None.

**1247**

**Chronic Inflammatory Responses in Rheumatoid Arthritis: The Vicious Circle Might Be Related to Interaction of Th17 Cells with FLS or Mesenchymal Stem Cells.** Assia Eljaafari1, Marie-Laurie Tartelin1 and Pierre Miосsec1. 1HIL and UCBL, Lyon, France, 2HIL and UCBL, France

**Introduction:** Th17 cells have been involved in the initiation and maintenance of several inflammatory and autoimmune diseases, such as Rheumatoid Arthritis (RA). More recently, they gained further interest, due to the demonstration of their involvement in anti-tumor responses.

**Hypothesis:** Here we postulated that if Th17 cells play a so preponderant role in inflammatory diseases, their development might be facilitated in this context. Therefore, using RA as a model of chronic inflammation, we hypothesized that interaction of T cells with mesenchymal cells, such as synovocytes (FLS), or mesenchymal stem cells (MSC) could participate in the activation of the Th17 pathway, with the help of the inflammatory environment.

**Methods:** To investigate this possibility, mononuclear cells (MNC) from healthy blood donors were co-cultured with MSC from healthy controls, or FLS from either RA or osteoarthritic (OA) patients, and were activated with PHA or A/CD3 + CD28 mABs, for 1 to 2 days. IL17A, TNFa, and/or IFNg were added or not to these co-cultures. Q-RT-PCR, ELISA, and cytofluorometry techniques were used to assess for IL17-A production.

**Results:** We observed that the interaction of MNC with healthy MSC resulted in an extinction of TH1 and TH2 cell activation, but was sufficient by its own to induce a strong production of TH17 cells, as soon as 24 hours post-activation, as assessed by the increase of IL17A at the mRNA and protein levels and by Th17 staining. The levels of IL17A further increased at 48 hours, and/or in the presence of IL17A, TNFa, and/or/IFNg. IL6, IL8, and IL1 mRNA levels increased as well. Interestingly, co-culture with FLS from either OA or RA patients, also resulted in a strong induction of IL17, but not in TH1 inhibition. Finally, TH17 production was partially inhibited in the presence of anti-IL6 mAbs, or CTLA4-Ig fusion molecules, demonstrating thus the major role of IL6 and co-stimulatory molecules in such a vicious circle, that may participate to the chronicity of inflammation.

**Disclosure:** A. Eljaafari: None; M.-L. Tartelin: None; P. Miосsec: None.
to a lower proportion of mature previously activated CD4+ T cells at later ages. We conclude that the number of regulatory T cells in the circulation is important in the function of inhibition of immune activation, probably both to endogenous and exogenous antigens. Therefore, lower numbers of regulatory T cells in the circulation might precede the onset of inflammatory disease.

Disclosure: H. Rabe; None. A.-C. Lundell; None. K. Andersson; None. L. Adlerberth; None. E. A. Wold; None. A. Rudin; None.

1249

Critical Role of IL-21 in Modulating Th17 Responses and Regulatory T Cells in Behçet Disease. Guillaume Geri1, Benjamin Terrier1, Michelle Rosenzweig1, Bertrand Wechsler2, Du Le Boutin1, Bahram Bodaghi1, Tu Anh Tran3, Nathalie Costedoat-Chalumeau1, Lucile Musset1, David Klatzman1, Patrice Cacoub1 and David Saadoun1. 1Pitié-Salpêtrière Hospital, Paris, France. 2Pitié-Salpêtrière Hospital, Paris, France

Background: Behçet disease (BD) is a systemic vasculitis of unknown origin. Infectious or environmental factors and Th1 cells producing IFN-γ have been involved in its pathogenesis, but these findings remain controversial.

Objective: To determine the implication of Th1, Th17 and regulatory T cells in the pathogenesis of BD.

Methods: Forty BD patients (20 active untreated [aBD] and 20 treated and inactive [iBD]) fulfilling the international diagnostic criteria and 20 healthy donors (HD) were included. Flow cytometric analysis of peripheral blood mononuclear cells (PBMCs) and purified CD4+ T cells was performed for cell surface markers, intracellular production of cytokines and FoxP3 transcription factor. Measurements of cytokine levels in serum and culture supernatants were also performed.

Results: A marked enrichment in IL-17A-producing CD4+ CD45RO+Foxp3− T cells (Th17) was found in peripheral blood of aBD compared with iBD and HD (3.1 vs. 1.0 and 0.6 %, P<0.0001 for both), whereas IFN-γ producing CD4+ and CD8+ T cells did not differ between aBD and HD. Th17 expansion was more pronounced in cells isolated in cerebrospinal fluid of aBD with central nervous system involvement. CD4+CD25highFoxp3+ T cell subset was decreased in aBD compared to HD (1.78 vs. 3.2%, P=0.02). We found an increase in serum IL-21 in aBD compared with iBD and HD whereas no significant difference was noted for others cytokines promoting Th17 differentiation. Expansion of IL-21-producing CD4+ T cells was observed in aBD compared with iBD and HD (5.5 vs. 2.8 and 1.8 %, P=0.002 and P<0.0001, respectively), that correlated positively with Th17 expansion (r2=0.43; P=0.0001) and negatively with activated Tregs (r2=0.45, P=0.009). Stimulation with anti-CD3/CD28 of purified CD4+ T cells, with human recombinant IL-21, significantly increased Th17 cells and decreased FoxP3 expression. The blockade of IL-21 using IL-21R/Fc chimera markedly decreased production of IL-17A and increased FoxP3 expression in sorted CD4+ T cells.

Conclusion: Taken together, these results are the first to demonstrate the implication of IL-21 in the pathogenesis of BD. IL-21 may exert a critical role to a lower proportion of mature previously activated CD4+ T cells while IL-21 is the major functional cytokine produced from Th17 cells. The purpose of this study is to determine how CXCL13-CXCR5 signaling is involved in the development of Tfh during the development of pathogenic GC response in BXD2 mouse model of autoimmune disease.


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Decreasing Fli1 Levels in Lupus T Cells Has Effects on Serum Immunoglobulin Levels and T Cell Infiltration in the Kidney. Erin Morris1, Maria I. Harrell1, John Svenson1, Laura Tonks1, John Zhang1 and Tamara K. Nowling2. 1MUSC, 2Ralph Johnson VAMC/MUSC, Charleston, SC. Ralph Johnson VAMC/MUSC.

Background: The Ets factor Fli1 is implicated as a key modulator of lupus disease expression. Over-expressing Fli1 in healthy mice, results in the development of an autoimmune kidney disease similar to that observed in lupus. Lowering the global levels of Fli1 in two lupus mouse models significantly improved disease and prolonged survival. Lowering the levels of Fli1 in hematopoietic cells only in MRL/lpr lupus mice resulted in significantly improved kidney disease. The cell type mediating this protective effect is unknown. Here we analyzed the effects of reducing Fli1 levels in MRL/lpr T cells on serum IgG and IgM levels, T cell infiltration in the kidneys and T cell proliferation.

Methods: T cells and B cells were isolated from spleens of lupus prone MRL/lpr Fli1+/+ and MRL/lpr Fli1−/− mice. The cells were mixed in all possible Fli1+/+ and Fli1−/− T and B cell combinations in a 1:1 ratio and adoptively transferred into Rag-1-deficient mice, which do not produce mature T and B cells. Various markers of autoimmunity were measured in the serum of the recipient mice at 2 and 4 weeks after transfer by ELISA and T cell infiltration in kidneys was examined 4 weeks after transfer by immunofluorescence. Next, we measured the various T cell subsets infiltrating the kidneys of MRL/lpr Fli1+/+ and MRL/lpr Fli1−/− mice by flow cytometry, CFSE staining and Annexin V staining were used to measure proliferation and apoptosis, respectively of Fli1+/+ and Fli1−/− T cells following ex vivo stimulation.

Results: Our adoptive transfer results demonstrated that recipient mice that received Fli1−/− T and +/- B cells or Fli1+/+ T and +/- B cells averaged 50–75% lower levels of IgG and 60–70% lower levels of IgM compared to recipient mice that received Fli1+/+ T and +/- B cells. The recipient mice that received Fli1−/− T and +/- B cells also had approximately 30% fewer T cells (CD3+) present in their kidneys compared to recipients that received Fli1+/+ T and +/- B cells. Analyses of kidneys from 14–16 week old MRL/lpr Fli1+/+ and MRL/lpr Fli1−/− mice demonstrated that the percent of CD4+ T cells

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present was significantly decreased by 25% (p<0.005) and the percent of CD8+ T cells present was significantly increased by 57% (p<0.01) in the MRL/pr Fli1+/− compared to MRL/pr Fli1+/+. A 37% decrease in the number of total T cells and 42% increase in the percent of CD25+ T cells present in the kidney also was observed in the MRL/pr Fli1+/− mice, but the differences did not reach statistical significance. Furthermore, T cells isolated from spleen of Fli1+/+ and Fli1+/− mice demonstrated that reducing Fli1 results in a 10–12% increase in T cell proliferation.

Conclusions: The adoptive transfer results demonstrate that reducing Fli1 levels in T cells alone may have a positive therapeutic impact on the progression of lupus nephritis. This positive impact may be mediated by changes in the number and subtypes of T cells infiltrating the kidneys. Mechanistically, the effects of altered Fli1 levels in T cells has yet to be fully explored. Preliminarily, our results suggest that Fli1 may have an effect on proliferation.

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1252


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Purpose: Tobacco smoking is the main environmental risk factor for the development of rheumatoid arthritis (RA). In established RA, smoking is associated with the increased production of rheumatoid factor (RF) and autoantibodies and with increased incidence of extra-articular manifestations that include the development of rheumatoid nodules. However, mechanisms linking smoking with the onset of RA, severity and/or progression of disease and that accommodate the genetic influence of the shared epitope are poorly understood. The aim of this study was to identify the pathogenic mechanisms within RA tissues which are triggered by smoking, with particular emphasis on the cells capable of responding via the aryl hydrocarbon receptor (AHR).

Method: Synovial membrane and subcutaneous nodule tissues were obtained at surgery from patients fulfilling ACR criteria for RA. Retrospective followup established whether patients were smoking at disease onset and/or continued to smoke at the time tissue was obtained, or had ceased smoking prior to tissue collection or had never smoked. All synovial samples were assessed using quantitative real-time PCR assays (Tagman; Applied Biosystems) to establish AHR expression and distinguish AHR activation, through CYP1A1 expression. Cryostat sections of synovial tissue were stained by double immunoﬂuorescence using cell specific antibodies recognising lineage specific markers, in combination with biotinylated AHR- or CYP1A1-specific antibodies to identify cells responding to continued smoking. Genomic DNA was isolated from cryosections or from peripheral blood and genotyping for HLA-DR shared epitopes (SE) allotypes was performed using sequence specific-primer-PCR.

Results: The combination of AHR and CYP1A1 gene expression in synovial membrane distinguishes patients with RA who continue to smoke. CYP1A1 protein was observed in synovia obtained from smokers. Cell-specific markers conﬁrmed both AHR and CYP1A1 were produced by CMRF56+ dendritic cells (DC) and CD3+ T lymphocytes in synovia from smokers. CD20+ B cells, CD14+ monocytes/macrophages CMRF44+ DCs did not produce either AHR or CYP1A1 protein. No CYP1A1 protein expression was detected in synovial tissues from non-smokers. Synovia obtained from RA patients who smoked and carried a single or double copies of SE genes were largely positive for CYP1A1 gene expression. By comparison CYP1A1 was mainly expressed in nodule tissues from patients who were non-smokers but who carried double copies of SE genes.

Conclusions: Our results show that in rheumatoid synovial tissue, dendritic cells are armed and responsive to the components of cigarette smoke. A subset of T cells is also capable of responding. The response requires continued smoking as CYP1A1 expression, reflecting AHR activation, ceases within months of smoking cessation. The AHR-mediated response to smoking in synovial tissue is heightened in individuals who smoke requiring only a single copy of the HLA-DR shared epitope. This may reflect an increased sensitivity/activity of participating dendritic cells.

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1253

DNA Methylation Affects Gene Expression in CD4+CD28- T Cells through microRNAs. Dipak R. Patel, Anura Hewagama, Sushma Yarlagadda and Bruce C. Richardson, University of Michigan, Ann Arbor, MI.

CD4+CD28- T cells are enriched in multiple autoimmune diseases such as rheumatoid arthritis. These cells are capable of enhanced cytotoxicity, and they are more resistant to apoptosis. Extra-articular disease manifestations and disease severity positively correlate with the relative abundance of these cells. Compared to their CD28+ counterparts, CD28- CD4+ T cells over-express CD70 and other molecules that potentially contribute to their phenotype. Hypomethylation of the DNA in these genes’ regulatory elements expresses their aberrant expression. Recently, changes in DNA methylation have been shown to affect microRNA (miRNA) expression. MicroRNAs are small non-coding RNA molecules that block the translation of messenger RNAs (mRNAs). The role of miRNAs in regulating gene expression in CD4+CD28- T cells is unknown.

We investigated the role of miRNAs in CD4+CD28- T cell gene expression. CD28+ and CD28- CD4+ T cells were generated by chronic re-stimulation in vitro. Peripheral blood mononuclear cells were stimulated overnight with phytohaemagglutinin. CD4+ T cells were then isolated by negative selection, and they were re-stimulated weekly with irradiated antigen presenting cells and IL-2. CD28+ and CD28- CD4+ T cells were separated by flow cytoometry after 4–6 weeks of culture. Total RNA, including the miRNA fraction, was then isolated (Qiagen). Expression of miRNAs in each population was compared using a quantitative real-time PCR kit (Systems Biosciences).

In four sets of chronically re-stimulated cell cultures, we found five miRNAs that are over-expressed at least 1.5 fold in CD4+CD28- T cells, compared to their CD4+CD28+ counterparts. Another four miRNAs were over-expressed in all four cultures, though the 1.5 fold threshold was exceeded in only three of the four cultures. Online tools, including TargetScan and miRanda, were used to predict potential interactions between these mRNAs and miRNAs. Two of the five miRNAs over-expressed in CD4+CD28- T cells did not have any predicted mRNA targets. The remaining three of five miRNAs over-expressed in CD4+CD28- T cells were predicted to interact with miRNAs encoding proteins that are required for DNA methylation and cytokine signaling.

Overall, these experiments identified several miRNAs that are over-expressed in CD4+CD28- T cells. These miRNAs potentially interact with genes encoding proteins required for DNA methylation. If miRNAs targeting DNA methylation are over-expressed, hypomethylation and over-expression of genes causing T cell activity could result. This could explain the increased disease severity seen when CD4+CD28- T cells are abundant in RA. The miRNAs we have identified could then be potential therapeutic targets.

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1254

Dys-Regulation of T-Cell Subsets and Cytokines Is Associated with the Development of Inflammatory Symptoms in ACPA-Positive Asymptomatic Individual. Richard J. Cuthbert1, Rekha Parmar2, Jackie Nam3, Edith Villeneuve4, Diane Corscadden5, Karen Henshaw2, Paul Emery6 and Frederique Ponche1. 1Chapel Allerton Hospital, Leeds, United Kingdom, 2University of Leeds, Leeds, UK

Background: We reported that T-cell subset dys-regulation can predict evolution towards rheumatoid arthritis (RA) from early symptoms, response to treatment in early disease as well as relapse in patients who achieved clinical remission. Naïve cells were the most informative circulating T-cells subset in early disease. Cytokine activated T-cells (IRC) were less informative as systemic inflammation is low in early disease. Asymptomatic ACPA-positive individual are at high risk of developing RA. The aim of the current study is to determine whether T-cell subset and cytokine analysis can predict future development of inflammatory symptoms in this group.

Methods: 35 asymptomatic ACPA+ individuals were enrolled; they were recruited if they had new onset musculoskeletal pain but no synovitis on clinical examination. 6 colour flowcytometry was performed using standard protocols. 36 healthy controls were used to build the age relationship with naïve cell frequency. ELISA were used to measure cytokines and chemokines.

Results: 35 individuals were recruited and followed for 12 months. There was clear difference at baseline between ACPA+ individuals and controls for...
naive (P<0.0001), CD25hiFoxp3+ Treg (P=0.020) and CD62L+ Treg (P=0.001). IRC were not increased in asymptomatic individuals. During follow-up, 6 individuals were diagnosed with undifferentiated arthritis (UA). 6 with RA, 9 with non-inflammatory osteoarthritis or connective tissue disease and 16 remained with non-specific musculoskeletal symptoms or arthralgia. Analysis based on follow-up showed reduced naive T-cell (P=0.007) and Treg (P=0.090) in arthralgia and CD62L+ Treg frequency were increased (P<0.0001). In the group developing IA, naive cells were reduced (P<0.0001) but Treg were not different from controls. CD62L+ Treg in contrast were significantly reduced (P=0.025). All OA/CTD individuals were close to controls. Furthermore, OA/CTD patients compared to the age-naïve frequency relationship in controls were above normal, the arthralgia group was close to controls and IA patients below. Serum levels of IL-12 and IL-7 cytokines differed in arthralgia individuals compared to controls (P<0.0001) but MIP-1α levels were not raised. On follow-up reduced IL-12 (P=0.007) and IL-7 (P=0.019) were observed in the arthralgia group. In the group developing IA, IL-12 (P<0.0001) and IL-7 (P=0.006) were even more reduced and MIP-1αpha raised (P=0.018). In OA/CTD individuals, only IL-12 levels were reduced (P<0.001).

**Conclusion:** In ACPA+ asymptomatic individuals, the future development of inflammatory symptom appears clearly associated with abnormal immunological parameters at baseline. Furthermore, data suggest that Treg’s involvement may be in the true pre-clinical phase and this battle is lost by the time symptoms develop. More work is needed to determine if loss of naïve cells is a cause or a consequence of this dys-regulation on T-cells, however, loss of CD62L+ Treg suggests a role for the thymus.

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**1255**

Expression of K5.1 Potassium Channels on CD4+ T Lymphocytes Correlates with Disease Activity in Rheumatoid Arthritis Patients.

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**Background:** CD4+ T cells express K5.1 (TASK2; KCNK5), a member of the two-pore domain potassium channel family, which has been shown to influence T cell effector functions. Recently, it could be shown that K5.1 is upregulated upon T cell stimulation. In addition, it has been shown that expression levels of this channel are strongly increased on CD8+ T lymphocytes from the peripheral blood from clinically active relapsing-remitting multiple sclerosis (MS) patients. The aim of this study was to analyze the expression of K5.1 on T cells in patients with rheumatoid arthritis (RA).

**Methods:** Expression levels of K5.1 were measured by RT-PCR in CD4+ and CD8+ T cells in the peripheral blood of 58 patients with RA and correlated with disease activity parameters (C-reactive protein levels, erythrocyte sedimentation rates, DAS28 scores). In a prospective study 20 patients were followed up for 6 months after changing DMARD therapy due to high disease activity. Additionally, synovial fluid was investigated for T lymphocytes expressing K5.1.

**Results:** K5.1 expression in contrast to MS is elevated in active RA only in CD4+ T cells in the periphery. Comparing synovial fluid and PBL, K5.1 expression levels of synovial fluid derived T cells are higher for both RNA level and protein level. In the cross-sectional study K5.1 expression levels in CD4+ T cells show a strong correlation to DAS-28 scores in RA patients (r=0.63). The correlation for serologic markers were r=0.39 for ESR, r=0.28 for CRP. In patients followed prospectively after a change of DMARD therapy for up to 6 months K5.1 expression levels in CD4 + T cells follow nicely the individual clinical response.

**Conclusion:** Disease activity in RA patients correlates strongly with K5.1 expression levels in CD4+ T lymphocytes in the peripheral blood in cross-sectional as well as in prospective, longitudinal observations. Further studies are needed to investigate the exact pathophysiological mechanisms and to evaluate the further use of K5.1 as a potential biomarker for disease activity in RA.

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**1256**

Fopx3+ CD4+ Tregs Prevent Arthritis by Promoting Clonal Anergy Induction in Self Ag-Specific CD4+ T Cells.

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Using a mouse model of self Ag recognition by naive CD4+ T cells, we have investigated the peripheral self tolerance mechanism that prevents the development of autoimmune arthritis in most individuals. As previously reported, an adoptive transfer of glucose 6-phosphate isomerase (GPI)-specific naïve KRN TCR-transgenic CD4+ T cells into lymphopenic TCRalphachain-deficient mice that naturally express GPI-A/B complexes led to an intense clonal expansion, the production of anti-GPI IgG1 autoantibody, and the development of severe polyarticular arthritis. Recognition of GPI-A/B in normal hosts, however, failed to elicit autoimmune disease, and instead was sufficient to stimulate only an abortive KRN CD4+ T cell clonal expansion and the induction of clonal anergy. Anergic KRN CD4+ T cells demonstrated a reduced proliferative responsiveness to Ag stimulation, the inhibition of IL-2, TNF-alpha, and IFN-gamma synthesis, and high-level expression of CD73 and Folate receptor 4 (FR4). Reconstitution of the T cell-deficient hosts with enriched CD25+Foxp3+ CD4+ T cells was sufficient to promote the induction of KRN T cell clonal anergy and prevent the development of arthritis. More importantly, use of diphtheria toxin to selectively eliminate Foxp3-expressing cells from T cell-deficient hosts that had been reconstituted with polyclonal CD4+ T cells from Foxp3-GFP-diphtheria toxin receptor transgenic mice, prevented the development of clonal anergy in the transferred naïve KRN CD4+ T cells, and led to their induction of autoimmune arthritis. These data suggest that during the initial encounter of naïve CD4+ T cells with peripheral self Ag, CD25+ Foxp3+ T regulatory cells ensure that clonal anergy will be induced early during clonal expansion, and autoimmune arthritis can be avoided. Individuals deficient in Foxp3+ T regulatory cell activity or number are prone to autoimmune arthritis as a consequence of euribivalent self Ag-specific CD4+ T cell clonal expansion and differentiation, and the provision of pathological helper activity that leads to a breakdown of self tolerance in the B cell compartment.

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**1257**

Gender and Sex Hormones Influence CD4+ Regulatory T Cells and Their Expression of Foxp3 in Healthy People and in SLE.

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**Purpose:** The goal of the present study was to determine the role of gender and the effect of sex hormones on the regulation of Foxp3 gene in healthy individuals and in patients with SLE.

**Methods:** Levels of sex hormones (17 b-estradiol, testosterone, cytokines, and chemokines were measured by ELISA in the serum/plasma of healthy donors and from the culture supernatant of peripheral blood mononuclear cells (PBMC) isolated from SLE patients and healthy controls. PBMC were immunophenotyped by flow cytometry, and mRNA gene expression was analyzed by intracellular staining and by Western blot analysis. The in vitro effect of sex hormones 17 b-estradiol (60–100, 500pg/ml), and testosterone (100pg/ml) were studied by culturing sorted CD4+ CD25hiCD127lo regulatory T cells for 24–72 hours followed by FACS/Western blot analyses.

**Results:** 1- The numbers of CD4+ CD25hiFoxp3+ and of CD8+ Foxp3+ regulatory T cells are significantly decreased in healthy females compared to healthy males (p<0.01). 2- Both CD4+CD25hi and CD8+CD25hi subsets of healthy males had 3-4 fold higher Foxp3 mRNA compared to healthy females. 3- Plasma 17b-estradiol levels are significantly increased in female SLE patients compared to healthy females (p<0.01).

**4-** The addition of 17 b-estradiol (physiologic cycling luteal phase concentrations of 60 pg/ml) for 24 hours to cultured PBMC from healthy women (but not men) increased the total numbers of cells expressing CD4, CD25 and Foxp3. These effects were not seen in cells in women with SLE. 5- Incubation of CD4+ regulatory T cells with 100 pg/ml of 17b-estradiol maintained Foxp3 expression in SLE women, in contrast to the usual increase in CD4+ Treg that occurs in healthy women at this concentration.
6-Testosterone (100 pg/ml) significantly increased FoxP3 expression in CD4+CD25hi cells from women with SLE. In fact, plasma concentrations of testosterone in those women correlated positively with the expression of FoxP3 in their CD4+CD25+ T cells (p < 0.04).

**Conclusions:** Women may be more susceptible than men to SLE and other autoimmune diseases in part because many healthy women have fewer regulatory T cells and less FoxP3 expression in those cells. In addition, women with SLE, compared to healthy women, seem to have less ability to generate CD4+ Treg in response to physiologic concentrations of 17 β-estradiol, whereas the testosterone metabolite increases the generation of Tregs. These data suggest that gender and sex hormones may influence susceptibility to SLE via their effects on regulatory T cells.

**Disclosure:** R. K. Dinesh: None; B. H. Hahn: None; R. P. Singh: None.

**1258**


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**Purpose:** The purpose of this study was to identify the T cell receptor (TCR) of autoantibody-inducing CD4+ T (αCD4+ T) cell that induces autoantibodies in naïve recipients with 100% efficiency upon transfer.

**Methods:** BALB/c mice were repeatedly injected i.p. with 25mg staphylococcal enterotoxin B (SEB) or PBS every 5 days and serum IgG of the recipients received a single i.p. injection of 25mg SEB 24 h after cell transfer and sera was studied 2 weeks afterwards. Statistical analyses were performed using Student’s t test and the correlation coefficient r was calculated.

**Results:** SEB-reactive Vβ8’CD4+ T cell was significantly decreased in the mice immunized 12x with SEB as compared with PBS (17.4% vs. 21.2%, P<0.001), probably due to clonal deletion because of anergy induction in the SEB-reactive T cell after 2x immunization with SEB. However, in these mice immunized 12x with SEB, the level of RF was positively correlated to the frequency of splenic Vβ8’CD4+ T cell (r=0.83, P<0.05), indicating that once-energized T cell re-proliferated and simultaneously produced RF. We then transferred either Vβ8’CD4+ T cell or Vβ8’CD4+ T cell from the mice immunized 12x with SEB into naïve mice. We found that Vβ8’CD4+ T cell, but not Vβ8’CD4+ T cell, induced RF (P<0.001), indicating that antigen-reactive CD4+ T cell acquires the ability to induce autoantibodies. Further analyses showed that, among series of Vα chains in the Vβ8’CD4+ T cell, a positive correlation existed between the selection of Vα13 chain and the level of RF (r=0.87, P<0.05), strongly suggesting that CD4+ T cell with Vβ8’Vα13’ TCR induces RF.

**Conclusion:** We have tried to identify the TCR of αCD4+ T cell that induces autoantibodies in naïve recipients with 100% efficiency upon transfer, and identified that Vβ8’Vα13’ TCR is its candidate.

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**1259**

IL-23 Suppresses IL-22 Levels and AHR Expression in Human CCR6+ Memory T Cells. Jerry Cornelliss, Jan Piet van Hamburg, Nadine Davelaar, Patrick Asmawidjaja, Anne-Marie Mus and Erik Lubberts. Erasmus MC, University Medical Center

**Background:** Human CCR6+ T helper (Th) cells were shown to preferentially express the cytokines IL-17A and IL-22 (1). Recently, it became clear that within the CCR6+ Th cell population, cells are present which exclusively expressed IL-22 (2, 3). Although IL-23 and IL-1b are involved in the differentiation of naïve T cells towards effector CCR6+ Th cells (4), their role in the regulation of IL-17A and IL-22 expression by effector CCR6+ Th cells is unknown.

**Objective:** To investigate the role of IL-23 and IL-1b on the expression of Th17 specific cytokines by human memory CCR6+ Th cells.

**Methods:** CD4+CD45RO+CCR6+ T cells were FACS sorted from PBMC obtained from healthy individuals. These cells were cultured in the absence or presence of IL-23, IL-1b or the combination of IL-23+IL-1b. After culture, intracellular cytokine stainings for IL-17A, IL-22, and IFN-gamma were analyzed by flow cytometry. Cytokine levels of IL-17A, IL-22, and IFN-gamma were determined in the supernatant by enzyme-linked immunosorbant assay (ELISA). Semi-Quantitative RT-PCR was performed to analyze gene transcription of genes involved in Th differentiation and function.

**Results:** IL-23 had no effect on the percentage of IL-17-positive and IFN-gamma-positive cells. However, IL-23 in contrast to IL-1b significantly decreased the percentage of IL-22-positive memory T cells. This was mainly due to a significant reduction in the proportion of IL-22+/IL-17A- and IL-22+/IFN-gamma- T cells. In line with this, significantly lower IL-22 levels were found in the supernatant of CCR6+ T cells incubated with IL-23 and significantly lower expression of the transcription factor aryl-hydrocarbon receptor (AhR) in these cells. In contrast to IL-23, IL-1b increased the percentage of IL-17A-positive and IFN-gamma-positive CCR6+ T cells. However, the combination of IL-23/IL-1b significantly and specifically increased the percentage of IL-17A+/IL-22- and IL-17A+/IFN-gamma- compared to IL-1b alone, although the suppressive effect on IL-22-positive cells was not increased by this combination compared to IL-23 alone. Significant higher levels of IL-17A but also IFN-gamma were detected after incubation with IL-23/IL-1b compared to IL-1b alone. This latter may be due to an increase in IL-17A+/IFN-gamma- double positive CCR6+ memory T cells by IL-23/IL-1b.

**Conclusion:** These data revealed that IL-23 specifically suppresses a Th2-like phenotype in CCR6+ memory T cells resulting in lower IL-22 levels and reduced AhR expression. Adding IL-1b to IL-23 resulted in a specific increase of a Th17/IL-17A-like phenotype in CCR6+ memory T cells resulting in higher levels of IL-17A. However, the total IFN-gamma level was increased by IL-23/IL-1b as well. These data suggest an important role for combination in IL-23 with IL-1b in the regulation of human IL-17-positive and IL-22-positive memory T helper cells.

**References:**

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**1260**

IL-23-Mediated RORγt Pathway Is Associated with Thymic Negative Selection of Autoreactive T Cells. Hao Li2, Hui-Chen Hsu2, Qi Wu3, PingAr Yang2, Jun Li2 and John D. Mountz1. 1Univ Alabama at Birmingham, AL, 2Univ Alabama at Birmingham, AL, 3Univ Alabama at Birmingham, AL

**Background:** BD2 mice develop erosive arthritis and high levels of autoantibodies. Spontaneously increased TγC17 cells and IL-23 production by follicular dendritic cells have been found in the periphery of BD2 mice. Since ROR gamma t (RORγt), the transcription factor downstream of IL-23, is expressed by CD4+CD8+ double positive (DP) thymocytes, we determined if IL-23 can regulate thymocyte selection via the RORγt pathway and if dysregulation of this pathway can be found in BD2 thymus.

**Methods:** Thymii from B6, DB/H-Y TCR transgenic (Tg), and BD2 mice were analyzed. FACS analysis was carried out to determine the expression of IL-23R and RORγt in subsets of thymocytes. TUNEL staining was carried out to determine apoptotic thymocytes. Subpopulations of different thymic cells were FACS sorted for qRT-PCR assay to determine the expression of IL23, IL23r and Rorc. In vivo overexpression of IL-23 was achieved by injection of mice with AdIL-23 using AdLa2 cz as the control (2 x 105 pfu/mouse, tail IV).

**Results:** DB/H-Y Tg mice treated with an anti-IL-23 antibody exhibited a defect in thymic negative selection of H-Y specific T cells in male mice and
an increased proliferative response of self reactive spleen T cells to the H-Y antigen. AdIL-23 but not AdLacZ, injection to B6 mice lead to increased apoptosis (12.0±1.7% vs 1.4±0.3%) and a massive reduction of DP thymocytes (18±3×10^3 vs 4±1×10^3) at day 5. This AdIL-23-induced thymocyte apoptosis response was partially prevented in RORγt^-/- mice. Consistent with this, there was dramatically increased expression of IL-23R (24± vs 1%) and RORγt (15± vs 2%) in DP thymocytes of AdIL-23 vs AdLacZ injected mice at day 6. Autoimmune BXD2 mice exhibited upregulation of IL-23R on DP thymocytes and down-regulation of IL-23 production by thymic CD11c^-/d dendritic cells compared with those in normal B6 mice. Consistent with this, there was lower IL-23 signaling in vivo indicated by a lower expression of RORγt in BXD2 thymocytes compared with B6 thymocytes at both the protein and the transcriptional levels. Administration of AdIL-23 resulted in upregulation of RORγt, leading to a 4-fold increase in apoptosis of DP thymocytes in BXD2 mice (20%) compared with that in B6 mice (5%) at day 3. Interestingly, CD4 single positive thymocytes in BXD2, but not B6 mice, failed to down-regulate IL-23.

Conclusions: Our results reveal a novel function of IL-23 in that IL-23 can regulate thymocyte negative selection of autoreactive T cells via the RORγt pathway. The IL-23-mediated DP thymocyte apoptosis may be deficient in BXD2 mice, leading to the generation of autoreactive T cells. This is significant since it suggests that although IL-23 has a pro-autoimmune effect in the periphery, it has an opposite action in the thymus to prevent development of self-reactive T cells.

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Immunoregulation by Peripheral Suppressor T Cells Induced upon Homotypic T Cell Interaction. Katja Thuemmler1, Leipe Jan2, Andreas Ramming3, Hendrik Schulze-Koops4 and Alla Skapenko5. 1Division of Rheumatology, LMU Munich, Germany, 2LMU Munich, Germany

The mechanisms by which regulatory T cells are generated in the periphery are incompletely understood. Interestingly, CD4 T cells up-regulate the expression of surface receptors specific for antigen-presenting cells during activation. The appropriate ligands of these receptors are physiologically expressed on resting CD4 T cells. Here, we tested the hypothesis, that activated T cells may interact with resting T cells and that this interaction results in the differentiation of the latter.

CD4 memory T cells (responders) were cultured together with activated stimulator T cells. After five days of co-culture the phenotype and function of the T cells resulting from the responder cells was analyzed both in vitro and in vivo. The mechanisms underlying this homotypic T cell interaction were determined in co-cultures of activators and stimulators in the presence or absence of neutralizing antibodies to surface receptors.

Activated stimulator T cells induced proliferation and production of various cytokines in the responder T cells. Whereas Th1 stimulator T cells promoted the development of IL-10 and IFNγ producing cells, T cells cultured with Th2 cells produced IL-4. T cells induced upon homotypic T cell interaction expressed CD25 and reduced levels of CD127, and produced TGFβ. T-T cell communication is both, anchored and tuned through interaction of LFA-1 and its ligands ICAM-1, ICAM-2 and ICAM-3. Blocking of ICAM-1 diminished IFNγ production, whereas ICAM-3 was important for IL-4 secretion. Functionally, homotypic T cell interaction-induced T cells were anergic and inhibited the proliferation of CD25 negative T cells as potently as natural occurring CD25 Tregs in vivo. The inhibitory effect was partly contact dependent and partly dependent on IL-10 secreted after T cell interaction. Moreover, in vitro generated T-T cell induced T cells with a TCR specific for OVA prevented clonotypic expansion of OVA TCR transgenic T cells in BALB/c mice upon antigen challenge in vivo. Together, the data suggest a negative feedback mechanism of specific immunity involving bystander-activated memory T cells.

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Late Complement Complex in T Cell Function and Cell Death. Anil Chauhan1, John P. Atkinson2 and Terry L. Moore3. 1Saint Louis University, 2St Louis University, St Louis, MO, 3Washington University School of Medicine, St Louis, MO

Purpose: Recently, complement systems role in T cell modulation has been suggested. Excessive complement activation results in cell death due to the formation of membrane attack complex (MAC). Lysis of nucleated cells by MAC is explained by the “multi hit hypothesis” that suggests formation of a large number of holes. We tested this hypothesis in human naive CD4^+ T cells by in situ assembly of MAC using purified C5b-6, C7, C8 and C9. Scanning electron microscopy (SEM) and confocal imaging revealed formation of MAC on a single site. Thus, we hypothesized that due to strong affinity of C9 for membrane phospholipids, sublytic MAC deposition resulted in reorganization of the T cell membrane. This resulted in the formation of a functional ‘IS’ synapse-like structure by lateral clustering of membrane rafts (MR). Thus, we explored the role of the structure formed by MAC in T cell physiology such as calcium channels, cell activation, proliferation and death.

Methods: MAC was assembled on human CD4^+ T cells by treating with equimolar ratio of purified late complement proteins along with fifteen molar excess of Alexa 594 labeled C9 protein. These cells were then examined for alteration in membrane structures by confocal and SEM. MR in these cells were localized using chola toxin B-FITC. Cell proliferation was studied with CFSC labeling and T cell activation by traditional methods. Calcium mobilization was examined using Fura-2 dye.

Results & Conclusions: Unlike present belief of multiple MAC generated holes in erythrocytes, in human T cells, MAC deposited on a single site. The SEM images showed a single hole surrounded by dense structures (A). These structures were also seen in confocal images (B).

The site of MAC was also the site of MR accumulation and formation of synapse-like structures. Signaling protein microclusters accumulated at this site and were phosphorylated. Such structures are also implicated in the function of NK cells. Sublytic doses of MAC trigger a number of events such as DNA synthesis, upregulation of cell cycle associated cyclins, CDK2, growth factors and proto-oncogenes such as NF-kB, c-jun, c-fos, jun-D, and protein kinase C. We have shown that in T cells these structures may participate in activation of the T cell receptor in the presence of immune complexes. However, in lytic doses of MAC, these structures that support cell function result in collapse of cell integrity, thus lysing the cell. Thus, we propose that ICs and MAC participate in the outcome of T cell differentiation by triggering and enhancing T cell activation. Complement activation and altered T signaling are observed in SLE. Here we link immune reactants observed in disease to the cells of adaptive immunity. Better understanding of these processes will allow us to delineate the disease process and design better therapeutic interventions.

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Linking Power Doppler Ultrasound with Th17 Cells in the RA Joint. Nicola J. Gullick1, Hayley G. Evans2, Leigh Church3, David Jayaraj2, Andrew Filer1, Bruce W. Kirkham1 and Leonie S. Taams1. 1CMCBI, King’s College London, London, United Kingdom, 2CMCBI, King’s College London, Rheumatology Research Group, University of Birmingham, 3Rheumatology, Guy’s & St Thomas’ NHS Foundation Trust

Introduction: Power Doppler ultrasound (PDUS) is increasingly used to assess synovitis in Rheumatoid Arthritis (RA). Prior studies have shown correlations between PDUS scores and vessel counts, but relationships with immunopathology have not been described. This study investigated the presence of Th1, Th17 and TNFα producing CD4^+ T cells in peripheral blood (PB), synovial fluid (SF) and synovial tissue (ST) from RA patients and related these data to PDUS scores of either single or multiple joints.

Methods: PB mononuclear cells were isolated from healthy controls or RA patients and stimulated with PMA and ionomycin for 3 hours in the
presence of Golgistop. Paired SF were analysed where available (n = 21). ST was obtained at arthroscopic synovial biopsy from six RA patients. Synovial blood flow was evaluated by power Doppler (PD) signal at 10 metacarpophalangeal (MCP) joints, wrists and knee joints. PD signals were graded on a semi-quantitative scale from 0 to 3 (where 0 = no synovial flow; 1 < 25% signal within ST; 2 = 25–50% signal; 3 >50% signal). Intracellular expression of IL17, IFNy, and TNFa was determined by multicolour flow cytometry. Serum, SF and fibroblast culture levels of vascular endothelial derived growth factor-A (VEGF-A) were assessed by ELISA.

**Results:** Th17 cells and dual IFNy+IL-17-expressing cells but not Th1 cells are increased in PB of RA patients vs. healthy controls. These cells are further enriched in both SF and ST relative to PB. The percentage of PB Th17 cells did not correlate with systemic parameters of disease. The percentage of Th17 cells, but not Th1 cells, in SF positively correlated with CRP (r = 0.51, p = 0.03) and local PDUS-defined synovitis (r = 0.62, p = 0.003), suggesting a specific role for Th17 cells in active synovitis in RA. Patients with high levels of IL-17+ CD4+ T cells in SF displayed increased levels of vascular endothelial growth factor-A (VEGF-A) in SF; this was not observed for IFNy+ T cells. The addition of IL-17 but not IFNy increased VEGF-A production by RA synovial fibroblasts in vitro.

**Conclusion:** Our data demonstrate a link between the presence of highly inflammatory Th17 cells and RA disease activity assessed by PDUS scores, and offer a novel immunological explanation for the clinical observation that rapid joint damage progression occurs in patients with persistent positive PDUS signal. Furthermore, our findings highlight PDUS as a possible surrogate marker of Th17 cells, which may identify patients who would benefit from early, aggressive therapy, including IL-17 antagonists.

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### 1264

**NKT Cell Is Required for the Break of T Cell Anergy, Inducing Autoantibody, and Generation of Autoantibody-Inducing CD4+ T Cell That Causes Systemic Autoimmunity.** Yoko Fujita1, Ken Tsuniyama2 and Shinichi Shiozawa3. 1Department of Biophysics, Kobe University Graduate School of Health Science, Kobe, Japan, 2Department of Biophysics, Kobe University Graduate School of Health Science, Kobe, Japan, 3Department of Biophysics, Kobe University Graduate School of Health Science/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

**Objective:** With regards to how autoantibody-inducing CD4+ T (orCD4+) T cell is induced, which is the key as the cause of systemic autoimmunity including SLE, we consider the recovery from anergy as the essential step in generating orCD4+ T cell. Here, we studied the contribution of NKT cell to the break of anergy, induction of autoantibodies, and generation of orCD4+ T cell.

**Methods:** BALB/c mice were repeatedly immunized with staphylococcal enterotoxin B (SEB), staphylococcal enterotoxin A (SEA) and/or a-galactosylceramide (a-GC). SEB stimulates NKT cell and T cells, whereas SEA stimulates only T cells. Mice were also immunized 2x with SEB to induce T cell anergy, and then repeatedly immunized with a-GC. Further, spleen cells of naïve BALB/c mice were stimulated with a-GC in vitro, and supernatant from a-GC-activated NKT cells herein termed NKT-sup. This NKT-sup was repeatedly immunized in CD1d KO mice, following immunization 2x with SEB to induce T cell anergy. Spleen cells were stimulated in vitro with SEB, and IL-2 and mitotic events were measured. Autoantibodies, phoshorylation of ZAP70, LAT, Akt, the expression of Cbl-b and Ca2+ influx in T cell were examined.

**Results:** The T cells of the mice immunized 2x with SEB were rendered into anergy. However, after further immunization 8x with SEB, this once-anergized T cells were re-activated from anergy to resume IL-2 production and proliferation. This re-activation was accompanied by induction of RF and anti-Sm antibody in 100% of mice, and this property can be transferred by CD4+ T cells into naïve recipients, thereby orCD4+ T cells are generated. Phosphorylation of ZAP70, LAT and Akt and Ca2+ influx were inhibited in anergic T cells of the mice immunized 2x with SEB as compared with PBS-immunized control. However, this inhibition was released after immunization 8x with SEB. Further, expression of Cbl-b, an anergy-inducible protein, was increased in the T cell of mice immunized 2x with SEB. The Cbl-b was subsequently down-regulated after further immunization 8x with SEB. As to the contribution of NKT cell to the break of T cell anergy and the generation of orCD4+ T cell, we found that spleen cells of mice immunized 8x with SEA neither induced RF nor secreted IL-2 because SEA did not activate NKT cell. When a-GC, a specific ligand for NKT cell, was co-immunized 8x with SEA, the once-anergized T cell was recovered from anergy and begun to secrete IL-2 and RF and resume proliferation. Sole 2x immunization with SEB followed by 8x immunization with a-GC was also sufficient for the break of T cell anergy and induction of RF. Further, the once-anergized T cells of CD1d KO mice lacking NKT cells could be recovered from anergy after 2x immunization with SEB followed by 8x treatment with the NKT-sup, a supramutant of a-GC-activated NKT cells. These results indicate that the NKT cells and its effector molecule can break T cell anergy and induce autoantibodies, finally leading to the induction of orCD4+ T cells.

**Conclusion:** We show that the activation of NKT cell is indispensable for the re-activation of once-anergized T cell and the induction of autoantibodies, finally leading to the generation of orCD4+ T cell that causes systemic autoimmunity.

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### 1265

**Peroxisome Proliferator-Activated Receptor α and γ Agonists Together with TGF-β Convert Human CD4+CD25+ T Cells into Functional Foxp3+ Regulatory T Cells.** Hitoshi Hasegawa1, Jin Le2, Takuya Matsumoto2 and Masaki Yaskuwada1. 1Ehime University Graduate School of Medicine, Toon, Ehime, Japan, 2Ehime University Graduate School of Medicine

**Background:** Regulatory T cells (Treg) play a crucial role in the prevention of autoimmune diseases. Human peripheral CD4+CD25+ T cells can be induced to express Foxp3 after TCR activation in the presence of TGF-β, but the induced cells (iTreg) lack a regulatory phenotype. Human T cells require multiple stimulations to become a regulatory phenotype. Moreover, induction of functional human Treg cells would have therapeutic implications. Therefore, we screened molecules that would enhance the TGF-β-induced conversion of human CD4+CD25+ T cells into functional Treg cells.

**Methods:** We obtained three peroxisome proliferator-activated receptor (PPAR) agonists (bezafibrate, GW7647, and 5,8,11,14-eicosatetraenoic acid) and two PPARγ agonists ( ciglitazone and 15-deoxy-prostaglandin L1) as molecules that increased Foxp3 expression in human iTreg cells from lipid and nuclear receptor ligand libraries. We analyzed the mechanism by which human CD4+CD25+ T cells are converted to functional Treg cells by PPARα and PPARγ agonists together with TGF-β.

**Summary of the Results:** These PPARα and PPARγ agonist-treated iTreg cells maintained a high level of Foxp3 expression and had suppressive properties. There were no significant differences in the suppressive properties of iTreg cells treated with the three PPARα and two PPARγ agonists, and all of them made iTreg cells increased DNA demethylation levels of the Foxp3 promoter and intronic CNS3 regions significantly compared with the control iTreg cells. Furthermore, both PPARα and PPARγ agonists together with TGF-β inhibited more strongly the expression of all three DNA methyltransferases (DNMTs), DNMT1, DNMT3a, and DNMT3b, in activated CD4+ T cells. These results demonstrate that PPARα and PPARγ agonists together with TGF-β elicit Foxp3 DNA demethylation through potent down-regulation of DNMTs and induce potent and stable Foxp3 expression, resulting in the generation of functional iTreg cells. In control, there are no differences of cytokine productions such as IL-10 and TGF-β between control and PPAR agonist-treated T cells. PPARα produced retinoic acid (RA) in human blood monocyte-derived DCs. Addition of PPARγ agonist in the presence of TGF-β may generate antigen-specific Treg cells such as ANCA-associated vasculitis more efficiently upon coculture with antigen-pulsed DC through a RA-dependent mechanism and epigenetic regulation of the Foxp3 gene.

**Conclusions:** PPAR agonists converted human CD4+CD25+ T cells into functional Foxp3+ regulatory T cells and may be beneficial for the treatment of human autoimmune diseases.

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Phenotype and Functional Stability of TGF-β-Induced CD4⁺Foxp3⁺ Regulatory T Cells in Steady and Inflammatory States. Ning Kong¹, Julie Wang², David Brand³, Hejian Zou¹, Xuehong Yu¹ and Song Guo Zheng¹. ¹Fudan University Medical School, ²H. Lee Moffitt Cancer Center and Research Institute, ³USC Keck School of Medicine, ⁴VA Medical Center, Memphis.

Background: Although both natural CD4⁺Foxp3⁺ regulatory T cells (nTregs) and TGF-β-induced CD4⁺Foxp3⁺ regulatory T cells (iTregs) share many similar phenotypes and biological activities in the prevention of autoimmune diseases, recent studies from several groups observed that Foxp3 expression by iTregs is unstable and adoptive transfer of these cells had poorly therapeutic effect on acute GVHD model in animal although these cells prevented and even treated other autoimmune diseases in animal models. Here we try to determine the phenotype and functional characteristics of iTregs in the steady and inflammatory states.

Methods: iTregs were induced from naive CD4⁺ cells with IL-2, TGF-β and anti-CD3/CD28 beads or plate-bound anti-CD3 and soluble anti-CD28 antibodies. nTregs were isolated from splenocytes of foxp3-GFP knock in mice and expanded with IL-2 and anti-CD3/CD28 beads. 0.5×10⁶ both Tregs were transferred to SCID mice. The mice were sacrificed in one and two months after adoptively transfer. 5×10⁶ Tregs from DBA/1J mice labeled with CFSE were adaptively transferred to normal or established collagen induced arthritis (CIA) mice and the mice were sacrificed in one, three and six weeks for monitoring donor Treg fates.

Results: Both Tregs had the same level of Foxp3 expression (near to 50%) in one and two months after cell transfer. In addition, both Treg subsets maintain the similar levels of Foxp3 expression (about 40%) in one month after transfer to naive mice. Both nTregs and iTregs donor cells sorted from recipient mice in three weeks after transfer displayed the similar suppressive activities. We observed that suboptimal TCR stimulation was required for the maintenance of Foxp3 expression by iTregs. Of great interest, nTregs but not iTregs in the spleens, particularly in draining lymph nodes mostly lost Foxp3 expression only one week after cell transfer to established arthritis mice. Conversely, iTregs not only maintained Foxp3 expression but also induced more Foxp3⁺ cells in recipient mice compared to CIA mice and iTregs received nTregs. We further observed that adoptive transfer of iTregs but not nTregs significantly suppressed the progression of the established arthritis.

Conclusions: iTregs are as stable as nTregs in immune deficient and normal states, and are more stable and functional than nTregs in an inflammatory milieu. We therefore conclude that manipulation of iTregs may have an advantage to treat the autoimmune diseases and inflammatory diseases.

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Plasmacytoid Dendritic Cells Control Peripheral Treg Conversion to the RNA-Binding Nuclear Self Antigen La/SS-B. A. Darise Farris¹, Christina Lawrence² and Zi-jiian Pan³. ¹Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, ²Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background: RNA-binding nuclear antigens are a major class of autoantigen targeted in systemic autoimmune diseases. Serologic tolerance to the RNA binding antigen human La/SS-B (hLa) is controlled primarily by CD4⁺ T cells in transgenic (Tg) mice expressing hLa gene under its natural promoter. The goal of the present study was to uncover peripheral mechanisms of T cell tolerance to this RNA-binding nuclear antigen.

Methods: Genetically marked splenocytes of TCR transgenic (Tg) mice, in which essentially all CD4⁺ T cells are specific for an I-Ek-restricted, immunodominant T cell epitope of hLa (hLa 67–76) but do not recognize the mouse La antigen, were transferred into lymphocyte replete hLa Tg and non-Tg recipients and their phenotype assessed after retrieval from recipients. Impacts of recipient B lymphocytes, plasmacytoid dendritic cells (pDC), and Type I interferon receptor (IFNAR1) on donor T cell phenotype were assessed by administration of depleting or blocking monoclonal antibodies to recipient mice prior to and following transfers.

Results: Donor CD4⁺ T cells of both CD25⁺ Foxp3⁺ and CD25⁻ Foxp3³ phenotypes were present in hLa Tg recipients on day 7 post-transfer and were absent in recipients that lacked expression of the hLa neo-self antigen. Donor cells retrieved from hLa Tg recipients were hypoproliferative and produced elevated levels of IL-10 following in vitro stimulation with irradiated splenocytes and hLa 61–84 peptide compared to donor cells retrieved from control recipients that lacked expression of hLa. Recipient pDC but not B cells directed the appearance of Foxp3 expressing donor T cells in hLa Tg recipients. Both conventional (c) DC and pDC purified from hLa Tg mice presented the hLa epitope constitutively as revealed by their capacity to stimulate IL-2 secretion from a hLa 67–76-specific T cell hybridoma. Treatment of hLa Tg recipients with an IFNAR1-blocking antibody resulted in significantly fewer Foxp3⁺ donor T cells at day 7 compared to recipients treated with an isotype control antibody.

Conclusions: These studies suggest that peripheral differentiation of antigen-specific Foxp3 Treg is a mechanism of T cell tolerance to a representative RNA-binding nuclear antigen and that pDC play an important role in this process.

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Protective Human CD4⁺CD25⁺FOXP3⁺ Regulatory T Cells Generated Ex-Vivo with IL-2, Retinoic Acid and TGF-bets Are Resistant to Pro-Inflammatory Cytokines. Xiaohui Zhou¹, Chin Lan¹, Juhua Wang², Song-suo Zheng³ and David A. Horwitz². ¹University of Southern California, ²University of Southern California, Los Angeles, CA

Purpose: The stability of CD4⁺CD25⁺ Foxp3⁺ regulatory T cells (Tregs) under inflammatory conditions has been questioned. These Tregs may lose Foxp3 and acquire proinflammatory effector functions. Therefore, for Tregs to be used as a potential T cell therapy, they must not only be functionally competent, but also resistant to proinflammatory conversion. We have previously reported that CD4 Tregs induced with IL-2 and TGF-β (iTregs) are resistant to conversion and our objective has been to generate similar Tregs using human naive CD4⁺ T cells. We have previously reported that human iTregs generated with IL-2, TGF-β and retinoic acid become fully functional Tregs in one week. Here we compare the functional properties of iTregs with expanded endogenous CD4 Treg after treatment with proinflammatory cytokines.

Methods: Naive human CD4⁺ cells prepared by negative selection were suboptimally TCR activated for 6 days with anti-CD3/CD28 coated beads with IL-2, TGF-β and all-trans retinoic acid (atRA). Autologous CD4⁺CD25hi T cells (nTregs) were also isolated and expanded with high dose IL-2 and rapamycin. Both iTregs and nTregs were then re-stimulated with with IL-1β and IL-6 and low IL-2 to bring out the inhibitory effects of these proinflammatory cytokines, the Treg subsets were examined for phenotype and function. To assess in vivo suppressive activity, sublethally irradiated NOD SCID IL-2R γ chain⁻² (NOG) mice were injected IV with human CD25 depleted PBMC and various Treg subsets.

Results: After 6 to 10 days of TCR stimulation with IL-2 and TGF-β and atRA naïve CD4⁺ cells had become CD25⁺ CD127lo, CD45RA⁺RO⁻, DR⁺, Foxp3⁺ cells that were anergic, produced low amounts of IL-2 and IFN-γ and exhibited strong in vitro suppressive activity. These cells protected NOG mice from a human xeno-GVHD as well as expanded nTregs. After restimulation of iTregs and nTregs with IL-1β and IL-6 nTregs Foxp3 and other Treg markers were down-regulated whereas these markers expressed by atRA/TGF-β induced iTregs were stable. While the protective effects of restimulated iTregs and nTregs was equivalent, the protective effects of nTregs treated with IL-1β and IL-6 decreased and was significantly less than iTregs.

Conclusion: These studies suggest that atRA TGF-β are not only important in the generation of iTregs, but also confer resistance when they are present in an inflammatory milieu.

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RANKL Expression in Human T-Lymphocytes Requires Cooperative Signaling through the T-Cell Receptor and Adhesion Molecule CD2. Bohdan P. Harvey and Zehra Kaymakcalan. Abbott Laboratories, Worcester, MA

Purpose: T-lymphocytes contribute to osteolysis in rheumatic diseases through their production of the osteoclastogenic cytokine RANKL. Mitogenic stimulation of lymphocytes has been shown to induce expression of RANKL;
however, the extracellular events leading to its production have not been fully identified. We sought to determine whether cell-to-cell interactions through adhesion molecules such as lymphocyte function-associated antigen 2 (CD2) were necessary to promote RANKL secretion from T-cells following T-cell receptor (TCR/CD3) engagement.

**Methods:** Healthy donor PBMC was isolated by Ficoll gradient. Human CD4+ and CD8+ T cells were purified by negative magnetic bead selection method. PBMC samples from rheumatoid arthritis (RA) patients were obtained from Conversant Healthcare Systems. Cells were cultured in medium supplemented with 2% human serum, IL-2, IL-7, M-CSF and 1alpha,25-dihydroxyvitamin D3 in the presence of various combinations of bead bound anti-CD3, anti-CD2 and anti-CD28 (co-stimulatory receptor) antibodies for 4 days. Total RANKL was determined in culture supernatants by osteoprotegrin (OPG) capture sandwich ELISA, and remainder of supernatants were used in Meso Scale Discovery Multi-spot assay system to evaluate the levels of IFN-γ, TNF-α, IL-10, IL-4, IL-8 and IL-13. T-cell activation was determined by flow cytometry using CD69 and CD25 as markers.

**Results:** RANKL secretion by healthy donor PBMC was first detected after 72 hr incubation with anti-CD3/CD2/CD28 antibody coated beads with maximal secretion levels being reached following 96 hr. Anti-CD3/CD28 antibody coated beads failed to induce detectable levels of RANKL. When purified T-lymphocyte subsets were evaluated, both CD4+ and CD8+ T-cells produced RANKL only in response to the combined cross-linking of CD3 and CD2 whereas cross-linking of CD3 and CD28 was insufficient to promote RANKL expression even though the T-cells were activated based on the high levels of CD69 and CD25. Those conditions (anti-CD3/CD2) that did not lead to RANKL production induced changes in expression levels of the IL-4, IL-8 and IL-13 as compared to the combinations of anti-CD3/CD28 or anti-CD3/CD28 antibodies. The combination of anti-CD2 and anti-CD8 antibodies neither induced RANKL secretion nor led to the activation of T-cells. PBMC from RA patients also secreted RANKL in a CD3/CD2-dependent manner and at levels similar to PBMC from healthy donors.

**Conclusions:** Our results clearly demonstrate that T-lymphocytes (both CD4 and CD8 subsets) can generate RANKL following the co-ligation of the TCR/CD3 and the adhesion molecule CD2 in the absence of the co-stimulatory receptor CD28, suggesting that interactions between T-cells and non-traditional APCs, such as synovial fibroblasts, could lead to the production of osteoclastogenic cytokines without the need for other co-stimulatory signals. Interestingly, the cross-linking of CD3 and CD2 induced RANKL secretion with minimal impact on most of the inflammation-associated cytokines, indicating that RANKL expression is activated by a signaling cascade(s) separate from most other cytokines.

**Disclosure:** B. P. Harvey: Abbott Laboratories, 3; Z. Kaymakcalan: Abbott Laboratories, 3.

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**Regulation of Human T Cell Activation and Effector Functions by Kv1.3 and KCa3.1 Channels**

Gang Chen1, Vaishali Patel1, Rothschild Soto1, Chen Shih-Chun2, Sandip Panicker2, Philip A. Nunn2, and Julie A. DeMartino2.

**Purposes:** Kv3.1 and Kv3.2 are major potassium (K+) channels expressed in T cells that have been suggested to play essential roles in the activation and effector functions of central memory T cells (Tem) and effector memory T cells (Tem), respectively. The goal of this study is to understand the relative contribution of these two K+ channels in human CD4+ T cell effector functions.

**Methods:** Selective small molecule inhibitors of KCa3.1 [TRAM-34, lecanin 17043 (Ica)], the Kv1.3-selective peptide inhibitor Shk(L5) and a CRAC channel inhibitor RO6712 were used in this study. The responsiveness of primary human T cells to K+ channel blockade was examined in the following manner: 1) Human mixed lymphocyte reaction: responder PBMC were co-cultured with Mitomycin C-treated stimulator PBMC for 4 days. Cell proliferation was measured by 3H-thymidine incorporation; 2) CFSE proliferation were co-cultured with Mitomycin C-treated stimulator PBMC for 4 days. Total RANKL was determined in culture supernatants by osteoprotegrin (OPG) capture sandwich ELISA, and remainder of supernatants were used in Meso Scale Discovery Multi-spot assay system to evaluate the levels of IFN-γ, TNF-α, IL-10, IL-4, IL-8 and IL-13. T-cell activation was determined by flow cytometry using CD69 and CD25 as markers.

**Results:** First, we found that neither resting Tem nor total CD4+ T cell proliferation could be fully blocked by TRAM-34, Ica or Shk(L5) alone. However, the combination of TRAM-34 or Ica with Shk(L5) could completely suppress resting T cell proliferation and cytokine production in the context of anti-TCR stimulation and MLR. In activated T cells, Ca3.1 blockade was able to suppress IL-2 production significantly. In addition, blockade of both Kv1.3 and Ca3.1 channels exerted similar extent of inhibition on T cell proliferation and cytokine production as CRAC channel blockade. Lastly, electrophysiological analysis showed that activated CD4+ T cells exhibited potassium currents consisting of varying contributions from both channels. Further analysis on the effect of K+ channel blockade on T cell calcium influx will be necessary.

**Conclusion:** We have demonstrated that in human CD4+ T cells, Ca3.1 and Kv1.3 function in concert in the regulation of the optimal activation and effector functions, possibly through maintaining a sustained CRAC current in these cells. Electrophysiological findings confirmed that human primary CD4+ T cells exhibit varying contributions of potassium flux from both Kv1.3 and Ca3.1 channels. Our data strongly suggest that in human inflammatory diseases driven by pathogenic T cells, targeting both Ca3.1 and Kv1.3 channels simultaneously could potentially provide therapeutic benefit to patients.


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**Role for IL-23 in Differentiation of Human Th17 Cells**

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**Purpose:** Th17 cells, which are crucial in host defense, play significant roles in many autoimmune diseases, including RA. In mice, the combination of TGF-beta and IL-6 induces Th17 cells from naive CD4T cells. Whereas TGF-beta was shown to also be essential for human Th17 differentiation, it is unclear what additional pro-inflammatory cytokines are required to induce human Th17 cells. We proposed that IL-23 was dispensable for human Th17 cell differentiation given the expression of IL-23 receptor only after induction of ROR-gammad (master regulator gene of Th17 cells) in mice.

**Method:** Naive CD4T cells were isolated from peripheral blood mononuclear cells (PBMCs) from healthy adult donors by a naive CD4T cell enrichment kit, and were cultured in RPMI culture media with 10% FCS, 1% Penicillin/Streptomycin, and 2% L-glutamine, with beads coated with anti-CD3/CD28 antibodies, anti-IFN-gamma and IL-23 antibodies (5ng/ml), TGF-beta (0.1, 1 or 10ng/ml), IL-1 (5ng/ml), IL-6 (10ng/ml), and IL-23 (0, 1 or 10ng/ml). Cells were collected on day 5 and incubated for 6h with phosphor ester and ionomycin followed by Golgi-Plug. After blocking Fc receptors, cells were fixed, permeabilized in PBS containing 0.5% Saponin, and stained with Phycoerythrin conjugated antibodies against IL-17A, IL-17F, IL-21, or IL-22. IL-17A in culture supernatants was measured by ELISA. On day 3, total cellular RNA was extracted to synthesize cDNA. Expression of RORc was assessed by RT-Q-PCR with GAPDH as a reference gene.

**Results:** Analysis of ELISA data from healthy subjects (n = 5) showed that IL-17A induction was more IL-23 dependent in lower TGF-beta: 0.1ng/ml: 162.8 ± 70.2pg/ml (no IL-23), 233.9 ± 133.0pg/ml (IL-23: 1ng/ml), 377.4 ± 249.8pg/ml (IL-23: 10ng/ml) vs IL-23: 1ng/ml: 233.9 ± 133.0pg/ml (no IL-23), 338.1 ± 168.0pg/ml (IL-23: 1ng/ml), 320.6 ± 155.2pg/ml (IL-23: 10ng/ml). RORc expression was IL-23 dependent at TGF-beta concentrations of either 0.1ng/ml or 1ng/ml, but was IL-23 independent in 10ng/ml TGF-beta. These data indicate that the role of IL-23 in contributing to human Th17 differentiation varies depending on the concentration of TGF-beta. On flow cytometry, induction of IL-17A+ and IL-22+ cells was relatively independent of the concentration of IL-23. However, induction of IL-17F+ cells was more IL-23 dependent in lower TGF-beta: 0.1ng/ml whereas induction of IL-21+ cells was more IL-23 dependent in higher TGF-beta: 1ng/ml.
Conclusion: Contrary to initial predictions, our data suggest that IL-23 might promote human Th17 differentiation either through distinct mechanisms that are in part independent of TGF-beta or through contribution to low TGF-beta driven pathway. Furthermore, each Th17-derived cytokine may be differentially regulated by IL-23. The level of secretion of Th17 cytokines is not entirely predictable by enumeration of Th17 cells that contain a specific cytokine intracellularly.

Disclosure: H. Kato: None; L. Cooney: None; J. Endres: None; D. A. Fox: None.

1272
Self-Organized Criticality Theory for the Cause of Autoimmunity. Ken Tsumiya1, Yumi Miyazaki1 and Shunichi Shinzawa2. 1Department of Biophysics, Kobe University Graduate School of Health Science, Kobe, Japan, 2Department of Biophysics, Kobe University Graduate School of Health Science/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Objective: Since 'clonal selection theory of immunity' of F. Macfarlane Burnet and subsequent molecular biologic discoveries on V(D)J recombination and the diversity and individuality of immune response, how autoimmunity arises remains unclear. Apart from the term 'autoimmunity' which is now ready-made in the present study, we tried to see the pathogenesis of autoimmunity from different angle and test the integrity of immune 'system'. The method we have chosen was to stimulate the system maximally by introducing mice not prone to autoimmune diseases were examined the T cell receptor (TCR) revision in spleen, maturation of CD8+ T cell and antigen cross-presentation in dendritic cell (DC).

Results: Repeated immunization with antigen caused systemic autoimmunity in mice otherwise not prone to spontaneous autoimmune diseases. Overstimulation of CD4+ T cells led to the development of a fully-matured autoantibody-inducing CD4+ T cell type (αCD4+ T cell) which had undergone T cell receptor (TCR) revision and became capable of inducing autoantibodies. The αCD4+ T cell was induced by de novo TCR revision but not by cross-reaction to immunizing antigen, and subsequently overstimulated CD8+ T cells, driving them to become MHC class I-restricted, antigen-specific cytotoxic T lymphocytes (CTL). These CTLs could be further matured by antigen cross-presentation, after which they caused autoimmune tissue injury. In fact, autoimmune tissue injury did not appear in CD8+ T cell-deficient mice after repeated immunization with antigen. Further, inhibi-

Conclusion: We show that systemic autoimmunity appears to be the inevitable consequence of over-stimulating the host's immune 'system' by repeated immunization with antigen, to the levels that surpass system's self-organized criticality. Thus, we propose here 'self-organized criticality theory' explaining the cause of autoimmunity.

Disclosure: K. Tsumiya: None; Y. Miyazaki: None; S. Shiozawa: None.

1273
SGN-70: Phase 1a Study of a Novel Humanized Antibody Targeting CD70 for the Treatment of Autoimmune Diseases. Jonathan G. Drachman1, Julie A. McEarchern2, Che-Lueh Law3, Luis Lopez-Lazaro1, Gabriele Fabian1 and Michael Seiberling1. 1Covance Clinical Research Unit AG, Basel, Switzerland, 2Seattle Genetics, Inc., Bothell, WA, 3Seattle Genetics, Inc., 1, 3;

Background: SGN-70 is a humanized IgG1 monoclonal antibody with high affinity for CD70 which can deplete CD70-positive cells via antibody effector mechanisms and can also block interaction of CD70 with its cognate receptor, CD27. CD70, a tumor necrosis factor family member, is expressed on activated T-cells, B-cells, and mature dendritic cells and co-stimulates immune responses. Based on these activities and preclinical studies, SGN-70 could reduce inflammation by targeting CD70+ immune cells while leaving the resting immune system intact.

Methods: A single-dose, dose-escalation, randomized, double-blind, placebo-controlled clinical trial was conducted in healthy volunteers (N=61) to evaluate safety, tolerability, PK, immunogenicity, and pharmacodynamic effects. Blood samples and clinical symptoms were collected for 50 days. Subsequently, a cohort of patients (N=8) with mild-moderate plaque psoriasis were evaluated at a single dose level. Upon randomization, 6 patients received SGN-70 (10 mg/kg) and 2 received placebo. This trial was conducted at a single site in Switzerland.

Results: SGN-70 was well tolerated over a wide dose range (0.0001 – 10 mg/kg) when administered without premedication as a single intravenous injection over 30 minutes (first 3 cohorts) or 60 minutes (higher dose levels). There were no serious adverse events or significant changes in laboratory values, vital signs, or ECGs, and a maximum tolerated dose was not established. Among healthy volunteers, the most frequent adverse events were URI symptoms, headache, and fatigue, which appeared to be balanced between treated and placebo subjects. Both Cmax and AUC appeared to increase linearly with dose level whereas terminal half-life increased at the highest dose levels. This resulted in a mean terminal half-life of 6–7 days for doses up to 1 mg/kg and 10 or 13 days at 3 mg/kg and 10 mg/kg, respectively. Low titer anti-therapeutic antibodies were detected in some subjects, but the effect of repeat dosing could not be assessed. In both the healthy volunteers and the psoriasis patients, a decrease in CD70+ B- and T-cells from peripheral blood could be demonstrated by qPCR or flow cytometry. Although the psoriasis patients had generally mild disease and were not eligible for more than 1 dose, preliminary evidence suggests that at least two of six patients experienced decreased skin thickness and cytokerin 16 expression as well as modest improvement in PASI scores.

Conclusions: SGN-70 is well tolerated up to 10 mg/kg and has on-target pharmacodynamic activity when administered as a single dose. Based on the novel mechanism of action and ability to impact multiple arms of the activated immune system, this is a promising novel monoclonal antibody for rheumatologic and autoimmune diseases that warrants further evaluation in a multi-dose clinical trial.

Disclosure: J. G. Drachman: Seattle Genetics, Inc., 1, 3; J. A. McEarchern: Seattle Genetics, Inc., 1, 3; C.-L. Law: Seattle Genetics, Inc., 1, 3; L. Lopez-Lazaro: None; G. Fabian: None; M. Seiberling: None.

1274
Vitamin D Suppresses the Pathogenic Behavior of Primary Th17 Cells from Patients with Early RA in Synovial Fibroblast Activation. Jan Piet van Hamburg1, Patrick Asmawidjaja1, Anne-Marie Mus1, Mieke Hazes1, Hans van Hamburg2, Jan Piet van Hamburg1, Edgar van der Valk3 and Eddy C. Vanden Bossche4. 1Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, 2Department of Rheumatology, Erasmus MC, University Medical Center Rotterdam, 3Departments of Rheumatology and Immunology, Erasmus MC, University Medical Center Rotterdam, 4Erasmus MC, Rotterdam, ZH, The Netherlands

Introduction: Vitamin D is a secosteroid hormone that is produced on the skin under the influence of sunlight or is obtained from the diet. In the liver, the inactive precursor vitamin D3 is converted to the hormonal precursor 25-hydroxyvitamin D3 (25(OH)D3). In the kidneys and extrarenal tissue, 25(OH)D3 is converted into its most active metabolite 1,25(OH)2D3. It has been shown that 1,25(OH)2D3 has immunomodulatory effects in many experimental autoimmune models. Recently, we showed that vitamin D modulated Th17 polarization and IL-22 expression by memory T cells from patients with early rheumatoid arthritis and stimulates IL-4 production by PBMC from early RA patients.

Objective: To identify the effect of vitamin D on the pathogenic behavior of primary Th17 cells on synovial fibroblast (RASF) activation both from patients with early RA.

Methods: From PBMC of patients with early RA, CCR6+ CD45RO+ CD4+ Th17 cells were FACS sorted and co-cultured with early RA synovial fibroblasts (RASF) in the absence or presence of Vitamin D. Supernatant of these cultures were analyzed for the production of inflammatory cytokines and matrix metalloproteases (MMPs) with ELISA. Transcript-
tion of genes involved in the differentiation and function of T cells or genes expressed by activated RASF were analyzed by quantitative RT-PCR analysis. In addition, TNF-alpha and IL-17A blocking experiments were performed in these co-cultures.

Results: Th17-RASF co-culture experiments revealed an increase of IL-6, IL-8, and MMP-1 and MMP-3. Vitamin D significantly suppressed the production of IL-6 and MMP-3 in these co-cultures. Interestingly, the specific enhanced autocrine production of IL-17 due to this Th17-RASF interaction was significantly inhibited by vitamin D. In addition, markedly suppressed expression of RORgammat and significantly enhanced expression of GATA3 was noted in the presence of vitamin D. No effect of vitamin D was observed on T-bet and FoxP3 expression. In addition, lower IL-22 and enhanced IL-10 production was found in the presence of vitamin D. The regulatory effects of vitamin D on IL-17 production in the Th17-RASF co-culture was comparable to neutralizing IL-17 and on IL-6 production comparable to neutralizing TNF or IL-17.

Conclusion: These data show that vitamin D modulates the pathogenic behavior of primary Th17 cells in their activation of synovial fibroblasts. In addition, vitamin D suppresses the pro-inflammatory IL-17 loop between Th17 and RASF cells. These data suggest that the activation of the vitamin D pathway may have therapeutic potential for the treatment or even prevention of persistent arthritis.

Disclosure: J. P. van Hamburg None; P. Asmawidjaja None; A.-M. Mus None; M. Hazes None; H. van Leeuwen None; E. Colin None; E. Lubberts None.

ACR Poster Session B
Large-Vessel Vasculitis and Behcet’s Disease I
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

1275
18F-Fluorodeoxyglucose Positron Emission Tomography Scanning (FDG-PET/CT) in Evaluation of Disease Activity in Takayasu Arteritis. Øyvind Palm1, Birgir Gudbrandsson2, Torhild Garen2, Kjersti Johnsrud1 and Jan Tore Graven3. 1Section for Nuclear Medicine, OUS, Rikshospitalet, 2Section for Rheumatology, OUS, Rikshospitalet, 3Section for Rheumatology, OUS, Rikshospitalet, Oslo, Norway

Purpose: To evaluate FDG-PET/CT findings and disease activity in patients with Takayasu arteritis (TA).

Background: The assessment of disease activity may be difficult in TA. Patients can have active and progressing disease in spite of normal levels of ESR and CRP. Unfortunately, specific markers of disease activity are still missing1. Edema-weighted MR does not seem to correlate well with development of new vascular lesions2 and angiographic methods will only reveal findings compatible with long-standing, irreparable disease.

Since the introduction of FDG-PET/CT, case reports and small studies have reported positive associations between pathological uptake in FDG-PET/CT and disease activity in TA3. However, a recent study failed to find such a correlation4. Obviously, further studies are needed to clarify the usefulness of FDG-PET/CT in assessing disease activity in patients with TA. In order to evaluate our experience, we retrospectively evaluated the results of FDG-PET/CT in our patients with TA.

Methods: Patients who fulfilled the ACR criteria for TA2 and had been consecutively investigated with FDG-PET/CT between 2003 and 2009 were included. They were recruited from the Norwegian Registry of connective diseases and systemic vasculitides (n=36) and by a systematic search in our hospital register of diagnoses (n=11). The FDG-PET/CTs were evaluated by nuclear medicine physicians. Semi-quantitative measurements were used to aid the visual evaluation. The scans were performed 60–90 minutes after injection of 370 MBq FDG. Disease activity was assessed by ESR and CRP measured within 15 days of the FDG-PET/CT investigation, by clinical evaluation by a rheumatologist prior to the FDG-PET/CT and by applying the NHI criteria for disease activity1.

Results: Totally, 45 female and 2 male patients were investigated. Their median age was 31 years (14–69). Disease duration was median 1 year (0–31). Among patients with pathological FDG-PET/CT uptake, the mean level of CRP (28 cases evaluated) was significantly higher compared to patients with normal FDG-PET/CT. Further, based on the clinician’s evaluations, 79% of those with increased FDG-PET/CT uptake had active disease compared to 29% among those with negative FDG-PET/CT. However, neither the ESR levels, nor the fulfilments of the NHI criteria for disease activity did not show significant difference between the groups (Table 1).

Table 1. Pathological FDG-PET/CT (PET/CT+) and normal FDG-PET/CT (PET/CT−) by markers of disease activity in Takayasu arteritis

<table>
<thead>
<tr>
<th>PET/CT+</th>
<th>PET/CT−</th>
</tr>
</thead>
<tbody>
<tr>
<td>n total</td>
<td>15</td>
</tr>
<tr>
<td>ESR median (range)</td>
<td>62 (3–100)</td>
</tr>
<tr>
<td>CRP median (range)</td>
<td>48.5 (1–145)</td>
</tr>
<tr>
<td>Clinical evaluation*</td>
<td>Active/Inactive 11 (79%/3) (21%)</td>
</tr>
<tr>
<td>Criteria for activity†</td>
<td>Active/Inactive 11 (73%/4) (27%)</td>
</tr>
</tbody>
</table>

* Totally, 5 cases could not be evaluated.
† Mann-Whitney test, ~ Fisher’s exact test

Conclusions: We found a significant association between FDG-PET/CT results and disease activity measured by CRP and clinicians evaluation, but not by ESR or the NHI criteria.

Reference List:
2. TSO E et al. Arthritis Rheum, 2002

Disclosure: O. Palm: None; B. Gudbrandsson: None; T. Garen: None; K. Johnsrud: None; J. T. Gran: None.

1276
A Double-Blind Placebo Controlled Trial of Infliximab in Patients with Corticosteroid-Dependent Polymyalgia Rheumatica. Víctor M. Martínez-Tahooro1, Francisco Javier López-Longo10, Rosario García de Vaca1a, Jordi Gratacos5, Georgina Espigol-Frigole5, Julio Medina5, Javier Narváez5, Rosa Roselló17, Luis Carreño3, Ifigo Rua-Figueroa4 and María Cintia Cid1
1Hospital Clinic, Barcelona, Spain, 2Hospital Clinic, 3Hospital de Bellvitge, Barcelona, Spain, 4Hospital Doctor Negrin, Spain, 5Hospital Parc Taulí, Barcelona, Spain, 6Hospital Rio Carrión, Palencia, Spain, 7Hospital San Jorge de Huesca, Spain, 8Hospital Universitario de la Princesa, Madrid, Spain, 9Hospital Universitario Gregorio Marañón, Madrid, Spain, 10Hospital Universitario Gregorio Marañón, Madrid, Spain, 11Hospital Universitario Marques de Valdecilla, Santander, Spain

Background: Corticosteroids (CS) constitute the standard treatment of polymyalgia rheumatica (PMR). However, a significant proportion of patients remain CS-dependent. Open label studies have suggested that tumour necrosis factor (TNF) antagonists led to sustained improvement and CS sparing effect in patients with refractory PMR. To confirm these observations, we conducted a randomised, double-blind, placebo controlled trial with infliximab in CS-dependent patients with PMR.

Methods: We randomly assigned patients with CS-dependent PMR (defined as requiring ≥ 5 mg/day after at least 2 years of treatment to maintain remission or ≥ 7.5 mg/day after at least 6 months) to receive Infliximab (5 mg/kg iv) at 0, 2, 6, 14 and 22 weeks (n = 11) or placebo (n = 11) together with CS that were reduced according to a predefined schedule. The primary outcome was the proportion of responder patients - defined as individuals with both complete clinical and analytical remission without receiving CS for at least three months- at 24 weeks. Secondary outcomes were cumulated CS doses and adverse events.

Results: Baseline characteristics were similar in the two groups. The majority of patients were women (81.8% in infliximab versus 63.6% in placebo, p = 0.6) with a mean age of 68.5±10.4 years in infliximab and 74.7±5.3 years in placebo group (p = 0.3). PMR duration (median: 30.0 months and 36.0 months in infliximab and placebo groups, respectively; p = 0.8) and CS dose at baseline (7.4±3.2 mg in infliximab versus 8.1±3.0 mg in placebo group; p = 0.5) were also similar. At week 24, 17 patients continued in the trial (8 in infliximab and 9 in placebo group), and only 1 patient in the infliximab group and 2 in the placebo group fulfilled the definition of responder (p, NS). During the 24-week period, CS dose was increased according to physician judgment at least once in 36.4% of patients in the infliximab group compared with 72.7% in the placebo group (p = 0.2). Patients in the infliximab group tended to have lower cumulated dose of prednisone during the first 24 weeks of treatment (533.7±366.8 mg versus 901.1±522.4 mg; p = 0.1) and received lower CS dose at week 24 (1.1±1.4 mg versus 3.6±2.6 mg; p = 0.06). There were 26 adverse events (24 mild/moderate) in patients treated with infliximab and 7 (all mild/moderate) in those patients treated with placebo.
Conclusion: The limited number of patients included in this trial does not allow definitive conclusions. The therapeutic role of infliximab in patients with CS-dependent PMR should be evaluated in trials enrolling larger patient cohorts. The medication of the study (infliximab) was provided by Schering-Plough S.A.

Disclosure: V. M. Martínez-Taboada: Pfizer Inc; 5, Roche; 5, UCB, Inc.; 5. F. J. López-Longo: None; R. García de Vicuña: Schering-Plough; 5; J. Gratacos: Schering-Plough; 5; G. Espigol-Frigola: None; J. Medina: None; J. Narváez: None; R. Roselló: None; I. Carreño: Schering-Plough; 5; I. Rua-Figueroa: None; M. C. Cid: None.

1277
Adverse Outcomes of Glucocorticoid Therapy among Patients with Giant Cell Arteritis. Laura López Vives, Javier Narváez, Paula Estrada, Carmen Gómez Vaquero and Joan Miquel Nolla. Department of Rheumatology, University Hospital of Bellvitge, Barcelona, Spain

Background: Glucocorticoids (GC) are currently the only agents in giant cell arteritis (GCA) with proven efficacy. Two studies have demonstrated that GC therapy carries an important long-term morbidity, with an incidence of GC adverse events ranging from 58% to 86% of the patients.1,2

Purpose: To evaluate the incidence and risks of adverse events associated with GC therapy in a series of patients with GCA diagnosed in an area of north-eastern Spain over a 23-year period.

Methods: Retrospective follow-up study of an unselected population of 140 patients with GCA diagnosed in 1 center between 1986 and 2008. Medical records of these patients were reviewed, and clinical variables, GC doses, and GC adverse events on each patient were recorded. Multivariate regression analysis were used to identify variables associated with the development of adverse events.

Results: The series included 94 women and 46 men with a mean age at time of diagnosis of 75 ± 7 years (range, 56 to 92). TAB was positive in 112 (80%) patients. For the total sample the mean duration of therapy after diagnosis was 41.6 months (range, 12.5 to 180) and the total median dose of prednisone was 10.2 gm.

Adverse events associated with GCs were recorded in 89 (63.6%) patients and 2 or more events occurred in 51 patients (36.4%). The main adverse events and their frequency are presented in the following table:

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Patients with the event, number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>22 (15.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (29.2%)</td>
</tr>
<tr>
<td>Hypoalimentia</td>
<td>49 (35%)</td>
</tr>
<tr>
<td>Total osteoporotic fractures</td>
<td>27 (19.3%)</td>
</tr>
<tr>
<td>Symptomatic vertebral fracture</td>
<td>15 (10.7%)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Colles’ fracture</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Insufficiency fracture of the pelvis</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Posterior subaortic cataract</td>
<td>30 (21.4%)</td>
</tr>
<tr>
<td>Glucocorticoid-induced myopathy</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Severe or opportunistic infections</td>
<td>25 (17.9%)</td>
</tr>
</tbody>
</table>

Among those patients experiencing and adverse event, the median duration of therapy was 48.7 months (range, 2 to 180), the total median dose of prednisone was 11.6 gm, and the average daily dose was 9.5 gm. The median time from initiation of therapy to the first adverse event was 8.5 months. In the multivariate analysis, only higher cumulative dose of prednisone (odds ratio = 1.17, 95% confidence interval: 1.05, 1.30) was associated with the development of adverse GC side effects.

Conclusion: The incidence of GC adverse events in patients with GCA is high, occurring at least in 63.6% of cases; being this percentage close to that observed in other populations. Adverse events may occur even in low-dose therapy and appear to be dose and duration dependent. Osteoporotic bone fractures and infections were as frequent as cardiovascular adverse events.

References:

Disclosure: L. López Vives: None; J. Narváez: None; P. Estrada: None; C. Gómez Vaquero: None; J. M. Nolla: None.

1278
Alemtuzumab (CAMPATH-1H) as Remission Induction Therapy in Behcet’s Disease. Rona M. Smith1, Yok W. Chow2 and David R. W. Jayne1. 1Addenbrooke’s Hospital, Cambridge, United Kingdom, 2Hospital Pantai Ayer Keroh Melaka, Malaysia

Introduction: Behcet’s Disease is a chronic, relapsing inflammatory disorder, characterised by recurrent oral and genital ulceration, but the more severe, life threatening manifestations are neurological, gastrointestinal or vascular in nature. The precise aetiology and pathogenesis are unclear, but there is increasing evidence that T cells play a key role in the development of disease, and thus T cell depleting agents, such as the anti-CD52 humanised monoclonal antibody, alemtuzumab (CAMPATH-1H) are a potential therapeutic strategy.

Methods: We present a retrospective review of 20 patients treated with alemtuzumab since 1998 in Addenbrooke’s Hospital, Cambridge, UK. Two dose schedules were used in this time period; a total dose of 134mg wasadministered prior to 2003, and 95mg in total in the latter years. Disease activity was measured using the Birmingham Vasculitis Activity Score (BVAS), and sequential evaluation of haematological and biochemical markers were performed.

Results:

Patient Characteristics
15/20 (75%) of patients were female, and the mean age at the time of alemtuzumab therapy was 36.2 years (range 18–59 years). All patients had oral and genital ulceration. 19 (95%) and 18 (90%) of patients had joint and skin involvement respectively. 11 (55%) had eye involvement, 13 (65%) gastrointestinal involvement and 9 (45%) central nervous system disease.

Less common features included vascular manifestations (25%), peripheral nervous system involvement (10%) and lung disease (1%). Prior to alemtuzumab, the average disease duration was 59.8 months (range 1–203 months), and the mean duration of steroid exposure was 22.7 months (range 1–84 months). 17/20 (85%) of patients had received one or more immunosuppressive agents (including anti-TNF agents, cyclophosphamide, anti-metabolites, calcineurin inhibitors and thalidomide) in addition to corticosteroids prior to receiving alemtuzumab. The average duration of follow up was 85.47 months (range 20–134 months).

Outcomes

Six months after treatment, 74% of patients were in complete remission. Many of these remissions have been sustained over years, but in those that did relapse, re-treatment with alemtuzumab was effective. There were significant reductions in prednisolone dose and BVAS after treatment (Figure 1).

Figure 1. Prednisolone doses, BVAs, and relapse free survival post alemtuzumab.

Adverse events

Alemtuzumab was well tolerated. 25% of patients experienced infusion reactions, but in only one did the reaction necessitate termination of the treatment. There were no infectious complications directly attributable to alemtuzumab, but six patients developed new autoimmune thyroid dysfunction. Autoimmune diseases following alemtuzumab, including thyroid disease and ITP, have also been reported in multiple sclerosis.
Ankylosing Spondylitis Associated with Takayasu Arteritis. Süleyman Yildirim, Gülen Hafetani, Sebahattin Yurdakul, Izzet Fresko and Huri Ozdogan. Istanbul University, Cerrahpasa Medical School, Rheumatology

Background: A number of case reports have been published on the association of Takayasu arteritis with ankylosing spondylitis. The aim of this study is to formally evaluate Takayasu patients for ankylosing spondylitis (AS).

Methods: All patients who were followed with a diagnosis of Takayasu arteritis in our clinic were evaluated. Apart from the 114 Takayasu patients who fulfill ACR criteria, 77 rheumatoid arthritis and 29 AS patients were included as controls. Patients were questioned for inflammatory back pain, arthritis and heel pain with a previously validated questionnaire for screening sero negative spondylarthropathies. Patients who gave an affirmative answer to at least one of the questions were further evaluated with physical examination and sacroiliac radiograms. Radiograms were evaluated twice on 2 separate days by 3 rheumatologists blinded to each others observations and graded according to modified New York criteria. Patients who had bilateral grade 2 or unilateral grade 3 or 4 sacroiliitis on at least 3 of 6 observations were diagnosed as ankylosing spondylitis.

Results: Among the 114 patients with Takayasu arteritis 14 had died. Two of these patients had been diagnosed as AS, and one of them also as Crohn’s disease before they died. Among the remaining 100 patients 44 already had a diagnosis of AS, one of them with accompanying Crohn’s disease. We were able to reach 75 of the remaining 96 patients. 36 gave an affirmative answer to at least one of the questions. 29 of these 36 patients agreed to come to the clinic for further evaluation. Two of these 29 patients had sacroiliitis. One of them had a diagnosis of Crohn’s disease. Among the controls 27/77 RA (3%) patients and 28/29 (97%) AS patients had sacroiliitis. Among the 114 patients with Takayasu arteritis a total of 8 (7%) patients had ankylosing spondylitis. Three of them were known to have Crohn’s disease. None of the remaining 5 patients had symptoms related to Crohn’s disease. The inter and intra-observer reliability of reading the sacroiliac radiograms was good. (kappa: inter-observer 0.89, 0.89, 0.69 and intra-observer 0.93, 0.69, 0.71)

Conclusion: The frequency of ankylosing spondylitis is increased in Takayasu arteritis. The association seems to include Crohn’s disease in at least some of the patients. The HLA B27 status and other features of spondylarthropathy in these patients remains to be studied.

Disclosure: S. Yildirim: None; G. Hafetani: None; S. Yurdakul: None; I. Fresko: None; H. Ozdogan: None.

Association of VEGF, NOS2, IL6, CCL2 and IL1RN Polymorphisms and Haplotypes with Susceptibility to Giant Cell Arteritis. A Simultaneous Study of 130 Potentially Functional SNPs in 14 Candidate Genes. Anna Enjuanes1, Yolanda Benavente1, Jose Hernandez-Rodriguez2, Carme Queralt3, Jordi Yague4, Pedro Jares5, Silvia de Sanjose6, Elias Campo7 and Maria C. Cid2. 1Department of Immunology, Barcelona, Spain, 2Department of Systemic Autoimmune Diseases, Hospital Clinic, Barcelona, Spain, 3Hematopathology Section, Department of Anatomic Pathology, Barcelona, Spain, 4Hematopathology Section, Department of Anatomic Pathology, Hospital Clinic, Barcelona, Spain, 5Department of Infection and Cancer, Cancer Epidemiology Research, Catalan Institute of Oncology, Barcelona, Spain, 6Unit of Infection and Cancer, Cancer Epidemiology Research, Catalan Institute of Oncology

Background: Giant cell arteritis (GCA) is an immune-mediated vasculitis involving large and medium-sized arteries, especially the aorta and its cervico-cranial branches. GCA is probably a polygenic disease and it seems plausible that frequent genetic variants with modest effects may be related to GCA susceptibility. To date, existing studies assessing genetic risk for GCA have only analyzed limited number of candidate genes and restricted number of genetic variants.

Purpose: To investigate the genetic susceptibility to GCA, we performed a case-control study genotyping 130 SNPs in 82 biopsy-proven GCA patients and 166 healthy controls from the Spanish population. The study evaluates SNPs in potentially functional regions (coding and regulatory gene regions) and some tag SNPs in 14 candidate genes related to the inflammatory response (CCL2, CCR7, IL10, IL12A, IL-1A, IL-1B, IL-1RN, IL6, IL8, INFG, IL12A, NOS2, TNF and VEGF).

Methods: Genomic DNA was isolated from peripheral blood mononuclear cells and genotyping was carried out using the Spanish National Genotyping Centre (CeGen) using an Illumina Bead Array System. Hardy-Weinberg equilibrium (HWE) for each SNP was evaluated in control subjects. To test the hypothesis of association we used multivariate methods based on logistic regression analyses under four inheritance models (codominant, dominant, recessive and log-additive) and adjusted for age and sex.

Results: We found that 9 SNPs located in five genes had a significant statistical association with disease risk (P < 0.05) for any of the inheritance models. These SNPs were located in NOS2 (rs2779251), VEGF (rs1885657, rs2010963, rs699946 and rs699947), IL1RN (rs17207494), IL6 (rs7805828 and rs1546766), and CCL2 (rs1860190) genes. The strongest associations were provided by rs2779251, rs1885657 and rs2010963 (P = 2.3 10^-7. P = 0.0078 and P = 0.0097, respectively). The association of rs2779251 and GCA risk was statistically significant after strong adjustment for multiple testing (P corr = 0.0024). The presence of the minor allele of NOS2 variant rs2779251 had a protective effect for the risk of GCA (OR = 0.27, 95% CI 0.14–0.52). Risk alleles for three of the four SNPs located in VEGF gene (rs2010963, rs699946 and rs699947), in homozgyous, showed an increase in the GCA risk (OR = 4.22, 95% CI 1.38–12.87; OR = 0.94, 95% CI 1.58– 51.81; and OR = 2.38, 95% CI 0.53–38.36, respectively). Minor allele for the other SNP in VEGF gene, the OR = 0.46, 95% CI 0.16–0.84). Moreover, we defined linkage disequilibrium blocks for each candidate gene included in this study and we explored the effect of haplotypes on disease risk. We found four haplotypes that showed significant association with susceptibility to GCA (IL6, OR = 0.51, 95% CI 0.28–0.94; VEGF, OR = 2.92, 95% CI 1.03–8.34; VEGF, OR = 0.42, 95% CI 0.20–0.92 and IL12A, OR = 4.22, 95% CI 1.29–13.67).

Conclusions: In summary, our results show that common genetic variants in NOS2, VEGF, IL6, ILRN1 and CCL2 genes are associated with risk for GCA, reinforcing a polygenic influence in susceptibility to this vasculitis.

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Behcet’s Disease and the Major Histocompatibility Complex: Looking beyond HLA-B51. Michael J. Ombrello1, Yohei Kirino2, Fulya Cosan3, Ahmet Gul1, Daniel L. Kastner2 and Elaine F. Remmers2. 1Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul, Turkey, 2Laboratory of Clinical Investigation, NIAMS, NIH, Bethesda, MD

Background: Behcet’s Disease (BD) is a complex genetic disease of unknown etiology that is characterized by inflammatory lesions of the eyes, skin, and oro-gential mucosa. Family studies reveal a genetic contribution to BD, with estimates of the sibling recurrence-risk ratio from 11–52. Though the class I MHC molecule, HLA-B51 (B51), is reportedly the strongest known genetic risk factor for BD, the gene immediately centromeric to HLA-B, MICA, has also been implicated in BD. Because of strong linkage disequilibrium (LD) between HLA-B and MICA, their respective contributions to BD susceptibility have been debated.

Methods: In an effort to clarify the roles of B51, MICA, and other MHC loci genes in BD, we performed B51 typing with sequence specific oligonucleotide probes, and examined MHC locus SNP genotypes determined with Illumina Human CNV370 SNP chips in the largest single collection of BD patients ever assembled, 1190 Turkish BD patients and 1257 geographically matched, healthy Turkish subjects. Genotype association testing and regression analysis was performed using SNP Variation Suite 7. Haplotypic analysis was performed using Haplview.

Results: We found that B51 was strongly associated with BD (allelic chi square p = 5.47E-50, OR = 5.0). Occurring at allelic frequencies of 0.159 in healthy Turkish individuals and 0.352 in Turkish BD patients. We found 228 statistically significant BD-associated SNPs within the MHC locus (p<2.00E-5). The most strongly associated SNP (rs2848713, p = 1.91E-45)
was located centromeric to MICA, and was contained within a cluster of 33 BD-associated SNPs within HLA-B and MICA. Analysis of LD and haplotype structure identified a BD-associated, B51-containing haplotype block (p=1.22E-46, OR =2.81) spanning the entire HLA-B and MICA genes. An otherwise identical B1-negative version of this haplotype also existed, although it occurred at identical frequencies, 0.04, in cases and controls. B51-containing haplotypes with recombiant events occurring between HLA-B and MICA continued to convey a risk of BD (OR=1.75, [95CI=1.15-2.68]). Further analysis accounting for the effects of both B51 and rs9260997 identified additional regions of BD association in PSORS1C1 (p=1.24E-5, OR =2.01), and HLA-B (p=1.18E-5, OR =1.46).

Conclusion: Our study demonstrates B51 to be the largest single contributor to BD susceptibility in Turkish individuals. We identify a common B51-containing BD-associated HLA-B/MICA haplotype. B51 was required on the haplotype for the conveyance of significant BD risk, whereas MICA variants were dispensable. Finally, we identified additional B51-independent BD associations in the HLA-A, PSORS1C1, and HLA-B regions.

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Circulating Adipokine, Ghrelin and Acylated Ghrelin Levels in Patients with Takayasu's Arteritis. Hatice Yilmaz1, Vedat Gerdan2, Didem Kozaci2, Servet Akar3, Gercek Can1, Aytaç Gulcu4, Faize Yuskel1, Volkân Cakır3, Yigit Goktay3, Merih Birlik3, Nurullah Akkoc4 and Fatos Onen4. 1Internal Medicine, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, 2Internal Medicine, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, 3Radiology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, 4Radiology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey.

Objective: In Takayasu arteritis (TA) with unknown etiology, it is very important to monitor the disease activity because intensive treatment is needed during active periods. Today's clinical and laboratory activity criteria alone are not very satisfactory for follow-up. This study aims to investigate the numbers of circulating endothelial cells (CEC) and endothelial precursor cells (CEPC) and also the correlation of these parameters with disease activity in patients with TA.

Patients and Methods: 32 patients with TA, 25 with systemic lupus erythematosus (SLE) (patient control group) and 30 healthy subjects were included in this study. Detailed medical history was obtained and full physical examination was done in all patients. The NIH activation criteria, DEITAK scoring and “DEITAK-physician’s global opinion (PGO)” and also radiological investigations (B-mode and Doppler USG and MR angiography) were used to evaluate disease activity in TA patients. The numbers of CEC and CEPC were measured by flow cytometry in patient and control groups.

Results: There were 29 female and 3 male patients with TA (mean age: 43.9 years). Mean disease duration was 5.4 years. According to NIH activation criteria in TA patients, 18.8% of patients were active; according to “DEITAK-physician global opinion”, 18.8% active, 28.1% persistent and 53.1% inactive and according to the radiological findings, 31% active. A significant correlation was determined between the NIH activation criteria and DEITAK scoring, “DEITAK-POG” and also radiological activity (r=0.529, p=0.002; r=0.540, p=0.002; and r=0.361, p=0.046 respectively).

Serum CRP levels in TA patients (p=0.018) and SLE patients (p=0.009) were significantly higher than in healthy control group. The numbers of CEC were higher in patients with TA (7.02 ± 2.78 n/µl) and patients with SLE (7.24 ± 2.06 n/µl) in comparison to healthy control group (4.90 ± 1.82 n/µl), p<0.001 and p<0.001, respectively. CEPC numbers were correlated positively with serum CRP levels (r=0.228, p=0.34). CEPC numbers were not different between the groups.

No difference was found between leptin and adiponectin levels in TA patients and healthy controls. However, a significant negative correlation was found between leptin levels and ghrelin and acylated ghrelin levels in TA patients (r=0.344, p=0.006 and r=0.389, p=0.002, respectively). Leptin and adiponectin levels were significantly lower in patients with coronary involvement (p=0.027, p=0.016 respectively). There was a significant positive correlation between mean carotid intima-media thickness (IMT) measurements and adiponectin levels in TA patients (p=0.001 and p=0.004, respectively).

Conclusion: Ghrelin levels were considered to be useful in monitoring the disease activity and adjusting the treatment plan in TA. DEITAK scoring, “DEITAK- PGO” and radiological activity indicators which are in accordance with NIH activation criteria can also be used for disease follow-up.

Disclosure: H. Yilmaz: None; V. Gerdan: None; D. Kozaci: None; S. Akar: None; G. Can: None; A. Gulcu: None; V. Cakir: None; Y. Goktay: None; M. Birlik: None; N. Akkoc: None; F. Onen: None.

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Circulating Endothelial Cells and Endothelial Progenitor Cells in Takayasu Arteritis. Serkan Dogan1, Dilek Solmaz2, Ozden Piskin3, Servet Akar4, Aytaç Gulcu4, Faize Yuskel1, Volkân Cakır3, Yigit Goktay3, Merih Birlik3, Nurullah Akkoc4 and Fatos Onen4. 1Hematology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, 2Internal Medicine, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, 3Radiology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, 4Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey.

Objective: In Takayasu arteritis (TA) with unknown etiology, it is very important to monitor the disease activity because intensive treatment is needed during active periods. Today’s clinical and laboratory activity criteria alone are not very satisfactory for follow-up. This study aims to investigate the numbers of circulating endothelial cells (CEC) and endothelial precursor cells (CEPC) and also the correlation of these parameters with disease activity in patients with TA.

Patients and Methods: 32 patients with TA, 25 with systemic lupus erythematosus (SLE) (patient control group) and 30 healthy subjects were included in this study. Detailed medical history was obtained and full physical examination was done in all patients. The NIH activation criteria, DEITAK scoring and “DEITAK-physician’s global opinion (PGO)” and also radiological investigations (B-mode and Doppler USG and MR angiography) were used to evaluate disease activity in TA patients. The numbers of CEC and CEPC were measured by flow cytometry in patient and control groups.

For comparison of the groups, Kruskall-Wallis analysis or chi square tests were used. When significance level was determined between the groups, they were recompared in pairs by way of Mann-Whitney U test. For the purpose of testing the correlations between the variables, Spearman’s correlation analysis was applied.

Results: There were 29 female and 3 male patients with TA (mean age: 43.9 years). Mean disease duration was 5.4 years. According to NIH activation criteria in TA patients, 18.8% of patients were active; according to “DEITAK-physician global opinion”, 18.8% active, 28.1% persistent and 53.1% inactive and according to the radiological findings, 31% active. A significant correlation was determined between the NIH activation criteria and DEITAK scoring, “DEITAK-POG” and also radiological activity (r=0.529, p=0.002; r=0.540, p=0.002; and r=0.361, p=0.046 respectively).

Serum CRP levels in TA patients (p=0.018) and SLE patients (p=0.009) were significantly higher than in healthy control group. The numbers of CEC were higher in patients with TA (7.02 ± 2.78 n/µl) and patients with SLE (7.24 ± 2.06 n/µl) in comparison to healthy control group (4.90 ± 1.82 n/µl), p<0.001 and p<0.001, respectively. CEPC numbers were correlated positively with serum CRP levels (r=0.228, p=0.34). CEPC numbers were not different between the groups.

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Conclusion: Ghrelin levels were considered to be useful in monitoring the disease activity and adjusting the treatment plan in TA. DEITAK scoring, “DEITAK- PGO” and radiological activity indicators which are in accordance with NIH activation criteria can also be used for disease follow-up.

Disclosure: H. Yilmaz: None; V. Gerdan: None; D. Kozaci: None; S. Akar: None; G. Can: None; A. Gulcu: None; V. Cakir: None; Y. Goktay: None; M. Birlik: None; N. Akkoc: None; F. Onen: None.
Clinical Characteristics, Treatment and Ethnic/Racial Differences in the Manifestations of 518 Behçet’s Syndrome Patients in the United States.

Yusuf Yazici, Maria T. Filopoulos, Elizabeth Schimmel, Andy McCraken and Christopher Swearingen. NYU School for Joint Diseases

Background: Behçet’s syndrome (BS) is a systemic vasculitis rare in northern Europe and the US. Previous reports have suggested that there may be ethnic and racial differences in disease presentation and possible clustering of manifestations. We started a dedicated Behçet’s clinic in 2004 and now report on the disease characteristics of the first 518 patients.

Methods: All patients seen at the center have completed a MDHAQ, and a questionnaire about past medical history, medication use, Behçet’s specific history, ethnic and demographic information. These data are prospectively collected and updated each visit. About 2/3 of patients live within driving distance of New York City while patients from over 45 states have been seen. Patients were analyzed as the whole cohort and then also separated into 2 groups: Group A = with ethnic background in northern Europe and North America and/or self declared Caucasians without background around the Mediterranean and/or the Far East; Group B = Patients with an ethnic background in the Mediterranean, Middle East, North Africa, and Far East. These groups were compared for disease manifestations, demographic information and medication use.

Results: 518 patients (398 (77%) female, mean (SD) disease duration 40.5) years, age 35 (13.6), 324 (60%) fulfilled International Behçet’s classification criteria) were analyzed. Disease characteristics of the whole cohort and those fulfilling criteria are given in Table 1. When divided by ethnic background, Group A had statistically more significant GI disease (47% vs. 28%, p<0.001) and more females compared to Group B (83% vs. 71%, p=0.005) for those meeting criteria. For the whole cohort, less eye disease and vascular involvement than other centers was reported. There was only one blind eye.

Most commonly used medication at baseline was low dose prednisone (62%), followed by colchicine (46%), TNF inhibitors (21%) azathioprine (19%) and methotrexate (10%).

Conclusions: In this cohort of 518 Behçet’s patients, largest cohort to be reported in the US, demographic and clinical differences were noted between patients with different ethnic backgrounds. There were significantly more female patients in the non-ethnic groups. The frequency of GI disease was also significantly more in this group. Eye disease prevalence for the whole cohort was far less than reported from other centers. These finding point to considerable heterogeneity in disease expression in BS at different geographic areas.

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Clinical Features of Behçet’s Disease with Vascular Involvement. Hirotoshi Kikuchi1, Kurumi Asako1, Maki Takayama1, Hajime Kono1, Shunsei Hirohata2 and Yasuo Ono1. 1Department of Internal Medicine, Teikyo University School of Medicine, 2Department of Microbiology and Immunology, Teikyo University School of Medicine, Ibaraki-ku, Tokyo, Japan

Background: Behçet’s disease (BD) is characterized by recurrent oral aphthous stomatitis, ocular involvement, genital ulcer, and skin lesions. Although one of the serious manifestations of BD is vascular involvement (VBD), its pathogenesis remains unclear. The current studies were therefore undertaken to delineate the clinical characteristics of VBD and to explore its pathological features.

Patients and Methods: The clinical records of 277 patients who satisfied the 1990 international criteria for Behçet’s disease and were hospitalized in Department of Internal Medicine, Teikyo University School of Medicine, from January 1989 to December 2009 were reviewed.

Results: Forty two patients (25 males and 17 females) had been diagnosed with VBD. The mean age of BD onset was 35.6±11.8 years (mean±SD), and the mean delay for the development of VBD was 5.8 years. The frequency of HLA-B51, HLA-A26, pathergy test and complete type was 34.4%, 13.3%, 42.9% and 38.1%, respectively. The vessels involved were as follows: the most frequent venous lesion was deep vein thrombophlebitis (42.9%), followed by deep vein thrombosis (40.5%), superior vena cava syndrome (9.5%), and inferior vena cava obstruction (4.8%) and frequent arterial lesions were aortic aneurysm (11.9%), pulmonary aneurysm (9.5%), femoral artery stenosis (7.1%), and subclavian arterial stenosis (4.8%).

Seven patients suffered from both venous and arterial lesions. Two patients died because of hemoptysis from pulmonary arterial aneurysms. One of 7 patients who were complicated with pulmonary embolism died.

Conclusion: These results indicate that the frequency of vascular manifestations tended to be higher for venous lesions (81.8%) compared with arterial lesions (28.6%). In particular, the main complication associated with death was pulmonary vessel involvement.

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Clinical Spectrum, Angiographic Findings and Outcome in Takayasu Arteritis. Using the Disease Extent Index for Takayasu Arteritis (DEI.TAK). Sivakumar M. Rajappa. Cerebrovascular and Vasculitis Research Foundation, Chennai, Tamilnadu, India

Background: Takayasu’s arteritis (TA) is a chronic, inflammatory large vessel vasculitis affecting the aorta and its major branches, pulmonary and
coronary arteries. Although more common in Asia, the disease has been found worldwide, with different vascular involvement patterns, clinical manifestations and outcome usually affecting young women. The disease involves all the three layers of the vessel walls and results in luminal abnormalities like intima medial thickening, stenosis, occlusion, and aneurysm formation. The Disease Extent Index for Takayasu Arteritis (DEI.Tak), is a validated instrument for assessment of the clinical involvement in Takayasu Arteritis (TA), without need for imaging. The index is also useful to study damage and outcome in TA.

**Objective:** To analyze data in TA, regarding demographics, race, clinical manifestations, angiographic findings by CT/MR/Digital Subtraction Angiograms, outcome of vascular interventions and mortality over a period of 20 years, using the DEI.Tak.

**Methods:** This is a prospective cross sectional study 222 TA patients who fulfilled the ACR diagnostic criteria for TA, seen at Chennai, India between January 1988 and March 2010. The clinical findings were entered into a database using the DEI.Tak. All the relevant laboratory parameters like ESR, CRP and imaging modalities like Carotid and Vertebral Duplex Ultrasound and Intima-Media Thickness (IMT), CT/MR/Invasive Angiograms and PET CT scans were performed to classify TA according to Nummano’s angiographic classification. The survival of grafts and interventional procedures like Carotid, Subclavian, Renal and Aortic angioplasty and stenting done on TA patients were analyzed. The outcome with treatment and surgery/ interventional procedures and mortality over a 22 year period is reported.

**Results:** A total number of 222 TA patients (151 women and 71 men) were seen with a mean age of 34.62 ± 14.8 years. The systems scored commonly were: Systemic-9(42.66%), Renal-84(38.33%) and Cardiovascular-83(37.92%). System rarely involved were skin, mucous membrane and abdomen. The mean Common Carotid Artery IMT was 0.845 cm. The long term survival of stents with effective immunosuppressive treatment pre and post stenting were 92%, 83% and 72% at the end of 5, 10 years and 15 years respectively. The 5 Angiographic distribution of involvement of the aortic arch and its branches were: Type I: 19, IIA: 26, IIB: 37, III: 43, IV: 33 and V: 64. During the follow up of over 20 years, 41 patients expired.

**Conclusions:** This study involving a large cohort of TA cases, followed up for more than two decades provides a comprehensive assessment of the extent and severity of TA using the DEI.Tak. CVS is the most important system affected and the presence of new pulse loss was a good indicator of active disease. With effective immunosuppressive therapy, there is good long term patency of stents in the Indian subjects with improved morbidity and mortality.

**Disclosure:** S. M. Rajappa: None.

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Cluster Analysis of Vascular Involvement in Takayasu Arteritis: Extension of the Lesions Is Contiguous in the Aorta and Symmetric in Paired Arteries

**Background:** The determinants of vessel targeting are largely unknown in vasculitides. The aim of this study was to identify patterns of vascular involvement in Takayasu’s arteritis (TA), using cluster analysis.

**Methods:** Peripheral vascular Doppler, CT angiography and angio-MRI data of 82 patients with TA (ACR criteria) were studied between Jan. 1995 and May 2006. Cross-involvement between 34 main arteries were assessed using the Phi correlation coefficient. Patterns of vascular involvement were identified using hierarchical cluster analysis.

**Results:** Data were obtained from 68 women (82.9%) and 14 men (17.1%). The median duration of follow-up was 5.1 years (range: 1 month to 30 years).

For 16 (80%) of 20 paired arteries, the highest correlation of involvement was observed with the contralateral artery (r=0.31 to 0.66). Conversely, the involvement of the abdominal aorta best correlated with that of the thoracic descending aorta (r=0.38, p=0.0005), and this latter best correlated with the aortic arch (r=0.44, p<0.0001). This suggests contiguous extension in the aorta.

Cluster analysis visually confirmed that all paired arterial beds, but the internal and external carotid arteries, clustered with their contralateral counterpart, and that the aortic arch, the descending thoracic aorta and the abdominal aorta clustered together.

**Conclusion:** Our study reveals that TA lesions mostly develop in a symmetric manner in paired vascular territories and that disease extension is contiguous in the aorta. This may prove useful for improving the radiological follow-up of patients with TA, and for providing a pattern for further investigations focusing on the mechanisms of vessel-specificity in vasculitides.

**Disclose:** L. Arnaud: None; J. Haroche: None; D. Toledano: None; P. Cacoub: None; N. Costedoat-Chalumeau: None; D. Le Thi Huong-Boutin: None; P. Chuelz: None; Z. Amoura: None.

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Colchicine Does Not Decrease the Need for Immunosuppressive Use at Long Term in Behcet’s Syndrome

**Objective:** To analyze data in TA, regarding demographics, race, clinical manifestations, angiographic findings by CT/MR/Digital Subtraction Angiograms, outcome of vascular interventions and mortality over a period of 20 years, using the DEI.Tak.

**Methods:** A total number of 222 TA patients (151 women and 71 men) were seen with a mean age of 34.62 ± 14.8 years. The systems scored commonly were: Systemic-9(42.66%), Renal-84(38.33%) and Cardiovascular-83(37.92%). System rarely involved were skin, mucous membrane and abdomen. The mean Common Carotid Artery IMT was 0.845 cm. The long term survival of stents with effective immunosuppressive treatment pre and post stenting were 92%, 83% and 72% at the end of 5, 10 years and 15 years respectively. The 5 Angiographic distribution of involvement of the aortic arch and its branches were: Type I: 19, IIA: 26, IIB: 37, III: 43, IV: 33 and V: 64. During the follow up of over 20 years, 41 patients expired.

**Conclusions:** This study involving a large cohort of TA cases, followed up for more than two decades provides a comprehensive assessment of the extent and severity of TA using the DEI.Tak. CVS is the most important system affected and the presence of new pulse loss was a good indicator of active disease. With effective immunosuppressive therapy, there is good long term patency of stents in the Indian subjects with improved morbidity and mortality.

**Disclosure:** S. M. Rajappa: None.

**Reference:**

**Disclose:** V. Hamuryudan: None; G. Hatemi: None; S. Yurdakul: None; C. Mat: None; K. Tascilar: None; Y. Ozayzgan: None; E. Seyahi: None; S. Ugurlu: None; H. Yazici: None.

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Diagnostic Value of Pathergy Phenomenon in Behcet’s Disease

**Objective:** To analyze data in TA, regarding demographics, race, clinical manifestations, angiographic findings by CT/MR/Digital Subtraction Angiograms, outcome of vascular interventions and mortality over a period of 20 years, using the DEI.Tak.

**Methods:** A total number of 222 TA patients (151 women and 71 men) were seen with a mean age of 34.62 ± 14.8 years. The systems scored commonly were: Systemic-9(42.66%), Renal-84(38.33%) and Cardiovascular-83(37.92%). System rarely involved were skin, mucous membrane and abdomen. The mean Common Carotid Artery IMT was 0.845 cm. The long term survival of stents with effective immunosuppressive treatment pre and post stenting were 92%, 83% and 72% at the end of 5, 10 years and 15 years respectively. The 5 Angiographic distribution of involvement of the aortic arch and its branches were: Type I: 19, IIA: 26, IIB: 37, III: 43, IV: 33 and V: 64. During the follow up of over 20 years, 41 patients expired.

**Conclusions:** This study involving a large cohort of TA cases, followed up for more than two decades provides a comprehensive assessment of the extent and severity of TA using the DEI.Tak. CVS is the most important system affected and the presence of new pulse loss was a good indicator of active disease. With effective immunosuppressive therapy, there is good long term patency of stents in the Indian subjects with improved morbidity and mortality.

**Disclosure:** S. M. Rajappa: None.

**Reference:**

**Disclose:** V. Hamuryudan: None; G. Hatemi: None; S. Yurdakul: None; C. Mat: None; K. Tascilar: None; Y. Ozayzgan: None; E. Seyahi: None; S. Ugurlu: None; H. Yazici: None.

**Background:** Pathergy phenomenon (PP) is used for the diagnosis of Behcet’s Disease (BD). It is an important criterion of many classification/diagnosis criteria. The sensitivity of PP was 83% in Russia, 77% in Morocco, 71% in Iraq, 62% in China and Egypt, 61.5% in Iran, 55% in Germany, 44%
in Japan, and 18% in Saudi Arabia. The sensitivity of PP is changing over the time. It has changed in Iran from 71.8% for the first 1000 patients to 33.9% for patients 5000 to 6000. The aim of this study was to look for the diagnostic value of PP in the present time, and its change over the past 35 years.

Patients and Methods: The Behcet’s Disease registry, has the data of 6607 BD and 4292 Control patients from the past 35 years. Patients were divided in 4 groups of 1650 BD and 1073 controls. Sensitivity, Specificity, Positive and Negative Predictive Value (PPV & NPV), Positive and Negative Likelihood Ratio (PLR & NLR), Diagnostic Odds Ratio (DOR), and Youden’s Index (YI) were calculated. The first and the 4th quartiles were compared.

Results: Positive PP changed from 64.2% to 35.8% (1st and 4th quartiles) in BD and from 13.4% to 1.6% in control patients (Table 1). Sensitivity, specificity, PPV, NPV, PLR, NLR, DOR, and YI are shown in Table 2.

Table 1. Details of Behcet’s Disease and control patients

<table>
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<th>Second Group</th>
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<tr>
<td>Control Patients</td>
<td>1–1073</td>
<td>1074–2146</td>
<td>2147–3219</td>
<td>3228–4292</td>
</tr>
<tr>
<td>PP Done</td>
<td>1069</td>
<td>1004</td>
<td>900</td>
<td>1061</td>
</tr>
<tr>
<td>Positive PP</td>
<td>143</td>
<td>96</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>% Positive</td>
<td>13.4%</td>
<td>9.0%</td>
<td>1.0%</td>
<td>1.6%</td>
</tr>
<tr>
<td>95% CI</td>
<td>11.5–15.6</td>
<td>7.4–10.9</td>
<td>0.5–1.9</td>
<td>1.0–2.6</td>
</tr>
</tbody>
</table>

Table 2. Performance and Diagnostic value of Pathergy Test

<table>
<thead>
<tr>
<th>Patients and Controls</th>
<th>First Group</th>
<th>Second Group</th>
<th>Third Group</th>
<th>Fourth Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD Patients</td>
<td>1–1650</td>
<td>1651–3300</td>
<td>3301–4950</td>
<td>4951–6607</td>
</tr>
<tr>
<td>PP'Done</td>
<td>1580</td>
<td>1639</td>
<td>1622</td>
<td>1643</td>
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<tr>
<td>Positive PP</td>
<td>1014</td>
<td>971</td>
<td>820</td>
<td>588</td>
</tr>
<tr>
<td>% Positive</td>
<td>64.2%</td>
<td>59.2%</td>
<td>50.6%</td>
<td>35.8%</td>
</tr>
<tr>
<td>95% CI</td>
<td>61.8–66.5</td>
<td>56.8–61.5</td>
<td>48.2–53.1</td>
<td>33.3–38.1</td>
</tr>
<tr>
<td>Control Patients</td>
<td>1–1073</td>
<td>1074–2146</td>
<td>2147–3219</td>
<td>3228–4292</td>
</tr>
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<td>1.0–2.6</td>
</tr>
</tbody>
</table>

Discussion: The sensitivity of PP decreased while the specificity increased. The difference was statistically significant (Table 2).

PPV shows the probability that the positive test is true positive. PPV is influenced by the prevalence of the disease in the tested population. The prevalence of BD in Iran is 0.08%. In BD clinic, 1/3rd of new patients have BD. PPV improved from 0.38% to 1.76% (population) and from 70.2% to 91.7% in BD Unit (between 1st and 4th quartile). Although the sensitivity of PP has decreased over the time, its value as a diagnostic test, when positive, has improved. NPV shows the probability that a negative test is truly negative. NPV lost a little in the BD Clinic, going from 83.1% to 75.7% (Table 2).

PLR shows the odds of having the disease. PLR improved from 4.8 to 22.4 (1st to 4th quartile), meaning the risk of having BD with positive PP is 22.4 times. The NLR deteriorated from 0.41 to 0.65, meaning the error rate of not having BD increased from 41 to 65%.

The diagnostic odds ratio (DOR) combines the results of PLR and NLR. A value of 1 means no discrimination between patients and controls. Higher values mean better discrimination. DOR improved from 11.6 to 34.3 (from 1st to 4th quartile).

Youden’s Index (YI) shows the accuracy of PP. Zero is the worse and one the best. The YI decreased from 0.5 to 0.34, showing a deterioration of precision rate over the time.

Conclusion: PP improved its diagnostic value.

Disclosure: F. Davatchi: None; C. Chams-Davatchi: None; F. Shahram: None; B. Sadegh Abdollahi: None; A. Nadji: None; M. Akhlaghi: None; T. Faizi: None; R. Larimi: None.

1290

Disease Activity Assessment in Large Vessel Vasculitidis. Luca Magnani1, Annabelle Versari1, Diana Salvo1, Massimiliano Casali1, Giuseppe Germaino1, Riccardo Meliccoli1, Lia Pulsatelli1, Debra Formisano1, Gianluigi Bajocchi1, Nicolò Pipitone1, Luigi Boiardi1 and Carlo Salvareni1. 1Arcispedale S Maria Nuova, Reggio Emilia, Italy, 2Istituti Ortopedici Rizzoli, Bologna, Italy, 3Università di Bologna, Italy

Purpose: Assessment of disease activity in patients with large vessel vasculitidis (LVV) is challenging because clinical, biologic and radiologic data do not always correlate. 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and serum interleukin-6 (IL-6) may be useful for the assessment of disease activity, however data on their usefulness are not well defined.

The aims of this study were to compare National Institute of Health (NIH) criteria and Indian Takayasu’s arteritis activity score (ITAS) with FDG-PET scan results, as well as with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum IL-6 values for the assessment of disease activity in a group of patients with LVV.

Methods: Fifty-eight patients with LVV (24 with Takayasu’s arteritis, 31 with giant cell arteritis according to the ACR criteria, and 3 with chronic psoasitis) underwent a total of 99 PET scans. Images were reviewed by a nuclear medicine physician (AV) who was unaware of the clinical diagnosis and assessed images for pattern and intensity of vascular uptake. LVV activity data, including laboratory tests, were obtained within 14 days of the PET scans.

Results: PET scanning revealed abnormal vascular uptake (≥ 2 on a 0–3 scale in at least 1 of the 7 vascular regions analyzed) in 57.6% of the 99 examinations. According to the NIH criteria, 27 patients had active and 72 inactive disease. Thirty-three patients had ITAS ≥ 1 and 66 equal to 0. ESR, CRP and IL-6 levels were stratified into 4 groups according to distribution quartiles. 12.5% of patients (9/72) with inactive disease according to NIH criteria had ITAS ≥ 1, while 11.1% of patients (3/27) with active disease according to NIH criteria had ITAS = 0. The agreement between ITAS and NIH criteria was 87.9% (87/99) (kappa value: 0.71). Abnormal FDG vascular uptake was present in 52.8% of patients (38/72) with inactive disease according to NIH criteria, while 30.8% of patients (8/26) with active disease according to NIH criteria had normal FDG vascular uptake. The total agreement between FDG vascular uptake and NIH criteria was 53.1%. Abnormal FDG vascular uptake was present in 53.6% of patients (35/66) with ITAS = 0, while 33.3% of patients (11/33) with ITAS ≥ 1 had normal FDG vascular uptake. The agreement between FDG vascular uptake and ITAS criteria was 53.5%. ESR and CRP levels were significantly associated with disease activity according to the NIH criteria and ITAS (p = 0.0001). In contrast, there was no association between IL-6 serum levels and disease activity according to NIH criteria and ITAS.

Conclusion: The agreement between NIH criteria and ITAS for disease activity assessment in LVV is excellent. ESR and CRP values are associated with disease activity as assessed by the NIH criteria and ITAS, while FDG vascular uptake and IL-6 serum values are not.

Disclosure: F. Davatchi: None; C. Chams-Davatchi: None; F. Shahram: None; B. Sadegh Abdollahi: None; A. Nadji: None; M. Akhlaghi: None; T. Faizi: None; R. Larimi: None.
Disease Assessment in Takayasu’s Arteritis: Data from a Literature Search and a Survey of Expert Opinion. Haner Direskeneli, Sibel Z. Aydin, Peter A. Merkel and Turkish Takayasu Study Group, 1 Istanbul, Turkey, 2 Boston University School of Medicine, West Newton, MA, 3Mar- mara University, School of Medicine, Istanbul, Turkey

**Purpose:** To study approaches to disease assessment in Takayasu’s arteritis (TAK) by summarizing published clinical studies and surveying current expert opinion in Turkey.

**Methods:** A literature search was conducted in “PubMed” with keywords “Takayasu’s arteritis”, “assessment”, “activity”, “remission”, and “relapse” for studies published in English between 1994–2010 (case reports and reviews excluded). Informed by the literature review, Turkish rheumatologists (n=34, 20 specialists/academicians and 14 rheumatology fellows) and two foreign experts completed a questionnaire on disease assessment in TAK.

**Results:** Of the 4004 articles with the key-word “Takayasu’s arteritis”, items associated with disease assessment and activity were present in 62 studies. Among these, 45% (n=28) focused on clinical issues (case series, treatment, outcome), 32% (n=20) on biomarkers/pathogenesis, and 22% (n=14) on vascular imaging. An NIH study (Kerr et al. 1994) was most commonly cited for a definition of active disease (48%, n=30). Acute-phase response (ESR/CRP) was part of an “active” disease definition in 84% (n=52), constitutional features in 73% (n=45), clinical features of vascular ischemia in 53% (n=33), and angiographic involvement in 58% (n=36). A consensus score of disease activity was used in 24% (ITAS=2, ITAS=1), and a patient-derived outcome tool (SF-36) in two studies.

After a presentation of the results of the literature search, experts were asked to define a “gold-standard” of disease activity in TAK. New vessel/organ involvement determined clinically or by imaging was chosen by 84%, physician global assessment by 13%, no expert named patient global assessment. The most commonly chosen items for a disease-assessment tool were new bruises or arterial tenderness (both 100%), arterial claudication (97%), acute-phase reactants (97%), arterial tenderness (94%), fever (88%), and constitutional symptoms (84%). Although experts felt that a dichotomous assessment (active vs. inactive) was not suitable (63%), they also agreed that damage vs. activity (83%) and grumbling vs. highly active disease (80%) cannot be reliably differentiated in TAK. Some organ manifestations present in BVAS and DEI.Tak (a recently-developed TAK-specific tool) were found suitable for TAK (cardiovascular-100%, CNS-93%, renal-87%, abdominal-83%, ocular-83%, musculoskeletal-72%) whereas others were felt to have a limited value (respiratory-50%, cutaneous-47%, ENT-24%, genitourinary-19%). The majority of experts (62%) agreed that an outcome measure could be developed for large-vessel vasculitis for use in research of giant-cell arteritis and TAK that incorporated manifestations of both diseases.

**Conclusion:** Outcome measures used in research for TAK vary considerably in content and do not consistently include clinical manifestations that experts give a high value to regarding disease assessment, including vascular imaging and biomarkers. These data are helpful in guiding the process of creating an internationally-accepted core set of outcome measures in large vessel vasculitis.

**Disclosure:** H. Direskeneli: None; S. Z. Aydin: None; P. A. Merkel: None; Turkish Takayasu Study Group: None.

1292

Effect of Glucocorticoids on Gelatinase expression (MMP-2 and MMP-9) Expression in Giant-Cell Arteritis (GCA) Using an Ex-vivo Temporal Artery Culture Model. Marc Corbera-Bellalta, Ana García-Martínez, Esther Planas-Rigol, Esther Lozano, Marta Segarra, Georgina Empigol-Frigóle, José Hernández-Rodríguez, Itziar Tavera and Marta C. Cid. Department of Systemic Autoimmune Diseases. Hospital Clinic. University of Barcelona, IDIBAPS, Barcelona, Spain

**Background:** GCA is the most frequent systemic vasculitis in the elderly. Increased gelatinase expression and proteolytic activity have been demonstrated in GCA lesions. Gelatinases may play an important role in the progression of inflammatory lesions given their proinflammatory functions and elastinolytic activity and may also participate in vascular remodelling in response to injury. Glucocorticoids (GC) are the cornerstone of GCA treatment but it is not know how GC treatment influences gelatinase expression.

**Purpose:** To explore the effects of GC on gelatinase expression in GCA lesions using an ex-vivo arterial culture system.

**Methods:** Fresh temporal artery sections obtained from 19 GCA patients and 10 controls were embedded in the reconstituted basement membrane Matrigel™ and cultured for 5 days as described (Arthritis Rheum 2008 (suppl) 58:9; S929–S929). Cultured sections were treated with medium alone or with medium supplemented with 0.5 mg/ml of dexamethasone. MMP-2 and MMP-9 mRNA was measured in recovered sections by quantitative real-time PCR (Applied Biosystems). Both gelatinases were also measured in the supernatant fluid by immunooassay (R&D Systems).

**Results:** MMP-9 mRNA was significantly more abundant in cultured sections from patients compared to controls (1283±1353 vs 304±222 relative units, p=0.039). Contrarily, no differences were observed in MMP-2 mRNA between normal and GCA cultured sections (2097±918 vs 3450±2800 relative units, p=0.738). MMP-9 and MMP-2 protein concentrations were higher in the supernatant from GCA sections compared to controls (48.9±30.3 vs 7.0±7.02 ng/ml, p=0.006 for MMP-9); although differences were not significant for MMP-2 (39.1±31.5 vs 15.3±16.6 ng/ml, p=0.192), Dexamethasone treatment for 5 days highly reduced MMP-9 expression both at the mRNA (861.2±1054 vs 88±110 p=0.018) and at the protein level (48.9±30.4 vs 8.6±5.4 ng/ml, p=0.003) whereas no effect was apparent on MMP-2 expression.

**Conclusion:** The pattern of gelatinase expression in cultured temporal artery sections parallels what has been observed in fresh biopsies (Ann Rheum Dis. 2007 Nov; 66(11):1429–35). In the present model, dexamethasone treatment in fully reduced MMP9 expression with a much lesser effect on MMP-2 expression. These findings reinforce a pro-inflammatory role for MMP9 during active disease and suggest a role for MMP2 in vascular remodelling before and after treatment. Supported by SAF 05/06250 and MTV3 06/0710.

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1293

Efficacy of Cerebrospinal Fluid Testing and Magnetic Resonance Imaging for Diagnosis of Neuro-Behcet’s Disease: A Multicenter Retrospective Analysis. Shunsei Hirohata, Hitoshi Kikuchi, Tetsuji Sawada, Hiroko Nagafuchi, Masataka Kuwana, Mitsuhiro Takeno and Yoshiaki Ishigatsubo. 1Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, 2Keio University School of Med, Tokyo, Japan, 3Kitasato Univ School of Med, Kanagawa, Japan, 4St Marianna University School of Med, 5Teikyo Univ School of Med, 6Tokyo Medical University, Shinjuku Tokyo, Japan, 7Yokohama City Grad Sch of Med, Yokohama, Japan

**Objective:** Central nervous system (CNS) involvement in Behcet’s disease (BD) is one of its most serious complications (neuro-Behcet’s disease [NBD]). Since there are factors causing neurological manifestations other than BD (non-NBD), the diagnosis of NBD is often difficult. The present study was therefore designed to delineate the clinical characteristics of NBD and to determine the reliable diagnostic parameters. Special attention was paid to cerebrospinal fluid (CSF) cell counts and interleukin-6 (IL-6) as well as magnetic resonance imaging (MRI) findings.

**Methods:** A multicenter retrospective survey was performed on BD patients who fulfilled the diagnostic criteria of the international study group and presented neurological manifestations between 1987 and 2008. The diagnosis of either NBD or non-NBD was confirmed by retrospective review of the clinical records. NBD was further classified into acute NBD and chronic progressive NBD, 35 with chronic progressive NBD, and 33 with non-NBD. Smoking status, smoking duration, smoking amount, presence of NBD, 35 with chronic progressive NBD, 33 with non-NBD. Smoking and HLA-B51 were correlated with chronic progressive NBD (p=0.0024 and p=0.016, respectively). CSF cell counts were most prominently elevated in acute NBD, but were within normal limits in approximately 15% of chronic progressive NBD. ROC curve analysis revealed that the sensitivity and specificity of CSF cell counts for diagnosis of acute NBD were 97.3% and 96.7%, respectively, at the cut-off value of 6.5/mm³. Whereas CSF IL-6 was elevated in both acute NBD and chronic progressive NB, it was decreased only in acute NBD after treatment. Moreover, the sensitivity and specificity of CSF IL-6 for differential diagnosis of chronic progressive NBD from
recovery phase of acute NBD were 86.7 % and 94.7 %, respectively, at the cut-off value of 16.55 pg/ml. High intensity lesions on MRI T2-weighted images were found in 60.5% of acute NBD, 54.2% of chronic progressive NBD, and 42.4% of non-NBD, whereas brainstem atrophy was observed in 7.5% of acute NBD, 71.4% of chronic progressive NBD, and 9.0% of non-NBD.

Conclusion: The results indicate that CSF cell count is a useful marker for diagnosis of acute NBD, whereas determination of persistent elevation of CSF IL-6 along with brainstem atrophy on MRI is pivotal for diagnosis of chronic progressive NBD. The data have also disclosed that T2 high intensity lesions on MRI are neither sensitive nor specific for diagnosis of NBD.

Disclosure: S. Hirohata: None; H. Kikuchi: None; T. Sawada: None; H. Nagafuchi: None; M. Kuwana: None; M. Takeno: None; Y. Ishigatsubo: None.

1294
Endothelin-1 (ET-1) Induces Collagen Type I and Type III Production by Temporal Artery-Derived Myointimal Cells. A Mechanism Potentially Leading to Intimal Hyperplasia in Giant-Cell Arteritis (GCA). Ester Planas-Rigol, Marc Corbera-Bellalta, Ester Lozano, Montserrat Butjosa, Sergio Prieto-González, José Hernández-Rodríguez, Marta Segarra and Maria C. Cid. Department of Systemic Autoimmune Diseases. Hospital Clinic. University of Barcelona, IDIBAPS, Barcelona, Spain

Background: GCA is a granulomatous vasculitis involving large and medium-sized arteries. The inflammatory process leads to intimal hyperplasia and vessel stenosis with the ensuing ischemia of supplied tissues. Intimal hyperplasia results from proliferation and matrix production by myointimal cells. Recent studies demonstrate up-regulation of the ET system in GCA lesions and increased ET-1 concentrations in plasma from patients with cranial ischemic complications (Ann Rheum Dis. 2010 Feb; 69(2):434–42). ET-1 is one of the most potent vasoconstrictor agents and may create a microenvironment prone to the development of vasospasm, contributing to ischemic events.

Purpose: To investigate whether ET-1 may additionally contribute to vascular occlusion by inducing pro-fibrotic responses in cultured human temporal artery-derived myointimal cells (HTAMC) potentially participating in the development of intimal hyperplasia.

Methods: HTAMC were obtained from cultured temporal artery sections from patients with GCA as described (Ann Rheum Dis. 2008 Nov; 67(11): 1581–8). Transforming growth factor b (TGFb), collagen type I (COL1) and type III (COL3) expression was assessed by quantitative real-time PCR (Taqman® Gene Expression Assay) from Applied Biosystems.

Results: ET-1 up-regulated TGFb and COL1 expression by HTAMC in a dose-dependent manner. A delayed increase in COL3 expression was also observed which was partially mediated by TGFb. Study of underlying mechanisms is in progress.

Conclusions: ET-1 may contribute to intimal hyperplasia directly by inducing collagen type I and indirectly by inducing the synthesis of the fibrogenic cytokine TGFb by human temporal artery-derived myointimal cells. These preliminary results suggest that ET receptor antagonists may prevent vascular occlusion in GCA.

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1295
Expansion of Peripheral Blood Plasma Blasts Reflects Disturbances of B Cell Homeostasis in Patients with Takayasu Arteritis and Success of B Cell Depletion Therapy. Bimba F. Hoyer1, Imitaz M. Mumtaz1, Udo Schneider2, Rolf Keitzer3, Gerd-Rüdiger Burnmester2, Andreas Radbruch1 and Falk Pieper4. 1Dep. Pediatric Rheumatology, Charité Universityhospital Berlin, 2Dep. Rheumatology and Clinical Immunology, Charité Universityhospital Berlin, 3Dep. Rheumatology and Clinical Immunology, Charité Universityhospital Berlin and German Rheumatism Reserach Center Berlin, Berlin, Germany, 4Dep. Rheumatology and Clinical Immunology, Charité Universityhospital Berlin and German Rheumatism Reserach Center Berlin, 5German Rheumatism Reserach Center Berlin

Purpose: Takayasu arteritis (TA) is a rare form of chronic large vessel vasculitis mainly affecting the aorta and its branches.

The etiology of TA is yet unknown but highly suggestive of T cell-mediated autoimmunity. The presence of autoantibodies against endothelial cells (AECA) however indicates that autoreactive B cells and plasma cells may be involved in the pathogenesis. Therefore, we comprehensively analysed the peripheral blood cell subpopulations from TA patients.

Methods: 14 patients suffering from TA (7 active, 7 inactive) were analysed. As controls, 10 patients with active SLE and 9 healthy donors were investigated.

PBMCs were surface stained for expression of CD27, CD19, CD20 and MHCII and analysed by flowcytometry. Plasmablasts were characterized as being CD19+CD20+CD27++ and MHCII++. All CD27++ CD20+ CD19+ cells represent both newly generated plasmablasts and plasma cells. Sera of patients were tested for the presence of Anti-Endothelial-Cell-Antibodies (AECA).

Data was analysed using FlowJo-Software. Statistical analysis was done with SPSS.

Results: Patients with active TA revealed significantly more peripheral blood plasmablasts compared to patients with inactive disease as well as healthy persons. Absolute numbers of plasmablasts in patients with active TA (mean 0,0068/nl, SD 0.0049/nl) were comparable to active SLE patients (mean 0,01908/nl, SD 0.02/nl) whereas inactive patients (mean 0,001629/nl SD 0.0016/nl) show numbers comparable to healthy persons (median 0,001057/nl, SD 0.0005/nl). The same is true for the frequency of plasma cells within the B cells.

In addition a significant correlation between the frequencies of CD27++ CD20+ CD19+ cells in the B cell population and Crp-level could be observed as well (r=0.731 p=0.0029, Pearson-Test).

No correlation could be found with the presence of AECA.

Based on these results we successfully treated three patients refractory to conventional immunosuppressive drugs and TNF blockers with B cell depletion.

Conclusion: For the first time disturbances in the B cell homeostasis in TA that might be crucial in the pathogenesis are described. Therefore B cells and plasma cells should be considered as a target for therapeutic approaches as successful treatment of three patients by B cell depletion underlines.

Disclosure: B. F. Hoyer: None; I. M. Mumtaz: None; U. Schneider: None; R. Keitzer: None; G.-R. Burnmester: Roche; 2, 5; 8; A. Radbruch: None; F. Hiepe: None.

1296
Expression and Function of Toll Like Receptors in Peripheral Blood Mononuclear Cells of Patients with Polymyalgia Rheumatica and Giant Cell Arteritis. Lorena Alvarez-Rodriguez2, Marcos Lopez-Hoyos3, Cristina Mata1, Ana Fontalba1, Jaime Calvo-Alen1, Maria Jose Marin4, Jose Luis Fernandez-Luna5, Jesus Agiero-Balbin5, Maitane Aranzamendi-Zaldunbide4, Ricardo Blanco5, Ignacio Villa5, Orlando Pomper5, Marien Peiro6, Teresa Ruiz7 and Victor M. Martinez-Taboada2. 1Hospital de Serrallana, Spain, 2Hospital de Serrallana, Spain, 3Hospital Universitario Marques de Valdecilla, Santander, Spain, 4Hospital Universitario Marques de Valdecilla

Objective: To investigate the expression and function of the TLR family in PBMCs of patients with polymyalgia rheumatica (PMR) and giant cell arteritis (GCA).

Methods: We analyzed 70 patients with PMR, 20 with GCA and 24 healthy controls (HC). TLR expression was assessed by flow cytometry. TLR function was studied by stimulating PBMCs with specific ligands.

Results: A significant increased expression of TLR7 in PBMCs of patients with active disease compared with HC was found. Despite an increased expression of TLR7, circulating monocytes from patients showed a significant lower in vitro response to TLR7 agonists. No amino acid substitutions predicted to be functionally damaging were found in TLR7. A normal response to specific TLR7 agonists in patients in complete remission eliminated a genetic defect. The expression profile on PBMCs from HC induced by plasma from PMR and GCA were marked by up-regulation of type I IFN-response transcripts, suggesting that the diminished response to TLR7 agonists in active disease was secondary to receptor saturation with natural ligands. We attempted to identify the presence of a set of respiratory virus in plasma from patients without conclusive results.

Conclusion: These data suggest the activation of TLR7 by a natural(s) ligand(s) in patients with PMR and GCA that is followed by a selective desensitization of the receptor. Despite the failure to identify a responsible virus in plasma from patients, the up-regulation of type I IFN-response genes
Extracellular HMGB1 Is Increased in Patients with Behcet’s Disease with Intestinal Involvement. Joong Kyong Ahn, You Sun Lee, Eun-Jun Park, Ji-Won Hwang, Ji-Min Oh, Jaejoon Lee, Chan-Hong Jeon, Eun-Mi Koh and Hoon Suk Cha, Bucheon Hospital, Soonchunhyang University College of Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Masan Samsung Hospital, Sungkyunkwan University School of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine

Objective: Behcet’s disease (BD) is a chronic multisystemic inflammatory disorder of unknown etiology consisting of orogenital ulceration, ocular inflammation, and skin lesions. HMGB1 (High-Mobility Group Box 1 protein) has been demonstrated to play an important role in chronic inflammatory diseases including rheumatoid arthritis, systemic lupus erythematosus, and inflammatory myositis. HMGB1 is a crucial cytokine that mediates the response to infection, injury and inflammation. HMGB1 activates macrophages and monocytes to release proinflammatory cytokines, upregulates endothelial adhesion molecules, and stimulates endothelial cell barrier failure. We performed this study to investigate the association between extracellular HMGB1 expression and disease activity and clinical features of BD’s disease.

Method: Extracellular HMGB1 expression from the sera of 42 BD patients and age- and sex-matched 22 healthy controls (HC) was measured using ELISA.

Results: According to the activity criteria based on clinical manifestation at the time of study, 42 patients with BD comprised 25 active and 15 inactive patients with mean age of 47 years (range 22–65 years). The HMGB1 concentration was significantly increased in BD patients compared to HC (78.70 ± 20.22 vs. 10.79 ± 1.90 ng/ml, p = 0.002). In addition, HMGB1 concentration was significantly elevated in patients with intestinal involvement compared to those without (179.61 ± 67.95 vs. 61.89 ± 19.81, p = 0.04). Patients with vascular involvement showed decreased trend of serum HMGB1 expression compared to those without vascular involvement (36.79 ± 12.63 vs. 95.47 ± 27.41 ng/ml, p = 0.059). There was no significant association between HMGB1 concentration and clinical manifestation, including genital ulcer, erythema nodosum, ocular involvement or musculoskeletal symptoms. No significant difference in the serum HMGB1 level was found between inactive and active BD patients (58.78 ± 18.46 vs. 92.26 ± 31.63 ng/ml, p = 0.367). No significant correlation was found between HMGB1 concentration and leukocyte counts, ESR, or CRP.

Conclusion: This is the first study to evaluate the expression of HMGB1 in Behcet’s disease. An important finding in our study is that extracellular HMGB1 concentrations are significantly increased in BD patients compared to HC, and are significantly increased in the sera of BD patients with intestinal involvement compared to those without intestinal involvement. These results suggest that extracellular HMGB1 may play an important role in the pathogenesis of BD.

Disclosure: J. K. Ahn: None; Y. S. Lee: None; E.-J. Park: None; J.-W. Hwang: None; J.-M. Oh: None; J. Lee: None; C.-H. Jeon: None; E.-M. Koh: None; H.-S. Cha: None.

1299 Glucocorticoid Therapy in Giant Cell Arteritis: Duration and Predictors for Long-Lasting Remission. Paula Estrada, Javier Narvaez, Laura Lopez Vives, Carmen Gomez Vaquero and Joan Miquel Nolla. Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain

Purpose: To analyze the clinical course and duration of glucocorticoid (GC) therapy in a series of patients with giant cell arteritis (GCA), identifying those predictors for the achievement of a long-lasting remission.

Methods: Retrospective follow-up study of an unselected population of 140 patients with GCA diagnosed in 1 center between 1986 and 2008. The end-point of patient follow-up was the date of the last clinic visit or the date of death. Long-lasting remission was recorded as the date of permanent discontinuation of treatment without recurrence of symptoms for at least 1 year. Possible correlations between the duration of therapy and demographic, clinical, laboratory and treatment variables were explored. Multivariate regression analysis were used to identify variables associated with the achievement of long-lasting remission.

Results: The series included 94 women and 46 men with a mean age at time of diagnosis of 75 ± 7 years (range, 50 to 92). TAB was positive in 112 (80%) patients. The median follow-up duration after diagnosis was 36.6 months (range, 12.5 to 180). All patients were treated with GCs and responded rapidly (mean initial dosage of prednisone: 50.1 ± 13.7 mg/day). The dosage was later reduced according to the treating physicians’ judgment. The median duration required to achieve a maintenance dose of less than 10 mg prednisone/day was 8.5 months. Relapses or recurrences occurred in 82 (52.6%) patients, with a mean of 2.7 ± 1.7 relapses per patient.

In 60 (42.8%) patients, GCs were discontinued and permanent remission achieved after a median of 26.7 months of treatment, with a range of 15 to 90 months. The median cumulative dose of prednisone taken by these patients was 8.51 gm. Only in 33.3% (20/60) of these patients GCs could be withdrawn within the first 2 years of treatment. This percentage increased to 73% (33/60) at 3 years, 81.6% (49/69) at 4 years, and 88.3% (53/60) at 5 years, with only 11.6% (7/60) of the patients requiring therapy for more than 5 years. At the time of last follow-up, 80 (57.2%) of the 140 patients were still taking GCs with a median treatment duration of 36 months; in 50% of these patients the duration of treatment was longer than 3 years. A significant correlation was found between the duration of therapy and (1) diagnostic delay (r = 0.240; p = 0.004), (2) age at disease onset (r = -0.237; p = 0.004), (3) the value of pre-treatment erythrocyte sedimentation rate (r = 0.154; p = 0.047), and (4) total dose of prednisone (r = 0.824; p < 0.0001). In the multivariate analysis, the only variables associated with the achievement of long-lasting remission were the age at disease onset fulfiling the International Behcet’s Classification Criteria were analyzed as one cohort and then in 2 groups: Group A = with ethnic background in northern/central Europe and North America and/or self declared Caucasians without Mediterranean, Middle Eastern and/or Far Eastern background; Group B = Patients with Mediterranean, Middle Eastern, North African, or Far Eastern ethnic background. These groups were compared for their prevalence, type of disease and outcome of ocular disease.

Results: 471 patients were seen for suspected BS. 296 (62.8%) fulfilled the International Behcet’s Classification Criteria and were included in the present study. Of those, 121 (40.9%) patients had eye disease, which included 56 (18.9%) with uveitis, 8 (2.7%) with retinitis, 11 (3.7%) with episcleritis, and 42 (14.2%) with other eye disease. There was no statistically significant difference between Groups A (n = 163) and B (n = 133) regarding the prevalence of eye disease (41.1% vs. 40.6%, p = 0.93), types of involvement: uveitis (19.6% vs. 18.0%, p = 0.729), retinitis (1.8% vs. 3.8%, p = 0.311), episcleritis (3.1% vs. 4.5%, p = 0.514), baseline disease activity and use of immunosuppressive medications. None of the patients presented with or developed blindness during the study period.

Conclusions: Eye involvement was less prevalent and seemed to have better outcomes in this North American cohort of BS patients than in cohorts studied in high-incidence/ endemic BS regions. Contrary to our expectations, there was no significant difference in prevalence or outcome of Behcet’s eye disease between North Americans of non-Mediterranean European ancestry compared to individuals of Mediterranean, Middle- or Far Eastern descent living in the US. These findings could suggest a role of environmental factors in the phenotype expression of BS in general, and in the pathogenesis of Behcet’s eye disease in particular.

Disclosure: J. Nowatzky: None; M. T. Filipoulo: None; C. Swearingen: None; Y. Yazici: None.
Objective: The purpose of this study was to assess the potential association between CD40 rs1883832 polymorphism and biopsy-proven GCA. We also studied whether this polymorphism might influence the phenotypic expression of this vasculitis, in particular the development of visual ischemic manifestations.

Methods: 305 Spanish patients with biopsy-proven GCA and 788 matched controls were assessed. DNA from patients and controls was obtained from peripheral blood. Samples were genotyped for the CD40 rs1883832 C/T polymorphism using a predesigned TaqMan allele discrimination assay and by polymerase chain reaction amplification.

Results: Biopsy-proven GCA patients showed a trend towards a higher frequency of the minor allele homozygote of rs1883832 (TT) compared to healthy controls (12.1% vs. 8.3%, respectively; p = 0.05, odds ratio-OR: 1.54 [95% confidence interval- CI: 0.98–2.40]). Also, a marginally significantly increased frequency of the minor allele T was observed in GCA patients with visual ischemic manifestations (36.9%) compared to those without visual ischemic manifestations (27.7%); OR: 1.53 [95% CI: 0.99–2.34], p=0.04). In this regard, biopsy-proven GCA patients carrying the minor allele T (either TT or TC) experienced visual ischemic manifestations more commonly than those carrying the CC genotype (58.5% versus 44.2%, OR 1.78 [95% CI: 0.99–3.22], p=0.04).

Conclusions: Our results suggest a potential implication of the CD40 rs1883832 C/T polymorphism in the susceptibility to visual ischemic manifestations in individuals with biopsy-proven GCA.

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1302
Large-Vessel Involvement in Newly-Diagnosed Giant Cell Arteritis: A Case-Control Study Using Color-Doppler Sonography. Alessandra Ghinoi, Luigi Boiardi, Nicolò Pipitone, Giovanna Restuccia, Alberto Nolli, Mauro Silingardi, Giuseppe Germani, Gianluigi Bajocchi, Ilaria Chiarolanza, Luca Magnani, Pierluigi Macchioni, Andrea Caruso and Carlo Salvatari. 1Arcispedale S Maria Nova, Reggio Emilia, Italy, 2Arcispedale S Maria Nuova, Reggio Emilia, Italy

Purpose: The prevalence of large-vessel vasculitis (LVV) in newly diagnosed giant cell arteritis (GCA) is still poorly documented. Two studies have estimated such prevalence at 30% and 83% using Color-Doppler sonography (CDS) (1) and 18F-FDG PET (fluorodeoxyglucose positron emission tomography) (2), respectively. CDS allows to visualize the temporal, axillary, and subclavian arteries, as well as the aortic arch, abdominal aorta and supra-aortic vessels. The presence of a hypoechogenic halo around the arterial walls is considered quite specific for GCA.

The aim of this study was to investigate the prevalence of LVV in newly diagnosed GCA using CDS and to compare the clinical findings of GCA patients with and without LVV.

Methods: Sixty-two consecutive patients with a diagnosis of new-onset GCA according to the American College of Rheumatology criteria who had a CDS performed were analyzed. The identified patients with LVV were randomly matched to an equal number of GCA patients without LVV.

Results: In 19 out of 62 patients (30.6%), CDS showed the characteristic halo sign in at least one vessel examined. Comparing patients with and without LVV, no significant difference was found for any of the following parameters: gender (male:female 0.0/100% versus 21.1%/78.9%), positivity of the temporal artery biopsy (82.4% versus 88.2%), presence of a transmural infiltrate (78.6% versus 86.7%), or periadventitial infiltrate (21.4% versus 13.3%), temporal arteries' abnormalities on inspection (85.7% versus 92.3%), cranial (77.8% versus 94.1%) and constitutional (66.7% versus 35.3%) manifestations. Similarly, the ESR was similar in both groups (91 ± 30 versus 72 ± 25 mm/1st hour).

Conclusion: LVV evidenced by CDS occurred in 30.6% pts with newly diagnosed GCA. This prevalence is very similar to that found in a previous study with a similar design. Constitutional manifestations were more frequent and cranial manifestations were less frequent in our GCA patients with LVV, although the difference did not reach significance. Early diagnosis of LVV in GCA can help tailor treatment accordingly and may prevent vascular complications.
References:


Disclosure: A. Ghinoi: None; L. Boiardì: None; N. Pipitone: None; G. Restuccia: None; A. Nicolini: None; M. Silingardi: None; G. Germani: None; G. Bajocchi: None; I. Chiarolanza: None; L. Magnani: None; P. Macchioni: None; A. Caruso: None; C. Salvaranì: None.

1303
New Disease Activity Indices in the Management of Behçet’s Disease: A Comparative Study of Patients from Turkey and the USA, Gonca Mumcu, Yusuf Yazici, Nevusun Inanc, Tulin Ergun, Maria Filopoulou and Haner Direskeneli. Faculty of Health Sciences, Department of Health Informatics and Technologies, Marmara School of Medicine

Purpose: The aim of this study was to evaluate and compare oral ulcer activity by Composite index (CI) and general disease activity by Behçet Syndrome Activity Score (BSAS) in patients from Turkey (TR) and the USA with Behçet’s disease (BD).

Methods: In this cross-sectional study, age- matched 30 Caucasian active female patients from TR (mean age: 41.10 ± 11.04 years) and 30 Caucasian active female patients from USA (mean age: 41.40 ± 11.56 years) with BD were included. Patients from TR were examined in Marmara University Hospital, Department of Rheumatology whereas patients from USA were examined in NYU, Hospital for Joint Disease in the same time span. Composite index (CI) was previously validated (1) for oral ulcer activity. It evaluates both pain scored by visual analogue scale (VAS) and functional status. Behçet Syndrome Activity Score (BSAS) (2) is a general disease activity index and evaluates clinical activities according to organ involvement in BD. CI and BSAS were filled by both patients from Turkey (TR) and USA. Scores could be between 0 and 10 in CI and 0 –100 in BSAS, (0=inactive disease). Oral health related quality of life was evaluated by oral health impact profile-14 (OHIP-14) in both groups. Better oral health-related quality of life was indicated with lower scores in OHIP-14 (range 0–56).

Results: No significant difference was found in OHIP-14 scores between patients from TR (21.4 ±3.7) and USA (21.9±12.7) (p=0.886). Although the number of oral ulcers was higher in patients from TR than patients from USA (4.3±2.5 and 3.3±2.8, respectively), this was not statistically significant (p=0.161). Yet, CI index score and pain score evaluated by VAS as its subscale score, were higher in patients from TR (7.8±1.6, 52.7±22.1) compared to the US patients (4.2±1.5, 35.9±27.8) (p=<0.001 and p=0.013, respectively). CI score was correlated with BSAS score in patients from TR (r=0.36 p=0.04) and USA (r=0.44 p=0.02).

BSAS score was higher in patients from USA (44.5±18.5) compared to patients from TR (21.4±15.4)(p<0.0001). In accordance with these results, majority of patients from USA (76.8 %) were treated with immunosuppressive medications compared to patients from TR (67 %) (p<0.0001).

Conclusions: CI and BSAS, two patient derived disease activity measures, showed moderate correlation with the manifestations of BD and moderate correlation with one another in these two different patient populations. They may be suitable tools for use both in routine clinical care and clinical studies in BD patients.

References:


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1304
Normal Sedimentation Rate and C-Reactive Protein at Diagnosis in Biopsy-Proven Giant Cell Arteritis, Tanaz A. Kermani, Cynthia S. Crowson, Steven R. Ytterberg, Gene G. Hunder and Kenneth J. Warrington, Mayo Clinic, Rochester, MN

Purpose: 1) To determine the frequency of normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at diagnosis in biopsy-proven giant cell arteritis (GCA) and 2) to evaluate clinical factors associated with discordant or normal ESR/CRP.

Methods: In this retrospective cross-sectional study, medical records of all patients with biopsy-proven GCA evaluated between January 1, 2000 and December 31, 2008 were reviewed. Only subjects with ESR and CRP available at the time of diagnosis were included. Clinical information was abstracted. Subjects with both ESR and CRP normal and those with discordant ESR/CRP were identified. We used our laboratory cut-off values for elevated ESR (>22 mm/hour for men and >29 mm/hour for women) and CRP (>8 mg/L). Fisher’s exact test was used to compare categorical variables between patients with discordant results to those with concordant ESR/CRP, and GCA patients with normal ESR/CRP to those with elevated ESR/CRP. Rank sum tests were used to compare continuous variables between the above two groups.

Results: Two-hundred and forty patients were diagnosed with biopsy-proven GCA at a single institution during the study period. Of these, 160 subjects (78%) had ESR and CRP available prior to GCA diagnosis. The final study population included 119 women (74.4%) and 41 men (25.6%); mean age at diagnosis 74.3 years (± 7.59). Nine patients (5.6%) had discordant ESR and CRP of whom 7 had Eleveted CRP but normal ESR. Mean age at diagnosis of GCA, mean duration of symptoms, clinical symptoms and laboratory findings at GCA diagnosis were similar in patients with discordant ESR/CRP compared to patients with concordant results (p>0.05).

Both ESR and CRP were normal in 18 patients (11.3%), 11 of whom were on prednisone and were excluded from the analysis. However, 7 patients (4%) had normal ESR and CRP at diagnosis in the absence of prednisone use. Table 1 compares the clinical manifestations and laboratory findings of these 7 patients to those with elevated ESR or CRP. A greater proportion of patients with normal ESR and CRP had polymyalgia rheumatica (PMR) symptoms compared to patients with elevated ESR or CRP (p=0.02). Furthermore, fewer patients with normal ESR and CRP had anemia (p<0.001) and there was a trend toward lower thrombocytosis (p=0.09) compared to subjects with elevated ESR or CRP.

Table 1. Clinical manifestations of GCA patients with normal ESR and CRP to those with elevated ESR and/or CRP

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>ESR, CRP elevated, No (%)</th>
<th>ESR and CRP normal, No (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Mean age at diagnosis, years</td>
<td>74.3 (±7.88)</td>
<td>70 (±5.87)</td>
<td>0.12</td>
</tr>
<tr>
<td>Median duration symptoms, days</td>
<td>53</td>
<td>113</td>
<td>0.32</td>
</tr>
<tr>
<td>Mean duration from laboratory testing to biopsy, days</td>
<td>6.1 (±8.34)</td>
<td>8.7 (±9.07)</td>
<td>0.52</td>
</tr>
<tr>
<td>New headache</td>
<td>79 (62.7)</td>
<td>45 (71.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Jaw claudication</td>
<td>61 (48.4)</td>
<td>2 (28.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>Scalp tenderness</td>
<td>10 (34.1)</td>
<td>0 (0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Permanent vision loss</td>
<td>11 (8.7)</td>
<td>1 (14.3)</td>
<td>0.49</td>
</tr>
<tr>
<td>Fever</td>
<td>3 (24.6)</td>
<td>0 (0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Anorexia</td>
<td>16 (12.7)</td>
<td>0 (0)</td>
<td>0.60</td>
</tr>
<tr>
<td>Weight loss</td>
<td>42 (33.3)</td>
<td>0 (0)</td>
<td>0.43</td>
</tr>
<tr>
<td>Polymyalgis rheumatica</td>
<td>33 (26.2)</td>
<td>5 (71.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>NSAID use</td>
<td>61 (49.6)</td>
<td>2 (28.6)</td>
<td>0.44</td>
</tr>
<tr>
<td>Anemia</td>
<td>89 (70.6%)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>43 (36.4)</td>
<td>0 (0)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Conclusions: CRP is considered a more sensitive marker in GCA. This is the largest, single center study to date evaluating the prevalence of normal CRP in biopsy-proven GCA. While ESR and CRP were concordantly elevated in most patients, discordant results were noted in 5.6%. More significantly, 4% of patients in this study had both normal ESR and CRP at diagnosis. They were more likely to present with PMR symptoms. Absence of a systemic inflammatory response does not exclude GCA and biopsy should be pursued in patients with high clinical suspicion of GCA, especially if PMR symptoms are present.

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Pediatric Behçet’s Disease, PED-BD: An International Cohort Study of 110 Patients. One-Year Follow-Up Data. Isabelle Kone’-Paut1, Martha Durce Bello1, Faraday Shahram1, Marco Gattorno1, Rolando Cimaz2, Seza Özen3, Michael Hofer4, Ilkman Tugal-Tukan5, Samir Assaad-Khalil6, Jasmin Kimmerle-Deschner6, Saida Benamour7, Soulaymane Al Mayouf8, Christine Pajot4, Jordi Anton3, Albert Fayé5, Susan Nielsen6, Alexia Letierce1 and Tu-Anh Tran11, 1Bicêtre University Hospital, Clinical Research Unit, Le Kremlin-Bicêtre, France, 2Hacettepe University, Department of Pediatrics, Ankara, Turkey, 3Hospital Alexandria Hospital, Alexandria, Egypt, 4IBN Rochid University Hospital, Casablanca, Morocco, 5Istanbul University-Ophtalmology, Istanbul, Turkey, 6Pediatric Clinic, Blegdamsvej, Copenhagen, 7Pediatric Rheumatology G. Gaslini Scientific Institute, Genoa, Italy, 8Pediatric Rheumatology King Faisal Hospital, Riyadh, Saudi Arabia, 9Pediatric Rheumatology Unit, Sant Joan de Dèu University Hospital, Esplugues de Llobregat, Spain, 10Pediatric Rheumatology, A. Meyer Institut Florence, Florence, Italy, 11Pediatric Rheumatology, Bicêtre University Hospital, Le Kremlin-Bicêtre, France, 12Pediatric Rheumatology, Robert Debré University Hospital, Paris, France, 13Pediatric Rheumatology, Toulouse University Hospital, Toulouse, France, 14Pediatric Rheumatology, Vaudois University Hospital, Lausanne, Switzerland, 15Rheumatology Research Center, Shariati Hospital, Tehran, Islamic Republic of Iran, 16Rheumatology, Childrens Hospital, University of Tuebingen, Tübingen, Germany

Aim of the Study: To set up an algorithm for definition of pediatric Behçet’s disease (PED-BD) based on international cohort of children suspected with BD

Patients and Methods: An international expert committee has defined the inclusion criteria as follows: Recurrent oral aphthosis (ROA) associated with at least one of following: genital ulceration (GU), erythema nodosum, folliculitis, pustulosis/acneiform lesions, positive pathergy test, uveitis, venous/arterial thrombosis, family history of BD. Onset of disease is before the 16th birthday, disease duration is ≤ 3 years, minimum future follow up duration is 4 years and to obtain informed consent. Clinical data are updated at the 16th birthday, disease duration is 4 years and to obtain informed consent. Clinical data are updated every year. Accordingly, the included patients are classified by the expert committee into 3 groups: definite PED-BD, probable PED-BD and no PED-BD. Statistical analysis are performed at the end to compare the 3 groups of patients. Centers specializing in PED-BD have been called to collaborate and document their patients into a single database, (available online).

Results: In January 2010, 110 patients (56M/54F) from 16 centres of 11 countries have been examined. Mean age, 11 years, and mean disease duration 3.1 years (median 8.2). Mean age at BD suspicion: 11.8 y. (median 14.4y). At inclusion 38 % of them had only 1 symptom associated with ROA, 31 % had 2 and 31% had at least 3. 106 first evaluations have been done. Chronology of symptoms at presentation: 59 patients with 1 symptom (ROA: 45, and fever:5 being the most frequent), 26 with 2 symptoms (OA + GU: 6), 14 with 3 and 3 with 4.

93% were receiving treatment: colchicine 59%, steroids 58% and azathioprine 14%. Fifty-seven patients underwent the first year evaluation and 36 had no new symptom, 12 had one, and 9 had 2. The expert committee has examined 48 files and classified 30 as definite and 18 as probable. Among our patients classified as definite, 26 (87%) fulfilled the ISG criteria. 17/18 classified as probable did not meet the international criteria (p< 0.001).

Table. List of symptoms in addition to oral aphthosis in patients classified as definite and probable by the committee of experts.

<table>
<thead>
<tr>
<th>Probable n=18</th>
<th>Confirmed n=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital ulceration*</td>
<td>21</td>
</tr>
<tr>
<td>Skin lesions**</td>
<td>22</td>
</tr>
<tr>
<td>Uveitis</td>
<td>16</td>
</tr>
<tr>
<td>Arthralgia/arthritis</td>
<td>11</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>12</td>
</tr>
<tr>
<td>Neurological***</td>
<td>12</td>
</tr>
<tr>
<td>Vascular</td>
<td>7</td>
</tr>
<tr>
<td>Urological</td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>13</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3</td>
</tr>
<tr>
<td>Family history</td>
<td>3</td>
</tr>
</tbody>
</table>

Significant values: \( p<0.03; \quad *p<0.0001; \quad **p<0.09 \)

Conclusion: The expert committee has classified the majority of patients in the BD group although they presented with few symptoms independently from BD classification criteria.

Disclosure: I. Kone’-Paut: None; M. Durce Bello: None; F. Shahram: None; M. Gattorno: None; R. Cimaz: None; S. Özen: None; M. Hofer: None; I. Tugal-Tukan: None; S. Assaad-Khalil: None; J. Kimmerle-Deschner: None; S. Benamour: None; S. Al Mayouf: None; C. Pajot: None; J. Anton: None; A. Fayé: None; S. Nielsen: None; A. Letierre: None; T.-A. Tran: None.

1306

Plasma Fibrinogen Is More Specific Than Either ESR or CRP for Confirmation of Response to Treatment in Patients with Active Poly- myalgia Rheumatica. Eoghan M. McCarthy1, 2, Paul A. MacMullan1, 2, Shibel Al-Madhaifer, 3, Anne Madigan, 3, Suzanne Donnelly, 3, Conor J. McCarthy1, Eamonn S. Molloy3 and Geraldine M. McCarthy1. 1Mater Misericordiae Univ. Hosp, Dublin, Ireland, 2Mater Misericordiae University Hospital, Dublin, Ireland, 3Mater Misericordiae University Hospital, Dublin, Ireland, 4Mater Misericordiae University Hospital, 5St Vincent’s University Hospital, Dublin, Ireland

Purpose: To evaluate fibrinogen as a marker of disease activity in polymyalgia rheumatica (PMR).

Background: Measurement of disease activity in PMR is challenging due to the subjective nature of symptoms and absence of consistent physical signs in an elderly population. ESR and CRP are used in clinical practice to guide therapeutic decisions. Both are non specific markers of inflammation. Disease activity in PMR has been shown to correlate with interleukin 6(IL6) levels. IL6 also regulates fibrinogen production. We sought to prospectively evaluate plasma fibrinogen as a biomarker of active inflammation in patients with PMR.

Methods: 60 patients with PMR (as per Jones Hazleman criteria) were divided into Active disease group (1, n=25) or Inactive disease group (2, n=35), based on symptoms, physician assessment and standard biomarkers ESR and CRP. Plasma fibrinogen was also assayed. Both groups underwent clinical and laboratory assessment at baseline and 6 weeks. The following disease activity data was collected: Duration of morning stiffness(mins), Visual Analogue Scale(VAS) for pain(Vaspain) and VAS for patient assessment of disease activity(VaDA). Demographic data and categorical variables were assessed using Fisher’s Exact Test. Between group disease activity data were assessed using Wilcoxon Signed Rank Test. Receiver operator curves (ROC), predictive values, and likelihood ratios were calculated for all biomarkers measured.

Results: Demographic data was similar in all groups. Median steroid dose was 15mg (range 10 –60mg) in the active group and 5mg (range 0–15mg) in the inactive group. There were significant differences in steroid dose between the two groups(p<.001).Mean scores for Vas pain (7.44 versus 2.8), Vas disease activity (7.38 vs 2.77) and duration of morning stiffness(72mins vs 9mins) improved significantly in the Active group between week 1 and week 6 (p<0.001).Mean fibrinogen reduced from 5.2g/L to 3.5g/L (normal<4g/L) between weeks 1 and 6. ESR and CRP reduced from 59.6 mm/hr to 24.3 mm/hr(normal ~20mm/hr) and 45.9mg/L to 12.66mg/L(normal~5mg/L). There was no significant difference between the mean disease scores at week 6 in the Active group and the Inactive group at either week 1 or 6.

ROC curve analysis revealed fibrinogen to be more specific than either ESR or CRP for the detection of response to treatment in patients with active PMR (Fig 1).
Prevalence of Behçet’s Disease in Southern Sweden. Aladdin Mohammad, Thomas Mandl, Gunnar K. Sturfelt, Mårten Segelmark, 1Helsingborg Hospital, Helsingborg, Sweden, 2Skåne University Hospital, Lund, Sweden, 3Skåne University Hospital, Malmö, Sweden

Background: Behçet’s Disease (BD) is a chronic inflammatory disease of unknown etiology characterized by recurrent oral and genital ulcerations and a variety of systemic manifestations, most of which are believed to be due to vasculitis. BD has a distinct geographic distribution with highest prevalence in the countries of East Asia, the Middle East and the Mediterranean (the old Silk Route). The epidemiology of BD in Sweden is largely unknown. Studies from other European countries have shown significantly higher prevalences among immigrants in comparison to populations with European ancestry.

Objectives: To estimate the prevalence of Behçet’s Disease (BD) in a well defined multiethnic population in southern Sweden.

Method: The study area is two health care districts in the southern part of Skåne, the southernmost county in Sweden. The study population (adult ≥ 15 years) at the date of prevalence estimate was 582,347 inhabitants (51% females). The majority of the population was Scandinavian but about 23% were of non-Scandinavian ancestry. Patients with BD living within the study area were identified by search in clinical registries at the departments of Rheumatology, Nephrology and Ophthalmology at the 3 hospitals within the study area. The search period was between 1997 and the end of 2009. All case records were reviewed to ascertain the diagnosis. Only patients fulfilling the criteria for diagnosis of BD according to the International Study Group for Behçet’s Disease were included. The date of point prevalence was January, 1st, 2010.

Results: A total of 21 patients (five women) fulfilling the diagnosis criteria for BD were included in the study. The main clinical and demographic features of all patients are summarized in Table 1. Eighty one percent of patients (17 of 21) were of non-Scandinavian ancestry, mostly from the Middle East, Iraq and Turkey. The prevalence of BD was 36.1/million adults, and was significantly higher among subjects of non-Scandinavian ancestry in comparison to subjects of Scandinavian ancestry (125.8 vs. 8.9/million adults, p<0.001). For the entire study population, the gender-specific prevalence rate of BD was significantly higher among men than women; 55.9/million vs. 16.9/million (p=0.013).

Table 1. Clinical and demographic characteristics of patients with Behçet’s Disease In southern Sweden

|                      | All patients (n=21) | Men (n=16) | Women (n=5) | P*
|----------------------|--------------------|------------|-------------|-----
| Prevalence/million  |                    |            |             |     |
| Adult (95% CI)      |                    |            |             |     |
| All patients, n=21  | 36.1 (20.6-51.5)   | 55.9 (28.5-83.3) | 16.9 (2.1-31.7) | 0.013 |
| Scandinavian, n=4   | 8.9 (0.2-17.7)     | 4.6 (0-13.5)  | 13.2 (0-28.1) | 0.336 |
| Non-Scandinavian, n=17 | 125.8 (66.0-185.5)| 223.9 (110.6-337.1)| 29.3 (0-70.0) | 0.001 |
| Diagnosis delay 1   | 42 (4-96)          | 48 (10-96)  | 36 (4-72)   | 0.618 |
| Age at diagnosis, yrs, median (range) | 30 (15-42) | 31 (15-42) | 24 (19-38) | 0.380 |
| Age at point prevalence, yrs, median (range) | 41 (27-66) | 42 (27-66) | 40 (31-54) | 0.809 |

1 men vs. women, *time from first symptom to diagnosis, occurring anytime throughout the disease course.

Conclusions: The prevalence of BD in our area was significantly higher among subjects of non-Scandinavian ancestry in comparison to subjects of Scandinavian ancestry. These findings are consistent with previous epidemiologic reports from other European countries.

Disclosure: A. Mohammad: None; T. Mandl: None; G. K. Sturfelt: None; M. Segelmark: None.

1308
Safe, Rapid-Onset, and Sustained Biological Activity of IL-1β Regulating Antibody XOMA 052 in Resistant Uveitis of Behçet’s Disease: Results of a Pilot Trial. Ahmet Gül, Baha Artim-Esen, Alan M. Solinger, Linda Giustino, Charles Dinarello, and Ilknur M. Tugal-Tutkun, 1Häftinge Hospital, Helsingborg, Sweden, 2Skåne University Hospital, Lund, Sweden, 3Skåne University Hospital, Malmö, Sweden, 4Häfteing Hospital, Helsingborg, Sweden.

Introduction: Behcet’s disease (BD) is a vasculitic multi-system inflammatory disorder of unknown etiology. Increased expression of proinflammatory cytokines, including IL-1β has been considered to play a critical role in the pathogenesis of BD. Uveitis is a major manifestation of BD, and recurrent attacks can cause permanent vision loss in patients resistant to immunosuppressive drugs. XOMA 052 is a recombinant humanized monoclonal antibody. It binds and regulates IL-1β activity, and its administration may produce rapid and sustained reductions in symptoms in IL-1β-mediated systemic inflammatory diseases.

Aim: To evaluate the safety and PK of XOMA 052 in BD uveitis.

Methods: This pilot open-label study enrolled patients who developed a posterior/panuveitis or retinal vasculitis attack despite cyclosporine and/or azathioprine treatment. XOMA 052 was administered as a single 0.3 mg/kg intravenous infusion. Subjects suspended their immunosuppressive treatments and maintained prednisolone at ≤10 mg/day (6 patients) or 20mg/day (one patient) without any increase.

Results: Seven patients enrolled in and completed the study period of 98 days. No adverse events related to XOMA 052 were observed. Preliminary PK analysis of the first 6 patients showed a clearance of 2.6 mL/day/kg, a beta half-life 26.7 days and a volume of distribution for the central compartment of 54 mL/kg. Intravenous infusion started to resolve in all patients on Day 1, and complete resolution of retinal findings and vitreous haze was achieved in 4 to 21 days. Five patients were in remission on Day 28, and one was still in remission at Day 98 with a single infusion. One of the patients received increased doses of prednisolone for new retinitis attack in the contralateral eye on Day 25, and other received intravitreal methyl pred-
S545

Severe and Opportunistic Infections during Giant Cell Arteritis Course: A Case-Control Study. Javier Narvaez1, Laura López Vives1, Paula Estrada2, Nuria del Castillo1,Montserrat Robustillo1 and Joan Miquel Nolla3. Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain,3Department of Rheumatology, Barcelona, Spain

Purpose: To assess the incidence of severe and opportunistic infections in GCA patients as compared to age- and sex-matched, population based randomly selected controls.

Methods: Case-control study including 140 cases with GCA diagnosed in 1 center from 1986 to 2008. Patients were diagnosed with GCA if they had a positive temporal artery biopsy (TAB) or, in cases with negative biopsy or no biopsy, if they fulfilled the 1990 ACR criteria for the classification of GCA and had a prompt and persistent response to glucocorticoid (GC) treatment. The end-point of patient follow-up was the date of the last clinic visit or the date of death. For each GCA patient, 2 subjects without GCA of the same sex and similar age an time of follow-up were randomly selected from the population of patients attended in our outpatient clinic due to osteoporosis, osteoarthritis or gout. Severe infection was recorded as any bacterial infection leading to hospitalization.

Results: The series included 94 women and 46 men with a mean age at time of diagnosis of 75 ± 7 years (range, 56 to 92). TAB was positive in 112 (80 %) patients. The median duration of follow-up after diagnosis was 36.6 months (range, 12.5 to 180).

All patients were treated with GCs and responded rapidly (mean initial dosage of prednisone: 50.1 mg ± 13.7 mg/day). The dosage was later reduced according to the treating physicians’ judgment.

During follow-up, severe and/or opportunistic infections were recorded in 17.9% (25/140) of GCA patients compared to 3.5% (10/280) in the control group (odds ratio (OR) = 5.87, 95% confidence interval (CI): 2.73, 12.61). Among GCA patients, opportunistic infections occurred in 5.7% (8/140) of the patients (including 1 case of tuberculosis, 6 cases of herpes zoster and 2 cases of candidiasis) compared to 1.4% (4/280) in the control group (OR = 4.18, 95% CI: 1.23, 14.14). Several bacterial infections occurred in 13.6% (19/140) of the cases compared to 2.14% (6/280) in the non-GCA subjects (OR = 7.17; 95% CI: 1.79, 18.4).

Interestingly, the incidence of tuberculosis (TB) in our GCA patients, in whom prophylaxis with isoniazid was not regularly administered, was 181/100,000 patient-years (1 case in 550 patient-years of follow-up). During the same period (1990–2008) the pooled annual incidence of TB infection in the general population of Spain ranged from 23 to 30 cases/100,000 individuals. This data reflects that the incidence of TB in GCA patients receiving GC is at least 6 times higher than in the general population.

Only one of the GCA patients died due to pulmonary TB complicated with upper gastrointestinal bleeding. The overall mortality was similar in cases and controls (p>0.05).

Logistic regression models identified the cumulative dose of prednisone (OR=6.19, 95% CI: 1.61, 23.71; p=0.007) and the presence of large-artery complication (aortic involvement and/or large-artery stenosis) (OR=11.35, 95% CI: 2.24, 57.33; p=0.003) as significant predictors of severe/opportunistic infections.

Conclusion: The incidence of severe and opportunistic infections is increased in GCA. This increased risk is mostly influenced by GC therapy. We found a 6-fold increased risk of TB infection in patients diagnosed with GCA.

Disclosure: J. Narvaez: None; L. López Vives: None; P. Estrada: None; N. del Castillo: None; M. Robustillo: None; J. M. Nolla: None.

1311

Significance of “Healed Arteritis” (HA) on Temporal Artery Biopsy. Rahul Sehgal, Elise Belilos, Matthew Geller, Lorna Ogden, Steven E. Carsons and George K. Turi, Winthrop University Hospital, Mineola, NY

Purpose: Although temporal artery biopsy (TAB) is the gold standard for the diagnosis of Giant Cell Arteritis (GCA), the presence of skip lesions, and atypical biopsy features limit its utility. In particular, the pathologic diagnosis of HA is controversial. Many changes described for HA may be seen in aging and atherosclerosis alone. We attempted to determine the significance of HA by comparing pathologic features, clinical and laboratory manifestations, and corticosteroid (CS) requirements of HA patients to those displaying classical GCA on TAB.

Methods: We performed a retrospective cohort study, comparing the clinical presentation, laboratory data and CS requirements of 8 cases having a
pathology report indicating HA to 12 cases of classical GCA. To validate the pathologic impression of HA for our cases, a literature review was performed to identify the pathologic features most commonly reported in HA. These were found to include intimal thickening, medial fibrosis, scarring and calcification and internal elastic lamina (IEL) fragmentation. If present, inflammatory cells must be focal or scant. All slides (~25 sections/patient) were reviewed by 3 pathologists to 1) quantitate the features of HA and GCA and 2) to ensure that any cases with inflammatory infiltrates graded more than scant or focal (0–1 on a scale of 0–4) were excluded from the HA group. Clinically, all 20 patients were treated for GCA. CS exposure prior to TAB was also recorded.

Results: Other than the presence of significant medial and/or adventitial inflammation in GCA, there were no significant differences in the pathologic features previously identified to be associated with HA when slides from HA and GCA were compared. Although there was slightly more medial fibrosis, scarring and calcification in the HA group, this was not significant. The proportion of headache, jaw claudication, visual symptoms, fever, weight loss and scalp tenderness did not significantly differ between groups. No difference was noted in ESR. A trend towards higher alkaline phosphatase levels in GCA vs. HA (36% vs. 0%; p = 0.11) was seen. Only the presence of PMR was significantly associated with HA (86% vs. 3.3%; p = 0.002). Although the mean CS dose at Day 1 was significantly higher for GCA (150mg GCA vs. 45 mg HA; p = 0.045), no significant differences in subsequent CS dosing at days 30, 60 or 90 was seen. Importantly, cumulative pre-biopsy CS exposure was nearly identical (357 GCA vs. 306 mg HA; p = 0.857).

Conclusion: The presence of only scant or focal inflammation on TAB and a significant association with PMR symptoms were the only pathologic or clinical features that distinguished HA from GCA. CS courses were similar as well. Pre-biopsy CS exposure is not responsible for this phenotype, thus, use of the term “healed arthritis” should be reexamined. “Mild arthritis” may be appropriate for biopsies demonstrating scant or focal inflammation. Intimal thickening, medial fibrosis, scarring and calcification in the absence of any inflammation appear indistinguishable from changes due to aging and atherosclerosis.

Disclosure: R. Sehgal: None; E. Belloï: None; M. Geller: None; L. Ogden: None; S. E. Carson: None; G. K. Turri: None.

1312

Some Manifestations Disappear Earlier Than Others in Behcet’s Syndrome (BS), Seyfi F. Sacti, Emire Seyahi, Yilmaz Ozaygazan, Cem Mat and Hasan Yazici. “Cerrahpasa Medical Faculty, Dermatology Department, Turkey,” “Cerrahpasa Medical Faculty, Internal Medicine Department, Turkey,” “Cerrahpasa Medical Faculty, Ophthalmology Department, Turkey,” “Cerrahpasa Medical Faculty, Rheumatology Department, Turkey.”

In a 20 year outcome study, we had observed that the frequency of all mucocutaneous lesions and arthritis decreased in frequency with the passage of time (1). In this study we investigated whether some manifestations disappeared before others.

Patients and Methods: We studied consecutive BS patients who were seen in the rheumatology outpatient clinic at Cerrahpasa Medical Faculty in Istanbul between February 2009 and April 2010. Only BS patients whose disease duration and follow-up were 10 years or longer were included in the study. With the help of a questionnaire, patients were asked whether skin mucosa lesions, arthritis and uveitis attacks occurred for the preceding one year. If not, they were asked about the date when the manifestation occurred for the last time. Information given by the patients was confirmed with the patient charts whenever it was possible. Also a pathergy test was done to those who volunteered.

Results: We studied 115 (60 M, 55 F) patients. The mean age of the patients was 48 ± 8 and the mean disease duration 20 ± 6 years. 63 patients had eye, 20 vascular and 6 neurological disease. Vascular and neurological attacks were not evaluated due to rarity. The frequency of those with any BS manifestation during the preceding one year including pathergy positivity was decreased significantly at the final visit compared to that found at the beginning.

Table. Frequency of BS manifestations

<table>
<thead>
<tr>
<th>Frequency n (%)</th>
<th>Initial visit</th>
<th>Final visit</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Oral ulcers</td>
<td>115 (100)</td>
<td>84 (73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genital ulcers</td>
<td>105 (115)</td>
<td>13 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Papulonodular lesions</td>
<td>104 (90)</td>
<td>61 (53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>72 (63)</td>
<td>23 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arthritis</td>
<td>39 (34)</td>
<td>8 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pathergy positivity</td>
<td>85/109 (78)</td>
<td>6/39 (15)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

As seen in the Kaplan-Meier curve, eye attacks were the first to cease followed by arthritis, genital ulcers and skin lesions.

Figure. Kaplan Meier survival plot for duration of BS manifestations.

This was most prominent among females. Oral ulcer was the most frequent lesion after 30 years of disease course.

Conclusion: In BS some disease manifestations disappear earlier than others. These findings may have important pathogenetic and clinical implications. Since our survey was cross-sectional to retrospective caution is required in interpretation.

Reference:

Disclosure: S. F. Sacti: None; E. Seyahi: None; Y. Ozaygazan: None; C. Mat: None; H. Yazici: None.

1313

Takayasu’s Arteritis Is Associated with HLA-B*52, But Not with B*51, in Turkey. Turkish Takayasu Study Group. Turkey.

Aim: HLA-B*51 and B*52 are two close HLA alleles with minor amino acid differences. However, they are associated with two different vasculitides (B*51 with Behcet’s disease and B*52 with Takayasu’s arteritis-TAK) with major clinical and immunological differences. This study aimed to screen a large cohort of TAK patients from Turkey for the presence of HLA-B*51 and B*52 and to examine the association of B*52 as susceptibility alleles for Takayasu’s arteritis.

Material and Methods: TAK patients (n = 305) followed by 15 centers were included in the study. The mean age of the patients was 37.8 years and 86% (n = 264) were female. DNA samples of the patients and healthy controls (n = 210) were isolated by salting-out technique. HLA-B*51 and B*52 were investigated by using polymerase chain reaction (PCR) with sequence specific primers (SSP). The presence of the alleles were compared by chi-square method.

Results: B*52 has shown a significant association with TAK (67/305 (22.3%) vs. 14/210 (6.6%), p < 0.0001, OR: 4.07, CI: 2.19-7.36). However, the distribution of B*51 did not differ between TAK and control groups (24.6% (75/305) vs. 24.8% (52/210), OR: 0.99). Trends towards an association of B*52 presence with limited aortic involvement (Type I: OR: 0.4, p = 0.05), medically refractory disease (OR: 1.8, p = 0.14) and late-onset (OR: 0.25, p = 0.09) were observed. No significant association of B*52 was present with surgical procedures.

Conclusion: In this study, the previously reported association of TAK with B*52 in Japanese and other populations was confirmed in patients from Turkey, whereas no association with B*51 was observed. This association might have implications about the functional relevance of B*52 in TAK pathogenesis, which has to be further explored.

Disclosure: Turkish Takayasu Study Group: None.
Treatment with Angiotensin Converting Enzyme Inhibitors (ACEI) or Angiotensin II Receptor Antagonists (ARA) Is Associated with Higher Frequency of Ischemic Complications but Better Response to Therapy in Patients with Giant-Cell Arteritis (GCA). Marco A. Alba1, Ana Garcia-Martinez2, Georgina Espigol-Frigole1, Iitzar Taveoa, Montserrat Butrosa, Sergio Prieto-Gonzalez2, Jose Hernandez-Rodriguez2 and Maria C. Cid*. 1Emergency Department, Hospital Clinic, Barcelona, Spain, 2Systemic Autoimmune Diseases, Hospital Clinic, Barcelona, Spain, 3Systemic Autoimmune Diseases. Hospital Clinic, Barcelona, Spain, 4Systemic Autoimmune Diseases. Hospital Clinic, Barcelona, Spain.

Background: GCA is a chronic inflammatory disease involving large and medium-sized arteries. Involvement of cranial arteries is particularly symptomatic. About 15–20% of patients develop cranial ischemic events derived from occlusion of involved vessels. Previous studies have shown that angiotensin receptor 1 is expressed in vascular lesions from patients with GCA (Ophthalmology 2009, 116: 990–6). Angiotensin II is an important mediator of angiogenesis.

Purpose: To investigate whether ACEI or ARB therapy is related to vascular complications or response to glucocorticoid therapy in patients with GCA.

Methods: Between 1995 and 2005, 160 patients were diagnosed with biopsy-proven GCA at our institution. Among them patients with the following criteria were selected: prospective treatment and follow-up by the authors according to uniform criteria, prospective recording of GCA-related complications, relapses and glucocorticosteroid doses, and a follow-up duration of at least 3 years. Eighty-four patients fulfilled the selection criteria and were eligible for this study. Although retrospective in design, the study was performed on a prospectively followed cohort. Fisher exact test and Kaplan-Meyer survival analysis/log-rank test were used for statistical comparison.

Results: Eighteen percent (21%) of patients were receiving ACEI (12 patients) or ARB (6 patients) at the time of diagnosis. GCA-related complications (amaurosis fugax, diplopia, anterior ischemic optic neuritis, transient ischemic attack or stroke) occurred in 18% (21%) of patients at disease presentation. Ischemic complications occurred in 5% (27.8%) of patients receiving ACEI or ARB compared to 5% (7.6%) of those not receiving these therapies (p = 0.033). The proportion of patients who relapsed at least once was lower among those receiving ACEI or ARB (54% vs 75%, p = 0.06). Patients with multiple relapses were significantly less frequent among the ACEI/ARB treated group (p = 0.03). Patients receiving ACEI/ARB tended to achieve a maintenance prednisone dose < 10 mg/day earlier than patients not receiving these therapies (71 vs 82 weeks, p = 0.07).

Conclusions: Previous ACEI/ARB use is associated with higher frequency of ischemic complications at the time of GCA diagnosis but is associated with better response to glucocorticoid treatment. These preliminary data suggest that ACEI/ARB effects on angiogenesis or vascular remodelling may be relevant to patients with GCA.

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Disclosure: M. A. Alba: None; A. Garcia-Martinez: None; G. Espigol-Frigole: None; I. Taveoa: None; M. Butrosa: None; S. Prieto-Gonzalez: None; J. Hernandez-Rodriguez: None; M. C. Cid: None.

1314

Use of Peri-Operative Glucocorticoids and Post-Operative Complications in Patients with Takayasu’s Arteritis Undergoing Vascular Surgical Procedures. Bijal A. Jayakar1, Gary S. Hoffman3 and Carol A. Langford2. 1Cleveland Clinic, Cleveland, OH, 2Cleveland Clinic Foundation, Cleveland, OH, 3Cleveland Clinic Foundation, Pepper Pike, OH.

Purpose: The risks and benefits of peri-operative glucocorticoids (POGC) in patients with Takayasu’s arteritis (TAK) undergoing vascular surgery have been unclear. We studied the relationship between POGC and disease activity in TAK patients who received vascular surgery to determine if these factors influenced the risk of infection, vascular events, and other complications.

Methods: Retrospective chart review of TAK patients undergoing vascular surgery at the Cleveland Clinic from 1979–2008. Standardized definitions were used for the diagnosis of TAK, disease activity, and POGC. POGC was defined as prednisone use within 1 month prior to or after surgery and analyzed as 0mg, < 20mg, and ≥20mg. Variables including POGC, other immunosuppressives, disease activity, age at diagnosis, age at surgery, disease duration at surgery and sex were examined by univariate and multivariate analysis using SAS 9.2.

Results: In this study we identified 40 TAK patients who underwent 56 vascular surgical procedures. Mean age at diagnosis was 35.5 years and at surgery was 40 years. Mean duration of disease at surgery was 6.2 years (0–28.3). Mean time between surgery and last follow-up was 2.1 years (0–8.7). Active disease was present in 24/56 procedures (43%). Histology was obtained in 42/56 (75%) procedures with 8/42 (19%) being histologically active. Discordance between clinical and histological activity was seen in 17/42 (40%). Erythrocyte sedimentation rate (ESR) was increased in 18/44 (41%) measurements including 12/20 (60%) with active disease and 6/24 (25%) with inactive disease. POGC doses were prednisone = 0 in 21/56 (37%), <20mg in 10/56 (18%), ≥20mg in 25/56 (45%). 28/56 (56%) were on other immunosuppressives. 42 complications occurred in 30 patients, consisting of 11 infections, 12 vascular events, and 19 other complications. Relapses occurred in 25/56 (45%) with 6 (11%) being within 3 months of surgery. There were 5 deaths, 2 from strokes in the immediate post-operative period. POGC were not associated with a higher frequency of infections (p = 0.84). For inactive TAK, total complications were no lower in those who did not receive POGC (p = 0.11). This lack of association remained present for each subgroup: infection (p = 0.90), vascular (p = 0.22), and other complications (p = 0.37). In active TAK, there was no difference in the occurrence of total complications between those on and not on POGC (p = 0.67). Although this lack of association was present for other complications (p = 0.74), subset analyses were not possible for infection or vascular complications because of absence of an event.

Conclusions: The absence of an increased risk of infection in this study support that POGC can be used in TAK patients felt to have active disease at the time of vascular surgery. These results did not support that POGC should be routinely used in all patients with TAK undergoing surgical procedures as the risk of complications was no different in patients who received this. Performance of surgery is not associated with a high rate of immediate relapse, although relapses are common over time in TAK. ESR and clinical definitions remain imperfect measures of disease activity and underscore the need for better biomarkers in TAK.

Disclosure: B. A. Jayakar: None; G. S. Hoffman: None; C. A. Langford: None.

ACR Poster Session B
ACR/ARHP Poster Session B - ARHP: Osteoporosis
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

1316

Application of the Generalizability Theory for Determining Inter-Rater and Inter-Trial Reliability of Spine Curvature Measures in Postmenopausal Women with Osteoporosis of the Spine Using the Flexicurve Ruler and the Digital Inclinometer. Norma J. MacIntyre1, Lisa Bennett2, Alison Bonnymann3 and Paul W. Stratford2. 1McMaster University, Hamilton, ON, Canada, 2McMaster University

Purpose: Spine curvatures are often measured in physical therapy practice using a flexicurve ruler to calculate kyphotic index (KI) and lordotic index (LI) or a digital inclinometer to quantify the angle at the cervicothoracic (CT), thoraco-lumbar (TL) and lumbosacral (LS) junctions. Generalizability theory (G-Theory) provides tools that characterize the sources of variation, or facets, in a measurement procedure and permit identification of a protocol that provides optimal reliability. The purpose of this study was to use the tools of G-Theory to investigate the inter-rater and inter-trial reliability of these spine curvature measures and to establish an optimal measurement protocol.

Methods: Nine postmenopausal women over the age of 60 years with established osteoporosis of the spine were recruited for this cross-sectional observational study. Two raters completed triplicate measures of spine curvatures using both the flexicurve ruler and the digital inclinometer according to a standardized protocol. G-Theory was applied through a Generalizability Study to estimate G-coefficients (analogous to the reliability coefficient in the Classical Test Theory). The facets included were participants (P), raters (R) and trials (T). Three-way ANOVAs were used to generate variance components for the following terms: P, R, T, PrT, PxT, RxT and error. G-coefficients were calculated as the proportion of the overall variance that can be attributed to the facets and interactions and the proportions of variance attributed to rater and trial. Follow-up Decision Studies were performed to identify a measurement protocol that minimized error and optimized reliability. G-coefficients ≥ 0.8 were considered desirable and 0.70 to 0.79 were considered acceptable.

Results: Inter-rater reliability is excellent for KI, LI, TL and LS (G-
coefficient = 0.97, 0.91, 0.85 and 0.80, respectively) and acceptable for CT (G-coefficient = 0.74) using our protocol for measuring spine curvatures. Three raters are required to achieve excellent inter-rater reliability for CT (0.81). A single trial would result in excellent reliability for all measures (G-coefficient = 0.94 for all except LI where G-coefficient = 0.84). Triplicate trials improve inter-trial reliability (G-coefficient = 0.98 for all except LI where G-coefficient = 0.94). Little gains are achieved by increasing trials beyond three; eight trials are needed to raise the inter-trial reliability of LI measures to 0.98.

Conclusions: This study demonstrates the application of G-Theory to identify a protocol for measuring spine curvatures in osteoporotic women which optimizes reliability by testing the gains achieved by increasing the number of raters or the number of trials. If more than one rater is involved in assessing spine curvatures, triplicate measures acquired using the flexicurve ruler will be most reliable. For a given rater, inter-trial reliability is optimized by measuring in triplicate whether using the flexicurve rater or the digital inclinometer.

Disclosure: N. J. MacIntyre: None; L. Bennett: None; A. Bonnyman: None; P. W. Stratford: None.

1317

Baseline Serum Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α) and C-Reactive Protein (CRP) Do Not Predict Subsequent Hip Bone Loss in Men or Women: The Framingham Osteoporosis Study. Robert R. McLean1, Xiaochun Zhang2, Joao D. T. Fontes3, James B. Meigs3, L. Adrienne Cupples1, Douglas P. Kiel4 and Marian T. Hannan5. 1Boston University School of Public Health, 2Framingham Heart Study and Boston University, 3Hebrew Senior Life, Boston, MA, 4Hebrew SeniorLife, 5Hebrew SeniorLife and Harvard Medical School, 6Hebrew SL & Harvard Med Sch, Boston, MA, 7Massachusetts General Hospital

In vitro studies suggest that several pro-inflammatory cytokines increase bone resorption and that their activity is amplified following estrogen withdrawal. Yet there is little epidemiologic evidence that circulating concentrations of inflammatory markers predict bone loss in men and women, or that estrogen status may influence this relation. We therefore examined the associations of serum concentrations of the cytokines IL-6 and TNF-α, and CRP, a marker of systemic inflammation, with bone loss among men and women in the Framingham Offspring Study. We hypothesized that increased baseline concentrations of inflammatory markers would be associated with greater bone loss, and that this association would be strongest among postmenopausal women not using hormone replacement therapy (HRT). Baseline fasting blood samples were obtained (1998–2001) from 501 men, 106 premenopausal women, 206 postmenopausal HRT users at baseline, and 334 postmenopausal not using HRT. Serum IL-6 (pg/mL) and TNF-α (pg/mL) were measured using ELISAs and CRP (mg/L) using a highsensitivity assay. Total femur bone mineral density (BMD; g/cm²) was measured at baseline with a Lunar DPX-L (1996–2001) and at follow-up using a Lunar Prodigy (2002-05), accounting for equipment change. Bone loss was calculated as percent BMD change per year. Within each of the 4 groups defined by sex, menopause status and HRT use, participants were categorized into tertiles of inflammatory markers. We used analysis of covariance to compare mean bone loss in each of the upper 2 tertiles to the lowest tertile and test for a linear trend across tertiles, adjusting for baseline age (y), BMI (kg/m²), height (in), physical activity, and current smoking (y/n). Mean age at baseline was 61 y (range 29–85 y), and mean follow-up time was 4.6 y (range 1.5–7.9 y).

Least squares-adjusted mean annual % change (SE) in total femur BMD for tertiles of inflammatory biomarkers in Framingham Offspring men and women.

<table>
<thead>
<tr>
<th></th>
<th>T1 (Low)</th>
<th>T2</th>
<th>T3 (High)</th>
<th>P trend</th>
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</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IL-6</td>
<td>-0.01 (0.08)</td>
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<td>-0.03 (0.08)</td>
<td>0.90</td>
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<td>TNF-α</td>
<td>0.08 (0.09)</td>
<td>-0.04 (0.09)</td>
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<tr>
<td>CRP</td>
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<td>-0.03 (0.07)</td>
<td>0.07 (0.08)</td>
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<td>Premenopausal women</td>
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<td>CRP</td>
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<td>IL-6</td>
<td>-0.23 (0.12)</td>
<td>-0.20 (0.11)</td>
<td>-0.29 (0.11)</td>
<td>0.72</td>
</tr>
<tr>
<td>TNF-α</td>
<td>-0.19 (0.13)</td>
<td>-0.23 (0.12)</td>
<td>0.07 (0.12)</td>
<td>0.12</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.37 (0.12)</td>
<td>-0.23 (0.11)</td>
<td>-0.13 (0.12)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

There were no statistically significant associations between inflammatory markers and total hip bone loss in any of the sex/menopause/HRT groups (Table). Our findings suggest that circulating biomarkers of inflammation are not associated with hip bone loss in men or groups of women categorized by menopause status and HRT use. Future investigations of inflammation and BMD should address limitations of our study by including longitudinal measures of inflammatory markers, more precise measures of estrogen status (e.g., sex hormones), and larger samples that could detect the small bone loss effects suggested by our results.

Disclosure: R. R. McLean: None; X. Zhang: None; J. D. T. Fontes: None; J. B. Meigs: None; L. A. Cupples: None; D. P. Kiel: None; M. T. Hannan: None.

1318

Development of a Motivational Interviewing Protocol for Clinical Application in Osteoporosis. Maura D. Iversen1, Laura Rekedal1 and Daniel Hal Solomon2. 1Boston, MA, 2Brigham and Womens Hospital, Boston, MA, 3Northeastern University, Boston, MA

Background: While many effective therapies exist for osteoporosis (OP), most people do not adhere to such treatments long-term. Few proven interventions exist to improve OP medication adherence. Motivational interviewing (MI) is a counseling technique that may improve adherence. We report on methods used to develop MI skills among 5 health educators to promote patient adherence to OP medications.

Methods: Five health educators (HE) participated in an initial 2 day educational session led by a rheumatologist, a behavioral scientist and a certified MI trainer which detailed information on MI techniques and OP. Reinforcement of MI was provided via semi-monthly calls with the study team over one year. Two additional telephonic MI training sessions were provided at the trial midpoint based on two 20–30 minute audio taped client conversations. A second certified MI trainer listened to tapes, coded the MI performance using the Motivational Interviewing Treatment Integrity code (MI) and then provided feedback using examples from the tapes. The MI contains 5 domains: evocation, autonomy, collaboration, direction and empathy and MI global spirit. Scores range from 0 (low) to 5 (high). Conversations with clients were also coded based on the ratio of total reflections to questions used. This information was then used to individually tailor feedback about the use of MI techniques for each health educator.

Results: All HEs were female. Mean age was 42 years and range of experience was 7 to 15 years. One health educator was a registered nurse, one a dietician, and one a social worker. At baseline, only one of the five health educators had any experience using MI; two were familiar with MI concepts but had not received training and one was not familiar with MI. Scores across the five MI domains suggested the HE performance was strongest in the areas of providing direction (all received scores of 3.5 or better) and empathy (average range 2.5–4.5).

### Table: MI Global Domains Performance Scores For Each Health Educator For MI Domains During Two Separate Audiotaped Conversations

<table>
<thead>
<tr>
<th>Global Domains</th>
<th>001</th>
<th>002</th>
<th>003</th>
<th>004</th>
<th>005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evocation</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Collaboration</td>
<td>2.5</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Average</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Direction</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Average</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Empathy</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Average</td>
<td>3.5</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Global Spirit</td>
<td>3.5</td>
<td>2.75</td>
<td>4.5</td>
<td>3.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Score</td>
<td>2.8</td>
<td>2.3</td>
<td>3.0</td>
<td>3.3</td>
<td>3.0</td>
</tr>
</tbody>
</table>

The areas which needed improvement were the domains of evocation, collaboration and autonomy/support. With respect to total reflection to...
Type of Activity Pacing Instruction Affects Physical Activity Variability in Adults with Symptomatic Knee or Hip Osteoarthritis

**Objective:** In a recent trial, we examined the effect of two different activity pacing interventions, general versus tailored, on symptom management for people with knee or hip osteoarthritis and found that fatigue was improved after the tailored compared to the general intervention. The current study was done to examine the secondary effect of activity pacing instruction on objective physical activity patterns (using ambulatory monitoring).

**Methods:** Thirty-two adults with knee or hip osteoarthritis, who were randomly stratified by age and gender, received either tailored or general activity pacing instruction. Both interventions involved two sessions with an occupational therapist. All participants wore an accelerometer for five days. Both interventions were sessions with an occupational therapist. All participants wore an accelerometer for five days that measured physical activity and allowed for repeated symptom assessment at baseline (which was used for tailored activity pacing instruction) and at the 10 week follow-up period. Activity patterns were assessed by examining: physical activity variability, measured using the standard deviation of 5-day average activity counts per minute, and average activity level, the 5-day average activity counts per minute.

**Results:** Physical activity variability decreased in the tailored group and increased in the general group. Participants in the tailored and general groups did not have significant changes in their average physical activity from baseline to 10 week follow-up.

**Conclusion:** The type of activity pacing instruction affected the objective physical activity of adults with symptomatic knee or hip OA. Tailored activity pacing was more effective at reducing high and low activity bouts corresponding to the message of keeping a steady pace to reduce symptoms.

Disclosure: S. L. Murphy: None; D. M. Smith: None; A. K. Lyden: None.

ACR Poster Session B
ACR/ARHP Poster Session B: ARHP: Behavioral Science

Tuesday, November 9, 2010, 9:00 AM–6:00 PM

A Prospective, Longitudinal Cohort Study Evaluating Psychosocial Risk and Protective Factors for Post Lyme Disease Syndrome

**Background:** Rarely do patients manifest objective evidence of ongoing infection with *B. burgdorferi* after antibiotic treatment and yet it has been estimated that at least one third of treated Lyme disease patients report chronic pain, fatigue, and cognitive problems. The condition referred to as Post Lyme Disease Syndrome, may be more appropriately thought of as fibromyalgia triggered by an infectious disease. There is evidence that illness factors at baseline, such as symptom severity and functional status are associated with symptom persistence and functional status after treatment; however, little is known about psychosocial risk and protective factors.

**Methods:** In a multicenter longitudinal study, 99 patients newly diagnosed with Lyme disease underwent comprehensive psychometric and medical/laboratory assessments at baseline. All patients received antibiotic treatment and at one year after diagnosis completed the Fibromyalgia Impact Questionnaire revised for Lyme disease (FIQ-LD) to evaluate the presence of chronic symptoms and functional status. Psychosocial factors assessed at baseline included: functional status (FIQ-LD), symptoms checklist, depression (PRIME-MD PHQ), catastrophizing (Coping Strategies Questionnaire; Catastrophizing subscale), negative affect and positive affect (Positive and Negative Affect Scale). At one year, patients with persistent symptoms ascribed to Lyme disease were compared to patients with resolved symptoms.

**Results:** Of the 74 patients who completed the 1-year assessment, 24 (32.4%) reported chronic symptoms – predominantly pain (VAS mean PLDS: 3.38±2.63 vs. Recovered: 0.43±0.85) and fatigue (VAS mean PLDS: 5.98±1.83 vs. Recovered: 1.56±1.96). Compared with patients who reported no chronic symptoms at one year, only functional status (45.00±18.23 vs. 31.90±21.19, p<0.01) and positive affect (31.57±5.63 vs. 35.92±4.96, p<0.005) at baseline differed between groups. After correcting for multiple comparisons, positive affect alone remained significant. Logistic regression showed that group membership (PLDS vs. recovered from Lyme disease) was predicted by positive affect (p=0.003, Somers’ Dxy rank correlation of 0.40) and baseline functional status (p=0.01, Somers’ Dxy rank correlation of 0.35). No other variables were predictive of group status at one year. At baseline, positive affect and functional status were not correlated (r=0.06).

**Conclusion:** Almost one third of Lyme disease patients will manifest chronic symptoms post antibiotic treatment. Consistent with others, we found worse functional status at baseline to be predictive of PLDS. Further, we found that a resilience factor, positive affect, was the most valuable factor for predicting outcome in this population. Patients with higher levels of positive affect were more likely to fully recover from Lyme disease after treatment. Typically, psychological batteries only measure negative factors, but these data are consistent with emerging data in other fields that suggest that positive factors at baseline may better predict outcomes than negative factors.

Disclosure: A. L. Hassett: None; T. Shlimbaum: None; D. C. Radvanski: None; D. J. Herman: None; R. Nahass: None; S. Buyske: None; L. H. Sigal: None.
key concepts specific to identity in current occupational therapy and rehabilitation theories that are intended to inform practice and clinical reasoning.

**Conclusion:** Metaphor was used to interpret stories of women living with RA. In the example presented here, changing shoes represents not only a physical adjustment to accommodate pain and apply joint protection principles, but also part of an internal process of reshaping identity. Appreciating how small changes carry greater meaning with regard to one’s identity may foster more effective patient-provider communication and client-centered practice.

**Disclosure:** C. L. Backman: None; A. Townsend: None; L. C. Li: None.

### 1322

**Emotional Response to Serial Doppler Echocardiography Examinations as a Screening Method To Detect Developing Congenital Heart Block in SSA/Ro Positive Pregnancy.** Joanna Tingström1, Mia Barimani2, Sven-Erik Sønnesson1, Marie Wahren-Herlenius1 and Elisabet M. B. Welin Henriksson2.

1Karolinska Institutet, Stockholm, Sweden, 2Karolinska Institutet CMM, Stockholm, Sweden, 3Karolinska Institutet Rheum, Stockholm, Sweden

**Objective:** Congenital heart block may develop in the fetus during pregnancy in SSA/Ro52 autoantibody positive women. The aim of this study was to investigate how women with SSA/Ro52 autoantibodies experience their pregnancy focusing on the period between gestational weeks 18–24 when serial Ultrasonic/Doppler examinations were performed to detect early signs of congenital heart block. The implementation of a new screening method has the benefit of detecting heart block early and allowing treatment at the stage when it is most effective, but may also cause negative side effects such as increased stress for the women.

**Methods:** Data were collected through individual semi-structured interviews with Swedish SSA/Ro52 positive women post pregnancy (n=14). None of the women gave birth to a child with congenital heart block. The interviews were audio taped, transcribed verbatim and analyzed by qualitative content analysis.

**Results:** Three categories emerged from the responses: information, emotional response and support. The information received prior to and during early pregnancy was focused on the need for attending a specialized antenatal clinic, and information on the risk for congenital heart block was scarce or missing. During gestational week 18–24 when the ultrasound/Doppler examinations were performed all women described increased stress in some way. However, nobody wanted to renounce the examinations and the interaction with the caregivers made the women feel more safe and secure. Several women described that they did not emotionally acknowledge the pregnancy and could not fully take in that they were pregnant until after gestational week 24. None had been offered psychological support.

**Conclusions:** There is a need for structured information and organized programs for surveillance of SSA/Ro52 positive pregnancy. Despite the increased stress the women described in connection with the ultrasound examinations, all women felt that the advantages outweighed the disadvantages of the procedure. Further, offering psychological support to the women and their families to give them tools to handle the stress and to facilitate the early attachment to the child should be considered.

**Disclosure:** J. Tingström: None; M. Barimani: None; S.-E. Sønnesson: None; M. Wahren-Herlenius: None; E. M. B. Welin Henriksson: None.

### 1323

**Psychological Factors but Not Clinical Markers of Disease Activity Predict Adherence Among Rheumatoid Arthritis (RA) Patients Receiving DMARDs and Adalimumab (ADA): Results from the British Society for Rheumatology Biologics Register (BSRBR).** C. Morgan1, J. McBeth2, L. Cordingly2, K. D. Watson1, BSRBR Control Centre Consortium, K. L. Hyrich2, D. P. M. Symmons2, I. N. Bruce2 and on Behalf of the BSR Biologics Register. 1The University of Manchester, Manchester, United Kingdom, 2The University of Manchester

**Background:** Drug adherence rates amongst RA patients are reported to be between 30–78%. Psychological factors such as illness perceptions and coping mechanisms are important predictors of adherence. The aim of this study was to establish the relative contributions of demographic, physical and psychological factors to adherence.

**Methods:** The analysis included 610 patients recruited between 01/05/07–30/04/09 to the BSRBR, a UK national observational cohort study monitoring the long term safety of biologic agents in RA patients receiving anti-TNF therapy. Two patient groups were identified for this analysis: (i) those taking ADA as a monotherapy or in combination with a DMARD and (ii) those taking a DMARD-only based regime as mono or combination therapy. At baseline, demographic data, DAS28, physical function (HAQ), quality of life (SF36) and psychological data including illness perception, coping strategies and belief about medication use were collected. Adherence was assessed indirectly using the validated 19-item patient self-complete Compliance Questionnaire Rheumatology (CQR) at baseline. The CQR yields a total score between 0–100, with higher scores indicating higher levels of adherence. Linear regression (adjusted for age, gender and disease duration) was used to investigate the relationships between baseline factors and CQR scores.

**Results:** A total of 358 ADA and 252 DMARD patients were available for analysis of which 75% were female. Compared to the DMARD group, ADA patients had a younger age at disease onset (median 44 v 51 years, p<0.001), longer disease duration (median 9 v 5 years, p<0.001) and higher disease activity (mean DAS28, SD: 6.5, 0.9 v 5.4, 0.9, p<0.001). 287 (80.2%) of the ADA group were also taking a DMARD, and in the DMARD-only group, 101 (40.1%) were taking ≥ 2 DMARDs at time of study. The median CQR score for the DMARD and ADA patients were 71.9 (IQR 64.9–78.9) and 75.4 (IQR 64.9–82.5), respectively. The DAS28 and HAQ did not predict CQR score in either group. In both treatment groups a lower CQR score was predicted by poor physical health (physical component summary (PCS) SF36). Perceiving RA to be a chronic illness, that medication was a necessity, and adopting positive coping mechanisms were all associated with higher CQR scores while increasing concern over medication use was associated with lower scores in both groups. Perceived control over treatment also predicted higher CQR scores in the ADA group alone.

Regression results* for significant associations with total CQR score

<table>
<thead>
<tr>
<th>Factor</th>
<th>DMARD group (n=252)</th>
<th>ADA group (n=358)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β co-efficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>Poor physical function (PCS, SF36)</td>
<td>−0.2</td>
<td>−0.3, −0.08</td>
</tr>
<tr>
<td>Perception of illness being chronic</td>
<td>0.7</td>
<td>0.3, 1.2</td>
</tr>
<tr>
<td>Necessity of medication</td>
<td>1.8</td>
<td>1.5, 2.2</td>
</tr>
<tr>
<td>Positive coping mechanisms</td>
<td>1.5</td>
<td>0.8, 2.3</td>
</tr>
<tr>
<td>Medication concerns</td>
<td>−0.3</td>
<td>−0.7, 0.06</td>
</tr>
<tr>
<td>Perceived control over treatment</td>
<td>−0.1</td>
<td>−0.7, 0.4</td>
</tr>
</tbody>
</table>

* adjusted for age, gender and disease duration

**Conclusion:** Wider recognition of the role of beliefs about medication adherence would have substantial clinical benefits in RA. In the biologics era, it may also have important health economic benefits. This study has identified modifiable psychological factors that are putative targets for strategies to improve adherence.

**Disclosure:** C. Morgan: None; J. McBeth: None; L. Cordingly: None; K. D. Watson: None; BSRBR Control Centre Consortium: None; K. L. Hyrich: None; D. P. M. Symmons: None; I. N. Bruce: None; on Behalf of the BSR Biologics Register: None.

### 1324

**Spousal Social Support and Well-Being among Persons with Rheumatoid Arthritis: Is Support in the Eye of the Beholder?** Allen J. Lehman1, Anita DeLongis1, Daniel D. Pratt1, John B. Collins2 and John M. Esdaile2.

1Arthritis Research Centre of Canada; Simon Fraser University, Vancouver, BC, Canada, 2Arthritis Research Centre of Canada; University of British Columbia, Vancouver, BC, Canada, 3University of British Columbia, Canada

**Background:** Much evidence suggests that social support is beneficial to persons with RA, both in terms of disease course and quality of life. It is essential that research identify the pathways through which support is beneficial. Several recent studies of people undergoing relatively chronic, but ultimately time-limited stress, suggest that spousal support is most health protective when it is “invisible” (the beneficiary of support is unaware that it has been provided). The stress associated with living with RA, however, is not time-limited. Whether extant findings on invisible support can be extended to couples in which one spouse has RA is unclear. Our study objective was to determine if invisible support for the person with RA is associated with significantly better well-being for the recipient than when both spouses agree that support was provided.

**Disclosure:** C. L. Backman: None; A. Townsend: None; L. C. Li: None.
Methods: English speaking adults with RA ≥ 6 months and their spouses (N=228 couples) independently completed standardized questionnaires that assessed the perceptions of each regarding social support received by the person with RA and support provided by the spouse, as well as relationship satisfaction, positive affect, and depression. A dummy-coded 2 x 2 table summarized spousal congruence or divergence on perceptions of support for the person with RA (present, absent). Couple congruence on support present for the person with RA served as the reference category. Separate hierarchical regression models tested the effects of spousal support congruence or divergence on RA's relationship satisfaction, positive affect, and depression, after adjusting for gender, RA severity, and spouse depression.

Results: Questionnaire response rate for couples was 82%. Of the persons with RA, 73% were female, the mean RA duration was 12 yrs, with mean relationship duration 31 yrs. Spousal congruence or divergence on perceptions of support explained additional variability in relationship satisfaction (R² = 0.492, p < 0.001), positive affect (R² = 0.099, p < 0.001), and depression (R² = 0.084, p < 0.001). Invisible support from the spouse showed a significant negative association with well-being in the person with RA, including poorer relationship satisfaction (β = -0.503, p < 0.001), less positive affect (β = -0.269, p < 0.001), and higher depression levels (β = 0.168, p < 0.01).

Conclusion: Perceptions of social support from the spouse were significantly associated with positive well-being among persons with RA, regardless of whether the spouse reported having provided support. Contrary to findings of previous studies in non-RA samples, invisible support was associated with poorer well-being. Our findings suggest that what is most important is the recipient’s perception of support received from the spouse. Such findings will be useful in designing evidence-based family and couple clinical interventions for those with RA and their families.

Disclosure: A. J. Lehman: None; A. DeLongis: None; D. D. Pratt: None; J. B. Collins: None; J. M. Esdale: None.

1325
Sustained Reduction in Fatigue Impact in Rheumatoid Arthritis: RCT of Cognitive Behavioural Therapy. Sarah E. Hewlett1, Nicholas Ambler2, Bey Knops2, Alena Cliss1, Celia Almeida3, Denise Pope3, Alison Hammond4, Annette Swinkels5, Karen Kitchen6 and Jon Pollock6. 1Frenchay Hospital, Bristol UK, 2Frenchay Hospital, Bristol, UK, 3University Hospitals Bristol, University of the West of England, Bristol UK, 4University of Salford, Matlock Derbyshire, United Kingdom, 5University of the West of England, Bristol, United Kingdom, 6University of the West of England, Bristol UK

Aim: Up to 90% of RA patients experience distressing, unmanageable fatigue that impacts profoundly on life. In other long-term conditions, fatigue self-management programmes of cognitive behavioural techniques (CBT) show benefit. This randomized controlled trial tested CBT for RA fatigue.

Methods: CBT was delivered by a clinical psychologist and specialist occupational therapist in 6 x 2hr weekly group sessions (1hr booster at wk 14), addressing thoughts, feelings and behaviours, underpinned by goal-setting. Included were activity pacing, self-monitoring diaries for energy management, achieving balance (prioritizing), stress, communication, assertiveness, sleep, and managing setbacks. The information-only control group comprised a 1hr group session based on the Arthritis Research UK fatigue leaflet. Entry criteria were fatigue VAS ≥60/100 and no change in major medication in previous 16 wks (steroids 6 wks). Assessments: VAS 0–10 for fatigue impact, severity and coping, Multi-dimensional Assessment of Fatigue (MAF 0–50), quality of life (RAQoL 0–30), sleep (good/poor), anxiety and depression (HADS 0–21), helplessness (AHI 5–35).

Results: Of 168 patients randomized, 41 withdrew before entry, 51 did not complete all datasets, 76 completed to wk 18 (no significant baseline differences for age, gender, disease duration). At baseline, the 76 patients (38 CBT, 38 Control) comprised 55F, 21M, mean age 60.4 yrs (95% CI 57.8–62.9), disease duration 11 yrs (10–15). All data were tested for normality and outcomes transformed where necessary. Analysis was adjusted for group and for baseline scores. At baseline, CBT and Control patients only differed by better RAQoL in CBT arm: 13.7 (11.8–15.6) vs 17.3 (14.8–19.9).

At the end of the programme (6 wks) the CBT group had significantly better scores than the Control group for every fatigue and every well-being outcome, which were maintained at 18 wks, except for RAQoL (see Table). More CBT than Control patients reported better sleep quality (6 wks 22/38 vs 19/38, p=0.024; 18 wks 30/38 vs 20/38, p=0.012).

Interim assessment at 10 wks showed the CBT group was still significantly better than the Control group in all except 3 outcomes which just failed to reach statistical significance (Anxiety p=0.057, Fatigue Coping p=0.066, Fatigue Severity p=0.064). The planned booster session was delivered at 14 wks. At 18 wks these outcomes were all significantly different again (Table).

Conclusion: CBT for fatigue self-management in RA significantly improves fatigue and well-being, maintained at 3 months. The loss of significance in three variables before the booster session and subsequent improvement afterwards may indicate the value of ‘top-up’ sessions in clinical practice. As a clinical psychology provision is often limited, the efficacy and cost of a lower-intensity CBT approach provided by the clinical team (with training and support) should be explored.

Disclosure: S. E. Hewlett: None; N. Ambler: None; B. Knops: None; A. Cliss: None; C. Almeida: None; D. Pope: None; A. Hammond: None; A. Swinkels: None; K. Kitchen: None; J. Pollock: None.

1326
The Effect of Social Support from Physicians and Partners on the Health-Related Quality of Life of Vasculitis Patients in Relapse and Remission. Delesha M. Carpenter1, Jessica A. Kadi2, Robert F. DeVellis2, Susan L. Hogan2 and Joanne M. Jordan1. 1Chapel Hill, NC, 2UNC, Chapel Hill, NC, UNC

Background: Although social support has been shown to positively impact the physical and mental health of chronic disease patients, few studies have explored whether the benefits of support vary by level of disease activity.

Objective: Our goal was to determine whether the disease status (relapse vs. remission) of vasculitis patients moderated the effect of physicians’ and partners’ social support on patients’ health-related quality of life (HRQOL).

Methods: Vasculitis patients (n=228) completed two online surveys. The baseline survey assessed demographic information, self-reported disease status (relapse vs. remission), and social support from physicians and partners. The 3-month follow-up survey measured 8 dimensions of HRQOL (SF-36): physical functioning (PF), physical role limitations (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role limitations (RE), and mental health (MH). Higher scores indicate better HRQOL. We compared the HRQOL of patients in relapse and remission. We also determined whether disease status moderated the effect of physician support and partner support on patient HRQOL; Wilks’ Λ indicated whether the physician support-by-disease-status and partner support-by-disease-status interaction terms were significant.

Results: Relapsing patients reported significantly worse health when compared with non-relapsing patients for 7 of 8 HRQOL dimensions: physical functioning, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health (Figure 1). Disease status did not moderate the effect of physician (Wilks’ Λ=0.49, p=.86) or partner social support (Wilks’ Λ=1.49, p=.16) on HRQOL. However, social support from
both physicians and partners was associated with better HRQOL. Specifically, physician support predicted better HRQOL for 6 of 8 dimensions (all except for except bodily pain and vitality). Partner support predicted fewer physical and emotional role limitations and better social functioning.

Conclusion: Vasculitis patients experience compromised HRQOL when compared with U.S. population norms, but the magnitude of the compromise is greater for patients experiencing a relapse. Social support from physicians and partners is beneficial for patient HRQOL regardless when compared with U.S. population norms, but the magnitude of the intervention.

### Foot Pain in Relation to the Foot Biomechanical Measures of Plantar Peak Pressures and Pressure Time Integral

**Introduction:** Foot pain is a major cause of mobility limitation, however, the mechanisms that lead to foot pain are not completely understood. Small laboratory studies have shown that uneven distribution of the forces applies to the foot during normal walking result in areas of high pressure, which are associated with foot pain. Yet, these relations between plantar peak pressures and pressure-time integrals have not yet been investigated in a large, population-based sample. Thus, we examined the associations between generalized foot pain and peak pressure (PP) and pressure time integral (PTI) in men and women of the population-based Framingham Foot Study. We hypothesized that individuals reporting foot pain would exhibit higher peak pressure in specified foot areas compared to those reporting no foot pain.

**Methods:** Foot pressure data were obtained from 200 men and 262 women enrolled in the Framingham Foot Study. Between 2002 and 2005, plantar pressure values were collected using a Tekscan Matscan pedobarographic system (resolution of 1.4 sensels/cm²) while participants walked at a comfortable pace barefoot across the mat. Pressure data were obtained from a subset of participants enrolled in the study. Novel software was used to calculate PP and PTI from 12 segments of the right foot (toes, submetatarsal heads 1–5, medial arch and heel, lateral arch and heel). Self-reported foot pain was determined by the response to the question: “On most days, do you have pain, aching or stiffness in either foot?” Two-tailed Student’s T-tests assessed differences in PP and PTI between those with and without foot pain, separately for men and women.

**Results:** Study participants were 66% female with mean age of 65 years, and mean BMI of 28. In women who reported foot pain, there was significantly greater PP at the 2nd and 3rd metatarsal heads (p<0.0001) compared to those who did not report foot pain. In men, significant differences in PP were only seen at the 5th metatarsal head (p<0.001). There were no significant findings for foot pain and PTI measures in either men or women.

<table>
<thead>
<tr>
<th>Foot Region</th>
<th>No Foot Pain</th>
<th>Foot Pain</th>
<th>P Value</th>
<th>No Foot Pain</th>
<th>Foot Pain</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submetatarsal head 1</td>
<td>17.8±6.1</td>
<td>22.6±4.7</td>
<td>0.01</td>
<td>18.3±3.9</td>
<td>21.0±5.1</td>
<td>0.73</td>
</tr>
<tr>
<td>Submetatarsal head 2</td>
<td>22.1±4.7</td>
<td>20.4±5.0</td>
<td>0.01</td>
<td>10.5±3.2</td>
<td>10.6±5.0</td>
<td>0.81</td>
</tr>
<tr>
<td>Submetatarsal head 3</td>
<td>17.3±4.6</td>
<td>16.5±4.8</td>
<td>0.28</td>
<td>7.8±2.9</td>
<td>7.6±2.6</td>
<td>0.65</td>
</tr>
<tr>
<td>Submetatarsal head 4</td>
<td>14.2±6.1</td>
<td>13.9±5.8</td>
<td>0.69</td>
<td>5.9±3.2</td>
<td>6.2±3.0</td>
<td>0.80</td>
</tr>
<tr>
<td>Male</td>
<td>n=164</td>
<td>n=36</td>
<td>0.61</td>
<td>9.1±5.1</td>
<td>9.5±4.7</td>
<td>0.61</td>
</tr>
<tr>
<td>Submetatarsal head 1</td>
<td>18.9±6.3</td>
<td>22.0±4.1</td>
<td>0.53</td>
<td>11.0±4.4</td>
<td>11.6±3.9</td>
<td>0.45</td>
</tr>
<tr>
<td>Submetatarsal head 2</td>
<td>22.8±4.1</td>
<td>23.5±4.5</td>
<td>0.34</td>
<td>11.0±4.8</td>
<td>11.5±3.5</td>
<td>0.46</td>
</tr>
<tr>
<td>Submetatarsal head 3</td>
<td>18.9±4.7</td>
<td>20.3±5.2</td>
<td>0.13</td>
<td>8.6±3.6</td>
<td>9.2±2.6</td>
<td>0.21</td>
</tr>
<tr>
<td>Submetatarsal head 4</td>
<td>15.4±6.2</td>
<td>17.8±5.0</td>
<td>0.03</td>
<td>6.9±4.8</td>
<td>7.7±2.9</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* Two-Tailed Students’ T-Test

**Discussion:** In a large population-based sample, general foot pain was associated with higher PP under several of the metatarsal heads, albeit differently in men and women. Significant findings were not observed for the pressure-time integral measures. It may be that the accumulation of pressure loading over time does not cross a pain threshold as easily as peak pressure. We are unaware of differences in gait between men and women, or other reasons for different PP and reports of foot pain. Future work should investigate specific foot pain location in relation to areas of plantar pressure loading to elaborate on potential mechanisms.

**Disclosure:** V. A. Casey: None; A. B. Dufour: None; R. R. McLean: None; R. R. Jordan: None.

### Hallux Valgus and Foot Biomechanics: Relation between Structure and Function

**Introduction:** Hallux valgus (HV), the etiology and biomechanics of the pathology remain poorly understood. Although previous studies have noted differences in peak plantar pressures in various regions of the foot between individuals with and without HV, results are inconsistent and have not been confirmed in larger studies.

**Methods:** Data were obtained from a subset of participants enrolled in the Framingham Heart Study (N = 464; 57% female; mean age, 65 years; mean BMI, 28). Between 2002 and 2005, plantar pressure values were collected using a Tekscan Matscan system (model 3150, resolution of 1.4 sensels/cm²) while participants walked at a comfortable pace barefoot across the mat. Data was imported into Novel software and masked into 12 segments (toes, submetatarsal heads 1–5, medial arch and heel, lateral arch and heel). Peak pressure and pressure time integral values were then calculated. Two-tailed Students’ T-tests assessed differences between those with and without HV.
Results:

<table>
<thead>
<tr>
<th>Foot Region</th>
<th>No Hallux Valgus</th>
<th>Hallux Valgus</th>
<th>P Value</th>
<th>No Hallux Valgus</th>
<th>Hallux Valgus</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEMALE</td>
<td>n=172</td>
<td>n=87</td>
<td></td>
<td>n=171</td>
<td>n=87</td>
<td></td>
</tr>
<tr>
<td>Hallux</td>
<td>18.5 ± 6.1</td>
<td>18.4 ± 6.1</td>
<td>0.84</td>
<td>7.9 ± 3.9</td>
<td>8.0 ± 4.6</td>
<td>0.90</td>
</tr>
<tr>
<td>Submetatarsal head 1</td>
<td>17.7 ± 5.8</td>
<td>17.1 ± 5.8</td>
<td>0.46</td>
<td>8.4 ± 3.7</td>
<td>8.0 ± 4.2</td>
<td>0.50</td>
</tr>
<tr>
<td>Submetatarsal head 2</td>
<td>22.2 ± 4.8</td>
<td>21.9 ± 5.1</td>
<td>0.67</td>
<td>10.7 ± 3.1</td>
<td>10.9 ± 5.1</td>
<td>0.72</td>
</tr>
</tbody>
</table>

MALE

<table>
<thead>
<tr>
<th>Foot Region</th>
<th>No Hallux Valgus</th>
<th>Hallux Valgus</th>
<th>P Value</th>
<th>No Hallux Valgus</th>
<th>Hallux Valgus</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallux</td>
<td>19.3 ± 7.0</td>
<td>18.0 ± 7.0</td>
<td>0.27</td>
<td>7.7 ± 4.5</td>
<td>8.2 ± 5.8</td>
<td>0.61</td>
</tr>
<tr>
<td>Submetatarsal head 1</td>
<td>18.9 ± 5.9</td>
<td>19.3 ± 7.6</td>
<td>0.8</td>
<td>8.7 ± 3.7</td>
<td>10.5 ± 7.9</td>
<td>0.15</td>
</tr>
<tr>
<td>Submetatarsal head 2</td>
<td>23.0 ± 3.9</td>
<td>22.8 ± 5.2</td>
<td>0.82</td>
<td>10.9 ± 3.1</td>
<td>11.9 ± 7.0</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Preliminary analysis revealed significant sex differences in plantar pressures. Therefore, subsequent analyses were stratified by gender. Since the right foot is considered more dominant, only these results are reported. Tables 1 and 2 present a subset of the 12 analyzed foot areas. Female subjects with HV exhibited greater peak pressure values under the lateral arch than those without HV (p = 0.046). No significant differences were found in pressure-time integrals for females with and without HV, regardless of foot area. Male subjects with HV exhibited greater peak pressure (p=0.007) and pressure-time integral (p=0.015) values than those without HV under groupings of the 3rd, 4th, and 5th toes.

Conclusions: Significant gender differences in peak pressures and pressure-time integrals were noted. The data did not support our hypothesis as analyses did not distinguish between those with and without HV based on pressure-related measures. It is possible that the accuracy and resolution of Tekscan, in comparison to other foot mat systems, may have affected our results. It is also possible, since both groups contain concomitant pathologies, the plantar loading effects for HV washed out. Future work may investigate whether consideration of additional foot disorders or deformities may better use the plantar pressure measures to distinguish foot pathologies.

Disclosure: A. M. Galica: None; A. B. Dufour: None; M. T. Hannan: None; V. A. Casey: None; J. C. Frey: None; M. W. Lenhoff: None; H. J. Hillstrom: None.

1329

Hallux Valgus and Pes Cavus Are Highly Heritable in Older Men and Women: The Framingham Foot Study

Mariam T. Hannan1, Yi-Hsiang Hsu1, L. Adrienne Cupples2 and Joanne M. Jordan3, 1Chapel Hill, NC, 2BUSPH, Boston, MA, 3Hebrew SeniorLife, HSPH and Harvard Medical School, Boston, MA, 4University of North Carolina at Chapel Hill

Foot disorders are common among adults, affecting 20–60% of adults and often linked to mobility limitations. Although genetics are commonly suspected in foot disorders, only one family aggregation study has been done, reporting that 90% of 350 participants with hallux valgus had a family history, and inheritance may be an autosomal dominant transmission. To our knowledge, no other studies have examined the association between foot disorders and genetics in humans. We have the unique opportunity to link data that we have collected on specific foot disorders to a wealth of genetic data in the community-based Framingham Study. Our aim was to evaluate the possible heritability of two common foot disorders, using the pedigree structure in the Framingham Study.

The Framingham Foot Study (n=2179) was designed to examine common foot disorders and functional limitations. A trained examiner used a validated foot exam to assess 20 foot disorders in 2179 participants between 2002–2005. Of participants, 959 men and 1220 women had been genotyped. We estimated overall, sex-specific and age (≤ 60, 60 + years) heritability of hallux valgus and pes cavus (our most common and least common foot disorders) in the Framingham participants. Hallux valgus (present/absent) was defined as the angular deviation of the hallux with respect to the first metatarsal toward the lesser toes at > =15°. Pes cavus was defined using a digital recording of foot pressure while walking (MatScan pedobarographic device, Tekscan, Inc. Boston MA), that allowed calculation of the ratio of arch width (medial to lateral, to nearest 0.01 cm) to heel width. Pes cavus was defined as either foot as having a weight-bearing arch width=0, regardless of heel width. We estimated heritability of hallux valgus and pes cavus by the threshold model of a standard quantitative genetic variance-components model implemented in the Sequential Oligogenic Linkage Analysis Routines (SOLAR) package. Mean age was 66y (range 39–99y); 57% were female. The prevalence of hallux valgus (HV) was 31% (675 hallux valgus cases with available pedigree structure). The overall HV heritability was 0.39 for women and 0.38 for men. For persons aged < 60y, the HV heritability was 0.89. The prevalence of pes cavus (PC) was only 7% (154 cases with available pedigree structure have pes cavus). The PC heritability was 0.68 for women and 0.20 for men. For individuals < 60y of age, the PC heritability was 0.99 for women and 0.63 for men. Thus, hallux valgus and pes cavus are highly heritable, especially for younger adults.

This study breaks new ground in an area that has received very little attention, yet is critically important to public health. Our study documented for the first time, the high heritability (strongly supported by many) of two specific foot disorders phenotypes. Foot disorders are common and it is important to identify persons at high risk, as effective interventions exist and may also be targeted to individuals to lessen the impact of foot disorders or prevent development. Genome-wide association analyses are planned to identify potential genetic determinants for these common foot disorders.

Disclosure: M. T. Hannan: None; Y.-H. Hsu: None; L. A. Cupples: None; J. M. Jordan: None.

1330

Racial Differences in Foot Disorders: The Johnston County Osteoarthritis Project

Yvonne M. Golightly1, Mariam T. Hannan1, Alyssa B. Dufour2 and Joanne M. Jordan3, 1Institute for Aging Research, Hebrew Senior Life, 2University of North Carolina at Chapel Hill

Background: Clinical impressions are that African Americans have pes planus (flat feet) and hallux valgus (bunions) more frequently than Caucasians, but few population-based studies exist. This cross-sectional analysis describes racial/ethnic differences in the prevalence of physical disorders of the foot in a large, bi-racial cohort of individuals 45 years of age or older.

Methods: Of the 1,540 Johnston County Osteoarthritis Project participants clinically evaluated in 2006–2010, four with lower extremity amputation were excluded, leaving 1,536 available for analyses (mean age 69 years, mean body mass index [BMI] 31.5 kg/m2, 68.4% female, 30.3% African American). Presence of specific foot conditions (coded as present or absent) were evaluated using the Foot Assessment Clinical Tool, a validated clinical examination with specific criteria to assess 10 foot disorders (Table). The most common foot disorders were identified (prevalence of > 10%), and logistic regression was used to compare each foot problem by race, controlling for age, BMI, and gender, as these factors may affect foot disorders. Effect modification between race (African American versus Caucasian) and age, BMI (categorized as > 30 or ≤ 30 kg/m2), or gender were examined (p<0.10 for interaction was considered statistically significant).

Results: In 1536 participants, the 5 most common foot conditions were hallux valgus (62.8%), hammer toes (35.6%), overlapping toes (31.8%), pes planus (22.5%), and corns (20.5%). In adjusted models, African Americans were almost 3 times as likely as Caucasians to have pes planus and corns (Table). Non-obese (BMI ≤ 30 kg/m2) African Americans were almost twice as likely as non-obese Caucasians to have hallux valgus (aHR=1.90, 95% CI=1.29–2.78) and over twice as likely to have hammer toes (aHR=2.30, 95% CI=1.62–3.27). These conditions did not differ significantly by race among the obese (BMI > 30 kg/m2). There were no other interactions by age or gender. African Americans were 70–80% less likely than Caucasians to have Tailor’s bunion and pes cavus (Table).

Table. Prevalence of Foot Disorders by Race.

<table>
<thead>
<tr>
<th>Foot Disorder</th>
<th>African American</th>
<th>Caucasian</th>
<th>Adjusted* Odds Ratio</th>
<th>(95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallux Valgus</td>
<td>40.3</td>
<td>28.4</td>
<td>Non-obese: 1.90 (1.29–2.78)</td>
<td></td>
</tr>
<tr>
<td>Hammer Toes</td>
<td>27.9</td>
<td>32.0</td>
<td>Obese: 1.28 (0.94–1.74)</td>
<td></td>
</tr>
<tr>
<td>Claw Toes</td>
<td>3.7</td>
<td>2.8</td>
<td>1.56 (0.85–2.89)</td>
<td></td>
</tr>
<tr>
<td>Overlapping Toes</td>
<td>33.5</td>
<td>31.1</td>
<td>1.16 (0.91–1.47)</td>
<td></td>
</tr>
<tr>
<td>Corns</td>
<td>32.0</td>
<td>15.5</td>
<td>2.89 (2.20–3.79)</td>
<td></td>
</tr>
<tr>
<td>Tailor’s Bunion</td>
<td>1.5</td>
<td>6.7</td>
<td>0.21 (0.10–0.47)</td>
<td></td>
</tr>
<tr>
<td>Morton’s Neurona</td>
<td>8.8</td>
<td>7.9</td>
<td>1.11 (0.74–1.65)</td>
<td></td>
</tr>
<tr>
<td>Planter Fasciitis</td>
<td>5.6</td>
<td>4.6</td>
<td>1.10 (0.67–1.82)</td>
<td></td>
</tr>
<tr>
<td>Pes Cavus</td>
<td>1.5</td>
<td>5.6</td>
<td>0.28 (0.12–0.61)</td>
<td></td>
</tr>
<tr>
<td>Pes Planus</td>
<td>37.6</td>
<td>16.0</td>
<td>2.89 (2.24–3.73)</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age, body mass index, and gender.
Conclusions: Foot disorders are common among adults 45 years of age or older, and these conditions tend to be more prevalent among African Americans than Caucasians. The racial differences in the prevalence of hallux valgus and hammer toes are most evident among those who are not obese, suggesting that obesity equalizes the odds of having these conditions, regardless of race.

Disclosure: Y. M. Golightly: None; M. T. Hannan: None; A. B. Dufour: None; J. M. Jordan: None.

1331

Risk Factors for Hallux Valgus (HV) in a Population-Based Study of Older Adults: The Framingham Foot Study. Alyssa B. Dufour1, Virginia A. Casey2, Andrew M. Galica1, David R. Gagnon1, Howard J. Hillstrom1 and Marian T. Hannan2. 1Boston University School of Public Health, Boston, MA, 2Hebrew SL & Harvard Med Sch, Boston, MA, +Henry Jackson Smith Foundation, New York, NY, 4Institute for Aging Research, Hebrew SeniorLife & Tufts University School of Public Health, Boston, MA, 5Institute for Aging Research, Hebrew SeniorLife, Boston, MA

HV is common in older adults, but its risk factors and relation with foot pain are understudied. The few studies of risk factors have reported conflicting results and had small samples, with limited age ranges. Our purpose was to determine if HV is associated with foot pain and potential risk factors in large numbers of community-dwelling older men and women.

This cross-sectional study included 341 ambulatory adults from the population-based Framingham Study. We used a validated foot exam done by trained examiners with criteria to assess hallux valgus, foot pain, pes planus, and current and past high heel use. HV was present if the angle of the hallux toward the lesser toes was observed to be >15°. Pes planus was defined using a weight-bearing ratio of arch width to rear-foot width on a computerized pressure mat (y/n if ratio > .75 on either foot). Foot pain (y/n) was queried: “On most days, do you have pain, aching or stiffness in either foot?” High heel use in women was determined by the subject choosing high heels/pumps from a list of 13 shoe types as the shoe most typically worn currently and in their past. Past high heel use was categorized into 3 groups: main shoe between ages 20–64y; main shoe at some ages between 20–64y; not worn between 20–64y. Age, sex, and body mass index (BMI, grouped < 25, 25–30, > 30 kg/m2) were also collected. Sex-specific multivariate logistic regression models were performed to examine the effect of the above risk factors on HV. 1498 men & 1917 women had mean age of 67 ± 10.6 y (range 40–100 y). 20% of men and 41% of women had HV. Current high heel use was not associated with HV in women and thus excluded. Table shows risk factors for HV by sex. Foot pain and older age increased the odds of having HV in both women and men (all p < 0.03), even after adjusting for other factors. In women only, having pes planus increased the odds of HV by 70% (p = 0.01); BMI > 30 was protective, decreasing the odds by 35% (p = 0.0007) and wearing high heels as main shoe during ages 20–64y increased the odds of HV by 22% (p = 0.01), after adjusting for other factors. To extend the BMI findings, we examined a biomechanical measure (1st met-head peak pressure) in a subset (n = 573) and found no interaction with BMI (p = 0.56). Adding peak pressure to the model did not change the effects of BMI (ORs = 0.99).

Risk Factors for Hallux Valgus (adjusted for all other risk factors)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence (Male %)</th>
<th>OR (95% CI)</th>
<th>Prevalence (Female %)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 year increment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt;25 (referent)</td>
<td>1.15 (1.01, 1.31)</td>
<td></td>
<td>1.20 (1.09, 1.31)</td>
<td></td>
</tr>
<tr>
<td>BMI 25–30</td>
<td>1.82</td>
<td>1.00</td>
<td>33.5</td>
<td>1.00</td>
</tr>
<tr>
<td>Foot pain (yes/no)</td>
<td>35.1</td>
<td>0.95 (0.67, 1.36)</td>
<td>0.96 (0.76, 1.21)</td>
<td></td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>36.9</td>
<td>0.72 (0.49, 1.06)</td>
<td>0.65 (0.51, 0.83)</td>
<td></td>
</tr>
<tr>
<td>Foot pain (yes/no)</td>
<td>31.4</td>
<td>1.36 (1.10, 1.69)</td>
<td>3.36 (2.84, 3.98)</td>
<td></td>
</tr>
<tr>
<td>Pos Planus (yes/no)</td>
<td>28.5</td>
<td>1.81 (1.33, 2.47)</td>
<td>1.36 (1.10, 1.69)</td>
<td></td>
</tr>
<tr>
<td>Past high heel use (never, referent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past high heel use (some)</td>
<td>6.4</td>
<td>1.45 (0.84, 2.25)</td>
<td>1.68 (1.13, 2.60)</td>
<td></td>
</tr>
<tr>
<td>Past high heel use (always)</td>
<td>38.9</td>
<td>3.19</td>
<td>1.45 (1.09, 1.93)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43.2</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>38.9</td>
<td>1.45 (0.84, 2.25)</td>
<td>1.68 (1.13, 2.60)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.0</td>
<td>1.22 (0.99, 1.51)</td>
<td>1.22 (0.99, 1.51)</td>
<td></td>
</tr>
</tbody>
</table>

We saw strong relations between HV and foot pain and increased age in both men and women. While current high heel use was not linked to HV, several other factors were associated with this structural foot disorder in women. Results for BMI>30 are in agreement with ≥1 previous study showing a protective effect. Perhaps this is due to differing weight distributions and thus different foot biomechanics in obese women versus those with BMI<25. Future studies should include additional risk factors such as occupational weight bearing load, pregnancies and toe box structure of shoe wear.

Disclosure: A. B. Dufour: None; V. A. Casey: None; A. M. Galica: None; D. R. Gagnon: None; H. J. Hillstrom: Stride Rite, 2; M. T. Hannan: None.

1332

A Model of Quality Patient-Health Care Provider Communication. Elizabeth Salt1 and Graham Rowles2. 1University of Kentucky, Lexington, KY, 2University of Kentucky

Background: Quality treatment of rheumatoid arthritis (RA) includes effective communication between patients and health care providers (Lempp, Scott, & Kingsley, 2006). Effective patient-health care provider communication may have a positive effect on health outcomes, medication adherence, and a trusting patient-health care provider relationship, and a negative effect on the number of complaints to medical regulatory authorities (Berrios-Rivera et al., 2006; Tamblyn et al., 2007; Viller et al., 1999; Wolfe, 1995). The purpose of this study is to develop a model of the patient’s perception of quality patient-health care provider communication.

Methods: Following Medical Institutional Review Board approval, a sample of 15 English-speaking patients with RA were recruited from a university rheumatology clinic to participate in two focus groups sessions (n = 6) and individual interviews (n = 9). Verified transcripts from the audio-recorded interviews were analyzed using constant comparative analysis (Straus & Corbin, 1990). The resulting codes were collapsed into themes which were organized into a model of the patient’s perception of quality patient-health care provider communication.

Findings: The model of the patient’s perception of quality patient-health care provider communication involves dynamic interactions between the patient and health care provider. Participants described entering the encounter with past experiences and outside influences. They explained their symptoms and concerns and asked their health care provider questions. Participants felt that their health care provider should both listen to them and believe the information reported. Participants reported that the health care provider, who can come to the encounter with assumptions, should disseminate information, ask questions, and make recommendations. The participants in this study felt that providers should be personable, empathetic, respectful, un-hurried and caring during this interaction. They also felt that health care providers should be honest, straightforward, positive, and decisive when providing accurate information using face-to-face conversation or visual aids.

Conclusion: A model of the patient’s perception of quality patient-health care provider communication has been developed. This model, if substantiated, can further our understanding of patient-health care provider communication and provide direction for future research.

Disclosure: E. Salt: None; G. Rowles: None.

1333

Comparison of Physician- and Nurse Prescriber-Led Dose Adjustment of DMARD Therapy in RA. Grainne Murphy, Mary Daly, John Ryan, Fergus Shanahan, Sinead Harney and Molloy Michael. Cork University Hospital

The advent of nurse prescribing has greatly enhanced the role of the specialist nurse in the care of the rheumatology patient. Patient education and monitoring of patients receiving disease-modifying (DMARD) therapies has been a pivotal part of the rheumatology nurse specialists (RNS) scope of practice. The importance of frequent review and DMARD dose adjustment in early RA has been repeatedly highlighted. Improved clinical responses in those seen on a monthly basis in comparison to those seen every 3 months were observed in patients treated with methotrexate (MTX). The ability of the advanced nurse practitioner (ANP) to review patients in this timely manner may be more feasible than that of physician directed clinics.

Objective: To assess the effectiveness of the ANP in the appropriate escalation of MTX and dose reduction of prednisone and to assess the patient response to such interventions.

Methods: We included all patients who attended the ANP-led clinic in a
12 month period who underwent a dose adjustment in either MTX or prednisone. Treatment records were retrospectively reviewed and the frequency and magnitude of dose escalation (MTX) or reduction (prednisone) were assessed. Patients were asked to complete a retrospective questionnaire to assess the effectiveness of the consultation. Consecutive patients attending a physician-led clinic were used as a control group. The ANP prescriptions were audited for appropriateness and safety.

**Results:** We identified 33 consultations for adjustment of MTX and 74 for prednisone. Of the 1282 attendees at the ANP clinic 107 included a consultation in which a medication dose adjustment occurred. The mean increase in MTX was 2.63mg/month (+/- 0.25mg) for the ANPs in comparison with 0.87mg/month (+/- 0.09) for the physician-led clinic, p=0.000. In relation to prednisone, the ANP achieved a 2.57mg/month dose reduction. All patients attending the ANPs clinic felt adequately informed about their treatment and, by recall, were educated in relation to the nature, administration and side-effects of their medication. Patients demonstrated high levels of confidence in the ANP; 83.3% were as likely to adhere to the ANP decision as the physician led approach and only 11.1% felt that they would have more confidence in a physician-prescribed adjustment. Interestingly, 61.1% felt they would have received less information in the physician-led clinic. No episode of inappropriate or unsafe treatment alteration was identified.

**Conclusion:** We demonstrated that ANPs can effectively and safely escalate DMARDs with the added benefit of steroid dose reduction. This is in contrast with the sub-optimal dose escalation previously demonstrated in physician-led clinics. This study supports the expanded role of ANPs in delivering optimal care or RA patients.

Disclosure: G. Murphy: None; M. Daly: None; J. Ryan: None; F. Shanahan: None; S. Harney: None; M. Michael: None.

**1334**

**Developing an Interactive Health Communication Application within Rheumatology: What Do Patients Want?** Rosalie van der Vaart1, Constance H. C. Drossaert2, Erik Taal3 and Mart A. F. J. van de Laar2. 1Arthritis Centre Twente, Institute for Behavioural Research, University of Twente & Medisch Spectrum Twente, Enschede, The Netherlands, 2Arthritis Centre Twente, Institute for Behavioural Research, University of Twente & Medisch Spectrum Twente

**Background:** The potential of Interactive Health Communication Applications (IHCA’s) to improve health care has been acknowledged and the development of online health applications is quickly evolving, for various chronic conditions. For rheumatic patients, however, no IHCA’s exist yet and research on online applications within rheumatism is scarce. In this project we aim to develop a hospital based rheumatology IHCA. To ensure acceptance and future use of it, a needs assessment among patients was conducted.

**Objectives:**
- To examine patients’ current disease related internet use and their intentions to use various online support tools on a rheumatology IHCA.
- Furthermore, we examined which variables are associated with the intention to use these support tools.

**Methods:** We conducted a survey among a random sample of patients of a large teaching hospital’s rheumatology clinic (N=484). Inclusion criteria were: having visited a rheumatologist in the past 6 months and an age below 70 years. Questions included demographics and health related variables as well as patients’ current disease related internet use and their intention to use seven different support tools: (1) disease and treatment information, (2) care and support information, (3) peer communication, (4) patient-provider communication, (5) symptom monitoring, (6) self-management support and (7) an online personal health record.

**Results:** The response rate was 47% (N=227). Current disease related internet use was mainly limited to searching information. Nevertheless, many patients reported they intended to use six of seven possible support tools when offered in a hospital rheumatology IHCA (49% - 68%). An exception was peer communication; only 11% of patients intended to use this tool. Of all support tools the personal health record was mostly preferred, followed by information provision. Although we found some small significant correlations between this reported intention and participants characteristics, these were all small (below 0.21) and showed no clear predictors.

**Conclusion:** Our results reveal a discrepancy between the low current health related internet use and the high interest to use online support tools offered by the hospital. Patients are especially positive about the option of an online personal health record. Demographics and health related variables showed no clear relation to intention to use.

Disclosure: R. van der Vaart: None; C. H. C. Drossaert: None; E. Taal: None; M. A. F. J. van de Laar: None.

**1335**

**Does an RA Peer Support Program Impact Disease Outcomes?** Melanie Zibit1, Jing Cui2, Christine K. Iannaccone3, Nancy A. Shadick4, Michael E. Weinblatt6, Meghan Courtney5, Margo Hanlan5, Huyen Tsoa1 and Anne Fossel1. 1Brigham & Womens Hospital, Boston, MA, 2Brigham and Womens Hospital, Boston, MA, 3Brigham and Womeens Hospital, Boston, MA, 4Brigham and Womeens Hospital, Boston, MA, 5Brigham and Womeens Hospital, Boston, MA

**Purpose:** A diagnosis of RA can lead to loss of function, increased pain, depression, and complex medical care. Peer support, used effectively in other illnesses, may provide support that can lead to improvement in RA disease outcomes. This pilot study evaluates whether a peer support program for RA patients can improve fatigue, health, and medication adherence.

**Methods:** RA patients at a hospital arthritis clinic seeking peer support enrolled in a peer support program. Patients wishing to provide support to others (mentors) were trained by a social worker to learn how to help other patients with concerns, coping strategies and medical decision-making. Mentors and mentees were partnered based on age, disease duration, comorbidities, lifestyle, physical activity, and employment status. Mentors contacted mentees by phone once a week for 6 weeks, with some email or a face-to-face meetings. To evaluate the efficacy of the program, mentees seeking support were compared with controls from an RA registry at baseline and at 6 month follow up. Both groups filled out questionnaires concerning fatigue and pain (VAS), flares, self-efficacy, emotional health and functional status (SF12 Health Status Survey), and medical adherence (ASK20). Univariate analyses were done to compare both groups at baseline and a linear regression model was used to compare differences after 6 months.

**Results:** 10 mentees and 6 controls, to date, have completed baseline and 6 month questionnaires. There were no differences in disease duration (p=0.98) and gender (p=0.89), but age distribution differed (p=0.02) between mentees and controls. Analysis at 6 months, using linear regression analyses, showed that mentees had a significant improvement in self-efficacy compared to the controls (p=0.05) (see Table 1). Subjects completing the program to date showed a trend toward less fatigue (p=0.11) and improvements in medical adherence (p=0.12).

**Conclusions:** This pilot study suggests that RA patients who have active disease and receive peer support show improvement in self-efficacy. Peer support programs may be effective in enhancing patients’ coping skills. Further analyses are needed to demonstrate the impact of the program on patient self-reported outcomes of fatigue and medical adherence.

**Table 1. Linear Regression Analysis Mentees (N=10) compared to Controls (N=6)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mentees Controls</th>
<th>Pre Mean (± SD)</th>
<th>Post Mean (± SD)</th>
<th>Pre Mean (± SD)</th>
<th>Post Mean (± SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>SF55</td>
<td></td>
<td>53.52 (± 21.56)</td>
<td>64.26 (± 16.75)</td>
<td>81.11 (± 14.32)</td>
<td>74.44 (± 9.87)</td>
<td></td>
</tr>
<tr>
<td>Fatigue (0–100)</td>
<td></td>
<td>55.5 (± 34.36)</td>
<td>56 (± 29.04)</td>
<td>29.17 (± 26.35)</td>
<td>51.67 (± 28.75)</td>
<td>0.11</td>
</tr>
<tr>
<td>Medical Adherence</td>
<td></td>
<td>42.9 (± 39.1)</td>
<td>39.1 (± 35.7)</td>
<td>35.7 (± 39.7)</td>
<td>12 (± 35.7)</td>
<td></td>
</tr>
<tr>
<td>ASK20 (20–100)</td>
<td></td>
<td>13.37 (± 13.39)</td>
<td>13.54 (± 13.54)</td>
<td>13.54 (± 14.10)</td>
<td>13.54 (± 14.10)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pain (0–100)</td>
<td></td>
<td>60.5 (± 24.77)</td>
<td>30 (± 36.62)</td>
<td>45.0 (± 25.50)</td>
<td>45.0 (± 25.50)</td>
<td>0.22</td>
</tr>
<tr>
<td>SF-12 (MCS)</td>
<td></td>
<td>44.19 (± 45.39)</td>
<td>54.44 (± 52.30)</td>
<td>52.30 (± 91.91)</td>
<td>52.30 (± 91.91)</td>
<td>0.91</td>
</tr>
<tr>
<td>SF-12 (PCS)</td>
<td></td>
<td>31.08 (± 34.83)</td>
<td>48.00 (± 40.38)</td>
<td>30.22 (± 13.20)</td>
<td>30.22 (± 13.20)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Disclosure: M. Zibit: Amgen Inc., 2; J. Cui: Biogen Idec, 2, Crescendo Bioscience, 2; C. K. Iannaccone: Biogen Idec, 2, Crescendo Bioscience, 2; N. A. Shadick: Amgen Inc., 2, Biogen Idec, 2, Crescendo Bioscience, 2; M. E. Weinblatt: Biogen Idec, 5, Crescendo Bioscience, 5; M. Courtney: Biogen Idec, 2, Crescendo Bioscience, 2; M. Hanlan: Amgen Inc., 2, H. Tsoa: Biogen Idec, 2, Crescendo Bioscience, 2; A. Fossel: Biogen Idec, 2, Crescendo Bioscience, 2.
Educational Needs Assessment among Patients with Rheumatic Diseases in Kenya. Ines Colmegna, Susan J. Bartlett, Sharon Kodhek, Omondi G. Oyoo and International League of Associations for Rheumatology East Africa Initiative. McGill University, Montreal, QC, Canada, Nairobi SLE Support Group, Nairobi, Kenya, University of Nairobi, Nairobi, Kenya

**Background:** In Africa, access to comprehensive musculoskeletal (MSK) health care is very limited. Patient education and self-management have been shown to reduce inequities and improve functional status, pain, psychological wellbeing, employment, and even disease activity. Educational interventions need to be tailored and contextualized to meet individuals’ specific needs.

**Objective:** To assess educational needs among patients with rheumatic conditions in Africa as a first step in developing interventions to reduce the gap in health service provision.

**Methods:** English-speaking patients who attended community lectures sponsored by ILAR in Nairobi on rheumatic diseases completed a questionnaire about demographics, diagnosis, pain and disability. Topics also queried included overall interest in learning about arthritis, specific needs, preferred learning modalities as well as internet access.

**Results:** The sample consisted of 61 patients, mostly female (87%) with a mean ± SD age of 41.4 ± 13.5 yrs and education of 14.6 ± 3.7 yrs. Most reported working full (76%) or part time (10%) and lived with family or others with only 14% living alone. Diagnoses reported included SLE (37%), RA (30%), other (19%), gout (17%) and gouty arthritis (6%). Nearly half (48%) reported having pain every day. The highest MHAQ scores were associated with RA (0.7 ± 0.7), “RA + SLE” (0.6 ± 0.6), and SLE (0.4 ± 0.5).

Across conditions, disease knowledge was suboptimal; only 33% reported having “enough” to a “great deal” of knowledge and almost all (95%) wanted to learn more about their condition. Most reported it to be “very” to “extremely important” to learn more about pain (100%), medications (98%), fatigue (98%), exercise (96%), expectations about disease (96%), use of heat and cold (94%), and coping with emotions (90%). One fourth expressed fatigue (98%), exercise (96%), expectations about disease (96%), use of heat to learn more about their condition. Most reported it to be “very” to “extremely important” to learn more about pain (100%), medications (98%), fatigue (98%), exercise (96%), expectations about disease (96%), use of heat and cold (94%), and coping with emotions (90%).

**Conclusions:** There is a clear need for rheumatic disease education among patients in Kenya. Participation in support groups does not appear to lessen interest or select for specific educational needs, a finding that is consistent with other studies showing that “experienced” patients are still eager to learn about their illness and treatment. Leaders in Rheumatology from developed countries have unique opportunities to empower patients in developing parts of the world using internet-based technologies.

**Disclosure:** I. Colmegna: None; S. J. Bartlett: None; S. Kodhek: None; O. G. Oyoo: None; International League of Associations for Rheumatology East Africa Initiative: None.

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Rheumatology Health Professionals’ Care: Current and Future Tasks and Education. Emilia J. Hurkmans, Rinie Geenen, John Verhoef and Thea P. M. Vliet Vlieland; 1. Clinical and Health Psychology, Utrecht University & University Medical Center, Utrecht, The Netherlands, 2. Department of Rheumatology and Orthopaedics, Leiden University Medical Center, Leiden, The Netherlands, 3. Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands, 4. Faculty of Health, University of Applied Sciences, Leiden, The Netherlands

**Background:** In the Netherlands, as in many other countries, advanced arthritis training for HPs (clinical nurse specialists, physical therapists, occupational therapists, social workers and psychologists) is organized separately for each discipline. A study of their actual and preferred tasks and education may lead to recommendations for improvement of education and, eventually, care provided by HPs.

**Objectives:** To examine which tasks currently are performed and preferred by Dutch HPs involved in the care of patients with rheumatic diseases, and to what extent the required knowledge and skills are and should be covered in advanced arthritis training.

**Methods:** For this cross-sectional study a questionnaire was developed, based on a comparable project of the UK Arthritis Research Campaign and interviews with experts from the various disciplines involved. The first part pertained to the current en preferred performance of 19 diagnostic and 27 therapeutic tasks (yes/no). The second part included the knowledge of 22 “items” and was asked whether the items were not, globally or in detail covered in their advanced arthritis training.

**Results:** The response rates were 44% for the HPs, 38% for the rheumatologists and 80% of the patients, respectively. On average clinical nurse specialists and physical therapists each perform 23 of the 46 included tasks, occupational therapists 21, social workers 17 and psychologists 12. Of the 46 included tasks, 35 were performed by >50% of two or more groups of HPs. The least provided tasks were medical tasks, such as ordering and judging X-rays and prescribing medication. The majority (>50%) of 4-5 groups of HPs indicated a wish to apply (more) measurement instruments and to provide (more) education. The majority of all knowledge and skills items (27/35) were not sufficiently covered in the current advanced arthritis training, according to >50% of 2 or more HP groups. According to >50% of the HPs and rheumatologists medical tasks should not or only globally be covered in the advanced arthritis training for HPs. In contrast, >50% of the patients thought that all tasks (including medical tasks) should be covered in the advanced arthritis training.

**Conclusions:** There is considerable overlap in the tasks performed by Dutch HPs in rheumatology. HPs did not express a need to expand their daily tasks with medical tasks. A large number of knowledge and skills items were found not sufficiently covered in the current advanced arthritis training. These findings suggest that there is room for the improvement of the current advanced arthritis training for Dutch HPs. Given the overlap in current tasks and preferences with respect to education, the development of common educational modules appears to be a good option.

**Disclosure:** R. Ariza-Ariza: None; B. Hernández-Cruz: None; V. Navarro-Compañ: None; F. Navarro-Sarabia: None.

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**Phone Administration Compared to Self-Administration on Paper of the Main Instruments Used To Evaluate Ankylosing Spondylitis Patients.** Rafael Ariza-Ariza, Blanca Hernández-Cruz, Victoria Navarro-Compañ and Federico Navarro-Sarabia, Hospital Virgen Macarena, Sevilla, Spain

**Background:** BASDAI, BASFI, and other instruments used to evaluate Ankylosing Spondylitis (AS) patients are usually self-administered on paper. However, it limits their use in daily clinical practice because paper forms are resource demanding regarding the time spending for filling them. A phone administration previously to the medical visit it would facilitate the use of these tools.

**Objective:** to assess the performance of the instruments used to evaluate AS patients when administered by phone in comparison with the traditional self-administration on paper.

**Methods:** Design: a test-retest study. Patients with AS (modified NY criteria) consecutively selected in a tertiary care center were included. Patient global assessment on numerical rating scale (NRS), patient global pain assessment on a NRS, patient global morning stiffness assessment on a NRS, BASDAI, BASFI, and ASQoL were administered by phone. 48 later the same instruments were self-administered on paper at the hospital. Descriptive statistics were done. Agreement between the two tests was assessed by the intraclass correlation coefficient. Spearman correlation coefficient was also calculated.

**Results:** 51 patients, 76% males, with age 47.7 ± 13 years were included. The time between phone administration and self-administration on paper was 1.5 ± 1.0 days. Mean ± SD values of the instruments obtained by phone administration and self-administration on paper, intraclass correlation coefficients (ICC) and Spearman correlation coefficients (rho) were as follows: patient global assessment on a NRS: 3.8 ± 2.8, and 3.8 ± 2.4, ICC: 0.80*, and rho: 0.80*; patient global pain assessment on a NRS: 3.9 ± 2.9, and 3.7 ± 3.0, ICC: 0.89*, and rho: 0.82*; patient global morning stiffness assessment on a NRS: 3.6 ± 3.0, and 3.4 ± 3.0, ICC: 0.90*, and rho: 0.87*; BASDAI: 3.9 ± 2.6, and 3.5 ± 2.5, ICC: 0.91*, and rho: 0.92*; and ASQoL: 6.2 ± 5.3, and 6.1 ± 4.9, ICC: 0.93*, and rho: 0.87*, respectively. *p < 0.001.

**Conclusions:** the phone administration of these instruments is comparable to their self-administration on paper. It can facilitate their use in daily clinical practice.

**Disclosure:** R. Ariza-Ariza: None; B. Hernández-Cruz: None; V. Navarro-Compañ: None; F. Navarro-Sarabia: None.
Accuracy of the Early Detection of Juvenile Idiopathic Arthritis Questionnaire—A Multicenter Study, Claudio A. Len1, Luciana T. P. Paulo2, Maria Teresa R. A. Terrell3, Silvana B. Sacchetti3, Virginia P. L. Ferriani5, Clovis A. A. Silva5, Cäsia M. P. Barbosa1, Simone Lotufo7 and Roberto Marini6

1Hospital Darcy Vargas, São Paulo, Brazil, 2Hospital Menino Jesus, São Paulo, Brazil, 3Santa Casa de São Paulo, São Paulo, Brazil, 4Universidade de São Paulo, São Paulo, Brazil, 5Universidade de São Paulo, Ribeirão Preto, São Paulo, Brazil, 6Universidade Estadual de Campinas, São Paulo, Brazil, 7Universidade Federal de São Paulo, São Paulo, Brazil

Background: Many factors are associated to the delay in the diagnosis of juvenile idiopathic arthritis (JIA), some of them related to the disease and other to the difficulty in referring patients to specialists. The Early Detection of Arthritis Questionnaire (EDA-12) was designed to be used as an auxiliary tool for screening of suspect cases in general practice. However, its reliability was tested only in a small number of subjects.

Objective: To assess the reliability of EDA-12 in the detection of suspect cases referred to outpatient pediatric rheumatology reference clinics in 3 large urban areas.

Methods: EDA-12 (score range 0–12) was applied to parents of children (0–18 y) who sought spontaneously or were referred for evaluation in 7 outpatient pediatric rheumatology clinics. Diagnostic suspicion was recorded in the first consultation (initial diagnosis), and definitive diagnosis was recorded after, at least, 6-month period of follow-up.

Results: Six hundred and sixty patients (57% girls) were included, with age (mean) of 9 years-old. JIA initial diagnosis was performed in 12% of the consultations, being also observed in the definitive diagnosis (12% of the consultations), with a high agreement between the first suspicion and the diagnostic confirmation (kappa coefficient = 0.872%). A ROC curve was used in the assessment of a score able to distinguish JIA children from non-JIA children, being obtained a value of 5 (five) in the first consultation, with sensitivity of 93% and specificity of 76%.

Conclusion: The EDA-12 has demonstrated reliability for discrimination of suspect cases of JIA and reinforces its relevance as an auxiliary tool in the first medical consultation.

Disclosure: C. A. Len: None; L. T. P. Paulo: None; M. T. R. A. Terrell: None; S. B. Sacchetti: None; V. P. L. Ferriani: None; C. A. A. Silva: None; C. M. P. Barbosa: None; S. Lotufo: None; R. Marini: None.

Engaging Youth in a Web Based Transition Intervention: Usability and Feasibility of Rheumtogrow.org, Peter Scal, Ann Garwick and Keith Horvath. University of Minnesota

Purpose: This pilot study tests the usability and feasibility of a theoretically grounded, internet based intervention for youth with Juvenile Arthritis (JA)

Method: We developed Rheumtogrow.org for youth with JA based on Self-Determination Theory (SDT) through a user centered and participatory process. This intervention seeks to increase the likelihood that youth will engage in behaviors that reduce the impact that arthritis has on their lives across multiple domains including the transition from child to adult focused care. We enrolled 32 youth (age 14–18) and provided them with access to the intervention site.

Results: Of the 32 enrolled youth, 1 (3.1%) did not complete pre-test and 2 (6.3%) completed the pretest but did not login to the intervention site during the trial. Pre and post test questionnaires were completed by 29 (90.6%). Most users agreed or strongly agreed that the intervention site was easy to understand (82.7%) and easy to use (72.4%) that it was contained creditable information (96.5%), was sensitive to teen issues (89.7%) and relevant to their life (71.4%). Most would use the site again (88.9%) and recommend it to a friend (88.9%). Open ended responses indicated that users most liked the site as being relevant and engaging, especially the opportunity to learn from the experiences of other teens. Users had a strongly stated preference for improving the youth-to-youth interactivity on the site which is consistent with their current patterns of use and expectations of technology. Interest in learning more about JA and the influence of others was associated with greater site use while expectations that the site would have real-time youth-to-youth interaction (when it did not) was associated with lower use. Youth engagement in a web-based intervention for JA is influenced by individual and social characteristics and the nature of the technology. Rheumtogrow.org offers a promising foundation on which to refine and test intervention for youth with JA.

Disclosure: P. Scal: None; A. Garwick: None; K. Horvath: None.

FEAR (False ELISA Associated Rheumatic) Syndrome in Children, Donald P. Goldsmith1, Carolann Martucci2 and Svetlana Lvovich3.

1St Christopher Hosp Children/Drexel University College of Medicine, Philadelphia, PA, 2St Christopher’s Hosp Children/Drexel University College of Medicine, Philadelphia, PA, 3St Christopher’s Hospital for Children, Philadelphia, PA

Introduction: Non specific arthralgias associated with a positive ANA remain a common referral source to the pediatric rheumatologist. Multiple studies have documented the unlikely progression to a recognizable inflammatory disorder and allow the pediatric rheumatologist to effectively alleviate parent and patient anxiety. There is now increased use of ANA reflex panels which use solid phase ELISA assays rather than indirect immunofluorescence. If positive, even without a reported quantitative titer, these panels automatically cascade (with increased cost) to additional antibody tests. Children are now being referred for isolated positive ELISA tests such as anti centromere, anti SS-A/B, anti SCL-70, anti Sm/RNP, and anti dsDNA antibodies.

Purpose: To characterize and bring to attention increasing numbers of children with a positive ANA screen without a quantitative titer and one or more positive additional specific antibody tests.

Methods: A retrospective outpatient chart review from 06/01/2008 to 01/01/2010

Results: Of 415 new patient assessments seen over this 18 month period we identified 20 (5%) children with a positive ANA screen and one or more additional positive antibody tests. All children had non specific complaints, primarily arthralgias, myalgias, and/or transient cutaneous eruption. These tests had been obtained prior to consultative assessment. There were 19 F, 1 M, 16 White, 3 African-American, and 1 Hispanic. Mean age 11.4 y (range 6–17). Within this group of children there were 6 positive tests for anti SS-A, 4 anti SS-B, 4 anti SCL-70, 3 anti centromere, 3 anti RNP, 2 anti Smith, and 2 anti dsDNA. Four children had more than 1 antibody present. The average duration of symptoms prior to laboratory assessment was 18 months (range 4–48). Prior to assessment 15(75%) of the parents had seriously web researched those disorders associated with each of these antibodies. None of these children have thus far developed a characteristic pediatric rheumatic disorder.

Conclusions: Although these children require careful follow-up observation, in view of the extended duration and non specific nature of symptoms prior to the recognition of each positive antibody as well as the lack of corroborative physical findings we predict it’s unlikely that significant morbidity will develop. As 5% of our recent new patient assessments/year, this represents a significant number of children. Parent/patient fear and anxiety is considerable and in our opinion lead to subtle variants of the evolvent and engaging, especially the opportunity to learn from the experiences of other teens. To minimize the creation of FEAR syndrome we need to better inform our referring physician base about the most suitable, if any, ANA tests to order. Commercial laboratories should fully disclose the nature of each panel and not solely offer cascading tests on pre-printed forms.

Disclosure: D. P. Goldsmith: None; C. Martucci: None; S. Lvovich: None.
Physiotherapy Management of Children with Hypermobility: A Review of an Out-Patient Self Management Exercise Programme. Susan M. Maillard1, David Adkins2, Elaine Haggart2 and Swati Bhagat2. Great Ormond Street Hospital, London, Maidenhead, United Kingdom, 2Great Ormond Street Hospital, London, United Kingdom

Background: The recognition of hypermobility in the paediatric population has increased and common complaints associated with this are pain and fatigue. Great Ormond Street Hospital, UK has implemented a self management exercise programme, which is specific and progressive to key muscle groups. It utilises open chain exercises with high repetitions (30) and low fatigue. Great Ormond Street Hospital, London, United Kingdom has increased and common complaints associated with this are pain and fatigue.

Method: A retrospective case note review of children who had attended the hypermobility out-patient service between Nov 2009 and March 2010 was completed (comparing initial assessment and follow up). Assessments of muscle strength, school attendance, Childhood Health Assessment Questionnaire (CHAQ), parental visual analogue scale (VAS) of general well being and pain VAS were collected on the children. All children were provided with an exercise programme at the initial assessment, based on 4–5 key exercises, focusing on increasing repetitions and weights. An excel database was used to compile findings.

Results: Data from 20 children (10 males:10 females) who had already been diagnosed with hypermobility (Beighton score of ≥4/9), was collected. The mean age was 11 years (range 5–16 years). The primary complaints within the cohort were of pain and fatigue longer than 6 months in duration. School attendance for all but one patient was 100%.

On initial assessment the mean muscle strength score was 3.5/5 (oxford manual muscle score) in hip abductors, hip extensors and inner range quadriceps (range 2.5–5) and 7.25/10 repetitions for plantar flexors (range 2–10). At 8–12 week follow up, all children were completing 30 repetitions and using an average weight of 1.5kg (range 0.5–2.5kg). There was an average increase in muscle strength of hip abductors (60%), hip extensors (70%), inner range quadriceps (55%) and plantar flexors (40%).

The average score of the CHAQ on assessment was 1.15/3, pain VAS was 4.6/10cm and parental VAS of general well being 3.9/10cm (10=most unwell). There was a 60% decrease in the score of CHAQ between visits. Pain and parental VAS diminished by 55% and 45% respectively and all parents reported an improvement in fatigue.

Conclusion: The use of a specific progressive resisted muscle strengthening programme using open chain exercise, with high reps and low weights has been shown to increase muscle strength, improve overall function and decrease pain in children with hypermobility. This can therefore considered to be an effective method of managing hypermobile children within an outpatient clinic.

Disclosure: S. M. Maillard: None; D. Adkins: None; E. Haggart: None; S. Bhagat: None.

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Stress in Adolescents with Idiopathic Musculoskeletal Pain. Juliana Molina1, Flavia H. Santos1, Maria Sylvia Vitale2, Maria Odete E. Hiliaro2, Maria Teresinha R. A. Terreri2, Simone G. L. Silva2 and Claudio A. Len2. 1Universidade Estadual de São Paulo, Assis, São Paulo, Brazil, 2Universidade Federal de São Paulo, São Paulo, Brazil

Background: Musculoskeletal pain syndromes are raising complaints at pediatric practice, affecting mainly children and adolescents from 5 to 14 years. Adjacent to the pain, reports of emotional and cognitive difficulties are also commonly reported.

Objective: To investigate the presence of stress in the attended population in a Pediatric Rheumatology outpatient clinic.

Method: Nineteen adolescents from 14 to 16 years with idiopathic musculoskeletal pain (IMP) were assessed regarding to stress symptoms through Lipp’s Inventory of Stress Symptom for Adults, and compared to a control group of 20 matched healthy adolescents.

Results: IMP adolescents had significantly higher stress scores comparing to the control group. Thus, 79% of IMP adolescents had complaints related to stress, while the same scores were observed in only 35% of the control group. The differences between groups (t-test) were notable in the intermediate stage of stress, known as resistance phase (p=0.009), followed by exhaustion phase (p=0.023), final stage of stress where the organism becomes vulnerable to diseases. Also, regarding to complaints, the differences were pointed out either for physical (p=0.013) or emotional (p=0.030) aspect.

Conclusion: Adolescents with chronic pain have physical, social, emotional, and behavioral aspects in their lives affected by a chronic process of pain. In our sample we have demonstrated that the complaints presented by adolescents and their parents also show a stress response in a worsening process.

Disclosure: J. Molina: None; F. H. Santos: None; M. S. Vitale: None; M. O. E. Hiliaro: None; M. T. R. A. Terreri: None; S. G. L. Silva: None; C. A. Len: None.

1344

To Explore the Use of the PedsQL Subjective Questionnaire To Assess Levels of Fatigue in Children with Juvenile Dermatomyositis. Susan M. Maillard1, Amy Todd2, Kiran Nistala2, Clarissa Pilkington2 and Abdul Hassan3. 1Great Ormond Street Hospital, London, Maidenhead, United Kingdom, 2Great Ormond Street Hospital, London, 3Institute of Child Health, London

Background: Fatigue is one of the regularly reported clinical features of Juvenile Dermatomyositis (JDM), however there is no standardised method of assessing the degree of fatigue. The PedsQL Fatigue score (FS) is a self reported questionnaire and a Visual Analogue Scale (FVAS) which has been developed to measure fatigue in children with paediatric inflammatory diseases. Great Ormond Street Hospital has a specialist service for children with JDM and the FS and FVAS were used to assess whether they were an effective measure of disease related fatigue.

Objectives: To establish if the PedsQL FS measures fatigue in children with JDM compared to clinical outcome measures of ACR including muscle strength and function.

Methods: All children attending the JDM clinic were routinely assessed using the Childhood Myositis Assessment Score (CMAS), manual muscle testing score (MT8), parental VAS score of general wellbeing (PaVAS), physicians VAS of disease activity (PVAS), 6 minute walk test (6MWT) and Childhood Health Assessment Questionnaire (CHAQ). The PedsQL questionnaire was given out separately to both parents and children and includes a fatigue VAS (FVAS), a pain VAS as well as specific questions about cognitive fatigue, physical activity and sleep. The data was analysed using SPSS v16.0.

Results: The patient cohort comprised of 52 children (39 F: 13 M). The mean age was 11.92 years (range 3–19). The mean disease duration was 9.42 years (range 0.2–13yrs).

The PedsQL FS (both parent and child) showed statistical significance with pain VAS, PaVAS and CHAQ however did not show significance with the objective markers- MT8 and CMAS. The child and parent FVAS shows statistically significant results with the pain VAS, MT8 and the CHAQ. Additionally, the child FVAS statistically shows a correlation with the CMAS. Neither the PedsQL FS or FVAS showed any statistical correlation with the 6MWT or the PVAS.

Table: Spearman’s Correlation

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<th>6MWT</th>
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<td>-.427**</td>
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<td>-.304</td>
<td>-.415**</td>
<td>.311</td>
<td>.004</td>
<td>.324</td>
</tr>
</tbody>
</table>

Conclusions: It appears that the PedsQL FS does not fully objectively measure fatigue but combined with the FVAS may be a reasonable tool for assessing fatigue in JDM. However it is also recognised that psychological and psychosocial factors also play a role in patient self reported fatigue and further research is required into this area.

Disclosure: S. M. Maillard: None; A. Todd: None; K. Nistala: None; C. Pilkington: None; A. Hassan: None.
Utilizing Social Media To Reach Young Arthritis Patients. Jane S. Brandenstein1, Emily Cope1, Allison J. Kerr2, Ashley M. Boynes3, Carol D. Popp4 and Lori Knapp. 1. Freedom, PA, 2. W Pa Arthritis Foundation, Pittsburgh, PA, 3. WPA Arthritis Foundation, Pittsburgh, PA

Background: Many people in their teens through thirty's affected by Arthritis can feel like they are the only one with this disease. Young people often have difficulty finding age appropriate resources and peers with similar chronic diagnoses. School, work schedules and family commitments make traditional arthritis exercise classes and self management programs challenging to access for this population. This isolation and lack of information can be very stressful and harmful to arthritis patients mental well being.

Objective: To create an online community and informative online resources for young people with arthritis.

Summary: Social media was used to connect to the target audience of young people affected with arthritis. To do this the organization created and regularly maintains accounts on Twitter, facebook, and YouTube. Since the online community's creation it has gained 1,634 followers on Twitter, 164 fans on facebook and uploaded 12 videos to YouTube.

The organization also created Rheum for Wellness, a blog, which serves as an outlet for all arthritis-related topics. The blog has featured posts on cooking, rare forms of arthritis, personal stories of hope, physical activity and much more. Another hugely popular feature of the blog is a series entitled The Journey to Wellness. In this series a young woman blogs about her personal battle with several inflammatory diseases and her quest to remain positive and reach out to others with similar issues. Rheum for Wellness has sparked online conversations and connected readers from all over the world. This blog has had 99 posts, 493 comments, and 73,775 views. There has been overwhelming feedback in support of the blog. Readers constantly comment that it makes them feel understood and not alone and that they have a voice. Mariah posted, "I want to say Thank You for writing this! I also 'live' with autoimmune disease, as well as other things. It is such a great feeling to know that someone out there knows how I truly feel everyday." Elizabeth said, "Thank You! Someone needed to express what we are all feeling, and you did it so eloquently.

Arthritis Radio, a podcast, was established showcase the many voices of arthritis. The podcast features interviews with health professionals, community leaders, physical therapists and many others. The goal of the show is to make knowledgeable experts accessible to all of those affected with arthritis. Arthritis Radio has had 16 episodes, 9,558 channel visits and 732 subscribers. Listeners have described this podcast as "a wonderful learning tool you have provided people who have arthritis" and state that the interviews on cutting edge research give them hope for the future.

Conclusion: Social media can be successfully utilized to provide information, resources and support to young arthritis patients. This target population benefits from supplementing traditional forms of communication with online communities and social networks.

Disclosure: J. S. Brandenstein: None; E. Cope: None; A. J. Kerr: None; A. M. Boynes: None; C. D. Popp: None; L. Knapp: None.

**ARHP Concurrent Abstract Sessions Physical and Psychosocial Challenges in Scleroderma**

Tuesday, November 9, 2010, 9:15 AM-10:15 AM

1345

Frequency and Impact of Symptoms Experienced by Patients with Systemic Sclerosis: Results from a Canadian National Survey. Marielle Basser1, Marie Hudson1, Suzanne S. Taittler1, Ort Schier2, Murray Baron2, and Brett D.Thombs3; 1. Jewish General Hospital, Montreal, QC, Canada, 2. McGill University, Montreal, QC, Canada, 3. McGill University and Jewish General Hospital, 4. SMBD Jewish General Hospital, Montreal, QC, Canada

Background: Patients with systemic sclerosis (SSc) report a number of problems that have been linked to disability and reduced quality of life. Due to the rarity and heterogeneity of SSc, not enough is known about the range of problems faced by individuals living with SSc. Several studies have assessed problems faced by patients with SSc, however, knowledge about the relative importance of these different problems is limited by the small number of studies that have been conducted, the relatively narrow scope of potential problems assessed in existing studies, and the small sample sizes in these studies. The objective of the present study was to identify, in a large SSc sample, symptoms of SSc that patients rated as frequent and that highly impacted their ability to carry out daily activities.

Methods: Patients with SSc were recruited to complete the anonymous Canadian Scleroderma Patient Survey of Health Concerns and Research Priorities through patient advocacy group websites, Canadian magazines, scleroderma-related newsletters, and support groups across Canada. The survey included questions regarding the frequency and impact of 69 SSc symptoms, which were generated from a panel of Canadian Scleroderma Research Group and Scleroderma Society of Canada members using existing questionnaires, symptom checklists and research articles. Descriptive analyses were performed dichotomizing symptom frequencies into never or rarely versus sometimes, most of the time or always and symptom impact on daily activities into no or minimal impact versus moderate to severe impact. In addition, for each item, among patients with symptom frequency of at least sometimes, the percentage of patients with at least moderate impact on daily activities was calculated.

Results: Our study included 464 Canadian persons with SSc. The 5 highest-rated symptoms in terms of frequency were fatigue (89%), Raynaud’s phenomenon (86%), hand stiffness (81%), joint pain (81%) and difficulty sleeping (76%). The same 5 symptoms were the highest-rated in terms of having a moderate to severe impact on daily activities, in the order of fatigue (72%), Raynaud’s phenomenon (67%), joint pain (64%), hand stiffness (59%), and difficulty sleeping (59%). In addition to these symptoms, items related to decreased hand function (difficulty making a fist; difficulty holding objects; difficulty opening hand; difficulty faucet) were frequently endorsed by more than 400 patients and of these patients, at least 67% endorsed a moderate to severe impact on daily activities.

Conclusion: The results of this study confirmed the importance of core symptoms of SSc with respect to quality of life, such as fatigue. Limitations in hand function, another area identified by patients as being significant, is common and contributes to overall disability levels. However, little literature exists testing the effectiveness of rehabilitation techniques to improve hand function among patients with SSc. Other areas with very little research that appear to play important roles in daily functioning include sleeping problems and male sexual functioning. A patient-researcher consensus is suggested in order to focus future SSc research.

Disclosure: M. Bassel: None; M. Hudson: None; S. S. Taittler: None; O. Schier: None; M. Baron: None; B. D. Thombs: None.

1347

Sociodemographic and Disease Correlates of Body Image in Systemic Sclerosis (SSc). Lisa R. Jewett1, Marie Hudson2, Murray Baron2, Brett D. Thombs2 and Canadian Scleroderma Research Group (CSRG), 1. Jewish General Hospital, Montreal, QC, Canada, 2. McGill University, Montreal, QC, Canada, 3. McGill University and Jewish General Hospital

Background/Objective: Systemic sclerosis (SSc) is a chronic disease that results in significant disfigurement to socially relevant body parts, including the face and hands. There is very little research, however, on body image concerns in SSc. The objective of this study was to identify sociodemographic and disease-related correlates of dissatisfaction with appearance and social discomfort among patients with SSc. Furthermore, the study aimed to identify disfigured areas of the body most closely related to body image dissatisfaction and social discomfort.

Methods: The sample of SSc patients came from the 15-center Canadian Scleroderma Research Group Registry. Sociodemographic information was based on self-report, and patients' medical histories and disease characteristics were obtained via clinical histories and examinations by study physicians. The Brief-SWAP was used to assess social discomfort and dissatisfaction with appearance. Structural equation models were conducted with MPlus to determine the relationship of the dissatisfaction with appearance and social discomfort factors of the Brief-SWAP with age, sex, marital status, total body skin involvement, disease duration, and telangiectasias. A secondary model assessed relationships between each factor and skin involvement scores from specific body areas, including face, hands/fingers, arms, chest/abdomen, thighs, and lower legs.

Results: A total of 788 SSc patients (94 men and 694 women) were included. Subjective dissatisfaction with appearance was significantly associated with greater skin involvement (standardized regression coefficient = .26, p < .01) and longer disease duration (.08, p = .04). Social discomfort was significantly associated with greater skin involvement (.02, p < .01), presence of telangiectasias (.06, p < .01), longer disease duration (.09, p = .03), younger age (-0.17, p < .01), and being unmarried (-.08, p = .04).

Model fit was good, (χ2(14) = 38, CFI = 0.99, TLI = 0.99, RMSEA = 0.05).
analysis found that skin involvement of the face, hands/fingers, and chest/abdomen were significantly related to both social discomfort and subjective dissatisfaction with appearance. Model fit was again good, $\chi^2(18)=42$, $CFI=0.99$, $TLI=0.99$, $RMSEA=0.04$.

**Conclusion:** This study found that appraisal of appearance (dissatisfaction with appearance) was related to SSc disease factors, most prominently skin involvement. Social discomfort, in addition to being associated with disease characteristics, was also linked to younger age and being unmarried, which is highly relevant for social interactions particularly in the context of establishing intimate relationships. The prominent association of disfigurement to the face and hands/fingers with body image concerns is not surprising. Chest/abdomen disfigurement, which is much less common, may be a proxy for overall severity of disfigurement. In sum, the results of this study underline the need to attend to both disease and social contexts in understanding the impact of disfigurement on body image distress among patients with SSc.

**Disclosure:** L. R. Jewett: None; M. Hudson: None; M. Baron: None; B. D. Thombs: None; Canadian Scleroderma Research Group (CSRGG): None.

1348

Development and Validation of the Brief-Satisfaction with Appearance Scale (Brief-SWAP) for Measuring Body Image in Systemic Sclerosis (SSc). Lisa R. Jewett¹, Marie Hudson, Jennifer A. Haythornthwaite, Leslie Heinberg², Fredrick M. Wigley³, Murray Baron⁴, Brett D. Thombs⁵ and Canadian Scleroderma Research Group (CSRGG). Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, ²Jewish General Hospital, Toronto, QC, Canada, ³Johns Hopkins University School of Medicine, ⁴McGill University, Montreal, QC, Canada, ⁵McGill University and Jewish General Hospital

**Background:** Systemic sclerosis (SSc) often results in disfiguring physical changes that commonly occur in visible and socially relevant areas of the body, including the face, mouth, and hands. The few studies that have investigated body image in SSc have found that patients with more severe SSc reported higher levels of body image dissatisfaction and low appearance self-esteem. These studies, however, used general measures of body image distress developed for use in eating disorders and not validated among patients with acquired disfigurement from disease or injury. Recently, a measure of body image originally developed for patients with burn injury, the Satisfaction with Appearance Scale (SWAP), was validated for use in SSc. The 14-item SWAP, however, which measures social discomfort and dissatisfaction with specific body parts, includes numerous items that are highly redundant and some that are less relevant for patients with SSc. The objective of this study was to develop and cross-validate a brief 6-item version of the SWAP in order to increase SSc-relevance, reduce item redundancy, and improve feasibility of body image assessment in SSc.

**Methods:** Female SSc patients in a developmental sample (Johns Hopkins Scleroderma Center) and a validation sample (Canadian Scleroderma Research Group Registry) completed the 14-item SWAP. Items for the 6-item Brief-SWAP were selected based on theoretical considerations and psychometric data from the developmental sample. In both samples, internal consistency reliability, convergent validity (depressive symptoms, physical and mental health function, pain), and the hypothesized two-factor structure (Perceived Social Impact and Subjective Dissatisfaction) were compared between the Brief-SWAP and SWAP. Confirmatory factor analysis models were conducted with MPlus.

**Results:** 217 women from the developmental sample and 654 women from the validation sample completed the SWAP. Cronbach’s alpha for the Brief-SWAP was 0.82 in both samples compared to 0.90 and 0.91 for the full SWAP. Correlations between the Brief-SWAP and SWAP were 0.94 and 0.95 in the developmental and validation samples. All correlations of the Brief-SWAP and SWAP with measures of convergent validity were substantially equal with no statistically significant differences in either sample. Based on confirmatory factor analysis, model fit for the Brief-SWAP was good in the developmental ($\chi^2(4)=9.0$, $CFI=0.99$, $TLI=0.99$, $RMSEA=0.07$) and validation samples ($\chi^2(4)=19.5$, $CFI=0.99$, $TLI=0.99$, $RMSEA=0.08$) and better than for the SWAP in both samples.

**Conclusion:** The Brief-SWAP is a reliable and valid measure of body image dissatisfaction and social discomfort related to disfigurement in SSc. Compared to the full 14-item SWAP, the 6-item Brief-SWAP reduced item redundancy, increased relevance to the experience of SSc patients, and demonstrated good psychometric properties including reliability and validity, thus providing a less burdensome and more feasibly administered scale. The results from the current study constitute a significant step towards the improvement of measurement of important body image constructs for individuals with SSc.

**Disclosure:** L. R. Jewett: None; M. Hudson: None; J. A. Haythornthwaite: None; L. Heinberg: None; F. M. Wigley: None; M. Baron: None; B. D. Thombs: None; Canadian Scleroderma Research Group (CSRGG): None.

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**Work as a Daily Challenge: Working with Scleroderma.** Cindy F. Mendelson¹, Janet L. Poole² and Saralynn H. Allaire³. ¹Boston Univ School of Medicine, Boston, MA, ²Univ of New Mexico, Albuquerque, NM, ³University of New Mexico, Albuquerque, NM

**Background:** Systemic sclerosis (SSc) may severely limit one’s ability to participate in paid employment, which may threaten an individual’s economic, social, physical, or mental well being. This study identified challenges in the work environment and adaptations made by persons with SSc.

**Study Sample:** 32 persons were recruited from the Scleroderma Foundation website. The participants mean age was 47.3 years, mean disease duration was 9.6 years and mean education level was 17.1 years. The majority of participants were in professional or managerial jobs and had been at their current jobs for mean of 9.8 years. 56.2% had diffuse scleroderma, 59.4% were married, and 71.9% worked 35 hours or more a week.

**Methods:** Each participant engaged in a single structured interview. Questions were posed about challenges getting to/from work, the work environment, managing the physical/mental demands of the job, working with others, performing essential job functions, balancing work/home activities, changes to work hours or job type, and adaptations made to keep working. Interviews were audio taped and transcribed. Interviews were coded using the interview guide questions as an initial framework. Content analysis were used to determine the key content of the code and a summary statement generated for each code. Working from the summary statements the data was aggregated into four themes and a single overarching theme.

**Results:** Employees with SSc experience work as a daily challenge. This overarching theme described the work experience for most participants, who, on a daily basis, dealt with the details of work, such as getting to work in the cold knowing that their Raynauds will be triggered or shuffling paper with limited hand mobility. Four subthemes describe their experiences. Their work environment presented options, opportunities and challenges. Participants discussed work options such as home offices, part-time or flex time schedules, and problems within the work environment such as the temperature or inaccessible buildings. Successful employees were skillful at managing the present while looking forward. Most planned to either stay at their current job or occupation. However, they also were mindful of future opportunities and potential problems and planned by watching for opportunities to move into less physically demanding positions. Participants remained hopeful about the future and the possibility to work until retirement. Managing the tasks of work described how participants performed their daily jobs. For most participants this was the least problematic part of their work, as they found ways to modify the job, use adaptations, found help, or left positions that were a poor fit.

Employees had a network that included family, friends, colleagues and their employer, who contributed to their success by lessening the load at home, providing a supportive emotional network, helping with tasks at work, and providing accommodations at work.

**Conclusions:** It is in the best interest of all of us that those who can work continue to work. We found that our participants wanted to continue to work, and were anxious to find win-win scenarios that allowed them to work and that benefited their employer.

**Disclosure:** C. F. Mendelson: American College of Rheumatology Research & Education Foundation, 2; J. L. Poole: American College of Rheumatology Research & Education Foundation, 2; S. H. Allaire: None.

**ACR Plenary Sessions**

**ACR Plenary Session II: Discovery 2010**

Tuesday, November 9, 2010, 11:00 AM–12:30 PM

1350

**Suppression of Collagen-Induced Arthritis in Mice by Anti-CD19 Antibody That Co-Engages BCR and Inhibitory Receptor FcγRIIb: Efficacy Does Not Require B Cell Depletion.** Saso Čemerski¹, Seung Y. Chu², Erik Pong³, Holly M. Horton⁴, John R. Desjarlais⁵ and David E. Szymbonski⁶. ¹Xencor, Inc., Monrovia, CA, ²Xencor, Inc.

S560
Background: The B cell is a clinically validated target in autoimmune disease, yet current therapeutic approaches that involve B cell depletion (such as anti-CD20 antibodies rituximab and ocrelizumab) are associated with increased infection risks, including viral reactivation leading to PML. On the other hand, approaches that target individual B cell survival factors including BLYS and APRIL (such as belimumab and atacicept) are reportedly safer but less efficacious, possibly due to redundant activities of other survival factors. We have therefore developed a new therapeutic antibody that globally suppresses B cells with minimal cell depletion. This biologic exploits the natural ability of immune complex to suppress humoral immunity by coengaging B cell receptor with the inhibitory receptor FcγRIIB.

Methods: XmAb5871, an anti-human CD19 antibody with >400-fold increased FcγRIIB affinity relative to native IgG1 Fc, was produced as described (Chu et al. Mol. Immunol. 2008; 45:3926). For use in mouse models, we generated surrogate antibodies against mouse CD19 and CD20 including XENP9206 (with identical Fc domain to XmAb5871), XENP8243 (a surrogate for rituximab), and their Fc and isotype controls. For humanized SCID mice, 3 × 10^7 human PBMCs were engrafted prior to immunization and treatment with therapeutic antibodies. For collagen-induced arthritis models, C57BL/6 mice transgenic for human FcRIIb were obtained from J. Ravetch (Rockefeller). CIA was induced in transgenic mice and littermate controls using chicken collagen as described in Inglis et al. (Arth. Res. Therap. 2007; 9:R113). Suppression of B cell activation was assayed by calcium flux, as described in Chu et al. (2008).

Results: Antibodies coengaging CD19 and FcγRIIB suppressed humoral immunity to foreign antigens in both human PBMC-engrafted SCID mice and huFcγRIIB-transgenic mice. XENP8206, but not control anti-CD19 antibodies with native IgG1 or Fcγ receptor knockout Fc domains, suppressed BCR-mediated activation of splenic B cells from transgenic mice. XENP8206 also suppressed joint inflammation in CIA induced in huFcγRIIB-transgenic C57BL/6 mice, an arthritis model known to possess a strong T cell-mediated disease phenotype. Notably, therapeutic efficacy of XENP8206 occurred without depletion of peripheral B cells in mice, in contrast to XENP8243 (mouse surrogate for rituximab), which potently depleted such B cells.

Conclusions: We show that a recombinant antibody engineered for enhanced binding to FcγRIIB via its Fc domain is a potent suppressor of B cell activation that inhibits humoral immune responses and arthritis in humanized mouse models. In contrast to other B cell-targeted therapeutic approaches, this antibody suppresses activated B cells without depletion, thus mimicking the natural function of immune complex. Our results demonstrate the critical role of FcγRIIB in regulating human and murine humoral immunity, and suggest that replication of immune complex-mediated immunosuppression by XmAb5871 has potential as a novel therapy for rheumatoid arthritis and other autoimmune diseases.


1351
Micro RNA 155 Deficiency Protects from the Development of Inflammatory Arthritis. Stephan Blümli1, Michael Bonelli2, Birgit Niedereiter3, Antonia Puchner1, Georg Mayr1, Marije Koenders4, Smolen Josef5 and Redlich Kurt1. 1Medical University Vienna, Austria, 2Medical University Vienna, Austria 3Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

Objective: Micro RNAs are a new class of regulatory elements in various biological processes. Altered expression of certain micro RNAs has been demonstrated in rheumatoid arthritis. However, the pathogenic role of micro RNAs is not known in the development of this disease. The aim of this study was to assess the role of microRNA 155 in the development of murine inflammatory arthritis.

Methods: Collagen-induced arthritis (CIA) as well as K/BxN serum transfer arthritis was induced in wild-type (wt) and microRNA 155 knock out (miR155^-/-) mice. Clinical scoring was performed on a weekly basis. Histological analysis of synovial inflammation as well as local bone destruction was performed. Cytokine production was measured in serum as well as from supernatants of cultured lymph node cells after immunization after induction of CIA. The humoral as well as T cell response to collagen as well as T cell polarization was assessed in serum, spleen and lymph node, respectively. The cellular composition of the draining LN in CIA was analyzed by flow cytometry.

Results: We show that mice miR155^-/- mice are protected from clinical as well as histological signs of CIA. Analysis of anti-collagen antibodies revealed strongly reduced levels in miR155^-/- mice compared to wt. However, relative numbers and expression of costimulatory molecules on B cells were not different between the two groups. Furthermore miR155^-/- mice showed reduced antigen-specific proliferation of T cells. In addition, T cells of miR155^-/- mice produced significantly diminished levels of the Th17 cytokines IL-17 and IL-22, whereas Th1 and Th2 cytokine IL-4 and IFN-γ were not different. Using K/BxN serum transfer arthritis, which is only dependent of innate effector mechanisms, we show that both wt and miR155^-/- mice develop arthritis. However, miR155^-/- mice showed significantly reduced local bone destruction due to reduced generation of osteoclasts.

Conclusions: MiR155 deficiency protects from the development of CIA by inhibiting the generation of pathogenic self reactive T as well as B cell responses. Furthermore, miR155 controls the development of local bone destruction by inhibition of osteoclastogenesis. These data identify miR155 as a possible novel target in the therapy of autoimmune arthritis.

Disclosure: S. Blümli: None; M. Bonelli: None; B. Niedereiter: None; A. Puchner: None; G. Mayr: None; M. Koenders: None; S. Josef: None; R. Kurt: None.

1352

Objectives: The underlying mechanism of epigenetic imprinting in SSC microvascular endothelial cells (MVEC) remains unknown. MicroRNAs (miRNAs), which are noncoding RNAs that regulate gene expression, are involved in diverse biological functions. In this study, we investigated whether miRNAs are aberrantly expressed in SSC-MVEC and if they are involved in the regulation of epigenetic imprinting in SSC.

Methods: The expression levels of the 376 most abundantly expressed miRNAs in the human genome were determined in Ssc and control MVEC (derived from 6 Ssc and matched control subjects) by RT2 microRNA PCR array. Control and Ssc MVEC were transfected with 1.0ug of miRNA isolated from Ssc or control MVEC. After 48 hours, cells were harvested and the expression levels of endothelial nitric oxide synthase (NOS3) and DNA methyltransferases 1 (DNMT1) were measured by real-time PCR. The expression levels of miR-152 were determined by quantitative PCR. Finally, miRNA-152 was forced expressed or inhibited in Ssc and control MVEC.

Results: Significant differences in the expression levels of miRNAs were noted in Ssc-MVEC. To understand the role of altered miRNAs expression in Ssc, control-MVEC were transfected with Ssc- derived miRNAs which resulted in significant increase expression of DNMT1 (2.5 ± 0.3 folds, mean ± SD) and reduced NOS3 expression level (25±9%, percent of control). While, the transfection of Ssc-MVEC with control miRNAs resulted in decreased expression of DNMT1 and increased expression of NOS3. Since DNMT1 is one of the predicted direct targets of miR-152, we investigated the expression levels of miR-152 in Ssc and control MVEC. Levels were frequently down-regulated in Ssc-MVEC and were inversely correlated to DNMT1 expression levels. Forced expression of miR-152 in Ssc-MVEC led to a reduction in DNMT1 expression at both the mRNA and protein levels in comparison with the negative control, while inhibition of miR-152 expression in control- MVEC enhanced DNMT1 expression levels in association with reduced NOS expression level.

Conclusions: Ssc-miRNAs transfection into control-MVEC can induce Ssc-MVEC phenotype. miR-152 expression is down regulated in Ssc-MVEC and inversely correlates with DNMT1 expression level. The forced expression of miR-152 corrected Ssc-MVEC phenotype and its inhibition induced Ssc phenotype in control MVEC. miR-152 may play a causal role in DNA methylation changes in Ssc-MVEC.

Disclosure: Y. Wang: None; O. R. Kahaly: None; B. Kahaleh: None.
Background: Toll-like receptor (TLR) signaling may contribute to the pathogenesis of rheumatoid arthritis (RA) resulting in the persistent activation of macrophages and the expression of inflammatory cytokines, mediated by endogenous TLR ligands produced and released locally within the joint. While a number of potential ligands have been identified, it is unclear which, if any, is clinically important. Therefore, a yeast-two hybrid system was employed to identify TLR2 and TLR4 binding proteins by screening a cDNA library generated from RA joint tissue.

Methods: In yeast-two hybrid system, the extracellular domains of TLR2 or TLR4 were used as bait. The prey was a cDNA library generated from highly inflammatory RA synovial tissues. Positive colonies were selected by growing yeasts on nutritional dropout agar plates. The plasmids from the positive yeast colonies were isolated and the cDNA inserts were sequenced. Co-immunoprecipitation was performed using HA-tagged in vitro translated SNAPIN with TLR2-Fc or TLR4-Fc fusion proteins. The agonistic function of SNAPIN was examined using HEK-TLR2 and HEK-TLR4 reporter cells.

Results: The TLR2 bait interacted with 60 protein sequences, which represented 11 unique proteins, while the TLR4 bait identified 54 sequences, which represented 34 unique proteins. 33 of the 60 sequences interacting with TLR2 and 7 of the 56 interacting with TLR2 represented SNAP-associated protein (SNAPIN), a protein important in endosomal fusion. SNAPIN co-immunoprecipitated with TLR4-Fc, but more strongly with the TLR2-Fc fusion protein. In the functional assays, recombinant SNAPIN activated HEK cell lines expressing TLR2 and TLR4. Heat inactivation of SNAPIN for 10 min at 96°C and pre-incubation with 50 μg/ml protease K completely abolished TLR activation, while treatment with polymyxin B did not inhibit TLR activation, suggesting that the effects were not due to endotoxin contamination. Furthermore, neutralizing anti-TLR2 antibody inhibited SNAPIN's effect on TLR2 signaling, suggesting the SNAPIN specifically targets TLR2. SNAPIN was expressed in synovial fluid macrophages, determined by immunoblot analysis.

Conclusion: We identified SNAPIN as a novel endogenous TLR2 and TLR4 ligand in the synovial tissue of patients with RA. SNAPIN is known to function as a regulator for membrane docking and fusion for synaptic vesicles as well as for late endosomal-lysosomal fusion. Studies are underway to determine the potential role of SNAPIN in the pathogenesis of RA.

Disclosure: B. Shi: None; Q. Huang: None; M. J. Vervoordeldonk: None; P. P. Tak: None; R. M. Poppe: None.

1354

TLR9 Induced Macrophage Activation Syndrome Is Driven by IFNγ Produced by Lymphocytes and Natural Killer Cells But Is Insuppressed by Lymphocyte Produced IL-10. Edward M. Behrens1, Katharine Slade1, Sheila Rao1, Portia A. Kreiger1, Michele Paessler1, Taku Kambayashi1 and Gary A. Koretzky2.1.1. A.I. DuPont Hospital for Children, 2Childrens Hospital of Philadelphia, PA, 3The Children’s Hospital of Philadelphia, 4University of Pennsylvania, Philadelphia, PA, 5University of Pennsylvania

Purpose: Macrophage Activation Syndrome (MAS) is a clinical entity consisting of macrophage inflammation, cytokine storm, and multi-organ failure associated with an overproduction of IFNγ. Previous murine models implicate genetic defects in CD8+ T-cell cytotoxicity as the cause of the syndrome. However, this model does not explain the link of MAS with genetically normal patients having rheumatologic disease or Epstein Barr Virus (EBV) infections. To investigate the pathobiology of MAS in inflamed, genetically normal animals, we utilized a system of chronic inflammation driven by Toll-like receptor (TLR) stimulation.

Methods: Mice treated with every other day i.p. injection of CpG (TLR9 agonist) for 10 days. Cytokines were measured by ELISA, cell surface markers by flow cytometry, and organs were taken for histology. Natural killer (NK) cells were depleted using the PK136 antibody (100 μg i.p. every day).

Results: CpG treated mice develop pancytopenia, splenomegaly, microthrombosis, hepatitis, hyperferritinemia, and elevated serum IFNγ consistent with MAS. None of these changes occur in PBS injected control mice. Only a small population of CD8+ T-cells are activated by the CpG treatment as measured by CD69 levels. In contrast, Natural Killer (NK) cells show a more robust CD69 upregulation. Consistent with previous MAS models, disease is dependent on IFNγ as IFNγ/−/− CpG treated mice are protected from disease. Unlike previous models, CpG treated β2m−/− mice lacking CD8+ T-cells develop disease to the same extent as wild type mice showing that CD8+ T-cells are not required. Furthermore, Rag−/− mice develop CpG induced disease, showing that all B- and T-cells are dispensable. NK cell depleted mice developed disease suggesting NK cells are dispensable. However, Rag/common gamma chain (Rag/gc−/−) doubly deficient mice missing B-, T- and NK cells have greatly reduced disease. Thus, in the absence of adaptive immunity, NK cells are required for full disease expression. Interestingly, consistent with incomplete protection, Rag/gc−/− CpG treated mice produce half as much IFNγ as Rag−/− mice suggesting that an IFNγ producing myeloid cell also contributes to disease. IL-10 is also produced by CpG treated mice, but is reduced in IFNγ−/− mice suggesting it is produced in response to IFNγ induced inflammation. IL-10 is also reduced in CpG treated Rag−/− mice, which develop enhanced liver disease, suggesting both that the source of IL-10 is from lymphocytes, and that its production is protective.

Conclusions: Our novel mouse model shows that MAS can result from TLR stimulation. This provides a rationale for the link between MAS and rheumatologic diseases such as Still’s Disease and lupus, both of which are associated with TLR activation, as well as the association of MAS with EBV. TLR9 stimulation virus. We show that NK cells are important mediators of disease, a cell population implicated in the etiology of Still’s Disease. We show that IFNγ is critical for driving disease, but that IL-10 from a lymphocyte origin is protective. Interestingly, these studies also suggest a role for an IFNγ producing myeloid cell, a population whose relevance has been controversial, in driving this disease process.

Disclosure: E. M. Behrens: None; K. Slade: None; S. Rao: None; P. A. Kreiger: None; M. Paessler: None; T. Kambayashi: None; G. A. Koretzky: None.

1355

Genome-Wide Association Study of Ankylosing Spondylitis Identiﬁes New Loci, a Tag SNP for HLA-B27, and an Interaction between HLA-B27 and Variants in ERAP1. Matthew A. Brown, on Behalf of the Wellcome Trust Case-Control Consortium 2 and Australo-Anglo-American Spondyloarthritides Consortium. The University of Queensland Diamantina Institute, Brisbane, Queensland, Australia

In order to identify genetic variants predisposing to risk of Ankylosing Spondylitis (AS), we performed a gwas of 1782 British and Australian cases fulfilling modified New York Criteria, and 5167 historical controls from the Wellcome Trust Case-Control Consortium 2 (WTCCC2). After imputing to Hapmap, the study was combined with existing results from the Australo-Anglo-American AS Consortium (TASC) involving a non-overlapping cohort of Australian, British and North American cases and ethnically matched controls, using inverse variance meta-analysis. Replication was then performed in 2109 cases and 4410 controls from Australia, Britain, and the Canadian SPARC consortium.

As well as confirming known associations at HLA, IL23R, ERAP1, KIR12, and TRADD (combined p = 1.2 × 10−6), and TBKBP1-TBX21 (p = 5.9 × 10−6), and found suggestive association at PTGER4 (p = 7.8 × 10−6) and TKBPI-TBX21 (p = 5.9 × 10−6), as well as providing further support for previously reported loci with suggestive association with AS, including ANT12 (p = 3.8 × 10−3), CARD9 (p = 4.6 × 10−7), and TLR4 (p = 3.1 × 10−7).

We also identified a single SNP, rs4349859 near the gene MICA, which tagged HLA-B27 with near perfect sensitivity (98%) and specificity (99%) in 531 cases and 729 controls of Australian and British origin. These findings were conﬁrmed in independent sets of Sardinian and Azorean cases, and show that whilst rs4349859 tagged the non-AS associated HLA-B*2707 subtype, it did not tag the AS-associated HLA-B*2707 subtype, indicating that rs4349859 is not AS causative, and further reducing the likelihood that a B27-linked gene is responsible for the association of B27 with AS.

In most common diseases the proposed genetic model involves interaction between loci, but to date no convincing examples of such interaction have been demonstrated. In the current study however, we identiﬁed an interaction between HLA-B27 and variants within ERAP1 in the WTCCC2 (p = 0.008), TASC (p = 0.004) and replication datasets (p = 0.004). Speciﬁcally, risk variants in ERAP1 increased odds of disease in HLA-B27-positive, but not B27-negative, cases (combined interaction p = 1.4 × 10−6). In contrast, IL23R was associated with disease in both B27+/+ and −/− cases. This result indicates that B27+ and B27−/− forms of disease have substantially different but overlapping aetiologies. The findings support mechanisms of association of B27 and ERAP1 with AS that involve peptide presentation, and that ERAP1 contributes to disease risk through its action in trimming peptides prior to loading into nascent HLA class I molecules, rather than by cleaving pro-inﬂammatory cytokine receptors on the cell membrane.

In summary, we have identiﬁed several new loci that affect risk of AS, bringing the total number of conﬁrmed AS genetic susceptibility loci to 14,
TLR-4 and Annexin A2 Involvement in Endothelial Cell Activation by Anti-Phospholipid Antibodies: Specific Silencing by Small Interfering RNAs, Elena Raschi1, Valentina Broggini1, Maria Orietta Borghi2, Claudia Grossi2 and Pierluigi Meroni1. 1Instituto G. Pini University, Milano, Italy, 2IRCCS Istituto Auxologico Italiano, Milano, Italy, University of Milan, Italy, University of Milan; IRCCS Istituto Auxologico Italiano, Milan, Italy

Background: Antiphospholipid Syndrome (APS) is characterized by recurrent fetal losses and arterial/venous thrombosis in the presence of antiphospholipid antibodies (aPL). aPL are directed against anionic phospholipid binding proteins: mainly prothrombin and b2 glycoprotein I (b2GPI). The complex formation between circulating aPL and b2GPI expressed on the cell membranes induces signalling and triggers cell activation. Accordingly, aPL mediated endothelial cell (EC) perturbation is thought to be a key pathogenic event leading to the prothrombotic diathesis as supported by in vitro and in vivo models. The exact nature of the EC receptors for b2GPI is still matter of research: b2GPI has been shown to bind heparan sulphate, Annexin A2 and apoER2 (on platelets). Furthermore there is also evidence that aPL trigger TLR-4.

Objectives: To address the role of TLR4 and Annexin A2 in anti-b2GPI mediated EC activation pathway.

Methods: we performed: i) in vitro experiments with or without blocking antibodies directed to Annexin A2 and TLR-4 ii) small interfering RNA experiments for silencing TLR-4 and Annexin A2 expression in suitably transfected HUVEC.

Results: aPL binding to HUVEC was partially inhibited by both anti-Annexin A2 and anti-TLR-4 blocking antibodies. Anti-TLR-4 also reduced aPL-induced E-Selectin and ICAM-1 expression. TLR-4 silencing by siRNA significantly inhibited both binding and activation of aPL-exposed HUVEC, while Annexin A2 silencing only affected binding.

Conclusion: Our results suggest that more than one receptor may be involved in aPL-mediated EC activation. As Annexin A2 is unable to transduce signals into the cells owing to the lack of a cytoplasmic tail, TLR-4 could act as co-receptor. Understanding the nature of the receptor/co-receptor and its interaction with b2GPI will lead to identify new strategies for treatment and prevention of pro-thrombotic and pro-inflammatory state in APS.

Disclosure: E. Raschi: None; V. Broggini: None; M. O. Borghi: None; C. Grossi: None; P. Meroni: None.

Peptide & NMR Spectroscopy Studies of Recombinant Domain I Confirm Conformationally Correct Domain I and Non-Linear Epitope Binding to Anti-Domain I Anti-Phospholipid Antibodies. Charis Pericleous1, Tolulape Dusi2, Jennifer Miles2, Diego Esposito3, Aycet Guza-Garcia3, Paul C. Driscoll2, David S. Latchman2, David A. Isenberg2, Ian Giles2, Anisur Rahman3 and Yiannis Ioannou1. 1National Institute of Medical Research, London, UK, 2University College London, London, United Kingdom, 3University of London, London, United Kingdom

Purpose: Recombinant Domain I (DI) is increasingly being utilised in the development of diagnostic assays and being developed as an inhibitor of pathogenicity. The critical epitope R39-R43 as well as the DI/DII interlinker region have been shown to be important in binding anti-phospholipid antibodies. We undertook NMR spectroscopy studies as well as linear peptide epitope binding assays to confirm that recombinant DI was indeed conformationally correct and ascertain the potential binding abilities of different linear peptides based on the defined epitopes.

Methods: Sera from 8 patients with APS (8/8 female; mean age 46.7±16.4; 7/8 Caucasian, 1/8 Asian; 8/8 with previous thrombosis, 4/8 with previous pregnancy morbidity) were tested in a standard direct anti-b2GPI assay and the appropriate dilution corresponding to 50% of maximal binding (MBD) was identified. Linear peptides containing region R39-R43 (PEP1, 9aa, 1kDa), DI-DII interlinker (PEP2, 9aa, 1kDa), or both (PEP3, 26aa, 3kDa) were designed and synthesised (Sigma, UK). 7kDa wild type recombinant human (WT) DI was expressed in E.coli cells and folded in vitro in a cysteine/cystine-rich buffer for disulfide bond formation. Sera at a dilution that conferred 50% MBD anti-b2GPI activity were incubated (2h, RT) with increasing doses of WT DI (0, 20, 40, 60, 80 or 100µg/ml) or equimolar doses of PEP1–3; and their anti-b2GPI activity was assessed. Percentage binding was calculated based on the change in OD405nm in the presence of inhibitor. To confirm WT DI was conformationally correct, NMR spectroscopy was employed following standard triple resonance 3D NMR protocols. The Chemical Shift Index (CSI) and TALOS computer programs were used to compare the secondary structure of WT DI alone with that in whole human b2GPI based on the published 3D crystal structure.

Results: The inhibitory ability of WT DI was statistically superior compared to all peptides, throughout the entire range of inhibitor concentrations tested (p<0.05 for 20µg/ml WT DI and equimolar PEP1–3; p<0.001 in all other cases). By calculating the mean percentage binding (+standard deviation) of all 8 sera tested, a clear positive correlation between the concentration of WT DI and level of inhibition was identified (from 75.7±29.9% with 20µg/ml WT DI to affinity purified IgG from 7 APS patients (aPL-IgG), or IgG normal human serum (IgG-NHS) from 7 healthy donors. Then, time and dose-dependent ROS production was analyzed. Inhibitory studies on ROS production were performed by preincubation of the treated monocytes 1h with antioxidants N-acetyl-L-cysteine (NAC), and vitamin C (vit C), as well as with the mitochondrial inhibitor, rotenone. Peroxides, peroxynitrite generation and mitochondrial membrane potential (MMP), were analysed by flow cytometry using specific fluorescent probes. As procoagulant/proinflammatory markers, cell surface TF, VEGF and Flt1 expression were evaluated by flow cytometry and western blot respectively.

Nitric oxide (NO) levels and Total Antioxidant Capacity (TAC) were measured in the supernatant of the cell cultures. N-Tyr, iNOS expression, p38MAPK activation and IkappaB degradation were evaluated by Western blot. NFKB activity was quantified by EMSA.

Results: Independent incubation of monocytes with aPL-IgG from 7 patients increased cellular ROS production and mitochondria depolarization, which were prevented by the antioxidants Vit C and NAC. Incubation by rotenone further indicated an involvement of the mitochondrial transport chain as a source of ROS. The reduction of supernatant TAC after aPL-IgG treatment was abolished by ROS inhibitors. Moreover, aPL-induced iNOS, N-Tyr, and NO expression levels were reduced by treatment with ROS inhibitors. ROS production by aPL-IgG treatment activated p38 MAPK and its subsequent target, the nuclear factor kappa B (NFkB), and controlled the up-regulation of TF, VEGF, and Flt1 in monocytes.

Conclusions: Our data indicate that the binding of aPL-IgG to the monocyte membrane elicits a redox-sensitive signalling pathway that controls the procoagulant phenotype of that cells in the setting of APS. Thus, oxidative stress by aPL-IgG represents a new pathway potentially contributing to the thrombotic complications of APS. Supported by JA0042/2007, JA0246/2009, P08CVB04234 and P099/01809.

Disclosure: C. Lopez-Pedrera: None; P. Ruiz-Limon: None; A. Aguirre: None; N. Barbarroja: None; A. Rodriguez-Ariza: None; C. Perez-Sanchez: None; E. Collantes-Estvez: None; J. M. Villalba: None; F. Velasco: None; M. A. Khamasha: None; M. J. Cuadrado: None.

The role of antiphospholipid antibodies (aPL) in the induction of a procoagulant state is clearly established; yet, the precise intracellular mechanisms are poorly understood. Besides their role in tissue vascular injury, reactive oxygen species (ROS) may act as important signalling molecules, activating redox-sensitive signalling cascades that potentially link the activation of receptors by their agonists to gene expression.

Aim: We investigated the relevance of ROS in the prothrombotic/proinflammatory state elicited by aPL and studied ROS-dependent downstream signalling pathways leading to monocyte activation.

Design and Methods: Monocytes from healthy individuals were treated with...
25.0 ± 22.0% with 100µg/ml WT DI), as opposed to PEP1–3 where binding did not fall below 91.3 ± 50.3% (with PEP3 at the highest dose). NMR-derived parameters of WT DI were entirely consistent with the secondary structure of crystallised DI in whole β2GPI. The 3D structure of WT DI superimposed well with the β2GPI crystal structure, indicating that in solution WT DI adopts the anticipated polypeptide fold.

**Conclusions:** NMR studies demonstrate that bacterially expressed recombinant DI adopts its native conformation supporting the use of this peptide in diagnostic assays and as an inhibitor of pathogenicity. Furthermore, whole DI peptide is necessary to inhibit as patient anti-DI sera failed to recognise linear epitope peptide derivatives.

Disclosure: C. Pericleous: None; T. Disu: None; J. Miles: None; D. Esposito: None; A. Garza-Garcia: None; P. C. Driscoll: None; D. S. Latchman: None; D. A. Isenberg: None; I. Giles: None; A. Rahman: None; Y. Ioannou: None.

### 1359

A Novel, Simple Fluid Phase Binding Assay for the Detection of Serum Anti-Domain I Antibodies in Patients with the Antiphospholipid Syndrome.


1National Institute of Medical Research, London, UK, 2University College London, London, United Kingdom 3University College London, London, United Kingdom 4University College London, London, UK

**Purpose:** Domain I (DI) of beta-2-glycoprotein I (β2GPI) has been established as a critical immunodominant region for pathogenic antiphospholipid antibodies (aPL) in patients with the antiphospholipid syndrome (APS). A direct enzyme-linked immunosorbent assay (ELISA) to detect anti-DI antibodies in APS sera could be affected by conformational changes in immobiised DI and has required considerable efforts to optimise by multiple groups including our own. Here we present an alternative concept for detecting anti-DI activity based upon inhibiting anti-β2GPI activity with recombinant DI in the fluid phase.

**Methods:** Sera from 15 anti-β2GPI positive patients fulfilling APS classification criteria (15/15 female; mean age 47.4 ± 11.9; 14/15 Caucasian, 1/15 Asian; 14/15 with a thrombotic history, 7/15 with previous pregnancy morbidity), and 5 patients with circulating anti-β2GPI aPL (but without APS, aPL+/APS-) were serially diluted (from 1:50) and tested in triplicate using a standard solid phase anti-β2GPI ELISA. The appropriate dilution of serum corresponding to 50% of maximal binding (MBD) was identified for each patient. In each case this gave an OD405nm ≥0.4. For the new anti-DI assay, each serum sample at the 50% MBD was firstly incubated (2hr, RT) with increasing doses of in-house bacterially-expressed recombinant human DI (0, 20, 40, 60, 80 or 100 µg/ml) and then tested in triplicate for binding with recombinant DI was performed. For each patient sample the percentage binding was calculated based on a change in OD405nm in the presence of DI.

**Results:** Mean percentage binding (± standard deviation, SD) to β2GPI for all 15 APS sera was calculated in the presence of increasing concentrations of DI; the same was performed for the 5 aPL+/APS- samples. The presence of DI significantly reduced binding for APS samples compared to aPL+/APS- samples, in a dose-dependent manner (Table 1).

**Table 1.** The inhibitory ability of recombinant human DI in the fluid phase

<table>
<thead>
<tr>
<th>Concentration of DI added (µg/ml)</th>
<th>Mean (SD) binding for APS samples as a percentage of binding in the absence of inhibitor (n=5)</th>
<th>Mean (SD) binding for aPL+/APS- samples as a percentage of binding in the absence of inhibitor (n=5)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>75.0 (20.3)</td>
<td>96.3 (12.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>40</td>
<td>62.0 (15.6)</td>
<td>97.9 (12.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>60</td>
<td>56.9 (18.1)</td>
<td>94.0 (11.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>80</td>
<td>44.3 (22.9)</td>
<td>89.1 (17.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>100</td>
<td>37.5 (21.7)</td>
<td>85.1 (16.1)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Conclusions:** Using the well-established direct anti-β2GPI assay, serum inhibition of anti-β2GPI activity by fluid phase recombinant DI is both remarkably simple and selective of pathogenicity in this small sample of patients. The ability to express recombinant human DI in a bacterial system allows for the cost-effective production of large amounts of DI for use in this assay. The findings from this proof-of-concept novel and simple approach to measuring anti-DI activity in an anti-β2GPI positive patient warrant further exploration to further characterise specificity and sensitivity, and hence clinical diagnostic and prognostic utility.

Disclosure: C. Pericleous: None; A. Garza-Garcia: None; P. C. Driscoll: None; D. S. Latchman: None; D. A. Isenberg: None; I. P. Giles: None; A. Rahman: None; Y. Ioannou: None.

### 1360

### Apolipoprotein E Receptor (apoER2) Is Involved for Thrombotic Complications in a Murine Model of Antiphospholipid Syndrome.


1Univ of TX Med Branch, Galveston, TX, 2University Hospital Utrecht, Utrecht, The Netherlands

**Background:** Antiphospholipid antibodies (aPL) recognize β2-glycoprotein I(β2GPI)-bound to receptor(s) in target cells (i.e.: endothelial cells [EC], platelets, monocytes) and trigger a pro-coagulant/pro-inflammatory phenotype (i.e.: up-regulation of tissue factor [TF] that lead to thrombosis). The interaction of β2GPI with target cells may involve more than one protein. Previous publications suggest that β2GPI-aPL antibody complex binds to apoER2 in cell surface, inducing activation of platelets or EC. Moreover, it has been shown that a soluble binding domain I of apoER2 (sBDI) inhibits the binding of β2GPI to apoER2.

**Objectives:** To determine whether apoER2 mediates pathogenic effects of murine and human aPL antibodies in vivo.

**Methods:** Wild type (apoER2+/+) and apoER2-deficient (apoER2−/−) mice were injected twice with IgG purified from one patient with "primary" antiphospholipid syndrome (IgG-APS) or with control IgG (IgG-NHS) or with a murine monoclonal anti-β2GPI antibodies (named E7) or with control murine monoclonal antibody [1kMPOC-21(Sigma Aldrich)](MuMoAbC).

**Results:** Significantly larger thrombi and increased TF activity in carotid artery homogenates and in peritoneal macrophages was observed in apoER2−/− mice treated with IgG-APS or E7 when compared to controls. Importantly, apoER2−/− mice treated with murine or human aPL antibodies shown partial but significantly abrogation of thrombogenic effects compared with their counterparts injected with control antibodies. In addition, thrombogenic effects of IgG-APS were significantly abrogated in apoER2−/− mice by sBDI, hence confirming the apoER2 involvement in vivo.

**Mice/ treatment** | Thrombi size (µm²) | TF activity carotid (pmol/mg · mL⁻¹ · protein) | TF activity macrophages (pmol/mg · mL⁻¹ · protein) | TF expression (AU) |
<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>apoER2+/+ IgG-APS</td>
<td>*904 ± 1037</td>
<td>*214 ± 8.4</td>
<td>*101 ± 1.2</td>
<td>*11.9 ± 2.8</td>
</tr>
<tr>
<td>apoER2+/+ IgG-NHS</td>
<td>287 ± 110</td>
<td>5.8 ± 0.9</td>
<td>3.2 ± 0.8</td>
<td>3.2 ± 0.4</td>
</tr>
<tr>
<td>apoER2−/− IgG-APS</td>
<td>**1675 ± 781</td>
<td>14.6 ± 1.8</td>
<td>**5.9 ± 1.5</td>
<td>4.8 ± 0.9</td>
</tr>
<tr>
<td>apoER2−/− IgG-NHS</td>
<td>514 ± 115</td>
<td>5.3 ± 1.7</td>
<td>2.7 ± 0.8</td>
<td>5.9 ± 0.9</td>
</tr>
<tr>
<td>apoER2+/+ IgG-APS + sBDI</td>
<td>**1665 ± 173</td>
<td>**14.7 ± 16.6</td>
<td>**4.4 ± 0.6</td>
<td>43.4 ± 0.3</td>
</tr>
<tr>
<td>apoER2+/+ IgG-NHS + sBDI</td>
<td>486 ± 164</td>
<td>4.5 ± 3.3</td>
<td>3.1 ± 2.5</td>
<td>3.2 ± 0.6</td>
</tr>
</tbody>
</table>

(**) statistically significant different from their negative controls in apoER2+/+ mice. (*) statistically significant different from their negative controls and apoER2−/− mice counterparts. (†) statistically significant different from apoER2−/− mice treated with IgG-APS.

**Conclusions:** Altogether these data show that apoER2 is a mediator of aPL thrombogenic effects in vivo. These data may have important implication in the design of new targeted treatments for APS.

Disclosure: Z. Romay Penabad: None; T. Shilagard: None; G. Vargas: None; R. Aguilar-Valenzuela: None; P. de Groot: None; S. Pierangeli: None.
C6-Deficient Mice Are Protected from the Pathogenic Effects of Antiphospholipid Antibodies. A. L. Carrera-Marin, R. Aguilar-Valenzuela, Z. Romay Penabad, E. Papalardo and S. Pierangeli. Univ of TX Med Branch, Galveston, TX

Background: The pathogenic mechanisms mediated by antiphospholipid (aPL) antibodies are partially understood. Recent studies have demonstrated the complement involvement in the thrombogenic effects of aPL antibodies. Furthermore, inhibitors for the C5 axis can abrogate aPL effects. The complement membrane attack (C5b-9 MAC) complex has been shown to induce tissue factor (TF) expression (procoagulant effect). However, whether C5b-9 MAC plays a role in the pathogenesis of thrombosis in Antiphospholipid Syndrome (APS) is unknown.

Objective: To study the effects of human and murine aPL antibodies on thrombosis in C6 deficient (C6−/−) mice.

Methods: C6−/− mice and the corresponding wild-type (C6+/−) were injected twice with either a) 500 μg/ml IgG isolated from two patients with APS (IgG-APS1 and IgG-APS2) or with normal IgG (IgG-NHS), b) 100 μg/ml murine anti β2GPI monoclonal antibodies (4G4) or with mouse IgG (LeMPOC-21(MuMoAb) (Sigma Aldrich) as control or c) 500 μg/ml IgM isolated from a patient with APS (IgM-APS3). Seventy two h after the first injection the size of induced thrombi in the femoral vein was determined. TF activity was determined in homogenates of carotids and peritoneal macrophages using a chromogenic assay. TF expression in macrophages was also determined using quantum dot nano crystals and two-photon excitation laser scanning microscopy.

Results: Thrombus sizes were significantly larger in C6+/− mice treated with all different IgG-APS and IgM-APS when compared with healthy controls (p<0.001). Similarly, MuMoAb 4G4 shown significant difference in thrombus size compared with control MuMoAb. Importantly, C6−/− mice treated with IgG-APS1 or IgM-APS or MuMoAb 4G4 had smaller thrombi compared to their C6+/− counterparts (p<0.001) and there were no significant differences among the control groups.

Conclusions: These data indicate that the C6 component of the complement system mediates aPL-thrombogenic effects. The data underscore the possibility of complement inhibition as a new therapy for clinical manifestations of APS.

Disclosure: A. L. Carrera-Marin: None; R. Aguilar-Valenzuela: None; Z. Romay Penabad: None; E. Papalardo: None; S. Pierangeli: None.

ACR Concurrent Abstract Sessions
Epidemiology and Health Services Research: Gout
Tuesday, November 9, 2010, 2:30 PM–4:00 PM

1361

Short-Term Effects of Caffeinated Beverage Intake on Risk of Recurrent Gout Attacks. Tuhina Neogi1, Clara Chen2, Christine Chaisson2, David J. Hunter1 and Yuying Zhang. 1Boston Univ Schl of Med, Boston, MA, 2Boston Univ School of Medicine, Boston, MA, 3Boston Univ School of Medicine, 4University of Sydney, Boston, MA

Purpose: Long-term caffeine intake has been associated with decreased risk for incident gout attacks and lower serum uric acid levels. Acute effects of caffeine, however, can potentially increase uric acid, for example, through a diuretic effect with volume depletion, and impaired glucose tolerance. Further, caffeine, which is a methyl xanthine, can competitively inhibit xanthine oxidase, and therefore may have effects similar to allopurinol in terms of precipitating a flare in the short-term. Given these potential conflicting effects on gout attack risk, we evaluated whether caffeinated beverage intake was associated with risk for recurrent gout attacks.

Methods: We conducted an internet-based case-crossover study to assess a set of putative risk factors thought to trigger recurrent gout attacks. This methodology uses each participant as his/her own control by comparing the frequency of a particular risk factor during periods of gout attacks with that during periods when they are not having an attack, thereby eliminating between-person confounding. Subjects with gout who had an attack within the past year were recruited online and asked to provide access to medical records pertaining to their gout diagnosis. Data were obtained on the amount of caffeine (coffee, tea, other caffeinated beverages) consumed over the 24-hour period before a gout attack and over a 24-hour period during an intercritical period, as well as non-caffeinated beverages (non-caffeinated coffee, tea, sodas, juices). We did not ask about use of sugar in the beverage. We examined the relation of amount of caffeinated beverage intake (0, 1, 2, 3, 4–5, > 6 servings per 24-hours) with the risk of recurrent gout attacks using conditional logistic regression adjusting for diuretic use, alcohol consumption, and purine intake, and additionally for all other fluid intake. We repeated the same analyses for non-caffeinated beverage intake.

Results: Of the 633 participants who experienced recurrent gout attacks during the study period, 78% were male, 89% were White, and 58% had a college education. Of the 486 medical records reviewed to date, 82% met the ACR classification criteria for gout. Higher levels of caffeinated beverage intake in the prior 24 hours were associated with increased risk for recurrent gout attacks, even after accounting for other fluid intake, while non-caffeinated beverages were not associated with risk for recurrent gout attacks (Table).

Table. Association of Caffeinated and Non-Caffeinated Beverage Intake, respectively, with Risk for Recurrent Gout Attacks.

<table>
<thead>
<tr>
<th>Caffeinated beverage servings, # (prior 24 hours)</th>
<th>Case/Control periods</th>
<th>Crude OR</th>
<th>Adjusted* OR (95% CI)</th>
<th>Adjusted** OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 214/279</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>1 154/223</td>
<td>1.08</td>
<td>1.14 (0.79–1.62)</td>
<td>1.13 (0.79–1.62)</td>
<td>1.13 (0.79–1.62)</td>
</tr>
<tr>
<td>2 238/366</td>
<td>1.25</td>
<td>1.23 (0.87–1.73)</td>
<td>1.22 (0.86–1.70)</td>
<td>1.22 (0.86–1.70)</td>
</tr>
<tr>
<td>3 195/256</td>
<td>1.56</td>
<td>1.38 (0.95–1.99)</td>
<td>1.37 (0.94–1.98)</td>
<td>1.37 (0.94–1.98)</td>
</tr>
<tr>
<td>4 174/191</td>
<td>2.09</td>
<td>1.78 (1.19–2.65)</td>
<td>1.76 (1.18–2.64)</td>
<td>1.76 (1.18–2.64)</td>
</tr>
<tr>
<td>5–6 160/194</td>
<td>2.10</td>
<td>1.66 (1.09–2.53)</td>
<td>1.65 (1.08–2.52)</td>
<td>1.65 (1.08–2.52)</td>
</tr>
<tr>
<td>&gt;6 112/80</td>
<td>4.85</td>
<td>4.35 (1.98–5.68)</td>
<td>3.33 (1.96–5.65)</td>
<td>3.33 (1.96–5.65)</td>
</tr>
</tbody>
</table>

For trend p<0.0001

Non-caffeinated beverage servings, # (prior 24 hours) | 0 443/568 | 1.0 | 1.0 |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1 215/307</td>
<td>0.90</td>
<td>0.83 (0.64–1.08)</td>
<td>0.84 (0.63–1.09)</td>
</tr>
<tr>
<td>2 219/298</td>
<td>0.96</td>
<td>0.78 (0.60–1.02)</td>
<td>0.79 (0.61–1.04)</td>
</tr>
<tr>
<td>3 118/169</td>
<td>1.01</td>
<td>0.78 (0.55–1.10)</td>
<td>0.81 (0.57–1.14)</td>
</tr>
<tr>
<td>4 87/110</td>
<td>1.10</td>
<td>0.85 (0.58–1.25)</td>
<td>0.88 (0.60–1.30)</td>
</tr>
<tr>
<td>5–6 94/56</td>
<td>1.56</td>
<td>1.02 (0.67–1.55)</td>
<td>1.06 (0.70–1.61)</td>
</tr>
<tr>
<td>&gt;6 71/51</td>
<td>1.81</td>
<td>0.93 (0.55–1.58)</td>
<td>0.96 (0.56–1.63)</td>
</tr>
</tbody>
</table>

P for trend p=0.6

* adjusted for diuretic use, purine and alcohol intake

** additionally adjusted for all other fluid intake (including non-caffeinated beverages, dairy, and water for the caffeinated beverage analyses: including caffeinated beverages, dairy, and water for non-caffeinated beverage analyses).
Conclusions: Increases in or episodic caffeinated beverage intake in the short-term appears to increase risk for recurrent gout attacks. In contrast, we did not find such associations with non-caffeinated beverages. Since these beverages may have had varying amount of fructose that we did not measure, further study is warranted to evaluate the effects of caffeine independent of fructose.

Disclosure: T. Neogi: None; C. Chen: None; C. Chaisson: None; D. J. Hunter: None; Y. Zhang: None.

1363
Yanyan Zhu1, Bhavik Pandya 2 and Hyon Choi 1. 1Boston University of School of Medicine, Boston, MA, 2Takeda Pharmaceuticals International, Inc., Deerfield, IL

Objective: There is a direct causal relation between serum urate (sUA) levels and the risk of gout. Thus, the population’s sUA levels are accurate surrogate indicators for the scope of the disease burden of gout in the population. Our objective was to estimate the trends of sUA levels and prevalence of hyperuricemia based on a recent, nationally representative sample of US men and women (NHANES 1999–2008).

Methods: Using data from 24,693 participants (11,816 men and 12,877 women) aged 20 years and older from NHANES 1999–2008, we estimated overall, gender-specific, and age-specific mean sUA levels and prevalence of hyperuricemia. sUA was measured by oxidation with the specific enzyme uricase to form allantoin and hydrogen peroxide, using participants’ blood samples collected during home interview or examination session. We used an NHANES definition of hyperuricemia (sUA level >7.0 mg/dL in men and >5.7 mg/dL in women). We estimated the number of people with hyperuricemia by applying our prevalence estimates to the corresponding US population estimates from the Census Bureau.

Results: The overall prevalence of hyperuricemia among US adults was 20.1%, which corresponded to an estimated 31.9 million individuals with hyperuricemia. The prevalence of hyperuricemia among men was 21.1% (16.1 million) and 19.2% (15.8 million) among women. The overall mean sUA level was 5.41 mg/dL (95% CI, 5.38 to 5.44 mg/dL). The mean sUA level was 6.10 mg/dL (95% CI, 6.06 to 6.14 mg/dL) among men and 4.77 mg/dL (95% CI, 4.73 to 4.80 mg/dL) among women. The prevalence of hyperuricemia increased with age, ranging from the lowest (15.6%, 4.5 million) in individuals aged 20 to 29 years to the highest (36.7%, 2.4 million) in individuals aged 80 years or older. The prevalence of hyperuricemia among individuals aged 65 years or older was 31.3%, which corresponded to an estimated 8.4 million US adults with hyperuricemia (Table).

Conclusions: These findings from the latest nationally representative sample of US adults in NHANES 1999–2008 suggest that the prevalence of hyperuricemia is substantial, particularly among older individuals.


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Obesity Is Associated with a Younger Age at Gout Incidence
Mara A. McAdams1, Janet W. Maynard2, Judith A. Bolton Hoffman3, Alan N. Baer4, Allan C. Gelber1 and Josef Coresh1. 1Baltimore, MD; 2Johns Hopkins Univ, Baltimore, MD; 3Johns Hopkins University, Baltimore, MD; 4Johns Hopkins, Bloomberg School of Public Health

Background: Obesity is an established risk factor for gout; however, the influence of obesity on the age of gout onset is unclear. We tested the hypothesis that obesity is associated with an earlier age of incident gout diagnosis in a population-based cohort, CLUE II.

Methods: At cohort entry (1989), CLUE II enrolled 26,147 individuals residing in Washington County, Maryland. We included participants who reported on 2003 and 2007 follow-up questionnaires that they had been diagnosed with gout by a healthcare professional and recalled their age at gout diagnosis. We limited this study to incident gout cases that developed gout after 1989. In 1989, participants reported their current weight and height as well as their weight at age 21. Body mass index was calculated (kg/m²) and obesity defined as BMI ≥ 30 kg/m². We compared the mean age at gout incidence by obesity status, both at baseline and at age 21, using t-tests. Multivariate linear regression was used to estimate the independent association of BMI with age at gout incidence.

Results: There were 281 participants with incident gout. 70% were male, and 49% reported alcohol consumption. At baseline, the mean BMI was 25.8 kg/m², systolic blood pressure was 126.5 mm Hg and the diastolic blood pressure was 80.7 mm Hg. After adjustment for sex, blood pressure and alcohol intake a one kg/m² change in BMI was associated with a 0.15 year decrease in the age at gout incidence (p-value = 0.38). For every one kg/m² increase in BMI at age 21 years, there was a 1.13-year, adjusted, decrease in the age at gout incidence (p-value < 0.001). Participants who were obese at baseline had a younger age at gout incidence compared to non-obese participants (Table, p-value = 0.009). The relationship was statistically significant in men and women but more significant in the group of men with gout. We compared the age at cohort entry, developed gout on average 5.5 years earlier than their non-obese counterparts. Obesity at age 21 was associated with a 12-year earlier age of gout incidence compared to non-obese participants (p-value < 0.001) in both men and women.

One limitation of the study is that participants had to be alive to report gout incidence on the 2003 and 2007 questionnaires. However, sensitivity analysis suggest that prevalent gout was not related to reporting on the 2003 and 2007 questionnaires. Age at gout incidence according to obesity status, at baseline and age 21, in CLUE II cohort

Table. Prevalence of Hyperuricemia and Mean sUA Levels in NHANES 1999–2008

<table>
<thead>
<tr>
<th>Hyperuricemia Estimates (in Millions)</th>
<th>Prevalence, % (95% CI)</th>
<th>Mean sUA Level, mg/dL (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>31.9</td>
<td>20.1 (19.2–21.0)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16.1</td>
<td>21.1 (19.8–22.4)</td>
</tr>
<tr>
<td>Female</td>
<td>15.8</td>
<td>19.2 (18.0–20.3)</td>
</tr>
<tr>
<td>Medicare Age Category (Yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–64</td>
<td>23.5</td>
<td>17.8 (16.8–18.8)</td>
</tr>
<tr>
<td>65+</td>
<td>8.4</td>
<td>31.3 (29.7–32.9)</td>
</tr>
<tr>
<td>Age Category (Yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>4.5</td>
<td>15.6 (13.9–17.2)</td>
</tr>
<tr>
<td>30–39</td>
<td>4.7</td>
<td>15.3 (13.4–17.2)</td>
</tr>
<tr>
<td>40–49</td>
<td>5.9</td>
<td>17.0 (15.3–18.6)</td>
</tr>
<tr>
<td>50–59</td>
<td>6.0</td>
<td>21.4 (19.4–23.4)</td>
</tr>
<tr>
<td>60–69</td>
<td>4.7</td>
<td>27.1 (24.7–29.5)</td>
</tr>
<tr>
<td>70–79</td>
<td>3.7</td>
<td>30.0 (27.8–32.2)</td>
</tr>
<tr>
<td>80+</td>
<td>2.4</td>
<td>36.7 (32.9–40.5)</td>
</tr>
</tbody>
</table>

Conclusions: Obese men and women are more likely to develop gout at an earlier age than non-obese counterparts. Those who were obese at age 21 years developed incident gout 12 years earlier than those who were not obese. Physicians should be aware that obesity impacts the age at gout incidence in this population-based cohort.

Disclosure: M. A. McAdams: None; J. W. Maynard: None; J. A. Bolton Hoffman: None; A. N. Baer: None; A. C. Gelber: None; J. Coresh: None.
Health Related Quality of Life (HRQOL) in Tophaceous vs. Non-Tophaceous Gout. Puja Khanna1, Jay Persselin2, Ron Hays1, Daniel Furst3, Harold Paulus4, Paul Maranian1 and Dinesh Khanna1. 1. UCLA, 2. UCLA and West LA VA, 3. West LA VA

Objective: Gout is a chronic disorder of uric acid metabolism resulting in acute painful episodes of arthritis. Tophaceous gout is associated with greater number of attacks, more erosive disease, inadequate pain control, and results in joint destruction when untreated. We assessed the impact of chronic tophaceous gout on HRQOL in an ongoing, prospective, 1-year observational study.

Methods: 71 patients with tophaceous and non-topheaceous gout were recruited at VA and University Hospitals. Tophi were assessed by a physician and HRQOL was assessed at baseline using SF-36 v2, HAQ-DI and a disease-specific Gout Impact Scale (GIS). Health utilities were elicited using computerized software, U-Maker® in structured interviews. Direct preference-based measures to evaluate disutility of gout included health rating scale (RS, 0–100), time tradeoff (TTO, 0.0–1.0), and standard gamble (SG, 0.0–1.0). Disutility was assessed by subtracting preference scores for current health states with gout from those for current health without gout. Patients were questioned on how much money they would be willing to pay out of pocket as a one time payment to cure their gout permanently. Patients were also asked to list their comorbidities and rank them from most to least concerning.

Results: Non-topheaceous were similar to topheaceous subjects in age (68 years), number of flares (3 per year), disease duration (12.9 years), Charlson comorbidity index (3.0) and serum urate levels (7.1 mg/dl, p > 0.05). Patients with tophi had greater evidence of radiographic damage (p < 0.05), worse HAQ-DI score (P = 0.06) and their gout as more severe (p = 0.0008). The 2 groups did not differ in SF-36 and GIS scores. However, topheaceous subjects assigned greater disutility to their gout on RS (12.4 vs. 7.4) and (SG 0.07 vs. 0.09), were willing to pay a significantly higher dollar amount out of pocket for a cure (p < 0.04), and had worse functional capacity to perform usual activities of daily living (p = 0.008) compared to the non-topheaceous. Gout was ranked as the top most health concern in 25% with topheaceous gout compared to 17% with non-topheaceous gout.

Conclusion: Although the patients with chronic tophaceous and non-topheaceous gout were comparable in demographics, the tophaceous group had worse functional disability, assigned higher disutility to gout, and was willing to pay more for a cure. SF-36 and GIS were not able to discriminate between 2 groups. Our data quantifies the decrement in quality of life of patients with tophaceous gout and their willingness to pay for treatment of a debilitating and disabling disease. Our finindings have implications for decision and cost-effectiveness analyses.


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Cherry Consumption and Risk of Recurrent Gout Attacks. Yuqing Zhang1, Clara Chen1, David J. Hunter2, Christine E. Chaisson1, Hyon K. Choi1 and Tuinhia Neogi2. 1. Boston Univ Medical Ctr, Boston, MA, 2. Boston Univ Schi of Med, Boston, MA, 3. Boston Univ School of Medicine, Boston, MA, 4. Sydney University, Sydney, Australia, 5. Univ of British Columbia, Vancouver, BC, Canada

Anecdotal evidence implicates that consumption of cherries and cherry products may reduce levels of serum uric acid (SAU) and the risk of gout attacks. A recent study of 10 healthy women reported that SAU levels were reduced by 15% 5 hours after consuming two servings (200 grams) of cherries. Other studies have also reported that cherry fruit/cherry products may provide anti-inflammatory benefits. To date, large-scale studies has examined whether cherry consumption reduces the risk of recurrent gout attacks.

Methods: We conducted an online case-crossover study to assess a set of putative risk factors for recurrent gout attacks. Subjects who had experienced a gout attack within the past year were recruited online and were asked to provide access to medical records for verification of gout diagnosis. Subjects were asked to log onto the study website when they experienced a gout attack. Risk factors, including cherry fruit and cherry products (i.e. cherry extract) intake, occurring each day over the two-day period prior to an acute gout attack (case-period) were assessed using an online questionnaire. The same questionnaire was used over each of the two days during an intercritical period (control-period). We examined the relation of cherry fruit and cherry products intake over the 2-day period to the risk of recurrent gout attacks using conditional logistic regression, adjusting for alcohol consumption, purine intake, and diuretic use.

Results: Included in this analysis were 633 subjects who experienced recurrent gout attacks during the study period. Participants were predominantly white (88%), men (78%), and 58% had a college education. Of the 468 medical records obtained to date, 82% fulfilled the ACR Classification Criteria for Gout. The median time between the onset of a gout attack and logging on to the website was 3 days. Compared with no cherry fruit intake over the 2-day period, the odds ratios (OR) of recurrent gout attacks were 1.0, 0.5, 0.4, and 0.6, respectively, for 1, 2, 3 and ≥4 servings (one serving is one-half cup or 10 cherries) over the past two days (p for trend <0.001). Intake of cherry products over the past 2 days was also associated with a decreased risk of recurrent gout attacks (OR=0.6, 95% CI: 0.3–1.0) (Table).

Conclusions: Intake of cherry fruit and cherry products over the past 2 days were associated with a reduction in risk for recurrent gout attacks. Cherry consumption may provide a safe, non-pharmacologic option that can help prevent recurrent gout flares among patients with preexisting gout.

Table 1: Intake over past 2 days

<table>
<thead>
<tr>
<th>Cherry Product</th>
<th>No. of Case-periods</th>
<th>No. of Control-periods</th>
<th>Crude OR</th>
<th>Adjusted OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 servings</td>
<td>1074</td>
<td>1318</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1 serving</td>
<td>51</td>
<td>71</td>
<td>0.9</td>
<td>1.0 (0.6–1.4)</td>
</tr>
<tr>
<td>2 servings</td>
<td>56</td>
<td>98</td>
<td>0.6</td>
<td>0.5 (0.3–0.8)</td>
</tr>
<tr>
<td>3 servings</td>
<td>16</td>
<td>35</td>
<td>0.5</td>
<td>0.4 (0.2–0.8)</td>
</tr>
<tr>
<td>≥4 servings</td>
<td>48</td>
<td>67</td>
<td>0.7</td>
<td>0.6 (0.4–1.0)</td>
</tr>
</tbody>
</table>

Use of cherry product

<table>
<thead>
<tr>
<th>No.</th>
<th>1212</th>
<th>1520</th>
<th>1.0</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>35</td>
<td>69</td>
<td>0.6</td>
<td>0.6 (0.3–1.0)</td>
</tr>
</tbody>
</table>

* Adjusted for diuretic use, purine and alcohol intake

Disclosure: Y. Zhang: None; C. Chen: None; D. J. Hunter: None; C. E. Chaisson: None; H. K. Choi: None; T. Neogi: None.

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Purpose: to determine if serum urate concentrations in young adults are associated with the subsequent development of hypertension.

Table 2: Serur Urate Levels in Young Adults

<table>
<thead>
<tr>
<th>Saturated Urate</th>
<th>Crude OR</th>
<th>Adjusted OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6–1.0</td>
<td>0.6</td>
<td>0.6 (0.5–0.8)</td>
</tr>
<tr>
<td>1.0–1.4</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1.4–1.8</td>
<td>1.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, smoking status, and alcohol intake

Methods: Women and men were analyzed separately because of intrinsic differences in their serum urate levels at the ages studied. Blood pressure (BP) was measured at cohort baseline (1985–1986) and at years 2, 5, 7, 10, 15, and 20 of follow-up. Using Cox-proportional hazard regressions, the associations between sex-specific categories of serum urate at baseline with subsequent development of hypertension (defined as BP ≥ 140/90 or being on blood pressure medication) were examined. Baseline covariates included in the models were age, race/ethnicity, body mass index, physical activity scores, total alcohol intake, smoking status, HDL and LDL cholesterol levels, serum triglyceride levels, serum insulin levels, education completed, and center of recruitment.

Results: 4933 participants free of hypertension at baseline were included in the longitudinal analysis. Mean age (standard deviation) at initiation of follow-up was 24.8 (3.6) years for men and 24.9 (3.7) years for women. The cumulative incidence of hypertension at 20 years of follow-up was 28.5% for men and 30.2% for women. Categories cutpoints of serum urate were higher in men than in women. After multivariable adjusted analyses men showed consistent dose-dependent increases in the risk of developing hypertension with higher levels of serum urate at the beginning of follow-up.

For women the increases in risk were inconsistent and did not conform with a linear trend, but the risk of incident hypertension did increased across all but the relatively small highest serum urate category.

Conclusions: We demonstrated an association between higher urate concentrations in young men and the subsequent risk for incident hypertension, even at concentrations considered to be within the normal range for concentrations in young men and the subsequent risk for incident hypertension. Our findings are consistent with previous reports generated in populations followed later in life and provide additional support to the hypothesis that higher levels of urate relate to their comparatively low concentrations of serum urate. Our findings are consistent with previous reports generated in populations followed later in life and provide additional support to the hypothesis that higher levels of serum urate play a role in the development of hypertension.

Disclosure: A. L. Gaffo: None; D. R. Jacobs: None; F. Sijtsema: None; C. E. Lewis: None; T. R. Mikalis: None; K. G. Saag: Savient Pharmaceuticals, 5, Takeda Pharmaceuticals North America, 5.

Statement of Purpose: To describe radiographic results of the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) Trial, a two-year, longitudinal, multi-center, randomized clinical trial that enrolled 755 early rheumatoid arthritis (RA) participants, comparing immediate combination treatment groups versus step-up from methotrexate (MTX) alone.

Methods: Participants that were enrolled in TEAR from 2004–2007 with early RA (≤3 years). In addition to demographic and clinical measures, hand/foot radiographs were obtained at weeks 0, 48 and 102 and scored using the modified Sharp/van der Heijde scoring system.

Results: A total of 755 participants were enrolled in TEAR with 476 (63%) completing 102 weeks. As of June 2010: 474 (99.6%) baseline films and 297 completed films sets have been scored (62% of all completers). At baseline, the mean radiographic score was 6.2±15.0 units (median 2.0, IQR 0.5–6.0) and 22.2% had no damage (p=0.30 by treatment group); 25.7% had erosions, 66.9% had no joint space narrowing (p=0.15 by group). The 297 with week 0 and 102 scores had a mean baseline score 5.4±12.7 (median 2, IQR 0.5–6.0, similar to entire cohort, p=0.11); 19.5% had no damage.

Table 1. Mean Radiographic Scores for Completers Cohort (N=297)

<table>
<thead>
<tr>
<th>Group</th>
<th>Observed Mean ± SD (Week 0)</th>
<th>Baseline Adjusted Change, Week 102-0</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IE</td>
<td>15.9 ± 8.3 (11.5)</td>
<td>2.9 ± 10.4 (10.4)</td>
<td>0.061</td>
</tr>
<tr>
<td>IT</td>
<td>12.7 ± 8.9 (11.5)</td>
<td>2.2 ± 10.4 (10.4)</td>
<td>0.068</td>
</tr>
<tr>
<td>SE</td>
<td>9.6 ± 8.0 (11.5)</td>
<td>1.6 ± 10.4 (10.4)</td>
<td>0.028</td>
</tr>
<tr>
<td>ST</td>
<td>10.2 ± 8.2 (11.5)</td>
<td>2.4 ± 10.4 (10.4)</td>
<td>0.037</td>
</tr>
<tr>
<td>TT</td>
<td>11.6 ± 8.4 (11.5)</td>
<td>2.3 ± 10.4 (10.4)</td>
<td>0.040</td>
</tr>
</tbody>
</table>

At week 102, the completers had a cohort mean score 6.5±14.5 (median, 3 IQR 1.0–7.5). 91% had no damage; 10.8% with no erosions, 40.3% with no joint space narrowing. The mean increase from week 0 to 102 was 1.1±6.1 (median 0, IQR 0–1.0) and was not different across the four groups (p=0.69). When only treatment is considered, pooling the two etanercept (ETN) groups and the two triple therapy (TT) groups, to assess main effects, there was a significant difference between those receiving ETN + MTX and TT (increase of 0.6 vs 2.4, respectively; p=0.02). There was no difference by the timing of treatment (immediate versus step-up, p=0.81). The difference between ETN + MTX and TT was also observed in the subgroup of individuals with baseline radiographic damage score >0 (increase of 0.6 vs 2.8, p=0.02). There was no change at week 102 among patients with no damage at week 0. In addition, 71.4% of participants achieved radiographic remission (change ≤ 0.5), which was not different by the timing or type of treatment. The remaining 38% of x-rays for trial completers are in the process of being scored.

Conclusions: While prior TEAR results showed no significant differences in clinical findings as assessed by DAS28, this preliminary analysis

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Two-Year Radiographic Results from the TEAR Trial. Larry W. Moreland1, James R. O’Dell2, Harold E. Paulus3, Jeffrey R. Curtis4, Joan M. Bathon2, E. William St Clair5, S. Louis Bridges6, Xiao Zhang7, George Howard2, Desiree M. Van Der Heijde8, Stacey S. Cotfield8 and for the TEAR Trial Investigators. 1Encino, CA, 2Duke University, Durham, NC, 3Johns Hopkins Univ Ste, Baltimore, MD, 4Leiden University Medical Center, Meerssen, The Netherlands, 5The University of Alabama at Birmingham, 6Univ of Alabama-Birmingham, Birmingham, AL, 7Univ of Pittsburgh Med Ctr, Pittsburgh, PA, 8University of Alabama-Birmingham, Birmingham, AL, 9University of Nebraska Medical Center, Omaha, NE
showed that treatment with ETN + MTX resulted in statistically significant radiographic benefit over TT, regardless of timing of treatment. All results to be updated to the full 476 completion cohort.

Disclosure: L. W. Moreland: Amgen Inc., 2; J. R. O’Dell: None; H. E. Paulus: Abbott Laboratories, 2; Amgen Inc., 2; J. R. Currie: Amgen Inc., 2; Centocor, Inc., 2; S. A. Comber: Amgen Inc., 2; S. Connor: Roche, 2; UCB Inc., 5; J. M. Bathon: None; E. W. St Clair: Genentech and Biogen IDEC Inc., 2; S. L. Bridges: None; X. Zhang: None; G. Howard: None; D. M. Van Der Heijde: None; S. S. Cofield: American Shoulder and Elbow Society, 5; GlaxoSmithKline, 5; for the TEAR Trial Investigators: None.

Development and Validation of an MRI Joint Space Narrowing Score for Use in Rheumatoid Arthritis: A Potential Adjunct to the OMERACT RA MRI Scoring System.

Mikkol Østergaard,1 Uffe Möller Dohn,2 Anne Duer-Jensen3, Merete L. Hetland3, Kim Hørslev-Petersen5, Kristian Stengaard-Pedersen1, Peter Junker6, Jan Pødenphant7 and Bo Ejbjerg7. 1Århus University Hospital, Åarhus, Denmark, 2Copenhagen University Hospitals at Hvidovre and Glostrup, Denmark, 3Copenhagen University Hospitals at Hvidovre and Glostrup, Hvidovre, Denmark, 4Diakonhjemmet Hospital, University of Oslo, Oslo, Norway, 5Division of Medicine, St. George Hospital, University of NSW, Sydney, Australia, 6Hôpital Pitié-Salpêtrière, Université PARIS VI-UPMC, Paris, France, 7Hôpital Pitié-Salpêtrière, Université PARIS VI-UPMC, Paris, France, 8Aarhus University Hospital, Maastricht, 9Sheba Medical Centre, Tel Aviv University, Tel Aviv, Israel, 10Spire Sciences LLC, Kentfield, CA, 11St. George Hospital, University of NSW, Sydney, Kogarah, Australia, 12University of Auckland School of Medicine, Auckland, New Zealand, 13University of California San Francisco, Tiburon, CA, 14University of Leeds, Leeds, UK, 15University of Rochester, Rochester, Rochester.

Background: Magnetic resonance imaging (MRI) is now frequently being used as an outcome measure in rheumatoid arthritis (RA) clinical trials. The OMERACT RA MRI score (RAMRIS), evaluating bone erosions, bone oedema and synovitis, is generally used in such trials. Cartilage damage is an important aspect of structural joint damage in RA, and a reliable MRI assessment system of joint space narrowing (JSN), reflecting cartilage damage, would further improve the usefulness of MRI in RA clinical trials.

Objective: The aim of the present initiative was to develop and validate an OMERACT RA MRI assessment method of JSN in RA, which may be a useful adjunct to the current OMERACT RAMRIS.

Methods: The project, which was undertaken by the OMERACT MRI in inflammatory arthritis group, had 3 phases:

Phase A: Exercise 1 (pilot study): Coronal T1-weighted gradient echo MR images of unilateral wrist and MCP-joints from 5 RA patients and 3 controls were scored for JSN at 15 sites in the wrist and each of the 2nd–5th metacarpophalangeal (MCP), without reader pre-training or calibration, by 8 readers (7 readers read once, 1 reader twice), after circulation by DVD.

Phase B: Discussion, review of images and consensus on exact definition and scoring system.

Phase C (Exercise 2): Coronal T1-weighted 3D gradient echo images (voxel size 0.4×0.4×0.4 mm) MR-images of unilateral wrist and 2nd-5th MCP-joints of 15 RA (80% female; age: median 51 (33–78) y, disease duration 7 (4–22) y and 4 controls (75% female; age: median 36 (34–57) y) were scored using a revised score sheet (22 sites, Figure). MRI results were compared with radiographic JSN scores from the same hand (Sharp-van der Heijde method).

Intraclass correlation coefficients (ICCs; single/average measure used for intraobserver/interobserver agreements), and smallest detectable differences (SDDs, for mean of readings) were calculated.

Results: Phase A: Interobserver agreement: ICC 0.93 and SDD 6.4 JSN units (9.9% of observed max). Intraobserver agreement: ICC 0.99 and SDD 2.8 JSN units (4.9% of observed max).

Phase B: Based on experiences from Phase A, agreement was reached on definition, scoring system, and reader rules (Figure).

Conclusion: An MRI scoring system of JSN in RA wrist and MCP joints was developed and showed good intra- and interreader agreements. The system may, after further validation in longitudinal data sets, be useful as an outcome measure of cartilage damage in RA, and may thereby further improve the usefulness of MRI in RA clinical trials.

Disclosure: M. Østergaard: None; P. Bøyesen: None; I. Eshed: None; F. Gandjbakhch: None; S. Lillegren: None; P. Bird: None; V. Foltz: None; A. Boonen: None; M. N. Lasserre: None; K.-G. Hermann: None; A. Anandarajah: None; U. Möller Dohn: None; J. Freeston: None; C. G. Peterly: Spire Sciences LLC, 1, 3, 9; Synarc, Inc., 1; H. K. Genant: Synarc, Inc., 1, 3; E. Haavardsholm: None; F. M. McQueen: None; P. G. Conaghan: None.

Patterns of MRI Bone Erosion in Rheumatoid Arthritis—Which Bones Are Most Frequently Involved and Show Most Change?

Mikkel Østergaard, Uffe Möller Dohn, Anne Duer-Jensen, Merete L. Hetland, Kim Hørslev-Petersen, Kristian Stengaard-Pedersen, Peter Junker, Jan Pødenphant and Bo Ejbjerg. 1Arhus University Hospital, Aarhus, Denmark, 2Copenhagen University Hospitals at Gentofte, Copenhagen, Denmark, 3Copenhagen University Hospitals at Hvidovre and Glostrup, Copenhagen, Denmark, 4Copenhagen University Hospitals at Hvidovre and Glostrup, Copenhagen, Denmark, 5King Christian X’s Rheumatism Hospital, University of Southern Denmark, Gråsten, Denmark, 6Odense University Hospital, Odense C, Denmark, 7Slagelse Hospital, Denmark.

Background: Magnetic resonance imaging (MRI) has been shown to be more sensitive for early bone damage than conventional radiography, and MRI of unilateral wrist and 2nd–5th metacarpophalangeal (MCP) joints is more sensitive to change for erosive progression than radiography of both hands, wrists and forefoot. However, data on the exact distribution of bone erosions, i.e. the pattern of bone involvement are minimal.

Objective: To investigate which bones in RA wrists and MCP-joints that most frequently show bone erosion and which bones most frequently show erosive progression, in early as well as established RA and during disease-modifying anti-rheumatic drug (DMARD) as well as anti-tumor necrosis factor (TNF) therapy.

Patients and Methods: MRI datasets from 258 RA patients (126 with early RA (disease duration <6 months)) were analysed. 223 patients (126 early RA) had 1-year follow-up MRIs. All patients had MRI of one wrist, whereas 86 had additional MCP-joint images, and 46 had additional images of the contralateral wrist. MRIs were evaluated according to the OMERACT RA MRI scoring system (RAMRIS) for erosions, and presence/absence of erosion at baseline was noted in each bone, as was presence/absence of erosive progression.

Results: The distribution of baseline erosions per wrist bone is shown in Figure 1a, whereas the distribution of bones with progression at year 1 is seen in Figure 1b. The capitates, ulna, lunate, triquetrum and scaphoid were the 5 bones with both most frequent baseline erosion and most frequent erosive progression, whereas metacarpal (M) base 3–4–5 were rarely involved. The patterns were similar in early RA and established RA.

In patients with bilateral wrist MRI available, no apparent major difference between dominant and non-dominant was found (269 versus 277 bones
Purpose of Study: We have published the importance of autoantibodies and MRI-proven joint damages of wrist and finger joints toward the prediction of development of rheumatoid arthritis (RA) from undifferentiated arthritis (UA) in Arthritis Rheum 2009: 65; 751–8. By using the same patients population, we have tried to find what variables at entry are able to predict the further plain radiographic progression in patients with UA.

Methods: Our cohort included 129 patients of UA. In the present study, we have focused on the 75 out of 129 patients who developed RA and UA among 75 patients, all of the 1 follow-up data, including serial plain radiography of both hands, were completed in 58 patients. We have examined, by univariate and multivariate analyses, to determine what variables at entry predict the plain radiographic progression at 2 years calculated by Modified Genant Sharp score. Annual progression value greater than 1 was considered as plain radiographic progression.

Results: After the follow-up of 2 years, eighteen patients were classified as having plain radiographic progression (progression group) whereas 40 were not (non-progression group). The multiple logistic regression analysis was conducted to determine the independent effects of variables on radiographic progression. The variables were included in the model if the p value was less than 0.20 in univariate analyses. Duration of morning stiffness, CRP, DAS28-CRP, MMP-3, anti-CCP antibodies, RF, MRI-proven symmetrical synovitis and MRI-proven bone edema were selected. Logistic regression analysis have revealed that MRI-proven bone edema is the first (p=0.023, Odds ratio 13.84) and RF is the second (p=0.049, Odds ratio 6.65) predictors toward plain radiographic progression.

Conclusions: Our data suggest that bone edema of wrist and finger joints at entry is the strongest predictor toward further radiographic progression in patients with UA.

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Conclusions: In this pilot study, there was no evidence that ZA influenced the progression of bone erosions in PsA. However, bone edema scores and number of involved sites fell over 1 year in ZA-treated patients, indicating potential suppression of osteitis. Further studies may be indicated to explore the therapeutic effect of ZA in PsA.


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1373

Cartilage Damage and Osteophytes: MRI-Defined Atrophic and Hypertrophic Phenotypes of Knee Osteoarthritis in the Framingham Cohort.
Frank Roemer, Ali Guermazi, Jingbo Niu, Yuqing Zhang and David Felson, Boston University

Purpose: Osteophytes (OPs) are a common feature of moderate to advanced radiographic osteoarthritis (OA). It is not known to what extent advanced cartilage damage detected by magnetic resonance imaging (MRI) correlates with severity of osteophyte formation. On the other hand, it is not known if knees without severe cartilage damage exhibit large osteophytes.

Our purpose was to describe the prevalence of osteophytes and concomitant cartilage damage in a population-based cohort using semi-quantitative MRI assessment. Focus of the investigation were a.) knees with severe cartilage damage and no or tiny concomitant osteophytes and b.) knees without substantial cartilage damage but with large OPs in order to characterize the atrophic and hypertrophic phenotypes of knee OA respectively.

Methods: Participants of the Framingham Knee Osteoarthritis Study were examined with a 1.5 T MRI system. Cartilage and OPs were assessed according to the WORMS scoring system. “Severe” cartilage damage was defined as cartilage morphology (CM) scores of 5 or 6 in at least 2 of 10 TF subregions. “Without substantial” cartilage damage was defined as none of 10 TF subregions exhibiting CM scores ≥3. Large OPs were defined as OPs grade 5–7. Absent or tiny OPs were defined as OP scores 0–2.

We first calculated the overall prevalence of knees with severe cartilage damage and described concomitant OP status. The odds ratios (OR) of severe cartilage damage according to OP size were estimated using a logistic regression model. Further the association of large OPs according to ROA status was analyzed. In addition we focused on knees with absent or only tiny osteophytes in all 10 TF subregions but with severe cartilage damage as defined above (atrophic phenotype) and knees with large osteophytes and without substantial cartilage damage (hypertrophic phenotype).

Results: 1597 knees of 1248 subjects were included. Mean age was 63.9 years, mean BMI 28.9, 58.3% were women. 197/246 (80.1%) knees with severe cartilage exhibited large OPs. The risk of severe cartilage damage increased in a linear fashion with increasing OP size when using the knees without or only tiny osteophytes as the reference. 21 knees showed an atrophic phenotype. Only 3 knees exhibited a hypertrophic phenotype.

Table 1. Association of osteophyte size with risk of severe cartilage damage

<table>
<thead>
<tr>
<th>Osteophyte status</th>
<th>Subregions with severe cartilage damage (n)</th>
<th>Crude model Odds ratio [95% CI]</th>
<th>Model adjusting age, sex, BMI, race, TF radiographic OA Odds ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPs absent (max. OP size 0–1)</td>
<td>1/498 (0.2)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>OPs present (max. OP size 2–7)</td>
<td>172/1099 (15.7)</td>
<td>92.9 [16.3, 528.9]</td>
<td>10.6 [1.8, 63.8]</td>
</tr>
<tr>
<td>Maximum OP size: 0 (reference)</td>
<td>1/498 (0.2)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>2</td>
<td>20/704 (2.8)</td>
<td>171.1 [1.9, 157.2]</td>
<td>4.2 [0.6, 28.4]</td>
</tr>
<tr>
<td>3–4</td>
<td>98/328 (29.9)</td>
<td>247.3 [27.7, 2208.5]</td>
<td>14.6 [2.2, 98.2]</td>
</tr>
<tr>
<td>5–7</td>
<td>54/67 (80.6)</td>
<td>2378.1 [249.8, 22,643.4]</td>
<td>108.8 [14.2, 834.9]</td>
</tr>
</tbody>
</table>

p-value for linear trend
- statistically significant, defined as p<0.05

Conclusion: The majority of knees with severe TF cartilage damage exhibit moderate to large TF OPs. A linear increase in risk of severe cartilage damage was observed with increasing OP size. A minority of knees exhibits the so-called atrophic phenotype, which also includes knees without ROA. The hypertrophic phenotype is extremely rare. MRI-based prevalence data on the different types of OA phenotypes contributes to understanding disease pathology.

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ACR Concurrent Abstract Sessions
Muscle Biology, Myositis and Myopathies: Insights into the Pathogenesis and Outcomes of Myositis

Tuesday, November 9, 2010, 2:30 PM–4:00 PM

1374

N. A. Young, R. Sharma, B. Kaffenberger, A. Friedman and W. N. Jarjour, The Ohio State University Medical Center, Columbus, OH

Background: Myositis is characteristically associated with an inflammatory process that results in pronounced muscle weakness. Myositis is observed in some regulatory T-cell (Treg) deficient mouse models. Scurfy mice lack Treg due to mutation in the X-linked forkhead box P3 (Foxp3) and its expression is required for negative selection of self-reactive T cells in the thymus. In the absence of Foxp3, T cells exhibit a mixed phenotype that includes Treg. However, the role of regulatory T cells in the development of myositis has not been fully explored.

Methods: RagI KO males were bred with scurfy mice to produce Syt VII deficient mice. The Syt VII KO mutation results in impaired membrane resealing and has been shown to lead to limited inflammation of muscle tissue. To investigate the role of muscle antigens and Treg deficiency in the development of muscle inflammation, we crossed scurfy mice with syt/VII deficient mice. The Syt VII mutation results in impaired membrane resealing and has been shown to lead to limited inflammation of muscle tissue. To investigate the role of muscle antigens and Treg deficiency in the development of muscle inflammation, we crossed scurfy mice with syt/VII deficient mice. The Syt VII mutation results in impaired membrane resealing and has been shown to lead to limited inflammation of muscle tissue.

Results: Double KO mice with Syt VII/Foxp3 mutations developed more severe myositis compared to mice with either mutation alone. Furthermore, IP adoptive transfer of double KO LN cells induced dramatic myopathy in Rag1 KO recipients. Conversely, a notably limited infiltrate was seen in the skeletal muscle of Rag1 KO mice that received LN cells from Syt VII/Foxp3 double KO.
sufficient scurfy mice. The muscle antigen effect was then examined through IP adoptive transfer of scurfy LN cells into Rag1 KO recipients with and without muscle tissue cell extract. These results were compared to Rag1 KO recipients of scurfy LN cells by IM injection, which readily exhibit severe muscle inflammation. Inflammatory myopathy could only be induced in the Rag1 KO recipients through IP injection of scurfy LN cells if the mice were co-injected with muscle extract.

**Conclusion:** This mouse model of myositis illustrates the interplay between two genetic defects in establishing a robust inflammatory process involving the muscle and that regulatory T cells are critical in limiting inflammation in muscles. The results suggest that endogenous muscle tissue antigen exposure either through injection of muscle extract or through leakage of endogenous antigen due to Syt VII mutation is essential in priming autoreactive cells. We have established a novel, reproducible model to study myositis that will be useful to define new autoantigens. Furthermore, extension of this model can be used to investigate autoimmune phenomena that are triggered by extrinsic factors such as ultraviolet light or exposure to certain drugs.

**Disclosure:** N. A. Young: None; R. Sharma: None; B. Kaffenberger: None; A. Friedman: None; W. N. Jarjour: None.

**1375**

**Blockade of TNFα or IL-1 Ameliorates Established C-Protein Induced Myositis of Mice.** Takahiko Sugihara1, Naoko Okiyama1, Naoto Watanabe1, Nobuyuki Miyasaka1 and Hitoshi Kohsaka1. 1Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan; 2Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Japan

**Objective:** Histological studies of the muscle biopsy specimens suggest that inflammatory cytokines are involved in pathology of inflammatory myopathy. Therapeutic effects of their blockade are controversial with anecdotal reports of clinical efficacy. Systematic pre-clinical studies can be performed by use of animal models. In this regards, C-protein induced myopathy (CPM) was studied as therapeutic targets of the myositis.

**Methods:** C57BL/6 mice were immunized with recombinant C protein fragments. IL-1 and TNF expression in the CPM muscles was evaluated with immunohistochemistry and real-time PCR. After onset of the myositis, CPM mice were treated with IL-1 receptor antagonist (IL-1ra), anti-IL-1 receptor monoclonal antibody (IL-1R mAb) and TNF receptor (p75)-fused with IgFc (TNFRFc), provided by Amgen as well as with anti-TNFα monoclonal antibody (TNFα mAb), provided by Centocor. Following completion of treatment, the muscles from the treated animals were examined for histological scoring.

**Results:** IL-1 and TNFα mRNA was expressed in the muscles as early as 7 days after the immunization. This was when mononuclear infiltration and muscle necrosis became appreciable. Their expression was up-regulated at the peak of the myositis. These cytokines were expressed primarily by infiltrating macrophages. To inhibit them in vivo, IL-1ra (0.24, 0.8 and 2.4 mg/day/mouse) was administered continuously with mini-pumps implanted subcutaneously for a week, starting 7 days after the immunization. These treatments suppressed pathology of CPM. While the continuous IL-1ra delivery of 0.8 mg/day/mouse was effective (a total of 5.6 mg/mouse), intermittent intraperitoneal injections (three times a week) of a total of 7.2 mg/mouse were not. In contrast, intermittent intraperitoneal injections (three times a week) of a total of 5.6 mg/mouse), intermittent intraperitoneal injections (three times a week) of a total of 5.6 mg/mouse) and TNFRFc (100 mg/mouse) were administered intraperitoneally three times a week for 2 weeks. Both of anti-TNF biological reagents suppressed pathology of CPM.

**Conclusions:** IL-1 and TNF blockade ameliorated ongoing CPM. Blockade of TNFα or IL-1 may be new strategies for treatment of PM. Previously, we reported that CPM developed in TNFα null mice but not in IL-1α/β null mice. Cytotoxic activity of anti-TNFα mAb does not account for this difference because TNFRFc treatment was also effective. TNFα null mice are reportedly susceptible to collagen-induced arthritis, which can be treated with anti-TNFα mAb. This paradoxical sensitivity of TNFα deficient mice to autoimmune holds true in CPM, which is driven by autoimmune CD8 T cells. As for the IL-1 blockade, anti-IL-1R mAb appeared clinically more feasible than IL-1ra presumably because of differences in affinities and pharmacokinetics.

**Disclosure:** T. Sugihara: None; N. Okiyama: None; N. Watanabe: None; N. Miyasaka: None; H. Kohsaka: None.

**1376**

**UPR Activation and IFNβ Production in Myocytes in Adult and Juvenile Myositis.** Ann M. Reed1, Molly S. Hein1 and Robert A. Colbert2. 1Mayo Clinic, 2NIH, NIAMS

**Background:** The unfolded protein response (UPR) to endoplasmic reticulum (ER) stress in myocytes may contribute to skeletal muscle damage and dysfunction in Inflammatory Myositis (IM). Overexpression of Interferon β (IFNβ) has been demonstrated in immune cells in Adult and Juvenile Dermatomyositis (DM JDM), and to a lesser extent in Polymyositis (PM) and Inclusion Body Myositis (IBM), and is hypothesized to contribute to the UPR through upregulation of MHC class I. Since the UPR can contribute to IFNβ upregulation in other cell types, we hypothesized that UPR activation in autoimmune myositis might correlate with IFNβ expression in myocytes in active disease.

**Methods:** Intracellular staining of IFNβ (Gp78/HSPA5), a marker of UPR activation, and IFNβ were assessed in muscle biopsy tissue from new onset IM subjects (n=5 each of DM, JDM, PM, IBM and control subjects). Myocyte regeneration marker (MYH3) expression was assessed using immunofluorescence (IF) staining. Co-localization of these proteins and inflammatory cell phenotyping, including CD3 (T cells), CD19 (B cells), CD20 (plasmacytoid dendritic cells (pDCs)), CD4 (T cells and pDCs) and CD19 (B cells), was performed by cell surface staining. Direct comparisons of the number of IF positive cells were normalized per 10X field.

**Results:** Co-localization of Bip and IFNβ expression was seen in 10–25% of the myocytes per high power field (HPF) in all IM subgroups and 20–50% of the mononuclear (MN) cells compared with rare <1% of myocytes and MN cells in control tissue (p=0.017 and 0.004). Bip staining in myocytes was seen rarely without IFNβ. The IFNβ levels were increased in all forms of myositis (JDM 25%, DM 8%, PM 7% and IBM 15%) versus 3% of controls with JDM having the highest values. Regenerating fibers express Bip in 80% of cases. MYH3 co-localized with Bip and IFNβ in ~80% of myocytes, with 20% staining for MYH3 alone. Bip+ pDCs were also greater in JDM (average of 44 cells/HPF vs. 6 in controls p<0.0001) and 7 cells/HPF in DM/PM/IBM). IFNb co-localized with pDCs (72 JDM, 23 DM, 25 PM, 15 IBM and 8 control cells per HPF (all groups vs controls p<0.003)). The co-localization of Bip and IFNb in myocytes suggests that non-immune cell production of IFNβ including regenerating cells, may be important in IM pathogenesis, and that the UPR may contribute to its production, possibly creating a positive feedback loop.

**Conclusions:** The UPR is associated with Type-I IFN (IFNb) expression in myocytes in several forms of IM.

**Disclosure:** A. M. Reed: None; M. S. Hein: None; R. A. Colbert: None.

**1377**

**A New ELISA System for Detecting Autoantibodies to aminoacyl-tRNA Synthetases: Usefulness in Myositis and Interstitial Pneumonia.** Ran Nakashima1, Yoshitaka Imura2, Shio Kobayashi1, Yuji Hosono3, Naohiro Yukawa4, Daisuke Kawabata5, Takaki Nojima2, Koichiro Ohmura2, Takashi Ushii4, Takao Fuji1, Minae Seto1, Akihito Murakami1 and Tsuneo Mimori1. 1Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Sakyo-ku Kyoto, Japan; 2Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan; 3Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan; 4Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan; 5Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan

**Purpose:** Aminoacyl-tRNA synthetases (ARS) are the most frequent myositis-specific antibodies and patients with anti-ARS antibodies show a spectrum of common clinical manifestations known as anti-synthetase syndrome. Detecting anti-ARS antibodies is useful in diagnosis, classification and management of polymyositis (PM)/dermatomyositis (DM) and interstitial pneumonia (IP). Immunoprecipitation assay is utilized currently to detect anti-ARS antibodies but can be
done only in limited numbers of laboratories. For easy detection of anti-ARS antibodies, we established enzyme-linked immunosorbent assay (ELISA) system using a mixture of five known recombinant ARS antigens for detecting anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ and anti-KS antibodies at once.

**Methods:** We prepared 6 recombinant ARS antigens; GST-Jo-1, His-PL-12, His-EJ and GST-KS expressed in E. coli, and His-PL-7 and His-OJ expressed in Trichoplusia Hi-5 cells. After confirming antigenic activity of all recombinant proteins except His-OJ using indirect ELISA, we made an ELISA system using mixture of the five recombinant ARS. In order to confirm the efficiency of this newly established ELISA, we screened a total of 241 sera from patients with various connective tissue diseases (PM 57, DM 46 and other diseases 138), 62 from idiopathic IP (IIP) and 30 from healthy controls. The results of ELISA were compared with those of standard RNA immunoprecipitation assay.

**Results:** Except for one false-negative and two false-positive samples, all of the results on anti-ARS positivity by ELISA were consistent with those by RNA immunoprecipitation. Sensitivity and specificity of the ELISA compared with RNA immunoprecipitation were 97.5% and 99.3%, respectively. Anti-ARS antibodies were detected in 33% (19/57) of PM, 36% (21/58) of IIP (IIP) and 30 from healthy controls. The results of ELISA were consistent with all of the results on anti-ARS positivity by ELISA. Our ELISA system will make possible to detect anti-ARS antibodies in patients with PM/DM and IP more easily and be used widely in daily practice.

**Conclusion:** We established the new anti-ARS ELISA system using a mixture of five recombinant ARS antigens and demonstrated that it detected anti-ARS antibodies as efficiently as RNA immunoprecipitation. This system will make possible to detect anti-ARS antibodies in patients with PM/DM and IP more easily and be used widely in daily practice.

**Disclosure:** R. Nakashima: None; Y. Imura: None; S. Kobayashi: None; Y. Hosono: None; N. Yukawa: None; D. Kawahata: None; T. Nojima: None; K. Ohmura: None; T. Usui: None; T. Fujii: None; M. Seto: None; A. Murakami: None; T. Minori: None.

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**Atherosclerotic Cardiovascular Disease among Hospitalized Dermatomyositis Patients in the US.** Eleni Linos1, David Fiorentino2, Bharathi Lingala2, Esvar Krishnan2 and Lorinda Chung1. Stanford Univ Medical Center, Palo Alto, CA, 2Stanford University, Palo Alto, CA, 2Stanford University School of Medicine

**Purpose:** Increasing evidence suggests that atherosclerotic cardiovascular disease is more prevalent among patients with rheumatologic diseases, including rheumatoid arthritis and systemic lupus erythematosus, compared with the general population. Cardiac involvement in patients with dermatomyositis (DM) has been reported and is associated with a poor prognosis, but the prevalence of atherosclerotic cardiovascular disease among hospitalized DM patients is unknown. Our aim was to evaluate the prevalence of atherosclerotic cardiovascular comorbidities and their associated mortality risk among hospitalized DM patients in the US.

**Methods:** We examined the in-hospital frequency and mortality rates of specific diagnoses and procedures associated with atherosclerotic cardiovascular disease among hospitalized adult patients with DM using data from the Nationwide Inpatient Sample (NIS) from 1993 to 2007. The NIS is a national, annual, representative survey of hospitalized patients in the US. The following diagnoses and procedures were identified by ICD-9 codes: coronary artery disease, congestive heart failure, angina, myocardial infarction, and cerebrovascular accidents; coronary artery bypass grafts, coronary catheterization, and percutaneous transluminal coronary angioplasty. We compared the odds of death among hospitalized DM patients with each cardiovascular diagnosis or procedure to those without using logistic regression. Analyses were weighted so results are standardized to the US population as a whole.

**Results:** A total of 50,323 hospitalizations of DM patients occurred in the US between 1993 and 2007. The mean patient age was 58 years, and 73% of patients were female. Of all DM hospitalizations, 20% were associated with a concurrent atherosclerotic cardiovascular diagnosis or procedure. The overall in-hospital mortality rate was 57 per 1000. DM patients with any of the specific atherosclerotic cardiovascular diagnoses or procedures were twice as likely to die during the inpatient stay compared to DM patients who did not have atherosclerotic cardiovascular disease (OR=2.95% CI 1.7–2.5, p<0.0001). The highest odds of death were noted for patients with congestive heart failure (OR=2.3 95% CI 1.9–2.8, p<0.001) and cerebrovascular accidents (OR=2.3 95% CI 1.7–3.3, p<0.001).

**Conclusions:** In this large US-based hospitalization database, approximately one fifth of hospitalizations in DM patients were associated with an atherosclerotic cardiovascular diagnosis or procedure. These patients have double the risk of in-hospital death, making identification of these groups important for both prognostic purposes and clinical care. Further prospective studies are necessary to confirm our findings and to analyze the relative contribution of disease activity, concomitant risk factors, and corticosteroid treatment.

**Disclosure:** E. Linos: None; D. Fiorentino: None; B. Lingala: None; E. Krishnan: None; L. Chung: None.

1379

**Predictors of Response to B Cell Depleting Therapy in Adult and Juvenile Myositis.** Ann M. Reed1, Kelly T. McNallan2, Cindy S. Crowson1 and Chester V. Oddis2. 1Mayo Clinic, 2University of Pittsburgh

**Background:** Idiopathic inflammatory myopathy (IIM) is associated with significant morbidity and mortality. There are no curative therapies and markers to predict therapeutic response are lacking. Type I interferon (IFN) regulated genes and cytokines/chemokines are known biomarkers of disease activity in IIM and predict response to therapy while autoantibody production and B cell survival factors including BAFF are hypothesized as important biomarkers in IIM. The Rituximab (Rtx) in Myositis (RIM) Study collected longitudinal patient (pt) samples and assessed the efficacy of Rtx in refractory adult polymyositis (PM) and dermatomyositis (DM) and juvenile DM (JDM) pts. We investigated if a biological signature predicts disease responsiveness to B cell depletion (BDE) therapy in the RIM Study.

**Methods:** Peripheral blood samples and clinical/laboratory data were collected at baseline and 16 and 24 weeks after Rtx in 75 RIM Study pts to: (a) determine biomarkers of disease activity, (b) predict treatment response, and (c) determine whether biomarkers predict disease flare. Multiplexed sandwich immunoassays (Meso Scale Discovery) quantified serum levels of IFN-regulated chemokines and other pro-inflammatory cytokines. B cell regulating factor transcripts were determined by quantitative PCR. Cytokines (IL-12, IL-2, IL-12, IFNγ, MIP1α, MIF and TNF-α), chemokines (MCP-1, MCP-2, ITAC and IP-10) and B cell regulating factors (BAFF, ΔBAFF, APRIL, BAFFR, BCMA, and TACI) were measured. Clinical response and disease activity were assessed utilizing a consensus-driven definition of improvement (DOI) in IIM and the Physician’s Global Activity (PGA). Spearman’s rank correlation coefficient (r) described the relationship between biomarkers and disease activity/response.

**Results:** Changes in serum biomarkers correlated with disease activity and response to Rtx. Disease activity measured by PGA at week 16 correlated with BAFF and TACI (r = 0.19; p = 0.007) and IP-10 (r = 0.21; p = 0.003), and TNF-α (r = 0.2; p = 0.028). Predictive treatment responses were detected in pts with higher IL-2 levels at week 0 who had an 80% likelihood of achieving DOI (hazard ratio: 1.84; 95% CI: 1.04, 3.27; p = 0.036). Serum levels of IFN regulated cytokines and chemokines declined from week 0 to 16 and correlated with change in PGA from week 0 to 16 and predicted responsiveness to Rtx [IL-12 (r = 0.19; p = 0.04), IL-12 (r = 0.21; p = 0.02), MIP1α (r = 0.21; p = 0.02), TNFα (r = 0.19; p = 0.03), ITAC (r = 0.26; p = 0.007) and IP-10 (r = 0.24; p = 0.01)]. Peripheral blood RNA levels of BAFFR, BCMA, CD20, and TACI decreased significantly between week 0 and 24 and clinical improvement (decrease in PGA) was significantly correlated with change in DBAFF (r = 0.26; p = 0.01) and full length BAFF (r = 0.25; p = 0.022). Markers of disease worsening, defined by a 10% increase in PGA between weeks 0 and 24, included BCMA/BAFFR ratio (p = 0.04) and BAFFR/TACI ratios (p = 0.06).

**Conclusion:** These studies show that cytokine and chemokine levels correlate with disease activity and physician-assessed worsening and predict response to BDE in adult and juvenile myositis.

**Disclosure:** A. M. Reed: None; K. T. McNallan: None; C. S. Crowson: None; C. V. Oddis: None.
Background: End-stage knee osteoarthritis (OA) is frequently treated by total knee replacement (TKR). In 40% of the cases this expensive treatment is performed under the age of 65 years, while the procedure has a higher risk of failure in younger patients, due to higher physical demands.

Knee joint distraction (KJD) is an experimental treatment for end-stage knee OA, aimed at unloading the joint cartilage and subchondral bone by use of a ‘fixateur exteme’. The technique proved to be clinically effective for end-stage ankle OA. The present study describes an exploratory, open, uncontrolled trial to verify whether KJD has the potency to postpone a TKR by inducing clinical improvement and cartilage repair.

Methods: Twenty patients, under 60 years of age, with end-stage knee OA were treated with KJD for 2 months. Two monotubes with internal coil springs were placed parallel (medial and lateral) bridging the knee joint and were distracted for 5 mm. Patients were encouraged to load the knee during distraction, in order to achieve intermittent intra-articular fluid pressures. During the treatment most patients (n=17) suffered from single or multiple pin tract infections, all being successfully treated with antibiotics.

After 2 months, tubes and pins were removed, and function was actively practiced.

The primary clinical outcome was pain and function by use of the WOMAC questionnaire. For secondary clinical outcome VAS pain was documented. Primary structural outcome was cartilage thickness by use of quantitative MRI and digital analyses of standardized X-rays. Secondary documented. Primary structural outcome was cartilage thickness by use of WOMAC questionnaire. For secondary clinical outcome VAS pain was documented.

Results: One year after distraction, the total WOMAC score improved significantly from 54% at baseline to 77% (p<0.001). This improvement is supported by a decrease in VAS pain score from 73 to 31 mm (p<0.001).

Complementary, quantitative MRI analysis showed an increase in cartilage thickness of the affected compartment from 2.4 to 3.0 mm (p<0.01), both femur and tibia. The total area of denuded bone decreased from 22% to 5% (p=0.01). Cartilage area and volume increased from 15.6 to 18.9 cm² and 2.3 to 2.8 cm³ (both p<0.05).

X-ray analysis corroborated the MRI findings by an increased mean, as well as minimum JSW from 2.7 to 3.6 mm (p<0.05) and 1.0 to 1.9 mm (p=0.01), respectively.

Increase in cartilage area and thickness and decrease in denuded bone area correlated with the increase in the mean radiographical JSW (r=0.571, r=0.553, r=-0.613 resp. all p<0.05)

Long term changes in biomarkers showed a decrease of collagen type II breakdown marker CTXII (~11%; p=0.04) and an increase of collagen type II synthesis marker PIIANP (~10%; p=0.03). The average change in the ration of PIIANP/CTXII of each patient was in favor of synthesis (p<0.03).

Conclusion: In treatment of end-stage knee OA it is proven to induce significant intrinsic joint cartilage repair by use of joint distraction, based on MRI, X-ray and biochemical marker analyses. These significant tissue structure changes are accompanied by clinical improvement in pain and function.
Patient Pain VAS
Baseline - (22 pts) 36.1 16 Months - (11 pts) 15.6 12 Months - (8 pts) - 11.7
Patient Global Assessment of Disease
Baseline - (22 pts) 34.4 6 Months - (11 pts) 21.4 12 Months - (8 pts) - 13.1
Physician Global Assessment
Baseline - (22 pts) 72.3 6 Months - (11 pts) 28.6 12 Months - (8 pts) - 16.1
50 Foot Walk Pain
Baseline - (22 pts) 27.7 6 Months - (11 pts) 14.6 12 Months - (8 pts) - 8.4
WOMAC
Baseline - (22 pts) 27.1 6 Months - (11 pts) 13.7 12 Months - (8 pts) - 8.0
Ultrasound measurement of patellofemoral cartilage thickness at 7 standard points (medial to lateral) was performed. Reproducibility error was reduced by confirming the original site and repeating measurements three times. Measurements showed:
Mean improvement from baseline to 6 months (11 pts) - 0.4 mm
Mean improvement from baseline to 12 months (8 pts) - 0.8 mm
While it is an uncontrolled study, GMSCL demonstrates some promise as a treatment for OAK. Further study is recommended.

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Increased Fat Mass Is Associated with High Levels of Low Back Pain Intensity and Disability. Donna Urquhart1, Patricia Berry2, Anita Wluka3, Boyd Strauss3, Yunnuyan Wang2, Joseph Proietto3, Graeme Jones4, John Dixon5, and Flavia Ciuffitton. 1Baker IDI Heart and Diabetes Institute, 2Menzies Research Institute, 3Monash Medical Centre, 4Monash University, 5University of Melbourne
Background: The relationship between obesity and low back pain and disability is unclear. No study has examined the role of body composition in low back pain and disability. The aim of the study was to determine whether body composition is associated with low back pain intensity and/or disability in a cross sectional study.
Methods: 135 participants (25 to 62 years), with a range of body mass indices (BMI) (18 to 55 kg/m2), were recruited for a study examining the relationship between obesity and musculoskeletal disease. Participants completed the Chronic Back Pain Grade Questionnaire, which examines individuals’ levels of low back pain intensity and disability. Body composition was assessed using dual x-ray absorbiometry.
Results: BMI was associated with higher levels of back pain intensity (Odds ratio (OR) 1.35, 95% CI 1.09, 1.67) and disability (OR 1.66, 95% CI 1.31, 2.09). Higher levels of pain intensity were positively associated with total (1.19, 95% CI 1.04, 1.38) and lower limb fat mass (OR 1.51, 95% CI 1.04, 2.20), independent of lean tissue mass. There were also positive associations between higher levels of low back disability and total (OR 1.41, 95% CI 1.20, 1.67), upper (OR 1.67, 95% CI 1.27 2.19) and lower limb (OR 2.29, 95% CI 1.51, 3.49) fat mass. Similar relationships were observed with trunk, android and gynoid fat mass. After adjusting for confounders, no measures of lean tissue mass were associated with higher pain intensity or disability (p=0.10).
Conclusions: Greater fat, but not lean tissue mass, was associated with higher levels of low back pain intensity and disability. While this needs to be confirmed in longitudinal studies, it suggests that weight loss strategies aimed at reducing fat mass may be important in the prevention of low back pain and disability. Understanding the mechanism for these relationships may provide novel approaches to managing low back pain.
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Creatine Supplementation Associated to Resistance Training in Post-Menopausal Women with Knee Osteoarthritis Improves Functional: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. Manoel Tavares Neves Junior1, Bruno Gualano2, Hamilton Roschel3, Marcelo Tatit Sapienza2, Fernanda Rodrigues Lima2, Ana Lucia de Sa Pinto2, Ricardo Fuller1, Rosa Maria Rodrigues Pereira1, Antonio Herbert Lancha Junior1, and Eloisa Silva Dutra de Oliveira Bonfa1, Universidade de Sao Paulo, Sao Paulo, SP, Brazil, 1Universidade de Sao Paulo
Background: Quadriceps muscle strength is associated with functional impairment in osteoarthritis (OA), reinforcing the relevance of strategies to optimize muscle strength in this disease. Creatine supplementation has been found to significantly increase muscle strength and hypertrophy in adults, particularly when associated with a resistance training regime.
Methods: We conducted a randomized, double-blinded, placebo-controlled trial investigating the efficacy and safety of creatine (CR) supplementation in sedentary post-menopausal women (50–65 years old) with knee osteoarthritis (grades II and III) submitted to resistance training. Subjects (n=16) were randomly allocated to receive treatment with either CR (5 g day-1 over 3 months) or placebo (PL) (dextrose). All of the subjects undertook moderate intensity resistance training, three times a week for three months. The patients were submitted to a physical function test (timed-stands test - measured by the number of repetitions performed over time), lower limb maximum dynamic strength test (1RM), body composition using a dual energy X-ray absorbiometry and renal function assessed by S1Cr-EDTA clearance before and after the training period. Data were analyzed by a mixed model for repeated measures.
Results: Functional testing revealed a significant improvement (pre to post) in the timed-stands test for the CR group (16.6 ± 1.06 vs. 19.1 ± 1.83 repetitions; p=0.02) while no change was observed for the PL group (15.1 ± 1.45 vs. 16.7 ± 1.11 repetitions, p=0.17). Additionally, between-group comparison revealed a statistically significant difference for CR when compared to PL (p=0.03). Body composition data showed a significant increase over time (pre to post) in total body weight (64.7 ± 7.65 vs. 67.1 ± 7.15 kg, p=0.02) and lean mass (3927.48 ± 5384.17, vs. 4059.16 ± 4932.96 g, p=0.01) for the CR group, whereas the PL group showed no alteration in any of the body composition parameters (p=0.95 and p=0.99, respectively). Moreover, 1RM significantly improved in both, CR (81.25 ± 16.71 vs. 98.83 ± 16.22 kg, p=0.02) and PL (85.98 ± 19.43 vs. 106.10 ± 27.43 kg, p=0.01) groups, thus indicating the efficacy of the training protocol in improving strength. Finally, renal function remained stable throughout the study (pre to post) for CR (88.00 ± 17.11 vs. 88.65± 16.45 mL/min/1.73 m2, p=0.89) and PL (83.43±6.62 vs. 83.05±5.29 mL/min/1.73 m2, p=0.99), groups, with no between-group differences. Creatine supplementation had no side-effects.
Conclusion: Our findings highlight that creatine is a promising treatment to help OA patients to perform daily living tasks since it safely improves lean mass and function. The underlying mechanism probably involves an additive effect of the CR supplementation and resistance training on the increase in muscle mass and work capacity, thus ameliorating muscle function. Clinical Trial Identification-NCT00749983
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Role of Central Sensitization in Persistent Pain Post-Knee Replacement: The MOST Study. Tuhina Neogi1, Jingbo Niu2, Laura Frey-Law2, Lars Arendt-Nielsen3, Javinder Singh4, Joachim Scholz5, Clifford Woolf6, Irina Tolstykh6, Jessica L. Maxwell7, Barton Wise8, and David T. Felson9, 1Aalborg University, Denmark, 2Boston Childrens Hospital, 3Boston Univ Schl of Med, Boston, MA, 4Boston Univ School of Medicine, Boston, MA, 5Boston University School of Medicine, Boston, MA, 6UCDavis, Sacramento, CA, 7UCSF, 8University of Alabama at Birmingham, Minneapolis, MN, 9University of Iowa
Purpose: Pain persists post-knee replacement (KR) in ~20–30% of patients. The reason for this pain persistence is unclear. One possibility is that long-standing mechanical and inflammatory stimuli in osteoarthritis (OA) can lead to changes in the peripheral and central nervous system, with subsequent peripheral and central sensitization resulting in heightened pain sensitivity. We hypothesized that central sensitization may be associated with persistent pain post-KR.
Methods: The Multicenter Osteoarthritis (MOST) Study is cohort study of persons with or at high risk of knee OA. This analysis was limited to those with KR at any time during the study, confirmed by medical records and/or x-ray. At the 60-month clinic visit, participants had knee x-rays, answered a knee-specific WOMAC pain questionnaire, and had temporal summation (TS) assessed at the wrist. TS is an augmented pain response to repetitive mechanical stimuli thought to reflect central sensitization. TS was defined as being present when, after touching the skin with a 60g monofilament repeatedly at a frequency of 1Hz for 30 seconds, the subject reported increased pain at the site being tested. For cross-sectional analyses, we defined...
presence of knee pain (of the KR knee) as moderate or greater pain vs none/mild based on the maximal score of any of the 5 WOMAC pain questions. For longitudinal analyses, we defined knee pain improvement post-KR as a decrease of ≥5.620 in WOMAC pain (of the KR knee) from pre-to post-KR (Escarb, OA&C, 2007) using the closest clinic visits to those time-points. We examined the relation of presence of TS with presence of knee pain among all persons with KR, and with having pain improvement post-KR among those with a new KR during follow-up, using Poisson regression and GEE to obtain prevalence ratios (cross-sectional) and risk ratios (longitudinal). All analyses were adjusted for age, sex, BMI, depressive symptoms, race, clinic site, and time since KR. Only the cross-sectional analysis could be adjusted for catastrophizing due to unstable estimates in the longitudinal analysis.

Results: There were 114 subjects with 151 knees that had a KR at baseline (22) or during follow-up (129) who also had TS measured at the 60-month visit (mean age 71.2, mean BMI 32.9, 74.6% female, mean time since KR 3.7 yrs (range <1–15 yrs). Maximal WOMAC knee pain was rated as ≥moderate in 26.5% of KR knees. Cross-sectionally, presence of TS was associated with 2.06 times higher prevalence of knee pain compared with no TS (95% CI 1.12–3.79, p = 0.02). Pain improvement from pre- to post-KR occurred in 42% of KR knees. In the longitudinal analysis, presence of TS was associated with a 67% lower chance of having a pain improvement post-KR (RR 0.33, CI 0.17–0.63, p = 0.009).

Conclusions: Temporal summation was associated with presence of, and less improvement in, post-KR pain. Central sensitization may therefore partially explain why some individuals have pain persistence post-KR. These findings suggest that consideration for performing KRs earlier in the course of OA, when central sensitization is still potentially reversible, may be warranted.

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Thrombin-Activatable Carboxypeptidase B (CPB) Plays a Central Role in Down-Regulating Inflammatory Responses in Rheumatoid Arthritis by Cleaving C5a, Jason J. Song, Henry Hwang, Tiffany Wang, Annette T. Lee, S. Louis Bridges, Peter K. Gregersen, Lawrence Leung and William Robinson. 1North Shore-LIJ Research Institute, Manhasset, NY, 2Stanford University School of Medicine, Stanford, CA, 3Stanford University, Palo Alto, CA, 4Stanford University, 5Univ of Alabama-Birmingham, Birmingham, AL.

Purpose: Thrombin-activatable CPB is known to play an anti-fibrolytic role by removing C-terminal lysine residues from fibrin, thereby preventing the cleavage of fibrin by plasmin. Recently, C3a, C5a, thrombin-cleaved osteopontin, and bradykinin have been identified as additional substrates of CPB. CPB removes arginine residues from the C-terminal of these inflammatory mediators, thereby altering their biological functions. Here we investigate the molecular mechanisms underlying the anti-inflammatory role of CPB in rheumatoid arthritis (RA).

Methods: We evaluated arthritis in CPB+/−, mice, osteopontin−/− mice, C5−/− mice, and bradykinin B2 receptor−/− mice after injection of anti-collagen antibody. Arthritis was assessed visually and by caliper measurement of paw thickness daily for 10 days after injections. To determine the effect of CPB on C3a-mediated chemotaxis in vivo, we injected intact C5a or CPB cleaved C5a into mouse peritoneum and assessed neutrophil migration. To study the role of CPB in human RA, RA, CPB and C5a levels were measured in synovial fluids derived from RA and osteoarthritis (OA) patients using commercial ELISA kits. To investigate the role of CPB genetic variants in RA, we genotyped two nonsynonymous CPB2 SNPs (rs1926447 and rs3742264) and evaluated the association with modified Sharp score (MSS) in the SONORA cohort (n=109, 70% female, 100% Caucasian) and the CLEAR Registry (n=118, 100 % female, 100% African-American).

Results: We found that anti-collagen antibody-induced arthritis was much more severe in CPB+/− mice than in wild-type mice. In contrast, C5−/− mice were protected from arthritis, while bradykinin B2 receptor−/− mice and osteopontin−/− mice developed arthritis equivalent in severity to that in wild-type mice. In vivo studies showed that C5a chemotactic effect is decreased with CPB incubation (peritoneal neutrophil of intact C5a vs CPB cleaved C5a; 15.66% vs 5.14%, p<0.01). We found that levels of CPB and C5a are increased in RA synovial fluid compared to OA synovial fluid (CPB 644.2 vs 374.1%, p<0.0001; total C5a 24.0 vs 9.6 ng/ml, p <0.05). CPB level is correlated with C5a level (p<0.01, r=0.41). CPB SNP rs1926447 is associated with radiologic progression of RA: (MSS for CT/TT vs CC; SONORA (year 2), 4.5 vs 8.4, p=0.03; CLEAR 1 (year 3), 1.8 vs 5.9 p<0.01).

Conclusions: These results suggest that thrombin-activatable CPB plays a critical role in down-regulating inflammatory responses in anti-collagen antibody-induced arthritis, and that CPB exerts its anti-inflammatory effects by cleaving, and thereby inactivating, C5a. We also demonstrate that CPB is elevated in RA synovial fluid, and is associated with synovial C5a level. Our SNP analysis results suggest that CPB variant 1064T (minor allele of rs1926447) that has been reported to produce a CPB protein with a two-fold longer half-life, results in less radiographic damage in Caucasians and African-Americans with RA, further suggesting that CPB plays a central role in down-regulating inflammatory responses in RA.

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The Liver X Receptor (LXR) Regulates Arthritis Fibroblast-Like Synoviocyte NFκB Activity, IL-6 Production and Cell Invasion. Carl Petrus Linge, Teresina Laragione3 and Percio S. Gulto1. 1Feinstein Institute Med Sch, Manhasset, NY, 2The Feinstein Institute for Medical Research, Manhasset, NY, 3The Feinstein Institute for Medical Research

Background: Fibroblast-like synoviocytes (FLS) produce several pro-inflammatory cytokines, chemokines, and proteases that mediate the development of synovial hyperplasia, inflammatory infiltration, and pannus invasions and destruction of cartilage and bone in rheumatoid arthritis (RA). We have recently determined that the expression and transcriptional activity of the anti-inflammatory nuclear receptor LXR is down-regulated in the synovial tissues of arthritis-susceptible and erosive DA rats, compared with resistant strains. Furthermore, two recent studies demonstrated that LXR agonists ameliorate rodent models of RA and reduce cytokine levels and joint erosions. Those observations led us to hypothesize that a state of deficient LXRs activity in the arthritic FLS could favor the increased production of pro-inflammatory cytokines such as IL-6 as well as the increased FLS invasive and destructive properties. We tested this hypothesis using an LXR agonist to modulate these cellular functions in FLS from DA rats and RA.

Methods: FLS were isolated from synovial tissues obtained from DA rats 21 days after the induction of pristane-induced arthritis (PIA), and from RA patients. Cells were passaged at least three times before use. The expression of LXR agonist T0901317 (10 μM) was determined in a) IL-1β-induced (100 ng/ml) IL-6 production (ELISA) using FLS culture supernatants; b) IL-1β-induced NFκB activation using DA FLS transfected with a NFκB luciferase reporter construct; c) FLS invasion using a well-established in vitro model through Matrigel-coated chambers; d) actin cytoskeleton distribution (phalloidin staining), lamellipodia formation and phospho-FAK expression and localization.

Results: T0901317 significantly increased LXR activity as evidenced by a 42-fold up-regulation of SCF1 expression, a known LXR target gene. T0901317 reduced the IL-1β-induced IL-6 production in DA FLS (n=7) by 61% (P=0.001, Mann-Whitney test). The reduction in IL-6 production also correlated with a significant reduction in the NFκB reporter activity. T0901317 nearly completely blocked DA FLS invasion, reducing it by 99% (P<0.001, n=8). A nearly identical major effect was observed in RA FLS where a 96% inhibition of invasion was determined (P=0.001, n=7), compared with control vehicle. The reduced invasion caused by T0901317 was associated with reduced levels of active MMP-2, reduced actin distribution and reduced polarized formation of lamellipodia (including reduced levels of phospho-FAK) both in DA and RA FLS.

Conclusion: This is the first time that LXR is implicated in the regulation of FLS production of IL-6 and FLS invasion. Our data show that this inhibitory effect is mediated, at least in part by NFκB, and suggest that LXR agonists have the potential to become useful therapies aimed at reducing both inflammation and FLS-mediated invasion and destruction in RA.

Disclosure: C. P. Linge; None; T. Laragione; None; P. S. Gulto; None.
Cadherin-11 Engagement Increases Matrix Metalloproteinase Production by Rheumatoid Arthritis Fibroblast-Like Synoviocytes. Erika H. Noss, Sook-Kyung Chang and Michael B. Brenner. Brigham and Women’s Hospital, Boston, MA

Background: Cadherin-11 is expressed on fibroblast-like synoviocytes (FLS) and mediates homophilic cell-to-cell adhesion by binding of cadherin-11 on one cell to cadherin-11 on an adjacent cell. Absence of cadherin-11 in mouse rheumatoid arthritis (RA) models led to a striking reduction of cartilage erosion independent of bone erosion, suggesting this molecule modulates the ability of FLS to degrade cartilage. Matrix metalloproteinases (MMPs) are a family of enzymes produced by FLS important in cartilage erosion. The aim of this study was to determine if FLS MMP production is regulated by cadherin-11, providing a possible mechanism to explain diminished cartilage erosion in the absence of cadherin-11 in RA models.

Methods: To test whether cadherin-11 engagement increases MMP production, human RA FLS were incubated with chimeric constructs containing human IgG1 Fc linked to the cadherin-11 extracellular domain (cad-11-Fc) in the presence or absence of tumor necrosis factor-a (TNF-a). MMP-1 and MMP-3 production were assessed by enzyme-linked immunosorbent assay (ELISA) and quantitative reverse transcription-polymerase chain reaction (qRT-PCR). Both autogenus to cad-11-Fc binding affinity and lentiviral short-hairpin RNA to silence cadherin-11 were used to test the specificity of cad-11-Fc stimulation for surface cadherin-11. Immunoprecipitation with phospho-specific antibodies was used to determine signaling protein activation, and specific chemical inhibitors of these proteins were used to examine their role in cad-11-Fc MMP activation.

Results: Human cad-11-Fc upregulated protein production of MMP-1 and MMP-3 in RA FLS culture supernatants both alone and in synergy with TNF-a. MMP upregulation by cad-11-Fc was specific for engagement of cell cadherin-11, as a cad-11-Fc mutant construct lacking two tryptophan residues impeded binding to cadherin bountly less MMP production. Also, cadherin-11 silencing by lentiviral shRNA infection almost completely reduced the ability of cad-11-Fc to stimulate MMP expression compared to control-infected cells. Cad-11-Fc stimulation increased MMP transcription as measured by qRT-PCR. Since mitogen-activated protein kinase (MAPK) signaling pathways are important for induction of MMP synthesis, the ability of cad-11-Fc to activate these pathways was tested. Phosphorylation of the MAPKs Jun N-terminal kinase (JNK) and extracellular signal-related kinase (ERK) was induced upon cad-11-Fc stimulation of RA FLS. Inhibitors of JNK and ERK phosphorylation partially blocked RA FLS MMP-3 expression by cad-11-Fc, providing evidence that these pathways help transduce the signal to upregulate MMP synthesis after surface cadherin-11 engagement.

Conclusions: Cadherin-11 binding by cad-11-Fc induced production of MMP-1 and MMP-3 by increasing MMP synthesis in RA FLS. Since MMPs are important mediators of cartilage degradation, these results point to a novel pathway by which cadherin-11 may influence joint destruction in RA.


Rheumatoid Synovial Fibroblasts Support Aid Expression and IG Class-Switching in B Cells Via a BAFF-Dependent TLR3-Stimulated Pathway. Michele Bombardieri1, Yvonne N. W. Kam1, Fabia Brentano2, Ken Choi3, Diego Kyburz4, Steffen Gay5, Iain B. McInnes2 and Costantino Pitzalis1.

Background and Aims: Rheumatoid arthritis (RA) is characterized by the presence of synovial niches of autoreactive B cells which express activation-induced cytokine deadenase (AID), the enzyme initiating Ig class-switching (CSR), and sustain in situ autoantibody production. Importantly, B cell niches remain functional in the RA-SCID model in the absence of recirculating cells, suggesting that autocrine mechanisms support ongoing B cell activation in the RA synovium. Here we investigated whether RA synovial fibroblasts (RASF), which are known to contribute to RA synovitis, are capable of directly regulating B cell activation, AID expression and CSR. In addition, we dissected the molecular basis of stromal cell/B cell interactions with particular emphasis on the role of Toll-like receptors (TLRs) signaling and B cell survival/proliferating factors.

Methods: mRNA and protein expression of B cell survival factors BAFF and APRIL in RASF and OASF stimulated with TLR2, TLR3 and TLR4 ligands was assessed by Taqman PCR (QT-PCR) and ELISA, respectively. Un-switched IgD+ B cells were isolated from human tonsils using magnetic cell sorting. Isolated B cells were co-cultured via transwell or cell-cell contact with RASF/OASF for 24h and 72h in the presence or absence of TLR ligands and with or without blocking of soluble BAFF/APRIL. AID mRNA expression and IgM/A/G production were measured to assess functional activation of B cells. In addition, IgG1 and IgE-C4 circular transcripts (CT, molecular by-products of ongoing CSR from IgM to IgG and IgM to IgE, respectively) were assessed by rt-PCR.

Results: In vitro stimulation of TLR3, and to a significantly lesser extent TLR4, but not TLR2 on RASF led to strong induction of BAFF (~1,000-fold increase with TLR3) and APRIL mRNA expression. In response to TLR3, BAFF was time-dependently released in the supernatant of RASF (~600pg/ml) and, to a lesser extent, OASF. TLR3 stimulation of RASF in co-culture with B cells strongly enhanced AID expression, ongoing CSR to IgG, but not IgA, as shown by detection of IgC4 and release of IgG. In contrast, TLR3 stimulation alone had no direct effect on B cells. Conversely, blockade of soluble BAFF/APRIL inhibited TLR3-induced RASF-dependent production of AID mRNA, 1gC4 CT as well as the secretion of IgG.

Conclusions: Here we demonstrated that RASF are able to release high levels of B cell survival factors upon TLR3 stimulation at both mRNA and protein level. The release of these factors was functional, as demonstrated by the capacity of RASF to directly modulate AID expression, CSR and production of class-switched antibodies in co-cultured un-switched B cells. This effect was abrogated by blockade of soluble BAFF and APRIL. Overall, these data strongly support a fundamental role for TLR3-dependent release of BAFF and APRIL by RASF in sustaining functional B cell activation and antibody production in the RA synovium.

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1390 Characteristic Oral and Intestinal Microbiota in Rheumatoid Arthritis (RA): A Trigger for Autoimmunity? Jose U. Scher1, Carles Ubeda2, Michael H. Pillinger3, Walter Brezis4, Yvonne Buisch5, Pamela B. Rosenthal6, Sourya M. Reddy7, Jonathan Samuels8, Peter M. Izmirly9, Rennie N. G. Howard7, Gary Solomon8, Yusuf Yazici8, Mukundan Attur7, Michele Equinda10, Nicholas Socci11, Agnes Viale12, Eric Pamer13, Dan R. Littman13, Gerald Weissmann14 and Steven B. Abramson15. 1Lucille Castori Center for Microbes, Inflammation, and Cancer/MSKCC, 2Memorial Sloan-Kettering Cancer Center, 3New York University Hospital for Joint Disease, New York, NY, 4New York University Medical Center, New York, NY, 5NYU College of Dentistry, 6NYU Hospital for Joint Diseases, New York, NY, 7NYU School of Medicine, 8NYU School of Medicine, 9NYU School of Medicine, 10NYU School of Medicine, 11NYU School of Medicine.

Purpose: The etiology of RA remains unknown, but genetic and environmental factors have been implicated. An infectious trigger has been sought but conventional microbiologic techniques have been uninformative. The human intestine contains a dense, diverse and poorly characterized (≥500 species) bacterial population whose collective genome (microbiome) is ≥100 times larger than its human host. We (DRL) have recently shown in mice that gut-residing bacteria drive autoimmune arthritis via Th17 cell activation (Immunity 2010). Multiple lines of investigation also suggest a link between RA and oral microbes.

Methods: As part of an NIH ARRA grant, the NYU Microbiome Center for Rheumatology and Autoimmunity was established to study gut and oral microbiota in RA and related conditions. A cross-sectional and prospective proof-of-concept antibiotic intervention trial are ongoing. Fecal samples are collected, periodontal status assessed and oral samples obtained by subgingival biofilm collection. To date, oral/intestinal microbiomes have been analyzed in 8 RA patients, 3 psoriatic arthritis (PsA) patients and 9 healthy controls. Periodontal status was characterized in 30 RA, 4 PsA and 8 controls. DNA was purified and variable 16s rRNA gene regions amplified. PCR products were pyrosequenced (454 Life Sciences), and DNA sequences were analyzed in 8 RA patients, 3 psoriatic arthritis (PsA) patients and 9 healthy controls.
**Results:** Prevotellaceae family was significantly overrepresented in fecal microbiota from ACPA+ RA patients (range 13%–85%; mean=38%) vs ACPA- individuals (mean=4.3%); p=0.003. One ACPA+ healthy individual and 1 ACPA+ PsA patient shared similar microbiomes with ACPA+ RA. Subgingival microbiomes in patients with new-onset drug-naive RA exhibited overabundance of the Spirochetaceae/Prevotellaceae/Porphyromonaceae families (mean=53%) compared to chronic-active RA and healthy controls (mean=18.5%). Periodontal assessment revealed 78% of examined sites bled upon probing in RA patients (mean age 39; 73% female), significantly more than controls (38% PsA, 12% healthy; p<0.001 vs RA); 66% of RA patients also presented with moderate periodontitis compared to PsA (25%) and controls (12%).

**Conclusions:** This is the first study using high-throughput technologies to assess oral and intestinal microbiota in RA. Our data corroborate prior reports demonstrating an underappreciated high prevalence of periodontal disease at a young age in patients with RA. Moreover, our preliminary data suggest that ACPA generation may be associated with larger populations of Prevotellaceae in both oral and intestinal microbiomes. In response to such altered microbial flora, certain predisposed individuals may develop auto-inflammatory disease, through mechanisms that may include the generation of cyclic citrullinated peptides or Th17 cell activation in the intestinal mucosa. Thus, the oral and intestinal microbiota merit further investigation as potential triggers for autoimmunity and clinical RA.

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### 1391

**Toll-Like Receptor 2 Activation Induces Angiogenesis, ICAM-1 Expression and EC Invasion in Rheumatoid Arthritis.** Tajvir P. Saber1, Sinead NicUltaigh1, Jennifer McCormick2, Douglas J. Veale2, Mary Connolly2 and Ursula Fearon2. 1Dublin, Ireland, 2Dublin Academic Medical Centre, Dublin, Ireland.

**Background:** Angiogenesis is a critical early event in inflammatory arthritis, facilitating leukocyte migration into the synovium resulting in invasion and destruction of articular cartilage and bone. This study investigates the effect of TLR2 on angiogenesis, EC adhesion and invasion using microvascular endothelial cells and RA whole tissue synovial explants ex-vivo.

**Methods:** Microvascular endothelial cells (HDEC) and RA synovial explants ex vivo were cultured with the TLR2 ligand, Pam3CSK4 (1μg/ml). HDEC tube formation was assessed using Matrigel matrix assays. Angiopoietin 2 (Ang2) was measured by ELISA. ICAM-1 cell surface expression was assessed by flow cytometry. Cell migration was assessed by wound repair scratch assays. ECM invasion, MMP-2 and 9 expression were assessed using transwell invasion chambers and zymography.

**Results:** Pam3CSK4 significantly increased angiogenicnic tube formation (p<0.05). Pam3CSK4 significantly upregulated Ang2 production in HDEC (p<0.05) and RA synovial explants (p<0.05). Pam3CSK4 induced cell surface expression of ICAM-1, from basal level of 149 ± 54 (MFI) to 617 ± 103 (p<0.01). TLR-2 activation induced an 8.8 ± 2.8 fold increase in cell invasion compared to control (p<0.05). Pam3CSK4 also induced cell migration and induced MMP-2 and -9 from RA synovial explants. Neutralisation of TLR2 with a blocking monoclonal antibody (OPN 301, 1μg/ml) inhibited Pam3CSK4-induced wound repair and EC tube formation.

**Conclusion:** Pam3CSK4 activation of TLR2 promotes angiogenesis, cell adhesion and invasion, key mechanisms involved in the pathogenesis of RA.

**Disclosure:** T. P. Saber: Centocor Ortho Biotech Inc., 2; S. NicUltaigh: None; J. McCormick: None; D. J. Veale: Abbott Laboratories, 2, 5, 8; Centocor Ortho Biotech Inc., 5, 8, GlaxoSmithKline, 2, 5, 8, Mundipharma, 2, 8, Opsona, 2, Pfizer Inc, 2, 5, 8, Schering-Plough, 5, 8; M. Connolly: None; U. Fearon: None.

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**ACR Concurrent Abstract Sessions**

**Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Existing Non-Biologic DMARDs**

Tuesday, November 9, 2010, 2:30 PM–4:00 PM

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**1392**

**Radiologic Progression in Patients with Early RA and a Good Clinical Response to MTX Monotherapy: Predictors and Clinical Implications.** Hamed Rezaei1, Ronald Van Vollenhoven2, Kristina Forslind3, Kristina Albertsson1, Helena Wallin1, Pierre Geborek5, Sofia Ernestam1, Ingmar Petersson4 and Johan Bratt1. 1Helsingborgs Hospital, 2Karolinska University Hospital, Stockholm, Sweden, 3Karolinska University Hospital, 4Lund University Hospital, 5Spenshult Hospital.

**Background:** In patients with early RA, several randomized trials have demonstrated the superiority of methotrexate (MTX) + anti-TNF over MTX alone. However, these trials also showed that some patients did have excellent responses to MTX monotherapy. In the SWEFOT trial, all patients were given an initial 3–4 months trial period with MTX alone; patients achieving a low disease activity state with this treatment were not randomized in the controlled portion of the trial. We previously demonstrated that this was the case for aprx. 30% of the patients. In a separate report (Wallin et al, abstract submitted) we showed that these patients had an excellent clinical course during the first two years, but that some radiological progression did nonetheless occur. Here, we investigated specific details of and predictors for radiological progression in this cohort.

**Objectives:** To analyze in detail the radiological course in patients from the SWEFOT study who responded adequately to initial MTX monotherapy and who were not included in the randomized trial.

**Methods:** A total of 487 patients with early RA (symptom duration <1 year) were started on MTX at a rapidly escalating dosage up to at least 20 mg/week. After 3–4 months, the 147 patients who had a DAS28<3.2 were not randomized but continued on MTX and followed in “regular care”, including 3-monthly assessments. These patients were analyzed here. Van der Heijde modified Sharp scores (SvDH) were done by two experienced readers. Scores at different times were compared by Wilcoxon paired test. Complete x-ray data were available for 114 patients.

**Results:** At baseline, the mean±SEM total SvDH score (median, IQR) was 3.8±0.7 (1, 0–5). After 1 year, it had increased to 6.0±0.8 (4, 0–8; p<0.0001 vs. baseline) and after 2 years to 7.9±0.9 (4, 0–8; p<0.0001 vs both BL and 1 year). Highly significant progression was seen for both erosion score and joint space narrowing score. The increase in total score after 2 years was 3.9±0.7 (2, 0–6). At baseline, 48.1% of patients had no x-ray damage (total score=0); at 1 year 26.9%, and at 2 years 20.2%. An increase in total score ≥ 10, was seen in 15% of patients. RF positive patients had a trend towards greater progression than RF-negative ones: 4.78±0.91 (2, 0–7) vs. 1.90±0.78 (0, 0–5; p=0.067). For ACPA positive vs. negative, a smaller, non-significant difference was seen. Double-positive patients had the highest progression: 5.27±1.21 (2, 0–9). Single-positive RF had significantly higher progression than single-positive ACPA. Men had numerically more progression than women (5.00±1.05 (2, 0–9) vs 3.88±0.88 (1, 0–3; p=0.119).

**Conclusions:** Patients who responded to an initial 3–4 months trial of MTX monotherapy with a DAS28<3.2 showed statistically significant (but on average numerically modest) radiological progression during the first 2 years of disease. Progression was associated with RF- and double-positive. About half of all patients had no damage at baseline but the majority of these did develop damage over 2 years. An initial good clinical response to MTX does not preclude a less favorable radiological course.

**Disclosure:** H. Rezaei: None; R. Van Vollenhoven: Schering-Plough, 2, K. Forslind: None; K. Albertsson: None; H. Wallin: None; P. Geborek: None; S. Ernestam: None; I. Petersson: None; J. Bratt: None.
In Early RA, Patients with a Good Initial Response to MTX Mono-therapy Have Excellent Clinical Outcomes over Two Years of Therapy, but Radiological Progression Is Not Completely Prevented. Helena Wal- lin1, Ronald Van Vollenhoven2, Kristina Albertsson, Kristina Forslind, Sofia Ernestam, Ingemar F. Peterson3, Pierre Geborek, Hamed Rezaei, Johan Bratt1 and The SWEFOT Study Group, 1Karolinska Univ Hosp Huddinge, Stockholm, Sweden, 2Karolinska University Hospital, Stockholm, Sweden, 3Lund University Hosp, Lund, Sweden, 4The Karolinska Institute, Stockholm, Sweden

Background: In the SWEFOT trial, all patients were initially given MTX monotherapy for 3–4 months; patients achieving a DAS28≤3.2 were not randomized in the controlled portion of the trial. We previously demonstrated that this was the case for 30% of the patients, most of whom maintained remission during the first year. Here, we investigated the clinical and radiological results in these patients over two years of follow-up.

Objectives: To analyze the clinical and radiological course in patients from the SWEFOT study who responded adequately to initial MTX monotherapy and were not included in the randomized trial.

Methods: A total of 487 patients with early RA (symptom duration <1 year) were started on MTX at a rapidly escalating dosage up to at least 20 mg/week. After 3–4 months, the 147 patients who had a DAS28≤3.2 were not randomized but continued on MTX and were followed in "regular care", including 3-monthly assessments. These patients were analyzed here. Complete data at 24 months were available for 65% of patients.

Results: The majority of patients continued on MTX monotherapy. In 15 patients MTX was replaced by or complemented with another DMARD or a biologic. DAS28 values in all patients are shown in the figure, and demonstrate lower values throughout. At the 6, 12, 18 and 24 months time-points, 61.1%, 61.0%, 64.2%, and 72.7% of patients, respectively, were in DAS28 remission, and 82.1 – 87.6% had a low disease activity state.

The mean progress in total Sharp-vdHeijde score at 24 months was 3.90 (0.68). For the subset of patients who had been in sustained remission at each time point from 3 to 24 months (n=18) the progression was 4.06 (1.85). Progression in patients on MTX monotherapy throughout follow-up was 3.97 (0.85).

Conclusion: Patients who respond to an initial 3–4 month trial of MTX monotherapy with a DAS28≤3.2 continue to have very good clinical responses for two years, and additional treatment is needed infrequently. However, radiographic progression does occur and is seen even in those patients who have sustained remission and/or stay on MTX monotherapy. An initial good response to MTX appears to portend a good clinical prognosis but close monitoring of radiological disease is warranted.

Disclosure: H. Wallin: None; R. Van Vollenhoven: Merck Pharmaceuticals, 2; K. Albertsson: None; K. Forslind: None; S. Ernestam: None; I. F. Peterson: None; P. Geborek: None; H. Rezaei: None; J. Bratt: None; The SWEFOT Study Group: None.

1394

Genetic Polymorphisms in Key Methotrexate (MTX) Pathway Genes Associated with Response to MTX Treatment in Rheumatoid Arthritis. Sally-Anne Owen1, Stephen Eyre2, Paul Martin3, Samantha Hider4, Ian N. Bruce5, Anne Barton6 and Wendy Thomson7. 1ARC National Primary Care Centre, Keele University, Staffordshire, United Kingdom, 2Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom.

Background: Methotrexate (MTX) is the cornerstone of treatment for rheumatoid arthritis (RA). However, up to a third of individuals will fail to respond to MTX treatment or suffer adverse events (AE). The main determinates of MTX response in RA remain unclear although evidence suggests that part of this variability is genetic. Genes within the MTX metabolic pathway represent good candidates as predictors of response. We investigated SNPs spanning 11 MTX pathway genes on the efficacy and occurrence of AE in MTX treated patients with RA.

Methods: Subjects included 309 RA patients with a defined response to MTX. Patients were included if they were (i) good responders (n=147) (with an ESR <20 and/or normal CRP and on a stable dose of MTX for at least 6 months) (ii) inefficacy failures (n=101) (physician statement and failure to reduce ESR/CRP by 20%) or (iii) AE failures (n=61) (verified by medical record review). Tagging SNPs were selected for genes: AMDP1, ATIC, DHFR, FPGS, GGH, ITPA, MTHFDI, MTHFR, SHMT1, SLC19A1 (RFC) and TYS using an r2 cutoff of 0.8 and MAF ≥ 0.05 within 10kb up and down stream of each gene. Genotyping was performed using the Sequenom iPLEX® MassARRAY platform. Three different analyses were conducted: 1) responders vs inefficacy failures 2) responders vs AE failures and 3) responders vs inefficacy and AE failures combined. Genotype frequencies were compared between the groups using the trend test implemented in PLINK and allelic odds ratios with 95% confidence intervals (CI) calculated in STATA 9.2.

Results: Of the 150 SNPs tested, 9 were found to be significantly associated (p-trend<0.01) with MTX response and 2 with MTX related AE. Interestingly 3 of these (rs12995526, rs7563206 and rs16858384) were found in the 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC) gene which encodes an enzyme that is important in the de novo purine synthesis pathway. Individuals carrying these SNPs had an increased risk of poor response to MTX (OR 1.48, 95%CI (1.01–2.17), OR 1.47, 95%CI (1.01–2.17) and OR 1.47 95% CI (1.01–2.76) respectively). Other associations were seen with 6 SNPs in the RFC gene (rs11702425, rs28338956, rs7499, rs2274808, rs9977268, rs7294445) all conferring an increased risk of poor response to MTX and two SNPs in the DHFR gene (rs12517451, rs10072026) were associated with AE. In addition there were a further 2 SNPs in the FPGS gene associated with AE under a recessive model (rs1054774, rs4451422) and 1 additional SNP in the ATIC gene approaching statistical significance (rs4673990) (p-trend<0.1) warranting further investigation.

Conclusion: Genetic variations in a number of key MTX pathway genes have been found to be significantly associated with MTX response and AE in RA patients. Further studies will be required to validate these findings. If confirmed these results could contribute towards a better understanding of and ability to predict MTX response in RA.

Disclosure: S.-A. Owen: Pfizer Inc, 3; S. Eyre: None; P. Martin: None; S. Hider: None; I. N. Bruce: None; A. Barton: None; W. Thomson: None.

1395

Observational Study To Evaluate the Relationship of Methotrexate to Interstitial Lung Disease in Rheumatoid Arthritis. Liron Caplan1, Anne E. Hines1,2, Jay R. McDonald3, Angelique L. Zeringue1, Alyse Mann4, Paul H. Sufta5, Kevin G. Osgood2, Ted R. Mikuls14, Jasvinder Singh3, Itziar Sufka13, Kevin G. Osgood 2, Ted R. Mikuls 14, Jasvinder Singh 3, Itziar Sufka 13, H. Walilin1, Ronald Van Vollenhoven2, Kristina Albertsson, Kristina Forslind, Ian N. Bruce1, Stephen Eyre2, Paul Martin3, Samantha Hider4, Ian N. Bruce5, Anne Barton6 and Wendy Thomson7. 1ARC National Primary Care Centre, Keele University, Staffordshire, United Kingdom, 2Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom.

Purpose: The relationship of methotrexate (MTX) to interstitial lung disease (ILD) remains controversial, with some studies supporting an association, while others dispute this association. We sought to identify risk factors for incident ILD in a population of veterans with rheumatoid arthritis (RA), with special attention on the disease modifying anti-rheumatic drug (DMARD) methotrexate (MTX).

Methods: We used a retrospective case-control study design where controls consist of subjects with RA and cases consist of subjects with both RA and ILD. We identified subjects based on ICD-9-CM diagnostic codes and prior DMARD or glucocorticoid treatment (n=442). Validation of ICD-9-CM codes for ILD relied upon medical records, as well as radiographic and pulmonary function results. All demographics, putative risk factors, and pharmaceutical data were abstracted using a detailed review of the medical record and defined abstraction algorithms. We performed unconditional multivariate logistic regression, controlling for multiple RA and ILD risk factors. Methotrexate was forced into the final model as the variable of...
interest. All analyses were performed using Stata software version 10.2. Confidence intervals were established at 95%.

**Results:** In the multivariate regression adjusting for all covariates, patients with ILD were no more likely to have been exposed to MTX than patients without MTX exposure. Conversely, rheumatoid factor, C reactive protein and history of emphysema were all associated with presence of ILD (see table).

**Conclusions:** Though markers of RA disease severity and activity are associated with ILD in patients with RA, MTX exposure does not demonstrate a relationship in our observational study. There is a strong association between prior emphysema and subsequent ILD in RA patients.

### Table 1. Factors associated with the odds of interstitial lung disease in rheumatoid arthritis patients

<table>
<thead>
<tr>
<th>Conceptual Block/ Domain</th>
<th>Multivariate Model</th>
<th>Final Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>Lower CI</td>
</tr>
<tr>
<td>Gender, male</td>
<td>0.96</td>
<td>0.97</td>
</tr>
<tr>
<td>Rheumatoid arthritis- associated Variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Factor level*</td>
<td>1.03</td>
<td>1.00</td>
</tr>
<tr>
<td>C Reactive Protein, mg/dL**</td>
<td>1.21</td>
<td>1.00</td>
</tr>
<tr>
<td>ILD-associated Variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of Emphysema</td>
<td>17.14</td>
<td>6.09</td>
</tr>
<tr>
<td>History of Previous Pneumonia</td>
<td>0.50</td>
<td>0.45</td>
</tr>
<tr>
<td>History of Recurrent Pneumonia</td>
<td>15.78</td>
<td>1.44</td>
</tr>
<tr>
<td>History of COPD</td>
<td>3.41</td>
<td>1.43</td>
</tr>
<tr>
<td>History of Bronchitis</td>
<td>0.56</td>
<td>0.22</td>
</tr>
<tr>
<td>DMARD exposure</td>
<td>0.48</td>
<td>0.36</td>
</tr>
</tbody>
</table>

**Ch² (df) = 23.95; Pseudo R² = 0.24 for final model**

**Disclosure:** L. Caplan: None; A. E. Hines: None; J. R. McDonald: None; A. L. Zeringue: None; A. Mann: None; P. H. Sufka: None; K. G. Osgood: None; T. R. Mikuls: None; J. Singh: Abbott Immunology Pharmaceuticals, 8, Allergan, 2, Amgen Inc., 2, Novartis Pharmaceuticals Corporation, 5, Saviem Pharmaceuticals, 2, Takeda Pharmaceuticals North America, 2, URL, Pharma, 5, Wyeth Pharmaceuticals, 2; I. Quinanzos: None; J. Mansoori: None; C. Pappa: None; L. M. Haverhals: None; A. R. Bankhuizen: None; D. Phelps: None; R. S. Hooker: None; H. Xian: None; F. Cunningham: None; S. Eisen: None.

### 1396


**Background:** Due to high costs, limited data, and the poor disease-modifying effect of MTX, the role of patients treated with MTX monotherapy is still controversial, and several studies have been performed to evaluate the role of combined treatment with MTX and prednisone in patients with recent onset RA. In the IMPROVED study, we investigated the role of low-dose oral prednisone as a co-medication for patients with very early arthritis.

**Methods:** This is a randomized, controlled, double-blind trial in which patients who fulfilled ACR 1987 criteria and fulfilled all clinical and demographic baseline criteria were randomized to receive MTX with prednisone or MTX monotherapy. Patients received MTX at a dose of 10 mg/week and prednisone at 60 mg/day tapered to 7.5 mg/day in 7 weeks, aimed at achieving DAS < 1.6, which will be followed by tapering to drug free if remission persists, or randomization to multi-DMARD or MTX alone. The primary endpoint was remission after 4 months, defined as DAS28 < 2.6 identified patients in clinical remission. The US assessment of patients included 12 joints (MCPs and MRs). A single operator unaware of the clinical findings carried out all scans.

**Results:** After 4 months of treatment with MTX and a tapered high dose of prednisone in patients with recent onset RA or UA, clinical remission (DAS < 1.6) was achieved in 63% of all patients, with similar outcomes for mean DAS and HAQ. Only in RA patients, ACPA positivity is an independent predictor for achieving remission. This suggests that ACPA negative UA patients, who did not benefit from treatment with MTX monotherapy in the PROMPT study, also benefit less from prednisone. ACPA negative UA may be a different disease that requires different therapy than ACPA positive UA.

### Table 1. Baseline characteristics, and clinical outcomes after 4 months of treatment of patients with UA or recent onset RA.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>UA N = 161</th>
<th>RA N = 261</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean, SD)</td>
<td>6.5 (13.3)</td>
<td>53.5 (14.2)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>% Female</td>
<td>64.6</td>
<td>66.3</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Symptom duration, months (median, IQR)</td>
<td>4.0 (2.0–7.0)</td>
<td>4.0 (2.0–7.0)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>% RF positive</td>
<td>33.4</td>
<td>61.1</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>% ACPA positive</td>
<td>48.4</td>
<td>59.7</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>ESR mm/hr (median, IQR)</td>
<td>17.0 (8.0–30.0)</td>
<td>29.0 (13.0–42.5)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CRP mg/l (median, IQR)</td>
<td>7.0 (3.0–19.0)</td>
<td>12.5 (6.0–34.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>DAS (mean, SD)</td>
<td>2.74 (0.74)</td>
<td>3.44 (0.91)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HAQ (mean, SD)</td>
<td>0.96 (0.62)</td>
<td>1.24 (0.64)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Follow up (4 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS (mean, SD)</td>
<td>1.43 (0.90)</td>
<td>1.54 (0.88)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>HAQ (mean, SD)</td>
<td>0.40 (0.49)</td>
<td>0.43 (0.52)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Improvement DAS</td>
<td>1.32 (0.95)</td>
<td>1.90 (1.05)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Improvement HAQ</td>
<td>0.57 (0.65)</td>
<td>0.81 (0.65)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>% Remission</td>
<td>66.5</td>
<td>58.6</td>
<td>0.12</td>
<td></td>
</tr>
</tbody>
</table>

**Disclosure:** K. V. C. de Boer: Abbott Laboratories, 2; K. Visser: None; H. K. Ronday: None; A. A. Schouffoer: None; J. H. L. M. Groenendaal: None; A. J. Peeters: None; I. Speyer: None; G. Colleé: None; P. B. J. Sonnaville: None; B. A. M. Grillot: None; T. W. J. Huizinga: None; C. F. Allaart: None.

### 1397

**The Role of Low-Dose Oral Prednisone Treatment in Early Rheumatoid Arthritis: Effects on Clinical and Ultrasonographic Remission and Functional Outcome.** Gafarilla Sakellariou1, Monica Todeorti2, Carlo A. Sciri2, Serena Bugatti2, Carlomaurizio Montecucco2 and Roberto Caporali2.

**Background:** Glucocorticoids are widely used in treating patients with rheumatoid arthritis (RA), providing rapid clinical improvement, reduction of radiographic progression and higher rates of clinical remission. Nevertheless, there is evidence of persistent subclinical synovitis even in clinical remission, and ultrasonography (US) is considered a sensitive tool to detect it. In this study we investigated the effect of low-dose oral prednisone co-medication on the occurrence of clinical and US remission, and the impact of these statuses on the development of future disability in a cohort of patients with early RA.

**Methods:** 210 patients with early RA (symptom duration < 1 year) were assigned to receive (P) or not (n-P) low-dose oral prednisone in association with a DAS-driven DMARD therapeutic protocol. Patients started with a dosage of 12.5 mg/day of prednisone, tapered to 6.25 mg/day after two weeks. Disease Activity Score 28 (DAS28) was assessed at the beginning of the study and after 12 months. A DAS28 < 2.6 identified patients in clinical remission. The US assessment of patients included 12 joints (MCPs and MRs). A single operator unaware of the clinical findings carried out all scans.
with a GE Logiq 9 scanner, using a multi-frequency linear array transducer (8–15 MHz), under standardized settings. Grey-scale (GS) and power Doppler (PD) synovitis were subjectively scored (0 to 3) for each joint. US remission was defined as absence of intra-articular PD signal (PD grade 0). Health Assessment Questionnaire (HAQ) was completed at the beginning of the study, at 12 and 24 months; disability (mild) was defined as a value of HAQ>0.5. Patients with complete data both on clinical and US variables were included in the analyses.

Results: Out of 210 patients, 105 were on prednisone plus DMARDs (P) and 105 on DMARDs alone (no-P). Age, disease duration, DAS28, HAQ, ESR, CRP, US findings did not differ between P and no-P at baseline. At 12 months, 44% of P patients and only 28% of no-P patients were in DAS28 remission (p = 0.018). US remission occurred in 71.2% of P patients, and in only 55.4% of no-P patients (p = 0.041). At 24 months, the odds ratio of progression to disability in patients who were in DAS 28 remission, compared to those with active disease, was 0.18 (95% confidence interval, CI, 0.063–0.55, p = 0.001). In this subgroup, patients who were also in PD remission carried the lowest risk of development of disability (OR 0.16, 95% CI 0.01–0.62, p = 0.005).

Conclusions: Low-dose oral prednisone co-medication gave an advantage over DMARD monotherapy in terms of higher rates of clinical and US remission. Patients in clinical and US remission showed the lowest rate of progression to disability at two years. These findings suggest a more complete suppression of joint inflammation in patients with early RA receiving glucocorticoids, resulting in a positive influence on functional outcome.


### ACR Concurrent Abstract Sessions

**Systemic Lupus Erythematosus - Clinical Aspects and Treatment:**

**Renal**

Tuesday, November 9, 2010, 2:30 PM–4:00 PM

#### 1398

**Repeat Kidney Biopsies Fail To Detect Differences between Azathioprine and Mycophenolate Mofetil Maintenance Therapy for Lupus Nephritis:**

**Data from the MAINTAIN Nephritis Trial.** Maria Stoeno1, Selda Aydin1, Carlos Vasconcelos1, Maria Tektonidou1, Isabelle Ravelingien1, Véronique le Guern2, Geneviève Depresseux1, Ricard Cervera3, Jean-Pierre Cosyns1 and Frédéric A. Houssiau1, 1Cliniques Universitaires Saint-Luc, Bruxelles, Belgium, 2Hôpital Cochin, Paris, France, 3Hospital Clinic, Barcelona, Spain, 4Hospital Santo Antonio, Porto, Portugal, 5National University of Athens, Athens, Greece, 6O.L. Vrouwenziekenhuis, Aalst, Belgium

**Introduction:** In the MAINTAIN Nephritis Trial, an investigator led randomized study, azathioprine (AZA) and mycophenolate mofetil (MMF) were compared as maintenance immunosuppressive treatment of proliferative lupus nephritis (LN) after a short course of low-dose (6 × 500 mg q2w; Euro-Lupus) intravenous cyclophosphamide. Although more renal flares were observed in AZA (25%) compared to MMF patients (19%), time to renal flare by Kaplan-Meier analysis did not statistically differ. No protocol repeat kidney biopsies were available in 26 patients. Here we compare the pathological findings between the two groups.

**Methods:** 105 lupus patients with biopsy-proven proliferative nephritides were included in the MAINTAIN Nephritis Trial. Per protocol repeat renal biopsies were performed between month 18 and 30 in 26 patients (all females; 15 AZA and 11 MMF). All 26 patients had been treated exactly according to the protocol, i. e. had stayed on the same immunosuppressant and had tapered the steroids as requested. Biopsies were classified according to the ISN/RPS classification. The activity index (AI, max 42) and the chronicity index (CI, max 6) were DMARDs alone (no-P). Age, disease duration, DAS28, HAQ, ESR, CRP, US findings did not differ between P and no-P at baseline. At 12 months, 44% of P patients, and only 28% of no-P patients were in DAS28 remission (p = 0.018). US remission occurred in 71.2% of P patients, and in only 55.4% of no-P patients (p = 0.041). At 24 months, the odds ratio of progression to disability in patients who were in DAS 28 remission, compared to those with active disease, was 0.18 (95% confidence interval, CI, 0.063–0.55, p = 0.001). In this subgroup, patients who were also in PD remission carried the lowest risk of development of disability (OR 0.16, 95% CI 0.01–0.62, p = 0.005).

**Conclusions:** Low-dose oral prednisone co-medication gave an advantage over DMARD monotherapy in terms of higher rates of clinical and US remission. Patients in clinical and US remission showed the lowest rate of progression to disability at two years. These findings suggest a more complete suppression of joint inflammation in patients with early RA receiving glucocorticoids, resulting in a positive influence on functional outcome.

**Disclosure:** G. Sakellariou: None. M. Todeti: None. C. A. Scirià: None. S. Bugatti: None. C. Montecucco: None. R. Caporali: None.

**Results:** Baseline and follow-up renal parameters of AZA and MMF patients did not differ. Time (SD) to repeat renal biopsy was 24.7 (1.7) and 25.1 (2.1) months in AZA and MMF patients, respectively. In both groups, the activity index dramatically and statistically decreased at follow up compared to baseline, while the chronicity index slightly but statistically increased. No between groups differences could be detected. In a second analysis, we added 4 patients for whom a repeat renal biopsy was also available, within the same time frame, but who had been switched to another immunosuppressant due to a renal flare which had occurred before the second biopsy. Baseline and follow up AI and CI on these 30 (26+4) paired renal biopsies were exactly comparable to the data obtained on the 26 patients.

**Conclusion:** No differences were observed on repeat kidney biopsies between patients treated with AZA or MMF.


#### 1399

**C4d on Circulating Cells and Renal Tissues in Lupus Nephritis as Novel Biomarkers.** Kelly V. Liang4, Ibrahim Batai2, Sheldon Bastacky4, Lawrence Kiss, Theresa McHale, Nicole Wilson, Barbara Paul, Apinya Lerttranatuk, Joseph M. Ahearn1, Susan Manzi2 and Amy H. Kao2, 1Wexford, PA, 2Pittsburgh, PA, 3Allegheny Singer Research Institute, Pittsburgh, PA, 4University of Pittsburgh, Pittsburgh, PA, 5West Penn Allegheny Health System, Pittsburgh, PA

**Background:** Immune complex deposition and complement activation via the classical pathway play a key role in the pathogenesis of lupus nephritis (LN), a severe manifestation of systemic lupus erythematosus (SLE). Traditional serologic tests such as anti-doubl-stranded DNA titers and serum complement levels (C3 and C4) are inconsistent predictors of renal pathology in LN. The complement activation product C4d bound to circulating erythrocytes (E-C4d), reticulocytes (R-C4d) and platelets (P-C4d) has been shown to reflect disease activity in SLE but has not been systematically studied in LN. The aims of this study were to: 1) compare C4d deposition on circulating cells and in renal tissues between LN subjects and two control groups (non-SLE renal disease and SLE subjects without LN), and 2) determine the association of C4d deposition with LN disease activity.

**Methods:** We prospectively evaluated C4d on circulating cells in 15 LN subjects and two control groups: 13 non-SLE renal subjects (control A) and 239 SLE subjects without LN (control B). Circulating cell-bound C4d levels were measured by flow cytometry. C4d deposition in different anatomic renal compartments was semiquantitatively assessed in LN and control A using immunoperoxidase staining performed on formalin-fixed, paraffin-embedded renal tissue.

**Results:** LN renal tissues had higher glomerular C4d scores than those of control A (p = 0.003). Glomerular C4d stain was detected in the majority (12/13, 92%) of LN samples and was associated with more frequent granular glomerular immunofluorescence staining and electron-dense, immune complex deposits (p < 0.001). C4d score in other anatomic compartments showed no differences. Compared to controls A and B, LN subjects had higher levels of E-C4d (p = 0.002 and p = 0.005) and R-C4d (p = 0.002 and p = 0.008), respectively. LN subjects were also more likely to have positive P-C4d compared to control A (p = 0.016) but not control B. In LN samples, E-C4d, but neither serum complement (C3, C4) nor renal tissue C4d, correlated with NIH activity index (r = 0.55, p = 0.04).

**Conclusions:** Glomerular C4d staining was associated with immune complex deposits in LN biopsies. LN subjects also had higher levels of E-C4d and R-C4d when compared to non-SLE renal subjects and non-LN SLE subjects. E-C4d levels correlated significantly with the NIH activity index (r = 0.55, p = 0.04). Larger prospective studies are needed to validate our findings and further investigate the role of C4d on circulating cells and renal biopsy tissues as biomarkers for LN.


#### 1400

**Are the Current Thresholds for SLE Proteinuric Flare Set Too High? Determining the 99% Confidence Intervals for Spontaneous Variation in Urine Protein/Creatinine Ratio in SLE GN Patients Who Are Clinically Stable (Not Flaring).** Stacy P. Ardoin1, Dan J. Birmingham2, Brad H. Rovin3, P. Hebert4, C.-Y. Yu1 and Lee A. Hebert1, 1Ohio State University, Columbus, OH, 2Ohio State University, 4University of Washington
Statement of Purpose: Proteinuria is the most common manifestation of a moderate or severe flare of SLE glomerulonephritis (GN). However, there is no general consensus on the threshold for proteinuric flare and the proposed criteria are based largely on expert opinion. The criteria that have been proposed can be categorized as having low, medium or high thresholds, depending upon the minimum increase in proteinuria deemed necessary to constitute a proteinuric flare. This study provides an evidence-based approach to validate the magnitude of proteinuria increase that should constitute a proteinuric flare.

Methods: This work involved analysis of data collected as part of the Ohio SLE Study (OSS), a prospective observational study of 106 SLE patients with recurrently active disease, 72 of whom had moderate or severe renal disease. Patients were managed by pre-specified protocols. Median follow up was > 46 months with over 2400 visits. >90% of visits occurred bimonthly, within pre-specified windows of ≥ 1 week. The renal OSS patients provided 24 hour urine collections at 84% of OSS visits and random spot urine collections at remaining visits. At each visit it was determined, using pre-specified criteria (JASN 16: 467–473, 2005), whether a renal or non-renal SLE flare had occurred at the previous OSS visit.

To assess spontaneous variation in protein/creatinine (P/C) ratio in patients with SLE under no-flare conditions, P/C ratios measured within 4 months of a renal flare were excluded. “P/C ratio datasets” were developed and required a minimum of 3 bimonthly consecutive urine collections spanning 4 months. At least 50% of the P/C ratios were required to be measured by 24 hour urine collection. The P/C ratio datasets were stratified into groups according to the mean P/C ratio of the dataset: group 1 (mean P/C ratio < 0.15), group 2 (mean P/C ratio ≥ 0.15 to ≤ 0.38), group 3 (mean P/C ratio > 0.38 to ≤ 0.77), group 4 (mean P/C ratio > 0.77 to ≤ 1.54), group 5 (mean P/C ratio > 1.54). For each group, 99% confidence intervals were developed.

Summary: Of 1168 urine collections in the OSS study, 895 met the above criteria. These were provided by 58 of the 72 SLE GN patients (mean age 34 ± 11 years, 91% female, 38% African American, 58% European American, 4% Other). Mean P/C ratio was 1.5 ± 2.4. 91% were taking prednisone and 88% an immunosuppressant. Confidence intervals (CI) for each group are displayed in Figure 1.

Conclusions: Most of the current thresholds for SLE GN proteinuric flare are set well above the 99% CI for spontaneous variation in P/C ratios under no-flare conditions. This suggests that SLE GN patients are exposed to unnecessarily prolonged periods of increasing proteinuria before flare is declared and treated. This work is hypothesis generating and needs to be confirmed in a prospective randomized trial to determine whether lowering proteinuric flare threshold would benefit SLE patients.
Discussion: There is a wide range of variation between immunosuppres-
sant studies including: study design (retropective versus prospective),
patient-selection, racial variation, and lack of standard steroid regimens. With
all these factors in mind, this pooled analysis was extremely challenging, but
important. Our results indicate that treatment with an immunosuppressive
agent (e.g., CYP, MMF, AZA, and CSA) should be strongly considered in
MLN patients. Subgroup analyses demonstrate a much better response with
AZA, CSA, CYP, or MMF when compared to the steroid alone group. The
results of this analysis are corroborated by the recently published randomized
controlled trials of MLN patients.

Conclusion: Overall, conventional immunosuppressive therapies appear to
be more effective than steroids alone for inducing partial or complete
remission in patients with MLN and should be considered in treatment of
nephritis in lupus MLN patients.

Disclosure: V. Majithia: None; J. T. Swan: None; D. Riche: None.

**1402**

**Treatment of Lupus Nephritis with Enteric-Coated Mycophenolate Sodium (EC-MPS)—MyLupus Exploratory Study, Andrea Doria. For the MyLupus Study Group, Padova, Italy**

The MyLupus study was designed to compare the non-inferior efficacy and
safety of EC-MPS using two different oral prednisolone regimens (standard SD or reduced dose RD) for the induction of remission of a lupus
nephritis (LN) flare.

**Methods:** A 24-week (W) exploratory, multi-center, open-label study
was conducted in patients with a LN flare (ISN/RPS Class III or IV
documented by renal biopsy within 24 months of study entry). All patients received EC-MPS 1440 mg/day for the first 2W, followed by 2160 mg/day for the remaining 22W, and methylprednisolone iv. (0.5 g/day) for the first 3 days. Patients were randomized to either SD or RD (starting dose of 1.0
mg/kg/day and 0.5 mg/kg/day for 2W, respectively, followed by pre-specified
dose reduction). Primary end-point was the proportion of patients with
complete response (urine protein/creatinine [P/C] ratio <0.5, urine sediment
normalized, and serum creatinine <10% normal value) of LN after 24W. Partial response was defined as urine P/C ratio reduced by at least 50% from baseline and serum creatinine stable (<10% of baseline value) or improved.

**Results:** 81 patients were enrolled, 42 in SD and 39 in RD group. Baseline characteristics were comparable between groups. After 24 W, a similar proportion of patients achieved complete response in both groups (19% SD vs. 18% RD), although non-inferiority was not demonstrated. A higher proportion of patients achieved partial response in SD (48% SD vs. 33% RD). Index scores decreased in both groups from 4 to 24W (British Isles Lupus Assessment Group [BILAG] index: mean change from baseline — 8.6
SD vs. —9.4 RD, Systemic Lupus Erythematosus Disease Activity Index
[SLEDAI]: —10.4 SD vs. —9.4 RD). There was greater improvement in
glomerular filtration rate (mL/min/1.73m²) in RD (mean change from baseline
9.0 SD vs. 15.2 RD). There were 2 deaths, both in SD group. The incidence of serious adverse events was 16.7% (SD) vs. 10.3% (RD).

**Conclusions:** This exploratory study suggests that EC-MPS in combina-
tion with steroids is a viable therapy for LN. The overall clinical results indicate that RD of CS may offer benefits in terms of tolerability compared to
SD of CS while maintaining efficacy.

Disclosure: A. Doria: None.

**1403**

**Machine Learning Models Using Multiple Low Abundance Protein Biomarker Levels Superior to Those Using Clinical Laboratory Values in Diagnosing ISN/RPS Class of Lupus Nephritis, Jim C. Oates*, Michelle A. Petri1, Jonas S. Almeida1, Thomas W. Fleury, Janech G. Michael1 and John M. Arthur1. 1Timonium, MD, 2Medical University of South Carolina, Charleston, SC, 3Medical University of South Carolina, The University of Texas M. D. Anderson Cancer Center**

**Objectives:** Treatment in lupus nephritis (LN) is often driven by renal
biopsy findings, and traditional biomarkers are not predictive of renal
pathology. We hypothesized that levels of multiple candidate low abundance
urine proteins, when analyzed by my multivariable machine learning techniques,
would create more effective models of International Society of Nephrology/
Renal Pathology Society class of nephritis (ISN/RPS Class) than traditional
biomarkers now available to clinicians.

**Methods:** Subjects from the Charleston and Baltimore LN inception
cohorts and the Rituxan in LN (LUNAR) study population were recruited.
ISN/RPS Class was determined prior to induction therapy. Urine samples
were collected at entry for analysis. Urine levels of 12 candidate low abundance
proteins (chemokines, growth factors, cytokines, and renal damage
markers) were determined by the multiplex bead array, ELISA or activity
assay for all patients. Levels of individual markers were used to create
multivariable models of LN Class at baseline. Diagnostic models were trained
using machine learning (artificial neural network (ANN) and nearest related
neighbor (NRN) algorithms). The diagnostic power of models was reported as
the receiver operating characteristics curve area under the curve (ROC AUC),
with AUC values for perfect and non-diagnostic tests being 1 and 0.5
respectively. Input variables were traditional biomarkers (anti-double stranded DNA antibodies (DNA), C3, C4, serum Cr) and/or the selected
biomarker panel. The output variables were the individual biopsy classes.

**Input variables**

| Biomarker Panel | Number of Subjects | Outcome (ISN/RPS Class) | ANN ROC AUC | S583
|
|------------------|-------------------|-------------------------|-------------|
| Novel biomarkers | 99                | II                      | 0.91        |
|                  |                   | III                     | 0.82        |
|                  |                   | IV                      | 0.75        |
|                  |                   | Proliferative           | 0.84        |
|                  |                   | V                       | 0.59        |
| Traditional Biomarkers | 66 | II                   | 0.82        |
|                  |                   | III                     | 0.64        |
|                  |                   | IV                      | 0.62        |
|                  |                   | Proliferative           | 0.63        |
|                  |                   | V                       | 0.64        |
| Novel and traditional biomarkers | 66 | II                   | 0.84        |
|                  |                   | III                     | 0.79        |
|                  |                   | IV                      | 0.82        |
|                  |                   | Proliferative           | 0.73        |
|                  |                   | V                       | 0.86        |

**Results:** Biomarker data were available for 99 subjects. Combined
biomarker clinical data were available for a subset of 66 subjects. In general, ANN and NRN models using biomarkers either alone or in combination with traditional biomarkers were superior to models with clinical variables alone. ANN models tended to have greater diagnostic power than NRN models. 93% of the predictive power from the ANN model of proliferative disease came from GM-CSF, IFN-γ MCP1, NGAL, IL-6, and IL-12 levels.

**Conclusions:** This study suggests that multiple biomarkers representing
diverse pathogenic mechanisms by machine learning modeling techniques are
effective in diagnosing ISN/RPS class of nephritis. It demonstrates that when
markers of multiple types of cell activation, migration, and damage are
combined into a single model, diagnostic power is improved over models
using traditional biomarkers alone.

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**ACR/ARHP Combined Abstract Session**

**ACR/ARHP Combined Pediatric Rheumatology - Clinical and Therapeutic Aspects Abstracts: Quality of Life in Children and Adolescents with Arthritis**

**1404**

**Investigating Medication Adherence in Pediatric Rheumatology Using a Medical Claims Database, Caitlin M. Sgarlab, Jorge M. Lopez-Benitez, Emily Cox, and Ira B. Wilson. 1Express Scripts Inc. Research and Analysis, St. Louis, MO, 2Tufts Medical Center and Floating Hospital for Children: Division of Pediatric Rheumatology, Boston, MA, 3Tufts Medical Center and Floating Hospital for Children: Division of Pediatric Rheumatology; Tufts University Sackler School of Graduate Biomedical Sciences, Boston, MA, 4Tufts Medical Center and Floating Hospital for Children; Tufts University Sackler School of Graduate Biomedical Sciences**

**Background:** Juvenile Idiopathic Arthritis (JIA) or Juvenile Rheumatoid Arthritis (JRA) is the most common pediatric rheumatologic disease. Pharmacologic therapy use in this population is important at the onset of disease as well as throughout its course and adherence to the planned treatment is critical for good outcomes. Adherence to treatment in these conditions and in
this population has not been well studied and little is known about an association between age and adherence. We hypothesized that medication adherence would be better in a younger pediatric population with JRA compared with an adolescent pediatric population with JRA because of parental medication administration and supervision and because of problems reported with medication adherence in adolescents with other chronic conditions.

Methods: We used The MarketScan® Commercial Claims and Encounters Database, a nationwide pharmaceutical database with 12 million enrollees that includes both medical and pharmacy claims. Pediatric patients were identified by ICD-9 codes for a medical claim of JRA from 7/1/07 to 12/31/07. Pharmacy claims were obtained for these patients up to 1 year after the medical claim was made. Claims included the following medications: non-steroidal anti-inflammatory agents, cytotoxic agents, corticosteroids, and biologic agents. For each medication a possession ratio (MPR) was calculated. The denominator for the MPR was the number of days between the first and last prescription in that year, and the numerator was the number of dispensed days of medication between those dates. For patients on more than one medication, the average of the MPRs of the individual medications was used. Age was dichotomized into patients aged 0 to 12 years and 13 to 18 years. T-tests were used to compare the MPR in the different age groups. The data was analyzed using statistical software SAS 9.2.

Results: Of 5,452 patients with a medical claim of JRA, 1,946 patients, or 36%, were on one or more medications. Of those on medication, 64.5% were females and 34.5% were males. 40.6% were 0 to 12 years old and 59.5% were between 13 and 18 years old. The overall MPR of all patients was 0.67 (SD 0.46). The mean MPR for the patients ages 0 to 12 years was 0.77 (SD 0.47) and the mean MPR for the patients ages 13 to 18 years was 0.60 (SD 0.44), p-value <0.0001. Adjusting for gender in a multivariable linear regression model did not change these results.

Conclusion: Adherence was significantly worse in teenagers with JRA than in younger children, but even in younger children whose medication taking is presumably supervised by an adult, it was surprisingly low. These low levels of adherence are a potentially serious problem for patients who are likely to have suboptimal clinical outcomes as a result. Pediatric rheumatologists need to be aware of the extent of nonadherence that these data reveal, and endeavor to communicate more effectively with their patients about the issues and problems that they are having taking medications as prescribed. While the challenges to taking care of adolescent patients are not unique to JRA or rheumatologic diseases in general, the need to address poor medication adherence in these patients appears particularly pressing.

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1405

Development of a Vision Related Quality of Life Instrument for Children with Juvenile Idiopathic Arthritis-Associated Uveitis

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Purpose: Studies on quality of life (QOL) in JIA-associated uveitis (JUA-U) focus on visual acuity (VA) and the presence of flare and cells during the ophthalmologic exam as a measure of visual function. However, these measures do not adequately assess the impact of disease activity on daily life from a child’s perspective. Assessment of QOL in JIA-U could improve by including both objective measures of visual function and subjective assessments of the impact of disease activity on daily functioning. However, there are no validated instruments that measure vision related QOL in children with arthritis (27 girls; 80.7% Caucasian; mean age 12.7 years, 45% with moderate arthritis (27 girls; 80.7% Caucasian; mean age 12.7 years, 45% with moderate

1406

Sleep in Polycarticular Juvenile Idiopathic Arthritis: An Electronic Daily Diary Study

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Purpose: In addition to joint pain and stiffness, children with arthritis may experience sleep problems. Recently, researchers have used electronic surveys to track symptom and behavior fluctuations, including sleep, in home settings. This study compares child- and parent- reported daily electronic surveys describing children’s sleep quality.

Methods: The sample consisted of 31 children with active polyarticular arthritis (27 girls; 80.7% Caucasian; mean age 12.7 years, 45% with moderate

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to severe disease severity) and their parents (87% mothers; mean age 41.7 years). As part of a larger study, all participants recorded symptoms on an electronic survey via a smartphone three times each day for one month, including ratings of child sleep each morning. Physicians completed disease severity ratings at baseline. Sleep quality was rated on an electronic visual analog scale with the anchors “Did not sleep well” and “Slept very well.” Daily sleep quality reports were aggregated, descriptive statistics were performed on all sleep variables, and compliance rates were calculated. Dependent sample t-tests were used to compare average parent and child sleep quality ratings.

Results: Children completed 65% and parents completed 72% of all possible electronic morning reports. Averaging all reports, children in the sample reported moderate to high sleep quality (m = 70.09, SD = 27.77). Parent ratings of child sleep quality were not significantly different (t = −0.59, p < 0.05). Children and parents’ individual sleep quality entries spanned the full range of 0–100mm. Poor sleep quality (>1SD below the mean) was reported by children on 18% and parents on 25% of all morning reports. Self-reported sleep quality did not vary by gender (t = −1.58, p = 0.05).

Neither child nor parent-reported average sleep quality scores correlated with physician-rated disease severity (r = −0.27, p = 0.05; r = −22, p > 0.05) or age (r = −25, p = 0.05; r = −18, p > 0.05). However, average self-reported pain (m = 28.6, SD = 21.9) and self-reported sleep quality were significantly correlated (r = −0.45, p < 0.05), as were parent-reported average pain (m = 28.42, SD = 20.66) and parent-reported average sleep quality (r = −0.41, p < 0.05). Children reported sleeping 4–8 hours on 55.7% of nights and 8–10 hours on 33.4% of nights, and reported mild difficulty with sleep onset and few night wakings.

Conclusions: Parents and children completed comparable numbers of morning electronic diary surveys, suggesting that children can adequately complete independent entries using this new technology. Self- and parent-ratings of child sleep quality were similar, supporting the use of child self-reported sleep ratings in future studies. Children generally reported adequate sleep duration and few sleep disruptions during the night. Although disease and demographic variables were not related to sleep quality scores, pain intensity reports correlated to sleep quality. Despite adequate sleep quality on average, children reported experiencing poor sleep quality on 18% of morning reports, suggesting daily variability. Additional research is needed to identify factors effecting daily sleep quality and to determine the clinical impact of sleep quality variability.

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1407 Clinically Meaningful Improvements in Health-Related Quality of Life, Pain and Sleep Quality in Children with Polyarticular Juvenile Idiopathic Arthritis Treated with Abatacept over the Long Term. Daniel J. Lovell1, Nicolina Ruperto2, Pierre Quatrefais3, Elitana Paz4, Nadina Rubio-Perez5, Closiv A. Silva6, Carlos Abud-Mendoza7, Ruben Burgos Vargas8, Valeria Gerloni9, José A. MeLo-Gomes10 (Andre Dos Santos)1, Claudia S. Magalhães11, Flavio Sztajnbok12, Claudia Goldenstein-Schneiber13, Morton Schneiber13, Immaculada Calvo Penades14, Michel Fischbach15, Javier Orozco16, Lisa Rosenblatt17, Monika Mody18, Marleen Nys19, Edward H. Giannini15 and Alberto Martini20.1 Bristol-Myers Squibb, NJ; 2Bristol-Myers Squibb, Braine-l’Alleud, Belgium; 3Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, 4Hospital Universitaire Hauteepierre, Strasbourg, France; 5Hospital Das Clinicas, Sao Paulo, Brazil; 6Hospital General Dr. Ignacio Morones Prieto, San Luis Potosi, Mexico; 7Hospital General de Mexico and Universidad Nacional Autonoma de Mexico, Mexico City, Mexico; 8Hospital Israelita Albert Einstein, Instituto de Investigation, Sao Paulo, Brazil; 9Hospital San Juan, Rheumatology, Guadalajara, Jalisco, Mexico; 10Hospital Universitario “Dr. J. E. Gonzalez”, Monterrey, Mexico; 11Hospital Universitario La Fe, Valencia, Spain; 12Hospital Universitario Pedro Ernesto, Rio de Janeiro, Brazil; 13Instituto de Salud del Nino, Lima, Peru, 14Centro Portugues de Reumatologia, Lisbon, Portugal, 15IRCSC G Gaslini, Pediatrica II-PRINTO, Universita di Genova, Genova, Italy, 16Istituto Gaetano Pini, Milan, Italy, 17Universidade de Sao Paulo, Sao Paulo, Brazil, 18Universidade Estadual Paulista, Botucatu, Brazil, 19Universite Paris-Descartes and Centre de Reference National Pour les Arthrites, Paris, France

Background: Systemic inflammation, chronic arthritis and possible joint damage can lead to functional impairment and diminished health-related quality of life (HRQoL) in children and adolescents with juvenile idiopathic arthritis (JIA). In a double-blind (DB), placebo-controlled, randomized withdrawal trial (RWT) 1 in subjects with polyarticular JIA, abatacept significantly improved multiple aspects of HRQoL, pain and sleep quality 2. Here we report follow-up data on these variables for up to 31 months of treatment, including 21 months of the long-term extension (LTE) of this trial.

Methods: Subjects in the RWT treated with abatacept who achieved an ACR Pedi 30 response in a 4-month open-label lead-in were randomized 1:1 to DB abatacept or placebo for 6 months or until flare 2. Subjects eligible to enter the open-label LTE (10 mg/kg abatacept) included ACR Pedi 30 non-responders (NR) from the lead-in who did not enter the DB period, and subjects randomized into the second phase with either flared or completed the 6-month DB period. HRQoL was assessed by the Child Health Questionnaire (CHQ), which includes 15 health concepts, sleep quality by the Children’s Sleep Habits Questionnaire (CSHQ) (score = 0–100) and parent global assessment of pain by 100 mm VAS. MECH component scores are also presented for healthy children 3. Data up to Month 21 of the LTE are presented for subjects who entered the LTE (either NR from the open-label lead-in or subjects treated with abatacept during the DB period), and who had data available at the visit of interest (as-observed).

Results: At study entry, subjects had considerably lower HRQoL than the general population 4. Mean changes in CHQ components from baseline to Month 31 generally indicated improvements in both patient cohorts, with differences in changes from baseline to Month 21 between DB abatacept versus NR cohorts: mean (95% CI) changes in CHQ total scores were −3.5 (−6.5, −0.5) versus −2.9 (−6.3, 0.6), and in parent global assessment of pain were −31.2 (−37.8, −24.6) versus −20.6 (−30.2, −10.9) (n = 28, n = 16, n = 50 and n = 22, respectively).

Conclusions: Treatment with open-label abatacept for up to 31 months resulted in improvements in multiple aspects of HRQoL, to within the range of healthy children, for subjects with JIA, including those who were ACR Pedi 30 non-responders in the lead-in period. These data suggest that long-term abatacept treatment can provide real-life tangible health-related benefits to children with polyarticular JIA.


Disclosure: D. J. Lovell: Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, Bristol-Myers Squibb, 2, 5, Centocor, Inc., 2, 5, Hoffmann-La Roche, Inc., 2, 5; Novartis Pharmaceuticals Corporation, 2, 5; Pfizer Inc, 2, 5, Regeneron Pharmaceuticals, Inc., 2, 5; X: N. Ruperto: Bristol-Myers Squibb, 2; P. Quatrefais: None; E. Paz: None; R. Rubio-Perez: None; C. A. Silva: None; C. Abud-Mendoza: None; R. Burgos Vargas: Abbott Laboratories, 5, 8; Bristol-Myers Squibb, 5, 8; MSD, 5, 8; Pfizer Inc, 5, 8, Roche, 5, 8; V. Gerloni: None; J. A. Melo-Gomes (Andre Dos Santos): Bristol-Myers Squibb, 2; C. S. Magalhães: None; F. Sztajnbok: Bristol-Myers Squibb, 2; C. Goldenstein-Schneiber: None; M. Scheinberg: None; L. C. Penades: None; M. Fischbach: None; L. Rosenblatt: None; R. Brown: Abbott Laboratories, 5, 8; Bristol-Myers Squibb, 5, 8; MSD, 5, 8; Pfizer Inc, 5, 8, Roche, 5, 8; V. Gerloni: None; J. A. Melo-Gomes (Andre Dos Santos): Bristol-Myers Squibb, 2; C. S. Magalhães: None; F. Sztajnbok: Bristol-Myers Squibb, 2; C. Goldenstein-Schneiber: None; M. Scheinberg: None; L. C. Penades: None; M. Fischbach: None; L. Orozco: None; L. Rosenblatt: Bristol-Myers Squibb, 1, 3; M. Mody: Bristol-Myers Squibb, 1, 3; E. Lilly and Company, 1, 3; M. Nys: Bristol-Myers Squibb, 3; E. H. Giannini: Bristol-Myers Squibb, 2; A. Martinis: Bristol-Myers Squibb, 5, UCB, Inc., 5.
Jointly Managing Arthritis: Information Needs of Children with Juvenile Idiopathic Arthritis (JIA) and Their Parents. Jennifer Stinson1, Brian M. Feldman1, Ciaran Duffy2, Adam Huber1, Lori Tucker1, Patrick McGrath3, Shirley M. Tse3, Ross Hetherington3, Lynn Spiegel4, Sarah Campbell5, Susan Pearson6, Navneet Gill5, Meghan E. White5 and Ali Vijenthira6
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Purpose: This study explores the information needs of children with JIA and their parents in order to develop a web-based program of disease-specific information, management skills, and social support aimed at improving their quality of life.

Methods: A qualitative study design was used. A purposive sample of children (n=41, 73% female) between 8 and 11 years of age diagnosed with JIA and one of their parents (n=48), was recruited from four Canadian tertiary care centers (Vancouver, Toronto, Montreal, Halifax). Parent-child dyad interviews (n=29) and 4 separate child and parent focus group interviews were conducted using semi-structured interview guides. Audio-taped interviews were transcribed verbatim. Nvivo 8.0 (QSR, 2009) was used to assist with sorting, organizing and coding data. The thematic analysis was a collaborative and iterative process. Data were organized into categories that reflected the emerging themes.

Results: Preliminary findings uncovered two major themes: “Living with Arthritis” and “Jointly Managing Arthritis”. Major subthemes for “Living with Arthritis” were: pain, maintaining friendships, communicating about the disease, and worry/distress. Two further sub-themes were found under worry/distress: parents expressed concern about their child’s future, and children wondered “why me?” Two sub themes were identified under “Jointly Managing Arthritis” where managing JIA was viewed as being a joint responsibility between the parent and child. The first sub theme, “desire for information and disease management strategies”, highlighted the need for further information on JIA, medications, tests and procedures, managing pain and emotions, and advocacy and communication strategies. The second sub theme was staying strong and seeking social support. Participants explained that staying strong as a family was essential, and they also wanted the opportunity to connect with others with JIA to help them feel that they are not alone. Finally, children and their parents felt that a web-enabled program of JIA information, disease management strategies and opportunities for social support would be the ideal way to meet their information needs.

Conclusions: In order to jointly manage JIA, children and their parents expressed the need for disease-specific information, management strategies, and social support. Web-enabled treatments are a promising avenue to improve the accessibility and availability of JIA information and disease management strategies for children and their parents. Findings from this study will be used to develop and test an on-line program to help children and their parents jointly manage arthritis.

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Follow-Up Survey on Adolescent Rheumatology Patients’ Online Activities and Social Support Systems: Opportunities for Transition Program Development. Peter Chira. Stanford University, Palo Alto, CA

Purpose: To evaluate current trends of social support systems and online behaviors of teen patients attending Stanford pediatric rheumatology clinic at Lucile Packard Children’s Hospital (LPCH) and to assess opportunities for a transition intervention.

Methods: We administered a written survey to consecutive teen rheumatology patients ages 13–22 during routine LPCH rheumatology clinic visits from April-June 2010. Informed consent and assent were obtained from parents (and participants ≥18) and teens <18, respectively. Stanford University’s IRB approved the study. The survey is based on one administered in 2003. Descriptive statistics are presented. Trends are compared between surveys.

Results: 120 patients completed the survey (Table 1). Most have discussed their disorder with another, typically parent (95%) or friend (81%); few had spoken to a peer with a similar rheumatic disease (22%), and this is an increase from 2003. Computer and internet use are pervasive: 89% use email but only 38% check daily, and 74% use social networking sites, with 54% checking daily. Online communications such as chat room and IM are used less often than in 2003 (16%, 51% vs 33%, 69%, respectively), with a drop in daily IM from 33% to 24%. 90% have cellphones, and calling (87%), texting (78%), and taking pictures (73%) are the most common uses. 44% send >50 text messages daily.

Discussion: The Pew Survey on Social Media in Young Adults in March 2010 revealed changing trends of teen internet practices. Our survey demonstrates that teen rheumatology patients have similar online habits, but they are more likely to go online for health information and for sensitive teen topics than the general adolescent population. We note increasing use of cellphones for communication and internet access, which have affected other interactive online modalities. Interest in online meetings with teens with similar conditions is declining, but our teens prefer website development and tools to collect their personal health information that also can be a reliable resource for medical information about their condition. While many teens commonly use online social networking sites, overall interest of their use as a social support resource may be limited.

Conclusion: Technology and social media use by teens with rheumatic diseases are evolving and follow the general young adult population. Further development of programs, especially those using mobile technologies such as cellphones, will help teens to learn about and track their rheumatic conditions, as well as to assist in peer communication– all potential opportunities in the creation of a teen transition program.

Disclosure: P. Chira: None.
ACR Concurrent Abstract Sessions
B-Cell Biology and Targets in Autoimmune Disease
Tuesday, November 9, 2010, 4:30 PM–6:00 PM

1410

TLR7 and IFNα Influence B Cell Selection in the Germinal Center. Ioana Moisini1, Weiqing Huang1, Tony Marion3 and Anne Davidson2. 1Feinstein Institute, 2Feinberg Institute for Medical Research, Manhasset, NY; 3University of Tennessee

Background: Male NZW/BXSby.Yaa (W/B) mice express two copies of the TLR7 gene and develop pathogenic autoantibodies whereas females with only one copy of TLR7 have attenuated disease. Vh3H9 is an autoreactive Ig heavy chain that can pair with a variety of light chains generating both autoreactive and non-autoreactive antibodies. Our goal was to analyze the regulation of the autoantibody response in male and female 3H9/W/B mice.

Methods: 3H9/W/B mice were bred and monitored for proteinuria. Some female mice received IFNα adenovirus at 3 months of age. Sera were analyzed for autoantibodies by ELISA. Mice were sacrificed at 8, 24 and 56 weeks of age and single cell PCR and sequencing of heavy and light chain Ig genes performed for all B cell subsets. Selected germline light chains were coexpressed with the 3H9 heavy chain and transfectant supernatants screened for autoreactivity by ELISA.

Results: IgM and IgG anti-CL antibodies appeared in the serum by 12 weeks of age in both males and females. Anti-dsDNA antibodies appeared in the serum of males at 12 weeks and most had high titer IgG anti-CL and anti-dsDNA antibodies performed for all B cell subsets. Selected germline light chains were coexpressed with the 3H9 heavy chain and transfectant supernatants screened for autoreactivity by ELISA.

Conclusions: Our studies are consistent with the hypothesis that TLR7 overexpression in females results in increased autoreactivity of the antigen driven B cell repertoire.

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1411

Impaired Somatic Hypermutation in Pre-Switch Memory B Cells and Modulation of Mutational Targeting in Memory B Cells during Tocilizumab Treatment in RA Patients. Khalid Muhammad1, Petra Roll1, Stefan Kleinert1, Thomas Seibold2, Martin Feuchtenberger3, Thomas Dönner2 and Hans-Peter Környay3. 1Department of Medicine II, Rheumatology/Immunology, University of Würzburg, Würzburg, Germany; 2Department of Medicine II, Rheumatology/Immunology, University of Würzburg, Würzburg, Germany; 3Depts of Medicine/Rheumatology and Clinical Immunology Charite Universitätsmedizin Berlin and DRFZ Berlin, Berlin, Germany

Purpose: Tocilizumab, a humanized anti-IL-6R antibody, is a novel anti-inflammatory drug with documented clinical effects in rheumatoid arthritis. Since IL-6 is a key differentiation factor of B cells, we analysed molecular effects of tocilizumab on pre- (IgD+CD27+) and post- switch (IgD-CD27+) memory B cells in vivo.

Methods: Memory B cell subsets were analysed from 10 RA patients by using single B cell sorting technique followed by nested PCR and Ig- VH/ VH sequencing. 6/10 received tocilizumab (8 mg/kg every 4 weeks) and 4/10 received as a control population anti-TNFα therapy with etanercept.

Results: Pre-therapy analysis of 344 rearranged IgR sequences from 10 RA patients revealed a diversified mutational pattern of pre-switch memory B cells containing mutated and non-mutated sequences. Patients receiving tocilizumab (n=6) showed a reduced mutational frequency in Ig-receptors of pre-switch memory B cells along with a marked reduction of the highly mutated Ig-receptor population at week 12 and 24 after tocilizumab. In detail, the mutational frequency of pre-switch memory B cells decreased from 4.1±0.2% (mean±SEM) to 2.9±0.1% (P=0.0001) at week 12 and 2.5±0.2% (P=0.0001) at week 24, respectively. Pre-switch memory B cells contained 50.6±2.3% highly mutated sequences (>9 mutations/sequence) before treatment which declined to 28.5±2.0% and 22.5±4.5% at week 12 and week 24 (P=0.0001), while low mutated sequences (<9 mutations/sequence) increased significantly from 43.1±2.7% to 65.1±1.8% and 63.6±4.0 (P=0.0001). This included a significant increase of unmutated sequences at week 24 (36.3±1.8 vs. 13.9±4.2, P=0.0001) after tocilizumab. The mutational frequency within post-switch memory B cells was unaffected. Analysis of the mutational hotspot RGYW/WRCY(R/A, G/T, C/A) motifs indicated significantly decreased targeting in pre-switch memory B cells (22.3±14% before therapy versus 17.2±1.0% and 14%±0.025) as well as in post-switch memory B cells (30.2±3.2% before therapy versus 17.2±2.0% and 16±0.5%, P<0.025) at week 12 and week 24 under tocilizumab.

In contrast, anti-TNFα therapy (n=4) had no effect on both, mutational frequency and mutational targeting of hotspot motifs in pre- and post-switch memory B cells.

Conclusions: Our data suggest that pre- and post-switch memory B cells are susceptible to IL-6R inhibition in vivo. Particularly, acquisition of mutations was substantially altered in pre-switch memory B cells, while targeting of mutational hotspots affected both pre- and post-switch memory B cells. The results indicate that pre- and post-switch memory B cells have a differential dependence on the IL6/IL6R system for differentiation in vivo which can be influenced by anti-IL6R therapy.

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1412

IL-17 Downregulates NF-κB/p50 and Upregulates BCL6 To Promote Germinal Center B Cell Differentiation in Autoimmune BJD2 Mice. Shutaoo Xie1, Hui-Chen Hsu2, Jun Li3, Qi Wu4, PingAr Yang5 and John D. Monta5. 1Univ Alabama at Birmingham, Birmingham, AL; 2Univ Alabama at Birmingham

Background: Suppression of NF-κB/p50 by transcription factor BCL6 has been shown to be associated with early germinal center (GC) B cell differentiation. BJD2 mice express high levels of IL-17 and spontaneously develop lupus and erosive arthritis. We previously showed that IL-17 can regulate the migration behavior of B cells via the canonical NF-κB P-65 signaling pathway to facilitate the close contact of B and T cells in spontaneous GCs. This study is to determine if IL-17 can promote GC B cell differentiation through its effects to modulate the expression of BCL6 and NF-κB/p50.

Methods: Purified splenic B cells from BJD2, BJD2-IgD+/−, B6 or B6/IgD−/− mice were incubated with or without IL-17 or IL-21 in vitro. NF-κB/p50 proteins were analyzed by western blot using antibodies against P-p65, p50, p105. Adenovirus (Ad)-IL-17RA:Fc, Ad-IL-17A, AdLacZ, an anti-IL-17 neutralization antibody and an isotype control antibody were administered into BJD2 mice. Expression of Rgs, Irf4, Bcl6 and Nkhi1 were determined by qRT-PCR. Expression of BCL6 in GC B cells was determined by FACs. B cells were stimulated in vitro with anti-CD40 (2 mg/ml) + anti-mouse IgG (4 mg/ml) in vitro.

Summary of the Results: IL-17 by itself upregulated the expression of Bcl6 and downregulated nuclear expression of p50 in BJD2 B cells in vitro. IL-17 also acted synergistically with IL-21 to upregulate the expression of Bcl6 in BJD2 B cells. In vivo blockade of IL17Ra signaling by administration of anti-IL-17 decreased BCL6 in BJD2 GC B cells. Consistent with this,
administration of AdIL-17A:Fc, which blocks IL-17/IL17R signaling, to BDX2 mice also resulted in significantly decreased BCL6, increased p50 and p105, and decreased P-p65 in B cells. Administration of AdIL-17A to BDX2 mice induced opposite effects. Both p50 and p105 in IL-17RA intact B cells were significantly lower than those in Il17ra−/− B cells from both B6 and BDX2 mice. BDX2-Il17ra−/− B cells also exhibited higher nuclear localization of p50, and when induced with anti-CD40 + anti-IgG, they showed dramatically lower expression of classical NF-κB responsive genes including Rgs (>10.0-fold, p<0.001) and If4 (>4.0-fold, p<0.01), compared with anti-CD40 + anti-IgG stimulated BDX2-Il17ra−/− B cells.

**Conclusion Reached:** Our results reveal a novel mechanism for IL-17 to regulate the development of GC B cells in autoimmune BDX2 mice in that: (i) IL-17 can directly upregulate BCL6 to facilitate GC B cell differentiation; (ii) IL-17 suppresses the NF-κB pathway facilitating GC formation and GC B cell development.

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**Targeting the Splicing of mRNA in Autoimmune Diseases:**

B-cell activating factor of the TNF family (BAFF) is a relevant target in autoimmunity. BAFF is increased in various animal models of autoimmune disease, and in patients with autoimmune diseases, including Sjögren’s syndrome. The efficiency of novel immunomodulatory therapies is, in part, determined by the ability of the BAFF system to induce or maintain regulatory B cells and to downregulate the function of autoreactive B cells. The use of exon skipping to promote the expression of one shorter variant over the predominant full length mRNA has shown encouraging effects for the treatment of the monoclonal disease Duchenne’s myopathy and offers exciting therapeutic opportunities for many other diseases.

**Methods:** Adeno-associated virus (AAV) and lentiviral vectors were constructed encoding U7 RNA with an antisense sequence targeting the exon of BAFF, which is absent in delta-BAFF. The expression of BAFF and delta-BAFF mRNA was assessed by PCR after infection of U937 and human lymphoma cell lines. Exon skipping-inducing AAV (AAV 161) or an AAV control vector encoding for beta galactosidase (LacZ) were administered by retrograde transduction of the submandibular glands of 19 NOD mice at the age of 10 weeks. Salivary gland function was assessed and expression of BAFF and SII inflammation was determined by quantitative immunohistochemistry 10 weeks post-treatment.

**Results:** In vitro transfection of U937 and human lymphoma cell lines with an exon skipping inducing lentivirus resulted in a marked decrease of BAFF and an increase of delta-BAFF mRNA and decreased BAFF protein in the supernatant.

**Conclusions:** These results demonstrate the efficacy of BAFF inhibition on features of SjS in NOD mice and offer a rationale to evaluate BAFF inhibition in patients with SjS. This study also represents a proof of concept of the efficacy of modulating mRNA splicing in autoimmune diseases.

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**Adaptive Transfer of Long-Lived Plasma Cells from NZB/W Mice Causes Immune Complex Nephritis in Recipient Rag1−/− Mice.** Quingyu Cheng1, Imitaz M. Muntaz2, Bimba F. Hoyer3, Andreas Radbruch4 and Falk Hippel4.

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**Background:** Previously, we showed that long-lived plasma cells refractory to immunosuppression significantly contribute to autoantibody production in NZB/W mice used as a model of lupus nephritis. Since immunosuppressive and B cell depletion therapy affecting only short-lived plasmablasts and plasma cells can induce remission of the disease, the role of surviving long-lived plasma cells in the pathogenesis of the disease is not well-defined.

**Objectives:** To elucidate the contribution of autoreactive long-lived plasma cells in the pathogenesis of lupus nephritis.

**Methods:** CD138+ plasmablasts and plasma cells were isolated by MACS technology from the spleens of >6-month-old NZB/W mice with high levels of anti-dsDNA antibodies and adoptively transferred to immunodeficient Rag1−/− mice (3 million cells/mouse). Contamination levels within the transferred plasmablast fraction did not result in the recipient mice were sacrificed 21 weeks after adoptive transfer for analysis of plasma cells, including anti-DNA-secreted cells, by flow cytometry and ELISPOT as well as for renal immunohistochemistry.

**Results:** Total IgG, total IgM and IgG and IgM anti-dsDNA antibody levels were measured in recipient mice starting one week after transfer and remained constant for the entire observation (21 weeks), even after cyclophosphamide treatment. Serum antibody levels in recipient mice were measured using ELISA. The recipient mice were sacrificed 21 weeks after adoptive transfer for analysis of plasma cells, including anti-DNA-secreted cells, by flow cytometry and ELISPOT as well as for renal immunohistochemistry.

**Conclusions:** Adoptive transfer of plasmablasts results in homing of long-lived plasma cells in spleen and bone marrow. Autoantibodies secreted by long-lived plasma cells can cause nephritis. This supports the suggestion to consider long-lived plasma cells refractory to conventional immunosuppression and B cell depletion as candidate targets for future therapeutic strategies.

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**B Cells Induced Proteinuria and Glomerulopathy in Absence of Immune Complexes Similar to Minimal Change Disease.** Alfred H. Kim1 and Andrey S. Shaw1.

1Washington Univ School of Med, St. Louis, MO, 2Washington Univ School of Med

**Purpose:** B cell depletion therapies have been efficacious in several immunopathologic glomerulopathies, such as minimal change disease. The contributions of B cells to proteinuria and podocyte foot process effacement remain unknown, although we test whether the glomerular localization of antigen, followed by adoptive transfer of antigen-specific B cells, can induce proteinuria and glomerular disease. This would enhance our understanding of immune-based kidney diseases.

**Methods:** The well-characterized B cell model antigen hen egg lysozyme (HEL) was biotinylated and complexed to avidin. Following intravenous injection in mice, purified naive HEL-specific B cells were adoptively transferred and proteinuria was assessed at various timepoints post-transfer.

**Conclusion:** These results demonstrate the efficacy of BAFF inhibition on features of SjS in NOD mice and offer a rationale to evaluate BAFF inhibition in patients with SjS. This study also represents a proof of concept of the efficacy of modulating mRNA splicing in autoimmune diseases.

**Disclosure:** N. Roescher: None; J. L. Vosters: Dutch Arthritis Foundation, 2; G. Al Sahih: None; P. Dreyfus: None; S. Jacques: None; L. Garcia: None; G. Chiocchia: None; A. Francois: None; J. Sibilia: None; P. P. Tack: Arthrogen B.V. Amsterdam, 9; J. A. Chiörini: NIH, 2; X. Mariette: None; J.-E. Gottenborg: None.
Kidneys were processed for immunofluorescence, H&E staining, and transmission electron microscopy. Intravitral two-photon microscopy was performed on exteriorized kidneys from live, anesthetized mice.

Results: HEL was found to be embedded within the glomerular basement membrane (GBM) within 30 minutes following intravenous injection as visualized with immunofluorescence microscopy. Induction of proteinuria occurred only after the transfer of HEL-specific B cells, as compared to wild-type polyclonal B cell transfer. The presence of HEL alone in the GBM did not induce proteinuria, nor did the transfer of HEL-specific B cells in the absence of HEL injection. The proteinuria is associated with podocyte foot process effacement as visualized on transmission electron microscopy. The absence of periglomerular infiltrates on H&E stained sections were noted in both proteinuric and control mice, indicating the absence of inflammation. There was no immune complex or complement deposition within the glomeruli during proteinuria. Intravitral two-photon microscopy demonstrated that HEL-specific B cells were retained only within the antigen-bearing glomeruli and became activated in situ as measured by calcium flux.

Conclusion: We have demonstrated that B cells were activated within antigen-bearing glomeruli, and induced proteinuria and podocyte foot process effacement in the absence of immune complex deposition, complement deposition, or inflammation. These are observations similar to those found in minimal change disease. These data provide additional evidence that B cells can generate pathophysiologic conditions seen in immune-based diseases in the absence of immune complexes. We hypothesize that B cell-derived cytokines are directly responsible for this phenotype, and this is currently being tested.


ACR Concurrent Abstract Sessions
Cell-Cell Adhesion, Cell Trafficking and Angiogenesis
Tuesday, November 9, 2010, 4:30 PM–6:00 PM

1416
Nuclear Factor-κB Inducing Kinase Is Preferentially Expressed in Rheumatoid Arthritis Synovial Tissue Containing Ectopic Lymphoid Neogenesis. Ae-Ri Noort1, Katinka P. M. van Zoest1, Mariagrazia Modesti4, Sander W. Tas2 and Paul P. Tak1. 1Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, 2Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, 3Academic Medical Center/University of Amsterdam, Amsterdam, 4University of Rome

Background: Approximately 30% of synovial tissues derived from rheumatoid arthritis (RA) patients is characterized by ectopic lymphoid neogenesis (ELN). This results in structures that may resemble germinal centers, containing dendritic cells and aggregates of B and T cells. This process also occurs in other chronic inflammatory diseases. Nuclear factor-κB (NF-κB) transcription factors are essential for the expression of pro-inflammatory cytokines, but can also induce regulatory pathways. These regulatory circuits are thought to be modulated by the non-canonical NF-κB pathway of which NF-κB-inducing kinase (NIK) is a key mediator. Non-canonical NF-κB signaling can be triggered by stimuli like CD40L and lymphotoxin that are abundantly present in ELN. Therefore, the non-canonical NF-κB pathway might play an important role in ELN.

Objectives: To investigate the expression and distribution of NIK in RA synovial tissue (ST) in relation to ELN and to study the functional role of non-canonical NF-κB signaling.

Methods: ST was obtained via mini-arthroscopy from inflamed knee or ankle joints of RA patients with active disease. RA ST samples were analyzed by microarray analysis. Next, we evaluated the expression of NIK in ST of 40 RA patients using immunohistochemistry. NIK expression was scored on a semiquantitative 5-point scale (0–4) by 2 independent observers. Furthermore, we analyzed NIK and von Willebrand Factor (vWF) expression using immunofluorescence microscopy, not only in RA ST, but also in Grawitz tumor and breast cancer tissue.

Results: Microarray analysis showed increased relative expression of non-canonical NF-κB pathway associated genes in ST containing ELN compared to tissue samples without ELN (p<0.05). Next, we confirmed these findings by immunohistochemistry. ELN was present in 15 out of 40 RA ST. NIK expression was significantly higher in ST with ELN and more abundantly present within lymphocyte aggregates (1.53±0.32 vs 0.62±0.19; p<0.05). Of interest, in the tissue away from the lymphocyte aggregates, NIK was expressed by vascular structures. Further analysis revealed that NIK positive cells were negative for the lymphatic vessel markers LYVE-1 and podoplanin. Immunofluorescence microscopy demonstrated that NIK co-localised with the endothelial cell marker vWF. We observed co-expression of NIK and vWF not only in RA ST, but also in Grawitz tumor and breast cancer tissue. Functional studies on the role of non-canonical NF-κB signaling in endothelial cells are currently being performed.

Conclusion: NIK is preferentially expressed in RA ST containing ectopic lymphoid aggregates. NIK expression in RA ST co-localised with vWF, indicating that NIK is expressed by blood vessel endothelial cells. These findings point towards an important role of the non-canonical NF-κB pathway in either blood vessel formation or in the activation of endothelial cells to attract immune cells. This could be exploited for the development of future new therapies, which would not only be applicable for RA but also for other diseases.

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1417
CXCL16 as an Early Response Chemokine in Rat Adjuvant and K/BxN Serum Induced Arthritis Models. Jeffrey H. Ruth2, Christian S. Haas1, M. Asif Amin3, G. Kenneth Haines III4 and Alisa E. Koch1. 1University of Luebeck - Department of Medicine I, Luebeck, Germany, 2University of Michigan Medical School, Ann Arbor, MI, 3University of Michigan, Ann Arbor, MI, 4Yale University Medical School

We and others have previously shown that the transmembrane chemokine CXCL16 and its counterpart CXCR6 are important in the pathogenesis of rheumatoid arthritis (RA) predominantly via recruitment and stimulation of mononuclear cells. However, the expression pattern of CXCL16 during the development of RA and the optimal time point for therapeutic targeting remain unclear. In the present study we determined the spatiotemporal expression of CXCL16-CXCR6 in rat adjuvant induced arthritis (AIA), a rodent model for RA. We also examined joint swelling in CXCR6 deficient (CXCR6−/−) and wild-type (WT) mice administered K/BxN serum, an acute model of RA.

Method: Rat AIA synovial tissues (STs) were immunostained to determine the percentage of cells expressing CXCL16 and CXCR6. CXCL16 levels were also determined in serum and ankle homogenates using ELISA assays. CXCR6 expression was evaluated on rat macrophages and tested to induce rat macrophage migration towards soluble CXCL16 using a modified Boyden chemotaxis system. Lastly, CXCR6−/− and WT C57BL/6 mice were proved to develop K/BxN serum induced arthritis and evaluated for joint swelling.

Results: CXCL16 showed constitutive expression on endothelial cells in rat AIA, and was upregulated on both lining cells (LCs) and macrophages on day 14, prior to arthritis onset (p<0.05). CXCR6 was virtually absent in normal ST but was expressed on LCs and macrophages on day 14. CXCL16 levels in serum and joints were increased on day 4 of rat AIA, suggesting that CXCR6 positive inflammatory cells migrate very early to the ST in rat AIA. Rat macrophages constitutively expressed CXCR6 in vitro and migrated in response to the ligand in a dose-dependent manner. Finally, using the K/BxN serum induced arthritis model, CXCR6−/− mice showed significantly reduced joint swelling compared to WT mice at day 5 after serum induction.

Conclusion: CXCL16 and CXCR6 are upregulated in the early course of rat AIA. CXCL16 positive macrophages and LCs are found predominantly prior arthritis onset. Rat macrophages express CXCR6 and migrate in response to CXCL16 in vitro. In addition, CXCR6−/− mice show significantly less joint swelling using in an acute model of RA, suggesting that CXCL16 and CXCR6 function early in disease development to recruit inflammatory cells to the joint. Our findings may help guide in vivo targeting strategies for the CXCL16-CXCR6 pathway in RA.

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Angiogenic Potential of HMECs is Driven by HIF-2α Overcoming the Effects of HIF-1α. Martin Hahne1, Steffi Luetkecosmann1, Cam Loan Tran1, Ferenz Lohanath2, Manuela Jakstadt1, Grit Kasper3, Georg Duda4, Paula Kolart5, Timo Gaber1, Gerd R. Burmester1 and Frank Buttgeriet1.

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Background: Hypoxia and angiogenesis are features of inflamed tissues. For the development of the rheumatoid pannus, subsequent synovial inflammation and joint destruction, the growth of new vessels is necessary. Inhibition of angiogenesis is one potential therapeutic approach to manage inflammatory diseases like rheumatoid arthritis (RA). In this regard the transcription factors Hypoxia inducible factor (HIF)-1α and (HIF)-2α control cellular response to decreased oxygen tension thereby promoting angiogenesis. Although HIF-1α and HIF-2α share structural similarities, they are supported to have distinct transcriptional targets with implications on the pathogenesis of RA.

Objective: We focused on the effects of HIF-2α in the process of angiogenesis. Therefore, we developed a stable human microvascular endothelial cells (HMEC) lentiviral based knockdown system for HIF-2α to overcome HIF-1α and (ii) to investigate the angiogenic and angiostatic growth factors, cytokines, and adhesion related genes

Methods: Specific knockdown of HIF-2α was achieved using lentiviral-based shRNA expression of hypoxia driven genes

Results: Evidencing the successful knockdown of HIF-2α, the gene expression levels of HIF2A were reduced by 69% under normoxia (scr vs. HIF2shRNA; p = 0.0045) with the same reductive effect of 69% under hypoxia. Moreover, strongly reduced HIF-2α protein levels were detected by Western blot. HIF-1α levels were not affected by HIF-2α knockdown. Targeting HIF-2α led to a significantly decreased node formation by factor 2 under normoxia (Nox) and factor 4.5 under hypoxia (Hox) incubation (Nox scr vs. Nox HIF2shRNA, p = 0.0255 and Hox scr vs. Hox HIF2shRNA, p = 0.0002). Similar effects were observed at tubuli and node formation under hypoxia (<1% O2). Furthermore, real-time RT-PCR was carried out for expression analysis of hypoxia driven genes HIF1A, HIF2A, GAPDH, PGK, GLUT1, LDHA and angiogenesis related genes VEGFA and IL8.

Conclusions: Our results show that sJAM-A is upregulated in RA and OA synovial fluid compared to normal serum. In addition, we show that sJAM-A promotes angiogenesis, which of this observation may provide a novel route for controlling angiogenesis in RA.

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Soluble Junctional Adhesion Molecule-A Promotes Angiogenesis in Rheumatoid Arthritis. Bradley J. Rabquer1, George Boychev1, Jeffrey H. Ruth1, Thilo Stehle2 and Alisa E. Koch1.

1University of Michigan, Ann Arbor, MI, 2University of Michigan, University of Tuubingen, University of Michigan, Ann Arbor, MI.

Purpose: Angiogenesis is a highly regulated process of new blood vessel formation that may occur from pre-existing blood vessels. Rheumatoid arthritis (RA) is characterized by synovial hyperplasia, inflammatory cell infiltration, and neovascularization. In RA, angiogenesis is regulated by the expression of angiogenic and angiostatic growth factors, cytokines, and adhesion molecules. Junctional adhesion molecule-A (JAM-A) is a novel member of the immunoglobulin supergene family expressed by epithelial cells and endothelial cells (ECs) and mediates EC permeability, leukocyte adhesion and migration, and angiogenesis. Interestingly, JAM-A was recently found in soluble form (sJAM-A). The aim of this study was to determine if sJAM-A is present in RA synovial fluid, if it mediates angiogenesis, and which signaling pathways sJAM-A utilizes to promote angiogenesis.

Methods: We designed and performed an ELISA to determine if sJAM-A was present in normal serum and synovial fluid from patients with RA and osteoarthritis (OA). To determine if sJAM-A mediates specific angiogenic events in vitro, human microvascular endothelial cell (HMVEC) chemotaxis assays and Matrigel EC tube formation assays were performed. To determine if sJAM-A mediates in vivo angiogenesis, we performed a Matrigel plug angiogenesis assay. HMVECs were stimulated with sJAM-A to determine which signaling pathways were activated.

Results: Our results indicate that sJAM-A is present in RA synovial fluid and that sJAM-A promotes angiogenesis. sJAM-A was detectable in normal serum (n = the number of patients = 8, 0.9 (mean) ± 0.2 (SEM) ng/ml) and was significantly elevated in OA (n = 9, 3.0 ± 0.5 ng/ml) and RA (n = 10, 2.3 ± 0.5 ng/ml) synovial fluid (both p < 0.05). sJAM-A stimulated HMEC migration in a dose dependent manner that was significantly greater than phosphate buffered saline (PBS, negative control) from 5 nM to 500 nM (n = 4 experiments, p < 0.05). In addition, at 50 nM sJAM-A induced significantly more EC tubes compared to PBS (n = 3 experiments, p < 0.05) in a Matrigel in vitro tube formation assay. In an in vivo Matrigel plug angiogenesis assay, plugs containing sJAM-A had significantly more hemoglobin than those with PBS (p < 0.05). Lastly, sJAM-A stimulated the phosphorylation of Mek1/2 and Erk1/2 kinases in HMVECs in a time dependent manner.

Conclusions: Our results show that sJAM-A is upregulated in RA and OA synovial fluid compared to normal serum. In addition, we show that sJAM-A promotes in vitro and in vivo angiogenesis. These results suggest that modulation of sJAM-A may provide a novel route for controlling angiogenesis in RA.

Disclosure: B. J. Rabquer: None; G. Boychev: None; J. H. Ruth: None; T. Stehle: None; A. E. Koch: None.

1420
Invasiveness of Rheumatoid Arthritis Synovial Fibroblasts Is Affected by Extracellular RNA and DNA. Birgit Zimmermann1, Silvia Fischer1, Stephanie Lefèvre1, Angela Lehr2, Jürgen Steinmeyer2, Henning Streit3, Thomas Umscheid1, Ulf Müller-Ladner3, Klaus T. Preissner1 and Elena Neumann1.

1Dept of Biochemistry, Justus-Liebig-University Giessen, 2Dept of Experimental Orthopedics, University Hospital Giessen and Marburg, 3Dept of Internal Medicine and Rheumatology, Justus-Liebig-University Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, 4Dept of Internal Medicine and Rheumatology, Justus-Liebig-University Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, 5Dept of Orthopedics and Orthopedic Surgery, University Hospital Giessen and Marburg, 6Dept of Orthopedics and Trauma Surgery, Markuskrankenhaus Frankfurt, Germany, 7Dept of Vascular Surgery, Helios William Harvey Klinik

Background: Activated synovial fibroblasts (SF) are one of the main cell populations in the inflamed joints of patients with rheumatoid arthritis (RA). RASF contribute to synovial neoangiogenesis and are cells central for cartilage destruction. In the SCID mouse model, we could recently show the potential of RASF to migrate out of a primary implantation site, to transmigrate through vessel walls, and to leave the vasculature again at a distant implanted cartilage site. Extracellular RNA has been shown to induce neoangiogenesis, increase endothelial cell (EC) permeability and to contribute to inflammation. Extracellular DNA is also known to induce inflammation. We therefore analyzed the effects of RNA/RNAse and DNA/DNAse on the invasiveness, migratory, and endothelial transmigratory potential of RASF.

Methods: RASF were treated for 15 h with RNAse, DNase or control medium. Monolayers of different human EC were cultured on transwell inserts. For the transmigration assay, 10% FCS served as chemoattractants. After 8 h, transmigrated cells were counted. Attachment of RASF and OASF to EC was measured in a cell-to-cell binding assay. As control cells, SF from osteoarthritis (OA) patients were used. In the SCID mouse model, healthy cartilage was implanted subcutaneously with RASF at the ipsilateral site (1). At the contralateral site (C), cartilage without RASF was implanted. Before implantation and every other day the animals received i.v. injections and were divided in 3 groups: (1) 42 µg DNase/kg body weight (2) 42 µg RNAse/kg body weight; (3) saline. After 45 days, implants were removed and scored for cartilage invasion.

Disclosure: B. J. Rabquer: None; G. Boychev: None; J. H. Ruth: None; T. Stehle: None; A. E. Koch: None.
Results: Stimulation of RASF with RNase and DNase resulted in reduced synthesis of pro-inflammatory, pro-destructive and pro-angiogenic factors (e.g. IL-6, IL-8, MMP-3, VEGF). RASF showed an increased medium-dependent adherence to EC monolayers in comparison to OASF. RASF were able to pass all investigated EC monolayers. The invasion of RASF at the ipsilateral cartilage was significantly inhibited by RNase as well as DNase in comparison to saline (I saline: 2.3 +/-0.7, I RNase: 1.2 +/-0.6, p=0.048; I DNase: 0.8 +/-0.3, p=0.007). In contrast, the invasion of the contralateral cartilage was not affected by RNase or DNase (Inv C saline: 1.3 +/-0.7 vs. C RNase: 1.2 +/-0.2, p=0.74; C DNase: 1.1 +/-0.6, p=0.73). RNase or DNase did not inhibit the migration of RASF to and invasion into the contralateral implant (Inv I RNase vs. C RNase: p=0.77; I DNase vs. C DNase: p=0.35).

Conclusion: RASF are able to attach to EC and to pass different EC monolayers, reflecting the ability for vascular transmigration. Extracellular DNA and RNA reduce the secretion of pro-inflammatory and pro-destructive factors by RASF. In the SCID-mouse model, the migration to the contralateral implantation site and the invasive behavior of RASF was not inhibited by RNase or DNase treatment, whereas RASF at the primary implantation site showed a significant decrease in their invasiveness. Interestingly, the results show different properties in the response to RNase and DNase treatment of migratory and non-migratory RASF in the SCID mouse model.

Disclosure: B. Zimmermann: None; S. Fischer: None; S. Lefèvre: None; A. Lehr: None; J. Steinmeyer: None; H. Stürze: None; T. Umscheid: None; U. Müller-Ladner: None; K. T. Preissner: None; E. Neumann: None.

1422 The Role of miR-155 in the Activation of RA and PsA Synovial Fluid Monocytes. Mariola S. Kurowska-Stolarska1, Lucy Ballantine2, Bartosz E. Stolarski2, John Hunter2, Foo Y. Liew2, J. Alastair Gracie1 and Iain B. McInnes1, 1Gartnavel General Hospital, United Kingdom, 2University of Glasgow, United Kingdom

Purpose: MicroRNA (miR) network has emerged recently as an important post transcriptional regulator of immune response. Each individual miRNA species is capable of targeting a large number of distinct mRNA transcripts often belonging to one pathway. In our previous study we identified miR-155 to be strongly up-regulated in RA and PsA synovial fluid (SF) CD14+ cells compared to matched peripheral blood (PB) CD14+ cells suggesting that this miR may be involved in regulation of inflammatory pathways in arthritic joints. The aim of our study was to investigate the impact of miR-155 on the cytokine production and transcriptomic signature of RA and PsA SF monocyte and macrophage.

Methods: CD14+ cells from SF or PB of RA patients (n=14), PsA patients (n=13) and CD14+ cells from PB of healthy controls (n=6) were purified using CD14 MACS MicroBeads. PB CD14+ cells were transfected with miR-155 or scramble mimics (20 nM). Total RNA was isolated by mirNeasy kit. TaqMan miRNA and mRNA assays were used for semi-quantitative determination of the expression of miR-155 and its targets. The expressions of U68 small nuclear RNA or beta-actin were used as endogenous controls. Target prediction program and miRNA target prediction software were used to identify the cellular targets of miR-155 in SF CD14+ cells.

Results: Overexpression of miR-155 in PB CD14+ monocytes and PB CD14+ derived macrophages triggered TNF production suggesting that miR-155 may indeed be involved in post-transcriptional control of inflammatory pathways in SF monocyte. A computational target ranking system (TargetScan human 5.1, aggregate Pct above 4.0) predicted 127 mRNA targets for miR-155. To identify mRNAs that are specifically targeted in SF monocytes we cross-referenced TargetScan predictions with a list of 2312 mRNAs that were differentially expressed in SF CD14+ cells compared to PB CD14+ cells of RA (n=8) and PsA (n=7) patients (GeneChip Affymetrix U133 plus 2). This approach produced a list of 26 mir-155 targets that were relevant to SF CD14+ activation. Among them, 24 genes were up-regulated and 2 genes were down-regulated in SF CD14+ cells compared to PB CD14+ cells. Since miRs exert their function by mRNA degradation, we focused on genes that were down-regulated in SF CD14+ cells, namely SHIP1 (Src homology-2 domain-containing inositol 5-phosphatase 1) and ZNF652 (zinc finger DNA-binding protein). Expression of SHIP1 was down-regulated by 9 and 3.9 fold in SF CD14+ cells from RA (n=8) and PsA (n=7) patients, respectively. ZNF652 was decreased by 4.43 and 2.97 fold in SF CD14+ cells from RA and PsA patients, respectively. The decrease of SHIP1 and ZNF652 expression in SF monocyte was confirmed by qPCR on additional patient samples. Experimental validation revealed that the expression of SHIP1 and ZNF652 was inhibited in PB CD14+ cells transfected with mir-155 mimic compared to control mimic transfected cells (48 ±10% and 43± 7%, respectively).

Conclusion: This study identified functional miRNA-mRNA network that may be responsible for pro-inflammatory activation of synovial fluid monocyte and macrophage in RA and PsA patients.

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Rapid Improvement in Health-Related Quality of Life (HRQoL) in Gouty Arthritis Patients Treated with Canakinumab (ACZ825) Compared to Triamcinolone Acetonide. A. So², M. De Meulemeester³, A. Pikhlak, A. E. Yücel⁴, U. Arulmani⁵, D. Richard⁶, K. Stricker⁷, A. Ferreira⁸, V. Murphy⁹, P. Sallstig³ and N. Schlesinger.²

Background: Gouty arthritis is a painful inflammatory disease with a significant impact on patients’ HRQoL. In gouty arthritis, the inflammatory response is initiated by interleukin-1β (IL-1β) release, due to activation of the NALP3 inflammasome by MSU crystals. Canakinumab, a fully human anti-IL-1β antibody has a long half-life and has been shown to control inflammation in gouty arthritis. This study evaluated changes in HRQoL in gouty arthritis patients following treatment with canakinumab or triamcinolone acetonide (TA).

Methods: This was an 8-week, dose-ranging, multi-center, active controlled, single-blind study. Patients (≥18 to ≤80 years) experiencing an acute gouty arthritis flare, refractory to or contraindicated to NSAIDs and/or colchicine, were randomized to canakinumab 10, 25, 50, 90, 150 mg sc or TA 40 mg i.m. HRQoL was assessed as an exploratory endpoint at baseline and different pre-specified time-points using patient reported outcomes assessing general mental and physical component summary scores and subscale scores of SF-36® (acute version 2) and functional disability (HAQ-DI). We report HRQoL results for canakinumab 150 mg, the dose that was selected for the Phase III studies.

Results: Baseline assessments showed a major impact on the HRQoL during acute gouty arthritis. Compared to TA, canakinumab 150 mg showed greater improvements in SF-36® physical and mental component summary and subscale scores at 7 days post-dose.

In the canakinumab 150 mg group, the most severe impairment at baseline was reported for physical functioning and bodily pain; levels of 41.5 and 36.0, respectively, which improved within 7 days to 80.0 and 72.2 (mean increases of 39.0 and 35.6) approaching levels of the general US population (84.2 and 75.2).

8 weeks post-dose patients reached levels of 86.1 and 86.6 (mean increases of 44.6 and 50.6 for physical functioning and bodily pain, respectively) and these levels were higher than levels seen in the general US population. This was in contrast to patients treated with TA, who showed less improvement within 7 days (mean increases of 23.3 and 21.3 for physical function and bodily pain, respectively).

None of the scores reached levels of the general US population 8 weeks post-dose. Functional disability scores, as measured by the HAQ-DI© decreased in both treatment groups (Table).

Table. Comparison of HRQoL scores of gouty arthritis patients treated with canakinumab and triamcinolone acetonide.

<table>
<thead>
<tr>
<th>Component</th>
<th>US population¹</th>
<th>Canakinumab 150 mg s.c. Baseline N = 27</th>
<th>7 days post-dose N = 26¹</th>
<th>Triamcinolone acetonide 40 mg i.m. Baseline N = 56</th>
<th>7 days post-dose N = 54¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 subscale scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>41.5</td>
<td>(29.3)</td>
<td>40.0</td>
<td>(25.5)</td>
<td>38.4</td>
</tr>
<tr>
<td>Role-physical</td>
<td>53.0</td>
<td>(32.5)</td>
<td>71.2</td>
<td>(28.5)</td>
<td>43.2</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>47.2</td>
<td>(22.5)</td>
<td>72.2</td>
<td>(20.5)</td>
<td>35.6</td>
</tr>
<tr>
<td>General health</td>
<td>71.9</td>
<td>(26.7)</td>
<td>65.4</td>
<td>(26.5)</td>
<td>46.6</td>
</tr>
<tr>
<td>Vitality</td>
<td>53.9</td>
<td>(24.9)</td>
<td>66.6</td>
<td>(23.9)</td>
<td>6.6</td>
</tr>
<tr>
<td>Social functioning</td>
<td>61.6</td>
<td>(20.5)</td>
<td>81.7</td>
<td>(18.0)</td>
<td>52.5</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>69.0</td>
<td>(22.7)</td>
<td>72.5</td>
<td>(23.7)</td>
<td>43.2</td>
</tr>
<tr>
<td>Mental health</td>
<td>74.7</td>
<td>(21.5)</td>
<td>77.8</td>
<td>(19.1)</td>
<td>61.8</td>
</tr>
<tr>
<td>HAQ-DI³</td>
<td>0.3</td>
<td>(0.7)</td>
<td>0.3</td>
<td>(0.7)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Mean (SD) values are presented through-out; t-test some scores were missing for up to 3 patients of the group; anormalized scores representing an average US person with no chronic disease; reached general population level. NA; not available. Reference: 1. Adapted from Ware J et al. SF-35 Physical and Mental Health Summary Scales: A User’s Manual, Boston, MA: The Health Institute, 1994

Conclusions: All canakinumab doses showed a rapid improvement in physical and mental well-being of gouty arthritis patients based on SF-36® scores, in particular the 150 mg dose. In contrast to the TA group, patients treated with canakinumab showed improvement within 7 days in physical function and bodily pain approaching levels of the general population. The 150 mg dose of canakinumab was selected for further development in Phase III studies.

Toll-Like Receptor Signals Modify the ER Stress Response. Jane C. Goodall¹, Louise McNeill², Lou Ellis¹ and J. Hill Gaston³,²

During cellular stress, the decrease in protein translation caused by eIF2α phosphorylation reduces protein load in the endoplasmic reticulum (ER) which allows the cell a window of time to instigate a program of gene expression coined as the unfolded protein response (UPR). To allow the recovery of protein translation, GADD34 is activated in a negative feedback loop which dephosphorylates eIF2α and enables more efficient protein translation and recovery from cellular stress. We have previously shown that ER stress signals are induced following bacterial infection and that these signals synergise with Toll-like-receptor (TLR) signals to enhance the expression of cytokines such as IL-23.

The aim of this study was to determine if TLR signals have a reciprocal activity and modify the ER stress response and in particular the expression of GADD34, the molecule involved in translation recovery from ER stress. Monocyte derived dendritic cells (mDC) were subjected to ER stress using thapsigargin (TP) or tunicamycin (TM) in the presence or absence of different pattern recognition receptor (PRR) agonists. The expression of GADD34 mRNA and protein was induced by the ER stress stimuli, but was substantially enhanced by costimulation with LPS (TLR4), Curdian (dectin 1) or peptidoglycan (TLR2 and NOD2) agonists.

MyD88 knockdown in the monocyte cell line THP-1, abrogated the ability of LPS to enhance GADD34 expression induced by ER stress stimuli, this effect was not seen in THP-1 cells expressing a control shRNA. This suggests that MyD88 dependent signals are required for LPS upregulation of GADD34 in the presence of ER stimulation. Using specific inhibitors for defined signalling pathways we identified that upregulation of GADD34 by LPS was dependent on the activity of p38Map kinase and ERK but not JNK and NF-κB. These inhibitors did not inhibit the upregulation of GADD43 by ER stress stimuli alone, suggesting that ER stress and LPS stimuli provide independent signals that synergise to enhance GADD43 expression.

ER stress and substantial upregulation of GADD43 expression was detected in mDC and THP-1 following infection with the intracellular bacterium, Chlamydia trachomatis (CT). To determine if the upregulation of GADD43 following intracellular bacterial infection was dependent on MyD88, THP-1 cells expressing MyD88 or a control shRNA were infected with CT and GADD43 expression was analysed. The upregulation of GADD34 was substantially reduced in THP-1 cells expressing MyD88 shRNA suggesting that MyD88 dependent TLR signals were required for this effect.

These data show that the regulation of protein translation has not only the potential to be modulated via ER stress but also via the stimulation of PRR pathways. This may have significant implications for the expression of pro-inflammatory or regulatory cytokines. We hypothesize that changes in GADD43 expression induced by TLRs can contribute significantly to the expression of myeloid cells to secrete pro-inflammatory cytokines in response to bacterial infection.

Disclosure: J. C. Goodall: None; L. McNeill: None; L. Ellis: None; J. H. Gaston: None.

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Background: Canakinumab (a fully human anti-interleukin-1β monoclonal antibody) has been recently approved by the FDA for the treatment of familial cold auto-inflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) and by the EU for the treatment of cryopyrin-associated periodic syndrome (CAPS). This spectrum of autoinflammatory disease is caused by overproduction of IL-1β and is associated with rash, constitutional inflammatory symptoms and marked fatigue. Health-related quality of life (HRQoL) was assessed during a phase III, open-label, multi-center study to evaluate the direct impact of the disease on patients’ well-being and to assess the long-term maintenance of HRQoL.

Methods: The 119 adult CAPS patients in this study were canakinumab naïve (n=71) or rolled-over from earlier Phase II/III studies (n=48). They received canakinumab 150 mg s.c. every 8 weeks and HRQoL was assessed using the following domains: general physical and mental health (SF-36® physical and mental component summary [PCS and MCS]), fatigue (FACIT-Fatigue®) and functional disability (HAQ-DI).

Results: Median duration of exposure to canakinumab in the study was 414 days (range 29–687 days). Of the 119 adult CAPS patients there were 25 FCAS, 80 MWS, 14 NOMID [6 NOMID] patients. In canakinumab naïve patients the baseline scores (mean [SD]) for physical function (SF-36® PCS: 41.2 [10.9]) and mental health (SF-36® MCS: 45.5 [10.7]) and fatigue (FACIT-F: 32.8 [11.7]) were considerably lower than those expected in the general population (50 [10] for SF-36® PCS and MCS and 43.6 [9.4] for FACIT-F), which demonstrates the significant impact that CAPS has on patients’ well-being. The scores improved rapidly after one single dose of canakinumab and approached levels of the general population after 8 weeks (SF-36® PCS, 48.4 [8.7] and MCS, 52.8 [7.7]; FACIT-F, 41.7 [9.3]). This improvement was maintained at one year, as shown by the SF-36® PCS (49.8 [8.6]) and MCS (51.2 [9.9]) and FACIT-F (42.9 [10]) scores. For patients who continued one year for up to two years HRQoL scores remained within the range of general population at the final visit. An improvement in functional disability was also observed as shown by HAQ-DI scores, although the level of functional disability in these patients as measured by the HAQ was not marked. Patients who rolled-over from previous studies while maintaining the 8 weeks dosing schedule already had HRQoL scores close to general population levels at baseline and these levels were maintained throughout the study.

Conclusions: Canakinumab administration improved the HRQoL scores to levels seen in the general population in a large cohort of CAPS patients across all severity phenotypes.

Disclosure: A. Dunne: None; L. Mielke: None; J. Tschopp: None; K. H. G. Mills: None; G. M. McCarthy: None.

Osteoarthritis-Associated Basic Calcium Phosphate Crystals Activate the NLRP3 Inflammasome in a Syk Kinase Dependent Manner. Aisling Dunne1, Lisa Mielke2, Jurg Tschopp3, Kingston H. G. Mills4 and Geraldine M. McCarthy5.

1Royal College of Surgeons, Ireland & Mater Hospital, Ireland, 2Trinity College Dublin, Ireland, 3University of Lusanne, Switzerland

Background: Basic calcium phosphate (BCP) crystals which were traditionally considered markers of osteoarthritis-associated (OA) tissue damage are now themselves considered potent drivers of pro-inflammatory cytokine production. In this study we investigated the ability of BCP crystals to activate IL-1β and IL-18 production through activation of the NLRP3 (NOD-like Receptor (NLR) Protein 3) inflammasome complex. In addition we assessed the ability of these crystals to induce neutrophil influx in an in vitro peritonitis model and to skew T cell responses towards a Th17 phenotype.

Methods: Murine and human dendritic cells (DC) were stimulated with BCP crystals, with or without priming with a Toll-like receptor (TLR) agonist and IL-1β and IL-18 production was quantified by enzyme linked immunosorbent assay (ELISA). Specific inhibitors of caspase-1 and NLRP3-deficient cells were used to determine the role of caspase-1 and the NLRP3 inflammasome complex while a role for Syk and PI3 kinase was determined with the use of the inhibitors piceatannol and LY294002, respectively. BCP-activated DC were tested for their ability to promote T cell responses using FACS analysis following treatment of splenocytes or purified CD4+ T cells with supernatants from BCP-treated DC. Finally, BCP-induced neutrophil infiltration was assessed using an in vivo peritonitis model.

Results: Physiological concentrations of BCP crystals (50µg/ml) induced robust IL-1β and IL-18 production in a caspase-1 and NLRP3 dependent manner. IL-1β was produced at an average concentration of 2 ng/ml following a 2 hour treatment of LPS-primed DC while IL-18 production averaged at 200 pg/ml under the same conditions. This activity is dependent on the synergistic action of IL-1α and IL-1β. Pre-incubation of sub-optimal doses of bafilomycin and quinidine, the potassium channel blocker, caused a 2-fold reduction in IL-1β levels. In addition, pre-incubation with specific Syk and PI3 kinase inhibitors abrogated both IL-1β and IL-18 production. In addition to IL-1β, BCP crystals greatly enhanced the production of the Th17 skewing cytokines IL-1α and IL-23 and incubation of splenocytes or purified CD4+ T cells with supernatants from BCP treated DC promoted Th17 cell differentiation. Finally, BCP crystals promoted robust neutrophil influx in a model of crystal induced peritonitis after 6 hours.

Conclusion: Our findings demonstrate that BCP crystals induce the pro-inflammatory cytokines IL-1, IL-18 and IL-17 via activation of the NLRP3 inflammasome and identify the inflammasome, Syk kinase and PI3 kinase as potential targets for the treatment of BCP crystal-induced inflammation and tissue destruction seen in OA patients.

Disclosure: A. Dunne: None; L. Mielke: None; J. Tschopp: None; K. H. G. Mills: None; G. M. McCarthy: None.

1427 Lipid-Cytokine-Chemokine Cascade Drives Neutrophil Recruitment in a Murine Model of Inflammatory Arthritis. Nancy D. Kim1, Richard C. Choi1, Christian Sadik2, Edward Seung2, Yinan Lan2, Yoichiro Iwakura4 and Andrew Luster1.

1Dartmouth-Hitchcock Medical Center, Lebanon, NH, 2Massachusetts General Hospital, 3Massachusetts General Hospital, Boston, MA, 4University of Tokyo

Purpose: A diverse array of chemotactic agents control leukocyte trafficking, but how these apparently redundant signals collaborate in vivo is still unknown. We previously demonstrated an absolute requirement for the lipid chemotactic agent leukotriene B4 (LTB4) and its receptor BLT1 for neutrophil recruitment into the joint in the development of immune complex-induced arthritis. The purpose of these studies was to further dissect the sequential roles of LTB4, IL-1β, and chemokine signaling in neutrophil recruitment in this model of inflammatory arthritis.

Methods: Using the K/BxN serum transfer arthritis mouse model, K/BxN serum was injected into C57Bl/6 (BLT1−/−, CXC2R−/−, CCR1−/−, and CXC2R−/−CCR1−/− mice, and arthritis was assessed by hind paw measurement and clinical scoring. Bone marrow neutrophils from IL-1α/β−/− mice were purified and injected for neutrophil adoptive transfer studies. On designated days, synovial fluid leukocytes and neutrophils and synovial tissue were isolated, and chemokine, chemokine receptor, and
cytokine transcription and production were analyzed by quantitative PCR and ELISA. Primary murine fibroblast-like synovocytes (FLS), endothelial cells, and macrophages were stimulated in vitro with recombinant murine IL-1β or TNF-α, and neutrophil-active chemokine expression was measured by qPCR.

**Results:** Synovial fluid analysis demonstrated that CCR1 was the predominant neutrophil chemokine receptor in the early phase of disease, and CXCR2 was the predominant neutrophil chemokine receptor in established disease. Synovial fluid neutrophils produced IL-1β and the neutrophil-active chemokines CCL3/MIP-1α and CXCL2/MIP-2. In contrast, synovial tissue expressed greater proportions of the neutrophil-active chemokines CXCL1/KC and CXCL5/LIX. Adoptive transfer of IL-1α/β−/− neutrophils into BLT1−/− mice was not able to restore disease or chemokine expression. In vitro IL-1β-stimulated FLS and endothelial cells expressed primarily CXCL5/LIX and CXCL1/KC, respectively. Finally, upon induction of K/BxN serum transfer arthritis, CCR1−/− mice had delayed and attenuated disease compared with wild-type mice, while CXCR2−/− mice had normal onset of disease that quickly waned. Importantly, deletion of both CCR1 and CXCR2 in the mice completely abrogated arthritis development.

**Conclusions:** In this model of acute autoantibody-induced arthritis, we uncovered a sequence of events in which a lipid receptor (BLT1) initiates disease by promoting the influx of neutrophils producing IL-1β, which then induces CXCL1/KC and CXCL5/LIX from surrounding synovial tissue. Synovial fluid leukocytes themselves also produce CXCL5/LIX and CXCL2/MIP-2, promoting further neutrophil trafficking into the joint. CCR1 and CXCR2 operate in series to mediate all chemokine-dependent neutrophil trafficking into the joint of arthritis. Thus, we have demonstrated that neutrophil trafficking into the joint is tightly regulated and dependent on the interplay of multiple cytokine and chemotactic pathways.

**Disclosure:** N. D. Kim: None; R. C. Chou: None; C. Sadik: None; E. Seung: None; Y. Lan: None; Y. Iwakura: None; A. Luster: None.

**ACR Concurrent Abstract Sessions**

**Education**

Tuesday, November 9, 2010, 4:30 PM–6:00 PM

**1428**

The Impact of Patient-Physician Relationship Components on Physician Trust and Treatment Adherence in Patients with Rheumatic Disease.

Sofia de Achaval1, Michael A. Kallen1, Vanessa L. Cox1, Marsha N. Richardson1 and Maria E. Suarez-Almazor2. 1The University of Texas M. D. Anderson Cancer Center, Houston, TX, 2University of Texas, MD Anderson Cancer Center, Houston, TX

**Background:** Treatment adherence plays a significant role in the successful management of rheumatic disease. Adherence itself may be influenced by patient-physician relationship factors and a patient's overall physician trust.

**Purpose:** We investigated whether specific components of the patient-physician relationship were directly associated with the more global concept of physician trust; we then assessed the extent to which these relationship components influenced treatment adherence via their impact on overall physician trust.

**Methods:** We performed a cross-sectional study of outpatient clinic patients with rheumatic disease, i.e., Rheumatoid Arthritis (RA) or Systemic Lupus Erythematosus (SLE). Six specific components of the patient-physician relationship were measured: doctor informativeness, sensibility to concerns, reassurance and support, patient centeredness, participatory decision-making, and patient disclosure of information. Patient’s physician trust was evaluated using the Wake Forest Physician Trust Scale, while treatment adherence was measured via the Compliance Questionnaire Rheumatology (CQR). A conceptual model was developed, with the relationship component variables predicting trust, and trust predicting adherence. We statistically assessed bivariate relationships across all model variables, using Pearson product-moment correlations. We then conducted a path analysis to test our conceptual model and identify statistically significant direct, indirect, and total effects of the conceptual model’s patient-physician relationship variables on physician trust and adherence. Path analysis’ particular strength lies in its capacity to model and then simultaneously estimate a number of regression equations when exploring complex relationships. For the path analysis we analyzed the model variable covariance structure.

**Results:** Our sample included 311 patients (201 with RA and 110 with SLE). Eighty percent of patients were female; mean patient age was 46 years. Bivariate correlations were all positive and statistically significant (p<0.05) and ranged from 0.25–0.79. In the path analysis, 4 of 6 relationship component variables (doctor informativeness, reassurance and support, patient centeredness and participatory decision-making) were found to have statistically significant direct effects on trust and indirect effects on treatment adherence; trust had a statistically significant direct effect on adherence. The overall path analytic model displayed good fit to the data (chi-square=2.56, p=0.63, RMSEA<0.01).

**Conclusion:** Patients’ perceptions of multiple specific components of their relationship with their physician are associated with patient trust in their physician, which is strongly related to treatment adherence, with greater trust enhancing adherence. Modifications to specific components of the patient-physician relationship, namely doctor informativeness, reassurance and support, patient centeredness and participatory decision-making, could potentially improve treatment adherence by increasing physician trust.

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**1429**

Development of an ACGME Core Competency-Based Electronic Portfolio at the USC-LAC Rheumatology Fellowship Program. Karina Mari- anne D. Torralba, Francisco P. Quismorio, Beatrice A. Boa teng and Shylaja Rachabattula. 1Arkansas Children’s Hospital-University of Arkansas for Medical Sciences, 2University of Southern California-Los Angeles County Medical Center, Pasadena, CA, 3University of Southern California-Los Angeles County Medical Center, Los Angeles, CA, 4University of Southern California-Los Angeles County Medical Center

Portfolios have been utilized in health sciences education over the past 10 years to document and assess progress in training, and as a vehicle for reflection on lifelong learning. The Accreditation Council for Graduate Medical Education (ACGME) has encouraged the use of core-competency based portfolios for postgraduate training, but current and convenient formats have not been widely available. The objectives of this study are to assess the effectiveness of paper-based portfolios in our program in demonstrating achievement of ACGME core competencies, and to develop an electronic portfolio that would conveniently document evidences according to these competencies. We conducted a systematic review of paper-based fellow portfolios over the past 7 years using the following parameters: evidence management, demonstration of fulfillment of core competency criteria, ability to show reflections of lifelong learning. Our fellowship program has 2-3 fellows at each training year level. Our review revealed that evidences of education and performance (eg. conference presentations, letters to patients and insurance companies, Mini-CEX, 360 degree evaluations) were not organized according to competency mainly due to 1) physical limitations of paper portfolios to adequately show that certain evidences had applicability to 2 or more than one competency, and 2) lack of perception by learners of what educational activities and evidences were pertinent to specific competencies. There was also a lack of reflection on self-assessment of educational progress. An institution-based software for residency management (Veriﬁn®) which is mainly used by faculty and fellows to access evaluations and procedure logs was inadequate to assess achievement of competencies. As a result, over the past 2 years, a Microsoft® Word-based portfolio was developed and implemented at our institution. We initially asked fellows and key faculty to identify the applicability of core competencies according to the various educational activities and evidences in the program. Activity/ evidence-based and competency-based rubrics were then developed to help establish levels of achievement that could help fellows understand criteria for improvement and allow faculty raters for evaluation. The electronic format permitted filing of evidences under multiple competencies using hyperlink and cross-referencing functions. Self-assessments using reflection were also developed. Our MS Word portfolio adequately demonstrates achievements of ACGME competencies. We seek to further evaluate the effectiveness of this portfolio and the evaluation rubrics as mentorship and career development tools.

**Disclosure:** K. M. D. Torralba: None; F. P. Quismorio: None; B. A. Boa teng: None; S. Rachabattula: None.
A Case-Controlled Study of a Multimodal Rheumatology Elective for Medical Residents. Deana M. Lazaro1, Sheen Yee Lim1, David R. Blumenthal1, Joshua Scheers-Masters1, Jeanne Macrè1 and Matthew Avital1.

SUNY Downstate Medical Center, SUNY Downstate-Brooklyn, Brooklyn, Medical Residents.

A Case-Controlled Study of a Multimodal Rheumatology Elective for Medical Residents. Deana M. Lazaro1, Sheen Yee Lim1, David R. Blumenthal1, Joshua Scheers-Masters1, Jeanne Macrè1 and Matthew Avital1.

Purpose: Basic immunology is a rapidly advancing area, with numerous clinical advances stemming from basic immunologic insights. Educating rheumatology fellows in training on basic immunology topics remains a challenge. Residents begin rheumatology programs having matriculated in widely different medical school and internal medicine environments. Balancing basic immunology concepts, experimental methods, and review of classic and recent immunology literature is a challenge, while maintaining a clinically relevant approach to the topic.

In an attempt to improve the basic immunology curriculum for our rheumatology fellows in training, we updated the immunology course to incorporate a clinically oriented text, lectures from clinical and basic research faculty, journal club style presentation of papers by fellows, and lectures by clinicians and basic researchers from industry.

Exam scores from a pre-test and post course test are compared.

Methods: 4 fellows (two 2nd year fellows, two 1st year fellows) completed the course. The course is taught from January to April. It consisted of 2 weekly sessions, 2 hours each, for 13 weeks. The text chosen for the course was Chapel et al Essentials of Clinical Immunology, 5th edition, 2006. Fellows were given weekly reading assignments from the text. One weekly session consisted of didactic lectures by immunology and clinical rheumatology faculty, covering key chapters from the text. The second weekly session consisted of discussion of journal papers from immunology literature. Papers were picked by rheumatology fellows to cover recent topics discussed in didactic lectures. Finally, clinical science liaisons and basic researchers from industry were invited to present unbranded talks covering basic immunology topics relevant to therapeutics in rheumatology. Participating fellows in training were given a pre-test at the start of the course, as well as a post-test at the conclusion of the course, with 30 multiple choice questions, written by immunology faculty. The pre and post tests included different questions, covering similar topics in basic immunology.

Results: Pre and post-test results were available for 3 fellows (1 fellow was absent on the pre and post test date). Results for the pre-test were 33 and 33% for both first year fellows, and 73% for 2nd year fellows with post-test results of 73 and 67% for first year fellows, and 87% for 2nd year fellow. All fellows showed an increase between pre to post test results, ranging from absolute increases of 15% to 34%.

Conclusions: Our experience suggests that rheumatology fellows’ understanding of immunologic topics, as reflected by increases between pre and post test exam results, showed improvement. Further longer term data, including measuring outcomes from the rheumatology in-service exams and board certification scores, would help support whether this approach can lead to long term successful education of fellows in training on immunologic topics.

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A Case-Controlled Study of a Multimodal Rheumatology Elective for Medical Residents. Deana M. Lazaro1, Sheen Yee Lim1, David R. Blumenthal1, Joshua Scheers-Masters1, Jeanne Macrè1 and Matthew Avital1.


Background: Training medical residents to treat patients with musculoskeletal complaints is highly desirable because of the aging United States population and relative shortage of rheumatologists. To address this concern, we tested whether first year medical residents who have clinical experience in Rheumatology clinic and an enhanced curriculum will perform better than residents without such experience on a multiple choice examination and an objective structured clinical examination (OSCE). We also surveyed the residents on their confidence and attitudes regarding musculoskeletal diseases.

Methods: Thirty-five SUNY Downstate first-year medical residents were randomized to participate in the ambulatory Rheumatology elective or another subspecialty experience for four weeks. All residents reviewed the MedStudy guide for Rheumatology and several Hopkins modules and received a copy of the Primer on the Rheumatic Diseases. The residents assigned to Rheumatology clinic were given access to 12 case-based learning modules with questions based upon the material, a video on the musculoskeletal physical examination, instruction on arthrocentesis and injection techniques using simulators, approximately 3 out-patient Rheumatology clinic sessions each week and weekly journal club. All residents completed a 45 question pre- and post-test, 4 OSCE stations focused on the evaluation and treatment of musculoskeletal diseases and completed a pre- and post-questionnaire to gather information on the confidence of the residents in their knowledge of Rheumatology.

Summary of the Results: All residents improved performance on the multiple choice examination after the clinical rotations, however, there was no significant difference in the improvement rate pre- and post- rotation between the groups (p = 0.18). Likewise performance on the OSCE was similar with the exception of the station on arthrocentesis. The residents who received a training session on arthrocentesis and injection technique and had the opportunity to interact with patients in the rheumatology clinic performed significantly better (p = 0.02). The residents assigned to the rheumatology clinic reported greater confidence in their ability to treat patients with arthritis (p = <0.001).

Conclusions: Exposure of medical residents to an enhanced curriculum and experience in rheumatology clinic improved performance of arthrocentesis as demonstrated on a simulator and increased their perception of their abilities. Rate of improvement on the multiple choice examination and the other OSCE stations were not significantly different between the two groups.

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Effect of Internal Medicine Resident Participation in Team-Based Learning on In-Training Exam Scores in Rheumatology. Karina Mari- anne D. Torralba1, Beatrice A. Boateng1, Ron Ben-Ari2 and Francisco P. Quismorio1.

1Arkansas Children’s Hospital-University of Arkansas for Medical Sciences, 2University of Southern California-Los Angeles County Medical Center, Los Angeles, CA, 3University of Southern California-Los Angeles County Medical Center.

Objective: Team-based learning (TBL) has been utilized as a teaching strategy for Rheumatology core curriculum learning sessions (CCLSs) of residents at the University of Southern California-Los Angeles County Internal Medicine Residency program since 2008. TBL is an interactive small group learning technique that encourages accountability, teamwork and has been demonstrated to improve board scores and patient care. This study seeks to examine if there is a correlation between attendance and participation in TBL sessions on the Rheumatology component of the Internal Medicine In-training exam (IM-ITE) scores.

Method: There have been 13 TBL-CCLSs over a two-year period (2008/09 and 2009/10) on various connective tissue diseases including rheumatoid arthritis, osteoarthritis, myopathies and spondylarthropathies. Resident attendance of TBL sessions and their ITE scores were recorded. Data was collected on two groups: group 1 represents residents who were in their year 1; residency when the TBL sessions started and group 2 are those who were in year 2. Of 129 residents, 117 participated in TBL-CCLSs over the 2-year period. Twelve residents did not participate in any TBL session; however their ITE scores are included in the analysis. ANOVA, T-test and Scheffe’s post-hoc analysis were used to analyze the data.

Results: TBL-CCLSs were required for residents however they are not always able to attend due to other responsibilities. Data were stratified into quartiles based on total attendance: no attendance; low, ≤4 times; medium, 5–9 times; high, ≥10. The average attendance was 3.17 ± 2.12 (SD). There was an increase in ITE scores over the two-year period. TBL participation had no significant effect on ITE scores (ANOVA). Scheffe’s post-hoc analysis was conducted to determine if there were any significant differences among the three levels of attendance in TBL. There was a significant difference in the mean ITE scores of residents with medium attendance (5–9 sessions) when compared to those with low attendance (1–4 sessions) (p < 0.05). This implies that residents that participated in 5–9 TBL-CCLSs over a two-year period were more likely to have significantly higher Rheumatology ITE scores than those who participated in less than 5 sessions.

Conclusions: There was no statistically significant increase in the overall ITE scores over the two-year period. However, residents participating in 5–9 TBL-CCLSs were more likely to have significantly higher Rheumatology ITE scores when compared to those that did not participate or participated in less than five sessions.

Disclosure: K. M. D. Torralba: None; B. A. Boateng: None; R. Ben-Ari: None; F. P. Quismorio: None.
**Tocilizumab in Patients with Systemic Juvenile Idiopathic Arthritis: Efficacy Data from the Placebo-Controlled 12-Week Part of the Phase 3 TENDER Trial**

**Title:** Tocilizumab in Patients with Systemic Juvenile Idiopathic Arthritis: Efficacy Data from the Placebo-Controlled 12-Week Part of the Phase 3 TENDER Trial

**Authors:** Fabrizio De Benedetti,1 Hermine Brunner,2 Nicola Ruperto,2 Immaculada Calvo,3 Ruben Cuttica,4,5 Clara Malattia,6 Rayef Schneidder,6 Patricia Woo,7 Carine H. Wouters,3 Ricardo Xavier,6 Lawrence S. Zemel,8 Helen Emery,1 and Gregory Gardner.2 1Seattle Therapeutics

**Purpose:** Systemic juvenile idiopathic arthritis (sJIA) is the most severe form of JIA and is characterized by arthritis and prominent systemic manifestations. Interleukin-6 (IL-6) plays a pivotal role in sJIA pathogenesis. Tocilizumab (TCZ), an anti-IL-6 receptor antibody, was shown to be effective in a Japanese phase 3 placebo-controlled, withdrawal-design trial in patients with sJIA. We report 12-week efficacy data from the global phase 3 TENDER trial in patients with sJIA.

**Methods:** Patients with active sJIA (age range, 2–17 years; disease duration, ≥6 months; inadequate response to previous NSAIDs and corticosteroids) were randomly assigned 2:1 to receive TCZ every 2 weeks (8 mg/kg for patients ≥30 kg body weight; 12 mg/kg for patients <30 kg) or placebo (control). Stable doses of NSAIDs and methotrexate were continued, and corticosteroid tapering was allowed from week 6. Patients who qualified for rescue therapy received standard of care, were offered open-label TCZ, and were considered nonresponders. Primary end point was the proportion of patients with JIA ACR30 response plus absence of fever at week 12 (ITT analysis).

**Results:** The ITT population consisted of 112 patients (37 controls, 75 TCZ). Baseline characteristics were similar between groups. By week 12, 32% of patients in both arms (1 control, 2 TCZ) withdrew from the study, and more control than TCZ patients required rescue therapy (54% vs 3%). Significantly more TCZ patients experienced JIA ACR30 response plus absence of fever at week 12 compared with controls (85% vs 24%, p=0.0001). Additionally, significantly more TCZ patients than controls achieved JIA ACR50/70/90 response (Table A). Of the patients who had fever at baseline, significantly more TCZ patients than controls had no fever at week 12. Similarly, of those patients with anemia or thrombocytosis at baseline, significantly more patients treated with TCZ than control had normal hemoglobin levels or normal platelet counts, respectively (Table A). A considerable proportion of TCZ patients achieved ACR70/90 responses, even in subgroups where baseline characteristics included a high number of active joints, fever, or a high platelet count, and in those treated with prior biologic therapy (Table B). Four serious adverse events were reported in 3 TCZ patients—angiodyema and urticaria (1), varicella (1), and bacterial arthritis (1)—all of which resolved without sequelae.

**Conclusions:** These results show that TCZ is highly effective in treating sJIA, as shown by the clinically relevant JIA ACR70 and ACR90 responses, irrespective of baseline characteristics such as active joint disease, fever, high platelet count, and previous biologic therapy.

Table A. Efficacy Outcomes at Week 12

<table>
<thead>
<tr>
<th>Control, n = 37</th>
<th>TCZ, n = 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>JIA ACR50 responses, n (%)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>JIA ACR70 responses, n (%)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>JIA ACR90 responses, n (%)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>No fever after having a fever at baseline, n (%)</td>
<td>5/24 (21)</td>
</tr>
<tr>
<td>Normal hemoglobin after having anemia at baseline, n (%)</td>
<td>2/29 (7)</td>
</tr>
<tr>
<td>Normal platelet count after having thrombocytosis at baseline, n (%)</td>
<td>1/26 (4)</td>
</tr>
</tbody>
</table>

Table B. Efficacy Outcomes at Week 12 by Select Baseline Characteristics, n/n (%)

<table>
<thead>
<tr>
<th>TCZ, n = 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 30 + absence of fever</td>
</tr>
<tr>
<td>ACR70</td>
</tr>
<tr>
<td>0–9</td>
</tr>
<tr>
<td>10–29</td>
</tr>
<tr>
<td>30–71</td>
</tr>
<tr>
<td>Fever status (last 7 d)</td>
</tr>
<tr>
<td>Fever present</td>
</tr>
<tr>
<td>Fever free</td>
</tr>
<tr>
<td>Platelet countb ≤ULN</td>
</tr>
<tr>
<td>&gt; ULN</td>
</tr>
<tr>
<td>Previous anakinra use Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Previous TNF-inhibitor use Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

**ITN analysis:** analysis adjusted for randomization stratification factors applied at baseline.

b p < 0.0001.

Data missing for 3 patients.

Study: Herein we report the long-term safety, tolerability, and efficacy of canakinumab 150 mg s.c. or 2 mg/kg s.c. (body weight) rolled-over from earlier Phase II/III studies. Patients received canakinumab every 8 weeks. In case of an incomplete response patients could be changed to a more intense dosing regimen (received an additional dose of canakinumab as: physician’s global assessment of disease activity and skin assessment minimal along with the physician’s global assessment of disease activity minimal or (b) physician’s global assessment of disease activity ≤ minimal and normal CRP and/or SAA values (≤ 10 mg/L). Relapse was defined as: serum levels of CRP and/or SAA >30 mg/L and (a) physician’s global assessment of disease activity > minimal or (b) physician’s global assessment of disease activity minimal along with the assessment of skin disease > minimal.

Results: Of 47 pediatric patients (3–17 years) (1 patient did not have CAPS and was discontinued [protocol violation] and of the remaining 46 patients there were 5 FCAS, 23 MWS, 18 MWS/NOMID [includes 8 NOMID] patients), 38 were canakinumab-naive, while 9 had been pre-treated with canakinumab. 43 (92%) completed the study and 3 patients discontinued the study (1 due to adverse event [AE]). The median duration of exposure to study drug was 290 days (range: 29–625 days). Complete response was achieved in most (n = 26, 68%) of canakinumab-naive pediatric patients. The majority of canakinumab treated pediatric patients were relapse free (29 out of 35 [83%]) and 6 patients experienced a relapse. Dose adjustments were required in 16 patients (34%). Amongst all NOMID patients (including MWS/NOMID overlap) 15 (47%) received at least one dose or frequency adjustment. In canakinumab-naive patients median CRP and SAA levels rapidly decreased within 7 days (2.5 and 7.4 mg/L [baseline levels were 14.8 and 40.6 mg/L, respectively]) and these levels were maintained at normal levels (<10 mg/L) during the study (both in naive and roll-over patients). The most frequent AEs were rhinitis, nasopharyngitis and headache. Serious AEs were reported in 6 pediatric patients. Most patients (n = 43, 91%) had no injection site reactions.

Conclusions: Canakinumab s.c. every 8 weeks induced rapid and sustained clinical and biochemical remission in pediatric patients across all severity of CAPS phenotypes. Adjustment of dose appears to be predominantly applied in pediatric and/or NOMID patients. Long-term tolerability and safety was good.

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Prevention of Flare Recurrences in Childhood Refractory Chronic Uveitis: An Open-Label Comparative Study of Adalimumab Versus Infliximab. GABRIELE Simonini 1, Andrea Taddeo 2, Marco Cattalini 1, Roberto Caputo 1, Cinzia De Libero 3, Cecilia Breschi 4, Monica Lorusso 5, Samuele Naviglio 6, Loredana Lepore 7 and Rolando Cimaz 8. 1Department of Sciences and Technology, University of Trieste, Trieste, Italy, 2Pediatric Clinic, University of Brescia, Brescia, Italy, 3Rheumatology Unit, U.S. Children’s Hospital, Firenze, Italy, 4Pediatric Clinic, Parma University, Parma, Italy, 5Pediatric Clinic, University of Florence, Florence, Italy.

Background: Up to now, no data are available about the comparison in efficacy and safety of Adalimumab versus Infliximab in treating chronic, refractory uveitis in childhood.

Objective: To compare the efficacy and safety of Adalimumab versus Infliximab in an open-label prospective, comparative, multi-centre, cohort study of childhood non-infectious chronic uveitis.

Methods: 33 patients (22 F, 11 M; median age: 9.17 years) with refractory vision threatening non-infectious uveitis, were enrolled, over 28 months, to receive, for at least 1 year, Infliximab (5 mg/kg at weeks 0, 2, 6 and then every 6–8 weeks) or Adalimumab (24 mg/sq.mt, every 2 weeks). Primary outcome was to assess, once remission was achieved, the time of a first relapse during time treatment. Time to remission, time to steroid discontinuation and the number relapses, were also considered.

Results: 16 children (12 with Juvenile Idiopathic Arthritis [JIA], 3 with idiopathic uveitis, 1 with Behçet’s disease) were recruited in the Adalimumab cohort; 17 children (10 with JIA, 5 with idiopathic uveitis, 1 with early-onset sarcoidosis, 1 with Behçet’s disease) into the Infliximab group. Cox-regression analysis did not show statistical significant differences between the two groups with regard to time to achieve remission, and time to steroid discontinuation, whilst showed a higher probability of uveitis remission on Adalimumab during the time of treatment entered for each cohort (Mantel-Cox \( \chi^2 \) 6.83, p < 0.001).

Adalimumab

Infliximab
Among children who relapsed, at 40 months follow-up, the median number of relapses resulted statistically significantly higher in Infliximab versus 1 range 1–5, respectively, p < 0.001.

Conclusion: Even if limited to a relatively small group, our study suggests that, at 3 year treatment, Adalimumab is more efficacious than Infliximab in maintaining remission of chronic childhood uveitis.

Disclosure: G. Simonini: None; A. Taddio: None; M. Cattalini: None; R. Caputo: None; C. De Libero: None; C. Bresei: None; M. Lorusso: None; S. Naviglia: None; L. Lepore: None; R. Cimaz: None; C. Bresci: None; R. Caputo: None; M. Cattalini: None; F. Baroni: None; J. F. Bonfa: None; G. Trudes: None; V. T. Viana: None; M. Timenetsky: None; A. R. Precioso: None; R. M. R. Pereira: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ) 301411/2009-3, 2; G. Trudes: None; A. C. M. Ribeiro: None; C. G. Saad: None; V. T. Viana: None; M. Timenetsky: None; A. R. Precioso: None; R. M. R. Pereira: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ) 300559/2009-7, 2.

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Mortality/Morbidity in Cardiac Neonatal Lupus and Associated Maternal/Fetal Risk Factors. Peter M. Izmirly1, Amit Saxena1, Zoey Smith1 and Jill P. Buyon1. NYU School of Medicine, New York, NY, 2NYU School of Medicine

Purpose: The classic cardiac manifestations of neonatal lupus (cardiac-NL) include a spectrum of conduction dysfunction (1st, 2nd, or 3rd degree heart block (CHB)) and more rarely cardiomyopathy which can be absent any conduction disease. This study was undertaken to update the mortality data of cardiac-NL in a large US based cohort and identify associated risk factors to further understand the pathogenesis of anti-SSA/Ro mediated injury and provide evidence based data for counseling women with these antibodies.

Methods: Three hundred and one children with cardiac-NL (295 with CHB and 6 with isolated cardiomyopathy) enrolled in the Research Registry for Neonatal Lupus (RRNL) had sufficient medical records for analysis. The RRNL database was analyzed for the following potential mortality maternal risk factors: age at pregnancy, race/ethnicity, anti-SSA/La antibody status, health status and fetal risk factors: time of diagnosis, exposure to maternal non-fluorinated and fluorinated steroids during pregnancy, method of delivery, and gender. In addition, morbidity was assessed by the frequency of pacemaker placement and cardiac transplant.

Results: Follow up of the children ranged from in utero death to adulthood. Of the 301 children with cardiac-NL, 53 (17.6%) died. Thirty children died in utero or at birth, 41% died prior to six months of postnatal life and the remaining 29% died after 6 months. Mortality was higher among children born to non-Caucasian mothers compared to Caucasian mothers (33% vs 15%, p = 0.003). Maternal age was equivalent between the groups (29.1 years vs 29.7 years). The maternal presence of anti-SSA/La antibodies was 74% for those whose children died and 63% for those whose children survived, which was not significant. A maternal diagnosis of Sjogren’s
Syndrome and/or Systemic Lupus Erythematosus was not significantly associated with cardiac-NL death (53% in death vs 44%) suggesting that prior knowledge of maternal antibody status did not influence mortality. With regard to fetal factors, 86% of those who died were diagnosed with cardiac-NL during pregnancy compared to 85% who survived. For those diagnosed during pregnancy there was a trend towards early gestational diagnosis for those children that died compared to those that survived (21 vs 23.5 weeks p=0.09). There was also a trend toward higher exposure to maternal fluorinated steroids after the diagnosis in children that died (53% vs 40% p=0.09), however there was no difference in maternal use of non-fluorinated steroids in those that died vs those that survived (19% vs 16%). Most fetuses were delivered by C-section and this was not significantly associated with death (70% dead vs 75% live). Female gender was also not associated with outcome (49% who died were female vs 52% live). Eighty-five percent of fetuses were delivered by C-section and this was not significantly associated with outcome (49% who died were female vs 52% live). Eighty-five percent of children received a pacemaker, 43% within 9 days of birth, 20% between 9 days and one year. Five children (2%) received a heart transplant.

Conclusion: Based on data from this large cohort, 17.6% of children born with cardiac-NL die from complications of the disease. Eighty-five percent required pacing and two percent required cardiac transplantation. Mortality was more prevalent in children born to non Caucasian mothers.

Disclosure: P. M. Izmirly: None; A. Saxena: None; Z. Smith: None; J. P. Buyon: NIAMS-NIH, 2, NIH, 2.

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Methotrexate in Children with Juvenile Localized Scleroderma: A Randomized, Double-Blind, Placebo-Controlled Trial.

A. Saxena,1 Cristina Vallongo2, Cristina Vidal-Fuente1, Maria Alessio3, Francesco La Torre4, Mario Cutrone5 Anna Belloni-Fortina6.
1Children’s Hospital of Mestre, 2Dermatology, IDI IRCCS, Rome, 3University Federico II Naples, 4University of Bologna, 5University of Florence, Florence, Italy, 6University of Messina, 7University of Padua, Padua, Italy, 8University of Padua, 9University of Turin

Background: Juvenile localized scleroderma (JLS) is a chronic progressive fibrotic process of the skin causing permanent disability and aesthetic damage. Although no universally accepted effective treatment is available, recent studies seem to support the use of methotrexate (MTX).

Objectives: We aimed to assess the safety and efficacy of methotrexate in patients with JLS.

Methods: We performed a double-blind, randomised controlled trial. Patients with active JLS, with linear, generalized or deep subtypes, were randomly assigned to receive oral MTX, at a dose of 15 mg/m² once a week (max 20 mg), for 12 months or until flare of the disease (MTX arm), or placebo at the same dose and timing (placebo arm). Oral prednisone (1 mg/Kg/day, max 50 mg), in a single morning dose for 3 months then tapered down to 10 mg in the next 9 months, was added to both groups. The randomization rate MTX:PLAC was 2:1. The extension of the skin lesions was evaluated by a computerized scoring system and changes were quantified by the skin score rate (SSR) (skin score at time, skin score at time). Clinical examination and serial thermographies monitored the changes of active lesions. The primary endpoint was the rate of response to treatment. Responders were defined those patients who satisfied the following 3 criteria: SSR<1; decrease of the temperature at thermography of at least 10% compared to baseline; absence of new lesions. Disease relapse was defined when present at least one of the following: SSR>1; unchanged or increased lesion temperature; appearance of new lesions. All analyses were intention-to-treat.

Results: 85 patients entered the screening phase and 70, aged 6–17 years, from 13 centres in Italy, were enrolled. 46 patients were randomized in the MTX arm and 24 in the placebo arm. Groups were homogeneous as far as clinical and immunological features, mean disease duration was 2.1 years in both groups. After an initial response in all patients, disease relapse occurred in 15 MTX patients (32.6%) and 17 placebo patients (70.8%) (p<0.005), mean SSR value decreased from 1 to 0.79 with MTX vs 1.1 with placebo. The mean target lesion temperature decreased 44% vs 12.1%. New lesions appeared in 3 MTX patients (6.5%) vs 4 on placebo (16.7%). 26 patients (56.5%) of MTX group and 11 patients of the placebo group (45.8%) presented mild side effects related to treatment. None was severe enough to stop treatment.

Conclusion: MTX is an effective and well tolerated treatment for patients with JLS.

Disclosure: F. Zulian: None; C. Vallongo: None; G. Martini: None; F. Falcini: None; A. Patrizi: None; M. Alessio: None; F. La Torre: None; M. Cutrone: None; A. Belloni-Fortina: None; M. Paradisi: None; S. Martino: None; F. Vittadello: None; G. Perillo: None.

Aim: To study the influence of anti-inflammatory treatments including methotrexate (MTX) and TNF-blockers on serological response following pneumococcal vaccination using 7-valent conjugate pneumococcal vaccine (Prevenar®) in adult patients with established arthritis.

Patients and Methods: Altogether 506 patients with rheumatoid arthritis (RA) or spondylarthropathy (SpA) including psoriatic arthritis were vaccinated. All patients were stratified into 6 prespecified groups based on diagnosis and type of anti-rheumatic treatment: 1. RA patients treated with methotrexate + in some cases other DMARDs (n=85; 79% female; mean age 62 years); 2. RA patients on TNF blockers as monotherapy (n=80; 88% female; mean age 60 years); 3. RA patients on anti-TNF +MTX + possibly other DMARDs (n=89; 78% female; mean age 60 years); 4. SpA patients on anti-TNF drugs as monotherapy (n=83; 34% female; mean age 49 years); 5. SpA patients on anti-TNF drugs +MTX (n=83; 53% female; mean age 50 years) and 6. SpA patients on NSAIDs and/or analgesics (n=86; 45% female; mean age 52 years). Group 5 served as a control group. All patients received one dose of 0.5 ml Prevenar intramuscularly. Levels of IgG antibodies against two pneumococcal serotypes (23F and 6B) were measured prior to and 4–6 weeks following vaccination using standardised ELISA.

Results: Postvaccination geometric mean IgG levels increased significantly for both serotypes in all groups compared to baseline (p<0.000). Immune response (IR); i.e ratio between post- and prevaccination antibody levels differed significantly between the groups. Patients with spondylarthropathy on NSAIDs and/or analgesics (controls) had better IR compared to groups treated with MTX or MTX combined with TNF blockers (group 1, 3 and 5). Patients treated with TNF-blockers as monotherapy (group 2 and 4) had numerically somewhat lower IR but not significantly different compared to controls for both serotypes.

Positive immune response (posIR) was defined as ≥ 2 times increase in antibody levels compared to baseline. Patients with RA exhibited reduced responsiveness compared to patients with SpA in univariate analysis. In multivariate analysis only older age and MTX treatment predicted reduced response while ongoing systemic prednisolone treatment elicited better posIR.

Conclusion: Higher age and treatment with methotrexate predicted an impaired immune response to the 7-valent conjugate pneumococcal vaccine in this cohort of patients with chronic arthritis. Concomitant prednisolone treatment was associated with better IR. TNF-blockers did not affect the immune responses significantly.

References:

ACR Concurrent Abstract Sessions
Rheumatoid Arthritis - Clinical Aspects: Outcomes Associated with Biologic Therapy for RA

Tuesday, November 9, 2010, 4:30 PM–6:00 PM
Table 1. Predictors of positive immune response (pos IR) for both 23F and 6B.

<table>
<thead>
<tr>
<th>B</th>
<th>p-value</th>
<th>Exp(B)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>−0.024</td>
<td>0.024</td>
<td>0.977</td>
<td>0.957</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>0.248</td>
<td>0.360</td>
<td>1.282</td>
<td>0.753</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>0.015</td>
<td>0.208</td>
<td>1.015</td>
<td>0.992</td>
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<td>RA diagnosis (yes/no)</td>
<td>−0.283</td>
<td>0.335</td>
<td>0.753</td>
<td>0.424</td>
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<tr>
<td>Swollen joint count (SJC28)</td>
<td>−0.037</td>
<td>0.618</td>
<td>0.963</td>
<td>0.832</td>
</tr>
<tr>
<td>Tender joint count (TJC28)</td>
<td>0.001</td>
<td>0.979</td>
<td>1.001</td>
<td>0.928</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>0.011</td>
<td>0.098</td>
<td>1.011</td>
<td>0.998</td>
</tr>
<tr>
<td>HAQ (0–3)</td>
<td>−0.316</td>
<td>0.179</td>
<td>0.729</td>
<td>0.460</td>
</tr>
<tr>
<td>Methotrexate (yes/no)</td>
<td>−0.726</td>
<td>0.003</td>
<td>0.484</td>
<td>0.297</td>
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<tr>
<td>Anti-TNF (yes/no)</td>
<td>0.039</td>
<td>0.882</td>
<td>1.039</td>
<td>0.625</td>
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<tr>
<td>Predisnolone (orally):</td>
<td>0.689</td>
<td>0.017</td>
<td>1.991</td>
<td>1.131</td>
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<tr>
<td>Pneumovax vaccination previously (yes/no)</td>
<td>−0.221</td>
<td>0.630</td>
<td>0.802</td>
<td>0.327</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>−0.268</td>
<td>0.394</td>
<td>0.765</td>
<td>0.413</td>
</tr>
</tbody>
</table>

Disclosures: M. C. Kapetanovic: None; C. Roseman: None; G. Jönsson: None; L. Trueblood: None; T. Saxne: None; P. Geborek: None.

1441

Lipid and Inflammation Parameters: A Translational, Randomized Placebo-Controlled Study To Evaluate Effects of Tocilizumab: The MEASURE Study. Ian B. McInnes2, Janet S. Lee3, Wen Wu4, Jon T. Giles5, Joan M. Batson2, Jane E. Salmon6, Andre D. Beaulieu7, Christine E. Codding1, Christian Delles1 and Naveed Sattar1. 1British Heart Foundation, Glasgow, United Kingdom, 2Centre de Rhumatologie St-Louis, Montreal, QC, Canada, 3Health Research of Oklahoma, Oklahoma City, OK, 4Hospital for Special Surgery, New York, NY, 5Johns Hopkins University, Baltimore, MD, 6Roche, Nutley, NJ, 7University of Glasgow, United Kingdom

Purpose: Mechanistic data describing changes in lipid parameters upon IL-6R inhibition with tocilizumab (TCZ) are lacking. We report initial results from a randomized, double-blind, placebo-controlled study to evaluate the impact of TCZ on lipid particle subclasses and markers potentially relevant to cardiovascular (CV) risk.

Methods: Serum lipid subclasses characterized by nuclear magnetic resonance (NMR) and a range of inflammatory biomarkers were measured in patients with active rheumatoid arthritis (RA) with an inadequate response to methotrexate (MTX). Changes from baseline (BL) to wk 12 were compared between TCZ and placebo (PBO) in patients with active rheumatoid arthritis (RA). The study was validated against the American College of Rheumatology criteria for response.

Results: Baseline values and changes from baseline for each lipid parameter are shown in the Table. Among inflammatory markers, Hs-CRP, HDL cholesterol (HDL-C), and sPLA2-IIA were reduced with TCZ treatment; the proinflammatory marker D-dimer was also reduced. The HDL-associated antioxidative enzyme, paraoxonase I was increased with TCZ treatment.

Conclusion: Small LDL particles, thought to be proatherogenic, did not increase with TCZ treatment, in contrast to large VLDL particles and in small HDL particles with statistically significant increases. The changes in lipid parameters that occur with TCZ treatment, coupled with reductions in a wide range of inflammatory markers, demonstrate the intrinsic linkage of inflammation and metabolic regulation in the context of RA. Furthermore, reductions in HDL-associated SAA and sPLA2-IIA along with increases in paraoxonase reflect qualitative changes in lipoproteins that may favor improvements in CV risk-benefit.
Conclusions: In this inception RA cohort, the use of TNF-α inhibitors was associated with a 60% reduction in risk of developing diabetes after controlling for confounders. These findings need to be confirmed by additional studies in this group of patients at high risk of cardiovascular disease.


1443

Superior Protection Against “Vulnerable” Coronary Plaque in Asymptomatic TNF-α Responders vs. DMARD Responders with Rheumatoid Arthritis (RA). George A. Karpouzas1, Naser Ahmed1, Tae-Young Choi2, Fereshteh Hajsadeghi2, Silvia Munoz1 and Mathew Budoff1. 1Harbor-UCLA, Long Beach, CA, 2Harbor-UCLA.

Background: A lower risk of myocardial infarction (MI) was recently reported in patients (pts) with RA exposed to Tumor necrosis factor-α inhibitors (TNFI). It is unclear, however, whether a good disease response is necessary for the observed benefit. Additionally, the mechanisms, as well as sequelae of disease response on coronary plaque quantity and composition are unknown. We prospectively evaluated the presence, total plaque burden (p<0.001 for TNFI vs. DMARDS alone), and the effect of TNFI against plaque progression, independent of RA disease activity.

Methods: We report on 74 RA pts recruited from a single center. Pt characteristics, including disease response, coronary risk factors and treatments are shown in table 1. Good EULAR response (DAS28≤3.2 and DAS28 change>1.2) distinguished responders (R) from non-responders (NR). Pts underwent 64+ slice cardiac Computed Tomography Angiography (CTA); this non-invasive modality includes an initial non-contrast phase assessing coronary calcium, followed by a contrast scan that detects plaque with equal accuracy to conventional angiography, and is superior in the assessment of non-calcified, lipid-rich, non-obstructive or “vulnerable” plaque. Individual coronary trees were evaluated for plaque volume and composition by standard methods (American Heart Association). Non-parametric tests were used for data analysis; regression models for plaque prevalence ratios (PR) and relative risk (RR) for plaque burden in TNFI R vs. NR and DMARD R vs NR, adjusted for conventional risk factors were constructed.

Results: No differences in coronary risk factors were present in DMARD vs. TNFI treated pts. Both TNFI and DMARD responders (R) had significantly less plaque prevalence than NR of both categories (table). Both R groups had lower numbers of diseased coronary segments vs. NR (p=0.008 for DMARD and TNFI respectively), and less total plaque burden (p=0.04 for DMARD and p=0.005 for TNFI vs. NR respectively). More importantly, R groups had less NC/mixed plaque (p=0.001 for DMARD and p=0.0001 for TNFI vs. NR respectively). TNFI R had 61% lower risk of having “vulnerable” plaque, and 23% less burden of it compared to DMARD R, after adjustment for age, sex and traditional risk factors. Interestingly, TNFI NR also had 38% lower risk of NC/mixed plaque and 21% less burden, insinuating a superior protective effect of TNFI against plaque progression, independent of RA disease response.

Conclusion: Good EULAR response to TNFI affords superior protection against total, but more importantly, “vulnerable” coronary plaque progression compared to good response to DMARDs. TNFI seem to have an independent- to RA clinical response- protective effect against plaque as evidenced by significantly lower volume and vulnerable plaque features in the TNFI NR group.

Table 1. Patient Features

<table>
<thead>
<tr>
<th>Model</th>
<th>DMARD-Responders</th>
<th>TNFI-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prev Ratio-any plaque</td>
<td>1 (ref)</td>
<td>0.89 (CI = 0.38–2.78) 0.61</td>
</tr>
<tr>
<td>non-calcified</td>
<td>1 (ref)</td>
<td>0.39 (CI = 0.1–0.6) 0.02</td>
</tr>
<tr>
<td>mixed calcified</td>
<td>1 (ref)</td>
<td>0.78 (CI = 0.2–1.3) 0.25</td>
</tr>
<tr>
<td>RRisk-total burden score*</td>
<td>1 (ref)</td>
<td>0.78 (CI = 0.6–0.9) 0.03</td>
</tr>
<tr>
<td>Non-calcified/</td>
<td>1 (ref)</td>
<td>0.77 (CI = 0.6–0.98) 0.04</td>
</tr>
<tr>
<td>mixed calcified</td>
<td>1 (ref)</td>
<td>1.12 (CI = 0.9–1.3) 0.3</td>
</tr>
</tbody>
</table>

Disclosure: G. A. Karpouzas: None; N. Ahmed: None; T.-Y. Choi: None; F. Hajsadeghi: None; S. Munoz: None; M. Budoff: None.

1444

Discontinuation of TNF-Inhibitor Treatment in Clinical Practice Has a Negative Impact on Radiographic Progression 2 Years after Initiation of Therapy. Results from the Nationwide Danish DANBIO Registry. Lykke M. Ørnbjerg1, Mikkol Østergaard2, Perinolle Boysen1, Anja Thormann1, Ulrik Tarp3, Wolfgang Böhme4, Ditte Dencker5, Hanne Lindegaard1, Uta Poulsen6, Anette Hansen7, Vibeke Ringsdal8, Anette Schlemmer9, Niels Graudal10, Anne R. Andersen11, Jakob Espersen1, Gina Kollerup1, Torben G. Christensen1, Randi Pelck3, Bente Glintborg2, Ole R. Madsen2, Dorte V. Jensen8, Ole Maigaard9 and Mereete L. Høtteland1. DANBIO Registry and Depts. of Rheumatology, Copenhagen University Hospitals at Hvidovre and Glostrup, Denmark, 2Dept. of Internal Medicine and Rheumatology, Gentofte University Hospital, Denmark, 3Dept. of Internal Medicine, Copenhagen University Hospital at Holbæk, Denmark, 4Dept. of Internal Medicine, Hospital Lillebaelt at Vejle, Denmark, 5Dept. of Rheumatology, Aarhus University Hospital at Alborg, Denmark, 6Dept. of Rheumatology, Arhus University Hospital, Denmark, 7Dept. of Rheumatology, Copenhagen University Hospital at Herlev, Denmark, 8Dept. of Rheumatology, Copenhagen University Hospital at Næstved, Denmark, 9Dept. of Rheumatology, Copenhagen University Hospital at Rigshospitalet, Denmark, 10Dept. of Rheumatology, Copenhagen University Hospital at Slagelse, Denmark, 11Dept. of Rheumatology, Copenhagen University Hospital at Glostrup, Denmark, 12Dept. of Rheumatology, Copenhagen University Hospitals at Hvidovre and Glostrup, Denmark, 13Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, 14Dept. of Rheumatology, Hospital of South West Jutland at Esbjerg, Denmark, 15Dept. of Rheumatology, King Christian Xth Hospital, Grästen, Denmark, 16Dept. of Rheumatology, Odense University Hospital, Denmark

Background: Randomised controlled trials have shown that tumour necrosis factor inhibitor (TNFI) treatment halts erosive progression in rheumatoid arthritis (RA). In clinical practice, patients often withdraw from or switch TNFI treatment. The impact of discontinuation or change of TNFI treatment on radiographic progression in RA clinical practice is unknown.

Objectives: To investigate and compare the annual radiographic progression rates on conventional radiographs (CR) 2 years before and after TNFI initiation in three subgroups of an observational cohort of RA patients, who (1) stayed on their first TNFI, (2) withdrew from TNFI treatment or (3) switched to another TNFI drug.

Methods: Conventional radiographs (CR) of hands and wrists were obtained ~2 years before start of TNFI (time-point A), at the start of TNFI (B) and ~2 years after start of TNFI (C). Clinical data from the DANBIO registry and the patientfiles were collected. The CRs were scored blinded to chronology (modified Sharp score). Annual radiographic progression rates during DMARD (delta A-B)
and TNF-I (delta B-C) treatments were calculated, stratified according to treatment status at timepoint C (Group 1–3, see above). Data were analysed with non-parametric analyses due to a skewed distribution.

**Result:** 522 patients (76% women, 80% rheumatoid factor positive, age 54(21–86) years (median(range)); disease duration 5 (0–67) yrs) had complete A-B-C series. At time-point B, patients who stayed on TNF-I had a higher rate of concomitant methotrexate (MTX) treatment, while patients who switched TNF-I had a higher DAS28. At time-point A, patients received DMARDS (90%) or no DMARDS (10%). At time-point B, patients started treatment with infliximab (61%), etanercept (15%), or adalimumab (24%). The TNF-I were given in combination with MTX(78%); other DMARDS(10%); or in monotherapy (12%). The duration of Period A-B was median 736 (Interquartile range, IQR 486–1006) days and of period B-C 562 (405–766) days. Patients who withdrew from treatment in 68% (mean) of the follow-up period, and withdrew due to lack of effect (LOE) (46%), adverse events (AE)(37%) or remission (2%), while patients who switched did so due to LOE(68%) and AE(26%), and were treated 99% of the follow-up period.

Radiographic data demonstrated significantly reduced progression rates during TNF-I therapy in all subgroups (Table), and that patients who continued treatment progressed less than patients who stopped.

**Conclusion:** In this observational study of 522 RA patients, initiation of TNF-I treatment reduced the rate of radiographic progression in the following 2 years, compared to the preceding 2 years of DMARD treatment, irrespective of treatment status after 2 years. The lowest level of radiographic progression was found in patients who continued treatment.

**Disclosure:** L. M. Ornbjerg: None; M. Ostergaard: Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, GlaxoSmithKline, 5, Pfizer Inc, 5, Roche, 5, Schering-Plough, 5, UCB, Inc., 5, Wyeth Pharmaceuticals, 5; P. Boyesen: None; A. Thormann: None; U. Tarp: None; W. Böhme: None; D. Dencker: None; H. Lindegaard: Abbott Laboratories, 5, Merck Pharmaceuticals, 5, Roche, 5; U. Poulsen: None; A. Hansen: Abbott Laboratories, 5, Schering-Plough, 5; V. Ringsdal: None; A. Schlemmer: Schering-Plough, 5; N. Graudal: None; A. R. Andersen: None; J. Espeen: None; G. Kollerup: Abbott Laboratories, 5; T. G. Christensen: None; R. Pelck: None; B. Glintborg: None; O. Majgaard: None; M. L. Hetland: Abbott Laboratories, 5, Centocor, Inc., 5, Roche, 5, Schering-Plough, 5, UCB, Inc., 5, Wyeth Pharmaceuticals, 5.

**Figure 1.** Development of AAA in percentages over 156 weeks follow-up.

**Figure 2.** Discontinuation of treatment due to failure to patients with and without ADA (P<0.0001).

**Table 1.** Mean TSS at 156 weeks follow-up for patients progressing, no patients progressing and ADA patients progressing.

- **Timepoint C treatment status**
  - TSS A-median (IQR) 15 (1–34)
  - TSS B-median (IQR) 15 (2–34)
  - TSS C-median (IQR) 15 (3–46)
  - Delta TSS A-median (IQR) 0.64 (0–2.9)
  - Delta TSS B-median (IQR) 0.0 (0–5.7)

- **Patients progressing A-B (%)**
  - Patients progressing A-B (%) 58
  - Patients progressing B-C (%) 7

- **P value**
  - 0.002

**1** Kruskal-Wallis tests

**2** Chi-square

**3** Paired Wilcoxon tests

1445

**Immunogenicity in a 3-Year Follow-Up Cohort of Adalimumab Treated Rheumatoid Arthritis Patients.** Geertje M. Bartels, Charlotte L. Kriekert, Michael T. Nurmoahmed, Pauline van Schouwenburg, Ben A. Dijkmans and Gerrit J. Wolbink.

**Background:** Short term data regarding the immunogenicity of adalimumab in adalimumab treated rheumatoid arthritis (RA) patients have been reported. After approximately 6 months follow-up anti-adalimumab antibody frequencies ranged from 17 to 44% in different studies, and were associated with low to undetectable serum adalimumab levels and non-response to treatment. [1–3] However, thus far long-term immunogenicity data for adalimumab have not been reported.

**Objectives:** To examine the course of anti-adalimumab antibody formation during long-term (3 year) follow-up and its effect on treatment.

**Methods:** Two-hundred-seventy-two consecutive RA patients with active disease were treated with adalimumab in a prospective observational cohort study. All patients were monitored at baseline and 4, 16, 28, 40, 52, 78, 104, 130 and 156 weeks. Trough serum samples were obtained at all visits. Serum adalimumab concentrations and anti-adalimumab antibody titres were determined retrospectively at the end of follow-up using an ELISA and RIA, respectively, designed by Sanquin Research Amsterdam. Patients were defined as positive for anti-adalimumab antibodies if titres were above 12 AU/ml on at least one occasion, in combination with serum adalimumab levels below 5.0 mg/L. A survival analysis including Cox regression analysis was performed.

**Results:** After three years 76 out of 272 patients (28%) developed anti-drug antibodies (ADA) against adalimumab. Figure 1 shows that 51 patients (19%) developed ADA during the first 28 weeks of treatment. One hundred twenty four patients dropped out of the study before the end of follow-up: 57 (46%) due to treatment failure, 30 (24%) due to adverse events, 11 (9%) due to a combination of failure and adverse events, and 26 (21%) due to other reasons. Patients with ADA significantly more often dropped out of the study due to treatment failure compared to patients without ADA in univariate analysis (figure 2, p<0.0001) and after adjustment for confounders MTX use, number of previous DMARDS and C-reactive protein (HR:3.0; 95%CI:1.6–5.5, p<0.0001).

**Conclusions:** Discontinuation of adalimumab treatment due to treatment failure was observed more frequently in patients who developed ADA compared to patients without ADA. The majority of the ADA positive patients developed ADA during the first 28 weeks of treatment. This suggests that monitoring immunogenicity is most effective during the first six months of treatment.
Fungal beta-Glucan Triggers Spondyloarthropathy and Crohn’s Disease in Skg Mice

G. Strutton, Merja Ruutu1, Bijesh Yadav2, Gelin Thomas3, Roland Steck4, Geoffrey Stratton5, Ai Tran6, Jared Velasco7, Mariapia Degli Esposti8, Martin Zinkernagel9, Matthew A. Brown8 and Ranjey Thomas8.

Lions Eye Institute, 2Queensland University of Technology, 3Queensland Health Pathology, 4University of Queensland Diamantina Institute

Background: Recent genome-wide association studies reveal candidate genes for ankylosing spondylitis, psoriatic arthritis and Crohn’s disease associated with polymorphamnflammatory cytokine production promoting T-helper 17 cells, including IL1R1, IL12B, IL23R, CCR6, JAK2, STAT3 and Card9. However, the functional correlates of these polymorphisms are unclear. This pathway is activated after death-1 signaling during fungal infection. Since skg ZAP70 mutant mice over-express these cytokines, and were reported as a model of rheumatoid arthritis triggered by fungal infection, we investigated whether skg mice develop spondyloarthropathy after systemic administration of fungal beta-glucan.

Methods: Skg mice and control BALB/c mice were injected i.p. or s.c. once with 3 mg 1,3-beta-glucan (curdulan). Arthritis, general appearance and weight loss were scored for 10 weeks. Organ pathology was determined by H&E staining of paraffin-embedded tissue sections at sacrifice between 1 and 10 weeks after injection of curdulan. Paws and spines were examined after sacrifice by radiography and micro-CT.

Results: After curdulan administration, BALB/c mice developed mild self-limiting arthritis of the ankles and wrists. By contrast, in skg mice, conjunctivitis, and progressive inflammatory arthritis of ankles and wrists, swelling of the soft tissue of the feet and typical sausage digits were evident from 3 weeks after injection. Over time, the mice developed hunching of the upper body, tail deformity, weight loss and abdominal bloating, but no diarrhea. Histologically and by imaging, we observed severe inflammation and progressive destruction of sacroiliac and vertebral facet joints, longitudinal ligaments and intervertebral discs with new bone formation, as well as enthesitis of Achilles tendon and plantar fascia in curdulan-treated but not naive skg mice. Analysis of tissues over time showed that inflammation first appeared in ankles, wrists and para-vertebral ligaments from 1 week after injection. Around 6 weeks later, mice began to develop unilateral uveitis and Crohn’s-like ileitis with granulomas and crypt abscesses. In contrast, the colon was not inflamed.

Conclusions: These characteristic features indicate that after systemic exposure to beta-glucan, skg mice develop a spondyloarthropathy closely resembling human spondyloarthropathy. Since the zap70 mutation decreases T cell receptor signaling and required for disease perpetuation, these data strongly suggest that polymorphisms enhancing signaling of the beta-glucan molecular pattern (present in pollens, fungi and many bacteria), coupled with defects in antigen presentation or T cell response, may increase spondyloarthropathy risk in humans.

Disclosure: M. Ruutu: None; B. Yadav: None; G. Thomas: None; R. Steck: None; G. Stratton: None; A. Tran: None; J. Velasco: None; M. Degli Esposti: None; M. Zinkernagel: None; M. A. Brown: None; R. Thomas: None.

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Autoimmunity to Sperm and Testicular Antigens Precedes Onset of Spondylarthropathy in HLA-B27/Hu-β2-Microglobulin Transgenic Rats.

Holly L. Rosenzweig1, Jelena M. Kezic2, Tibor T. Glant5, Robert Thomas2, None; Mark Degli Esposti3, None; R. Thomas: None;

Tuesday, November 9, 2010, 4:30 PM–6:00 PM

Purpose: Due to increased auto-reactive T cells recognizing the proteoglycan (PG) aggrecan in order to elucidate the onset and severity of eye disease as it relates to the joint and spine. We further tested the functional contribution of the Th-1 cytokine (IFNγ) versus the Th-2 cytokine (IL-4).

Methods: BALB/c mice transgenic for the T cell receptor specific for a dominant epitope of aggrecan (TCR-Tg mice) or TCR-Tg mice lacking IFNγ or IL-4 were immunized with PG. Ocular inflammation was assessed by intravitreal microscopy and histological analysis. Corresponding joint and spine inflammation was examined using an established clinical scoring system, histology and NIR-fluorescence imaging. Immunofluorescence staining of eye tissue was performed to further identify the cellular mediators and the presence of PG in the eye.

Results: Immunofluorescence staining of whole mounts revealed the presence of PG on nerve fibres in the cornea, retina, iris and optic nerve. Upon immunization with PG, a progressive mild uveitis was observed. Intravitreal microscopic imaging revealed an increased number of rolling, adhering and infiltrating leukocytes within the iris vasculature within 3 weeks post immunization, whilst deficiency in IL-4 significantly impaired the severity of uveitis. By comparison, mice lacking IFNγ expression showed a marked exacerbation of eye disease with a higher number of rolling and adherent cells within the iris. Histological analysis revealed a florid cellular infiltrate in the absence of IFNγ for both the anterior and posterior segments of the eye, with cells in the vitreous, iris, ciliary body, and choroid; along with retinal vasculitis, retinal folding and photoreceptor damage. Immunofluorescence studies have identified a predominance of neutrophils and mononuclear MHC-II-positive cells within the eye. Interestingly, The protective role for IFNγ in the eye is in direct contrast with the joint and spine, wherein we find IFNγ-null mice have reduced severity of arthritis.

Conclusions: We present a newly described model of ocular disease that occurs in the context of murine arthritis/spondylitis. IFNγ and IL-4 appear to play opposing roles within the eye. IFNγ promotes joint disease, yet somewhat surprisingly our findings demonstrating exacerbated uveitis in the absence of IFNγ supports a protective role for IFNγ the eye. The disparity in mechanisms between the eye and joint may have potential implications for the treatment of systemic diseases accompanying uveitis.

Disclosure: H. L. Rosenzweig: None; J. M. Kezic: None; T. T. Glant: None; S. R. Planck: None; T. M. Martin: None; M. P. Davey: None; J. T. Rosenbaum: None.
Gene Silencing of ERAP1 and ERAP2 Displays Differential Effects on Intracellular Free Heavy Chain Accumulation and Peptide Presentation in B*27 Subtypes Associated with Ankylosing Spondylitis (AS). Nigil Haroon, Florence W. Tsui and Robert D. Inman, Toronto Western Hospital and Research Institute. University of Toronto, Toronto, Canada

Introduction: Ankylosing spondylitis (AS) demonstrates differential association with different HLA subtypes: B*2704 and B*2705 are associated with AS while B*2706 and B*2709 are not. With the recognition that ERAP polymorphisms are associated with AS, we investigated the interaction of AS-associated genes ERAP1 and ERAP2 with HLA B*27 subtypes.

Methods: C1R cells stably transfected with the respective B*27 subtypes (B*2704, *2705, *2706 and *2709) were used. For gene silencing, two duplexes each of Stealth RNAi™ for ERAP1 and ERAP2 or a negative control (NC) siRNA were nucleofected into the respective transfected cells. For flow cytometry, ME1, HIC10, W6/32 and MARB4 antibodies were used respectively for intact B27, MHC-I free heavy chains (FHC), intact MHC-I and B27 presenting abnormally long peptides (B27lp). For intracellular FHC (iFHC) HC10 was used after cell permeabilization. The change in FCM was calculated as a ratio of the MFI with specific siRNA to NC for each antibody. Western blot showed more than 80% suppression of ERAP with specific siRNAs but no suppression with NC.

Results: Silencing of ERAP1/2 was associated with a significant increase in iFHC in B*2704 and *2705 cells compared to *2706 and *2709 cells (p = 0.002). The median (IQR) increase in iFHC (ΔFHC) in the B*2704 and *2705 cells was 2.5 (1.8, 4.2) compared to 1.3 (1.1, 1.5) in the *2706 and *2709 cells. There was no significant difference in the level of surface FHC, B27 or MHC-I expression. The median ΔB27lp expression with ERAP1/2 silencing in B*2704 and *2705 cells was 1.2 (1.1, 1.4) and was significantly higher (p < 0.03) than the median ΔB27lp of 0.9 (0.8, 1.0) in *2706 and *2709 cells. There was no significant difference in the results whether ERAP1 or ERAP2 was suppressed.

Conclusion: ERAP1/2 silencing causes accumulation of more iFHC and higher B27lp in AS-associated B*27 subtypes cells compared to non-associated subtypes. This suggests that interaction of B*27 with ERAP1/2 could be a key determinant underlying the B*27 subtype specific associations with AS.

Disclosure: N. Haroon: None; F. W. Tsui: None; R. D. Inman: None.

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of the seminiferous tubules. Indirect IF showed that the serum autoantibodies bind to antigens in the testis cell cytoplasm, sperm acrosome, and sperm tail. Thus both T cell and antibody-mediated mechanisms participate in the autoimmune EO, but the T cell-mediated processes appear first and are primary.

Conclusion: The B27/Huβ2m transgenes initiate characteristic T cell-mediated inflammation in the ductus efferentes that becomes granulomatous. Orchitis appears later, coinciding with the appearance of anti-sperm and anti-testis cell antibodies in serum, presumably as a result of an ongoing autoimmune response to sperm and other testicular antigens. As previously shown, bilateral castration prevented subsequent development of SpA if carried out before the age of onset of arthritis, even if advanced EO was already present. The data therefore suggest that the process of prolonged inflammation and antigenic stimulation within the tests and epididymis is an essential precursor of SpA in (21-3×283-2) F1 B27/Huβ2m TG rats. More generally, persistent autoimmune inflammation in one site seems linked causally to autoimmunity targeting a second site.

Disclosure: J. D. Taurog: Taconic, Inc. T. C. Rival: None; M. Dorris: None; N. Satuntrita: None; M. Sun: None; K. S. K. Tung: None.

1449

Mast Cells Contribute to Synovial Inflammation in Non-Psoriatic and Psoriatic Spondyloarthritis. Troy Noordenbos1, Nataliya Yeremenko1, Tineke Cantaert2, Christine Teitsma3, Marleen van de Sande1, Paul P. Tak1, Juan Canete4 and Dominique Baeten1. 1Academic Medical Center/University of Amsterdam, 2University Hospital Barcelona

Objective: We recently observed a striking synovial infiltration with cells positive for C-Kit, a marker for mast cells, in psoriatic arthritis (PsA). As mast cells have potent inflammatory functions, including the production of pro-inflammatory cytokines, we performed a systematic analysis of mast cell infiltration in different forms of chronic inflammatory arthritis.

Materials and Methods: Synovial tissue biopsies from active rheumatoid arthritis (RA) (n=21), non-psoriatic spondyloarthritis (SpA) (n=16), and PsA (n=23) was stained by immunohistochemistry and double immunofluorescence. Synovial fluid (SF) from RA (n=18), SpA (n=19), and PsA (n=16) was analyzed by ImmuNoCap and ELISA. The effect of C-Kit inhibition by imatinib mesylate on proinflammatory cytokine production was tested in vitro on fresh SpA synovial biopsies.

Results: C-Kit positive mononuclear cells were found in the synovial sublining in all disease groups. Double stainings with tytrpase confirmed that it persisted in SpA synovial biopsies taken after 12 weeks of successful treatment with TNF blockers. SF levels of factors involved in chemotaxis and differentiation of mast cells such as SCF, IL-3, and IL-33 were similar in all groups but sST2, the soluble decoy receptor for IL-33, was significantly decreased in SpA. As to the function of mast cells in synovial inflammation, double staining of the c-kit positive cells with toluidine blue and anti-trypstatine and SF analysis for mast cell products did not show evidence for enhanced degranulation in SpA versus RA synovitis. Preliminary data, however, show IL-17 signal in the synovial mast cells. Accordingly, C-kit inhibition in ex-vivo synovial cultures strongly reduced the production and secretion of pro-inflammatory cytokines.

Conclusion: There is an increased synovial infiltration with C-kit positive mast cells in non- psoriatic and psoriatic SpA. Inhibition of C-kit in vitro leads to a reduction of proinflammatory cytokine production by synovial biopsies. These data suggest a role for mast cells in driving and/or sustaining the synovial inflammation in SpA.

Disclosure: T. Noordenbos: None; N. Yeremenko: None; T. Cantaert: None; C. Teitsma: None; M. van de Sande: None; P. P. Tak: None; J. Canete: None; D. Baeten: None.

1451

Multiplex Assay of a Panel of 58 Biomarkers in Ankylosing Spondylitis: Identification of High Priority Candidates for Prediction of Structural Damage. Walter P. Maksymowych1, Nathalie Morency1, Stephanie Wichuk1, Proton Rahman2, Dafna D. Gladman2 and Robert D. Inman3. 1Memorial University Newfoundland, St. Johns, NL, Canada, 2Toronto Western Hospital, Toronto, ON, Canada, 3Toronto Western Hospital, Toronto, ON, Canada, 4University of Alberta, Edmonton, AB, Canada

Purpose: Radiographic progression in ankylosing spondylitis (AS) requires 2 years before it can be reliably detected and prospective studies have consistently identified only baseline radiographic damage as an independent predictor of radiographic progression in AS. This presents a major challenge to the study of disease modifying therapies and to the identification of patients at risk for damage progression. We aimed to simultaneously analyze a large panel of serologic biomarkers reflecting pathophysiological processes in AS as potential predictors of radiographic progression.

Method: We used multiplexed sandwich immunoassays (Eve Technologies) to simultaneously quantify a panel of 58 biomarkers that comprised 8 markers reflecting bone turnover, calcium homeostasis and osteoclast, 8 metalloproteinases (MMP), 6 joint tissue growth factors, 23 cytokines known to regulate inflammation, 9 chemokines, and 4 factors reflecting miscellaneous immunological processes such as T-cell co-stimulation and endothelial activation. Serum was obtained at a single time point from 60 patients with AS and 60 age- and sex-matched controls. Selection of 30 AS patients was based on phenotypic characterization of their progression status as measured by the modified Stoke AS Spine Score (mSASSS) after patients had been followed for at least 2 years. Progressors were defined as those patients where the baseline mSASSS was at least 10 units, progression over 2 years was at least 5 units, and included at least one new syndesmophyte. Non-progressors were patients meeting all 3 of the following: disease duration at baseline of at least 10 years, baseline mSASSS of less than 5 units, and no change in the baseline mSASSS was at least 10 units, baseline mSASSS of less than 5 units, and no change in mSASSS over 2 years. Unpaired t-test analyses were stratified according to radiographic phenotype.

Results: A total of 23 biomarkers demonstrated significant differences between AS patients and controls, the most significant being osteocalcin and Rantes (both p<0.0001). Ten biomarkers only demonstrated significant differences from controls when analysis was stratified according to radiographic phenotype: in the progressor subgroup MMP-9, transforming growth factor alpha, and tumor necrosis factor alpha were significantly elevated compared to controls (all p<0.0001) while eotaxin, interferon-alpha-2, and...
monocyte chemotactic protein-3 were significantly increased in the non-progression subgroup. Three biomarkers, interleukin-17, interferon-gamma, and macrophage inhibitory protein-beta, demonstrated significantly increased levels in AS patients that were further increased in the progression subgroup. Six biomarkers were significantly increased only in male patients and particularly the progression subgroup, especially macrophage derived chemokine and CD40 ligand (both p<0.0001).

**Conclusion:** Multiplexed assay of an extensive panel of biomarkers reflecting pathophysiological processes implicated in AS has identified several biomarkers of high priority candidates for prospective validation studies aimed at predictors of structural damage in AS.

**Disclosure:** W. P. Maksymowych: None; N. Morency: None; S. Wichu: None; P. Rahman: None; D. D. Gladman: None; R. D. Inman: None.

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### ACR Concurrent Abstract Sessions

**Systemic Lupus Erythematosus - Clinical Aspects and Treatment: New Therapies**

Tuesday, November 9, 2010, 4:30 PM–6:00 PM

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### 1452

**Epratuzumab Demonstrates Clinically Meaningful Improvements in Patients with Moderate to Severe Systemic Lupus Erythematosus (SLE): Results from EMBLEM™, a Phase IIb Study.**

**Study:** Daniel J. Wallace,1 Kenneth C. Kalunian,2 Michelle A. Petri,3 Vibeke Strand,4 Brian Kilgallen,5 Lexy Kelley6 and Caroline P. Gordon6. 1West Hollywood, CA, 2Timonium, MD, 3Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, CA, 4UCB, Smyrna, GA, 5UCSD School of Medicine, La Jolla, CA, 6University of Birmingham, Birmingham, United Kingdom

**Background:** Epratuzumab is a humanized anti-CD22 monoclonal antibody under development for the treatment of patients with moderate to severe SLE. This 12-week, double-blind, Phase IIb study (NCT00624351) was designed to evaluate the efficacy and safety of epratuzumab in SLE, and identify an optimal dose and regimen.

**Methods:** Patients with moderate/severe SLE (≥1 BILAG 2004 A or ≥2 B) were randomized to 1 of 6 intravenous regimens: placebo (PBO, standard of care) or cumulative dose (cd) epratuzumab (200, 800, 2400 or 3600 mg in equal divided doses using 2 every other week [EOW] infusions or 2400 mg cd as 4 equal infusions 1 week apart). Both 2400 mg cd groups (600 mg weekly and 1200 mg EOW) were also combined for analysis. Primary end point was a combined responder index of clinical disease activity at Week 12, defined as reduction of all baseline BILAG A to B/C/D and BILAG B to C/D in all body systems, no BILAG worsening in other organ systems, and no deterioration in SLEDAI or physician’s global disease activity assessment, with no increase in corticosteroids, immunosuppressives or anti-malarials over baseline. The combined responder index was analyzed using logistic regression. All drop-outs were considered nonresponders.

**Results:** At baseline, in the entire population (N=227) mean age was 38.8 years, 94% were female; with high disease activity (71% with ≥1 BILAG A, mean total scores: BILAG 15.2, SLEDAI 14.8). Combined responder index rates were higher in all epratuzumab groups than in the placebo group (Table), reaching statistical significance in the epratuzumab 600 mg weekly group (2400 mg cd) and the combined group of all 74 patients who received a cd of 2400 mg (600 mg weekly and 1200 mg EOW). In both groups, responder rates were twice those of placebo. Differences in responder rates between the epratuzumab 600 mg weekly and 1200 mg EOW groups, and the placebo group were observed at Week 8, with further improvement to Week 12 (epratuzumab 600 mg weekly vs 1200 mg EOW vs PBO; Week 8: 37.8% vs 35.1% vs 21.1%; Week 12: 45.9% vs 40.5% vs 21.1%). By Week 12, 37.9% and 35.3% of patients in the epratuzumab 600 mg weekly and 1200 mg EOW groups, respectively, achieved enhanced BILAG improvement (improvement of all body systems to BILAG C or better on consecutive visits, with no worsening) vs 22.2% in PBO. Epratuzumab was well tolerated; incidence of serious adverse events and infusion reactions was similar to PBO.

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### 1453

**Aspreva Lupus Management Study (ALMS): Extra-Renal Activity Results from the Maintenance Phase.**

**Study:** David A. Isenberg,3 Gerald B. Appel,1 Mary Anne Doyley1, Ellen M. Ginzlzer2, David Jayne2, David Wofsy,5 Neil Solomons and Laura Lisk.1 Columbia University, 2Renal Unit, Addenbrooke’s Hospital, 3SUNY-Downstate Medical Center, Brooklyn, NY, 4University College London, London, United Kingdom, 5University of California, San Francisco, San Francisco, CA, 6University of North Carolina at Chapel Hill, Chapel Hill, NC, 7Vifor Pharma (formerly Aspreva Pharmaceuticals), Canada, 8Vifor Pharma, UK

**Background:** The 36-month maintenance phase of the ALMS study (NCT00377637) compared the efficacy and safety of mycophenolate mofetil (MMF) with azathioprine (AZA) in patients with lupus nephritis (LN) classes III, IV and V achieving a clinical response in the induction phase with corticosteroids (CS) and either MMF or cyclophosphamide (IVC).

**Methods:** Patients were re-randomized 1:1 to a double-blind comparison of either placebo plus either oral MMF (2 g/day) or oral AZA (2 mg/kg/day). Patients were permitted to receive corticosteroids (maximum dose: 10 mg/day prednisone or equivalent). The primary efficacy outcome measure was time to treatment failure (death, end-stage renal disease, sustained doubling of serum creatinine, and/or renal flare [proteinuric or nephritic]). Patients who withdrew before reaching the primary endpoint were censored at the time of withdrawal. Although this was primarily an LN population, substantial extra-renal assessments were performed. Extra-renal secondary parameters included time to major extra-renal flare (British Isles Lupus Assessment Group [BILAG] score category A in one extra-renal system or three systems with concurrent category B scores) and the characterization of extra-renal activity. Immunology secondary parameters (levels of complement proteins C3 and C4, and titers of antibodies to double-stranded DNA [anti-dsDNA]) and adverse events (AEs) were also assessed.

**Results:** Of 227 patients randomized (intent-to-treat population), 127 completed the full 3 years (MMF, 73/116 [62.9%]; AZA, 54/111 [48.6%]). MMF was superior to AZA in the primary endpoint (p=0.036). Extra-renal disease characteristics and immunology parameters were similar across groups at baseline. There were very few occurrences of major extra-renal flare in either group during the study (8 [6.9%] for MMF, 7 [6.3%] for AZA), and time to major extra-renal flare did not differ between groups (p=0.936). However, there were differences in the characteristics of extra-renal activity. The most common manifestation of major extra-renal flare in the MMF group was maculopapular and in the AZA group was hematological. In the MMF group, 75 subjects (65.2%) experienced lupus-related AEs compared with 79 (71.2%) in the AZA group, with musculoskeletal events being the most common in both groups (MMF, 39/115 [33.9%]; AZA, 37/111 [33.3%]). At the end of the study, in patients who had completed 3 years, mean C3 and C4
Conclusion: In BLISS-76, belimumab significantly improved SRI response rate and reduced SLE disease activity in seropositive SLE patients at wk 52. Response rates at wk 76, while not statistically significant, were consistent with wk-52 results. Overall AEs, including serious AEs, and infusions, were comparable across groups.

Table. BLISS-76 Results Through Wk 76a

<table>
<thead>
<tr>
<th>SOC + Belimumab</th>
<th>SOC + Placebo</th>
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<tbody>
<tr>
<td>Response (SRI 7b,c wk 76, n (%))</td>
<td>91 (33.5%)</td>
</tr>
<tr>
<td>SRI-7b,c</td>
<td>30 (13.9%)</td>
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<tr>
<td>SRI</td>
<td>60 (26.4%)</td>
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<tr>
<td>SRI-7b</td>
<td>39 (17.5%)</td>
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<tr>
<td>Positive to negative, n (%)</td>
<td>11/112 (9.8%)</td>
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<tr>
<td>Patients with All flares, n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Patients with SLE flares, n (%)</td>
<td>27 (10.5*)</td>
</tr>
<tr>
<td>Median change at wk 76 (%):</td>
<td>16.7 38.5***</td>
</tr>
<tr>
<td>C3 n</td>
<td>70 n</td>
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<tr>
<td>C4 n</td>
<td>271 n</td>
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<tr>
<td>C1q n</td>
<td>272 n</td>
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<tr>
<td>C2 n</td>
<td>269 n</td>
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<tr>
<td>C5 n</td>
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<td>C6 n</td>
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<td>C8 n</td>
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<td>CD64 n</td>
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<td>CD16 n</td>
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<td>CD56 n</td>
<td>272 n</td>
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<tr>
<td>CRP n</td>
<td>271 n</td>
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<tr>
<td>Fibrinogen n</td>
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<tr>
<td>GFR n</td>
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<tr>
<td>Hb n</td>
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<td>HCT n</td>
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<td>TSH n</td>
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<td>T3 n</td>
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<td>T3 resin n</td>
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<tr>
<td>Proteinuria n</td>
<td>272 n</td>
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<tr>
<td>SLEDAI n</td>
<td>272 n</td>
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<tr>
<td>SRI wk 52 93 (33.5%) 110 (40.6%) 118 (43.2%)</td>
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<tr>
<td>4-point reduction 93 (33.8%) 114 (42.1%) 113 (41.4%)</td>
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<td>ESPRIT n</td>
<td>272 n</td>
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<tr>
<td>CRP n</td>
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<td>TSH n</td>
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<td>T3 n</td>
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<td>Proteinuria n</td>
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<td>SLEDAI n</td>
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<td>SRI wk 52 93 (33.5%) 110 (40.6%) 118 (43.2%)</td>
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<td>Proteinuria n</td>
<td>272 n</td>
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<tr>
<td>SLEDAI n</td>
<td>272 n</td>
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</table>

aPatients who withdrew from study prior to wk-76 visit or used protocol-prohibited medications were considered treatment failures.

Methods: In BLISS-76 (NCT00410384), a 76-wk, double-blind, interna-
tional, phase 3 study, 819 seropositive SLE patients (ANA ≥1:80 and/or
classic anti-dsDNA ≥30 IU/mL) with SELENA-SLEDAI (SS) score ≥6 on stable
care-of-care (SOC) therapy for ≥30 d were randomized to belimumab 1 or
10 mg/kg IV SOC vs placebo plus SOC or on d 14, 28, and 21, and then
cQ2d, for 72 wk. Efficacy analyses included SS, BILAG, and SS Flare Index
(SFI). SLE Responder Index (SRI) response rate at wk 52: SS improvement
(≥5-point decrease), no new BILAG A or new B flares, and no worsening
(<0.3-point increase) in Physician’s Global Assessment (PGA) vs baseline.
SRI at wk 76 was a secondary endpoint.

Results: Belimumab 10 mg/kg plus SOC met the primary efficacy
endpoint by achieving a significantly greater response rate vs placebo plus
SOC at wk 52 (43% vs 34%; p=0.017); the rate with belimumab 1 mg/kg was
41% (p=0.09). Statistical significance with either belimumab dose was not
achieved at wk 76 (32%, 39% [p=0.11], and 39% [p=0.13] for placebo,
and belimumab 1 and 10 mg/kg, respectively). In post-hoc sensitivity analyses
evaluating more rigorous response thresholds for the SS component of the
SRI endpoint (ie, ≥5-point reductions), robust and consistent effects
were achieved with belimumab 10 mg/kg at multiple time points, including
statistically significant effects at wk 52 and 76. Between wk 24 and 76,
belimumab reduced all flares (10 mg/kg: p<0.05) and severe flares (1 mg/kg:
p<0.05). Fatigue improved in both belimumab treatment groups at wk 76 (1
mg/kg: p<0.05). Although not statistically significant, there were numeric
trends favoring steroid sparing with belimumab. Belimumab was associated
with reduction in SLE-specific and short-lived plasma cells, as well as additional
B-cell subsets including CD20+ activated, and plasmacytoid cells. Moreover,
significant normalization of low complement was achieved with belimumab
10 mg/kg. Overall adverse events (AEs), laboratory abnormalities,
and infections, as well as serious AEs including infections, malignancies,
and deaths, were comparable across groups. Serious or severe infusion
reactions occurred in 1.5% of patients with belimumab 10 mg/kg vs 0.7%
with placebo.

1454

Belimumab, a BLYS-Specific Inhibitor, Reduced Disease Activity and
Severe Flares in Seropositive SLE Patients: BLISS-76 Study Results
through Wk 76. R. Fusie, O. Zamani, D. Wallace, D. Tegzova, M. Petr
T. Merrill, W. Chatham, W. Stohl, A. Schwartz, S. Cooper, Z. J. Zhong,
W. Freimuth, D. Hough, and R.F. van Vollenhoven, for the
BLISS-76 Study Group. 1North Shore-LIJ Health System, Lake Success,
Karolinska Institute, Stockholm, Sweden. 2North Shore-LIJ Health System,
Lake Success, NY. 3North Shore-LIJ Health System, Lake Success, NY.
4Cephalon, Genentech and Biogen IDEC Inc, 5Gerson Lehrman Group, 6Guidepoint
Global, 7Human Genome Sciences, Inc., 8Human Genome Sciences, Inc., 9Medimmune,
10W. Chatham, 11W. Stohl, 12A. Schwartz, 13S. Cooper, 14Z. J. Zhong,
15W. Freimuth, 16D. Hough, 17R. F. van Vollenhoven; for the
BLISS-76 Study Group.

Patients with Active Proliferative Lupus Nephritis (LN): Results from the
BLISS-76 Study Group: A. Schwarting, R. Guzman, M. Bijl, D. Jayne,
van Vollenhoven, for the BLISS-76 Study Group. 1Addenbrookes Hospital,
2Dept Rheumatology, 3Genentech, 4MedImmune Limited, 5North Shore Long
Island Jewish Health System, Lake Success, NY, 6OMI, Buenos Aires, Argentina,
7Roche, 8Univ of Groningen, 9Universidad NacionTucuman, Yerba Buena Tucuman,
Argentina.

Purpose: Beliefs are believed to contribute to LN pathogenesis. Occlu-
slization (OCR), a humanized monoclonal antibody that selectively targets
CD20+ B cells, was studied to determine the benefits and risks of OCR
compared to placebo (PBO) in patients (pts) with active class III/IV LN also
receiving corticosteroids plus standard of care (SOC) of mycophenolate
mofetil (MMF) or Europlas (EL) cyclophosphamide (CYC) regimen.
Methods: Pts with active proliferative LN were randomized equally to PBO, OCR 400 mg, or OCR 1000 mg IV on days 1 and 15; single infusions were then given every 16 wks. Pts received either MMF (up to 3 g/d) or EL (IV CYC 500 mg q2 wks infusions were then given every 16 wks. Pts received either MMF (up to 3 g/d) or EL (IV CYC 500 mg q2 wks

Table. Efficacy and Safety; Renal

<table>
<thead>
<tr>
<th>Renal Response at Week 48</th>
<th>All ‘32 Wks’ Pts</th>
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<tbody>
<tr>
<td></td>
<td>PBO</td>
</tr>
<tr>
<td>Number (%) Pts</td>
<td>N = 74</td>
</tr>
<tr>
<td>ORR (CRR + PRR)</td>
<td>38 (51)</td>
</tr>
<tr>
<td>CRR</td>
<td>24 (32)</td>
</tr>
<tr>
<td>PRR</td>
<td>14 (19)</td>
</tr>
<tr>
<td>Ulv/Cr (≥50%) reduction</td>
<td>43 (58)</td>
</tr>
<tr>
<td>Ulv/Cr ≤0.5</td>
<td>27 (36)</td>
</tr>
<tr>
<td>MMF Pts</td>
<td>N = 46</td>
</tr>
<tr>
<td>ORR</td>
<td>26 (57)</td>
</tr>
<tr>
<td>CRR</td>
<td>17 (37)</td>
</tr>
<tr>
<td>PRR</td>
<td>9 (20)</td>
</tr>
<tr>
<td>EL Pts</td>
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</tr>
<tr>
<td>ORR</td>
<td>12 (43)</td>
</tr>
<tr>
<td>CRR</td>
<td>7 (25)</td>
</tr>
<tr>
<td>PRR</td>
<td>5 (18)</td>
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Interim Safety Results (Safety Population)

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<tr>
<th></th>
<th>PBO</th>
<th>OCR 400 mg</th>
<th>OCR 1000 mg</th>
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</thead>
<tbody>
<tr>
<td>Number (%) Pts</td>
<td>N = 125</td>
<td>N = 126</td>
<td>N = 127</td>
</tr>
<tr>
<td>Adverse Events (AEs)</td>
<td>104 (83)</td>
<td>101 (80)</td>
<td>98 (77)</td>
</tr>
<tr>
<td>Serious AEs (SAEs)</td>
<td>36 (29)</td>
<td>45 (36)</td>
<td>30 (24)</td>
</tr>
<tr>
<td>Eurolypsis</td>
<td>16/44 (36)</td>
<td>13/47 (28)</td>
<td>10/48 (21)</td>
</tr>
<tr>
<td>MMF</td>
<td>20/81 (25)</td>
<td>32/79 (41)</td>
<td>20/79 (25)</td>
</tr>
<tr>
<td>Infections</td>
<td>65 (52)</td>
<td>78 (62)</td>
<td>71 (56)</td>
</tr>
<tr>
<td>Serious infections (SIEs)*</td>
<td>18 (14)</td>
<td>31 (25)</td>
<td>21 (17)</td>
</tr>
<tr>
<td>Eurolypsis</td>
<td>5/44 (11)</td>
<td>6/47 (13)</td>
<td>6/48 (13)</td>
</tr>
<tr>
<td>MMF</td>
<td>13/81 (16)</td>
<td>25/79 (32)</td>
<td>15/79 (19)</td>
</tr>
<tr>
<td>Infusion related reactions (IRRs)</td>
<td>6 (5)</td>
<td>14** (11)</td>
<td>15 (12)</td>
</tr>
</tbody>
</table>

Conclusion: In this ‘32 wks’ population, the ORR rate at 48 wks was overall 12% higher in the OCR group. The addition of OCR 400mg to MMF did not generate additional benefit, with an increased observed rate of serious infections (SIEs). The OCR + EL regimen had a higher ORR rate vs EL alone, in both dose groups, with a lower PBO + EL ORR rate compared to the

PBO + MMF group. Incidence of SAEs, SIEs, and IRRs was lower in EL pts compared to MMF pts.

Disclosure: E. F. Myster: Genentech and Biogen IDEC Inc, 6, Roche, 5, 6; A. J. Spindler: None; R. Guzman: None; M. Bijl: Roche, 2; D. Jayne: Roche, 2, 5, R. A. Furie: Genentech and Biogen IDEC Inc, 2; S. Shahdad: Roche; 3; D. Close: None; P. Brunetta: Genentech and Biogen IDEC Inc, 3, J. Drappa: Genentech and Biogen IDEC Inc, 3.

1456

Belimumab, a BLYS-Specific Inhibitor, Reduced Disease Activity across Multiple Organ Domains: Combined Efficacy Results from the Phase 3 BLISS-52 and -76 Studies. S. Manzi10, J. Sanchez-Guerrero2, J. T. Merrill9, R. A. Furie3, D. Gladman4, S. Navarra11, E. M. Ginzler1, D. D’Cruz2, A. Doria3, S. Cooper1, Z. J. Zhong4, D. Hough1, W. Freimuth1, M. Petr1 and on Behalf of the BLISS-52 and -76 Study Groups. 1Human Genome Sciences, Inc, Rockville, MD, 2Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico, 3North Shore LIJ Health System, Lake Success, NY, 4Oklahoma Medical Research Foundation, Oklahoma City, OK, 5St. Thomas’ Hospital, London, London, United Kingdom, 6SUNY Downstate Medical Center, Brooklyn, NY, 7Toronto Western Hospital, Toronto, ON, Canada, 8Universita’ di Padova, Padova, Italy, 9University of Pittsburgh School of Medicine, PA, 10University of Santo Tomas Hospital, Manila, Philippines

Purpose: To assess the efficacy of belimumab in individual organ domains using BILAG and SELENA SLEDAI (SS) in SLE patients after 52 wk of treatment.

Methods: 1684 seropositive (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL) SLE patients with SS ≥6 on stable standard-of-care therapy for ≥30 d were enrolled in the phase 3, randomized, double-blind, placebo-controlled, international studies of belimumab 1 or 10 mg/kg vs placebo, plus standard of care (NCT00424476; NCT00410384). Participants were dosed on d 0, 14, and 28, and then q28d, for 48 or 72 wk. Efficacy analyses included SS and BILAG measured every 4 wk. SLEDAI domain scores were determined using methods described by Bombardier et al (1992); traditional scoring methods were used for BILAG domains. Positive shifts in total SS domain scores between baseline and wk 52 defined worsening; negative shifts defined improvement. Improvement in BILAG domain scores was defined as a shift from A or B scores at baseline to a lower score; worsening was defined as a shift to a higher score from B, C, D, or E at baseline. Patients who withdrew and/or took protocol-prohibited/restricted medication were considered to have no improvement. In worsening analysis, missing data were analyzed with last-observation-carried-forward imputation methods, using the last available observation at or prior to withdrawal, or dropout due to use of a protocol-prohibited/restricted medication (whichever occurred earlier).

Results: SS and BILAG organ system involvement at baseline was generally similar in the belimumab and placebo groups, and between studies (table). The most common SS domains involved were dermal (82%), immunologic (80%), musculoskeletal (65%), and renal (16%). The most common BILAG domains involved were muscular-skeletal (60%), mucocutaneous (59%), hematology (16%), renal (11%), and general (11%). For SS, there was significant improvement from baseline at wk 52 in the central nervous system (CNS), vascular, muscular-skeletal, immunologic, and dermal domains with belimumab (≥1 dose) vs placebo. In patients without involvement at baseline in a specific organ system, there was significantly less worsening at wk 52 in the immunologic, renal, and hematologic domains with belimumab vs placebo. For BILAG, there was significant improvement from baseline at wk 52 in muscular-skeletal and mucocutaneous domains, and a trend (p<0.07) in the vasculitis domain with belimumab (≥1 dose) vs placebo. There also was significantly less worsening from baseline at wk 52 in the hematology domain, and a favorable trend in the vasculitis and renal domains, with belimumab vs placebo.

Conclusion: Belimumab demonstrated beneficial effects, with reductions in disease activity and prevention of worsening across several SS and BILAG organ systems.
Purpose: To examine 5-year safety of belimumab in an open-label extension study of SLE patients and evaluate long-term efficacy in a subgroup similar to those in recent phase 3 trials.

Methods: 449 SLE patients with SELENA-SLEDAI (SS) ≥4 enrolled in a phase 2, 52-wk, randomized, double-blind study of belimumab 1, 4, or 10 mg/kg q28d vs placebo, plus background SLE therapy (NCT00071487). At wk 56, placebo patients initiated belimumab 10 mg/kg; prior belimumab patients received the same dose or 10 mg/kg. At wk 80, 256 patients (60%) entered an uncontrolled continuation study (belimumab 10 mg/kg; NCT00583362). The 5-y dataset was divided into ten 6-mo intervals for reporting efficacy and adverse events (AEs). Analyses of disease activity included the SS Flare Index (SFI) and SLE Responder Index (SRI): improvement in SS (>4 pt), no new BILAG A or <2 new B flares, and no Physician's Global Assessment worsening (<0.3 pt) vs baseline. All efficacy assessments were limited to the seropositive (ANA titer ≥1:80 and/or anti-dsDNA ≥30 IU/mL) patient subgroup (n = 321), who were similar to those patients enrolled in the phase 3 trials. Safety assessments were performed in all patients.

Results: 19% of patients dropped out during the placebo-controlled portion of the study, 296 enrolled in the open-label extension at wk 80, and the discontinuation rate has been 3%–9%/y. Total belimumab exposure was 1415 patient-years (pys). Incidence rates (per 100 pty) of AEs remained stable or decreased over 5 y (table). In seropositive patients, SRI rate was 46% at wk 52 (vs 29% with placebo; p < 0.05), increased to 55% by wk 76, and was maintained through wk 272 (50%). In this study, adjustments in background SLE therapy were permitted. The frequency of 1 new BILAG A or 2 new B flares decreased from 30% over the 1st 6 mo to 23% over the 2nd 6 mo (vs 33% and 25%, respectively, with placebo) and declined to 11% at the 4.5–5.0-y interval. The frequency of SFI flares decreased from 72% (severe 13%) over the 1st 6 mo to 62% (severe 8%) over the 2nd 6 mo (vs 76% [severe 9%] and 73% [severe 11%], respectively, with placebo) and further declined to 22% (severe 1%) at the 4.5–5.0-y interval. Autoantibody levels (anti-Sm, anti-dsDNA, anti-cardiolipin immunoglobulin-G) decreased over time with belimumab.

Table. Acute Adverse Events with 1:5 or More

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SOC + Placebo, n (%)</th>
<th>SOC + Belimumab 1 mg/kg, n (%)</th>
<th>SOC + Belimumab 10 mg/kg, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BILAG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>1/5 (20%)</td>
<td>1/5 (20%)</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td>Worsening</td>
<td>4/5 (80%)</td>
<td>4/5 (80%)</td>
<td>6/8 (75%)</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alergy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening</td>
<td>1/5 (20%)</td>
<td>1/5 (20%)</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td><strong>Neurology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>2/5 (40%)</td>
<td>2/5 (40%)</td>
<td>3/8 (38%)</td>
</tr>
<tr>
<td>Worsening</td>
<td>3/5 (60%)</td>
<td>3/5 (60%)</td>
<td>5/8 (63%)</td>
</tr>
</tbody>
</table>

**Conclusions:** Belimumab added to standard-of-care therapy was well tolerated over 5 y. Seropositive patients treated with belimumab showed sustained improvement in disease activity, and a decline in BILAG and SFI flares over 5 y, without changing the background treatment rules.


**AUC RREF Special Session**

**REF Marshall J. Schiff, MD, Memorial Lectureship:** Everything a Rheumatologist Should Know About Spine Surgery but Was Afraid to Ask

Tuesday, November 9, 2010, 4:30 PM–6:00 PM
Purpose: The purpose of this study was to evaluate the effectiveness of the Global Posture Reducation method (GPR) and segmental stretching exercises in the treatment of chronic back pain.

Methods: A randomized controlled blinded assessor trial was conducted. One hundred and fifty patients of both sexes were selected, with a mean age of 40.15 ± 11.55 years-old, who had pain in some segment of the spine for at least three months. They were randomly distributed into three groups (n=50, each): G1 – submitted to GPR method; G2 – received the segmental stretching; and G3 – control. Patients in G1 and G2 received 16 individual treatment sessions, twice a week, for eight weeks. The outcomes measured were pain (visual analogue scale), function (Roland Morris questionnaire), quality of life by the Brazilian Portuguese version of Short Form-36 (SF-36), and pain medication consumption (all patients were instructed to register in a suitable form every time they consume any pain medication). Besides the evaluations before and after the end of the intervention, a follow up was conducted two months after the end of the treatment. Data were statistically analyzed at a significance level of p<0.05. An intragroup and intergroup comparison was performed.

Results: The baseline assessment demonstrates the homogeneity of the groups. The outcomes showed significant pain level reduction in the three groups, but in the intergroup’s comparison, treated groups were better than control, and G1 (GPR) was still better than G2 (segmental stretching), presenting the largest pain intensity reduction. In quality of life in G1 and G2, there was significant improvement in all SF-36 domains (functional capacity, physical, emotional and social aspects, pain, general health status, vitality, and mental health). In G3 this improvement occurred in pain, social and emotional aspects, and functional capacity. In the intergroup’s comparison, G1 and G2 were significantly superior to G3 in physical aspects, pain, and vitality components. The G1, treated with GPR, was still better than G3 when comparing social aspects and mental health. In Roland Morris questionnaire there were significant improvements in all groups, but in the comparison among them, G1 and G2 were significantly better. Regarding the consumption of pain medication, it was observed in the treated groups, G1 and G2, that the drug intake was significantly lower than in the control group (G3).

Conclusion: Based on the findings of our study, we conclude that both methods were effective and superior to control group in pain reduction, in the improvement of function and quality of life, and in the decrease of medication consumption, however, the GPR method proved to be superior to the segmental stretching for the treatment of chronic back pain.

Disclosure: M. M. dos Santos: None; L. S. Guimarães: None; L. O. Souza: None; M. M. Vasconcelos: None; T. M. Camargo: None; P. G. Develly: None; B. L. F. Fernandes: None; V. F. M. Trevisani: None.

1459
Epidemiology of Restricting Back Pain in Older Persons and Associations with Age, Sex, Obesity, and Depressive Symptoms. Una E. Makris1, Liana Fraenkel1, Ling Han2 and Thomas M. Gill3. 1Department of Veterans Affairs, West Haven, CT, 2Program on Aging, New Haven, CT, 3Yale University School of Medicine

Background: Despite the considerable morbidity and costs attributable to back pain, longitudinal data describing the clinical course and risk factors associated with this complaint in older persons are sparse.

Purpose: To describe the epidemiology of restricting back pain in community-living older persons and to evaluate the association of age, sex, obesity, and depressive symptoms with development of restricting back pain.

Methods: Participants, identified from the Yale Precipitating Events Project, included 550 nondisabled, community-living persons, aged 70 years or older, who did not report restricting back pain at baseline. Data were collected monthly for over 10 years. Restricting back pain was defined as staying in bed for at least half a day and/or cutting down on one’s usual activities due to back pain. One or more consecutive monthly reports of restricting back pain defined an episode. We first determined the number and duration of restricting back pain episodes. We used Cox regression models to evaluate the association between age, sex, obesity, and depressive symptoms and the development of the first occurrence and recurrence of restricting back pain episodes. Interaction terms between sex and these baseline factors were tested using Cox models in first-event and recurrent events models.

Results: The mean age of our sample was 78.6 years, 63% were women, 92% were white, 19% were obese (BMI ≥30 kg/m2), and 15% reported depressive symptoms. During a median follow-up of 107 months, 126 (61.8%) of the men and 251 (72.5%) of the women participants developed restricting back pain. Among the 377 (68.5%) participants with restricting back pain, the median (interquartile range) number of episodes was 2.0 (1–4) for men and 3.0 (1–5) for women (p = 0.01). The median duration of restricting back pain episodes was one month. Of the 1528 total episodes of restricting back pain, only 6.4% were chronic (lasting three or more months). There were no differences in number or duration of restricting back pain episodes by age. The association between restricting back pain and age, sex, obesity, and depressive symptoms are listed in Table 1. Women with depressive symptoms had the highest risk of developing recurrent restricting back pain episodes (HR 2.89, 95% CI 2.03, 4.11) compared to men without depressive symptoms.

Table 1. Association between selected risk factors and restricting back pain (N = 550) estimated using Cox proportional hazard model

<table>
<thead>
<tr>
<th>Effect*</th>
<th>Outcome</th>
<th>Model 1 (1st event)</th>
<th>Model 2 (Recurrent events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 85</td>
<td>HR (95% CI)</td>
<td>1.28 (1.01–1.62)</td>
<td>1.03 (0.82–1.29)</td>
</tr>
<tr>
<td>Female Sex</td>
<td>HR (95% CI)</td>
<td>1.27 (1.02–1.57)</td>
<td>1.41 (1.10–1.80)</td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>HR (95% CI)</td>
<td>1.34 (1.05–1.72)</td>
<td>1.60 (1.21–2.12)</td>
</tr>
<tr>
<td>Depressive Symptoms</td>
<td>HR (95% CI)</td>
<td>1.73 (1.29–2.34)</td>
<td>2.04 (1.53–2.72)</td>
</tr>
</tbody>
</table>

* Both models simultaneously included these four variables.

Conclusion: Among community-living older persons, restricting back pain is common, short-lived, and frequently episodic. Women with depressive symptoms are most likely to develop restricting back pain. Additional research is warranted to further investigate the relationship between depressive symptoms and back pain, especially in older women.

Disclosure: U. E. Makris: None; L. Fraenkel: None; L. Han: None; T. M. Gill: None.

1460
Life Course Socioeconomic Position and Health Outcomes in People with Self-Reported Arthritis. Jack H. Shreffler1, Britta Schoster2, Kathryn Remmes Martin1 and Leigh F. Callahan3. 1Univ of North Carolina, Chapel Hill, NC, 2University of North Carolina at Chapel Hill, Chapel Hill, NC, 3University of North Carolina, Chapel Hill

Purpose: Childhood and adult socioeconomic status (SES) positions have been demonstrated to be independently associated with health status outcomes in cardiovascular and other chronic diseases. The purpose of this study is to determine if current SES and childhood caregiver SES positions are independently associated with health outcomes, including measures of disability, physical health, and mental health status, in people with self-reported arthritis.

Methods: A practice-based research network of 22 family medicine practices in rural and urban areas of a southeastern state was established in 2001. Participants completed telephone surveys assessing health status, chronic conditions, community characteristics, health attitudes and beliefs, and socio-demographic variables in 2004 and again in 2006. The 2006 follow-up questionnaire obtained participants’ current SES and the SES of their parent or caregiver during childhood. Regression models were conducted on 937 people with arthritis for health outcomes including adult/childhood pairs of single SES variables (education, occupation, or homeownership) as main explanatory variables with adjustment for age, BMI, and gender. Outcomes were SF12v2 Physical (PCS) and Mental (MCS) Component Summary scores, Health Assessment Questionnaire disability scale (HAQ), Center for Epidemiological Studies-Depression depressive symptoms scale (CES-D), and the CDC Health Related Quality of Life 5-item general health response (dichotomized to fair/poor versus good/very good/excellent).

Results: The average age of participants was 61 years (23–94) and 74% were female. 16% did not complete high school (NHS), non-homeownership (NHO) was 18%, and low occupational status (LOC) was 42%. The 3 SES measures for the participants were considerably higher than those reported for their primary caregiver during childhood. PCS score, 38(13) [mean (sd)], was significantly (p<0.05) reduced by –4.2, –2.7, and –2.7 for caregiver NHS, LOC, and NHO, respectively. General health self-reported as fair/poor (39%)
was more likely, OR = 1.54 (95% CI = [1.17, 2.05]), for caregiver NHO, and nearly significantly, OR = 1.6 (95% CI = [0.99, 2.70], p = 0.056), for caregiver NHS. CES-D score, 11.9(12), was significantly increased by 2.6 and 2.5 for caregiver NHS and NHO, respectively. In addition, CES-D was nearly significant, $\beta = 1.6$ (95% CI = $(-0.1, 3.25)$, ($p = 0.051$) for LOC. Neither HAQ nor MCS was found to have independent, significant association with the three caregiver SES variables when the adult measures were included in the model. In the regression models producing the results above, SES measures for the adult participants were strongly associated with all outcomes, with the notable exceptions of PCS and MCS for homeownership.

Conclusions: SES measures at childhood show significant association with PCS, general health, and CES-D, independent of the participant’s current adult SES levels. Healthcare providers should consider the potential influence of patients’ SES as children when evaluating their current health status.

Disclosure: J. H. Shreffler: None; B. Schoster: None; K. R. Martin: None; L. F. Callahan: None.

1461
Perceived Helplessness as a Mediator between Household Income and Health Status in People with Self-Report Arthritis. Kathryn Remmes Martin$^2$, Britta Schoster$^3$ and Leigh F. Callahan$^1$. $^1$ Univ of North Carolina, Chapel Hill, NC, $^2$ University of North Carolina at Chapel Hill, Chapel Hill, NC, $^3$ University of North Carolina at Chapel Hill

Purpose: Lower income is associated with poorer health status among people with chronic disease. This study aimed to examine the role of perceived helplessness as a mediator in the relationship between household income and health status in people with self-report arthritis.

Methods: In 2004 and 2005, 439 people with self-reported physician-diagnosed arthritis were recruited from a southeastern Family Medicine Research Network and completed a telephone survey assessing health status, chronic conditions, neighborhood characteristics, health attitudes and socio-demographic variables. Six health status outcomes were: Health Assessment Questionnaire (HAQ), disability index; SF-12v2 Physical Component Summary (PCS), physical functioning; SF-12v2 Mental Component Summary (MCS), mental health; and 3 CDC Health Related Quality of Life Healthy Days measures: mental, physical and limited activity days. The proposed mediator, perceived helplessness, was assessed with the Rheumatology Attitudes Index (RAI). Path analyses were constructed with MPlus to examine the relationship between income, perceived helplessness, and each health status outcome, adjusting for age, race, gender, body mass index (BMI), education, occupation, homeownership, and block-group poverty-level.

Results: Participants were on average 56 years old, female (76.3%), non-Hispanic white (75.9%), had a mean BMI of 31.5, earned less than $45,000 (72.7%), had at or lower than a high school education (51.9%), had lower occupational status (54.7%), and were homeowners (74.3%). Income was directly and indirectly related to health status. Income was directly related to physically unhealthy days ($\beta = -2.42$, p = 0.003), mentally unhealthy days ($\beta = -2.17$, p = 0.002), lower MCS ($\beta = 1.96$, p = 0.03), limited activity days ($\beta = -3.66$, p < 0.001), PCS ($\beta = 3.40$, p < 0.001), and disability ($\beta = -0.27$, p < 0.001). Income was also indirectly related through helplessness. Individuals with lower income have greater perceived helplessness regarding their condition ($\beta = -0.33$, p < 0.001). Those with greater helplessness reported greater number of physically unhealthy days ($\beta = 5.24$, p < 0.001), mentally unhealthy days ($\beta = -4.48$, p < 0.001), limited activity days ($\beta = 4.44$, p < 0.001), greater disability ($\beta = 0.33$, p < 0.001) and lower scores on MCS ($\beta = -6.15$, p < 0.001) and PCS ($\beta = -3.98$, p < 0.001). The Sobel test showed a significant indirect effect for physically unhealthy days ($\beta = -1.74$, p < 0.001), mentally unhealthy days ($\beta = -1.49$, p < 0.001), limited activity days ($\beta = -1.48$, p < 0.001), MCS ($\beta = 2.04$, p < 0.001), PCS ($\beta = 1.32$, p < 0.001), and disability ($\beta = -0.11$, p < 0.001).

Conclusions: Our findings indicate that lower levels of helplessness partially mediate the relationship between lower levels of income and poorer mental and physical health status outcomes in people with self-report arthritis. Enhancing perceived control in individuals with lower income levels may be a mechanism for reducing health disparities.

Disclosure: K. R. Martin: None; B. Schoster: None; L. F. Callahan: None.

1462
An Examination of How Coping with Prescription Medication Costs and Medication Underuse Influences Physical and Mental Health of Individuals with Arthritis. Kathryn Remmes Martin, Britta Schoster, Jack Shreffler and Leigh F. Callahan, University of North Carolina at Chapel Hill

Purpose: Our purpose is twofold: 1) to identify the overall frequency and characteristics of individuals who self-report prescription medication cost coping strategies, and 2) to examine the association between coping strategies and medication underuse and physical and mental health outcomes among a cohort of participants with arthritis from a southeastern state.

Methods: In 2006 and 2007, 729 people with self-reported physician-diagnosed arthritis completed a telephone survey assessing health status, chronic conditions, neighborhood characteristics, health attitudes and socio-demographic variables. Five health status outcomes used were: Health Assessment Questionnaire (HAQ), disability index; SF-12v2 Physical Component Summary (PCS), physical functioning; SF-12v2 Mental Component Summary (MCS), mental health; Center for Epidemiological Studies-Depression (CES-D) (<16, ≥16), depressive symptoms; self-rated health (excellent, very good, & good; fair & poor). Helplessness was also assessed with the Rheumatology Attitudes Index (RAI). Linear and logistic regression analyses using Stata v11 were conducted for each outcome to explore associations with the medication cost coping strategies while adjusting for age, race, gender, body mass index (BMI), co-morbid conditions, income, occupation and homeownership.

Results: Participants were on average 61 years old, female (75.0%), non-Hispanic white (76.8%), had a mean BMI of 30.2, and a median income of below $45,000 (55.7%). Overall, participants reported spending less on food, heat, or basic needs (22.4%), borrowing money from a friend or relative outside of their household (16.1%), increased the amount of credit-card debt carried month-to-month (11.7%) to pay for medications and taking fewer medications than prescribed due to medication costs (20.2%). Individuals who borrowed money had lower mental health (MCS) ($\beta = -3.87$, p = 0.003) and greater disability ($\beta = 0.14$, p = 0.044). Individuals increasing credit card debt had worse physical functioning ($\beta = -4.63$, p = 0.001), and self-rated health (OR = 0.43, p = 0.005), and reported greater helplessness associated with their condition ($\beta = 0.47$, p < 0.001). Individuals who reported medication underuse had worse mental health ($\beta = -4.24$, p = 0.001), greater disability ($\beta = -0.13$, p = 0.028), depressive symptoms (OR = 2.03, p = 0.004), and a trend for worse self-rated health (OR = 0.62, p = 0.066). Age, race, BMI, comorbid condition count, education, and income were statistically significant covariates in some of the models dependent on the outcome.

Conclusions: Our findings indicate that individuals with arthritis do use strategies to cope with medication costs, one of which is medication underuse, and that these strategies have adverse mental and physical health outcomes. Health care practitioners should be alert to issues of medication cost to ensure optimal patient health and medication adherence.

Disclosure: K. R. Martin: None; B. Schoster: None; J. Shreffler: None; L. F. Callahan: None.

1463
Disability and Knee Osteoarthritis: Associations with Individual and Community Socioeconomic Status. Leigh F. Callahan, Joshua B. Knight, Jack H. Shreffler, Britta Schoster, Jordan B. Renner and Joanne M. Jordan, University of North Carolina, Chapel Hill

Purpose: Individual level socioeconomic status (SES) measures have been shown to be associated with disability and restricted function in osteoarthritis (OA), and limited studies have also demonstrated associations with community level SES measures independent of one’s individual SES. To date this has not been evaluated in persons with knee OA. This study examined associations between educational attainment, occupation, and community poverty with disability in persons with knee radiographic OA (rOA) or symptomatic OA (sOA) in a population-based OA cohort in a southeastern state.

Methods: A cross-sectional analysis was conducted on individuals (64% Caucasian, 36% African American) with knee rOA (n = 733) or knee sOA (n = 487) who were assessed in the 2001–2003 time period. rOA was defined as Kellgren-Lawrence grade ≥ 2 at least one knee. sOA was defined as K-L grade ≥ 2 and symptoms (pain, aching or stiffness) in the same knee. Educational attainment (<high school (HS) or ≥HS) and occupational status (managerial or non-managerial) were individual SES measures. Census block group poverty rate (<12%, 12–25%, >25%) was the community SES
measured. Disability was measured by the Health Assessment Questionnaire (HAQ). Covariates were age, gender, race, BMI, occupational activity score, and presence of hip symptoms. Race was not an effect modifier and was included as a covariate. Unadjusted and adjusted analyses were used to find associations of disability with each SES effect separately. Multivariable analyses were conducted using all SES variables, adjusting for covariates.

Results: In persons with knee rOA, education (β=0.24, C.I. = [0.11, 0.32]), occupation (β=0.15, C.I. = [0.05, 0.25]) and >25% poverty (β=0.22, C.I. = [0.07, 0.36]) were all significantly associated with disability in unadjusted models. All SES variables were also significantly associated with HAQ disability in persons with SOA: education (β=0.22, C.I. = [0.09, 0.35]), occupation (β=0.16, C.I. = [0.03, 0.29]) and >25% poverty (β=0.23, C.I. = [0.05, 0.41]). In adjusted models, occupation and community poverty were no longer significantly associated with rOA or SOA. In multivariable models, education was the only SES variable (in both rOA and SOA) significantly associated with disability (β=0.18, C.I. = [0.08, 0.29]) and (β=0.22, C.I. = [0.09, 0.36]), respectively. Covariates positively associated with disability were hip symptoms, female gender, obesity, and strenuous occupational activities.

Conclusions: In persons with knee rOA or knee SOA, education remained the important SES predictor of disability after adjusting for key risk factors. Occupation and community poverty were not independently significant when education was a main explanatory variable. These data underscore the importance of educational attainment with outcomes in knee OA.

Disclosure: L. F. Callahan: None; J. B. Knight: None; J. H. Shreffler: None; B. Schoster: None; J. B. Renner: None; J. M. Jordan: None.

Radiographic Knee Osteoarthritis and Knee Pain: Findings from 5 Ethnically Diverse Populations. Ke Wang2, Noriko Yoshimura3, Ling Xu1, Jianhao Lin6, Inje Kim4, Michael Nevitt8, Hiroshi Kawaguchi7, David Felson1, Xiaozheng Kang6, Yuqing Zhang1 and Hyun Ah Kim3. 1BU. Sch. of Med., Boston, 2BU. Sch. of Med., 3Hallym Univ., Sacred Heart Hosp., Anyang, Korea, Republic of, 4Hallym Univ., Sacred Heart Hosp., Korea, 5Wuchuan, China, 6Wuchuan (Rural), 7The University of Tokyo, Tokyo, Japan, 8Univ. of California at San Francisco, San Francisco, CA.

Background: There is a consensus that the association between knee radiographic osteoarthritis (ROA) and knee pain is modest and only limited to knees with severe ROA. However, utilizing a novel approach comparing knees discordant for pain, recent results from both Framingham OA Study and Multicenter OA Study suggested that ROA was strongly associated with both frequent knee pain (FKP) and pain severity, even among knees with moderate ROA. To investigate whether such findings are consistent in other ethnic populations, we examined the relation of knee ROA to FKP and pain severity, even among knees with moderate ROA.

Methods: Subjects included were from 5 studies: urban Chinese (Beijing OA Study, BOA), rural Chinese (Wuchuan OA Study, Wuchuan), Japanese (Research on OA Against Disability, ROAD), Korean (Hallym Aging study, HAS), White (OA Initiative, OAI), and African American (OAI). Participants in each study were asked knee-specific questions regarding presence of FKP (i.e., pain lasting for ≥ a month in the past 12 months) and pain severity. We performed a within-person knee-matched case-control analysis among subjects whose FKP status or pain severity categories (no pain, mild/moderate pain, severe/extreme pain) were discordant between the two knees. We examined the relation of knee ROA to prevalence of FKP using a logistic regression model and to pain severity using a stratified proportional odds model by amalgamating conditional likelihood.

Results: Included were 252 urban Chinese (71% female, mean age 68, mean BMI 26), 221 rural Chinese (55% female, mean age 57, mean BMI 23), 297 Japanese (71% female, mean age 71, mean BMI 24), 98 Koreans (54% female, mean age 70, mean BMI 25), 556 Whites (46% female, mean age 62, mean BMI 29), and 141 African Americans (71% female, mean age 62, mean BMI 32). As shown in Table, knee ROA is strongly associated with presence of FKP across all 5 racial/ethnic populations (p for trend for all studies <0.01). The association is strong even for knees with moderate ROA: knees with K/L=2 had 6.8 (BOA), 3.8 (Wuchuan), 6.6 (HAS), 3.0 (ROAD), 7.2 (OAI White), and 17.6 (OAI African American) times higher prevalence of FKP than those with K/L=0. Knee ROA was also strongly associated with knee pain severity (p for trend for all studies <0.01).

Conclusion: Severity of knee ROA was strongly associated with FKP and pain severity in all ethnic groups.

Impact of Buenos Dias, Artritis, a Spanish Health Communications Campaign Promoting Physical Activity among Spanish-Speaking People with Arthritis. Teresa J. Brady2 and Jed Lam1. 1Aeffect Inc., 2Center for Disease Control, Atlanta, GA.

Background: Buenos Dias, Artritis is a health communications campaign designed to promote physical activity among Spanish-speaking people with arthritis. The purpose of this campaign was to evaluate the effects of the campaign as implemented by 4 state health departments.

Methods: A quasi-experimental design was used. 4 state health departments conducted the campaign in one community in their state by placing radio ads and/or outdoor advertising, brochures in community locations and newspaper ads or other print materials. Data were collected from these Test communities (TC) and well as 2 Control communities (CC), selected to have similar proportions of Hispanic populations, at baseline (T1), immediately following campaign completion (T2) and 6 months after baseline (T3). Data were collected by random-digit dial telephone survey from purchased lists of randomly generated telephone numbers in geographic areas known to have higher rates of Hispanics with lower income and education levels. T1 respondents were ineligible for T2 survey.

Results: By design, T1 and T2 data were collected for approximately 1200 respondents (1213 and 1167 respectively), and 600 T3 respondents. Characteristics of T1 sample: 41% ages 55–64, (range 45–75), 68% from Mexico, 69% education less than high school graduate, and 75% female.

Changes in knowledge and confidence were seen. TC demonstrated significant increase in the percentage who believed that "moderate exercise can help you beat arthritis" at T3, (T1=84%, T3=89%)but control respondents also had a significant increase (T1=84%, T3=91%). However, the TC significant increase in beliefs that "moderate exercise can be helpful even if done 10 minutes at a time" (T1=84%, T3=91%), and that they could "reduce my arthritis pain by exercising regularly" (T1=76%, T3=82%) were not matched by increases in CC.

Exercise behavior increased significantly in TC but not CC at both T2 and T3. TC demonstrated significant increases in percentages "exercising at least 10 minutes per day" at T2 and T3 (T1=72%, T3=76%, T3=86%), and "exercising at least 3 days per week" at T2 and T3 (76%, 82%, 81% respectively). No comparable increase was seen in the CC.

Conclusion: Buenos Dias, Artritis health communications campaign produced significant increases in physical activity at T2 and T3, though few significant changes in knowledge or confidence were found. Unaided recognition of campaign sponsors increased at T2, but these increases did not persist at T3.

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A Novel Serum Biomarker of Cartilage Destruction, Measured in OA and RA Patients, Is Significantly Associated with Kellgren-Lawrence Score. Anne C. Bay-Jensen1, Erik B. Dam1, Inger Byrjalsen2, Tanja Schubert1, Philipp Vergnaud3, Per Qvist1 and Morten A. Karsdal1, 1Cartilage Biology and Biomarkers, Denmark, 2CCBR-Synarc, Denmark, 3Nordic Bioscience Imaging, Denmark, 4Synarc-Lyon, France

Background: Type II collagen is the primary matrix protein in articular cartilage. In joint degenerative diseases, such as osteoarthritis (OA) and rheumatoid arthritis (RA), the collagens are degraded by matrix metalloproteinases (MMPs) and fragments of the protein are released into the circulation. We identified one such fragment of MMP-derived type II collagen (CIIM).

Methods: Type II collagen was cleaved with MMP in vitro and analyzed by mass spectrometry. A collagen type II specific neoeptope, CIIM, was identified (RDGAAG1653). Monoclonal antibodies were raised against the neoeptope and used to develop an ELISA. CIIM assay was measured in the synovial fluid of 18 OA patients aged 62–81 and in serum of an adult population aged 21–80 (n=156). Knee OA was graded by standard Kellgren-Lawrence (KL) score. Serum levels were measured in serum samples from RA patients and age-matched controls (n=66).

Results: The CIIM ELISA showed good technical performance; a quantification range of 0.2–14.9ng/ml, inter- and intra assay variations below <15% and a dilution recovery of approximately 100%. CIIM was immunolocalized to classical arthritis features in OA cartilage. A high median level of CIIM [1.2ng/ml] was found in synovial fluid. Serum CIIM levels were significantly higher (p<0.05) in those individuals with OA detected by KL scores of 1–2 [0.9ng/ml] and 3–4 [1.0ng/ml] than in those with KL score of 0 [0.6ng/ml] (Fig. 1). The level of CIIM in RA serum [0.284ng/ml] was significantly higher (p<0.01) than age-matched controls [0.532ng/ml].

Conclusion: We developed and validated an ELISA for CIIM; a novel biomarker which we demonstrated is derived from MMP-degraded type II collagen. We found serum CIIM levels to be highest in those with the lowest KL score and with RA.

Purpose: c-Fos/activator protein-1 (AP-1) is an important transcription factor for cytokine production and joint destruction in rheumatoid arthritis (RA) and a potential target for the treatment of RA. We have previously reported a small molecule c-Fos/AP-1 inhibitor T-5224 prevented the development of arthritis and joint destruction in mouse collagen-induced arthritis (CIA). The purpose of this study was to investigate the effects of T-5224 on the osteoclastogenesis and bone resorption.

Methods: 1) in vitro: Macrophage-osteoclast precursor RAW264.7 cells were cultured with receptor activator for nuclear factor B ligand (RANKL) (50 ng/mL) and/or T-5224 for 6 days. Osteoclastogenesis was examined by tartrate-resistant acid phosphatase (TRACP)-staining and pit formation assay. The expressions of cathepsin K, c-Fos, and NFATc1 were determined by Western blot analysis. 2) in vivo: CIA was induced in DBA/1J mice by the immunization with bovine type II collagen twice on day 0 and 21. T-5224 was orally administered once daily. The levels of serum TRACP 5b were measured using ELISA, and the mRNA expressions of RANKL and osteoprotegerin (OPG) in the hind paw were measured by RT-PCR. Bone mineral density (BMD) of the femur was assessed using micro-CT. The region of interest was positioned at a metaphyseal region at a point of 3% of the length of the femur from the growth plate.

Results: T-5224 suppressed the induction of TRACP-positive multinucleated cells under the RANKL-stimulation in RAW264.7 cells. The expressions of cathepsin K and NFATc1 were also inhibited by T-5224 in RANKL-stimulated cells. Meanwhile, the expression level of c-Fos was no difference with or without T-5224. Furthermore, T-5224 inhibited the formation of bone resorption pits in vitro. In mice with CIA, the marked elevation of serum TRACP 5b, a bone resorption marker, was observed on day 35, and this change was significantly suppressed by the administration of T-5224 from day 21. In addition, T-5224 dose-dependently inhibited the increase of RANKL mRNA and the decrease of OPG mRNA in the arthritic hind paws. The BMD of the femora of mice with CIA was lower than that of normal mice on day 50, and T-5224 inhibited the trabecular bone loss.

Conclusions: These findings suggest that T-5224 inhibits the osteoclastogenesis and bone resorption in arthritic lesions and is able to correct the imbalance of RANKL-OPG which leads to bone loss. Thus, c-Fos/AP-1 inhibitor appears to be a promising drug for rheumatoid bone destruction.


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Activation of Wnt and Bone Morphogenetic Protein Signalling Pathways in the Articular Cartilage in Frzb−/− Mice. Liesbet Lodewyckx1, Jeroen Eyckmans1, Frank P. Luyten2 and Rik Lories1, 1KU Leuven, Leuven, Belgium, 2KU Leuven, Leuven, Belgium, 3KU Leuven

Objective: Frizzled related protein (FRZB/sFRP3) is a secreted Wnt antagonist isolated from articular cartilage and expressed in developing skeletal elements. Polymorphisms in the human FRZB gene are associated with susceptibility for osteoarthritis. Induction of experimental osteoarthritis in Frzb−/− mice results in enhanced cartilage degradation associated with increased Wnt signaling, Mmp3 expression, Mmp activity and cortical bone thickness. In this study we used a whole mouse genome micro-array analysis and a bioinformatics approach to investigate differences between healthy cartilage in wild-type and Frzb−− mice.

Methods: Articular cartilage from the tibia was isolated from 6 weeks old Frzb−/− mice and wild-type littermates. RNA was isolated using the Rneasy Fibrous tissue mini kit (Qiagen). RNA quality was assessed using an Agilent 2100 Bioanalyzer and RNA nanochips (Agilent technologies Inc). The transcriptional profiles were analysed using the whole genome Affymetrix GeneChip® Mouse Genome 430 2.0 Array. Articular cartilage from one tibia from 3 wild-type mice and 2 Frzb−/− mice was used (3 vs 2 chips comparison). Gene expression analysis was based on the RNA expression values and the MAS 5.0 detection calls. PANTHER Classification System software, DAVID bioinformatics resources and FUNNET transcriptional analysis were used for pathway analysis.

Results: Using Benjamini-Hochberg corrected P-values (p<0.001) in combination with a cut-off fold change log2-ratio>1 the analysis showed that 696 transcripts were significantly upregulated in the Frzb−/− sample group. PANTHER pathway analysis identified overrepresentation of genes linked to the Integrin, Wnt and Cadherin signalling pathways (corrected p-values 3x10−3, 5x10−3 and 6x10−3 respectively). Not surprisingly, genes linked to skeletal development and extracellular matrix were enriched in the

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analysis. DAVID analysis similarly identified the Wnt and Integrin pathways but also EGF signalling. FUNNET identified both Wnt and TGF/BMP signalling. With the Wnt signalling pathway both different Frizzled receptor, Wnt9a ligand and distinct intracellular and extracellular antagonists were upregulated suggesting compensatory mechanisms in the absence of Frzb. In addition, upregulation of bone morphogenetic protein and other transforming growth factor beta superfamily members and receptors suggests compensatory upregulation of this pathway. The link with integrin upregulation further supports our earlier data that support of role for Frzb in mechanobiology.

Conclusions: In this study we demonstrated that loss of Frzb results in the upregulation of the WNT signalling pathway and a possible compensatory upregulation of BMP signalling. The upregulation of the integrin and cadherin signalling pathway suggest an important role for Frzb in the interactions of cells with surrounding cells and extracellular matrix.

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Adenosine A1 Receptors Regulates RANKL-Induced Osteoclast Formation Via Regulation of c-fos and NFATc1 Expression. Wenjie He1, Tuere Wilder2 and Bruce N. Cronstein1. 1New York Univ Med Ctr, New York, NY, 2NYU School of Medicine

Purpose: Adenosine is a purine molecule necessary for normal cell metabolism and growth. Recent work from our laboratory using adenosine A1-deficient mice has demonstrated that adenosine A1 receptors play a critical role in regulating bone turnover, raising the intriguing possibility of targeting A1 receptors for therapeutic advancement in osteoporosis and other bone diseases. In the present study, we investigated the mechanism by which A1 receptors regulate mouse osteoclast differentiation induced by macrophage-colony stimulating factor (M-CSF) and the receptor activator of NF-kappB ligand (RANKL) from monocyte/macrophage cell lineage of bone marrow cells.

Methods: Osteoclast differentiation was studied in vitro as the M-CSF/RANKL stimulated formation of multinucleated (>3 nuclei), TRAP-positive cells from primary murine (C57Bl/6) bone marrow-derived precursors. Signaling events were studied by Western Blot for activated (phosphorylated) signaling molecules and changes in message were determined by RT-PCR.

Results: As we have previously demonstrated, the A1 –receptor specific antagonist 8-Cyclopentyl-1,3-dipropylxanthine (DPCPX) dose-dependently inhibited RANKL-stimulated tartrate-resistant acid phosphatase (TRAP)-positive osteoclast formation from bone marrow cells and the bone-resorptive activity of mature osteoclasts (p<0.001, n=3, IC50=0.1 μM). This inhibition is accompanied by reduction of osteoclast-specific target genes including MMP9, Integrin β3, Cathepsin S, Runx2 and TRAP. DPCPX also dose-dependently suppressed RANKL-induced gene expression of nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) at day 4 in bone marrow cells (p<0.05, n=3). Among the RANKL signaling MAPK pathways, DPCPX (1μM) inhibited phosphorylation of JNK (p<0.001, n=4), which is upregulated in response to RANKL in bone marrow macrophages.

Conclusion: Collectively, these data suggest that Adenosine A1 receptor blockade inhibits RANKL-induced osteoclast formation by inhibiting activation of JNK/c-Jun pathway, thereby suppressing the gene expression of c-fos and NFATc1 in osteoclast precursors. These results are consistent with the hypothesis that endogenously released adenosine, acting at A1 receptors, is critical for the expression and activation of critical signaling intermediates required for osteoclastogenesis. Moreover, these results further support the notion that blockade of adenosine A1 receptors may be useful in the treatment and prevention of osteoporosis and premature bone loss.

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Adenosine A2A Receptor Agonists: Can They Prevent/Treat Joint Prosthesis Loosening? Aranzazu Mediero1, Sally R. Frenkel2, Tuere Wilder2, Igor Immerman1, Scott Hadley2, R. Damani Howell2, Maya Hawly2, Elie Sellam1 and Bruce N. Cronstein1. 1Department of Medicine, NYU Langone Medical Center, New York, NY, 2Department of Orthopaedic Surgery, NYU Hospital for Joint Diseases, New York, NY, 3Department of Orthopaedic Surgery, NYU Hospital for Joint Diseases, 4Institut Supérieur des Bio-Sciences de Paris, France, 5New York Univ Med Ctr, New York, NY

Purpose: Survival of bone implants depends on biological fixation, and prosthesis loosening can be catastrophic leading to replacement of prostheses. Inflammation and osteoclast-mediated bone resorption in response to wear particles near prostheses contribute to loosening. Because we have demonstrated that adenosine A2A receptor activation is anti-inflammatory and prevents osteoclast formation and function we hypothesized that adenosine A2A receptor agonists might prevent osteoclast-mediated bone resorption at the site of prosthesis wear in a calvarial model of wear particle-induced bone resorption.

Methods: Eighteen C57Bl/6 mice age 6–8 weeks were anesthetized with intraperitoneal injection of ketamine and xylazine and a 1 cm midline sagittal incision was made over the calvarium anterior to the line connecting both ears. Six animals received no particles (control), and 12 received 15 μl of polyethylene particle suspension. Of the 12 mice receiving particles, 6 were injected subcutaneously at the surgical site with 20 μl of 10 μM CGS21680 (A2A receptor agonist), and 6 mice were injected with saline 0.9%, beginning immediately after incision closure and continuing every other day until sacrifice. Animals were sacrificed after 14 days and the calvaria were removed, fixed, and prepared for microCT and histological staining with TRAP.

Results: Histologic examination of calvaria demonstrated lymphocytic infiltration in both particle-exposed groups. TRAP staining revealed a reduction in osteoclast differentiation after treatment with CGS21680. mCT showed pitting and increased porosity in both particle-exposed groups compared to controls, although in CGS21680-treated mice the reduction in cortical bone was significantly less than in the untreated particle-exposed mice (p<0.01). Control bone volume/trabecular volume was significantly greater (p<0.005) than in either particulate group, however, calvarial bone from CGS21680-treated mice had significantly greater mean bone volume than did the untreated group (p<0.0005). Trabecular thickness was significantly reduced in both CGS21680-treated and untreated particle-exposed groups as compared to control mice (p<0.05). Finally, digital morphometric analysis of microCTs of RANKL shows that CGS21680 significantly reduced the area of bone pitting compared to control particle-treated mice (p<0.05).

Conclusions: Adenosine A2A receptor activation reduces inflammation and bone destruction due to prosthetic wear particles. This observation suggests that delivery of an adenosine A2A agonist in the cement may enhance orthopedic implant survival, delaying or eliminating the need for revision arthroplasty surgery.

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Adenosine A2A Receptor Ligation Inhibits Osteoclast Formation. Aranzazu Mediero1, Firas M. Kara2, Maya Hawly2, Elie Sellam1 and Bruce N. Cronstein1. 1Department of Medicine, NYU School of Medicine, New York, NY, 2Institut Supérieur des Bionuclides de Paris, Creteil, Ile de France, France, 3New York Univ Med Ctr, New York, NY

Purpose: Adenosine is a nucleoside that is generated at sites of injury and hypoxia and which mediates its physiologic and pharmacologic effects via activation of one or more G protein-coupled receptors (A1, A2A, A3, and A4). We have previously reported that adenosine A1 receptor ligation is required for osteoclast formation and that blockade or deletion of adenosine A1...
receptors leads to increased bone density. Because all four adenosine receptors are expressed on osteoclasts and osteoclast precursors we determined whether adenosine A2A receptors also regulate osteoclast formation in vivo and in vitro.

Methods: Osteoclast differentiation was studied in vitro as the GM-CSF/RANKL stimulated formation of multinucleated (≥3 nuclei), TRAP-positive cells from primary murine (C57Bl/6) bone marrow-derived precursors. Signaling events were studied by Western Blot for activated (phosphorylated) signaling molecules and changes in message were determined by RT-PCR. Histological examination of bones from A2A knockout and wild type mice was carried out with TRAP and alcin blue stains. Murine bone was further analyzed by micro CT and electron microscopy.

Results: The highly selective A2A receptor agonist CGS21680 inhibited osteoclast differentiation as much as 38±1% with an EC50 of approximately 50nM (p<0.05), reversed by the selective high affinity antagonist ZM241385. CGS21680 (1μM) stimulated phosphorylation of ERK1/2 (122±3 and 134±5% of control at day 3 and 7 of differentiation, p<0.001 for both) and JAK1 (107±1% of control phosphorylation at day 7 of differentiation, p<0.01), activation that was reversed by ZM241385 (not shown). Moreover, CGS21680 inhibited NFκB translocation to the nucleus (nuclear NFκB decreased by 44±5% at day 3, p<0.001). There was also a marked increase in cellular IkB levels (maximal IkB increased by 19±1% at day 7, p<0.001) whereas pretreatment with ZM241385 increased phosphorylation of IkB (maximal IkB increased by 13±0.4% at day 6, p<0.001) and enhanced nuclear translocation of NFκB (by 14±2% at day 3, p<0.01). MicroCT analysis of femurs from A2A-KO mice showed significantly decreased bone volume/total volume ratio (17.49±0.95 for A2A-KO vs. 22.61±2.15 for wild type, p<0.05), trabecular number (4.4±0.2 for A2A-KO vs 5.8±0.07 for wild type, p<0.001) and increased trabecular space (0.19±0.004 for A2A-KO vs. 0.13±0.004 for wild type, p<0.001). There were more osteoclasts in the TRAP-stained femurs of A2A-KO (50±13/lpf) than wild type mice (35±1/lpf, 6 fields each from femurs of 2 different mice each). Electron microscopy of osteoclasts in femurs from A2A-KO mice showed marked osteoclast membrane folding and increased osteoclast bone resorption.

Conclusions: These results indicate that adenosine A2A receptors inhibit GM-CSF/RANKL-stimulated osteoclast differentiation and thereby regulate bone turnover. Because adenosine mediates the anti-inflammatory effects of methotrexate we further speculate that the capacity of methotrexate to inhibit GM-CSF/RANKL-stimulated osteoclast differentiation and thereby regulate bone erosion in patients with Rheumatoid Arthritis may be mediated by methotrexate-stimulated increases in adenosine concentration.

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Alarmins S100A8 and S100A9 Skew Human Chondrocytes towards a Cartilage Breakdown Phenotype. Rik F. P. Schellbergen1, Peter L. van Lent2, Arjen B. Blom3, Annet Sloetjes4, Thomas Vogt4, Johannes Roth4 and Wim B. Van Den Berg3.

Background: Alarmins S100A8 and S100A9 are members of the S100 family of Ca2+-binding proteins that are associated with inflammation and cartilage and bone erosion during human rheumatoid arthritis (RA). Recently, we found that S100A8 and S100A9 are also associated with cartilage degradation in murine collagenase-induced osteoarthritis (OA). We also showed that S100A8 and S100A9 stimulate expression and activity of matrix metalloproteinases (MMPs) and pro-inflammatory cytokines in murine chondrocytes. We now investigated whether S100A8, S100A9 and/or the S100A8/S100A9 complex could also activate human chondrocytes from OA patients and skew them towards a cartilage breakdown phenotype.

Methods: Cartilage was collected from human OA patients undergoing joint replacement. Immunostaining was performed on paraffin sections of OA cartilage using antibodies against S100A8 and S100A9 and against VDIPEN and NITEGE, which are MMP- and A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-induced cartilage breakdown neoepitopes. Chondrocytes were isolated from OA cartilage and stimulated with recombinant S100A8, S100A9, S100A8/A9 heterodimer and/or interleukin 1β (IL-1β). mRNA levels of MMPs, cytokines and cartilage matrix molecules were determined with RT-qPCR and protein levels of MMP and cytokine using Lumines.

Results: Immunostaining on OA cartilage showed that both S100A8 and S100A9 protein were expressed in and around chondrocytes. Furthermore, immunostaining of breakdown neoepitopes VDIPEN and NITEGE was found in the same areas as the S100 proteins.

Advancement of OA chondrocytes with the monomers S100A8 and S100A9 for 24 hours strongly stimulated cartilage degrading molecules like MMPs and cytokines. mRNA expression of MMP1, -3, -9 and -13 was upregulated 6.0, 5.2, 4.3, and 2.8-fold respectively. Protein levels of MMP1, -3 and -13 were upregulated 3.4, 1.3 and 2.4-fold respectively. Moreover, particularly interleukin 6 (IL-6) were strongly upregulated on mRNA level (11-fold) and protein levels reached 10 ng/ml.

Apart from stimulating cartilage degradation, S100A8 and S100A9 monomers also inhibited new formation of cartilage matrix molecules. mRNA levels of aggrecan and collagen type II were significantly decreased 2- to 3-fold, suggesting that these proteins inhibit repair.

The S100A8/A9 heterodimer neither had effect on cartilage degradation nor on cartilage matrix production. The effect of S100A8 and S100A9 was similar to IL-1β effects, but there was no additive effect of S100 with IL-1β, suggesting independent mechanisms.

Conclusions: S100A8 and S100A9 expression is found in areas with cartilage breakdown. Moreover these proteins inhibit new formation of matrix molecules and stimulate production of cartilage degrading molecules in vitro thereby skewing human chondrocytes towards a cartilage breakdown phenotype.

S100A8 and/or S100A9 may serve as therapeutic targets for the treatment of cartilage damage.

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Analysis of Secretome from Mesenchymal Stem Cells from Human Umbilical Cord Stroma during the Chondrogenesis. Maria C. Arufe1, Alexandra De la Fuente1, Jesús Mateos2, Patricia Fernandez-Puente3, Esther Rendal4, Silvia Díaz2, Isaac Fuentes2, Francisco J. De Toro5 and Francisco I. Blanco5. 1TNIBIC-Universidad de A Coruña, A Coruña, Osteoarticular and Aging Research Laboratory, Proteomics Unit-Associated Node to ProteoRed-Biomedical Research Center (INIBIC), Hospital Universitario A Coruña, La Coruña, Spain, 2INIBIC-Universidad de A Coruña, A Coruña, Spain, 3INIBIC-Universidad de A Coruña, A Coruña, Spain, 4Osteoarticular and Aging Research Laboratory, Proteomics Unit-Associated Node to ProteoRed-Biomedical Research Center (INIBIC), Hospital Universitario A Coruña, La Coruña, Spain, 5Osteoarticular and Aging Research Laboratory, Proteomics Unit-Associated Node to ProteoRed-Biomedical Research Center (INIBIC), Hospital Universitario A Coruña, La Coruña, Spain.

Our goal is study the secreted proteins from Mesenchymal Stem Cells –MSCs- from umbilical cord stroma during their differentiation towards chondrocyte-like cells to discern the pathways which could be determinant in this chondrogenesis.

Material and Methods: Umbilical cord tissues were obtained from caesareans from normal women in the Maternity Facility at Complejo Hospitalario Universitario de A Coruña under the supervision of the hospital ethic committee. We isolated and growth MSCs from umbilical cord stroma by enzymatic digestion and cultured the cells adhered to the plastic plate(1). The cells were characterized (2) using flow cytometry, immunohistochemistry and RT-PCR techniques. Chondrogenic process was performed using our previously published model (3). Briefly, we grow the cells during two days in medium supplemented with FCS 10%. After 2 days we washed the cells with PBS and added medium supplemented with KO serum and TGF-β3. Spheroids were formed by two days in culture and this three-dimensional structure help to produce the characteristic proteins which form part of the extracellular matrix of the cartilage. The spheroid were situated in a well with the chondrogenic factors plus RPMI during 12 h to recover the protein secreted to the medium by the spheroids at 4, 7, 14, 28 and 46 days of differentiation avoiding the serum contamination.

SDS-PAGE was done using pre-cast NuPAGE® NOVEL gels (Invitrogen) to ensure reproducibility in the separation of the proteins. Gels were stained with Silver Nitrate and the entire lane was divided in 16 sections. Each section was excised and subjected to in-gel digestion with trypsin. The peptide mixture was cleaned and desalted with home-made Poros R2
columns, injected and separated in a nanoLC system, mixed with α-cyano and deposited in a MALDI plate using an automatic MALDI spotter. The MS run for each fraction was analyzed in an ABI 4800 MALDI-TOF/TOF instrument and fragmentation was done using a CID system.

Results: 87 identified proteins were related to the chondrogenic differentiation process from a total of 209 proteins. Some of the proteins related with chondrogenesis obtained with this method were:

Conclusions: 1. This technique is suitable to analyze medium complexity samples as secretome.

2. The chondrogenesis differentiation designed through spheroid formation have revealed be an excellent method to obtain chondrocyte-like cells from mesenchymal stem cells of human umbilical cord stromal tissue.

3. Pathways related with differentiation process are been activated during the chondrogenesis process.

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Biochemical Markers of Bone Balance (CTX-II/Osteocalcin) Improve with Tocilizumab Treatment in a Population of RA Patients with an Inadequate Response to Anti-TNF Therapy. Morten Karsdal2, Thasia G. Woodworth3, Andy Kenwright4, Inger Byrjalsen1, Adam Platt4 and Georg Schett5. 1CCBR Synarc, Ballerup, Denmark, 2Nordic Bioscience, Herlev, Denmark, 3Roche Products Ltd., Welwyn, Welwyn Garden City, Hertfordshire, UK, 4GlaxoSmithKline, 5, Merck-Serono, 5, Nordic Bioscience Diagnostic, 3, Novartis Pharmaceutical Company, 5, Nycomed, Roche, 5, sanofi-aventis, 5, Services, 5, G. Woodward: Roche; 5, A. Kenwright: Roche; 3, I. Byrjalsen: None; A. Platt: Roche, 1, 3; G. Schett: None.

Background: Bone resorption and bone formation are maintained in a dynamic equilibrium required for optimum bone and joint maintenance and integrity. In active RA, inflammation is associated with bone resorption, which characteristically dominates bone formation, resulting in osteopenia, bone fragility, and fracture. Biochemical markers of bone and cartilage turnover can provide an assessment of the effect of therapeutic intervention on the restoration of the balance between bone resorption and formation; indeed, previous analyses of tocilizumab (TCZ)-treated MTX inadequate response populations from OPTION and LITHE studies demonstrated dose-dependent improvement in markers of bone formation (osteocalcin [OC], PINP) and bone balance (CTX-II/OCT).

Objectives: To evaluate changes in biochemical markers of bone metabolism in an anti-TNF refractory RA patient population utilizing the 24-week RADIATE study, in which TCZ 8 mg/kg and 4 mg/kg every 4 weeks showed efficacy superior to that of weekly MTX/pbo in patients refractory to one or more anti-TNF agents. In addition, MMP-3 and ICTP, a biochemical marker of MMP activity, were measured.

Methods: Assays for OC, PINP, ICTP, CTX-I, and MMP-3 were conducted on serum acquired from 299 consenting patients (out of 499 in RADIATE) at BL and week 16. Approximately 50% were receiving low-dose corticosteroids (<10 mg qd).

Results: Patients were refractory to at least one anti-TNF with highly active RA (mean DAS28 ~6.8) and had mean disease duration of 12 years. Both TCZ doses decreased CRP and significantly inhibited cathepsin K–mediated bone resorption, as measured by decrease in CTX-I. OC levels remained stable, resulting in an overall improvement in bone balance with TCZ added to MTX, as measured by CTX-I/OCT ratio. Further, MMP-3 and ICTP levels decreased, consistent with lower type I collagen turnover in joint tissue.

Conclusions: In these anti-TNF refractory patients, TCZ and MTX significantly reduced the levels of biochemical markers of cathepsin K bone resorption and MMP-mediated tissue destruction. This observation suggests that this treatment regimen has a positive effect on bone balance, the equilibrium between formation and resorption, which will ultimately lead to improved joint health. TCZ dose-related decrease in CRP provides further evidence that TCZ treatment may limit joint damage in these patients.

Table 1. Baseline Characteristics (ITT population)

<table>
<thead>
<tr>
<th>N</th>
<th>Placebo + MTX</th>
<th>TCZ 4 mg/kg + MTX</th>
<th>TCZ 8 mg/kg + MTX</th>
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<tbody>
<tr>
<td>Female, n (%)</td>
<td>76 (78)</td>
<td>82 (81)</td>
<td>87 (86)</td>
</tr>
<tr>
<td>Age, y</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
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<tr>
<td>TCJC/SJC</td>
<td>31/19</td>
<td>16/11</td>
<td>32/19</td>
</tr>
<tr>
<td>DAS28</td>
<td>6.8</td>
<td>1.1</td>
<td>6.9</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>3.9</td>
<td>4.5</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Table 2. Percentage Change (geometric mean) in Biochemical Markers and CRP: Baseline to Week 16 (ITT population)

<table>
<thead>
<tr>
<th>N</th>
<th>Placebo + MTX</th>
<th>TCZ 4 mg/kg + MTX</th>
<th>TCZ 8 mg/kg + MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMean</td>
<td>±1 SEM</td>
<td>Range</td>
<td>GMean</td>
</tr>
<tr>
<td>CTX-I</td>
<td>−3.3</td>
<td>−8.4, 1.8</td>
<td>−25.5</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>0.7</td>
<td>−4.7, 6.1</td>
<td>−2.3</td>
</tr>
<tr>
<td>CTX-I/OC</td>
<td>−4</td>
<td>−9.1, 1.2</td>
<td>−23.8</td>
</tr>
<tr>
<td>PINP</td>
<td>1.5</td>
<td>2.8, 5.7</td>
<td>1.8</td>
</tr>
<tr>
<td>MMP-3</td>
<td>3.6</td>
<td>−3.9, 11.1</td>
<td>−30.9</td>
</tr>
<tr>
<td>ICTP</td>
<td>7</td>
<td>3.3, 10.8</td>
<td>−18.2</td>
</tr>
<tr>
<td>CRP</td>
<td>85</td>
<td>90</td>
<td>90</td>
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<tr>
<td>GMean</td>
<td>22.1</td>
<td>9, 35.1</td>
<td>−37.9</td>
</tr>
</tbody>
</table>

* p < 0.01 vs placebo; † p < 0.001 vs placebo.

Disclosure: M. Karsdal: Baxter, 5, Bristol-Myers Squibb, 5, CCBR/Synarc, 5, GlaxoSmithKline, 5, Merck-Serono, 5, Nordic Bioscience Diagnostic, 3, Novartis Pharmaceuticals Corporation, 5, Nycomed, 5, Roche, 5, sanofi-aventis, 5, Services, 5, G. Woodward: Roche; 5, A. Kenwright: Roche; 3, I. Byrjalsen: None; A. Platt: Roche, 1, 3; G. Schett: None.

1475

Chondrogenic Differentiation of Bone Marrow Mesenchymal Stem Cells Grown on Type I Collagen and Heparan Sulfate Scaffolds. Silvia Diaz-Prado1, Emma Muñoz1, C. G. Trejo-Irurte1, D. Lozano1, N. García-Hondavilla1, Isaac Fuentes1, Francisco J. De Toro1, P. Espri1, Julia Bujain1 and Francisco J. Blanco3. 1Department of Medical Specialties, University of Alcalá de Henares, Madrid, Spain, 2Laboratory of Bone and Mineral Metabolism. Fundación Jiménez Díaz (Capio Group), Madrid, Spain, 3Osseointegration and Aging Res. Lab. CIBER-BBN, Rheumatology Div, INIBIC-Complejo Hosp, Univ. A Coruña, A Coruña, Spain, 4Osseointegration and Aging Res. Lab. CIBER-BBN, Rheumatology Div. INIBIC-Complejo Hosp. Univ. A Coruña, Coruña, Spain.

Background: Articular cartilage lesions are not able to repair. To avoid the need for prosthetic replacement different cell treatments were developed with the aim of generating a repaired tissue. The transplantation of mesenchymal stem cells (MSCs) has been suggested as an alternative therapeutic approach for treatment of cartilage defects.

Aim: Evaluate the chondrogenic potential of bone marrow mesenchymal stem cells (BM-MSCs) grown on type I collagen and different concentrations of heparan sulfate (HS) scaffolds.

Materials and Methods: BM-MSCs and chondrocytes were cultured on type I collagen and different concentrations of heparan sulfate (HS) scaffolds. 1 SEM

Results: BM-MSCs and chondrocytes were able to proliferate on type I collagen and various concentrations of HS scaffolds, since cells showed high percentages of positivity for PCNA proliferation marker. Increased cell proliferation has been associated with a high rate of scaffold degradation, although the thicker collagen fibers take longer to be degraded. The results indicated that BM-MSCs proliferated better in chondrogenic medium than in the usual growth medium (DMEM 20%). The study groups with BM-MSCs
grown in chondrogenic medium +100 nM PTHrP, regardless the HS concentration, showed high percentages of cells regarding the scaffold area (more than 80% after 16 days in culture and more than 90% after 30 days in culture). Moreover, they also showed high percentages of positivity for safranin O (Safo), aggrecan (Agg) and type II collagen (Col II) (Table 1 and Figure 1). Masson’s trichrome (Mt) staining showed that cells formed aggregates and produced extracellular matrix. Von Kossa (VKos) stainings, performed in BM-MSCs grown for 30 days in chondrogenic medium, exhibited the presence of calcifications.

Conclusions: Our data demonstrated that type I collagen and heparan sulfate scaffolds were optimal for BM-MSCs and chondrocyte growth and that BM-MSCs cultured over these scaffolds on chondrogenic medium were able to differentiate to chondrocyte-like cells.

Acknowledgements: B. Parma; CIBER BBN CB06-01-0040; SDP is beneficiary of IPP contract and stays grant (IN809 A 2007/193, 2008/237 and 2009/23) from XUGA, Spain.

Disclosure: S. Diaz-Prado: None; E. Muiños: None; C. G. Trejo-Iriarte: None; D. Lozano: None; N. Garcia-Honduvilla: None; I. Fuentes: None; F. J. De Toro: None; P. Esbrit: None; J. Buján: None; F. J. Blanco: None.

Figure 1. Histochemical and immunohistochemistry analysis of BM-MSCs cultured over type I collagen and 3% HS scaffolds on chondrogenic medium after 30 days in culture.
trations by NO donors exerts anti-inflammatory effects. Cyclooxygenase-Inhibiting Nitric Oxide Donators (CINODs) are anti-inflammatory compounds designed to inhibit both COX-1 and COX-2 while releasing nitric oxide, an important modulator of vascular tone. We studied the effect of naproxen and the CINOD NCX 429 in human chondrocytes and cartilage tissues from OA patients, to understand whether NO donation from CINODs may modulate the inflammatory/metabolic response.

**Methods:** The experiments were performed with human cartilage and chondrocytes isolated from OA cartilage. Isolated chondrocytes stimulated with IL-1β to induce inflammation, followed by measurement of inflammatory and matrix parameters, such as iNOS, COX-2, MMP1 and 13, PGE2, NO, matrix metalloproteinases, collagen degradation and NF-κB nuclear translocation. Reference NSAIDs naproxen and celecoxib were used in comparison to NCX 429 (10 and 50 μM), and incubated 16 h before IL-1β challenge. Cartilage explants culture supernatants (untreated and treated with modulators) were harvested at 24 and 72 hours post-treatment. RNA was extracted from chondrocytes and estimated by qPCR. NF-κB binding was assessed using Marligen Bioscience kit and both cytoplasm and nuclear p65 subunit of NF-κB was also assessed by Western blot.

**Results:** The reference NSAIDs and the CINOD similarly upregulated MMP1 but inhibited MMP13, showing comparable net effect on collagen and proteoglycan degradation. They similarly inhibited AD-MMP1 but inhibited MMP13, showing comparable net effect on collagen degradation as assayed by CTX-II ELISA. They similarly inhibited TIMP3-mediated induction of apoptosis involves the inhibition of MAPK/p90RSK and Akt.

**Conclusion:** Taken together, these findings demonstrate that TIMP3 directly induce apoptosis in mesenchymal cells, which is independent of death receptor ligands. The fact that the withdrawal of serum leads to an enhanced TIMP3-induced indicates the importance of serum-derived survival factors. TIMP3-mediated induction of apoptosis involves the inhibition of MAPK/Erk1/2 as well as the Akt signaling pathway.

**Disclosure:** C. Wunrau: None; D. Wendholt: None; N. Pundt: None; T. Pap: None; B. Dankbar: None.

1479

Endogenous Joint Repair after Damage in the Red-Spotted Newt, Matthias Geyer1, Thilo Borchardt2, Carina Schreyæk3, Ulf Müller-Ladner1 and Robert Dinser1. 1Department of Rheumatology, Justus Liebig University Giessen, Kerckhoff-Klinik, Bad Nauheim, 2Max Planck Institute for Heart and Lung Research, Bad Nauheim

**Background:** Mammalian joint structures fail to repair after severe trauma or in osteoarthritis. Adult newts are able to regenerate lost extremities. We have previously shown that they are also able to rebuild a damaged knee joint after induction of joint instability through intraarticular injection of collagenase. We wanted to extend this observation on other modes of damage and start studying molecular mechanisms.

**Methods:** To induce apoptotic cell death in chondrocytes, monooiodoacetate was injected into the knee joints of red spotted newts. Alternatively, the femoral cartilage was removed surgically. The time course of clinical and histological damage was analysed. In parallel, RNA was extracted from whole joints 10, 20, and 40 days after damage with collagenase or surgery and hybridized to a CDNA array derived from regenerating newt hearts.

**Results:** Monooiodoacetate induced chondrocytic cell death predominantly in the deep zone of the articular cartilage in newts, associated with a loss of proteoglycans, in the absence of clinical disease. Histology returned to normal after 20 days. Surgery induced severe joint damage associated with complete loss of function of the joint, reflected in severe histological changes. Within 40 days, clinical function normalised. Histologically, cartilage reformed, leading to intact joint structures within 90 days. A number of genes was found to be deregulated. No gene was downregulated in both damage models, but several genes were found upregulated. These include matrix proteins like fibronectin, decorin, and collagens I, II, and III. Several complement factors and clusterin were found in addition to factors like peristin and olfactomedin that have not been previously associated with joint formation. Several enzymes of vitamin A metabolism that have been implicated in chondrogenesis were also upregulated.

**Conclusion:** Newts are able to regenerate joint structures irrespective of the exact mode of damage (apoptosis, instability, surgical loss of tissue). A CDNA analysis reveals several genes that may be key factors determining the enhanced repair potential of newts compared to mammals.

**Disclosure:** M. Geyer: None; T. Borchardt: None; C. Schreyæk: None; U. Müller-Ladner: None; R. Dinser: None.

1480

Experimental Osteoarthritis in Rats Is Attenuated by Treatment with a Selective Inhibitor of Sphingosine Kinase 2. Leo R. Fitzpatrick1, Cecelia Green1, Lynn W. Mairnes1 and Charles D. Smith2. 1Apogee Biotechnology Corporation, 2Apogee Biotechnology Corporation and Medical University of South Carolina, 3Penn State College of Medicine, Hummelstown, PA

Osteoarthritis (OA) is a progressive degenerative disease characterized by cartilage degradation and chondrocyte apoptosis, which may involve aberrant sphingolipid metabolism. Sphingosine kinases (SK1 and SK2) catalyze the formation of sphingosine-1-phosphate (SIP) from sphingosine, and are potential drug targets for a variety of hyperproliferative and inflammatory diseases. ABC294640 (ABC) is a novel orally bioavailable compound that selectively inhibits SK2, and has therapeutic activity in models of rheumatoid arthritis.

**Aims:** The goals of the present study were to utilize the Monosodium iodoacetate (MIA) model of OA to assess the effects of ABC294640 on: 1) cartilage and bone destruction in the knee joints of MIA-treated rats; and 2) the resultant pain to the animals.

**Methods:** Differential hind-limb weight-bearing (measured with an inac-
ments) was used as an indicator of knee pain throughout the study, and baseline data were collected on Day 0. To induce OA, anesthetized male Wistar rats (n = 22) were injected with 3 mg of MIA into the R knee joint and saline into the L knee. A control group of rats (n = 4) received saline injections in both knees. On Day 0, MIA-treated rats were randomized to receive either sham oral dosing (n = 13), ABC (50 mg/kg bid, n = 9) or Tramadol (100 mg/kg, one hr before incapacity readings only, n=4). Oral ABC dosing continued until study Day 27. Incapacitance readings were obtained weekly during this period. On Day 28, the R knee joints were harvested for histological evaluations. Safranin-O was used to evaluate cartilage proteoglycan staining in the knee joints. Cartilage thickness measurements were done from images of the joint histology sections.

**Results:** Weight bearing (%) in sham/MIA rats significantly (p < 0.01) decreased from 48.8 ± 0.8 (Day 0) to 41.9 ± 2.9 (Day 28). In contrast, these values in ABC-treated rats were virtually the same on Day 0 (49.0 ± 0.5%) and Day 28 (48.8 ± 2.6%). The ABC results were similar to data with Tramadol treatment. Knee joint histology scores (48 point scale) were reduced from 30.9 ± 3.3 (sham treatment) to 24.1 ± 4.0 (ABC treatment) demonstrating that ABC-treated rats had less evidence of cartilage and bone destruction. There was a significant (p=0.0036) inverse correlation between histological damage and weight-bearing in rats. Of note, proteoglycan staining in the tibia (figure 1) and femur were less disrupted in ABC/MIA animals than in sham/MIA rats.

Similarly, cartilage thickness in the knee joints of ABC/MIA-treated rats (0.30 ± 0.05 mm) was not different from control rats (sham/saline, 0.36 ± 0.03 mm); whereas that of sham/MIA rats was substantially decreased (0.21 ± 0.03 mm).

**Conclusion:** The selective SK2 inhibitor ABC294640 attenuated histological damage and joint pain in the MIA-induced OA model in rats. Therefore, clinical studies of this agent may be warranted.

**Disclosure:** L. R. Fitzpatrick: Apogee Biotechnology Corporation, 9; C. Green: Apogee Biotechnology Corporation, 3; L. W. Maines: Apogee Biotechnology Corporation, 3; C. B. Smith: Apogee Biotechnology Corporation, 4.

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**1482**

**Histamine Contributes to Inflammatory Joint Disease by Regulating the Expression of RANKL and OPG through Altered NR4A Activity in Human Chondrocyte Cells.** Viviana Marzaioli, Jason P. McMorrow, Alice McEvoy, and Evelyn P. Murphy. Dublin Institute of Technology, Kevin Street, Dublin, Ireland, UCD Veterinary Sciences Centre and Conway Institute for Biomolecular and Biomedical Research, University College Dublin, Ireland

**Background:** Mast cells, a major source of histamine in vivo, are found in increased numbers in rheumatoid arthritis synovial tissue. In the K/BxN arthritis model, mast cells are required to promote autoantigen-induced inflammatory arthritis. It has recently been shown that IL-33 enhances autoantibody-mediated articular inflammation via IgG mast cell degranulation and pro-inflammatory mediator release. Furthermore, histamine stimulates chondrocyte production of matrix metalloproteinases and osteoclast differentiation directly, and indirectly, through altered RANKL and OPG expression in osteoblasts. The aim of this study was to elucidate the receptor mediated signalling pathways and transcriptional events regulated by histamine in human chondrocytes.

**Methods:** Histamine receptors (HR1,-2, 3, 4), nuclear transcription factors (NR4A1,2,-3), RANKL and OPG mRNA levels were measured in human chondrocytes using real-time PCR (qPCR). HR subtype involvement was monitored using selective HR antagonists. NR4A protein levels and transactivity were evaluated by western blot, immunocytochemistry and luciferase reporter assays. ShRNA for control and NR4A1, 2, 3 were generated using lentivirus transduction.

**Results:** Differential expression of histamine receptor subtypes (HR1–4) was detected. HR1 and HR2 receptors are highly expressed in chondrocyte cells with minimal expression of HR3 and HR4. Histamine robustly modulates RANKL and OPG levels, in a time- and concentration-dependent fashion, leading to significantly increased RANKL/OPG expression ratio (p<0.005). Histamine rapidly and differentially modulates expression of all three NR4A transcription factors. Within 2-hours, histamine maximally modulates NR4A3 (300-fold), NR4A2 (100-fold) and NR4A1 (10-fold) transcript levels. The study of HR receptor antagonists reveals that histamine selectively signals through HR1 and HR2 in chondrocyte cells to modulate RANKL, OPG and NR4A1–3 expression. Our data further demonstrates histamine-dependent activation of NF-kB and CREB signalling pathways through HR1 and HR2 receptors, respectively. Consistent with mRNA analysis, histamine promotes NR4A nuclear localization and significantly enhances the capacity of NR4A proteins to mediate target gene expression. Specific knockdown of NR4A1,-2,-3 mRNA and protein levels (>50%) results in significantly reduced endogenous production of OPG (>60%) by chondrocytes. Finally, in NR4A-depleted cells, histamine regulation of RANKL and OPG expression is completely lost.

**Conclusion:** These data reveal that histamine, through HR1 and HR2, contributes to the development of inflammatory joint disease by regulating the expression of RANKL and OPG through altered NR4A activity in human chondrocyte cells.

**Disclosure:** V. Marzaioli: None; J. P. McMorrow: None; A. McEvoy: None; E. P. Murphy: None.

Introduction: Human amniotic membrane (HAM) is a highly abundant and easily accessible tissue that may potentially be an important chondrocyte carrier for cartilage regeneration in vitro. 

Objective: Develop an in vitro repair model of focal injuries of human articular cartilage, based on the usefulness of cryopreserved HAM as support for chondrocyte proliferation.

Materials and Methods: Four in vitro repair models of focal injuries of human articular cartilage were developed. For this purpose chondrocytes, isolated from cartilage slices obtained from femoral heads, were grown on the basement layer of HAM for 3–4 weeks. Then a chondrocyte pellet was implanted into 2 mm focal defects of human articular cartilage and the HAM providing chondrocytes was placed in direct contact with the cartilage surface to be repaired. These implants were cultured in DMEM supplemented with 10% FBS for 8 weeks. The repair tissues were analyzed by histochemistry (hematoxylin-eosin, Masson’s trichromic, toluidine blue and safranin O) and immunohistochemistry for type I and II collagen and aggrecan.

Results: Human chondrocytes cultured on HAM and transplanted onto focal injuries of human articular cartilage penetrated into the nearby surface of the chondral defect producing a more regular area and contributed on the closing of the chondral defect. The chondrocyte pellet implanted in the lesion filled the chondral defect and showed good integration between the repair tissue and native cartilage. Stainings were done to detect specific major components of the extracellular matrix to obtain more detailed information about the structure and composition of the repair tissue. Type II collagen, safranin O, toluidine blue and Masson’s trichromic stainings of repair tissue were positive, whereas aggrecan and type I collagen stainings were weak (Table 1 and Figure 1). The morphology of the newly-formed tissue exhibited a fibrocartilaginous appearance and high cellularity.

Table 1. Semi-quantitative histochemical and immunohistochemistry analysis of the in vitro human articular cartilage repair model.

<table>
<thead>
<tr>
<th>TYPE STAIN</th>
<th>Native Cartilage</th>
<th>Focal Injure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Matrix</td>
<td>Cells</td>
</tr>
<tr>
<td>Modified Masson’s trichrome</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Safranin O</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Toluidine Blue</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Type I Collagen</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Type II Collagen</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Aggrecan</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Figure 1. Histochemical and immunohistochemistry analysis of the in vitro human articular cartilage repair model. A. Toluidine blue. B. Safranin O. C. Col I. D. Col II.

Conclusions: These results indicated that cryopreserved amniotic membrane could be used as support for chondrocytes proliferation in cell therapy to repair focal injuries of human articular cartilage.

Support: Project funded by Servizo Galego de Saúde (PS07/84), Catedra Bioiberica de la Universidade da Coruña and Instituto de Salud Carlos III CIBER BBN CB06-01-0040. Silvia Díaz Prado is beneficiary of an Isidro Parga Pondal contract from Xunta de Galicia, A Coruña, Spain.

Disclosure: E. Muñoz-López: None; S. M. Díaz-Prado: None; T. Hermida-Gómez: None; E. Rendal-Vázquez: None; I. Fuentes-Boquete: None; M. C. Arufe-Gonda: None; F. J. De Toro: None; F. J. Blanco: None.

1484

Increased Expression of Arthritic Marker Genes in the Cartilage of SirT1 Null Mice. Odile H. Gabay1, Eun J. Lee2, Richard Booth3, Viktoria Gagarina4, Monia Dvir-Ginzberg5 and David J. Hall1. Hebrew University, Jerusalem, Israel, 2NIH, Bethesda, MD

Background: Osteoarthritis (OA), the most frequent age related disease present in the west, is a multi-factorial imbalance between cartilage anabolism and catabolism. To understand the mechanisms underlying OA, we focused on the protein deacetylase SirT1, a factor known to prolong organism lifespan. SirT1 has been previously shown to regulate apoptosis and cartilage-specific gene expression in human chondrocytes. Recent data also indicates that SirT1 is a potent inhibitor of the matrix metalloproteinases (MMPs). MMPs are the most well known of arthritis marker genes that play a central role in cartilage degeneration. In order to evaluate the role of SirT1 in cartilage homeostasis, we assessed MMP and ADAMTS expression in the cartilage of SirT1 null mice.

Method: We used SirT1 Wild-type (WT) and SirT1 Null mice in the analysis. The SirT1 Null mice do not express SirT1. Articular cartilage was harvested from hind paws in 1 to 3 week and 4 months old mice. The cartilage was processed for both immunohistochemistry and subculture of chondrocytes.

Results: Articular cartilage tissue sections from SirT1 Null mice exhibited low levels of type 2 collagen, aggrecan and glycosaminoglycans (GAG) compared to SirT1 WT mice at 1 week or 3 weeks. Protein levels of aggrecan and type 2 collagen were also decreased in the chondrocytes derived from SirT1 Null mice. In contrast, protein levels of MMP-3, MMP-8, MMP-9 and MMP-13 were elevated in the chondrocytes derived from SirT1 Null mice. Finally, DBC1 (deleted in breast carcinoma 1), a known Sir1 associated protein that represses SirT1 enzymatic activity, was found to be elevated in the SirT1 Null mice compared to WT.

Conclusion: The data from this animal model indicate that SirT1 is a negative regulator of the genes responsible for cartilage degradation in arthritis; namely the MMPs and DBC1. The role of SirT1 as a putative anti-arthritic gene is consistent with its general function as an anti-aging/anti-inflammatory protein.

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1485

Increasing Osteoclastic Bone Loss Inspite of Fewer Osteoclast Precursors during Chronic Autoimmune SKG–Arthritis Evaluated by 3D Stereological Estimators. Kresten K. Keller1, Kristian Steengaard-Pedersen1, Frederik Dagnæs-Hansen2, Jens R. Nyengaard3, Shimon Sakaguchi1 and Ellen-Margrethe Hauge4. Department of Experimental Pathology, Institute for Frontier Medical Science, Kyoto University, 2Dept. of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, 3Dept. of Rheumatology, Aarhus University Hospital, Århus, Denmark, 4Dept. of Rheumatology, Aarhus University Hospital, Denmark. 1Institut of Medical Microbiology and Immunology, Aarhus University, Denmark, 2Stereology and Electron Microscopy Research Laboratory, Aarhus University, Denmark

Background: Bone destruction in rheumatoid arthritis (RA) is the result of osteoclastic bone resorption and is mediated through the receptor activator of NF-κB ligand (RANKL) system. Experimental models and designs that allow detailed studies of osteoclast number and activity are therefore important. The aim of this study was to quantify arthritic changes in a new mouse model of rheumatoid arthritis focusing on osteoclast number using new 3D design-based stereological methods.

Methods: Arthritis was induced in 7-week-old female SKG-mice with intraperitoneal injection of 2 mg Zymosan A. Quantitative histology was...
made on 4 control mice and 4 arthritic mice euthanized after 6 and 12 weeks. The right hind paw was embedded undecalcified in methylmethacrylate and cut exhaustively generating 7-µm-thick vertical uniform random sections from approximately 10 section levels spaced by 350–800 µm depending on the random rotation of the sectioning plane. Sections were stained with Masson-Goldner Trichrome and enzymatic TRAP staining. A computer controlled microscope and stereological software (NewCAST) was used for histological quantification. Total volumes were estimated according to the Cavalieri principle, total surfaces were estimated using the vertical sections design, and the number of TRAP-positive cells was counted in a physical dissector. TRAP-positive cells on the bone surface were defined as active osteoclasts and TRAP-positive cells in inflammatory tissue were defined as osteoclast precursors. All analyses were performed blinded by a single observer. Spearman’s rank correlation or the Kruskal-Wallis test followed by the Mann-Whitney U-test were used. Data are given as the correlation coefficient (r) or median(range).

Results: The arthritis score increased during the 12-week period and was paralleled by an increase in the volume of inflammatory tissue ($r=0.90$, $p<0.001$). The number of osteoclasts on bone ($r=0.77$, $p<0.05$) and osteoclast-covered bone surface ($r=0.62$, $p<0.05$) increased significantly leading to a decrease in the volume of bone ($r=-0.65$, $p<0.05$). However, the number of osteoclast precursors declined between week 6 (14072 (10869–19040)), and 12 (7610 (3126–7893)) ($p<0.05$). Furthermore, the total cartilage surface ($r=-0.74$, $p<0.05$) and cartilage volume ($r=-0.65$, $p<0.05$) decreased during the 12 weeks of arthritis.

Conclusions: We showed that the SKG-model of autoimmune polyarthritis in mice developed osteoclastic bone erosion leading to loss of bone. The loss of bone and the bone surface attacked by actively resorbing osteoclasts continued in the chronic stage although fewer osteoclast precursors were present in the inflamed synovium. Thus bone erosion may progress although osteoarthrogenesis is slowing. Bone loss was prominent, but loss of cartilage also occurred. Furthermore, for the first time 3D quantitative histology has been applied in a mouse model of RA. The methods proved valuable, and are expected to be important for studying the in vivo effect of anti-inflammatory and anti-resorptive interventions in experimental arthritis.

Disclosure: K. K. Keller: None; K. Stengaard-Pedersen: None; F. Dagnas-Hansen: None; J. R. Nyengaard: None; S. Sakaguchi: None; E.-M. Hauge: None.

1486

Influence of NPP1 on Osteoarthritis (OA)-Associated Cartilage Calcification

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Background: Calcification of cartilage is a common finding during osteoarthritis and is directly linked to the severity of cartilage degradation. The pyrophosphate pathway functions to keep a sensitive balance of pyrophosphate (PPi) and pyrophosphate (Pi), thereby preventing the generation of calcium crystals. Based on previous data that have linked the expression of the nucletide pyrophosphatase phosphodiesterase (NPP1) to pathological matrix calcification and have demonstrated a regulation of NPP1 by inflammatory mediators, we sought to study the expression of NPP1 in OA cartilage and its association with calcification.

Methods: In a cohort of 120 consecutive OA patients, we analysed the calcification of cartilage using digital contact radiography (dCR). We used cartilage samples of these patients to isolate RNA and assessed the NPP1, ANK and TNAP expression by quantitative real time PCR. The tip-toe walking (ttw/ttw) mouse that carries a mutation in the enpp1 gene encoding NPP1 was used as an animal model. The calcification of cartilage was analysed using advanced imaging technology, including fluorid PET-scanning and μCT. Using van Kossa in combination with safranin orange staining of knee sections we assessed the calcification of articular cartilage and meniscus histologically. We analysed the expression of NPP1 in an ACL model of induced OA using immunohistochemical staining.

Results: In our cohort of OA patients, we found a correlation of NPP1 expression with cartilage calcification ($p<0.05$), whereas we found no correlation for ANK. These data could be confirmed in the ttw/ttw mice, in which we could show an enhanced calcification activity in the joint regions as well as in cartilage of non weight bearing areas such as in ear cartilage. Using both histological analysis and in vivo imaging, we found typical OA like changes in the knees of these mice, such as formation of osteophytes and roughening of the cartilage surface. In addition we could show that NPP1 expression was also increased in the animal model of OA in comparison to uninduced controls.

Conclusion: We conclude from our data, that NPP1 is an important player in OA associated cartilage calcification and might constitute a promising target for the development of novel therapeutics for the disease.

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Inhibitory κBα Is a Direct Bone Morphogenetic Protein Target Gene and an Essential Mediator of Anti-Catabolic Effects of BMPs.

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Background: Loss of cartilage in the joints and structural changes to the intervertebral discs, are common problems in patients with degenerative spine and joint disease, but also in those with chronic inflammation-driven arthritis. Increasing evidence supports a role for BMP7 in preventing joint and intervertebral disk damage and in disk regeneration in part by reducing the catabolic effects of TNF-α and IL-1β. The precise molecular mechanism mediating the preventive and regenerative effects of BMP7 is unknown. NF-κB signaling is a major pathway triggered by proinflammatory cytokines. Our transcriptional profiling studies revealed that the activation of BMP signaling leads to increased expression of Inhibitory κBα (IκBα), that is a key negative regulator of the NF-κB pathway. We therefore explored whether anti-catabolic effects of BMPs on cartilage and bone are mediated by BMP-induced IκBα expression.

Methods: cDNA microarrays-based gene expression profiling was used to identify novel BMP target genes. Positive hits were confirmed using Northern and Western blotting and Real-Time PCR. Luciferase reporter assays and ChIP assays were used to characterize the BMP-responsive region in the IκBα promoter. Anti-catabolic effects of BMPs were validated in vitro using preosteoblastic cell lines and primary human bone marrow-derived mesenchymal stem cell (hMSC) osteoblast differentiation, EMISA and lentiviral shRNA approaches.

Results: Real-Time PCR showed that activation of IκBα mRNA by BMPs does not require de novo protein synthesis, thus suggesting IκBα is a direct BMP target gene. Using ChIP assays we demonstrated that intracellular mediators of BMP signals Smad1/5 and Smad4 bound to the highly conserved proximal region of the IκBα promoter. A proximal fragment of the IκBα promoter was found to be activated by BMP2 and BMP7. EMISA assay showed that BMP7-induced IκBα expression blocked formation of the TNF-α-induced NF-κB transcriptional complex. Furthermore, BMP treatment was found to inhibit the TNF-α and LPS-induced NF-κB transcriptional response in mouse osteoblasts and hMSC and rescued the differentiation of MSC from inhibition by proinflammatory stimuli. shRNA-mediated knockdown of IκBα expression confirmed an essential role of IκBα in mediating the anti-catabolic effects of BMPs. Anti-catabolic effects of BMPs in vivo and their mechanism were further validated using transgenic TNF-α mice model.

Conclusion: BMP-induced IκBα expression is a key mechanism mediating preventive and regenerative effects of BMP7 on cartilage and bone. These results may lead to the development of novel strategies for cartilage and bone regeneration, using the combination of BMP7 with pharmacological agents.

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Interleukin-10 Regulates Bone Metabolism by Suppressing Osteoclastogenesis In Vivo.

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Interleukin-10 (IL-10) is an immunoregulatory cytokine that functions to suppress inflammation. IL-10 is capable of inhibiting proinflammatory cytokine production and as such may play a role in the regulation of osteoclastogenesis. In this study, we investigated the role of IL-10 in bone metabolism and the mechanism by which IL-10 regulates osteoclastogenesis in vivo. We found that IL-10 treatment significantly inhibited osteoclast formation and bone resorption in a mouse model of osteoclastogenesis. Furthermore, we found that IL-10 treatment suppressed the production of proinflammatory cytokines and inhibited the expression of RANKL, osteoclast precursor differentiation, and osteoclast survival. These findings suggest that IL-10 may have therapeutic potential in the treatment of osteoclast-mediated bone diseases, such as osteoporosis.
Background: Interleukin (IL-10) is a potent anti-inflammatory cytokine which is produced primarily from T cells and activated macrophages and acts on the macrophage lineage. IL-10 also has potent inhibitory effects on osteoclastogenesis, but the molecular basis of its action is poorly understood.

Recent studies showed IL-10 may down-regulate osteoclastogenesis through inhibition of the expression of NFATc1, c-Fos and c-Jun (1) and inhibition of calcium signaling downstream of RANK by inhibiting transcription of TREM-2 (2). However, there has been no study about the role of IL-10 in osteoarthritis in vivo and under inflammatory condition such as TNF-α induced osteoarthritis.

Objective: To elucidate the role of IL-10 in osteoclast formation under physiological and pathological condition.

Methods: 3-month old male IL-10 KO and WT littermates were used (n = 7 mice/group). We compared the bone phenotype by microcomputed tomographic analysis, histologic analysis and TRAP staining. And we conducted in vitro induction of osteoclast formation by bone marrow monocytes from IL-10 KO and WT mice.

Results: We analyzed the IL-10−/− mice for abnormal bone phenotypes. Microcomputed tomographic analyses showed that these mice had severe osteoporosis accompanied by markedly lower trabecular bone volume, number, and thickness, as well as a smaller number of bone nodules compared to wild-type mice. Histomorphometric analysis also revealed reduced bone mass in the IL-10−/− mice. Notably, TRAP stain showed higher osteoclast numbers and larger osteoclast surface areas in these mice. Moreover, we observed a higher rate of bone formation accompanying the accelerated bone resorption rate in the IL-10−/− mice, suggesting that their osteoporosis was caused by enhanced bone turnover and remodeling. Together, these observations indicated that IL-10−/− has a suppressive role in osteoclastogenesis during in vivo bone remodeling.

We then attempted to investigate the roles of IL-10 in the processes underlying pathological bone destruction. We examined the effect of TNF-α on osteoclastogenesis using IL-10−/− precursors, because TNF-α is a major mediator of inflammation induced by TLRs and has been suggested to be able to induce osteoclastogenesis. Consistent with previous reports, TNF-α induced the development of a small number of osteoclasts in cultures of wild-type precursor cells. Notably, osteoclastogenesis was enhanced in cultures of IL-10−/− precursor cells treated with TNF-α. The mRNA expression levels of Nfatc1 and Acp5 in the IL-10−/− osteoclast precursors were also augmented by TNF-α, indicating that IL-10 also has a suppressive role in TNF-α-induced osteoclastogenesis.

Conclusion: Our results show that IL-10 inhibits osteoclast formation under physiological and pathological conditions and suggest a model where downregulation of IL-10 contributes to RANKL-mediated osteoarthritis.

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Interleukin-1-Induced Cyclooxygenase-2 and Inducible Nitric Oxide Synthase Expression in Human OA Chondrocytes Is Associated with Histone H3K4 Methylation. Fatma Ezzahra El-Mansouri, Najd Chabane, Nadia Zaouali, Joanne Martel-Pelletier, Jean-Pierre Pelletier and Hassan Fahmi.

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Objective: Increased expression of inducible NO synthase (iNOS) and cyclooxygenase (COX)-2 plays a key role in the pathogenesis of osteoarthritis (OA). Methylation of lysine 4 on histone H3 (H3K4) was shown to be of fundamental importance in the regulation of gene expression. In the present study, we investigated the role of H3K4 methylation in interleukin-1b (IL-1)-induced COX-2 and iNOS expression in human OA chondrocytes.

Methods: Chondrocytes were stimulated with IL-1 for various time periods and the expression of iNOS and COX-2 mRNAs and proteins were evaluated using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) and Western blotting, respectively. H3K4 methylation at the iNOS and COX-2 promoters was evaluated using chromatin immunoprecipitation (ChIP) assays. The role of histone methylation was further evaluated using the methyltransferase inhibitor, 5′-deoxy-5′-(methylthio) adenosine (MTA).

Results: IL-1 induced iNOS and COX-2 mRNA and protein in a dose- and time-dependent manner. The induction of iNOS and COX-2 expression by IL-1 was associated with H3K4 di- and trimethylation at the iNOS and COX-2 promoters, whereas the levels of H3K4 monomethylation remained unchanged. Treatment with MTA inhibited IL-1-induced H3K4 methylation as well as IL-1-induced iNOS and COX-2 expression.

Conclusion: These results indicate that H3K4 methylation contributes to IL-1-induced iNOS and COX-2 expression and suggest that this pathway could be a potential target for pharmacological intervention in the treatment of OA.

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miR-7 and miR-130b Are Differentially Regulated during Mesenchymal Stem Cell Commitment. Glynn Palmer, Laura S. Danielson, Mukundan Attur, Steven B. Abramson and Eva Hernando.

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Purpose: Stem cell-based therapies aimed at introducing progenitor cells into cartilage lesions hold great promise for the restoration of damaged articular surfaces following joint injury or osteoarthritis. Key to the generation of a functional repair tissue is the controlled differentiation into the desired phenotype. To this end microRNAs (miRNAs) may be important molecules that regulate this process. By acting as transcriptional repressors, their modulation during differentiation may enable commitment to a specific lineage by suppressing the expression of other lineage markers. In this study we profiled MSCs for miRNA expression following induction into the chondrocyte (C), osteoblast (O) and smooth muscle (SM) lineages.

Results: Human bone marrow-derived Mesenchymal Stem Cells (MSCs) were obtained from NHI, or from the discarded hips of patients undergoing joint replacement surgery. SM differentiation was induced by treating monolayer cultures with 1 mM thromboxane-A2 [DPI] in the presence of 0.25% serum. C differentiation was induced by seeding MSCs in aggregate cultures in the presence of dexamethasone and TGF-b1 (10 ng/ml). O differentiation was induced by treatment of monolayer cultures with dexamethasone, ascorbate and beta-glycerolphosphate. Profiling of miRNAs by microarray (Agilent) or QPCR (SA Biosciences) revealed differential regulation of miR-7 and miR-130b, among 376 probes. Following SM and C differentiation, miR-7 expression was down-regulated up to 6.9-fold and 3-fold respectively. Conversely, during O differentiation, its expression was induced approximately 7-fold. Analysis of theoretical mRNA targets using TargetScan online software (www.targetscan.org) identified conserved sites in several genes associated with chondrocyte and myoblast lineages. Putative chondrogenic targets were found to include COL2A1, IGFR1, and GDF5, while potential smooth muscle modulators included EGRF1, PK3CD, IRS1/IRS2, KLF4, C1NN3 and IGFR1. Following a similar trend to miR-7, miR-130b was down-regulated up to 3.2-fold and 3.1-fold in C and SM differentiation respectively, while O differentiation induced its expression 2-fold. TargetScan analysis identified putative chondrogenic targets, TGF-BRII, Sox5, BMP-2 and IGFL1; Potential smooth muscle regulators included ESRI, TGF-BRII, MBLN1, TGFBR1 and IGFBP2. Together these observations suggest that miR-7 and miR-130b act to negatively regulate myogenic and chondrogenic cell fates via regulation of lineage specific genes.

Conclusion: Our findings suggest that miR-7 and miR-130b, via the targeting of lineage specific molecules, regulate cell fate in adult human MSCs by inhibiting smooth muscle and chondrocyte differentiation, thereby promoting ‘default’ differentiation into the osteoblast lineage.

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Purpose: MMP-3 and DKK-1 are markers of cartilage and bone breakdown, respectively. Prior studies in children and adults with arthritis have shown that MMP-3 levels are elevated and correlate with markers of disease activity(1,2). In RA, DKK-1 has been shown to be a marker of radiographic progression(3). There are no published studies of DKK-1 levels in children, healthy or otherwise.

Methods: For DKK-1 measurements, serum was obtained from 29 children with oligoarticular JIA and 11 healthy control subjects. For MMP-3...
measurements, serum was obtained from 67 children with JIA and 12 healthy control subjects. MMP-3 and DKK-1 values were measured through ELISA assays using kits provided by the manufacturer (Alpco).

Results: MMP-3 levels were significantly elevated in each JIA subtype as compared to the healthy controls (Figure 1), and among JIA patients showed a modest but statistically significant correlation with joint count (r = 0.294, p = 0.007) and ESR (r = 0.344, p = 0.005) at the time of the study. Differences between the arthritis sub-groups were not statistically significant. 8/27 oligoarticular JIA children, but none of the other arthritis patients, had undetectable MMP-3 levels (p = 0.004); this difference remained significant when the three subjects in long-term remission, all of whom had undetectable levels, were excluded (p = 0.032). One subject thought to be a healthy control based upon her physical exam had an elevated MMP-3 level, and subsequently had an MRI and physical exam that were consistent with inflammation arthritis. Another subject thought to have oligoarticular JIA had negative MMP-3 levels; MRI revealed a synovial cyst. DKK-1 levels were only measured in oligoarticular JIA patients and healthy controls. Values were comparable, with median levels of 25.3 (IQR 22.8–36.6) and 27.9 ng/ml (IQR 22.5–30.4) in patients and controls, respectively (p = 0.942). These levels were an order of magnitude higher than those reported in most prior studies in adults.(4,5). There was no association with DKK-1 levels and the age of the child.

Conclusions: Measurement of serum MMP-3 may be a useful biomarker in children with an unclear presentation of joint pain and may help assess severity of the condition. However, perhaps because growing children have considerable bone turnover at baseline, DKK-1 may be a less useful biomarker in this population as compared to adults.

RANKL induces DC-STAMP<sup>Δ</sup> OCPs to function as master fusogens, and DC-STAMP<sup>Δ</sup> OCPs to serve as mononuclear donors that cannot fuse on their own to form mature OCs. In order to investigate the molecular mechanisms by which DC-STAMP contributes to OCP fusion and OC formation, we aimed to isolate and characterize Raw cell clones with OCP master fusogen vs. mononuclear donor phenotypes based on their DC-STAMP expression before and after RANKL stimulation.

Methods: Raw 264.7 cells were cloned by limiting dilution: diluted 50 cells in 10ml alpha-MEM media, seeded 100ul/well in 96 well-plate and selected single cell clones. The clones were treated with 100ng/ml RANKL, and their osteoclastogenic potential was assessed by TRAP staining. The surface expression of DC-STAMP was determined by flow cytometry following 7AAD staining to gate the live cells, and FITC-conjugated 1A2 monoclonal anti-DC-STAMP antibody.

Results: Seven Raw cell clones were obtained and their QC formation and DC-STAMP surface expression were examined. Clone 5 formed large multilaminated TRAP<sup>+</sup> OCs three days after RANKL treatment, while it took five days for the parental raw cell line to form OCs under a same culture condition. Clone 5 also expressed a low basal level of surface DC-STAMP (MFI= 32.0), which was similar to DC-STAMP<sup>Δ</sup> (MFI=16.5) identified in the parental cells following three days of RANKL treatment. In contrast, the Clone 1 could not form OCs after five days of RANKL treatment. Clone 1 also had a high basal level of surface DC-STAMP expression (MFI= 60.8), which was similar to RANKL-induced DC-STAMP<sup>Δ</sup> (MFI=55.4) of the parental cells.

Conclusions: Two Raw 264.7 cell sub-clones were isolated to investigate DC-STAMP-mediated OCP fusion in response to RANKL treatment. Clone 5 forms OCs faster and has low basal DS-STAMP expression while Clone 1 forms OCs much slower, and expresses high basal DC-STAMP. These clones mimic the heterogeneous DC-STAMP expression levels and OC forming potential of the parental Raw cells, and can be used as cell models of master fusogens (Clone 5) or mononuclear OCP donors (Clone 1). Our ongoing studies to clone DC-STAMP ligand using these clones via differential microarray analysis will be discussed.

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Purpose: Osteoclasts (OC) are multinucleated bone-resorbing cells derived from mononuclear osteoclast precursors (OCP) following stimulation with RANKL and M-CSF. Raw264.7 cells are a heterogeneous murine monocyte/macrophage cell line, of which some can form OCs and others cannot. DC-STAMP is a receptor on OCP, and is required for cell fusion to form multinucleated OC. Recently we demonstrated that the surface expression of DC-STAMP by RANKL+ OCPs defines OCP fusion potential.

250nM) dose-dependently reduced osteoclast numbers. Furthermore, numbers of pre-osteoclasts were also significantly decreased after addition of PKC412, indicating an effect of PKC412 on early stages of osteoclastogenesis. In line with this finding, we could show a dose-dependent reduction of pre-osteoclast proliferation using MTT proliferation assays. Moreover, we detected a significant time- and dose-dependent increase in the ratio of apoptotic cells in the PKC412-treated cells by Annexin V and 7-AAD staining. Additionally, in the presence of PKC412 we obtained a significant reduction in osteoclastogenesis and nuclear number, as well as in the size of the resorption pits on dentin slices. This indicates that the bone resorbing capacity of osteoclasts is altered by PKC412. Consistently, we were able to demonstrate a dose dependent downregulation of mRNA coding for osteoclast resorption pit formation on bone.

Conclusion: These results suggest a regulatory role of PKC412 in pre-osteoclast differentiation and osteoclastogenesis through apoptosis induction.

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Potential Role of the LKB1-AMPK and CaMKKb-AMPK Pathways in Controlling the Progression of OA. Robert Terkeltaub1, Bing Yang2, Martin K. Lotz3 and Ru L. Bryan4.

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Purpose: LKB1, a tumor suppressor, and CaMKKb (Ca2+/calmodulin-dependent protein kinase kinase beta) are serine/threonine protein kinases that act upstream of AMPK (AMP-activated protein kinase), a super-regulator of energy homeostasis. AMPK exists as a heterotrimer composed of an alpha catalytic subunit and two regulatory beta and gamma subunits. Phosphorylation of AMPK (Thr172) within the catalytic domain of the a subunit by upstream kinases is essential for AMPK activation. We have previously observed that articular chondrocytes express functional AMPK, and activation of AMPK attenuates pro-catabolic responses of chondrocytes to inflammatory cytokines. In addition, phosphorylation of AMPKα is significantly decreased in human OA knee articular chondrocytes. Here, we investigated the role of two AMPK upstream kinases LKB1 and CaMKKb in regulation of chondrocyte matrix catabolism.

Methods: Expression and activation status (Ser428 phosphorylation) of LKB1 were examined in cultured human knee articular chondrocytes (first passage) and in human knee articular cartilage sections from different normal and OA (grade I to IV) donors. Knockdown of LKB1 and CaMKKb in human chondrocytes was achieved via transfection with LKB1 and CaMKKb siRNA. Activation of AMPK (AMPKa Thr172 phosphorylation) and pro-catabolic responses including nitric oxide (NO) generation and expression of MMP-13 in response to IL-1β and TNFα in normal human chondrocytes were assessed and compared. Expression of the chondrocyte hypertrophy marker type X collagen was also examined.

Results: Expression and constitutive phosphorylation of LKB1 were observed in normal and low grade OA human knee articular chondrocytes. However, both expression and phosphorylation of LKB1 were markedly decreased in OA chondrocytes beyond grade III, which correlated with decreased expression and phosphorylation of AMPKα. Treatment of articular chondrocytes with IL-1β and TNFα induced de-phosphorylation of LKB1 and AMPKα. Importantly, knockdown of LKB1 and CaMKKb in articular chondrocytes attenuated phosphorylation of AMPKα, and resulted in significant enhancement of MMP-3 release and nitric oxide (NO) generation induced by IL-1β and TNFα. In addition, type X collagen protein expression induced by TNFα was markedly enhanced in chondrocytes with knockdown of LKB1 or CaMKKb.

Conclusions: Human knee OA articular chondrocytes with grade III and beyond exhibit markedly decreased LKB1 and CaMKKb phosphorylation that correlates with decreased AMPK phosphorylation. Knockdown of LKB1, as well as CaMKKb, by RNAi enhanced chondrocyte hypertrophy and pro-catabolic responses of articular chondrocytes to inflammatory cytokines, and was closely linked with decreased AMPK activation defined to regulate the pro-catabolic responses. These findings identify therapeutic potential of activation of the LKB1-AMPK and CaMKKb-AMPK pathways in order to inhibit the progression of OA.

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dinal serum samples (baseline and year 1) with imaging results and clinical data from 160 patients followed in the BeSt trial, a 5-year blinded study comparing four different treatment arms (sequential monotherapy, step-up combination, combination therapy with prednisone, and combination therapy with infliximab) in aggressive early RA. The concentrations of individual biomarkers were assessed for their association with change in total Van der Heijde-modified Sharp Scores (mSS) at 2 years. Statistical models using combinations of serum biomarkers were built to predict the rate of change of total mSS. Good disease control may influence the computation of mSS rate of change; hence additional analyses incorporating therapy change information into the biomarker model were also performed. Various models built by conventional measures were compared to the serum biomarker model. Performance of the models was evaluated by the Pearson correlation coefficient between actual and predicted rates of change and by the area under the ROC curve (AUC) in cross-validated test sets. Mean mSS rate of change in the test sets was used to dichotomize patients into high and low groups for AUC calculation.

**Results:** Candidate serum biomarkers predicted damage better at Year 1 than at baseline, probably because baseline samples were collected before therapy took effect. We identified serum biomarker combinations (cor (0.60, AUC = 0.75) that predicted change in mSS from Year 1 to Year 2 and were superior to DAS28ESR (cor (0.33, AUC = 0.61), CRP (0.38, AUC = 0.67), DAS28ESR with CCP (cor (0.22, AUC = 0.61), or DAS28ESR with RF (cor (0.37, AUC = 0.62) in predicting radiographic progression. In total, 35 individual biomarkers were associated with joint damage progression with false discovery rate (FDR) <0.1, 18 at FDR<0.05. Incorporating therapy information into the biomarker model didn’t change model performance.

**Conclusion:** The best performing models included markers of bone and cartilage destruction, pro-inflammatory cytokines and acute phase proteins. Combining markers were able to achieve improved radiographic outcomes despite therapy changes and good control of disease activity. Serum biomarker-based indices have the potential to improve prediction of structural damage progression over standard clinical measures of disease activity in RA patients.

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### 1498

**Study of Chondrogenic Potential of Subpopulations of Cells Expressing Mesenchymal Stem Cell Markers Derived from Human Synovial Membranes**

Maria C. Aute, Aleksandre De la Fuente, Silvia Diaz, Isaac Fuentes, Francisco J. de Toro and Francisco J. Blanco.


**Introduction:** Synovial membrane mesenchymal stem cells (MSCs) have been demonstrated to be a good source of cells for the study of cartilage tissue engineering. Multiple stem cells markers have been found by flow cytometry and immunofluorescence in MSCs from human synovial membrane pools. In this study we analyzed the chondrogenic potential of subpopulations of MSCs derived from human synovial membranes enriched for CD73, CD106 and CD271 markers.

**Material and Methods:** Subpopulations of human synovial membrane MSCs enriched for CD73, CD106 and CD271 markers were isolated using a monoclonal antibody and characterized by flow cytometry for MSC markers. The expression of Sox9, Nanog and Runx2 genes by these cells was measured by reverse transcriptase-polymerase chain reaction. The chondrogenesis of each subpopulation was assessed by culturing the cells in a defined medium to produce spontaneous spheroid formation and differentiation towards chondrocyte-like cells. The examination of the spheroids by histological and immunohistochemical analyses for collagen type II (COL2), aggrecan, collagen type I (COL1), metalloproteinase 13 (MMP13) and collagen type X (COLX) levels were performed to assess their chondrogenesis capacity. The adipsogenesis and osteogenesis potential of each subpopulation was determined using commercial media; the resulting cells were stained with oil red O or red alizarin to test the degree of differentiation.

**Results:** The subpopulations had different profiles of cells positive for the MSC markers CD44, CD69, CD73, CD90 and CD105, and showed different expression levels of the genes Sox9, Nanog, Runx2 involved in chondrogenesis, undifferentiation and osteoblastogenesis, respectively. Immunohistochemical analysis demonstrated that COL1, COL2, COLX, MMP13 and aggrecan were expressed in the spheroids as soon as 14 days of culture. The CD271+ subpopulation expressed the highest levels of COL2 staining compared to the other subpopulations. CD105 and Runx2 were shown by immunohistochemistry and genetic analysis to have significantly higher expression CD271+ subpopulation than the other subpopulations.

**Conclusions:** Spheroids formed from CD271-enriched and CD73-enriched MSCs from normal human synovial membranes mimic the native cartilage extracellular matrix more closely than CD106+ MSCs and are...
possible candidates for use in cartilage tissue engineering. Both cell types have potential for promoting the differentiation of MSCs into chondrocytes, presenting new possibilities for achieving intrinsic cartilage repair.

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TGF-β-Induced CD4+CD25+Foxp3+ Regulatory T Cells Suppress Bone Erosion in Collagen-Induced Arthritis through Restraining the Osteoclastogenesis. Ning Kong1, Ziyun Yang2, Julie Wang3, Ryan Park4, Grant Dagliyan5, Peter S. Conti6, Hejian Zou2 and Song Guo Zheng7.1Fudan University Medical School, 2UCLA Department of Biomed, 3USC Keck School of Medicine.

Background: It is well-known that osteoclasts are responsible for the bone destruction in rheumatoid arthritis (RA) and collagen induced arthritis (CIA). Previous study has demonstrated that activated natural CD4+ CD25+ regulatory T cells (nTregs) can inhibit osteoclastogenesis and CIA in a factor receptor activator of NF-κB ligand (RANKL)-dependent pathway by blocking osteoclast differentiation from osteoclast precursors (OCP). Since we and other groups have identified that TGF-β-induced CD4+ CD25+Foxp3+ regulatory T cells (iTregs) have the similar phenotypic and functional characteristics as nTregs, here we try to learn if iTregs also have the suppressing capacity on osteoclastogenesis and CIA.

Methods: In vitro, osteoclasts were induced from bone-marrow cells with RANKL and macrophage colony-stimulating factor (M-CSF). Naïve CD4+ T cells were isolated from splenocytes of normal DBA1/J mice and stimulated with anti-CD3/CD28 coated beads with IL-2 (Tcon) or IL-2 + TGF-β (iTregs) for five days. On day 0, Tcon and iTregs were added to cultures for the induction of osteoclasts formation at different ratios in the presence of anti-CD3 monoclonal antibody. Osteoclast formation was determined by staining with tartrate-resistant acid phosphatase (TRAP), identified and counted by microscopes. In vivo, 3×106 iTregs were adaptively transferred to DBA1/J mice on d14 after immunization with CFA and bovine CII. The prevalence and severity of CIA mice were monitored every other day. After four-week transfer, mice accepted CT scanner on joints. The histological analysis of joints was performed and joints were stained for the identification of osteoclasts.

Results: Addition of 10% of iTregs almost completely suppressed osteoclast formation in cultures with addition of similar doses of Tcon cells. Addition of anti-TGF-β or anti-IL-10 antibody to cultures blocking osteoclast differentiation from osteoclast precursors (OCP). Since we and other groups have identified that TGF-β-induced CD4+CD25+Foxp3+ regulatory T cells (iTregs) have the similar phenotypic and functional characteristics as nTregs, here we try to learn if iTregs also have the suppressing capacity on osteoclastogenesis and CIA.

Conclusions: iTregs can inhibit osteoclastogenesis in vitro and in vivo, and eventually suppress bone erosion in CIA diseases. This study implicates that manipulation of iTregs may have a therapeutic effect on rheumatoid arthritis and other autoimmune diseases.

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1501

The Enhanced Expression of Suppressor of Cytokine Signaling (SOCS3) in Human Pathological Chondrocytes Impairs the TLR4 and IGF-1 Signaling in These Cells. Fons A. J. van de Loo, Miranda B. Bennink, Onno J. Arntz, Henk M. van Beuningen, Peter M. van der Kraan, Sharon S. Veenbergen and Wim B. van den Berg. Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Introduction: Osteoarthritis (OA), a degenerative joint disease, and Rheumatoid arthritis (RA), an inflammatory joint disease, are both characterized by progressive loss of the articular cartilage matrix due to an imbalance between matrix synthesis and degradation. Loss in the chondrocytes ability to respond to growth factor stimulation may be a key factor contributing to the development of OA and RA. We recently found that enforced expression of SOCS3 caused IGF-1 resistance in chondrocytes, thereby preventing upregulation of matrix proteoglycan synthesis. This study is designed to determine the expression of SOCS3 in human pathological chondrocytes and unravel the biological/functional consequences.

Methods: Chondrocytes were isolated from cartilage of patients undergoing surgical joint replacement. The mRNA and protein levels of SOCS1 and SOCS3 were measured by qPCR and westernblotting. Levels of SOCS3 were compared to a human immortalized chondrocyte cell-line (G6), mesenchymal-stem cells differentiated chondrocytes, and primary chondrocytes isolated from healthy bovine cartilage or from a SLE patient. The regulation of SOCS1 and 3 expression was studied in OA chondrocytes by incubation with different cytokines and TLR agonists. To determine the functional consequences the cytokine and TLR ligand induced nitric-oxide production and IGF-1-stimulated proteoglycan (PG) synthesis was studied.

Results: The SOCS3 mRNA expression in articular chondrocytes and cartilage was markedly upregulated (32-fold) in 21/24 OA, 5/5 RA patients, and 3/3 trauma patients tested, as compared to the G6 cell-line, stem cell-differentiated chondrocytes, and primary chondrocytes isolated from healthy bovine cartilage or from a SLE patient. The regulation of SOCS1 and 3 expression was studied in OA chondrocytes by incubation with different cytokines and TLR agonists. To determine the functional consequences the cytokine and TLR ligand induced nitric-oxide production and IGF-1-stimulated proteoglycan (PG) synthesis was studied.

Disclosure: P. Chen-An: None; Y. Li: None; B. C. Sondergaard: None; T. Silvestra-Segovia: None; P. Qvist: None; M. A. Karsdal: None; A. C. Bay-Jensen: None.
IL-1β, IFNγ, IL-17, Pam2Cys, Poly(I:C), and especially with the combination of IFNγ and Poly(I:C), SOCS3 expression in OA chondrocytes was confirmed at the protein level. This means that the SOCS3 and SOCS1 genes are independently regulated and that SOCS3 has reached the maximal expression level. In the OA chondrocytes, the TLR4 ligand LPS was unable to induce NO production and IGF-1 failed to stimulate PG synthesis. Forced expression of SOCS3 in bovine cartilage-derived chondrocytes blocked the LPS (NO) and IGF-1 (PG-synthesis) response in these cells.

**Conclusion:** We found increased SOCS3 but not SOCS1 expression in human pathological chondrocytes. SOCS3 could block TLR4 and IGF-1 activation in chondrocytes. This suggests that SOCS3 modifies normal chondrocyte function and this could play a major role in the development of cartilage pathology seen in osteoarthritis and rheumatoid arthritis patients.

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**1502**

The HCO3⁻/Cl⁻ Anion Exchanger SLC4A2 Regulates pH and Actin Organization within Osteoclasts.

**Fabiennes Courey**, Andrew K. Stewart, Sebastien Stephenson, Lynn Neff, William C. Horne, Seth L. Alper, Roland Baron, and Antonios O. Aliprantis. Department of Immunology and Infectious Diseases, Harvard School of Public Health, and Department of Medicine, Harvard Medical School, Boston, MA. 1Department of Oral Medicine, Harvard Dental School, 2Division of Nephrology, Beth Israel Deaconess Medical Center

Overactivation of bone resorption by osteoclasts occurs in numerous rheumatic diseases such as osteoporosis and rheumatoid arthritis. To resorb bone, osteoclasts secrete acid into a resorption lacuna between their apical ruffled membrane and the bone surface. This process is facilitated by reorganization of their actin cytoskeleton to form a sealing zone, which, like a gasket, seals off the resorption lacuna to prevent acid leakage. To prevent cytoplasmic alkalization during lacunar acid secretion, electroneutral exchange of bicarbonate for chloride occurs through an anion exchanger, Solute carrier family 4, anion exchanger, member 2 (SLC4A2, AE2). We recently showed that in the absence of Slc4a2, mice develop osteopetrosis due to impaired osteoclast function. Accordingly, SLC4A2-deficient osteoclasts are unable to secrete acid and resorb bone. Here, we show that SLC4A2 may serve an additional and previously unrecognized function in the osteoclast: the regulation of actin dynamics and podosome organization. In vitro, SLC4A2-deficient osteoclasts display a delay in actin belt formation. The actin belts ultimately formed by SLC4A2-null osteoclasts are thicker and made up almost completely of punctuate, large podosomes lacking the diffuse actin cloud characteristic of wild-type belts. Furthermore, the average podosome life span is significantly longer in the actin belts of null osteoclasts, while actin polymerization is increased. Interestingly, while SLC4A2 was not required for microtubule assembly, we show it is required to recruit c-Src to the actin belt. c-Src is a major intracellular mediator of osteoclast activation, coordinates organization of the actin belt and is required for osteoclast function in vivo. We also show that SLC4A2 is exclusively expressed at the basolateral membrane of mouse osteoclasts. In addition, in its absence, osteoclasts are unable to exchange Cl⁻ for HCO₃⁻, and display intracellular alkalinization. Taken together, our results indicate that SLC4A2 regulates two cell biological processes required for mature osteoclasts to efficiently resorb bone: reorganization of the actin cytoskeleton and acid secretion. Whether the effect of SLC4A2 deficiency on the osteoclast cytoskeleton represents a direct function of Wnt signaling leading to osteoarthritis. Wnts signal through β-Catenin/TCF or through non-canonical pathways involving Ca⁴⁺/CamKII, PKC, PKA, and the planar cell polarity pathway. Individual Wnt ligands are known to signal through different pathways depending of the cellular context. Canonical and non canonical signalling are active in cartilage and may play distinct roles in osteoarthritis. The purpose of the study was to systematically dissect WNT3A signaling in chondrocytes and understand the mechanisms through which disruption of this signaling leads to cartilage breakdown.

**Methods:** Articular chondrocytes were isolated from preserved cartilage of patients undergoing knee arthroplasty for osteoarthritis. Mouse cartilage explants were obtained from the femoral head of adult mice. The activation of the canonical and calcium dependent pathways upon Wnt3a stimulation was evaluated by the SUPERSTOP/Flash, CREB, and NF-AT reporter assays, calcium mobilization assay, Western blotting for β-catenin or p-CAMK2, and Axin-2 mRNA expression.

**Results:** Wnt3a induced the simultaneous activation of the canonical and CaMKII-dependent pathways. More importantly, using a systematic strategy of stimulation of Wnt3a and blockade of individual pathways, we have been able to demonstrate reciprocal inhibition of the two pathways and to separate specific downstream effects. We have built a model that, through such reciprocal inhibition, explains why excessive Wnt3A stimulation or blockade leads to cartilage destruction through different mechanisms.

**Conclusions:**

- Wnt3A signals simultaneously through the canonical and CamKII dependent pathways in cartilage
- The β-catenin and the CamKII-dependent pathways are reciprocally inhibitory and have distinct outcomes.

**Disclosure:** G. Nalesso: None; C. Pitzalis: None; F. Dell’Accio: None.

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**A Novel Role for Inducible Fucosyltransferase2 as a Regulator of Angiogenesis.**

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**Purpose:** Fucosyltransferases (Futs) are involved in the synthesis of fucosylated glycans and blood group antigens. A number of studies have shown the role of some Futs in angiogenesis and inflammation. The importance of angiogenesis is well established in diseases such as rheumatoid arthritis (RA). This is a novel study which demonstrates that Fut2, heretofore not known to regulate angiogenesis, is cytokine inducible in human dermal microvascular endothelial cells (HMVECs) and plays an essential role in inflammatory angiogenesis.

**Methods:** We performed reverse transcriptase polymerase chain reaction (RT-PCR) and quantitative PCR to determine Fut2 mRNA expression in HMVECs after stimulation with interleukin-1β (IL-1β). To determine the role of signaling molecules in Fut2 mRNA expression, we stimulated HMVECs with IL-1β in the presence or absence of chemical signaling inhibitors and collected RNA to examine the role of signaling molecules in Fut2 expression. We harvested endothelial cells (ECs) from Fut2 null and wild type (wt) mice and performed Matrigel tube formation assays in vitro. We also used Matrigel plug and the inflammatory sponge granuloma angiogenesis assays in vivo to elucidate the significance of Fut2 in angiogenesis by employing Fut2 null and wt mice. To evaluate the mechanism by which Fut2 contributes to angiogenesis, we stimulated Fut2 null and wt mouse ECs with IL-1β, and performed enzyme linked immunosorbent (ELISA) assays to determine if Fut2 deficient ECs produced lower amounts of angiogenic factors than their wt counterparts.

**Results:** IL-1β enhanced Fut2 mRNA expression in HMVECs compared to nonstimulated cells with a maximum increase at 60 minutes. Phosphatidylinositol 3 kinase and p38 were critical in HMVEC IL-1β stimulated Fut2 mRNA expression. Fut2 null ECs exhibited a significant 2 fold decrease in tube formation compared to wt ECs, indicating that Fut2 may be an important factor in angiogenesis in vivo. To determine whether Fut2 contributed to angiogenesis in vivo, we performed mouse Matrigel plug and inflammatory sponge granuloma angiogenesis assays using Fut2 null and wt mice. Fut2 null
mice were deficient in angiogenesis in both the Matrigel plug and the sponge granuloma compared to wt mice (p<0.05). To determine the mechanism of impaired angiogenesis in the absence of Fut2, ECs harvested from Fut2 null and wt mice were stimulated with IL-1β. Vascular endothelial growth factor (VEGF) was less in Fut2 null ECs at both the mRNA and protein levels, suggesting a novel role for Fut2 as regulator of angiogenesis.

**Conclusions:** These data suggest an intriguing role for Fut2 as regulator of angiogenesis. Fut2 may be a potential therapeutic target controlling production of angiogenic factors such as VEGF in angiogenesis-dependent diseases such as RA.

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**1505**

**CD86 Is Involved in the Intercellular Contacts between IL15 Activated Natural Killer Cells and THP-1 Cells That Result in TNF Production.** Amalia Lamana, Belen Diaz-Sanchez, gips. Ortiz, Santos Castañeda, Rosario Garcia-Vicuña and Isidoro González-Alvaro. Rheumatology Department. HU La Princesa. IIS Princesa, Madrid, Spain

**Background:** We have previously described that the interaction between NK cells activated with interleukin 15 (IL15) and macrophages leads to persistent TNF production and may be relevant in the perpetuation of rheumatoid arthritis in a subset of patients (1). Abatcept, an effective drug for controlling this disorder, inhibits the costimulatory signal induced by the interaction of CD28 expressed on T cells with CD80 and CD86 expressed on macrophages.

**Aim:** To study the pattern of CD28 expression on NK cells and its potential implication in the interactions that result in TNF secretion in cultures of NK and THP-1 cells.

**Methods:** We studied by flow cytometry the expression of CD16, CD28 and CD56 on different NK lineage tumor cell lines (NKL, NK1.1 and YT line obtained from ATCC) and on NK cells from peripheral blood (PB) of 33 healthy donors (HD). In addition, PB lymphocytes (PBL) were stimulated or not with IL15 (50 ng/ml) for 16 h. Resting and activated cells were washed twice with medium and cocultured with THP-1 cells (10 PBL by each THP-1 cell) in the presence or absence of CTLA4-Ig, anti CD64 and anti CD80 (as a control since THP-1 cells do not express this molecule) blocking monoclonal antibodies (mAb). After 24 hours, supernatants were harvested and TNF production was measured by ELISA. In some conditions, cells were separated by a permeable support (transwell) that allowed the passage of soluble mediators but not cells. Furthermore, we performed experiments with PBL depleted in CD86 or CD16 positive cells.

**Results:** NKL and YT line tumor cell lines expressed CD28. NK cells from HD could be classified according on their pattern of CD16 and CD56 expression as: group 1 (GR1) is CD56dim CD16high; group 2 (GR2) is CD56dim CD16negative; and group 3 (GR3) is CD56 high CD16low/negative. The most abundant population was GR1 (median 60% of NK; interquartile range [IQR] 48–75%) where cells lack CD28. The median percentage of NK subpopulation with GR2 profile was 17% (IQR 12–34%). A subset of GR2 NK cells, ranging from 5 to 50%, expressed CD28. The GR3 subpopulation represented about 5% of PB NK cells and did not express CD28. Supernatants from PBL and THP-1 cells showed TNF production that increased (80 /−15%, p=0.001) when PBL were pre-treated with IL15 and was abrogated when the two cellular types were separated by transwells. Interestingly, the presence of anti-CD86 mAb in the culture medium decreased TNF production (50 /−30%; p=0.02) mainly when PBL were pre-activated with IL15. CTLA4-Ig decreased TNF production only in a subpopulation of HD. On the other hand, IL15 did not increase the CD28 expression on NK cells and the depletion of CD28 positive cells did not impair TNF production, whereas depletion of CD16 positive cells abrogated its production.

**Conclusions:** In this study we have described that blockade of CD86 decreases the production of TNF in a model that is mediated by IL15 activated NK cells. Although we have detected a subpopulation of NK cells expressing CD28, this subset do not seem to be involved in the model. More studies are needed to determine the CD86 ligand on CD16+ NK cells since in a subset of donors CTLA4-Ig was also able to decrease TNF production.

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**1506**

**Characterization of CCR7 and Its Ligands CCL19 and CCL21 in Rheumatoid Arthritis,** Sarah R. Pickens 5, Michael V. Volin, Richard M. Pope, Arthur M. Mandelin and Shiva Shahrara. 1Midwestern University, 2Northwestern University, Chicago, IL, 3Northwestern Univ Feinberg, Chicago, IL, 4Northwestern Univ Med School, Chicago, IL, 5Northwestern University, Chicago, IL

**Introduction:** The aims of this study were to characterize the expression of CCR7 and its ligands CCL19 and CCL21 in rheumatoid arthritis (RA) synovial tissue (ST) and synovial fluid (SF) and to demonstrate the role of CCL19 and CCL21 in RA pathogenesis.

**Methods:** Immunohistochemistry was employed to determine expression patterns of CCR7, CCL19 and CCL21 in RA and NL STs. CCL19 and CCL21 expression levels were also determined in normal (NL) osteoarthritis (OA) and RA ST, as well as in SF from OA, juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA) and RA patients using ELISA. CCL19 and CCL21 mRNA levels were quantified in NL and RA peripheral blood (PB) monocytes and macrophages, as well as in RA SF macrophages by real-time RT-PCR. Next, we identified proinflammatory factors that modulate expression of CCL19 and CCL21 in PB differentiated macrophages using real-time RT-PCR. Finally, production of proinflammatory factors was examined in CCL19 and CCL21 activated macrophages and RA ST fibroblasts employing ELISA.

**Results:** We found that ST lining and endothelial cells positively stained for CCR7 and that the immunostaining was 2 fold higher in RA compared to NL STs. Consistently, CCL19 and CCL21 expression was significantly increased in RA ST lining (1.3 and 3 fold respectively) and endothelial cells (1.8 and 2.5 fold respectively) compared to NL STs. Further, CCL19 and CCL21 levels were elevated in RA (2.5 and 1.5 fold respectively) and PsA SFs (2 and 1.6 fold respectively) compared to OA SFs. Interestingly, CCL19 levels were significantly increased in RA SF macrophages compared to RA and NL PB macrophages, while CCL21 expression was upregulated in RA SF and PB macrophages compared to controls. Next, we showed that CCL19 expression levels were generally higher in RA and OA STs compared to CCL19. However, NL ST had similar levels of CCL19 and CCL21. Further, CCL19 and CCL21 levels were elevated in RA (2.5 and 1.5 fold respectively) and PsA SFs (2 and 1.6 fold respectively) compared to OA SFs. Interestingly, CCL19 and CCL21 were generally similar in RA compared to OA SFs. However, only RA SF stimulation (2.5 fold) upregulated levels of CCL21 in macrophages compared to untreated cells. Additionally we found that CCL19 and CCL21 were capable of inducing the production of VEGF and Ang-1 from RA ST fibroblasts and secretion of IL-8 and Ang-1 from macrophages.

**Conclusion:** Our results suggest that CCR7 and its ligands CCL19 and CCL21 are elevated in RA ST lining and endothelium, and ligation of CCR7 may play an important role in mediating angiogenesis in RA synovium.

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**1507**

**Chemerin Levels Are Increased in Rheumatoid Arthritis Patients Who Smoke, Correlate With Disease Activity, and Decrease after Adalimumab Treatment,** Marieke Herenius 2, Cristina Lebre 3, Ana Oliveira 3, Carla Wijnbrants 3, Daniëlle Gerlag 3 and Paul P. Tak 1. 1Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, 2Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Utrecht, The Netherlands, 3Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

**Background:** Chemerin is a recently discovered chemokine that modulates chemotaxis and activation of dendritic cells and macrophages. The expression of chemerin in rheumatoid synovial tissue strongly suggests involvement of chemerin in the migration/accumulation of dendritic cells and macrophages in the inflamed joint. Furthermore, we have recently shown in synovial biopsy explant cultures that chemerin levels are upregulated by TNF-a and that chemerin can induce TNF-a. Elevated chemerin levels have also been related to dyslipidemia and hypertension in obesity, thereby linking it to the metabolic syndrome.

**Objective:** To explore the role of chemerin in rheumatoid arthritis (RA) in relationship to known cardiovascular risk factors and to evaluate the effects of anti-TNF treatment on serum levels of chemerin.

**Methods:** 49 patients with active RA (disease activity score evaluated in 28 joints (DAS28) ≥3.2) were started on adalimumab therapy (40 mg subcutaneously every other week). Blood was drawn from patients while on anti-TNF treatment on serum levels of chemerin. In relationship to known cardiovascular risk factors and to evaluate the effects of anti-TNF treatment on serum levels of chemerin.

**Disclosure:** S. R. Pickens: None; M. V. Volin: None; R. M. Pope: None; A. M. Mandelin: None; S. Shahrara: None.

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levels were measured by ELISA. Known risk factors for cardiovascular disease were determined at baseline.

Results: Baseline chemerin levels correlated with DAS28 and ESR (r = 0.38, p = 0.007 and r = 0.40, p = 0.005, respectively). Of interest, we found chemerin levels to be significantly higher in current smokers (n = 9, median 162 ng/ml, IQR 159–168 ng/ml) than non-smokers (n = 33, median 143 ng/ml, IQR 130–169 ng/ml, p = 0.03). Baseline chemerin levels were not related to sex, age, BMI, serum lipids levels (TC, HDL, LDL, TG, Apo A-I, Apo B, Lp(a)) or cardiovascular events in the medical history. After 16 weeks of adalimumab treatment there was a significant reduction in DAS28, ESR, CRP (p < 0.001, p < 0.001, and p < 0.001, respectively) associated with a reduction of serum levels of chemerin from 152 ng/ml (± 34 ng/ml) to 141 ng/ml (± 29 ng/ml) (p = 0.025).

Conclusions: Levels of chemerin are related to disease activity and reduce after adalimumab treatment. Interestingly, smoking might increase levels of chemerin, a potent chemoattractant for dendritic cells and macrophages, promoting clinical signs and symptoms of RA and perhaps also the metabolic syndrome.

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1508

Contribution of NR4A2 Gene Expression in Modulation of Thrombospondin-1 in Human Joint Disease. Jason P. McMorrow, Ursula Fearon, Douglas J. Veale, Oliver M. FitzGerald and Evelyn P. Murphy. 1St Vincent’s University Hospital, Dublin, Ireland, 2University College Dublin, Ranelagh Dublin, Dublin, Ireland

Background: During joint inflammation perpetuation of angiogenesis leads the reorganisation and increase in blood vessel number. During early stages of disease an angiogenic switch occurs which shuts off angiogenic inhibitors such as Thrombospondin-1 (TSP-1) and leads to increased production of pro-angiogenic mediators. The NR4A subfamily of orphan nuclear receptors have recently emerged as novel transcriptional regulators of angiogenic growth factor and cytokine action in inflammatory diseases. The aim of this study was to examine the levels of TSP-1 in human serum, expression of TSP-1 in synovial tissue and to monitor the effects of anti-TNFα therapy on both systemic and local TSP-1 levels.

Methods: TSP-1, VEGF, NR4A, and IL-8 mRNA levels were determined in using real-time PCR. TSP-1 protein levels were quantified in synovial tissue (ST) by immunohistochemistry (IHC) in a cohort of patients (n = 10) pre and post anti-TNFα therapy. TSP-1 serum levels were measured by ELISA in healthy volunteers (n = 5) and 2 cohorts of patients (n = 12; n = 15) receiving anti-TNFα treatment. TSP-1 promoter activity was monitored by luciferase reporter assays.

Results: TSP-1 protein levels were measured in patient serum at baseline (n = 12) and compared to levels in healthy volunteers (n = 5). A significant decrease in TSP-1 expression was observed in patients with active disease (p = 0.007). Following anti-TNFα treatment, TSP-1 serum levels were restored (p < 0.001). TSP-1 and NR4A2 expression and localisation was measured in the ST of patients (n = 10) receiving anti-TNFα therapy. Our findings demonstrate that low expression levels of TSP-1 in inflamed tissue in the lining layer and sublining endothelial cells. TSP-1 expression was highly cell associated. High levels of NR4A2 were quantified in all patient tissue. Post-treatment, NR4A2 levels are significantly reduced, while TSP-1 protein levels are enhanced demonstrating a significant diffuse pattern of expression.

Using primary synoviocyte cells (n = 9), analysis revealed negligible levels of TSP-1 mRNA, high levels of NR4A1–3 and IL-8 transcripts in low passage cells. In high passage cells, reciprocal levels of TSP-1, NR4A and IL-8 expression were observed. Stable NR4A2 expression in normal synoviocyte cells resulted in decreased TSP-1 mRNA and protein levels. To determine whether NR4A effects on TSP-1 expression occurred at the transcriptional level, we evaluated transactivation of the hTSP-1 (2872 bp) promoter using a series of promoter deletions cotransfected with NR4A2. NR4A2 reduced TSP-1 promoter activity by approx. 50%. Within the promoter deletions we identified a repressor region. Deletion of this promoter region resulted in NR4A2 activity transformed from a repressor to transcriptional activator of TSP-1 expression.

Conclusion: These data reveal that moderate expression of TSP-1 in human joint inflammatory disease can be significantly enhanced during anti-TNF treatment and identifies a novel role for NR4A2 as a transcriptional repressor of TSP-1 expression in human synovial tissue.

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1509

Role of the Metalloproteinase ADAM-8 in the Regulation of the Inflammatory Response. Jason P. McMorrow, Ursula Fearon, Douglas J. Veale, Oliver M. FitzGerald and Evelyn P. Murphy. 1St Vincent’s University Hospital, Dublin, Ireland, 2University College Dublin, Dublin, Ireland

ADAM (a disintegrin and metalloproteinase domain) proteins are a family of transmembrane proteases with heterogeneous functions and expression profile. One of its members, ADAM-8 is constitutively present at both cell surface and intracellular granules levels in human neutrophil, and it has been implicated in the L-selectin shedding. However, the potential role of this metalloproteinase in the regulation of other “sheddable” proteins involved in the initial phase of the inflammatory response such as PSGL (P-selectin glycoprotein ligand)-1, had not been investigated.

Objective: To study the capability of ADAM-8 to process the ectodomain of PSGL-1 in human neutrophils.

Methods: In this study we have used human peripheral blood neutrophils from healthy donors, HL-60 cells (human promyelocytic leukemia cells) and CEM (T-lymphoblastic leukemia cell line). The association PSGL-1/ADAM-8 was studied by co-immunoprecipitation assays in HL60 cells. The membrane and intracellular expression of these two proteins in neutrophils was assessed by flow cytometry and confocal immunofluorescence microscopy. Supernatant concentration of PSGL-1 was determined by ELISA. Native and catalytically inactive ADAM-8 was expressed in CEM line (not possess endogenous ADAM-8) by nucleofection. PSGL-1 function was evaluated in a flow chamber by the dynamic behavior of CEM cells preincubated with termolysin-activated recombinant ADAM-8 over a P-selectin-coated surface.

Results: Both confocal microscopy studies and co-immunoprecipitation assays showed the association ADAM-8/PSGL-1 in human neutrophils and HL60, respectively. Pull-down assays established that the binding capacity of ADAM-8 to PSGL-1 was lost if cytoplasmic tail of PSGL-1 was truncated before amino acid 18. Incubation of human neutrophils with thermolysin-activated recombinant soluble ADAM-8 resulted in PSGL-1 shedding assessed by ELISA respect to cells incubated with inactive soluble ADAM-8 (t-student, p < 0.05). In addition, CEM cells transfected with native ADAM-8 showed a reduction in PSGL-1 surface expression (by flow cytometry) and a decrease in the number of cells that roll on recombinant P-selectin (in flow chamber) respect to cells transfected with a catalytic-inactive ADAM-8 (t-student, p < 0.05).

Conclusions: Both the membrane and soluble form of ADAM-8 are able to regulate the PSGL-1 and L-selectin surface expression in human neutrophils. All these data support a potential relevant role for ADAM-8 in the recruitment of neutrophils into tissues during the inflammatory response.

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ACR Poster Session C
Cytokines, Mediators, Gene Regulation II
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1510

In Vitro Hypoxia-Induced Mitochondrial Genome Mutagenesis and Dysfunction. Monica Binicică, Edward Fox, Chin T. Ng, Wei Gao, Ursula Fearon, Douglas Veale and Jacintha O’Sullivan. 1Department of Pathology, University of Washington, Seattle, WA, 2Translation Research Group, Dublin Academic Medical Centre, St. Vincent’s University Hospital, Dublin, Co. Dublin, Ireland

Background: Hypoxia is characterized by an inadequate supply of molecular oxygen and has been associated with increases in reactive oxygen species (ROS) production. O2 sensing and ROS source in response to hypoxia is though to be mediated by Electron Transport Chain, hence mitochondrial genome is highly susceptible to attack by oxygen radicals. Oxidative stress is postulated as a primary source of mitochondrial DNA mutations (mtDNA)

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and clonally expanded mitochondrial mutagenesis has been detected in patients with rheumatoid arthritis. In this study we examine whether in vitro hypoxia induces mitochondrial dysfunction resulting in mitochondrial genome mutagenesis and we examine the role of HIF-1x and NF-kB in mediating these events.

**Method:** K4 cells (immortalised human synoviocyte cells) were exposed to normoxia (21%) or hypoxia (1%). Levels of mtDNA point mutations were quantitatively evaluated using Random Mutation Capture assay. Intracellular ROS and mitochondrial membrane potential (MMP) were measured using fluorescent molecular probes. Markers of oxidative DNA damage (8-oxo-dG) and lipid peroxidation (4-HNE) were determined in cell culture supernatants by ELISA. Protein expression of HIF-1α and NF-kB were assessed by Western blots. The effect of antioxidant treatment on mitochondrial mutagenesis and dysfunction were examined by culturing cells under normoxic (21%) and hypoxic (1%) conditions in the presence or absence of manganese superoxide dismutase (MnSOD) or N-Acetyl Cysteine (NAC) or a hydroxylase inhibitor dimethyloxaloylglycine (DMOG).

**Results:** Hypoxia significantly increases the level of mitochondrial DNA point mutations (p < 0.05), ROS production (p < 0.05) and MMP (p < 0.01) in comparison to normoxia. Treatment with MnSOD, NAC and DMOG significantly reduced hypoxia-induced mtDNA mutation, intracellular ROS production and attenuated MMP hyperpolarization (all p < 0.05). Levels of 8-oxo-dG and 4-HNE were significantly higher in K4 supernatants exposed to hypoxia (p < 0.0002 and p < 0.0005 respectively) than to normoxia and cell stimulation with MnSOD, NAC and DMOG suppressed hypoxia secretion of these oxidative stress markers (all p < 0.002). MnSOD, NAC and DMOG stabilized HIF-1α protein accumulation under hypoxia. There was no difference in the levels of NF-kB protein expression between all oxygen and antioxidant treatment groups.

**Conclusion:** Hypoxia drives mitochondrial dysfunction manifested by ROS overexpression and altered MMP. Hypoxia-induced mtDNA mutations are a source of elevated oxidative damage indicating ROS as a primary source of mitochondrial mutagenesis. Early detected oxidative stress and mitochondrial genome instability are transient and can be rescued after treatment with MnSOD, NAC and DMOG. Hypoxic HIF-1α activation after antioxidants and hydroxylase inhibitor treatment may contribute to gene expression that prevents mtDNA damage following oxidative stress thus HIF-1α antagonizes hypoxia-induced mitochondrial mutagenesis.

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### 1511

**Allograft Inflammatory Factor-1 Facilitates the Migration of Fibroblasts and Has a Correlation with the Pathogenesis of Skin Fibrosis in a Murine Model of a Murine Model of Scleroderma-like Disease.**

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Allograft inflammatory factor (AIF)-1 is an IFN-γ-inducible, Ca²⁺-binding EF-hand protein that is encoded within the HLA class III genomic region in the direct vicinity of TNF-α. AIF-1 has been identified in chronic rejection of rat cardiac allografts and is thought to be involved in the immune response. We previously showed that AIF-1 was strongly expressed in synovial tissues in rheumatoid arthritis and that rAIF-1 increased the IL-6 production of synoviocytes and peripheral blood mononuclear cells. Recently, the expression of AIF-1 has been reported in systemic sclerosis (Ssc) tissues, whose clinical features and histopathology are similar to those of chronic graft-vs-host disease (GVHD). To clarify the pathomechanism of fibrosis, we underwent bone marrow transplantation and made sclerodermatous (Scl) GVHD mice. We examined the expression and function of AIF in Scl GVHD mice on day 21 after BMT. We demonstrated that immunoreactive AIF-1 and IL-6 were significantly expressed in infiltrating mononuclear cells and fibroblasts in thickened skin of Scl GVHD mice compared with control. The immunohistochemical findings were confirmed by Western blot analysis. Wound healing assay also revealed that rAIF-1 increased the migration of normal human dermal fibroblasts (NHDF) directly, but cell growth assay didn’t showed rAIF-1 increased the proliferation of them. These findings suggest that AIF-1, which can induce the migration of fibroblasts and the production of IL-6 in affected skin tissues, is an important molecule promoting fibrosis in GVHD. Although the biological function of AIF-1 has not been completely elucidated, AIF-1 can induce IL-6 secretion on mononuclear cells and fibroblast chemotaxis. AIF-1 may accordingly provide an attractive new target for anti-fibrotic therapy in SSc as well as Scl GVHD.

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**1512**

**Bach1 Regulates Heme Oxygenase-1 Expression of Human Monocytes in Response to LPS: Implication in Behcet’s Disease.**

Mitsuhiro Takeno, Takuya Miyazaki, Yohei Kirino, Sei Samukawa, Maasa Hama and Yoshiaki Ishigatsubo. Yokohama City University Graduate School of Medicine

**Background:** Heme oxygenase (HO)-1 is an inducible anti-inflammatory protein which regulates innate immune functions and involved in pathogenesis of various rheumatic diseases. We have found that increased TLR4 expression is associated with defective HO-1 expression in leukocytes from Behcet’s disease patients, leading to an augmentation of inflammatory responses. However, effects of lipopolysaccharide (LPS), a TLR4 ligand, on HO-1 expression have been controversial in mononcytic cells: both enhancing and reducing effects have been reported. We here investigated the regulatory roles of the transcriptional repressor Bach1 and the activator Nr2f2 in HO-1 expression of human monocytes in response to LPS.

**Methods:** Peripheral blood mononuclear cells (PBMC) were isolated from healthy donors. Expressions of HO-1, Bach1, and Nr2f2 were semiquantitatively analyzed by immunoblotting at the protein level nd real-time PCR techniques at the mRNA level, respectively. Transcriptional activity of HO-1 gene was determined by luciferase assay. The binding of Bach1, and Nr2f2 to Nrf2-recognition elements (MARE) was determined by chromatin immunoprecipitation assays.

**Results:** Immunoblotting studies showed that freshly isolated peripheral monocytes expressed substantial amounts of HO-1, along with nuclear Nr2f2 and cytoplasmic Bach1. In contrast, HO-1, Nr2f2 and Bach1 proteins were little expressed in unstimulated human myelogenous leukemic cell lines such as U937. In response to LPS, HO-1 was reduced in primary monocytes, but upregulated in U937 cells. The differences were associated with distinct kinetics of Nr2f2 and Bach1. Immunoblotting studies in cytoplasmic and nuclear fractions, and chromatin immunoprecipitation assays revealed that, in peripheral monocytes, Nr2f2 predominantly bound to MARE, the upstream enhancer lesions of HO-1 gene, while LPS promoted nuclear translocation of Bach1 and preferential bindings of Bach1 to MARE. On the other hand, Bach1 was highly bound to MARE in U937 cells under a resting condition, whereas treatment with LPS reversed the binding proportions of the two proteins. Thus, HO-1 expression level is regulated by the binding proportion of Nr2f2 and Bach1 to MARE. Furthermore, the LPS-mediated HO-1 reduction was abrogated by Bach1 siRNA.

**Conclusions:** The present study demonstrates that LPS suppresses HO-1 expression through nuclear translocation of Bach1 in human peripheral monocytes and suggests that Bach1 is a possible therapeutic target in inflammatory diseases including Behcet’s disease.

**Disclosure:** M. Takeno: None; T. Miyazaki: None; Y. Kirino: None; S. Samukawa: None; M. Hama: None; Y. Ishigatsubo: None.

**1513**

**BMS-582949 Is a Dual Action p38 Kinase Inhibitor Well Suited To Avoid Resistance Mechanisms That Increase p38 Activation in Cells.**

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**Purpose:** Multiple p38 kinase inhibitors (p38i) have been reported to show tachyphylaxis (only transient benefit) in clinical studies of RA, suggesting the induction of resistance mechanisms. By contrast, BMS-582949 has demonstrated clinical efficacy in a PhIIA RA study without tachyphylaxis. Potential kinase resistance pathways in cells and the effect of BMS-582949 on such pathways were investigated to better understand the mechanism by which BMS-582949 avoids tachyphylaxis.

**Methods:** The phosphorylation of p38 in the cells was measured with phospespecific antibodies to measure effects on p38 activation. Cells were
Results: BMS-582949 was found to inhibit p38 activation in cells, as measured by phosphorylation of p38. Furthermore, BMS-582949 treatment of cells in which p38 had been activated by LPS rapidly reversed p38 activation as shown by loss of phosphorylation of p38. BMS-582949 is therefore a dual action p38 kinase inhibitor, inhibiting both p38 kinase activity and p38 activation in cells. By contrast, SCIO-469, a p38i that was reported to show tachyphylaxis, did not inhibit p38 activation in cells. In gene expression analysis of cells treated with SCIO, all changes observed for p38 pathway components were consistent with cellular feedback to drive p38 activation more strongly. Treatment of either hepatocytes or monocyes with p38i alone resulted in up to 80% increased MKK6 expression, and treatment of monocyes with p38i plus LPS (compared to LPS alone) resulted in increased expression of several upstream activating kinases and p38a itself, while decreasing expression of MKP-1 which dephosphorylates and deactivates p38. X-ray crystallography revealed that BMS-582949 binding to p38a results in a conformational change of the activation loop which is phosphorylated by upstream kinases, whereas SCIO-469 had little effect. BMS-582949 may therefore inhibit phosphorylation of p38 by upstream MKK by inducing a less accessible conformation of the activation loop.

Conclusions: BMS-582949 acts as a dual action kinase inhibitor in cells, inhibiting both p38 kinase activity and activation of p38. Treatment of cells with a variety of p38 inhibitors resulted in changes expected to drive cellular p38 activation more strongly. Increasing activation of p38 may be a resistance pathway by which cells can overwhelm effects of p38 inhibitors that only inhibit p38 kinase after it is activated. By blocking activation of p38 kinase, BMS-582949 appears to be well suited to resist such cellular responses that would drive p38 activation more strongly.


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Both Insulin Receptor and Nampt Activity Are Implicated in Visfatin/ Nampt Induced PGE2 Synthesis in Articular Chondrocytes. Marjolaine Gosset1,2, Francis Berenbaum2, Colette Salvat2, Alain Sautet2, Martin Holzenberger3 and Claire Jacques4. 1Faculty of Medicine P&M Curie, UR4 Paris Universitas, Paris, France, 2Faculty of Medicine P&M Curie, Paris, France, 3Inserm U893, Paris, France, 4UR4 Paris Universitas, Paris, France

Purpose: We recently reported on visfatin expression in articular chondrocytes and its role in prostaglandin (PGE2) release in cartilage. However, the signaling pathways of visfatin remain unclear. Visfatin was first reported as a protein that binds to the insulin receptor (IR). More recently, a nicotinamide phosphoribosyltransferase (NAMPT) enzymatic activity involved in nicotinamide mononucleotide (NMN) production, a precursor of the cofactor NAD+, has been demonstrated. The aim of this study was to decipher the signaling pathways implicated in visfatin induced PGE2 release in chondrocytes.

Methods: IR expression from OA human chondrocytes and immature murine articular chondrocytes (iMACs) were assessed using real-time RT-PCR, immunoblotting and immunocytofluorescence. A highly specific monoclonal antibody raised against IR was used. Phosphorylation of IR and Akt were analyzed using Western Blot. IR tyrosine kinase activity was inhibited by clonal antibody raised against IR. Phosphorylation of IR and AKT was assessed using Western Blot and real-time RT-PCR, immunoblotting and immunocytofluorescence. A highly specific monoclonal antibody raised against IR was used. Phosphorylation of IR and AKT were analyzed using Western Blot. IR tyrosine kinase activity was inhibited by clonal antibody raised against IR

Results: Visfatin is known to bind to, and to activate IR in various cell types. However, IR is not considered to be usually present on chondrocytes. We therefore tested the implication of IR-1, a close homologue to IR, in visfatin signaling. When stimulated with 5μg/ml visfatin, IR-1+/- chondrocytes unexpectedly exhibited higher PGE2 release than IR-1+/- controls (228±4 compared to 86±29 pg/ml, p<0.05), ruling out a direct role of IR-1 in the visfatin effect. Moreover, visfatin (5μg/ml – 24h) induced PGE2 release in iMACs treated with 2 and 5μg/ml IR-1 blocking antibody compared to control cells (respectively a 1.3 and a 1.9 fold, p<0.05 – visfatin treated cells released 110±16 pg/ml PGE2, n= 3). (2) IR was expressed in cultured human chondrocytes from healthy (n=3) and OA patients (n=7) and in iMACs (n=3). (3) Insulin (100nM - 24h) did not trigger PGE2 release in iMACs (control: 118±68 pg/ml and insulin-stimulated cells: 130±79 pg/ml, n=3, NS). (4) Dose-responses of insulin from 0 to 1μM was performed in term of phosphorylation of IR and Akt. Moreover, insulin (100nM) from 0 to 60min triggered IR and Akt phosphorylation. (5) Blocking IR expression using HNMPA-AM(3) and a siRNA strategy was used to investigate the role of IR in visfatin-induced PGE2 release (54% decrease, n=3, p<0.05). Moreover, blocking IR expression by siRNA inhibited visfatin-induced PGE2 release (5μg/ml visfatin+IR siRNA2: 930±216 pg/ml versus visfatin + IR siRNA1: 184±515 pg/ml and visfatin + IR siRNA2: 930±216 pg/ml corresponding to a 48% and 74% decrease respectively, n=2, p<0.05). (6) Inhibition of the NAMPT activity of visfatin using APO866 from 0 to 1μM gradually induced a decrease in PGE2 release up to 32% (visfatin treated cells released 95±30 pg/ml PGE2, n=3, p<0.05). Conclusions: In chondrocytes, visfatin exerts pro-inflammatory events by both activation of its cognate receptor and Nampt activity.

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Comparison of IL-17F and IL-17A Effects and Signaling in Human Rheumatoid Arthritis Synoviocytes. Arnaud Hot, Saloua Zrioual, Anne Tournadre, Vanina Lenief and Pierre Miossec. Immunogenomics and Inflammation Research Unit and Department of Immunology and Rheumatology, Hospital Edouard Herriot, Lyon, France

Objective: IL-17A is implicated in rheumatoid arthritis (RA) pathogenesis; however the contribution of IL-17F remains to be clarified. Using microarrays and gene specific expression assays, we compared the effects of IL-17A versus IL-17F on gene expression and signaling in human RA synoviocytes.

Methods: IL-17A and IL-17F expression was studied in OA and RA synoviocytes by immuno-histochemistry. The comparison between IL-17A and IL-17F stimulatory effect on RA synoviocytes was assessed at the protein level by ELISA and at the mRNA level by microarrays (Affimetrix U133 +2) and real-time RT-PCR. IL-17RA and IL-17RC inhibition was achieved by small interfering RNA (siRNA). Western blotting, qRT-PCR, and DNA binding assay were used to evaluate mitogen-activated protein kinase (MAPK), activator protein 1 (AP-1) and nuclear factor kappa B (NF-κB) expression and activation. TNFRII expression was studied by real-time RT-PCR and immunofluorescence, and neutralizing antibody was used to analyse its contribution to CCL20 secretion.

Results: IL-17A and IL-17F were detected in plasma cell like cells in RA but not OA synovioum. In microarrays, IL-17A and IL-17F alone had very similar but not identical regulatory effects, IL-17F being less active. Indeed, IL-17A was more potent to induce IL-6 or IL-8 secretion than IL-17F, which was inactive alone. Both cytokines induced a rather similar expression pattern in the presence of TNF-α. Based on a cooperation index, 130 and 203 genes were synergistically induced by IL-17A or IL-17F plus TNF-α, respectively. Among these, the new target genes CXC4R, LPL and IL-32 were validated by real-time RT-PCR. Virtually all IL17A and IL17F inducible genes were dependent on NF-κB activation, whereas a minor number was modulated by p38. IL-17A induced activation of all three MAPK (ERK, p38 and JNK) and downstream transcription factors AP-1 and p65 NF-κB. IL-17F was less potent but induced activation of p30 NF-κB, IL-17A and IL-17F induced TRAF 6 but not MyD88. Inhibition of either IL-17RA or IL-17RC expression via siRNA led to near complete abrogation of IL-6 expression mediated by IL-17A and the combination of IL-17F and TNF-α. IL-17A and IL-17F upregulated TNFRII expression, but had no effects on TNFRI, IL17RA or IL17RC. TNFRII blockade inhibited the synergistic induction of CCL20 by IL-17A or IL-17F and TNFα.

Conclusion: IL-17A and IL-17F are both expressed in RA synoviotes. In the presence of TNF-α, they induced very similar but not identical pattern expression pattern in RA synoviocytes. The enhanced expression of TNFRII contributes to the synergistic effect of IL-17A and F with TNF-α. Targeting IL-17F could be a promising treatment of RA.

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Down-Regulation of Pyrin Promotes Up-Regulation of the Anti-Apoptotic Gene, BCL2, Via the Signal Transducer, gp130, and Leads to the Activation of the PI3K/Akt Pathway. Geryl M. Wood1, James Balow, Jh2, Hong-Wei Sun3, Ivona Aksentijevich2, Jae Jin-Chae2, Nitza Shoham1 and Daniael L. Kastner3.1Allergy Immunology Laboratory, Mtir Hospital, Kfar-Saba, Israel, 2Biodata Mining and Discovery, Office of Science and Technology, National Institutes of Health, NIAMS, 3Laboratory of Clinical Investigation, National Institutes of Health, NIAMS, Laboratory of Clinical Investigation, National Institutes of Health, Bethesda, MD

Purpose: Familial Mediterranean fever (FMF) is a periodic fever syndrome characterized by episodes of self-limited fever and localized inflammation. The gene causing FMF, MEFV, encodes a protein, pyrin, which is expressed in myeloid cells and in the myeloid leukemia cell line, THP-1. Identification of several pyrin-interacting proteins has led to the conclusion that pyrin participates in at least three cellular pathways that are connected to inflammation: cell death, cytokine secretion and cytoskeletal signaling.

Methods: RNA interference (RNAi) technique was employed to compare gene expression profiles between the human myeloid leukemia cell line, THP-1, expressing endogenous pyrin (scrambled control, SC) and cells in which the gene had been knocked down (siMEF1). Affymetrix cDNA microarray analysis was used to identify potential novel pyrin-dependent pathways. Western blot and qRT-PCR analyses were used for validation. Flow cytometry and kinase inhibition assays were used to study functionality and mechanism.

Results: Among our differentially expressed genes, we identified two up-regulated genes involved in cell survival, BCL2 and gp130. Consistent with these findings, pyrin truncated mice showed impaired macrophage apoptosis after IL4/LPS stimulation, independent of IL1b. Western blot and qRT-PCR analyses using independent samples, confirmed the THP-1 microarray data. Western blots comparing BCL2 expression in PBMCs from healthy controls and FMF patients revealed a significantly higher level of BCL2 in FMF patients compared to controls. These data were in agreement with the Bcl2 expression found in CD11b+ cells from knock-in mice expressing human mutations. The influence of pyrin knockdown on apoptosis was explored. Inducing apoptosis after staurosporine stimulation showed 1.8-fold less apoptosis in siMEF1 cells compared to SC. To examine the involvement of gp130 in siMEF1 up-regulation of BCL2, we co-transfected siRNA for gp130 and MEFV. We demonstrate reduction in BCL2 after the addition of siRNA for gp130 compared to siMEF alone. Since the PI3K/Akt survival pathway is activated thru gp130 signaling, we investigated this pathway as a possible mechanism of action. Western blot detection showed no difference in expression of PI3K phosphorylation between SC and siMEF1, in contrast to Akt, which revealed increased levels of phosphorylation in siMEF1 treated cells compared to SC. Also, the PI3K/Akt inhibitor LY294002 was able to reduce BCL2 up-regulation by siMEF1 with further reduction evident when Akt IV, a specific Akt inhibitor was employed.

Conclusion: These data support the hypothesis that knocking down pyrin in myeloid cells down-regulates apoptosis in part via the gp130 receptor, which activates the PI3K/Akt pathway and leads to an increase in BCL2 expression. It suggests that in some cases, the human mutations may function like the knocked down system.

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Effect of the PEG Component of Certolizumab Pegol on Calcium Flux in Cellular Systems. Gianluca Fossati1 and Andrew Nesbitt1. 1New Medicines, UCB, Slough, Berkshire, United Kingdom, 2New Medicines, UCB, Slough, UK

Background: Certolizumab pegol (the only PEGylated Fab alpha-TNF antagonist) has a very low incidence of injection site pain (ISP) in all clinical studies. It has been hypothesized that this could be due to inhibition of mast cell degranulation by the PEG component of CZP. Mast cells (from human peripheral blood monocytes) could be involved in mediating ISP as they are present at high numbers in the skin and can rapidly secrete many inflammatory mediators in preformed granules. Changes in Ca2+ flux from intracellular stores or by influx from outside the cell are primary indicators of cell activation and when mast cells degranulate, this is preceded by a calcium flux into the cell. PEG has been shown to bind metal ions (in particular calcium ions) and, therefore, the aim of this study was to determine if PEG could inhibit calcium flux in a cellular system.

Methods: Peripheral blood monocytes, positively isolated using MACS beads, were incubated for 30 min with the fluorophore Fluo-4 which changes its fluorescence emission when it chelates calcium. Calcium flux was measured using flow cytometry by detecting the Fluo-4 emission at 515–535 nm. Ionomycin was added at 2 μg/mL and the emission measured over a 4-min period relative to background, which was assessed for 1 min prior to ionomycin addition. The effect of a range of concentrations of the 40 kDa PEG component of CZP on calcium flux induced by ionomycin was assessed. In addition, the effect of PEG on an ionomycin-induced calcium flux in cultured mast cells was determined by a similar method except that the flux was measured using a fluorometer.

Results: Ionomycin caused a dramatic flux of calcium in the monocytes. PEG caused a dose-dependent inhibition of calcium flux in these cells over a range of concentrations from 0.01 μg/mL to a minimum of 40 μg/mL. This is 15 min prior to ionomycin addition. The effect of PEG on ionomycin-induced calcium flux in cultured mast cells was determined by a similar method except that the flux was measured using a fluorometer.

References:

1518 Expression of the Wnt Inhibitor sFRP-1 in Synovial Fibroblasts Is Regulated by the Histone Methyltransferase EZH2. Michelle Trenkmann1, Matthias Brock2, Renate E. Gay3, Christoph Kolling4, Rudolf Speich5, Beat A. Michel6, Steffen Gay7 and Lars C. Huber8. 1Center of Experimental Rheumatology, University Hospital Zurich/Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, 2Center of Experimental Rheumatology, University Hospital Zurich/Zurich Center of Integrative Human Physiology (ZIHP), Switzerland, 3Center of Experimental Rheumatology, University Hospital Zurich/Zurich Center of Integrative Human Physiology (ZIHP), Switzerland, Department of Internal Medicine, University Hospital Zurich, Switzerland, 4Department of Internal Medicine, University Hospital Zurich, Switzerland, 5Schulthess Clinic, Zurich, Switzerland

Background: Methylithione of histone 3 lysine 27 (H3K27) by the histone methyltransferase EZH2 is associated with silencing of affected gene promoters. We have previously reported that EZH2 expression is increased in rheumatoid arthritis synovial fibroblasts (RAF) compared to osteoarthritis (OA) SF and further induced by TNF-α. Here we identified secreted frizzled-related protein (sFRP)-1, an inhibitor of the Wnt signalling pathway, as a specific target gene of EZH2 in SF.

Methods: sFRP-1 (n=5) were transfected with a vector containing the EZH2 coding sequence or an siRNA targeting EZH2. After 72h and 96h, cells were analyzed for SFRP1 expression at mRNA (by quantitative real-time PCR) and protein levels (by ELISA). Constitutive and TNF-α stimulated expression of SFRP1 was measured in OASF and RAF for both mRNA and protein. To investigate the level of histone methylation within the SFRP1 gene promoter in RAF (n=10) and OASF (n=7), chromatin immunoprecipitation (ChIP) was performed by using antibodies specific for H3, H3K4me3 and H3K27me3.

Results: Overexpression of EZH2 in RAF resulted in a reduction of SFRP1 mRNA (15±17%; p=0.086 after 72h; 18±9%; p=0.05 after 96h, respectively). Secretion of sFRP-1 protein decreased from 689±216 pg/mL to 507±56 pg/mL (p=0.01) after 72h and from 1095±101 pg/mL to 830±150 pg/mL (p=0.05) after 96h. Conversely, silencing of EZH2 in RAF led to an increase of SFRP1 mRNA level by 15±12% (p<0.005) after 72h and of 15±35% (p=0.38) after 96h.

Conversely, silencing of EZH2 in RAF led to an increase of SFRP1 mRNA level by 15±12% (p<0.005) after 72h and of 15±35% (p=0.38) after 96h.

The constitutive expression of SFRP1 mRNA was strongly reduced in RAF by 86% as compared to OASF (delta Ct RAF: 7.1±2 (n=15), OASF: 4.5±1.7 (n=12), p<0.005). These findings could be confirmed on the protein
level by ELISA (566±354 pg/ml for RASF. 1285±845 pg/ml for OASF, p<0.01) and Western blot (n=10 and 7). Stimulation with TNF-α significantly reduced SFRP1 mRNA after 24h and 48h in RASF (by 56±13% and 85±6%, p<0.0001, n=6) and OASF (by 48±14% and 82±7%, p<0.0001, n=7). ChiP analysis revealed that the promoter of SFRP1 is trimethylated at H3K27 in SF (H3K27me3/H3 ratio RASF: 0.45±0.36, OASF: 0.22±0.08, p<0.12). Conversely, the H3K4me3/H3 ratio, which is a mark of active gene transcription, was reduced in RASF (0.31±0.27) compared to OASF (0.66±0.32, p<0.05). The mRNA expression of SFRP1 correlated positively with occupation of the activating H3K4me3 (R=0.71, p<0.0001) and negatively with occupation of the repressing H3K27me3 mark (R=0.4, p<0.01) in its promoter.

Conclusion: Our data strongly indicate that EZH2 regulates the expression of the Wnt inhibitor sFRP-1 in SF. We show that the levels of sFRP-1 are constitutively decreased in RASF and further reduced by stimulation with TNF-α. Wnt signalling has been shown to be activated in RASF and to contribute to the invasive and aggressive behaviour of these cells. We provide here the first evidence that this aberrant Wnt activation appears to be, at least in part, due to an epigenetic dysregulation of its inhibitor sFRP-1.

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Fms-Like Tyrosine Kinase 3 Ligand (Flt3L) Levels Are Elevated in Arthritis: Role of Flt3L in Regulating Monocyte Migratory Pattern in RA, Inès Ramos1, Ana Oliveira2, Geurt Schilders3, Saida Aarrass4, Cristina Lebre3 and Paul P. Tak1. 1Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, 2Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, 3Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands

Background: Fms-like tyrosine kinase 3 ligand (Flt3L) is a potent endogenous growth factor for myeloid (m)DC and plasmacytoid (p)DC. Its administration to mice and humans leads to dramatic increases of various DC subsets while Flt3L administration to mice and humans leads to dramatic increases of various DC subsets while Flt3L is released by synovial fibroblasts into the synovial fluid and its expression is upregulated on FLS by ELISA, with a significant (p<0.0001) increase in CD13 in RA synovial fluids (119±121.6 ng/ml) when compared to OA (646.1±46.64 ng/ml). Similar to previously published data we also found a significant difference in CD13-type enzymatic activity between RA and OA synovial fluids (3402±239.6 nmoles of substrate cleaved per hour per ml of synovial fluid versus 2250±93.18 nM/hr, p<0.0001). This activity was depleted by 1D7 immunoprecipitation. Recombinant CD13 was chemotactic for T cells.

Conclusion: CD13 is released by synovial fibroblasts into the synovial fluid and its expression is upregulated on FLS by IL-17. These findings suggest a mechanism by which IL-17 may enhance synovial inflammation in RA independent of TNFα. We have shown that the CD13 protein is present in significant amounts and accounts for most of the L-leu-AMC cleavage activity in synovial fluids. These data support the concept of CD13 as a multifunctional pro-inflammatory mediator that can serve as a T cell chemoattractant in the RA joint.

Disclosure: R. Morgan: None; J. Endres: None; D. A. Fox: None.

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Functional Expression of CD13/Aminopeptidase N by RA Synovial Cells In Vitro and In Vivo. Rachel Morgan, Judith Endres and David A. Fox. University of Michigan

Purpose: Aminopeptidase N (CD13, EC 3.4.11.2) is a metalloproteinase expressed on and secreted by myeloid cells and fibroblasts. Previously published data has documented increased CD13-related enzymatic activity in RA synovium compared to OA, and has proposed a role for CD13 as a T cell chemoattractant. The mechanisms whereby T cells become localized to the synovial lining and contribute to synovial inflammation and joint destruction remain incompletely understood. While CD13 has been identified on synovial fibroblasts (FLS), ELISA assay of CD13 in synovial fluid, serum or culture supernatants has not yet been reported. The purpose of this study was to critically examine CD13 expression and function in RA synovium.

Method: Novel monoclonal antibodies (mAb) were developed from splenocytes of mice immunized with an RA FLS line that had been treated with IL-17. Hybridoma supernatants were screened by flow cytometry to detect cell surface structures upregulated by IL-17 but not TNF. This approach yielded one mAb, termed 591.D7,34, which was used to immunofluorometry purify a protein that was identified as CD13 by amino acid sequencing. ID7 and another anti-CD13 mAb, WM15, were then used to create a sandwich ELISA for CD13. CD13 enzymatic activity was measured in parallel by cleavage of L-Leucine 7-amido-4-methyl coumarin hydrochloride (L-leu-AMC) to release the fluorescent molecule AMC.

Results: We detected substantial amounts of CD13 in synovial fluids and synovial fibroblast cell lysates and culture supernatants by ELISA, with a significant (p<0.0001) increase in CD13 in RA synovial fluids (119±121.6 ng/ml) when compared to OA (646.1±46.64 ng/ml). Similar to previously published data we also found a significant difference in CD13-type enzymatic activity between RA and OA synovial fluids (3402±239.6 nmoles of substrate cleaved per hour per ml of synovial fluid versus 2250±93.18 nM/hr, p<0.0001). This activity was depleted by 1D7 immunoprecipitation. Recombinant CD13 was chemotactic for T cells.

Conclusion: CD13 is released by synovial fibroblasts into the synovial fluid and its expression is upregulated on FLS by IL-17. These findings suggest a mechanism by which IL-17 may enhance synovial inflammation in RA independent of TNFα. We have shown that the CD13 protein is present in significant amounts and accounts for most of the L-leu-AMC cleavage activity in synovial fluids. These data support the concept of CD13 as a multifunctional pro-inflammatory mediator that can serve as a T cell chemoattractant in the RA joint.

Disclosure: R. Morgan: None; J. Endres: None; D. A. Fox: None.
Lastly, adhesion studies show that stretching of dermal fibroblast monolayers overnight in the presence of exogenous recombinant osteopontin results in a 2.3-fold increase in the binding of TIP-1 human monocytes (p<0.0001). Overall, we propose that stretch-induced expression of CD44v7 over joints, in concert with IFN-γ induction of osteopontin, provides a unique molecular signature of Gottron’s papules in DM and may contribute to their pathogenesis.

Disclosure: J. Kim: None; V. P. Werth: None.

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Identification of the NR4A Family of Orphan Nuclear Receptors as Mediators of Adenosine A2A Receptor Activation. Jason P. McMorrow1, Evelyn P. Murphy2 and Bruce N. Cronstein1. 1New York Univ Med Ctr, New York, NY, 2University College Dublin, Dublin, Ireland

Background: The effects of adenosine signalling on the regulation of inflammation suggest that targeting adenosine receptor activation/inactivation could have important therapeutic implications in wound healing and inflammatory disease. In recent studies we report that adenosine, acting at A2A receptors, plays an important role in bleomycin-induced dermal fibrosis, a model for scleroderma. Activation of A2A receptors on cultured human dermal fibroblasts directly stimulates collagen production. What remains to be elucidated are the cell-specific signal transduction events and the transcriptional mediators that act to promote adenosine receptor-mediated responses during these processes.

Aim: To establish cell-specific effects of a selective A2A receptor agonist, CGS-21680, on the expression of the NR4A family of transcription factors in the presence of signaling inhibitors and inflammatory stimuli.

Methods: THP-1 monocyte cells were differentiated to macrophages by stimulation with PMA (10 ng/mL) for 48 h. Normal human dermal fibroblasts (NHDF) and macrophage cells were treated for 1 hour with medium or the selective adenosine A2A receptor agonist, CGS-21680 (10-8-10-6 M), in the presence or absence of the A2A receptor antagonist, ZM241385 (10-6 M). In some experiments NHDF were pretreated with the MEK inhibitor, U-0126 or the p38 inhibitor, SB202190 for 1 hour before treatment with CGS-21680. Protein and total RNA was harvested and NR4A levels measured by western analysis and real-time PCR.

Results: Treatment of human macrophage-derived THP-1 cells and dermal fibroblast NHDF cells with increasing concentrations of CGS-21680 robustly induces the expression of all three NR4A family members (NR4A1, 2 and 3) in a time dependent manner. The temporal effects of CGS-21680 on NR4A transcription are abolished in cells pretreated with the A2A antagonist ZM241385 (1 μM) and blocked by protein inhibitors directed against PAK and MEK1/2. In THP-1 cells, co-treatment with CGS-21680 and LPS or IL-4 resulted in significantly (p<0.005) enhanced NR4A1, 2 and 3 transcription. In contrast, minimal effects on NR4A expression are measured in cells co-treated with TGF-β or IL-1. Furthermore, in LPS- and IFN-γ-treated NHDF cells, CGS-21680 effects on NR4A1, 2 and 3 expression is significantly reduced while, in cells co-treated with TGF-β, levels remain unchanged.

Conclusion: This study identifies the NR4A family as novel transcriptional mediators downstream to adenosine A2A receptor activation. In addition, these data reveal that cytokine-specific effects on A2A receptor mediating signaling are cell-type dependent.

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1524
Increased Levels of Soluble Programmed Death Ligand 1 (sPD-1) and Its Soluble Ligand (sPD-L1) in Early Rheumatoid Arthritis Are Associated with Disease Activity and Progression. Simone R. Greisen1, Tue K. Rasmussen2, Kristian Stengaard-Pedersen2, Merete L. Hetland3, Kim Horslev-Petersen2, Malene Hvid4 and Bent Deleuran1. 1Aarhus University Hospital, Aarhus, Denmark, 2Copenhagen Univ Hosp Hvidovre, Hvidovre, Denmark, 3Institute of Medical Microbiology and Immunology, University of Aarhus and 2Department of Rheumatology Aarhus University Hospital, 8000 Aarhus C, Denmark, 4Institute of Medical Microbiology and Immunology, University of Aarhus, 8000 Aarhus C, Denmark, 5Institute of Medical Microbiology and Immunology, University of Aarhus, 8000 Aarhus C, Denmark and Department of Dermato-Venerology, Aarhus University Hospital, 8000 Aarhus C, Denmark, 6King Christian X Hospital for Rheumatic Disease, University of Southern Denmark, Graasten, Denmark

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease. Disturbance of the balance between immune modulatory and inflammatory factors results in joint inflammation progressing to destruction. The regulatory molecules Programmed Death 1 (PD-1) and its ligand (PD-L1), expressed by antigen presenting cells, are believed to negatively regulate T cell induced activation. They are both regulatory molecules Programmed Death 1 (PD-1) mainly expressed on inflammatory cells, synovial hyperplasia, and the destruction of the articular cartilage and bone in CIA group. ASIC1, ASIC2, and ASIC3 were markedly increased compared with those in control. The concentrations of anti-type II collagen antibody in CIA were significantly higher than those in control (P<0.05). Serum concentrations of TNF-α (P<0.005) and IL-6 (P<0.05) in CIA group were also increased. ERK pathway activation was noted by increased p-ERK expression.

Objective: To investigate the presence of sPD-1 and sPD-L1 in early RA patients and their correlation with clinical and radiographic progression as well as to the follicular CD4 T cells (TFH) cytokine IL-21 and dendritic cell associated cytokine IL-23.

Methods: In a longitudinal sample set of early RA patients (n=40, < 6 months’ disease) we measured plasma levels of sPD-L1 and sPD-1 by ELISA (R&D systems), at baseline (0 month) and after 9 months of treatment with methotrexate, and investigated for correlations with disease activity in 28 joints (DAS28), C-reactive protein (CRP), and total Sharp score (TSS). To remove heterophillic antibodies, heat aggregated goat IgG (25μg/ml) was added to buffers. Statistical correlations were assessed by Spearman’s rho, and data are expressed as median with IQR in parenthesis. In a transverse sample set (n=30) of chronic RA patients (>8 years of disease) we measured sPD-1 and sPD-L1 in plasma.

Results: In patients with early RA, plasma levels of sPD-L1 and sPD-1 were both significantly higher at 0 months than after 9 months of treatment. Treatment reduced sPD-L1 from 29.9 ng/ml (10.5–85.3) to 16.8 ng/ml (4.8–35.2), p<0.001 and sPD-1 from 421 pg/ml (40.0–2560.0) to 40.0 pg/ml (40.0–840.0), p<0.05. In chronic RA patients levels of sPD-1, but not sPD-L1 tended to be lower than in early RA patients. In early RA, the change in sPD-1 was associated with DAS28 at 9 months (r2=0.401, p=0.021), and TSS at 2 years (r2=0.468, p=0.02). No association to CRP was observed. Plasma levels of sPD-1 as well as sPD-L1 at 0 months strongly correlated (ASIC) isoforms have been identified and critical for development of secondary hyperalgia in peripheral sensory neurons innervating skin and muscle. This study was aimed to investigate the ASIC expression in mouse anti-type II collagen antibody-induced arthritis (CIA) and its association with ERK expression.

Methods: Mice were divided into 2 groups; control, CIA. Histological and X-ray assessment of arthritis were done. Measurement of type II collagen specific antibodies, TNFα, IL-17, and IL-6 were done. Both mRNA and protein levels of ASIC1, ASIC2, and ASIC3 were evaluated. We examined ERK/MAPK expression and its activation in the knee joint with or without CIA.

Results: Histological and X-ray assessment revealed increased infiltration of inflammatory cells, synovial hyperplasia, and the destruction of the articular cartilage and bone in CIA group. ASIC1, ASIC2, and ASIC3 were markedly increased compared with those in control. The concentrations of anti-type II collagen antibody in CIA were significantly higher than those in control (P<0.05). Serum concentrations of TNF-α (P<0.005) and IL-6 (P<0.05) in CIA group were also increased. ERK pathway activation was noted by increased p-ERK expression.

Conclusion: Taken together, these results implicate that increased ASIC involved in the joint pain in mice anti-type II collagen antibody-induced arthritis. Activation of ERK pathway could be related to ASIC expression in arthritis.

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Disclosure: E. P. Murphy: None; B. N. Cronstein: None.
with IgM-RF (PD-1; \( t_2 = 0.737, p = 0.0001 \)) and PD-L1; \( t_2 = 0.417, p = 0.016 \)). PD-1 at 0 months additionally correlated with anti-CCP antibodies \( t_2 = 0.515, p = 0.002 \). Interestingly, plasma levels of both IL-21 and IL-23 at 0 months correlated with plasma levels of sPd-1 and sPD-L1 at 0 months in early RA (all \( p < 0.05 \)).

**Conclusion:** The significantly elevated plasma levels of both sPD-1 and sPD-L1 in early RA patients, point to strong activation of antigen presenting cells and T cells in the initial phases of the disease. The fact that we observed association to core disease parameters as well as IgM-RF, anti-CCP antibodies and IL-21 and IL-23, further supports PD-1 pathways involvement in this central mechanism in RA. We believe that decrease in sPD-1 together with the unchanged presence of sPD-L1 in chronic patients compared with early RA supports a shift from T cells to antigen presenting cells as the predominant cell types, involved in perpetuating the inflammation in RA.

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**1525**

**Lack of IL-17RA Signaling Prevents Autoimmune Inflammation of the Joint and Give Rise to a Th2-Like Phenotype in Collagen-Induced Arthritis.** Anne-Marie Mus, Odilia Corneth, Patrick Asmawidajaja and Erik Lubberts, Erasmus MC. University Medical Center

**Introduction:** IL-17A plays an important role in collagen-induced arthritis (CIA). On the other hand, CIA developed normally in IL-17F deficient mice. This could be due to IL-17A that is still expressed in these mice. It has been shown that around 20% of the IL-17A deficient mice still develop marked collagen-induced arthritis with a somewhat lower severity than the mice. However, it is still not fully clear how important the role of the IL-17A is in CIA. On the other hand, CIA developed normally in IL-17F deficient mice. IL-17A that is still expressed in these mice. It has been shown that around 20% of the IL-17A deficient mice are still develop marked collagen-induced arthritis with a somewhat lower severity than the mice. However, it is still not fully clear how important the role of the IL-17A is in CIA.

**Objective:** To examine the role of the IL-17RA signaling in the development of CIA.

**Methods:** Since the IL-17RA deficient (IL-17RA/−/−) mice can not signal for IL-17A and IL-17F these mice were used in this study and were compared to control mice and the CIA resistant IL-23p19 deficient (IL-23p19/−/−) mice. All mice were immunized intra-dermally with chicken type II collagen (CII) in CFA at days 0 and 21. The arthritis incidence and severity were scored macroscopically. In a set of experiments, mice were given a third CII/CFA injection at day 50. At days 20, 34, and 69 sera was collected for CII-specific IgG1’s measurements by ELISA. In addition, at days 10 and 69, splenic CD4^+^ T cells were isolated and intracellular flow cytometry of different cytokines was performed.

**Results:** CIA-immunized control mice developed CIA from day 24 onwards with an incidence between 40–60%. As expected, the IL-23p19/−/− mice did not develop CIA. Interestingly, the IL-17RA/−/− mice were completely protected and did not develop CIA even after a third CII/CFA injection. In contrast to the low percentage of IL-17A/−/− CD4^+^ T cells in the IL-23p19/−/− mice, there was a significant increase in the percentage of these cells in the IL-17RA/−/− group compared to the control group at day 69. No significant difference was found in the percentage of IFN-gamma / CD4^+^ T cells between all three groups. Interestingly and in contrast to the IL-23p19 knockout mice, the IL-17RA deficient showed a Th2-like phenotype in splenic CD4^+^ T cells at day 69. No difference was noted for FoxP3 expression in the splenic CD4^+^ T cells between the three different mouse groups. Moreover, the CII-specific IgG2a levels in the sera of IL-17RA/−/− mice was significantly lower than the CIA control group at day 20 and lower although not statistically significant at day 69. At this latter time point, CII-specific IgG1 levels in the sera of IL-17RA/−/− mice was increased although not statistically significant compared to the control.

**Discussion:** These data revealed a critical role for the IL-17RA signaling in the development of autoimmune inflammation of the joint. Moreover, these data show a Th2-like phenotype in IL-17RA/−/− mice immunized with CIA, suggesting that IL-17 receptor signaling is involved in the suppression of Th2 cytokines in autoimmune collagen arthritis.

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**1526**

**Lower Expression of Fli-1 Leads to Decreased Inflammatory Cell Infiltration in the Kidneys from NZM2410 Mice.** Sarah Williams, Emmanuel Reyes-Cortes, Eva Karam, Eiji Suzuki, Gary S. Gilkeson and John Zhang, Med Univ of South Carolina, Charleston, SC, Medical University of South Carolina, Charleston, SC, Medical University of South Carolina, Charleston, SC, Ralph H. Johnson VA Medical Center, Charleston, SC, Ralph H. Johnson VA Medical Center and Medical University of South Carolina, Charleston, SC

**Background and Purpose:** Fli-1 expression levels, a member of the Ets family of transcription factors, are a mitigating factor in the development of nephritis in murine models of systemic lupus erythematosus (SLE). Lupus nephritis is a major cause of death in both models and human patients, and is characterized by immune complex formation and inflammatory cell infiltration. Overexpression of the Fli-1 protein in transgenic mice resulted in the development of a lupus-like disease with nephritis. Expression of Fli-1 in SLE patients and animal models of lupus is higher compared to normal controls. In this study, we examined the effects of reduced Fli-1 expression on inflammatory cell infiltration in conjunction with nephritis development in NZM2410 mice, an animal model of SLE.

**Methods:** We generated Fli-1 heterozygous knockout NZM2410 mice (Fli1^+/−; Fli-1 homozygous knockout is embryonic lethal) and wild-type (WT) littermate (Fli1^+/+) mice for use as controls. The expression levels of monocyte chemotactic protein-1 (MCP-1) and Chemokine (C-C motif) ligand 5 (CCL5, also known as RANTES) in the kidneys from 18-week-old mice were analyzed by real-time PCR. Pathological scores of the kidneys from 12-week-old mice were assessed and the number of macrophages, neutrophils, T cells and B cells in the kidneys were stained with specific antibodies and counted in 10 random high power fields (HPF). These numbers were averaged and directly compared between WT and Fli-1^+/− NZM2410 mice. The MCP-1 in serum was measured by ELISA.

**Results:** Since expression of CCL5 and MCP-1 were demonstrated to initiate inflammatory cell infiltration in the kidneys of lupus mice, we first examined the expression of MCP-1 and CCL5 in the kidneys from both Fli-1^+/− and WT controls. Expression of MCP-1 and CCL5 in the kidneys from 18-week-old Fli-1^+/− NZM2410 mice was significantly decreased compared to that from WT littermates. Fli-1^+/− NZM2410 mice also had significantly reduced renal pathology scores compared to those from WT littermates (WT mice: 6.846 ± 0.9635; Fli-1^+/− mice: 3.882 ± 1.043, p < 0.05). The number of macrophages, neutrophil granulocytes, T cells and B cells in the kidneys from both Fli-1^+/− NZM2410 mice decreased by 44 – 75% compared to WT littermate controls. The serum MCP-1 levels in Fli-1^+/− NZM2410 mice were significantly lower at the age of 34 weeks compared with WT littermates (WT mice: 118.9 ± 17.7 pg/ml; Fli-1^+/− mice: 67.7 ± 7.1 pg/ml, p < 0.01).

**Conclusion:** Our data indicate that lower expression of Fli-1 results in decreased expression of CCL5 and MCP-1 in the kidneys with significantly reduced infiltration of inflammatory cells, which leads to overall kidney pathological scores in NZM2410 mice. Therefore, Fli-1 plays an important role in the development of nephritis in NZM2410 mice.

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**1527**

**Mechanisms and Clinical Relevance of TRAIL-Triggered Responses in Synovial Fibroblasts of Rheumatoid Arthritis Patients.** Rachel Audo, Flavia Calmon Hamaty, Dominique Baeten, Bernard G. Combe, Michael Hahne and Jacques Morel, 1Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, 2Department of Rheumatology, Teaching Hospital of Lapeyronie, Montpellier, France, 3Department of Rheumatology, Teaching Hospital of Lapeyronie, Montpellier, France, 4IGMM, UMR5535, CNRS, Montpellier, Montpellier, France, 5IGMM, UMR5535, CNRS, Montpellier

**Background:** Studies in mice suggest a protective role for the TNF-related apoptosis-inducing ligand (TRAIL) in arthritis. We investigated the role of TRAIL in rheumatoid arthritis (RA) patients. We have shown that exposure to TRAIL induces apoptosis only in a portion of RA Fibroblast-Like Synovocytes (FLS) and that in the surviving cells, TRAIL induced proliferation. In the present study, we compared FLS resistant and RAFLS-sensible to TRAIL-induced apoptosis including levels of the TRAIL receptors...
(TRAIL-R) and clinical features of respective patient. Furthermore, we evaluated TRAIL levels in RA patients.

**Method:** FLS were extracted from synovial tissue of RA patients (n=30) and analyzed by FACS for expression of TRAIL-receptors. We obtained DAS28 within the 3 months of surgery for 13 patients. TRAIL-responses of FLS were analyzed by FACS for apoptosis and thymidine-incorporation for proliferation. TRAIL receptor activity was assessed by RNA silencing. HIC were performed to evaluate TRAIL level in synovial tissues from RA (n=7) and OA patients (n=4). ELISA was used to determine TRAIL-levels in synovial fluid of osteoarthritis (OA; n=20), spondylarthritis (SpA; n=20) and establish RA patients (n=30). Serum levels of TRAIL and its soluble decoy-receptor osteoprotegerin (OPG) were measured by ELISA in 72 patients fulfilling the ACR criteria (1987) with recent (<2 years) and active (>3 swollen joints) RA that were not treated or had a stable background treatment for at least 1 month (M0). 48 of the RA patients were followed up at 6 months (M6).

**Results:** Depending on the patient, we observed variability in RAFLS sensitivity to TRAIL-induced apoptosis. We therefore classified the cultures depending on their sensitivity (<10%; RAFLS-R, n=10 and > at 30%, RAFLS-S, n=11). Disease activity of RA patients inversely correlated with susceptibility of FLS to TRAIL-induced apoptosis (r=-0.688, p=0.0092, n=13). TRAIL-S cells expressed significantly lower levels of TRAIL-R1 (p=0.014) and silencing of TRAIL-R1 increased TRAIL-induced apoptosis in RA FLS (p<0.005; n=7). TRAIL levels were elevated in the arthritic joints of patients with established RA and synovial fluids displayed elevated TRAIL levels compared to those of OA and SpA patients (p<0.0001 and p=0.0022 respectively). In early RA, patients in remission at M6 (DAS28<2.6) (n=14) had a lower percentage of TRAIL at baseline than patients without remission (n=13) (0.54 ± 0.25 and 0.94 ± 0.71 respectively, p=0.028), but high serum levels of TRAIL at M6 were associated with joint damages (p=0.0063).

**Conclusion:** Surprisingly, TRAIL-R1 seems to be a survival factor protecting RAFLS against TRAIL-induced apoptosis. Furthermore, we found a negative correlation between TRAIL sensitivity RAFLS in vitro and RA activity, suggesting that RAFLS develop resistance to TRAIL-induced apoptosis to escape TRAIL protective role. Indeed, in early RA patient, a low OPG/TRAIL ratio at baseline was associated with remission at 6 months but persistent TRAIL serum levels are associated with joint damage. These findings suggest a dual role for TRAIL in RA and resistance of RA FLS to TRAIL-induced apoptosis is associated with a disease promoting activity of TRAIL in RA.

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1528

Pro-Inflammatory Activity of SIRT1 in Monocytes. Fabienne Niederer1, Caroline Ospelet1, Fabia Brentano1, Beat A. Michel2, Christoph Kolling2, Michael O. Hottiger3, Renate E. Gay4, Steffen Gay2 and Diego Kyburz.1 Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, 2Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, 3Institute of Veterinary Biochemistry and Molecular Biology, University Zurich, Switzerland, 4Schulthess Clinic, Zurich, Switzerland

**Purpose:** Sirtuins are a conserved family of NAD-dependent histone deacetylases (HDAC) and mono-ADP-ribosyltransferases. The human sirtuins are critical regulators of many cellular processes, including cell survival and inflammation. Here we focused on the expression of SIRT1 in monocytes and tissues from patients with rheumatoid arthritis (RA) and osteoarthritis (OA) and assessed the function of SIRT1 in monocytes.

**Methods:** To study the expression of SIRT1 in RA and OA tissues, Western blot and immunohistochemistry were performed. Monocytes from peripheral blood were negatively isolated from healthy donors or RA patients using magnetic MicroBeads (MACS separation). Levels of SIRT1 mRNA were measured with SYBR green Real-time PCR. Healthy monocytes were stimulated with Toll-like receptor 4 (TLR4) ligand LPS (10 ng/ml) for 8 hours in the presence or absence of a SIRT1 inhibitor, EX-527 (9 μM). Moreover, freshly isolated monocytes (n=5) were transfected to overexpress a wild type or an enzymatically inactive mutant form of SIRT1 for 18 hours, following LPS-stimulation (10 ng/ml) for 8 hours. The levels of TNF-α protein were measured in the supernatants of stimulated monocytes by ELISA (BD Bioscience).

**Results:** Performing Western blot analysis of SIRT1 in RA and OA tissues, we found an upregulation of SIRT1 in whole RA tissues. Immunohistochemistry in synovial tissues showed the expression of SIRT1 in monocytes/macrophages. Consistently, levels of SIRT1 mRNA in monocytes from RA patients were expressed at dCT = 7.55 ± 0.31 and in healthy controls at dCT = 8.69 ± 0.72, p=0.12. Treatment of LPS-stimulated monocytes with the SIRT1 inhibitor EX-527 significantly reduced TNF-α production by 37 ± 17% (p<0.01). Monocytes transfected with a vector encoding an enzymatically inactive form of SIRT1 showed a prominent downregulation of TNF-α by 81 ± 21% (p=0.04) compared to wild type SIRT1 transfected cells.

**Conclusion:** SIRT1 is overexpressed in RA tissues and monocytes. The inhibition of SIRT1 activity significantly reduced the production of TNF-α in monocytes. Thus, SIRT1 appears to contribute to the characteristic inflammatory phenotype of synovial cells in rheumatoid arthritis.

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Ras GTPase Homologs Make Redundant Contributions to RA FLS Activation and Broad Silencing of Ras Proteins Decreases Inflammation and Joint Destruction in Experimental Arthritis. Daphne de Launay1, Jeroen Vreijling1, Joana Abreu1, Aleksander Grabiec1, Marjolein van Maanen2, Marjolein Sanders2, Margriet Vervoordeldonk2, Henrik Oerum2, Kees Fluiter3, Paul Tak1 and Kris Reedquist1. 1Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, 2Academic Medical Center, University of Amsterdam, The Netherlands, 3Santaris Pharma A/S, Horsholm, Denmark.

Changes in expression and activation of Ras proteins are thought to contribute to the pathologic phenotype of stromal fibroblast-like synoviocytes (FLS) in rheumatoid arthritis (RA). Here we examined the expression of each Ras protein in the synovial tissue of RA patients and disease controls, and the contributions of H-, K-, and N-Ras homologues to FLS activation in vitro and experimental arthritis in vivo.

**Methods:** Synovial Ras homolog expression was determined by immunohistochemistry and digital image analysis in patients with RA (n = 10), inflammatory osteoarthritis (n = 4) and reactive arthritis (n = 7). In a second cohort consisting of patients with RA (n = 20) and psoriatic arthritis (PsA) (n = 19), Ras homolog expression was monitored by immunohistochemistry and mRNA expression. Ras protein and mRNA expression was examined in RA and PsA FLS. The activation status of Ras homologues in RA FLS following stimulation with TNF and IL-1 was determined by affinity precipitation and immunoblotting. RA FLS were transfected with active mutants of H-, K-, and N-Ras, and Ras protein expression was specifically or broadly silenced using locked nucleic acids (LNA), and effects on basal and IL-1-dependent cytokine and MMP-3 production assessed. The potential therapeutic effects of broad, pan-Ras silencing in murine collagen-induced arthritis (CIA) were examined using pan-Ras and control LNA (1 mg/kg, 3 times weekly ip, 8 mice per group).

**Results:** Similar levels of each Ras homolog were expressed in RA and disease control synovial tissue, although H-Ras protein and mRNA expression was significantly elevated in RA synovial tissue and FLS compared to PsA. Each Ras protein was also expressed in RA FLS and activated by TNF and IL-1. H-Ras, but not other Ras homologues, was sufficient and required for spontaneous FLS MMP-3 production (P < 0.05), while multiple Ras proteins induced IL-6 and IL-8 induction, and each silencing of each Ras homolog suppressed IL-1-induced IL-6 production (P < 0.05). The three Ras homologues also redundantly activated overlapping sets of MAP kinase, NF-kappaB and PI3-kinase intracellular signalling pathway in FLS. In vivo, pan-Ras LNA, which significantly suppressed synovial expression of H- and N-Ras, decreased clinical severity of CIA in mice compared to control LNA (P < 0.05), as well as cartilage destruction (P < 0.05), bone erosion (P < 0.05), and the ratio of anti-collagen IgG2a/IgG1 auto-antibodies (P < 0.01).

**Conclusions:** Overlapping contributions of Ras homologues to global inflammatory parameters of RA FLS activation and pathology in CIA, suggesting a therapeutic potential in broadly, rather than specifically, targeting closely related Ras proteins may be effective in treating RA.

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Autoimmune diseases are characterized by progressive inflammation manifested with overexpression of matrix metalloproteinases (MMPs) and pro-inflammatory cytokines such as TNFα. IL-1β. Blockade of TNFα or IL-1β signaling has been successfully applied to clinical therapy of some autoimmune diseases such as rheumatoid arthritis. Resveratrol, a natural phytoalexin, has been shown to have anti-inflammation properties. However, the mechanism is not fully understood. Here, we investigated whether resveratrol attenuates TNFα-induced inflammation and potential mechanism in NIH/3T3 fibroblasts. Upregulation of MMP-9, MMP-13 and IL-1β were observed 6 hours or 24 hours after TNFα treatment in NIH/3T3 fibroblasts examined by gel zymography and/or quantitative real-time PCR. Increase of phosphorylated Akt, mammalian target of rapamycin (mTOR) and S6 ribosomal protein (S6RP) were also detected in the cells. Nevertheless, resveratrol suppressed TNFα induced upregulation of MMP-9, MMP-13, IL-1β. Resveratrol also inhibited phosphorylation of Akt, mTOR, S6RP induced by TNFα. However, Rapamycin, a special mTOR inhibitor, failed to attenuate overexpression of MMP-9 induced by TNFα. Our results indicate that resveratrol inhibits TNFα-induced inflammation via a mTOR-independent fashion. Resveratrol may be a potential therapeutic candidate for treatment of autoimmune diseases, although its mechanism remains to be further elucidated.

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dium of synovial explants from different OA patients to the murine chondrocyte cell-line with the lowest NF-kappaB-P65 level, resulted in more than 60% chondrocyte death in 3 of the 5 conditioned medium samples tested which could be prevented by preincubation of these media with soluble-TNFFR1 (Enbrel). TNFalpha was detected using a Luminex assay in the same samples that caused cell death. **Conclusions:** This study clearly demonstrated that lower levels of NF-kappaB-P65 makes chondrocytes more vulnerable for TNFalpha, a cytokine which can be produced during OA, and that this anti-apoptotic transcription factor is downregulated in chondrocytes in murine OA and in 50% of OA patients.

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**1533**

**TLR2 Mediates Acute Serum Amyloid A Induced Pro-Inflammatory Effects in Rheumatoid Arthritis.** Mary Connolly1, Ashwini Maratha1, Sinead Nic an Ualtaigh3, Sinead Miggins1, Ursula Fearon3 and Douglas J. Veale1. 1Institute of Immunology, National University of Ireland Maynooth, Maynooth, Ireland, 2Institute of Immunology, National University of Ireland Maynooth, 3Translational Research Group, Dublin Academic Medical Centre, St Vincents University Hospital, Ireland

**Introduction:** Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by progressive joint destruction. Serum amyloid A (A-SAA) is an acute phase protein with cytokine-like properties. Previously we have shown that A-SAA correlates with RA disease activity, is produced at high levels locally in the joint and promotes synovial tissue angiogenesis, migration and MMP production. Recently, A-SAA was identified as a ligand for Toll Like Receptor 2 (TLR2), however no study has examined a role for TLR2 in mediating A-SAA-induced inflammation in RA.

**Objective:** To examine A-SAA-induced inflammation via TLR2 in rheumatoid arthritis

**Methods:** A-SAA and TLR2 expression were observed in synovial tissue (ST) was examined by immunohistochemistry. Human embryonic kidney (HEK) 293 cells overexpressing TLR2/TLR4 were transfected with the NF-κB luciferase reporter gene plasmid. After 24 hr, cells were stimulated with A-SAA (10 and 50μg/ml), the TLR2 ligand Pam3CSK4 or the TLR4 ligand LPS. After 8 hr, ligand-induced reporter gene activity was assessed. Primary fibroblasts (RASFCs) isolated from synovial biopsies obtained at arthroscopy and human microvascular endothelial cells (HMECs) were stimulated with A-SAA (10μg/ml) ± anti-TLR2 (OPN 301, 1μg/ml). IL-8 was measured by ELISA. Proliferation, invasion and ICAM expression were quantified by crystal violet assay, transwell invasion assays and flow cytometry. Migration and angiogenesis were examined using wound repair and tube formation assays respectively.

**Results:** A-SAA and TLR2 expression were observed in the lining layer and perivascular regions of RA synovium. A-SAA induced a 12-fold increase in NF-κB reporter gene activity in HEK293-TLR2 cells (p<0.05), an effect greater than that observed with Pam3CSK4/Pam3CSK4. In contrast, A-SAA failed to induce NF-κB reporter gene activity in HEK-TLR4, confirming specificity for TLR2. A-SAA induced IL-8 expression in RASFCs from 2.5±1.5 pg/ml to 3453.9±1715.3 pg/ml, an effect inhibited in the presence of anti-TLR2, where IL-8 levels fell to 1461.5±819.0 pg/ml. A-SAA induced HMEC proliferation by 60.9% (p<0.001) which was significantly reduced by 38.2% in the presence of anti-TLR2 (p<0.05), similar to RASFCs. A-SAA increased ICAM expression on HMECs and RASFCs by 65.4% and 64.3% respectively, which was dramatically inhibited by 59.8% and 38.8% in the presence of anti-TLR2 (p<0.05). Furthermore, A-SAA-induced invasion and wound repair were inhibited by anti-TLR2, with no effect on TNFα-induced events. Finally, A-SAA induced angiogenic tube formation by 31.7%, an effect that was inhibited in the presence of anti-TLR2 by 24.5%.

**Conclusion:** A-SAA mediates pro-inflammatory events in RA including chemokine induction, adhesion, migration and angiogenesis, via TLR2. TLR2 blockade may represent a therapeutic strategy for the treatment of arthritis.

Disclosure: M. Connolly; None; A. Maratha; None; S. Nic an Ualtaigh; None; S. Miggins; None; U. Fearon; None; D. J. Veale; Abbott Laboratories, 2, 5, 8, Centocor, Inc., 5, 8, GlaxoSmithKline, 2, 5, 8, Mundipharma, 2, 8, Ospona, 2, 8, Pfizer Inc, 5, 8, Schering-Plough, 5, 8, Wyeth Pharmaceuticals, 2, 5, 8.

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**1534**

**TNF-a and Chemerin Cross-Talk in Rheumatoid Arthritis.** M. C. Lebre2, M. I. Ramos3, C. Hofstra1, H. van Enenenna1, S. Aarrassa1 and Paul P. Tak1. 1Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, 2Division of Clinical Immunology & Rheumatology, Academic Medical Centre/University of Amsterdam, Amsterdam, The Netherlands, 3Merck Research Laboratories, Oss, The Netherlands

**Background:** Rheumatoid arthritis (RA) synovium is characterized by a dense infiltrate, consisting of macrophages, T and B cells, plasma cells and dendritic cells (DC). Inflammatory chemokines present in RA synovium may contribute to the accumulation of these immune cells. We have recently shown that plasmacytoid DC (pDC) are enriched in RA synovial tissue (ST) compared to CD1c+ myeloid DC. In line with these observations, we have shown that chemerin (and its receptor chemR23) expression is upregulated in RA ST compared to non-RA arthritis patients. Moreover, in RA ST ChemR23 was specifically expressed by CD68+ macrophages and pDC, while chemerin expression was confined to endothelial cells (CD31 and vWF positive).

**Objective:** To investigate the regulation of chemerin expression in an ex-vivo model of human RA.

**Methods:** Arthroscopic synovial tissue biopsies were obtained from patients with active RA and cultured in medium or in the presence of recombinant (r)-TNF-a or r-chemerin. After 6 days, cell-free supernatants were harvested and the levels of TNF-a or chemerin were analyzed by Luminex or ELISA, respectively. When indicated, anti-chemerin or anti-ChemR23 neutralizing antibodies were added to cultures.

**Summary of the Results:** RA synovial biopsies released chemerin spontaneously. Interestingly, TNF-a stimulation induced significantly higher levels of chemerin compared to medium control. In addition, RA synovial biopsies released TNF-a spontaneously and addition of chemerin to the cultures strongly induced TNF-a release, suggesting a vicious cycle. Of importance, spontaneous and TNF-a-induced chemerin could be blocked by the addition of neutralizing antibodies against chemerin or against ChemR23. Moreover, spontaneous TNF-a could also be blocked by the addition of neutralizing antibodies against chemerin.

**Conclusion:** These findings suggest that elevated levels of chemerin in RA synovial tissue might regulate local TNF-a release and vice-versa in a positive feedback loop. The reciprocal interplay between chemerin and TNF-a is novel and might represent an attractive candidate for future drug development by blocking the chemerin/ChemR23 system to disrupt disease perpetuation.

Disclosure: M. C. Lebre; None; M. I. Ramos; None; C. Hofstra; None; H. van Enenenna; None; S. Aarrass; None; P. P. Tak; None.

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**1535**

**Toll-Like Receptor 4 Signalling Is Specifically TAK1-Independent in Synovial Fibroblasts.** Fons A. J. van de Loo1, Ben T. van den Brand1, Shahla Abdollahi-Roodsaz1, Onno J. Arntz1, Michael Kracht2, Jeroen Geurts1 and Ursula Fearon1. 1Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, 2Rudolf-Buchheim-Institute of Pharmacology, University of Giessen, Hannover, Germany

**Introduction:** Activated synovial fibroblasts are key players in the pathogenesis of rheumatoid arthritis (RA) by driving inflammation and joint destruction. Numerous molecules including cytokines and toll-like receptor (TLR) ligands induce pro-inflammatory signalling and gene expression through a hierarchical network of kinases. Upstream mitogen-activated protein kinase kinase kinases (MAP3Ks) represent an attractive target for RA treatment. In this study we sought to determine the role of the MAP3K transforming growth factor-β activated kinase1 (TAK1) in cytokine and TLR-mediated signalling.

**Methods:** TAK1 activity was inhibited using either a small molecule inhibitor or lentivirally expressed kinase-inactive TAK1-K63W mutant in murine embryonic and human dermal and synovial fibroblasts. Fibroblasts were stimulated with IL-1, TNF, TLR2 or TLR4 agonists and responses were evaluated using transcriptional reporters and analysis of gene expression of collagenases (MMP13), cytokines (IL-1β, IL-6) and chemokines (IL-8, MCP-1).

**Results:** TAK1 inhibition abrogated cytokine- and TLR-induced activation of NF-κB and Saa3-promoter reporters in murine and human dermal fibroblasts. In synovial fibroblasts, TAK1 crucially regulated IL-1 and...
TNF-mediated NF-κB, but not Saa3 promoter activation. Furthermore, TAK1 was required for inducible mRNA expression of IL-1β, IL-6, IL-8, MMP13, but not MCP-1, in response to IL-1, TNF and TLR2 agonist. Unexpectedly, TLR4-induced NF-κB activation and gene expression was fully TAK1-independent.

Conclusion: In general, TAK1 plays a prominent role in regulation of IL-1β- and TNF mediated signalling in fibroblasts. Interestingly, TLR4 signalling is specifically TAK1-independent in synovial fibroblasts. Consequently, therapeutic TAK1 inhibition in arthropathies may not dampen the damage-associated molecular pattern-mediated TLR4 activation of synovial fibroblasts.

Disclosure: F. A. J. van de Loo: None; B. T. van den Brand: None; S. Abdollahi-Roodsaz: None; O. J. Arntz: None; M. Kracht: None; J. Geurts: None; W. B. van den Berg: None.

1536
Tyrosine Kinase Inhibitors Reduce NMDA Receptor NR1 Expression, Nuclear Translocation and Thermal Hyperalgesia/Central Sensitization in a Rat Arthritis Model.

1Amgen Inc, Austin, TX, 2MD Anderson Medical Center, Houston, TX, 3University of Kentucky, Lexington, KY, 4University of Texas Medical Branch, Galveston, TX

Objective: This study was designed to determine if the central changes of the spinal cord in response to a peripheral inflammatory knee joint arthritis in rats are mediated by non-receptor tyrosine kinase. Methods: Spinal microdialysis administration of non-receptor tyrosine kinase inhibitors was used to measure their impact on secondary thermal hyperalgesia upon application of nociceptive radiant heat to the ipsilateral footpad in a kaolin and carrageenan (k/c)-induced knee arthritis model. NMDA NR1 cellular expression and nuclear localization by immunocytochemistry and Western blot analysis of the lumbar spinal cord were also measured. Statistics: Student’s t-tests and one-way ANOVA. Results: Tyrosine kinase inhibitors genistein and lavendustin (but not lavendustin or diadzein) effectively reduced 1) the development of secondary hyperalgesia, 2) the increases in glutamate NMDA receptor subunit NR1 expression in spinal cord that normally ensue 4 hours after intra-articular k/c-induced knee joint inflammation and 3) nuclear translocation of NR1. Genistein or staurosporin also inhibited the upregulation and shift of NMDA NR1 protein staining to the nuclear membrane and nucleus that is notable within 4 hours after treatment of neuroblastoma (SH-SY5Y) cell cultures with glutamate. Nuclear translocation of the NMDA NR1 subunit was also evident with activation of human primary and clonal synoviocytes. Nucleotide sequencing from clonal synoviocyte cDNA confirmed a putative nuclear localization sequence, similar to sequences derived from neuronal cells. Conclusion: Tyrosine phosphorylation is necessary for spinal cord responses to peripheral inflammation including centrally mediated nociceptive sensitization producing secondary hyperalgesia. Tyrosine phosphorylation is required for NMDA receptor mediated NR1 subunit nuclear translocation, upregulation and perhaps other long term plastic changes. These studies implicate NR1 in direct interactions with the nucleus suggesting a role for NR1 as a fast intracellular mediator.

Disclosure: T. A. McNeary: None; Y. Lu: None; Z. Ye: None; L. Zhang: None; G. Taglialetela: None; T. Pappas: None; W.-R. Zhang: None; K. N. Westlund: None.

1537

1Amgen Inc, Austin, TX, 2MD Anderson Medical Center, Houston, TX

Purpose: To evaluate the medication prior authorization process for rheumatology prescriptions. Method: Cases were acquired through the prescription insurance coverage prior authorization process in the Rheumatology Section between March 1, 2010 and June 18, 2010. Each case was charted in a table to reflect the length of time it took to receive the outcomes including: specific medication prior authorization patient diagnosis as on or off label (using FDA standards) whether the insurance company requested a peer to peer or step therapy (alternate medication). Results: The Dartmouth-Hitchcock Rheumatology Clinic referred 65 patients for insurance carrier prior authorization between March 1, 2010 and June 18, 2010. This population represents 16% of the total number of patients seen in clinic during that timeframe. The prescription prior authorization process averaged to two hours per patient from initial referral to completion. Time spent per request ranged from twenty minutes to three hours, 100% of the cases needed more than one phone call to determine the outcome; 62.5% of the total cases required a peer to peer (medical provider required to contact an insurance company physician), 75% of the cases were approved. Out of the 75% approved, 12.5% were found not to need a prior authorization, 50% of the cases that were approved were denied once the claim was submitted through billing. These cases are now in an appeal process. 37% of the cases were for off label use and out of those 50% were approved then denied when the claim was submitted. Categories of problems include: 1) FDA approved medications not covered 2) Insurance company representative conveyed incorrect information about coverage 3) Approval given then subsequently withdrawn (denied) 4) Medication denied then approved without appeal 5) Insurance company confused about their own appeal process 6) Pharmacy told patient prior approval needed when it wasn’t and vice versa. Conclusion: There is no consistent prescription prior authorization process within the insurance company industry. The lack of standardization creates problems such as an approval is initially granted and then upon review the approved medication coverage is denied. Insurance carriers also may initially approve a medication but then require reauthorization at the time of renewal. Patients are frequently required by the insurance company to trial one or more medications before approval will be given for the prescribed treatment plan.

The current lack of process amongst the insurance company industry for prescription medication prior authorization is time consuming, inefficient and costly for physicians, clinic staff, patients and insurance carriers.

Disclosure: D. C. Crate: None; D. A. Albert: None.

1538
Arthritis Prevalence and Access to Care in Indigenous People: Results of a Population-Based Study.

1Amgen Inc, Austin, TX, 2MD Anderson Medical Center, Houston, TX, 3University of Kentucky, Lexington, KY, 4University of Texas Medical Branch, Galveston, TX

Purpose: North American Indigenous people are believed to have a high prevalence of arthritis yet limited research has examined the burden of arthritis and access to care. Our objectives were to: 1) identify the prevalence of chronic pain in peripheral joints, neck or back with functional limitations; 2) identify the prevalence of reported diagnoses of arthritis; and, 3) evaluate access to care for arthritis, in three on-reserve Indigenous populations. Methods: A household survey of all adults living in three on-reserve communities was performed using a community case-finding strategy. Band Council support was provided and public forums were held to obtain community feedback prior to survey. Surveys were administered face-to-face by three trained interviewers residing in the community. The interview administered to each community member asked about chronic pain in the joint, neck, and back, and related functional limitations. Those indicating functional limitations secondary to arthritis/joint problems were then asked.
about their access to health care services and barriers to care. Descriptive analyses were conducted.

Results: Of 536 residents of these communities, 402 (75%) completed the initial interview. Participants’ mean age was 46 yrs (range = 19–93), 52% were female, 61% were married and 23% were never married. Thirty-percent (n = 119/402) reported a physician or health professional diagnosis of arthritis (excluding fibromyalgia), with 79 identifying specific type(s), including rheumatoid arthritis (n = 27), hip osteoarthritis (OA; n = 24), knee OA (n = 33), hand OA (n = 25), neck/back arthritis (n = 15), or other (n = 12). In comparison, non-age adjusted prevalence estimates reported in national surveys using the same question was 19% for off-reserve Indigenous People and 16% for non-Indigenous people. Chronic joint, neck, or back pain and functional limitations were reported by 41% (166/402). Of these 166 individuals, 140 reported at least one health care professional visit for their problem: family doctor = 75%; physical therapist = 28%; occupational therapist = 20%; rheumatologist = 16%; traditional healer = 15%; dietician = 13%; counsellor or psychologist = 7%. Assistive devices were used by 39%, and 70% used medications in the past 12 mos. Difficulties obtaining care in the past 12 mos were reported by 28% (n = 47/166), such as long wait lists (n = 20), difficult access to rheumatologists (n = 19), poor transportation availability and/or high costs (n = 16), lack of awareness of health care professional to see (n = 12), high treatment costs (n = 11), and perceived inadequate or culturally inappropriate health care (n = 10).

Conclusions: The burden of arthritis was high in the three Indigenous communities evaluated. The prevalence of reporting a diagnosis of arthritis exceeded that reported in national surveys for off-reserve Indigenous People and non-Indigenous people; and a large proportion (41%) reported chronic joint, neck or back pain and functional limitations. Along with suboptimal access to care, these findings suggest the need for further research to determine the specific types of arthritis and to identify solutions for improving health equity and access to care.

Disclosure: A. J. Lehman: None; M. H. Liang: None; L. Li: None; J. M. Esdaile: None; C. L. Baekman: None; P. Jorgensen: None; K. Roberts: None; L. Lavender: None; D. Lacaille: None.

1539
Aspirin vs. Low Molecular Weight Heparin for Prophylaxis Against Venous Thromboembolism after Total Knee or Hip Replacement in Lower Risk Individuals: A Cost-Utility Analysis. John T. Schousboe1 and Gregory A. Brown2. 1Park Nicollet Institute, Minneapolis, St Louis Park, MN, 2Park Nicollet Institute, Minneapolis, MN

Introduction: Venous thromboembolism (VTE) is common following total joint replacement (TJA) surgery, but there is substantial disagreement as to the best way to prevent VTE events. The American Academy of Orthopedic Surgeons guideline recommends aspirin after TJA for patients at average or lower risk of VTE or at high risk of bleeding. The American College of Chest Physicians guideline recommends stronger anticoagulants (adjusted dose warfarin, low molecular weight heparin, or fondaparinux) for VTE prophylaxis after TJA, and specifically recommends against aspirin. Our objective was to estimate the lifetime incremental costs per quality adjusted life year gained for 10 days of low molecular weight heparin (LMWH) vs. aspirin 160 mg daily following joint replacement surgery.

Methods: A Markov cohort model allowing 6 transient events following TJA (deep vein thrombosis, pulmonary embolism, operative site hemorrhage, non-operative site major hemorrhage, intracranial hemorrhage, and thrombo-cytopения), and 5 chronic health states (healthy post TJA, post TJA VTE without post-phlebitic syndrome, post TJA VTE with post-phlebitic syndrome, post intracranial hemorrhage, prosthetic joint infection). Costs and quality of life associated with each event and chronic health state were derived from the medical literature. The absolute risks of VTE and bleeding events on LMWH following TJA were derived from a pooled analysis of clinical trials, and the relative risks of VTE and major bleeding on aspirin vs. LMWH were derived from literature estimates of each drug vs placebo. LMWH and aspirin were compared for four sets of individuals; those without any additional risks for VTE (non-obese, no personal or family history of VTE), obese individuals but without additional risk factors, and those with a family history of VTE.

Results: The costs (2008 U.S. $) per QALY gained for LMWH compared to aspirin prophylaxis post TJA for those age 55 to 85 are as follows:

<table>
<thead>
<tr>
<th>Age</th>
<th>No Added VTE Risks</th>
<th>Family History of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>Aspirin Dominant</td>
<td>S$35,762</td>
</tr>
<tr>
<td>65</td>
<td>$635,488</td>
<td>$31,644</td>
</tr>
<tr>
<td>75</td>
<td>$326,842</td>
<td>$31,819</td>
</tr>
<tr>
<td>85</td>
<td>$246,044</td>
<td>$27,310</td>
</tr>
</tbody>
</table>

Results were highly sensitive to the relative risks of VTE and major bleeding events on aspirin vs LMWH, modestly sensitive to the risks of and quality of life loss associated with post-phlebitic syndrome.

Conclusion: Aspirin may be a cost-effective reasonable choice for VTE prophylaxis following TJA for those individuals with no additional risk factors for VTE events, based on currently available data. For those with one or more additional VTE risk factor, LMWH is preferred over aspirin. A randomized controlled trial of aspirin vs LMWH post TJA might clarify the relative risks and benefits of these two strategies.


1540

Purpose: While incremental or attributable costs of osteoporosis (OP)-related fractures have been reported, data on the economic impact of OP-related fractures in commercial health plan populations are limited. The objective of this study was to quantify the incremental cost of OP-related fractures among women in a large U.S. managed care plan between 2004 and 2008.

Methods: Female patients were identified from a large, commercially-insured population with integrated pharmacy and medical claims. Patients were included if they were age 45 to 65 years, had an OP medication claim between 1/1/2005 and 4/30/2008 (first claim defines index date), and had continuous coverage for 12 months pre-index. Patients were excluded if they had: pre-index Paget’s disease or malignant neoplasm, were in a skilled nursing facility, on combination therapy at index, or had a fracture ≤ 6 months post-index. Clinically-diagnosed and coded fractures were identified using published claims criteria; total direct costs were assessed in the 6 months pre- and post-fracture event date. Event dates were assigned to patients with no fracture; propensity score weighting was used to increase comparability of fracture and non-fracture patients. A generalized linear model was used to compare differences in 6 months pre- vs post-event cost for patients with fracture and those without fracture. Covariates included demographics, prior fractures, comorbidities, and other potential confounders. Generalized estimating equations methods were used to account for repeated measures.

Results: The study population included 47,650 women (N = 2,461 with a fracture) with a mean (± SD) age of 56.4 ± 4.7 years. Mean unadjusted total costs showed minor variation in the 6 months pre-event vs post-event for non-fracture patients. Mean pre-post-event cost differences were substantially larger for patients with vertebral, hip, or other fractures (Table).

<table>
<thead>
<tr>
<th>Table. Unadjusted Mean Total Direct Costs Per Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Total Direct Costs Per Patient (95% Confidence Interval) for Patients With:</td>
</tr>
<tr>
<td>Fracture</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>OP Pre-Event</td>
</tr>
<tr>
<td>(5,542, 17,395)</td>
</tr>
<tr>
<td>OP Post-Event</td>
</tr>
<tr>
<td>(21,088, 33,517)</td>
</tr>
</tbody>
</table>

After adjusting for covariates, OP-related fractures were associated with an estimated $9,512 (95% CI: $8,364, $10,660, p < 0.0001) per patient in...
additional direct health care costs across all fracture types during the 6 months immediately after the fracture.

Conclusion: On average, women with an OP-related fracture incurred nearly $10,000 in additional health care costs in the 6 months post-fracture compared with patients with no fracture. Efforts to reduce fracture risk may ultimately lower associated direct health care costs.

Disclosure: H. Viswanathan: Amgen Inc., 1, 3; J. White: None; S. W. Wade: Amgen Inc., 5; J. Yu: Amgen Inc., 2; J. R. Curtis: Novartis, Eli Lilly, 2, 5, 8; Novartis, Merck, Procter & Gamble, Eli Lilly, 2, 5, 8; B. Stolshek: Amgen Inc., 1, 3; C. Merinar: Amgen Inc., 1, 3; J. Kallich: Amgen Inc., 1, 3; A. Balasubramaniam: Amgen Inc., 1, 3; J. Adams: Amgen Inc., 5.

1542
Bending the Cost Curve in Early RA: Sick Leave and Disability Pension before and after Initiation of Biologics or DMARD Combination Therapy. Martin Neovius1, Julia F. Simard1, Johan Asking2 and ARTIS Study Group3, 1Karolinska Institute, Stockholm, Sweden, 2Karolinska Institute, Sweden

Background: Biologic treatment is effective but expensive. Increased work force participation arguably holds the greatest potential for offsetting some of the treatment cost. It has been speculated that treatment may improve productivity in patients with RA, and early RA in particular, but long-term work ability development in this patient segment in relation to intensified anti-rheumatic treatment is not well-described.

Objective: To estimate the sick leave and disability pension trajectory over seven years in patients with early RA before and after treatment initiation with biologics or combo-DMARDs.

Methods: Patients aged 16–59 years old and a disease duration of less than five years at treatment initiation with biologics or combo-DMARDs were included. The counties with biologics combined or the DMARDs were matched general population comparators were sampled. Sick leave and disability pension data from 1997 to 2007 were retrieved from national registers.

Results: During the year of treatment initiation, patients selected for biologic therapy had a mean 194 (136±59) days of sick leave and disability pension registered, compared to 159 (133±26) days in patients starting combo-DMARDs, and 52 (20±32) days in matched general population comparators. A rapid increase in annual days of sick leave and disability pension was observed before start of intensified anti-rheumatic therapy, but thereafter the number of days/year decreased for patients who had either initiated biologics or combo-DMARDs. However, the gap compared to the general population remained wide and three years after treatment start patients in the treatment groups had a mean of near or above 150 days of sick leave and disability pension registered annually.

Conclusion: Using seven years of real world data in patients with less than five years RA duration, rapidly increasing productivity losses were observed before initiation of intensive drug treatment. Treatment initiation was associated with a breakpoint in and small reversal of this development, but a large unmet need remained in these patients compared to general population comparators.

Disclosure: M. Neovius: None; J. F. Simard: None; J. Asking: Bristol-Myers Squibb, 9; ARTIS Study Group: Schering-Plough, 9.

1543
DXA Screening and Use of Osteoporosis Medications in Two Large Regional Healthcare Systems. Amy Warner1, Ryan C. Quinlan2, Jeffrey R. Curtis2, Adrian Feldstein3, Harry Glauber3, Junling Ren4, Douglas Robinson3, Anna Rosales1, Robert Unitan1 and Kenneth G. Sang3, 1Kaiser Permanente Center for Health Research, Portland, OR, 2Kaiser Permanent Center for Health Research, Atlanta, GA, 3Kaiser Permanente Northwest, 4Univ of Alabama at Birmingham, Birmingham, AL

Statement of Purpose: To compare the effect of a patient panel-support tool (PST) vs. standard of care on dual energy x-ray absorptiometry (DXA) screening in two large healthcare systems. Despite U.S. guideline recommendations for all women 65 years and older to have a screening bone density scan with central DXA, less than one-third of eligible U.S. women have undergone DXA testing.

Methods: We evaluated DXA receipt and use of prescription osteoporosis medications among women aged 65–90 in two large healthcare systems. Women were eligible for inclusion in the analysis if they had at least 24 months of enrollment at Kaiser Permanente Georgia (KPGA) or Northwest (KPNW). Primary outcomes included a DXA scan in the past 5 years and use of osteoporosis medications in the past year. The analysis included data...
obtained in 6 month intervals from January 2005 through July 2009. From this data, we examined the effect of a PST (KPNW) vs. standard of care (KPGA). The PST uses EMR data to graphically display “care gaps” for each patient, based on current evidence. Through this mechanism, primary care physicians within the KPNW system are alerted to order a DXA in patients without a DXA in the previous 5 years (start date February 26, 2007).

Summary of Results: The number of women undergoing screening DXA increased significantly in the KPNW group with the proportion increasing from 25.3% in January 2005 to 58.7% in July 2009 (Risk Difference [RD] 33.3%, 95% CI 32.5 – 34.1%). This differs from KPGA, in which minimal change in DXA scan use occurred between January 2005 and July 2009, 43.1% and 45.3%, respectively (RD 2.2%, 95% CI 0.6 – 3.9%). The majority of the increased DXA use was seen following the implementation of the PST, Figure 1.

![Figure 1](image)

**Figure 1.** Percentage of women aged 65–90 receiving DXA screening or prescription of osteoporosis medications in 2005–2009 in KP Northwest and KP Georgia.

However, the number of women taking an osteoporosis medication did not increase significantly over the 5 year period in either region, +3.4% in KPNW and +1.3% in KPGA.

**Conclusions:** Among older women, DXA testing increased incrementally over the past 3 years in the KPNW healthcare system, following the implementation of a PST. However, despite the increased screening, the use of osteoporosis-specific medications for fracture risk reduction did not increase significantly. In a similar health plan that did not implement such a program, the rates of DXA testing remained relatively flat. Further randomized studies are needed to confirm effectiveness of methods to improve appropriate DXA utilization.

**Disclosure:** A. Warriner: None; R. C. Outman: None; J. R. Curtis: Eli Lilly and Company, 2, 8, Merck Pharmaceuticals, 2, 5, Novartis Pharmaceuticals Corporation, 2, 8, Proctor and Gamble, 2, 5; A. Feldstein: Amgen Inc., 2, Merck Pharmaceuticals, 2, sanofi-aventis, 2; H. Glauber: None; J. R. Ren: None; D. Rohlin: None; A. Rosales: None; R. Uitman: None; K. G. Saag: Amgen Inc., 2, 5, 8, Aventis Pharmaceuticals, 5, Eli Lilly and Company, 2, 5, GlaxoSmithKline, 2, Merck Pharmaceuticals, 2, 5, Novartis Pharmaceuticals Corporation, 2, 5, Proctor and Gamble, 5, Roche, 2, 5.

**1544 Erectile Dysfunction Is Associated with Gout in the Campaign Against Cancer and Heart Disease (CLUE II).** Janet W. Maynard, Mara A. McAdams, Alan N. Baer, Judith Hoffman-Bolton, Allan C. Gelber and Josef Coresh. Johns Hopkins

**Purpose:** Erectile dysfunction (ED) is related to a variety of chronic medical conditions, including hypertension, obesity, and cardiovascular disease. We sought to identify whether gout was associated with ED independent of risk factors for cardiovascular disease in a community-based setting.

**Methods:** The CLUE II cohort consists of individuals, aged 13 to 87 years, who resided within or surrounding Washington County, Maryland. All participants received follow-up questionnaires (1996, 1998, 2000, 2003, and 2007). At baseline in 1989, participants were asked to self-report gender, race, age, and height. On the 2007 follow-up questionnaire, participants self-reported weight and a physician or health professional diagnosis of gout, ED, diabetes, and hypertension. This study was restricted to CLUE II participants who responded to the 2007 questionnaire (7,142) and were male. We assessed whether having gout was associated with ED. The distributions of variables among the men with gout versus those who did not have gout were compared using chi-squared or t-tests, as appropriate. We assessed the relationship between gout and ED with odds ratios from logistic regression.

**Results:** Of the 2,605 male participants responding to the 2007 questionnaire, 256 (9.8%) had gout and 779 (29.9%) had ED. A significantly greater proportion of participants with gout had ED (102, 39.8%) compared to participants without gout (677, 28.8%), p<0.001. The mean age of participants with gout was significantly greater than those without gout (68.7±11.3 years vs. 65.0±12.3 years, p<0.001). A significantly greater proportion of participants with gout were obese (BMI ≥ 30 kg/m²) (47.9%) compared to those without gout (32.1%), p<0.001. Similarly, a significantly greater proportion of participants with gout were hypertensive (72.0%) compared to those without gout (47.8%), p<0.001. A greater proportion of gout participants were diabetic (15.2%) than participants without gout (8.6%), p<0.001. There was a statistically significant association between gout and ED, even after adjustment for age (Table). However, this association was not observed after adjustment for hypertension, obesity, and diabetes.

**Table.** Association between Gout and Erectile Dysfunction.

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unadjusted</td>
<td>1.64 (1.25, 2.13)</td>
</tr>
<tr>
<td>2</td>
<td>Age</td>
<td>1.38 (1.05, 1.83)</td>
</tr>
<tr>
<td>3</td>
<td>Model 2 + hypertension</td>
<td>1.24 (0.94, 1.64)</td>
</tr>
<tr>
<td>4</td>
<td>Model 3 + obesity</td>
<td>1.19 (0.90, 1.59)</td>
</tr>
<tr>
<td>5</td>
<td>Model 4 + diabetes</td>
<td>1.15 (0.85, 1.53)</td>
</tr>
</tbody>
</table>

Significant values (p <0.05) are bold. Abbreviations: OR (odds ratio), CI (confidence interval)

**Conclusion:** In a community-based cohort we found that men with gout are more likely to have ED than men without gout, even after adjustment for age. However, this relationship may be mediated by obesity, diabetes, and hypertension, which are known risk factors for ED. Potential causal mechanisms need to be investigated, but even in their absence, the association suggests that physicians should explore this common treatable condition with their gout patients.

**Disclosure:** J. W. Maynard: None; M. A. McAdams: None; A. N. Baer: None; J. Hoffman-Bolton: None; A. C. Gelber: None; J. Coresh: None


**Background:** The spectrum of physical function ranges from high-level nursing home to long-distance runner, and improvement anywhere along this continuum represents an improvement in health. Yet, our measurement tools, from the SF-36 and the HAQ to the IRT-based new PROMIS tools, do not contain floor items sufficiently basic to assess low levels of function nor sufficiently difficult ceiling items to test function above the average. In many populations more than half may be beneath the floor or above the ceiling. As a result, instrument performance might suffer at population extremes, leading to much larger sample size requirements. We sought to estimate the size of this effect and to suggest remedies.

**Methods:** We initially performed a simulation study that estimated the sample size requirements of an IRT-calibrated 8 item questionnaire at 3 separate settings: general population, and populations where physical function was 1 standard deviation worse and 1 standard deviation better than general population. Based on the results we performed a prospective observational study of 451 patients with RA (rheumatoid arthritis). Mean 12-month score changes (A) in Physical function short form (PF10), PF-10 improved using IRT techniques, and PROMIS PF short form were measured and used to compute sample size needed for a 2.5% change with 80% power at a p value of 0.05.

**Results:** Whereas 50 patients were needed for detecting a change at 80% among those with physical function worse than general population (typical of patient populations) the corresponding sample size needs in the general population setting was 140. In samples of individuals with physical function 1 standard deviation superior to general population,(positive health), the sample size need was 325. In the empirical study the median sample size needs for those with no measurable disability at baseline (HAQ-DI =0), and those at progressively higher baseline disability categories (0.01<HAQ-DI<1.50; and HAQ-DI ≥1.6) the median estimated sample sizes were 146, 228 and 284 respectively.

Purpose: Estimate the prevalence of fragility fractures and investigate factors associated with this condition in Brazilian community-dwelling elderly.

Methods: 1075 elderly subjects (659 women/416 men) from São Paulo, Brazil, were evaluated using specific questionnaire including risk factors for osteoporotic fractures. Fragility fractures were defined as those resulting of a fall from standing height or less after 50 years of age at sites characteristic of bone fragility. Fractured fractures and those occurring at the face, skull, ankle, elbow and finger were not considered. Anthropometric data was obtained by physical examination and body mass index (BMI) was calculated. Bone mineral density (BMD) was measured by DXA in hip and lumbar spine. Laboratory tests were also determined.

Results: The prevalence of fragility fractures was of 11.9% (127) and the main fracture sites were forearm (50.4%), humerus (19.7%), femur (11.2%) and ribs (8.7%). Women had higher prevalence (15.3%; 95%CI 12.6–18.1) than men (6.5%; 95%CI 4.1–8.9) (P<0.001). The main factors associated with fractures were Caucasian race (OR=1.7; 95%CI 1.1–2.8; P=0.027), BMI (OR=0.9; 95%CI 0.89–0.98; P=0.002) and femoral neck T-score (OR=0.7; 95%CI 0.5–0.9; P<0.001). After adjustment for these significant variables, the logistic-regression analyses revealed that Caucasian race (OR=1.7, 95%CI 1.03–2.7 P=0.038) and femoral neck T-score (OR=0.7, 95%CI 0.51–0.86; P=0.002) remained a significant factor for fragility fractures in women. In men, the main factors associated with fragility fractures were smoking (OR=3.2; 95% CI 1.4–7.6; P=0.007), diabetes mellitus (OR=3.1; 95%CI 1.3–7.1; P=0.008), chronic faller (OR=2.9; 95%CI 1.1–7.6; P=0.033) and femoral neck T-score (OR=0.4, 95%CI 0.2–0.6; P<0.001). The logistic-regression analyses revealed that current smoking (OR=2.5, 95%CI 1.2–6.2; P=0.048), diabetes mellitus (OR=4.5; 95%CI 1.8–11.1; P=0.001) and femoral neck T-score (OR=0.4, 95%CI 0.2–0.6; P=0.001) were independent factors in predicting fragility fractures in men.

Conclusions: Our results suggest that fragility fractures are common in Brazilian community-dwelling elderly, and a low hip BMD was an important risk factor for this condition in both genders. In men, diabetes and smoking are also related to this complication. The identification of these factors may improve the prediction of fracture risk and enhance the evaluation of patients with osteoporosis.


1547

Higher Serum Urate Levels Correlate with Increased Prevalence of Comorbidities in the US General Population: NHANES 1999–2008. Yan Yan Zhu1, Bhavik Pandya2 and Hyoung Cho1. 1Boston University School of Medicine, Boston, MA; 2Takeda Pharmaceuticals International, Inc, Deerfield, IL

Objective: To estimate the prevalence of major comorbidities according to individuals’ serum urate (sUA) levels based on a recent, nationally representative sample of US men and women regardless of whether or not they had gout.

Methods: Using the National Health and Nutrition Examination Survey (NHANES) 1999–2008 data from 24,693 participants (11,816 men and 12,877 women) aged 20 years and older, we determined the prevalence of major comorbidities according to individuals’ sUA levels, including hypertension, diabetes, myocardial infarction, heart failure, stroke, renal impairment, and obesity, regardless of whether or not they had gout. Obesity was defined as body mass index ≥30 kg/m². Comorbidities were defined based on an affirmative answer to a question asking if a physician or other health professional had diagnosed the corresponding condition.

Results: The prevalence of major comorbidities correlated with an increase in sUA levels. Among individuals with sUA levels ≥10 mg/dL, 66% had hypertension, 32% diabetes, 23% history of myocardial infarction, 33% history of heart failure, 12% history of stroke, 18% renal impairment, and 65% obesity (Table).

Table. Prevalence of Comorbidities According to sUA Level Categories in NHANES 1999–2008

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>sUA Level (mg/dL)</th>
<th>Prevalence, % (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>&lt;4.0</td>
<td>26.6 (25.7–27.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.0–4.9</td>
<td>34.4 (33.6–35.2)</td>
</tr>
<tr>
<td>Depression</td>
<td>5.0–5.9</td>
<td>41.4 (40.6–42.3)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>6.0–6.9</td>
<td>49.0 (48.2–49.7)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>7.0–7.9</td>
<td>56.7 (55.9–57.5)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>8.0–8.9</td>
<td>64.4 (63.6–65.2)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>9.0–9.9</td>
<td>71.7 (70.9–72.5)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>≥10.0</td>
<td>78.3 (77.5–79.1)</td>
</tr>
</tbody>
</table>

Conclusions: These findings from the latest nationally representative sample of US adults indicate that the prevalence of comorbidities proportionally increases with increasing levels of serum urate.


1548

How Large Are the Productivity Losses in Contemporary Patients with RA, and How Soon in Relation to Diagnosis Do They Develop? A Six-Year Nationwide Cohort Study. Martin Neovius1, Johan Asklung2 and ARTIS Study Group3. 1Karolinska Institute, Stockholm, Sweden, 2Karolinska Institute, Stockholm, Sweden, 3Karolinska Institute, Stockholm, Sweden

Background: Marked changes in the therapeutic approaches to early RA have taken place the last decade. Whether the increasing treatment intensity and number of treatment options have led to improvements in work ability is unclear. Furthermore, nationwide assessments of the societal burden due to reduced work ability in contemporary patients with RA are lacking.


Methods: Patients of working age diagnosed with early RA in 1999–2007 were identified in the Swedish Rheumatology Quality Register (early RA cohort: n=3,084; mean age 46y; 73% women). Additionally, prevalent patients on Jan 1, 2008, were identified in the National Patient Register and the Swedish Rheumatology Quality Register (prevalent RA cohort: n=25,934; mean age 52y; 73% women). For each patient with RA, five age-, sex-, education-, county- and time period-matched general population comparators were sampled. Sick leave and disability pension days were retrieved from national registers for 1997 to 2007.

Results: In the early RA cohort, sick leave and disability pension increased from a mean 44 to 118 days/year (mean difference 74, 95%CI 69–79) from the year before to the year of RA diagnosis. A further increase to 133 days/year (mean difference 15, 95%CI 11–20) was observed the following year, followed by a rebound to 118 and 115 days/year the subsequent two years. During the three years following RA diagnosis, sick leave halved from a mean 103 to 51 days/year while disability pension doubled from 30 to 64 days/year.

Table: Comorbidities According to sUA Level Categories in NHANES 1999–2008

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Conclusions: These findings from the latest nationally representative sample of US adults indicate that the prevalence of comorbidities proportionally increases with increasing levels of serum urate.
Incidental Capture of Chikungunya Associated Chronic Rheumatism along with Other Rheumatic Musculoskeletal Disorders in a Rural Community in South India: A BJD India WHO COPCORD (Community Oriented Program for Control of Rheumatic Diseases) Project.

Ashish J. Mathew, Vinay Goyal, Elizabeth George, Dany Varughese, along with Other

Results: Painful RMSD, the predominant self-reported ailment, was present in 30% of the community (Mean age of 53.24±15.3 years, 72% women). Common pain sites were knees (83.5%), elbows (36%), low back (31.1%) and shoulders (29.5%). Cases were broadly classified as ill-defined aches (28%), soft tissue rheumatism (21%), degenerative joint disease (20%), post-infectious arthropathy (19%), inflammatory arthritis (4%) and miscellaneous (8%). The crude point prevalence rates of RMSD are shown below.

### Table 1. Crude prevalence rates of RMSD in each group

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Prevalence (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue rheumatism</td>
<td>10.13</td>
<td>9.3–10.96</td>
</tr>
<tr>
<td>Periarthritis shoulder</td>
<td>2.16</td>
<td>1.83–2.49</td>
</tr>
<tr>
<td>Plantar fascitis</td>
<td>1.56</td>
<td>1.28–1.84</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>1.29</td>
<td>1.03–1.55</td>
</tr>
<tr>
<td>Degenerative arthropathy</td>
<td>9.72</td>
<td>8.91–10.53</td>
</tr>
<tr>
<td>Knee OA</td>
<td>5.77</td>
<td>5.23–6.31</td>
</tr>
<tr>
<td>Nodular OA</td>
<td>1.85</td>
<td>1.54–2.16</td>
</tr>
<tr>
<td>Infection related arthropathy</td>
<td>9.16</td>
<td>8.37–9.95</td>
</tr>
<tr>
<td>Post CHIK polyarthalgias</td>
<td>5.73</td>
<td>5.2–6.26</td>
</tr>
<tr>
<td>Post CHIK reactive arthritis</td>
<td>2.45</td>
<td>2.1–2.8</td>
</tr>
<tr>
<td>Post CHIK tenosynovitis</td>
<td>0.95</td>
<td>0.73–1.17</td>
</tr>
<tr>
<td>Infectious arthritis</td>
<td>1.79</td>
<td>1.43–2.15</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>0.51</td>
<td>0.35–0.67</td>
</tr>
<tr>
<td>SSA</td>
<td>0.58</td>
<td>0.41–0.75</td>
</tr>
</tbody>
</table>

CHIKV related RMSD was classified in 14% cases, of which 283 (Mean age: 45.64±11.37 years, 76% women) were naïve for RMSD prior to the epidemic. Polyarticular onset (OR = 4.35; 95% CI 2.77–6.83), wrist pain at onset (OR = 4.23; 95% CI 2.62–6.45) and female sex (OR = 2.74; 95% CI 1.76–4.28) were predictors of chronic rheumatism in this group. Similar to Bhigwan COPCORD the prevalence of RA and SSA was conspicuous. Significant HAQDI was scored by 17% respondents. Difficulty in the HAQ items of walking, squatting and sitting cross-legged corresponded with the dominant pain sites in knees and lower back. In the age group 25–54 years, 9% had ceased work due to RMSD.

Conclusion: Though ill defined rheumatism remained the dominant category in this rural community, a wide spectrum of RMSD was observed. Such has been the conclusion of several COPCORD surveys. In the current study, CHIKV enhanced the community burden of RMSD. A long term follow up is warranted to study the future impact.

Funded by Bone and Joint Decade - India.

Disclosure: A. J. Mathew: Bone and Joint Decade – India, 2; V. Goyal: None; E. George: None; D. Varughese: None; J. Antony: None; A. Chopra: Bone and Joint Decade–India, 6.

1550

Mortality Outcomes amongst Patients with Rheumatoid Arthritis with and without Joint Surgery: A Comparative Study. Courtney A. Shourt1, Cynthia S. Crowson2, Sherine E. Gabriel3 and Eric L. Matteson4. 1Department of Medicine, Mayo Clinic College of Medicine, 2Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic College of Medicine, 3Division of Epidemiology, Department of Health Sciences Research, and Division of Rheumatology, Mayo Clinic College of Medicine, 4Division of Rheumatology, Mayo Clinic College of Medicine.

Objective: To examine the association between joint surgery and mortality in patients with rheumatoid arthritis (RA).

Methods: A retrospective medical record review was performed of all cases of adult onset RA incident from a defined geographic population base who fulfilled criteria for RA in 1980–2007. The arthritis related surgeries included in the study were primary total joint arthroplasty (TJA), joint reconstructive procedures (JRP), soft tissue procedures (STP) and revision arthroplasty. Cox models with time-dependent covariates for surgery occurring during follow-up were used to examine the influence of surgery on mortality.

Results: The study included 814 RA patients (mean age: 56 years; 68% female) with mean follow-up of 9.6 years, during which 204 died. A total of 190 patients underwent ≥1 surgical procedures involving joints during follow-up. The presence of any joint surgery was significantly associated with mortality (hazard ratio [HR]: 1.4; 95% confidence interval [CI]: 1.01, 1.96; p = 0.04) compared to patients not requiring joint surgery. This association was more pronounced among patients with JRP (HR: 2.77; 95% CI: 1.85, 4.16; p < 0.001). Following additional adjustment for risk factors known to be associated with mortality in RA patients (age, sex, calendar year, body mass index, smoking, rheumatoid factor positivity, severe extra-articular manifestations, comorbidities [cardiovascular disease, renal disease, liver disease, dementia, cancer, alcohol abuse] and use of glucocorticoids), the mortality risk associated with any joint surgery was somewhat attenuated.
(HR: 1.37; 95% CI: 0.96, 1.97; p = 0.08), but the association with JRP persisted (HR: 2.86; 95% CI: 1.89; 4.33; p < 0.001).

**Conclusion:** Overall, there were significant differences in survivorship in patients with RA undergoing joint surgeries compared to patients who did not require joint surgery, especially among patients with JRP. This association persisted following adjustment for known risk factors for mortality possibly indicating a higher disease burden in these patients.

**Disclosure:** C. A. Shourt: None; C. S. Crowson: None; S. E. Gabriel: None; E. L. Matteson: None.

**1551**

**Oral Tobacco Use Is Significantly Associated with Rheumatic Musculoskeletal (RMSK) Pain: Result of a WHO ILAR COPCORD (Community Oriented Program for Control of Rheumatic Diseases) Rural Population Study in India**, Arvind Chopra,1 Sarika Chaturvedi,2 Manjit Saluja2, Vajjayanti Lagoo Joshi2 and Sanjiv Sarmukadam.1 Center for Rheumatic Diseases, Pune, India, 2Center for Rheumatic Diseases, 4FCRC, Pune, India

Tobacco is a risk factor for RA and osteoporosis but its role in RMSK pain is not reported. Oral tobacco is a popular custom in India with alleged benefits of enabling work (or bearing pain) in a socioeconomically challenged scenario.

We reported significant oral tobacco use in patients with RMSK pain from 4000 village Bhigwan (South Pune) COPCORD survey (Chopra, J Rheumatol 2003; 29: 614). In 2004, we completed 4000 urban population COPCORD survey in Pune (West India) and though there were urban rural differences (Joshi, Chopra. J Rheumatol 2009; 36: 614), oral tobacco use remained significant (OR 1.78, 95% CI 1.30, 2.4; not published). In 2008, we completed another 4775 non-random population (90% response, 95% Hindu Maharashtrian ethnic) survey in village Balegan Sidhi (East Pune) using Bhigwan model. Surveys were cross sectional and populations matched well with Indian census 2001. Phase I Ralegan data analysis results are presented.

**Methods:** The methodology of COPCORD Bhigwan has been published (see above ref). The screening question was “Have you suffered from pain/swelling/stiffness in the joints or musculoskeletal soft tissues within the last seven days (considered current) or sometime in the past (last 3 months)?” Respondents marked pain sites on a human mannequin. All evaluations were carried out free of cost. Data was entered in MS Excel format and analyzed using statistical package (SPSS). 11 of the 19 variables from phase I database were selected in a step wise procedure for logistic regression analysis; RMSK (past or current) was the dependent variable. Variables discarded in the final run were *marital status, *literacy (read and write), alcohol use, *combined farm and house work, *vehicle accident, *stransport, *fracture and *sprain/ fracture; *found significant in univariate analysis.

**Results:** 1513 population (32%) reported RMSK pain; women preponderant(2:1). In 85% cases, pain lasted >4 weeks at multiple sites (>3). 37% men and 32% women used oral tobacco (rubbed tobacco powder on teeth and gums at least twice daily) and recalled several years of past use. 49.8% cases recorded tobacco use (p = 0.05). Table shows OR.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (female)</td>
<td>1.54</td>
<td>1.27, 1.87</td>
</tr>
<tr>
<td>Diet (Non-vegetarian)</td>
<td>0.741</td>
<td>0.643, 0.855</td>
</tr>
<tr>
<td>Religion (Hindu)</td>
<td>1.70</td>
<td>1.20, 2.41</td>
</tr>
<tr>
<td>Attended school</td>
<td>0.704</td>
<td>0.601, 0.825</td>
</tr>
<tr>
<td>Oral Tobacco Use (past/current)</td>
<td>1.28</td>
<td>1.09, 1.49</td>
</tr>
<tr>
<td>Farming</td>
<td>1.20</td>
<td>1.01, 1.41</td>
</tr>
<tr>
<td>Household work</td>
<td>2.01</td>
<td>1.66, 2.43</td>
</tr>
<tr>
<td>Intense Labour</td>
<td>1.40</td>
<td>1.20, 1.64</td>
</tr>
<tr>
<td>Accident, any type</td>
<td>4.55</td>
<td>3.60, 5.75</td>
</tr>
<tr>
<td>Agriculture related trauma</td>
<td>1.59</td>
<td>0.947, 2.67</td>
</tr>
</tbody>
</table>

**Conclusion:** In this rural COPCORD, oral tobacco use was a significant risk factor for RMSK pain. This validates our earlier conclusion from previous urban and rural COPCORD in the Pune region. Not surprisingly, history of accident trauma was a significant risk factor in the current report. Tobacco and trauma have important preventive bearing in public health, more so in developing economies.

**Disclosure:** A. Chopra: None; S. Chaturvedi: None; M. Saluja: None; V. Lagoo Joshi: None; S. Sarmukadam: None.

**1552**

**Osteoporosis Medication Adherence and Fracture Risk Among Women in a Large U.S. Health Plan.** Hema Viswanathan,1 Sally W. Wade2, Jeffrey R. Curtis3, Jingbo Yu4, Jeffrey White5, Bradley Stolshoke, Claire Merinard,6 Akhila Balasubramanian,2 Joel Kallich2 and John Adams5.1 Amgen Inc., Thousand Oaks, CA, 2Amgen Inc., 3HealthCore, Inc., 4University of Alabama at Birmingham, 5Wade Outcomes Research and Consulting, 6WellPoint, Inc.

**Purpose:** Osteoporosis (OP) poses a significant economic and clinical burden. Low adherence may mitigate treatment efficacy, including fracture risk reduction. This study examined the association between OP medication adherence during the first year on therapy and subsequent fracture risk using recent data from a commercially insured population.

**Methods:** Female patients were identified from a large, commercially insured U.S. population with integrated pharmacy and medical claims. Patients were included if they were ≥ age 45, new to OP therapy (no OP medication claims in prior year) with first (index) OP medication claim between 1/1/2005 and 4/30/2008, and had continuous coverage for ≥ 12 months pre- and post-index. Patients were excluded if they had: pre-index Paget’s disease or malignant neoplasm, or were in a skilled nursing facility, or on multiple OP medications at index. Clinically-diagnosed and coded fractures were identified using published claims criteria. Patients who had a fracture in the first year on therapy were excluded. This ensured that the time periods for assessing exposure (medication) and outcome (fracture) did not overlap. Logistic regression was used to assess the association between the medication possession ratio (MPR: < 0.5, 0.5 to 0.8, > 0.8) during the 12 months post-index and fracture risk thereafter in bisphosphonate users. Covariates included baseline demographic and clinical characteristics including comorbidities and prior fracture.

**Results:** The analysis included 35,958 patients who were new to OP therapy, had a mean age (± SD) of 59.4 ± 9.2 years (range: 45 to 102 years), and had a mean post-index follow up of 834.3 days. At index, 99.6% of patients used a bisphosphonate. Over 12 months post-index, the mean MPR was 0.57 (95% CI: 0.57, 0.58). Mean 12-month MPR was lower among patients with fracture (N = 1,006) compared with those without fracture (N = 34,952; 0.54 vs 0.57, respectively; p < 0.001). Patients were clustered at the upper and lower ends of the MPR range. In multivariate modeling, bisphosphonate users with a MPR > 0.8 (N = 12,318) over 12 months had a 18% lower risk of subsequent fracture compared with those with a MPR < 0.5 (N = 13,878), even after controlling for demographic characteristics, insurance type, prior fracture, select comorbidities, and other potential confounders (p = 0.007; Table).

**Conclusion:** In this study, female patients in a large, commercial health plan had a mean 12-month MPR of 0.57 for OP medications. Women with low adherence (MPR < 0.5) experienced an increased fracture risk even after controlling for a large number of fracture-related covariates.

**Disclosure:** H. Viswanathan: Amgen Inc., 1, 3; S. W. Wade: Amgen Inc., 5; J. R. Curtis: Novartis, Eli Lilly, 2, 5, 8, Novartis, Merck, Procter & Gamble, Eli Lilly, 2, 5, 8, Procter & Gamble, Merck, 2, 5, 8, J. Yu: Amgen Inc., 2; J. White: None; B. Stolshoke: Amgen Inc., 1, 3; C. Merinard: Amgen Inc., 1, 3; A. Balasubramanian: Amgen Inc., 1, 3; J. Kallich: Amgen Inc., 1, 3; J. Adams: Amgen Inc., 5.
Patient Age, Ethnicity and Wait Times Determine the Likelihood of Non-Attendance at a First Specialist Rheumatology Assessment. Valerie Milne, Robin Kearns and Andrew A. Harrison. University of Auckland, New Zealand, New Zealand, University of Otago, Wellington, New Zealand, New Zealand

Purpose: Failure to attend first specialist assessment in rheumatology clinics not only results in lost opportunities for early diagnosis and treatment with DMARDs but also wastes health resources. Long wait times and deprivation have been linked with non-attendance at outpatient appointments. This study aims to identify factors that predict non-attendance at rheumatology FSA with a view to optimising use of resources and patient outcomes.

Method: Administrative data for 1,953 new referrals over a 2-year period were collected from a public rheumatology unit that provides rheumatology services for three New Zealand health boards. Bivariate odds ratios were generated to test the association between attendance and geographic, demographic and clinic referral variables. Variables that were significant at the 0.05 level were included in linear regression models that tested their association with outcomes.

Results: Referral appointments were completed for 87 percent of patients. Of the uncompleted referrals, 6 percent cancelled in advance and 7 percent failed to attend without prior warning. Patient age (p<0.001) and ethnicity (p=0.002) predicted failure to attend. New Zealand Maori (OR 0.74, CI 0.54–0.95) and Pacific Island (OR 0.72, CI 0.54–0.95) patients were less likely to attend their FSA than New Zealand Europeans, and patients in the 20–29 age group were less likely to attend than 40–49 year olds (OR 0.55 CI 0.41–0.74). Gender was not a significant factor in attendance.

Likelihood of failing to attend was also associated with longer wait times (p<0.002). However, although age and ethnicity affected attendance, wait times were independent of these factors, with referral location and clinic location being significant predictors of long wait times (p<0.001). Patients referred from locations near to the hub of the rheumatology service had shorter mean wait times than those living further away. Patients referred from the health board providing the service were significantly more likely to have a shorter wait to the FSA than patients from within the other two health boards (OR 0.56 CI 0.51–0.61 and OR 0.40 CI 0.34–0.47).

Conclusion: In this study age, ethnicity, wait times and location of services were important predictors of non-attendance at FSA. Attendance rates could potentially be improved by focussing clerical resources on at-risk demographic groups and by restructuring the clinical service to reduce wait times and geographic barriers. This could result in more efficient use of clinic resources and more timely intervention in inflammatory arthritis.


Disclosure: V. Milne: None; R. Kearns: None; A. A. Harrison: None.

Predictors of Vitamin D Deficiency among Veterans. Joshua Baker, Alexis Ogdie, Li Yun Zhang, Jan Dinella, H. Ralph Schumacher and Sally W. Pullman-Moor. Philadelphia, PA, Second Hospital of Shanxi Medical University, China, University of Pennsylvania, Philadelphia, PA, University of Pennsylvania, VA Medical Center - 151K, Philadelphia, PA

Introduction: Due to a number of factors, vitamin D deficiency is increasingly recognized as highly prevalent in many populations and of increasing concern among rheumatologists due to its noted effects on bone, immunity, and cardiovascular health. It remains unclear which patients are of highest risk for vitamin D deficiency.

Methods: 4076 patients with vitamin D levels performed at our VA Medical Center were extracted within a 24-month period, between 2007 and 2008, from the electronic medical record. Diagnosis codes and other demographic data were also extracted. A predictive model was created using multivariable logistic regression analysis with vitamin D deficiency (<20 ng/mL) as the outcome.

Results: Patients with vitamin D deficiency were more likely to be younger, black, female, and have arthritic joint pain. Vitamin D deficiency was strongly associated with the number of additional diagnoses including diabetes, obesity, stroke, and renal disease. The lowest levels of vitamin D were found in patients with CKD, diabetes, degenerative disc disease, and stroke. The patients with calcium pyrophosphate deposition disease (CPPD) had the lowest levels of vitamin D of all diagnoses evaluated. In multivariable logistic regression, the strongest independent predictors of deficiency were younger age, black race, winter month, elevated systolic blood pressure, obesity, and a history of stroke, renal disease, and diabetes. Interestingly, patients with osteoporosis, RA, and SLE had significantly increased levels of vitamin D compared to other groups, possibly secondary to supplementation practices within those groups. These findings were similar when a cutoff of <30 ng/mL was used (not shown).

Conclusions: Our results suggest that, among veterans, increased attention should be paid to the risk of vitamin D deficiency in patients who are black, obese, and have multiple co-morbidities, including a history of hypertension, renal disease, stroke, and diabetes. Further study in patients with CPPD disease is indicated. Our limitations include indication bias and lack of data on supplementation.

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Projecting the Effects of a 5-Point Reduction in Body Mass Index on Knee or Hip Osteoarthritis and Health-Related Quality of Life in a Closed Population to 2031: A Microsimulation Study. Eric C. Sayre, Jacke A. Kope, Behnam Shari, William M. Flanagan, Philippe Fines, Moshfikur Rahman, Michal Abrahamowicz, David Buckridge, Sam Harper, John Lynch, Douglas Manuel, Jillian Oderkh and Michael Wolfson. Arthritis Research Centre of Canada, Vancouver, BC, Canada, McGill University, Canada, Statistics Canada, Canada, University of British Columbia, Canada, University of British Columbia, Canada, University of Ottawa, Canada, University of South Australia, Canada

Purpose: Body mass index (BMI) is a risk factor for knee or hip osteoarthritis (OA). Obesity (BMI >/= 30) increased from 10 to 15% in Canada between 1990 and 2000. BMI reduction is expected to reduce OA and improve health-related quality of life (HRQoL). The purpose of this study is to project in a national cohort the effect of a risk-targeted 5-point reduction in BMI on OA and HRQoL between 2001 and 2031.

Method: We used the Population Health Model (POHEM) platform to develop a stochastic continuous-time microsimulation model of physician-diagnosed OA. Incidence rates were calibrated to agree with administrative data for British Columbia, Canada. Projected upward trends in BMI under the base case (no intervention), the effect of obesity on OA incidence and the impact of OA on HRQoL were modeled using Canadian national surveys and
hospital data. The effect of BMI on OA was fit categorically: underweight (<18.5), normal (<25.0), overweight (>30.0) and obese (≥30.0). A closed population weighted for 2001 Canada that reflected projected mortality was followed in PÔHEM to 2031, aged 20+. BMI was reduced by 0 or 5 points in 2001 in persons with BMI≥25. Outcomes included OA prevalence and incidence (per 1000 person years), average Health Utilities Index Mark 3 (HUI), and health-adjusted life years (HALE). Monte Carlo error was estimated via subsamples. HRQoL models included BMI only indirectly through risk of OA.

Results: There were 22,483,400 in-scope subjects in the simulated population in 2001, 14,317,129 in 2031. Average age in 2001 is 45.89% (Monte Carlo CI=45.79, 45.99), in 2031 is 67.43% (67.37, 67.50). In 2001, average BMI is 25.55 (25.53, 25.58), OA incidence 7.42 (7.35, 7.49), OA prevalence 12.23% (12.00, 12.46), average HUI 0.874 (0.872, 0.875), proportion obese 14.99% (14.77, 15.20) and proportion overweight 33.66% (33.38, 33.94).

Under the base case, in 2031, average BMI is 27.79 (27.75, 27.82), OA incidence 21.03 (20.89, 21.16), OA prevalence 33.11% (32.98, 33.25), average HUI 0.752 (0.750, 0.753), proportion obese 26.82% (26.6, 27.04) and proportion overweight 37.15% (36.97, 37.33), with the rest normal or underweight. HALE for 20 year-olds is 27.06 (26.79, 27.21), for 24 year-olds 24.71 (24.61, 24.80) and for 60 year-olds 16.94 (16.81, 17.07).

With a 5-point targeted reduction in BMI, in 2031, average BMI is 25.56 (25.53, 25.58), OA incidence 19.29 (19.16, 19.42), OA prevalence 30.69% (30.55, 30.82), average HUI 0.756 (0.754, 0.758), proportion obese 11.57% (11.4, 11.74) and proportion overweight 38.19% (38.01, 38.36). HALE for 20 year-olds is 27.14 (26.99, 27.28), for 40 year-olds 24.81 (24.72, 24.91) and for 60 year-olds 17.00 (16.87, 17.12).

Conclusion: Reducing at-risk BMI by 5 points in 2001 would lead to a moderate reduction in OA (1.74 incidence and 2.42% prevalence) by 2031, but only very small improvements in HRQoL attributable to rates of OA. Lowering BMI will have additional direct benefits on HRQoL. Monte Carlo error was small; future studies should incorporate additional error such as around parameter estimates. Future studies should vary BMI reduction and the target group, and simulate open populations including births and immigration.

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1556
Racial Differences in Gout Risk and Uric Acid Levels in Both Men and Women in the Atherosclerosis Risk in Communities (ARIC) Study. Janet W. Maynard, Mara A. McAdams, Alan N. Baer, Allan C. Gelber and Josef Coresh. Johns Hopkins

Purpose: Gout is a common form of inflammatory arthritis; yet, few studies have evaluated the relationship between race and gout in both women and men. We evaluated the association of race with gout and uric acid levels in the Atherosclerosis Risk in Communities (ARIC) Study, a large population-based and racially-diverse cohort.

Methods: ARIC is a population-based cohort study of 15,792 individuals (55% women) recruited in 1987–1989. Our study population consisted of African-American and Caucasian men and women with and without gout. A participant was considered to have gout if 1 or more of the following criteria were met: a) gout was self-reported, b) surveillance of hospital discharge summaries revealed an ICD-9 code for gout (274.0, 274.1, 274.8, or 274.9), or c) the participant reported use of a medication taken primarily to treat gout (allopurinol, colchicine, or probenecid) at any study visit. The distributions of baseline variables among the men with gout versus those without gout were compared using chi-squared or t-tests, as appropriate. We stratified by gender and used multivariate logistic regression to model the association of race and prevalent gout. The multivariate models included baseline age, BMI, protein, organ meat, shellfish, and alcohol intake, hypertension, anti-hypertensive medication use, income, education, tobacco use, diabetes, and renal function. Lastly, we generated a multivariate model with the previously mentioned confounders and uric acid.

Results: 399 women (4.6%) and 702 men (9.9%) had gout in the ARIC cohort. In both men and women, a significantly higher proportion of African-Americans had gout (p<0.001). After stratifying by gender, the mean serum uric acid level was higher in African-Americans compared to Caucasians (p<0.001 in women and men). The mean difference in uric acid levels for African-Americans versus Caucasians was 0.57 mg/dL (0.50, 0.64) in women and 0.31 mg/dL (0.22, 0.40) in men. African-American race was associated with an increased risk of gout even after adjusting for known confounders in both men and women (Table). However, after further adjustment for uric acid levels at baseline, the effect was not statistically significant.

Table. Association of Race with Gout in the Atherosclerosis Risk in Communities (ARIC) Study.

<table>
<thead>
<tr>
<th></th>
<th>Caucasians</th>
<th>African-Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gout cases, n (%)</td>
<td>203 (3.4)</td>
<td>196 (7.4)</td>
</tr>
<tr>
<td>Uric acid level (mg/dL) (mean ± SD)</td>
<td>5.3 ± 1.4</td>
<td>5.9 ± 1.5</td>
</tr>
<tr>
<td>Age-adjusted OR (95% CI)</td>
<td>1.00 (Ref)</td>
<td>2.42 (1.97, 2.96)</td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1.00 (Ref)</td>
<td>1.57 (1.17, 2.10)</td>
</tr>
<tr>
<td>Multivariate Model including uric acid OR (95% CI)</td>
<td>1.00 (Ref)</td>
<td>1.34 (0.99, 1.80)</td>
</tr>
</tbody>
</table>

Key: OR=odds ratio; CI=confidence interval

Conclusions: African-American race is associated with a greater than 50% increase in risk of gout in both men and women, even after adjustment for known confounders. This suggests that above and beyond differential prevalence of medical comorbidities, including hypertension, race increases gout risk. This increased gout risk may be mediated by higher uric acid levels in African-Americans compared to Caucasians.

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1557
Racial/Ethnic and Sex Differences in Somatosensory Abnormalities in Subjects with or at High Risk of Knee Osteoarthritis: Preliminary Analysis of the Multicenter Osteoarthritis (MOST) Study. Jasvinder Singh1, Niu Jingbo2, Laura Freylaw2, Joachim Scholz3, Lars Arendt-Nielsen4, Cora E. Lewis5, Clifford Woolf6, Larry Bradley6, David T. Felson7, Michael C. Nevitt7, Irina Tolstykh7 and Tuhina Neogi8. 1Aalborg University, Aalborg, Denmark, 2Birmingham VA Medical Center and University of Alabama, Birmingham, Minneapolis, MN, 3Boston Univ Schl of Med, Boston, MA, 4Boston University School of Medicine, Boston, MA, 5Birmingham VA Medical Center and University of Alabama, Birmingham, Minneapolis, MN, 6Boston Univ Schl of Med, Boston, MA, 7UCSF, San Francisco, CA, 8University of Alabama, Birmingham, University of Iowa

Objective: There may be racial/ethnic and sex differences in the pain experience of knee OA, which may be reflected in differences in somatosensory abnormalities. Our objective was to assess differences in somatosensory findings between Caucasians and African-Americans (AA), and between men and women.

Methods: MOST is a cohort study of persons aged 50–79 years of age, with or at high risk of knee OA. At the 60-month clinic visit, participants underwent knee radiography, answered pain questionnaires, and had the following somatosensory assessments: static allodynia using a 26g monofilament, and hyperalgesia using a pin. Temporal summation (TS), an augmented pain response to repetitive mechanical stimuli thought to reflect central sensitization, was also assessed. These assessments were carried out separately over each patella and wrist. An abnormal response to 26g or pinprick was defined as the participant experiencing pain or a non-response on 3 out of 4 trials, respectively. TS was defined as being present when, after touching the skin with a 60g monofilament repeatedly at a frequency of 1Hz for 30 seconds, the subject reported increased pain or new pain at the site being tested. Univariate and multivariate-adjusted prevalences (age, BMI, clinic and race and sex, as applicable) of the somatosensory tests were obtained for each site and summed as being present overall at any site, stratified by race/ethnicity and gender.

Results: Of the 770 with somatosensory data, there were 652 Caucasians (438 women, 214 men) and 118 AAs (73 women, 45 men). Mean age, BMI and K-L grade was similar for all groups (Table 1).
Adjusted prevalence of static allodynia with 26g was higher in African-American women and almost achieved statistical significance (p = 0.06) (Table 2). Adjusted prevalences of the pin-prick and temporal summation somatosensory evaluations were not significantly different among the sex and racial groups.

Table 2. Age, BMI- and clinic-adjusted prevalence rates (95% CI) of pain and Temporal summation (any site, person-based).

<table>
<thead>
<tr>
<th></th>
<th>White men</th>
<th>White women</th>
<th>Black men</th>
<th>Black women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), year</td>
<td>65.9 (8.3)</td>
<td>68.1 (7.2)</td>
<td>62.8 (7.0)</td>
<td>65.2 (8.0)</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>30.0 (5.3)</td>
<td>28.5 (5.4)</td>
<td>31.3 (6.0)</td>
<td>32.6 (5.8)</td>
</tr>
<tr>
<td>P-value is from an Analysis of variance</td>
<td>0.073</td>
<td>0.080</td>
<td>0.025</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Adjustment for presence/absence of osteoarthritis did not impact the results for the pinprick and temporal summation tests; however this model did not converge for static allodynia for 26g.

Conclusions: African-Americans and women had greater prevalence of somatosensory abnormalities compared with Caucasians and men, but most of these differences were not statistically significant. This preliminary study is the first to demonstrate racial/ethnic difference in response to the 26g von Frey hair stimulus in patients with knee OA. Further exploration regarding factors that may contribute to such differences is warranted.

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1558

Relationship between Physical Activity and Health-Related Utility in Knee Osteoarthritics Patients. Larry Manheim1, Jing Song2, Rowland W. Chang1 and Dorothy D. Dunlop2. 1Northwestern Univ, Chicago, IL, 2Northwestern University, 3Northwestern University Medical School, Chicago, IL

Purpose: Cost Effectiveness analysis relies on health utility measurement to evaluate the relative effectiveness of many interventions. We examine the relationship between health-related utility and physical activity levels in persons with Knee Osteoarthritis (KOA), to address the following questions: 1) do individuals who meet Center for Disease Control (CDC) recommended levels of physical activity have higher levels of health-related utility? 2) is it necessary to meet CDC guidelines to have higher utility levels or is utility positively related to physical activity at more modest levels of physical activity? 3) is it necessary to meet CDC guidelines to have higher utility levels or is utility positively related to physical activity at more modest levels of physical activity? 4) is it necessary to meet CDC guidelines to have higher utility levels or is utility positively related to physical activity at more modest levels of physical activity?

Methods: This study uses baseline data from 143 subjects with radiographic knee OA (KL grade 2) enrolled in the IMPAACT study, a randomized controlled trial to evaluate a tailored physical activity intervention. The SF-36 health-related quality of life measure was used to derive the SF6-D utility measure over the follow-up period (3, 6 and 12 months) which yields values between zero (death) and one (perfect health). Baseline physical activity was assessed by accelerometer worn over one week. Each person completed a set of baseline questionnaires, used to measure subject demographics, comorbidities (based on reported medication use), BMI, disability level, and level of pain. The relationship of physical activity to subsequent health utility over one year was assessed using multiple regression with general estimating equations (GEE) multiple regression.

Results: Health-related utility was significantly higher for persons who met CDC guidelines (≥ 150 minutes of moderate/vigorous activity per week in bouts lasting more than 10 minutes), relative to those who were inactive. However, only 11% of individuals meet guidelines and 40% of the sample had no bouts of moderate/vigorous activity. We therefore asked whether higher levels of any intensity activity (as measured by accelerometer counts) were positively associated with higher utility. We found that even moving above the lowest quartile of accelerometer counts to the next quartile was associated with a significant increase in utility of 0.051 points (p = 0.025), after controlling for KL grade, pain, number of comorbidities present, level of disability, and demographics. Among these other factors only level of pain remains a significant predictor of utility level when all variables are included in the regression.

Table. Partial Association of Physical Activity with Utility after controlling for Disease Severity, Pain, Comorbidities, Disability, Intervention, Demographics

<table>
<thead>
<tr>
<th>Level of Physical Activity</th>
<th>Average Utility (Adjusted)</th>
<th>Partial Coefficient (Adjusted)</th>
<th>Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest Quartile</td>
<td>0.765</td>
<td>reference group</td>
<td></td>
</tr>
<tr>
<td>Lower Middle Quartile</td>
<td>0.816</td>
<td>+ 0.51</td>
<td>p = 0.025</td>
</tr>
<tr>
<td>Highest Middle Quartile</td>
<td>0.838</td>
<td>+ 0.073</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>Highest Quartile</td>
<td>0.845</td>
<td>+ 0.080</td>
<td>p = 0.003</td>
</tr>
</tbody>
</table>

Conclusion: Higher levels of physical activity at baseline were related to higher subsequent levels of health-related utility in KOA. This result holds for those meeting CDC guidelines. Importantly even persons not meeting guidelines but doing some activity had better utility that persons in the bottom activity quartile (largely inactive) Thus, even modest increases in physical activity levels may provide a significant improvement in health utility.

Disclosure: L. Manheim: NIH, 2; J. Song: NIH, 2; R. W. Chang: NIH, 2; D. D. Dunlop: NIH, 2.

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Reporting of the Recruitment Process in Randomized Clinical Trials of Biological Agents for the Treatment of Rheumatoid Arthritis. Ismail Simsek and Yusuf Yazici. NYU Hospital for Joint Diseases

Purpose: Before using the results of a randomized controlled trial (RCT) for treating an individual patient, a clinician must determine whether the patient differs from those who participated in the trial in a meaningful way. Therefore it is important to evaluate how the RCT sample was assembled from the general patient population. The trial recruitment process can be described with qualitative and quantitative data, both of which can contribute important information about the generalizability/external validity. The adequacy of reporting in RCTs has received increased attention and culminated in the publication of guidelines such as CONSORT. We tried to assess the adequacy of reporting of the recruitment process and quantify the levels of RA patients participating in RCTs of biological agents.

Methods: PubMed was searched for all reports of RCTs involving etanercept, infliximab, adalimumab, golimumab, certolizumab, abatacept and rituximab in RA patients in the English language published before 12/31/2009. Extension studies, interim analysis, and secondary analysis of previously published data were excluded as were phase I and phase II trials. Data recorded were: (1) eligibility fraction (proportion eligible of those screened), (2) enrolment fraction (proportion randomized of those eligible), (3) recruitment fraction (proportion of potential participants actually randomized), and (4) number of patients needed to be screened (NNS) in order to randomize one participant.

Results: A total of 45 RCTs were identified. Seventeen (37%) reported the number of patients who were evaluated by the investigators for eligibility, 14 (31%) reported the number eligible for participation, and all reported the actual number recruited. Only 9 (20%) of the RCTs reported recruitment process completely. Of the studies that reported quantitative recruitment information, the median eligibility fraction was 81% (IQR 71% to 91%), and the median enrolment fraction was 99% (IQR 82.25% to 100%). The median NNS was 123 (IQR 1.16 to 1.42), with most trials reportedly recruiting every patient screened for eligibility. We found no associations between provision of sufficient recruitment data and funding source, publication year, and the journal where the article was published.

Conclusions: A substantial majority of RCTs did not provide sufficient information about the patient recruitment process which makes assessments of external validity difficult. Furthermore, the rate of reporting of the recruitment process in this study was found to be lower as compared to similar studies conducted in different specialties or disease settings. Our finding of low NNS levels also suggests that once screened for eligibility patients are likely to be randomized. However, this finding needs to be treated with caution as it may actually present inadequate reporting of the eligible population.

Rheumatologists Practise Evidence Based Medicine, an Observational Study. Stephen Hall1, Adam Moreton2, Kathryn A. Gibson2, Barry A. Kane3, Vivek Thakkar1, J. Hanrahan1, Evange Romain1, Timothy Godfrey4, Marie Feletar5, Alexander Stockman2, Jennifer Harmer1, Rani Axten2, Peter Ryan1, Andrew Gibbons2, Christopher Mack3, Robert J. Moots6 and Geraldine Hassett1. 1Department of Medicine, Cabrini Health, Melbourne, Australia, 2Rheumatology Department, Liverpool Hospital, Sydney Australia, 3School of Clinical Sciences, University of Liverpool, Liverpool United Kingdom, Liverpool, United Kingdom, 4School of Clinical Sciences, University of Liverpool United Kingdom

Background: Evidence-based medicine (EBM) is used to inform treatment guidelines and in decision-making about funding for medicines and procedures. The extent to which evidence exists and EBM is employed in clinical rheumatology practice is unclear.

Objectives: To assess the extent to which rheumatologists in office practice follow EBM in their treatment recommendations.

Methods: The medical records of 190 patients attending rheumatology clinics with participating physicians (Liverpool Hospital, Sydney, Australia, private practices in Melbourne, Australia and University Hospital Aintree, Liverpool, UK) on or after 2nd July 2007 were reviewed and interventions were identified for each diagnosis made. A standardized search protocol was utilized to identify randomized controlled trials (RCT) in Medline (1950– present) and EMBASE (1980–present) supporting these interventions. In addition the Cochrane Database of Systematic Reviews was searched. Where there was no RCT evidence to support a treatment recommendation a subsequent adjudication process was undertaken to assess the recommendation by expert opinion.

Results: A total of 332 interventions were recommended. This generated 251 literature searches. Approximately 50% of interventions in clinical rheumatology were supported by EBM. The adjudication process supported 64% of non EBM based recommendations. Only 20% of interventions were neither supported by EBM or at adjudication. This occurred more often for soft tissue and non-inflammatory conditions compared to inflammatory conditions and osteoporosis. Adherence to EBM was similar in the private and public sector in Australia and across the public sectors of Australia and the United Kingdom.

Conclusion: Approximately 50% of rheumatology practice is supported by RCT data. Where RCT data does not exist, expert opinion supports 64% of the recommended interventions; thus only 20% of all interventions in rheumatology office practice lack evidence. The extent to which evidence exists varies across the rheumatic diseases. There is no difference in the rate of EBM across the public and private sectors of rheumatology.

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Screening and Treatment of Glucocorticoid Induced Osteoporosis in a Large U.S. National Pharmacy Database. Ryan C. Outman1, Nathan J. Markward1, Mona Khalid2, Ronald E. Aubert1, Jeffrey R. Curtis2, Robert S. Epstein1, Felix W. Freuh1, Eric J. Staneck1, Amy Steinkeller2, Amy H. Warriner1 and Kenneth G. Saag3. 1Medco Health Solutions, Inc., 2Univ of Warriner and Kenneth G. Saag2. 1Medco Health Solutions, Inc., 2Univ of

Purpose: To estimate the prevalence of being overweight/obese, among Canadians with arthritis, and to describe the arthritis self-management strategies among these individuals.

Methods: The 2009 Survey on Living with Chronic Diseases in Canada (SLCDC) was developed by the Public Health Agency of Canada in collaboration with Statistics Canada, to provide information on how arthritis affects Canadians, and how it is managed. A nationally representative sample of 4,565 Canadians aged 18 and older, who reported having diagnoses with arthritis has been conducted in the 2009 Canadian Community Health Survey (CCHS) was interviewed. Data from the 2009 SLCDC, was linked with data from the 2008 CCHS to analyze self-management strategies (including exercise, weight control/loss, classes, community based programs) among overweight (BMI=25.0-29.9) or obese (BMI≥30) Canadians with arthritis.

Results: The over-all response rate for the SLCDC survey was 78%. Within the SLCDC sample with arthritis(N=4,565), the majority were female(63.2%), aged 45+(88.6%), reported post-secondary education(68.7%) and were unable to report type of arthritis(42.4%).

Almost a third (27.4%) of the 4,565 was obese, with an additional 39.9% overweight. The overweight/obese individuals were mostly (59.5%) female and aged >45(89.7%). Regardless of weight category, about 75% had accessed a health professional in the past year, to manage their arthritis. Just under half (49.5%) of the overweight/obese individuals reported being told by a health professional to exercise, and a similar number (45.5%) were told to control/lose weight. A slightly smaller percentage of the overweight/obese versus under/ normal weight individuals (60.9% versus 67.1%, respectively) reported engaging in exercise to manage their arthritis symptoms. About 68% of overweight/obese individuals reported using weight control/loss to manage their arthritis symptoms.

Univariate analyses of overweight/obese individuals, we found no correlation between engaging in any arthritis self-management strategies and any of the following factors: age, income, marital status, region of residence, and time since diagnosis. Factors independently associated with not engaging in arthritis self-management strategies included: male sex; not having a

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Self-Management Strategies in Overweight/Obese Canadians with Arthritis. Sasha R. Bernatsky1, Corneliu Rusu2, Siobhan O’Donnell3, Gillian A. Hawker5, Crystal Mackay4, Louise McRae2, Mayilee Canizar4 and Elizabeth M. Badley3. 1Toronto, ON, Canada, 2University of Toronto, 5Women’s College Hospital, Toronto, ON, Canada

Purpose: To estimate the prevalence of being overweight/obese, among Canadians with arthritis, and to describe the arthritis self-management strategies among these individuals.

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medical doctor; not taking medications; no reported recommendation by a health professional to exercise, control/lose weight or use assistive devices; the presence of co-morbidities; worse self-reported health; and less disability in activities of daily living.

Correlates of NOT engaging in ANY self-management activities, for overweight/obese (BMI>25) individuals with arthritis (N = 273)

<table>
<thead>
<tr>
<th>Correlates</th>
<th>Crude RR</th>
<th>95% CI</th>
<th>Adjusted RR*</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Sex</td>
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<td></td>
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<tr>
<td>Female</td>
<td>Referent</td>
<td></td>
<td>Referent</td>
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</tr>
<tr>
<td>Male</td>
<td>1.64</td>
<td>1.12–2.40</td>
<td>1.71</td>
<td>1.16–2.52</td>
</tr>
<tr>
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<td>Non-white</td>
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<td>White</td>
<td>3.48</td>
<td>1.49–8.15</td>
<td>2.87</td>
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<td>Less than post-secondary</td>
<td>1.78</td>
<td>1.20–2.64</td>
<td>2.01</td>
<td>1.23–3.28</td>
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<tr>
<td>Medication use</td>
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<td></td>
<td></td>
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<tr>
<td>No medication</td>
<td>Referent</td>
<td></td>
<td>Referent</td>
<td></td>
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<tr>
<td>Prescription meds only</td>
<td>0.62</td>
<td>0.35–1.12</td>
<td>0.91</td>
<td>0.71–1.16</td>
</tr>
<tr>
<td>Non-prescription meds only</td>
<td>0.38</td>
<td>0.24–0.61</td>
<td>0.90</td>
<td>0.68–1.19</td>
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<tr>
<td>Both</td>
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<td>0.19–0.62</td>
<td>0.88</td>
<td>0.64–1.23</td>
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<td>Any medication (excl. natural treatments)</td>
<td>0.43</td>
<td>0.28–0.64</td>
<td>0.90</td>
<td>0.68–1.19</td>
</tr>
<tr>
<td>Any medication (incl. natural treatments)</td>
<td>0.33</td>
<td>0.22–0.52</td>
<td>0.90</td>
<td>0.58–1.38</td>
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Knowns type of arthritis

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<tr>
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<th>Referent</th>
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<th>Referent</th>
<th>Referent</th>
<th>Referent</th>
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<tr>
<td>Doesn’t know</td>
<td>1.50</td>
<td>1.01–2.24</td>
<td>1.47</td>
<td>1.1–1.95</td>
<td></td>
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<td>No not receiving clinical recommendation</td>
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<td></td>
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<tr>
<td>Exercise</td>
<td>3.09</td>
<td>2.02–4.72</td>
<td>1.26</td>
<td>0.61–2.62</td>
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<tr>
<td>Control/lose weight</td>
<td>2.47</td>
<td>1.52–4.03</td>
<td>1.31</td>
<td>1.07–1.60</td>
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<tr>
<td>Using assistive device</td>
<td>1.52</td>
<td>0.83–2.77</td>
<td>2.35</td>
<td>1.14–4.83</td>
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<tr>
<td>No recommendation at all</td>
<td>3.16</td>
<td>2.10–4.77</td>
<td>1.30</td>
<td>1.08–1.55</td>
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<tr>
<td>Co-morbidities</td>
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<tr>
<td>Migraine</td>
<td>0.28</td>
<td>0.15–0.52</td>
<td>0.22</td>
<td>0.07–0.67</td>
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<tr>
<td>Ulcer</td>
<td>0.50</td>
<td>0.24–1.04</td>
<td>0.42</td>
<td>0.21–0.83</td>
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<tr>
<td>Self rated general health</td>
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<tr>
<td>Fair or poor general health</td>
<td>0.69</td>
<td>0.45–1.07</td>
<td>0.74</td>
<td>0.57–0.97</td>
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<tr>
<td>Health somewhat worse/much worse than 1 year ago</td>
<td>0.53</td>
<td>0.33–0.86</td>
<td>0.64</td>
<td>0.43–0.94</td>
<td></td>
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<tr>
<td>Satisfaction with life</td>
<td>0.54</td>
<td>0.27–1.01</td>
<td>0.46</td>
<td>0.22–0.95</td>
<td></td>
</tr>
<tr>
<td>Activity of Daily Living Limitations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe limitation in at least one ADL</td>
<td>0.49</td>
<td>0.32–0.74</td>
<td>0.88</td>
<td>0.56–1.39</td>
<td></td>
</tr>
<tr>
<td>Medical doctor</td>
<td>0.39</td>
<td>0.23–0.66</td>
<td>0.79</td>
<td>0.67–0.92</td>
<td></td>
</tr>
</tbody>
</table>

RR = Relative Risk
* Adjusted for sex, age, race/ethnicity, education, marital status, income and region of residence.

Conclusion: Sub-sets of overweight/obese Canadians with arthritis are at risk for non-engagement in self-management activities. Ways that health professionals might encourage individuals with arthritis to engage in self-management may include providing more informed advice and targeted clinical recommendations.

Disclosure: S. R. Bernatsky: None; C. Rusu: None; S. O’Donnell: None; G. A. Hawker: None; C. Mackay: None; L. McRae: None; M. Canizar: None; E. M. Badley: None.

1563

State-Specific ICF Disability Profiles among US Adults with Arthritis.
Jennifer M. Hootman3, Kristina A. Theis1, Julie Bolen2 and Charles G. Helmick1.

Background: Population level estimates of arthritis-related disability are needed to define the burden, identify target populations for intervention, and monitor effectiveness of public health programs. The International Classification of Function (ICF) is a standard framework used to describe health and disability and may be useful for population surveillance.

Methods: Data were from the 2009 Behavioral Risk Factor Surveillance System, an annual telephone health survey conducted in all 50 states and the District of Columbia (DC; n = 424,592 adults). Arthritis (ARTH) was defined as a ‘yes’ response to “Have you ever been told by a doctor or other health care professional that you have arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?”. Three outcome measures, based on ICF domains, were created: 1) impairment = severe pain (PAIN), 2) limitation = activity limitation (AL), and 3) restriction = social participation restriction (SPR). PAIN was defined as 7 or higher on a 0–10 point scale. AL was defined as a limitation in usual activities due to arthritis. SPR was defined with a question asking about the extent that arthritis interfered with social activities such as shopping, going to movies or social gatherings. Respondents reporting “A lot” (versus “A little/Not at all”) were defined as having SPR. State-specific prevalence estimates (%) and 95% confidence intervals (CI) among adults with arthritis were calculated for each of the ICF domains by state using statistical weights to account for the complex sample design. An overall state disability profile for each state was created using tertiles for each ICF domain. States in the highest tertile for all 3 ICF domains were classified as HIGH disability profile states and in the lowest tertile for all 3 ICF domains were classified as LOW. All others were classified as MOD.

Results: Median prevalence for all 50 states/DC for each ICF domain were: PAIN = 23.9% (CI 22.3 – 26.2: state range 17.4% AK to 38.3% MS), AL = 44.6% (CI 43.5 – 46.1: state range 35.5% HI to 56.6% TN), and SPR = 14.8% (CI 14.0 – 15.9: state range 10.8% HI to 28.7% TN). Ten states (19.6%) were classified as having a LOW, 27 states (52.9%) were classified as MOD, and 14 states (27.5%: AL, AR, CA, KY, LA, MS, NV, NM, NC, OK, SC, TN, TX, WV) were classified as having a HIGH disability profile state. Tennessee, had the worst disability profile of all states/DC, ranking 50th in PAIN (35.7%), 51st in AL (53.6%) and 51st in SPR (14.8%). An estimated 14.5 million US adults with arthritis live in states with HIGH arthritis-related disability profiles.

Conclusions: These data identify states with poor disability profiles which may be high priority targets for widespread dissemination of evidence-based public health interventions that improve pain and function among adults with arthritis.

Disclosure: J. M. Hootman: None; K. A. Theis: None; J. Bolen: None; C. G. Helmick: None.

1564

Statistical Methods Analyzing Count Data with Excessive Zeros in Arthritis Research. Bin Zhang1, Jingbo Niu2, Yanyan Zhu1, Tuhina Neogi2, Ling Xu1, David T. Felson1, Michael P. LaValley2 and Yuqiu Zhang2.

Background: Arthritis research data are often collected in multiple joints within a person (i.e., number of hand joints with Radiographic Osteoarthritis (ROA)) or multiple sub-regions of a joint (i.e., number of sub-regions with cartilage loss in a knee). It is common that the outcome measures contain excessive zeros (zero-inflated data), e.g., the majority of the study subjects have zero count of hand joint ROA. When assessing the relationship between outcome measure of interest (e.g., number of hand joint ROA) with risk factors (e.g., obesity), commonly used statistical methods, including Poisson regression and generalized estimating equations (GEE) model, fail to account for the zero-inflated data, resulting in not only producing biased effect estimates but also creating artificial association between disease outcomes and their risk factors.

Methods: We use zero-inflated models, mixture models that have two parts: one part deals with the excessive zeros and the other part with a usual random variable (RV) such as a negative binomial (NB), to analyze zero-inflated data. We simulated 1000 zero-inflated negative binomial RV Y, where Y=0 with proba-
bility only related to predictor x3, otherwise Y has NB distribution associated with predictors x1 and x2. We used 3 statistical models: the GEE model, the Zero-inflated Poisson regression model (ZIP), and the zero-inflated NB regression model (ZINB) to analyze the simulated data. We applied the same three models to examine the relation of body mass index (BMI) to the prevalence of ROA among participants in the Beijing Osteoarthritis Study.

Results: As shown in Table 1, the effect estimates (i.e., β1, β2, β3) obtained from ZINB model is closer to true values than those from either GEE or ZIP model. Furthermore, GEE model generated a false association between X3 and Y, whereas no such an association was found using ZIP or ZINB models. Among participants of the BOA study, 70.8% of subjects had no ROA in any hand joints. The prevalence ratio or hand OA (PR) is significantly associate with BMI, per 5 unit BMI increase PR = 1.12 (95% CI: 1.12–1.28, P < 0.001) from GEE model and 1.12 (95% CI: 1.03–1.22, P < 0.001) from ZIP model, and no significant associate found, PR = 1.10 (95% CI: 0.95–1.27, P = 0.2) from ZINB model, adjusting for age and sex. A goodness-of-fit test suggests that the ZINB model should be used instead of the ZIP or Poisson regression models. Thus, the positive association between BMI and hand ROA obtained from GEE model may be false due to ignoring the zero-inflated phenomenon.

Table 1. Simulation Results

<table>
<thead>
<tr>
<th>β1</th>
<th>β2</th>
<th>β3 (when Y is NB)</th>
<th>β3* (when Y=0)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>True Values</td>
<td>Can not be estimated</td>
</tr>
<tr>
<td>0.8</td>
<td>0.5</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>GEE</td>
<td></td>
<td>0.77 (0.73, 0.82)</td>
<td>0.39 (0.35, 0.44)</td>
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<tr>
<td></td>
<td></td>
<td>0.70 (0.67, 0.73)</td>
<td>0.19 (0.17, 0.21)</td>
</tr>
<tr>
<td>ZIP</td>
<td></td>
<td>0.70 (0.67, 0.73)</td>
<td>0.47 (0.40, 0.54)</td>
</tr>
<tr>
<td>ZINB</td>
<td></td>
<td>0.75 (0.71, 0.80)</td>
<td>0.001 (0.06, 0.07)</td>
</tr>
</tbody>
</table>

Conclusion: We demonstrated the superiority of zero-inflated models analyzing count data with excessive zeros. We show that zero-inflated models are important not only to discover the unbiased associations between outcomes and their risk factors but also to avoid introducing false association when there is none.

Disclosure: B. Zhang: None; J. Niu: None; Y. Zhu: None; T. Neogli: None; L. Xu: None; D. T. Felson: None; M. P. LaValley: None; Y. Zhang: None.

1565
The Association of Race with Gout: A Broadly Representative Inpatient Survey. Allan C. Gelber, Janet W. Maynard and Carlton Haywood, Jr. 1Baltimore, MD, 2Johns Hopkins University, Baltimore, MD

Purpose: Gout is a leading cause of inflammatory arthritis. Established risk factors for gout include age, gender, hypertension and obesity. Relatively few studies have examined the association of race with gout status. We sought to determine, in a large, nationally representative survey of inpatient hospital stays, whether race was independently related to gout risk.

Method: We examined the 2004 Nationwide Inpatient Sample. In that calendar year, 37 states contributed data to the survey. For each hospital stay, one or more ICD-9 diagnoses were recorded, as well as race, age, gender, socioeconomic status (SES) measures of health insurance and median household income for ZIP code. Hospital size and teaching status were recorded. Overall, the study population was 62% female, 22.3% black and 77.7% white. None; None; None.

Results: A total of 323 articles were evaluated from the primary search; 27 were included. Excluded articles did not focus on corticosteroid AEs (n=70), were case studies (n=50), evaluated corticosteroid efficacy (n=38), or evaluated therapy to alleviate corticosteroid AEs (n=13). The secondary search added 20 studies. Overall, 25 were retrospective in design, 13 were conducted in the US and 21 in Europe. The AEs for which the literature contained the greatest number of reports were psychiatric events (18 reports), infections (15), gastrointestinal (GI) conditions (14), and fracture (11). Common AEs (>30% incidence) with a greater number of reports were sleep disturbances, lipodystrophy, adrenal suppression, and hypertension. The incidence of fracture varied by location: wrist fracture, Colles’ fracture, and lower limb fracture were generally low (incidence 3–5%). Vertebral fractures were more common (range, 21–30%). Severe GI AEs were less frequent (ulcers, 1–5%; bleeding, 3–5%). Despite wide variability in study design, population, daily dose, conditions treated, and treatment duration, most AEs (fracture, myocardial infarction (MI), weight gain, infections, glaucoma, and psychiatric events) demonstrated a dose-response pattern with increasing daily dose. Studies of fractures and MIs demonstrated the clearest dose-response relationship. As such, reducing daily dose requirements may reduce AE clinical and economic burden. For example, dose reduction from 7.5–15 mg/day to <7.5 mg/day may avoid 96 fractures per 10,000 elderly patients at $18,358 per fracture and a reduction from >10 mg/day to <10 mg/day avoid 19 MIs per 10,000 patients at $26,472 per MI (US $ 2009).

Conclusions: The clinical and economic burden of corticosteroid AEs is substantial; lowering the daily dose requirements may lower the incidence of many AEs.


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The Clinical and Economic Burden of Corticosteroid Adverse Events (AEs): A Systematic Literature Review. Evelyn F. Sarnes and Maria E. Watson. 1GlaxoSmithKline, Research Triangle Park, NC, 2Xcenda, Palm Harbor, FL

Background: Systemic corticosteroids are an important and commonly used therapy; however, their use must be balanced against a set of side effects. This study evaluated the clinical and economic burden of systemic corticosteroid AEs in a wide variety of patient populations. A secondary objective was to consider the clinical and economic impact of reducing daily corticosteroid doses.

Methods: A systematic review of 2007–2009 studies retrieved by a predefined search strategy in Medline, EMBASE, and Cochrane Library, as well as AHRQ, NICE, and NHS HEED (free text) was performed to supplement an existing literature review. Relevant articles (observational and intervention studies) evaluated incidence/relative risk of AEs following corticosteroid use or the relationship between dose/duration and AEs. Case studies, studies in infants, and studies with inhaled corticosteroids were excluded. Titles/abstracts of retrieved articles were screened for eligibility. A secondary search, based on citations from other systematic reviews and including pre-2007 articles, was conducted to obtain data on psychiatric conditions, infections, and peptic ulcers. Information about dose-response relationships was combined with cost data from the literature to estimate the cost implications of a dose reduction for two corticosteroid AEs.

Results: A total of 323 articles were evaluated from the primary search; 27 were included. Excluded articles did not focus on corticosteroid AEs (n=70), were case studies (n=50), evaluated corticosteroid efficacy (n=38), or evaluated therapy to alleviate corticosteroid AEs (n=13). The secondary search added 20 studies. Overall, 25 were retrospective in design, 13 were conducted in the US and 21 in Europe. The AEs for which the literature contained the greatest number of reports were psychiatric events (18 reports), infections (15), gastrointestinal (GI) conditions (14), fracture (11). Common AEs (>30% incidence) with a greater number of reports were sleep disturbances, lipodystrophy, adrenal suppression, and hypertension. The incidence of fracture varied by location: wrist fracture, Colles’ fracture, and lower limb fracture were generally low (incidence 3–5%). Vertebral fractures were more common (range, 21–30%). Severe GI AEs were less frequent (ulcers, 1–5%; bleeding, 3–5%). Despite wide variability in study design, population, daily dose, conditions treated, and treatment duration, most AEs (fracture, myocardial infarction (MI), weight gain, infections, glaucoma, and psychiatric events) demonstrated a dose-response pattern with increasing daily dose. Studies of fractures and MIs demonstrated the clearest dose-response relationship. As such, reducing daily dose requirements may reduce AE clinical and economic burden. For example, dose reduction from 7.5–15 mg/day to <7.5 mg/day may avoid 96 fractures per 10,000 elderly patients at $18,358 per fracture and a reduction from >10 mg/day to <10 mg/day avoid 19 MIs per 10,000 patients at $26,472 per MI (US $ 2009).

Conclusions: The clinical and economic burden of corticosteroid AEs is substantial; lowering the daily dose requirements may lower the incidence of many AEs.

Disclosure: A. C. Gelber: None; J. W. Maynard: None; C. Haywood, Jr: None.
Objective: Corticosteroid injection is a useful and low-cost therapy for carpal tunnel syndrome. This randomized controlled study addressed whether two different low-cost injection techniques affected the outcomes and cost-effectiveness of carpal tunnel injections.

Design: Prospective, randomized, controlled, single-blinded interventional trial.

Setting: Hospital outpatient musculoskeletal clinic.

Patients: 64 subjects with symptomatic carpal tunnel syndrome.

Interventions: 64 wrists with carpal tunnel syndrome were randomized to palpation-guided anatomic carpal tunnel injection with 80 mg triamcinolone acetonide by: 1) a conventional technique, or 2) injection by a mechanical syringe, the RPD (the reciprocating procedure device) syringe. A one-needle, two-syringe technique with hydrodissection by 1% lidocaine was used.

Main Outcome Measurements: Baseline pain by 10 cm Visual Analogue Pain Scale (10 cm VAS), procedural pain, pain at outcome (2 weeks and 6 months), responders, therapeutic duration, reinjection rates, total cost/patient/year, and cost/responder/year were determined.

Results: Both methods reduced pain scores by greater than 50% from baseline at 2 weeks (p<0.001). Relative to the conventional method, the mechanical syringe resulted in 62% greater reduction in injection pain (p<0.02), a 68% increase in responder rate (p<0.02), 50% reduction in non-responder rate (p<0.02), 57% increase in therapeutic duration (p<0.001), a 25% increase in time to next procedure, a 36% ($43 US) reduction in cost/patient/yr for a patient treated in a physician office (p<0.001), and a 34% reduction ($33 US) in cost/patient/year for a hospital outpatient (p<0.001) as well as reduced cost/responder/year (p<0.001).

Conclusion: Cost-effectiveness and outcomes of corticosteroid injection for carpal tunnel syndrome can be significantly improved by using low-cost alterations in technique.

Disclosure: S. L. DeLea: None; J. L. Poole: None; N. Chavez-Chiang: None; W. L. Sibbitt: Abbott Intravascular, Inc, 1, 9, Apple, Inc, 1, 9, Avanca Inc, 1, 9, Avanca Medical Devices, Inc, 1, 9, Avasca Medical, Inc, 1, 9, Avasca, Inc, 1, 9, Becton Dickinson, 9, Celgene, 1, Ferring Pharmaceuticals Inc., 9, Intellige; A. D. Bankhurst: None.

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The Prevalence and Characteristics of Fluorosis Causing Skeletal Deformities in Rural Tanzania. Helen G. Jarvis2, Peta S. Heslop2, John Kissima1 and Richard Walker3. 1Hai District Hospital, Kilimanjaro Region, Tanzania, East Africa, 2Newcastle upon Tyne NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, 3Northumbria Healthcare NHS Foundation Trust, Tyne & Wear, United Kingdom
Introduction: Excessive ingestion of fluoride affects bone during growth causing a condition known as skeletal fluorosis (SF). This process can distort the congruence of joints, particularly weight bearing joints, leading to bone and joint pain. Previous small case series have reported rheumatological deformities in areas with high fluoride concentrations in the drinking water. Due to the harmful effects of excessive fluoride to teeth and bone the WHO (2004) recommended that fluoride levels in drinking water be < 1.5 mg/L. The area in Tanzania where the study was based had reported levels of fluoride as high as 35 mg/L in the ground water.

A survey was carried out to estimate the prevalence of SF in a Northern Tanzania village and the study was designed to focus on identifying those with deformity and disability due to SF.

Methods: Using census information a door to door survey was conducted to identify cases of SF. Based on literature review and expert opinion, a diagnosis of severe SF was made if the following were identified on clinical examination: abnormal coronal tibio-femoral angle, sabre tibia or juvenile kyphosis/scoliosis with no alternative cause. Cases were then examined for other clinical manifestations, and disability/pain levels were estimated using a 4 point Likert scale. Social & educational exclusion were also assessed as part of the estimate of disease burden.

Results: A population of 1435 were studied 762 (53%) Female & 673 (47%) Male, of whom 1135 (79%) were under 30 years of age. We identified 56 cases (22 (39%) female & 34 (61%) male) of severe SF (aged 2 – 30 yrs). This gives a crude prevalence of 3.9% of severe deforming disease. 52 (93%) had evidence of coronal tibio-femoral joint deformities - 45 valgus & 7 varus. Sabre tibia was identified in 18 (32%) and juvenile scoliosis/kyphosis in 3 (5%) of the cases. Combinations of the above diagnostic criteria were common with 2 cases having all 3 conditions. Pain was reported in 37 (66%) cases using the ascending 4 point Likert severity scale. 25 (45%) reported moderate to severe pain & 36 (64%) reported limitation of normal activities. 97% had knee and lower limb pain with only 32% of those reporting pain in other skeletal sites. 17 (30%) felt their school attendance had been affected & 5 (9%) felt they were treated differently by their peers due to their SF.

Financial constraints meant only those with the worst deformities were referred for corrective surgery. 11 children have been operated on to date.

Conclusion: In this area with very high levels of fluoride in the ground water, SF is a common condition. The prevalence of nearly 4% in this village represents only the most severe end of the spectrum, being an estimate of the disability and burden that this condition causes in a community ingesting excessive amounts of fluoride. It appears that only the under 30’s in the population have been affected by severe SF, most likely due to the time of construction of the deep wells in the area, which carry higher fluoride levels than surface water. Severe SF also seems to be more common in males than females, possibly due to hormonal effects. The study group is currently investigating why, despite endemic exposure, only a minority appear to develop severe deforming disease.

Disclosure: H. G. Jarvis: None; P. S. Heslop: None; J. Kissima: None; R. Walker: None.

Thiazide and Loop Diuretics Are Associated with Incident Gout in the Atherosclerosis Risk in Communities (ARIC) Study. Mara A. McAdams1, Janet W. Maynard1, Allan C. Gelber2, Alan N. Baer3 and Josef Coresh4.

Background: While there is a clear association between diuretic use and the development of gout, it is unclear whether both thiazide and loop diuretics are associated with an increased incidence of gout. We quantified the association between incident gout and diuretic use in a population based multi-ethnic sample reporting gout incidence.

Methods: The ARIC is a prospective population-based cohort study of 15,792 individuals recruited in 1987–1989 from four US communities. It consists of 1 baseline visit (visit 1) and 3 follow-up visits administered 3 years apart. At ARIC visit 4, participants were asked, “Has a doctor ever told you that you had gout?” Participants were excluded if they did not attend visit 4 or had gout prior to visit 1. At baseline, blood pressure values were measured. Participants were asked to bring all medications that they had taken in the past 2 weeks to the baseline visit. Medication data, including diuretic use and class, were obtained by trained interviewers reviewing prescription bottles. Hypertension (HTN) was defined by the report of a medication to treat HTN or a blood pressure measurement > 140/90 mm Hg.

We examined whether baseline diuretic use was associated with incident gout over 9 years of follow-up. We used logistic regression to calculate the odds of incident gout associated with diuretic use in the whole population and the subset with baseline HTN. All models were adjusted for age, sex, race, HTN and baseline body mass index, estimated glomerular filtration rate, diabetes, and protein and alcohol intake. The models for loop diuretics were also adjusted for CHF diagnosis.

Results: There were 10,872 participants who met the study criteria; 1,643 (15%) took a diuretic, 3,248 (30%) had HTN at baseline and 43% of the HTN patients were taking a diuretic. The study population was 57% female and 22% African-American. There were 286 gout cases. Per 1000 participants, the cumulative incidence of gout was 28 overall, 61 among those who reported diuretic use in the 2 weeks prior to the baseline visit, 21 for those not exposed to a diuretic, and 51 for those with HTN. Baseline use of any diuretic, including thiazide and loop diuretics, was associated with an approximately 2-fold increased risk of incident gout, after adjustment for confounders. Among the participants with HTN, the risk of gout was increased approximately 1.5-fold compared to non-diuretic users. Results were similar by sex and race, except for the association of loop diuretics (African-American, Adjusted OR=0.76, not significant) and (White, Adjusted OR= 3.6, p-value< 0.001).

Table. Odds of gout by diuretic use and class

<table>
<thead>
<tr>
<th></th>
<th>Any diuretic use</th>
<th>Thiazide</th>
<th>Loop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout</td>
<td>86</td>
<td>43</td>
<td>11</td>
</tr>
<tr>
<td>No gout</td>
<td>1,299</td>
<td>799</td>
<td>158</td>
</tr>
<tr>
<td>Age adjusted OR</td>
<td>1.50 (1.09, 2.05)</td>
<td>1.22 (0.85, 1.74)</td>
<td>2.25 (1.18, 4.28)</td>
</tr>
<tr>
<td>Fully adjusted OR</td>
<td>1.49 (1.06, 2.10)</td>
<td>1.44 (0.99, 2.10)</td>
<td>1.29 (0.57, 2.93)</td>
</tr>
</tbody>
</table>

Note: OR refers to odds ratios and we presented 95% Confidence Intervals. We did not calculate odds ratios for the exposure to thiazide diuretics because there was only one exposed case.

Conclusion: Our results suggest that diuretic use is associated with incident gout. Thiazide and loop diuretics were associated with twice the risk of gout. This study supports the previously reported association of diuretic use with gout and suggests that this association occurs with both loop and thiazide diuretics in a population based multi-ethnic sample reporting gout incidence.

Disclosure: M. A. McAdams: None; J. W. Maynard: None; A. C. Gelber: None; A. N. Baer: None; J. Coresh: None.

Trends in Orthopedic Surgery Utilization among Patients with Rheumatoid Arthritis: A Focus on Surgery Type and Gender. Courtney A. Shourt1, Cynthia S. Crowson2, Sherrine E. Gabriel3 and Eric L. Matteson4.

1Department of Medicine, Mayo Clinic College of Medicine, 2Division of Biostatistics, Department of Health Science Research, Mayo Clinic College of Medicine, 3Division of Epidemiology, Department of Health Science Research, and Division of Rheumatology, Mayo Clinic College of Medicine, 4Division of Rheumatology, and Division of Epidemiology, Mayo Clinic College of Medicine.

Objective: To describe current trends in arthritis related orthopedic surgery utilization amongst a population based cohort of patients with rheumatoid arthritis (RA).

Methods: A retrospective medical record review was performed of all incident cases of adult onset RA from a defined geographic population base who fulfilled criteria for RA in 1980–2007. Orthopedic surgeries occurring after the incidence date were recorded, including primary total joint arthroplasty (TJA), joint reconstructive procedures (JRP), soft tissue procedures (STP) and revision arthroplasty, classified according to joint involved (hip, knee, wrist, shoulder, elbow, hand, ankle, foot, cervical spine and temporomandibular). Cumulative incidence of surgery was estimated using Kaplan-
Meier methods. Time trends and gender differences were examined using Cox models.

**Results:** The study included 814 RA patients (mean age: 56 years; 68% female; mean follow-up 9.6 years). A total of 190 patients underwent ≥1 surgical procedures involving joints during follow-up. The cumulative incidence of any joint procedure at 10 years for 1980–1994 was 30.4% compared to 21.9% for 1995–2007 (p = 0.08). The cumulative incidence of all joint surgeries was lower in the 1995–2007 cohort compared to the 1980–1994 cohort, with the greatest reduction in soft tissue procedures (synovectomies, tendon repairs, tendon transfers, meniscus repair, ligament release, cartilage repair), which decreased from 13.4% in 1980–1994 to 7.3% in 1995–2007 at 10 years after RA incidence (p = 0.018). Knee surgeries were less common in patients diagnosed in 1995–2007 compared to those diagnosed in 1980–1994 (hazard ratio [HR]: 0.56; p = 0.045), as were hand surgeries (HR: 0.45; p = 0.059), but there was no change in hip surgeries (p = 0.68). There were more surgeries performed (across all surgery types) amongst female patients with a cumulative incidence of 29.4% at 10 years compared to 23.5% for men during the same time period (p = 0.057).

**Conclusion:** The rates of arthritis related surgery continue to decrease for patients more recently diagnosed with RA, especially soft tissue procedures and knee surgeries. This trend is particularly noticeable in women. This decrease in rates may reflect improved treatments or secular trends in disease expression or changes in practice patterns.

**Disclosure:** C. A. Shour: None; C. S. Crowson: None; S. E. Gabriel: None; E. L. Matteson: None.

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**Objectives:** Administrative data are increasingly used for research purposes. Accuracy of diagnostic codes used in billing data is a common concern, especially for data from family physicians (FPs). The objectives of our study were: 1) To understand the process used by FPs from different practice settings for billing and assigning diagnostic codes; 2) To identify the specific diagnostic codes commonly used by FPs for various rheumatologic diseases.

**Methods:** A sample of 343 FPs were randomly selected from the list of all FPs in the province; while ensuring a representative distribution of gender, time since graduation, and geographic location (health authority). FPs with specialized practices, in fully administrative roles, or not in active practice were excluded. Self-administered surveys were sent by fax. Reminders were sent to non-responders twice, at two week intervals. The survey elicited information about their practice setting, the process they used for billing and for assigning diagnostic codes, as well as information about their choice of diagnostic codes for selected rheumatologic conditions. Descriptive analysis was performed.

**Results:** Of the 343 FPs invited to participate, 74% (52%) were ineligible, and 130 (48%) participated. The sample included 79% in full-time practice, 61% in urban areas, 67% with ≥20 years since graduation and 37% who used electronic medical records (EMR). Results indicated that 67% of FPs select the diagnostic code themselves, 15% use EMR to assign the diagnostic code, and 10% have their MOAs assign the code. When coding themselves, 76% of FPs reported using a specific code for each type of arthritis, while 24% reported using the same code for all arthritis. Of those, commonly used codes included 781 (MSK symptom) [41%], 715 (OA) [22%], 716 (unspecified arthritis) [16%] and 714 (RA) [13%]. When patients present with multiple complaints, 46% of FPs reported submitting the code for the complaint which took the most time. When asked which code they used for specific types of arthritis, FPs provided the correct code for RA in 83% of respondents, OA (76%), Gout (83%), AS (63%), PsA (14%) with 23% using the code for psoriasis, SLE (13%). Subgroup analysis showed that practice setting (rural vs urban), but not other practice characteristics, influenced use of diagnostic codes. FPs in rural settings were more likely to use specific codes for each type of arthritis [86% vs 63% of urban FPs], and to select accurate codes (RA: 93% vs 75%, rural vs. urban resp., OA: 85% vs. 69%, Gout: 83% vs. 60%, p < 0.05).

**Conclusion:** Most FPs selected the diagnostic code themselves, use specific codes for each arthritis, and use the code for the complaint which took the most time. Selection of the accurate code for specific types of arthritis occurred in greater than 70% of respondents for OA, RA, and gout, but was inadequate for PsA and SLE. However, the use of a single code for all types of arthritis by nearly a quarter of FP, with some using OA and RA, as well as misclassifications when specific codes were used, may lead to false positive cases of OA and RA. Further research is needed to validate diagnostic codes used by FPs in order to fully understand the impact of coding errors on estimates of prevalence.

**Disclosure:** D. Lacaille: None; J. Chang: None; P. Rogers: None.

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Urate-Lowering Therapy in Chronic Gout Results in Clinically Important Improvements in Health-Related Quality of Life—SF-36 Is Responsive to Change in Chronic Gout. Puja Khanna1, Fernando Perez-Ruiz2, Paul Maranian1 and Dinesh Khanna2. 1Hospital de Cruces, 2UCLA

**Purpose:** SF-36 is a validated outcome measure to assess generic health-related quality of life (HRQOL) in patients with gout. We assessed HRQOL in patients with gout in an academic outpatient rheumatology setting.

**Methods:** SF-36 was administered at baseline, then at yearly intervals. Patients who had a gout flare within the past 1 month were excluded. We assessed statistical significance and the minimal clinically important differences (MCID) at the first and second year. Statistical significance was evaluated using paired t-test for changed scores of the SF-36 scales. MCID for SF-36 scales and summary scores was defined as improvement of ≥5 points and ≥2.5 points at 12 months, respectively. We assessed responsiveness to change (effect size) and interpreted it based on Cohen’s criteria: 0.20–0.49 as small, 0.50–0.79 as moderate, and >0.80 as large, and the predictors for improvement in the SF-36 scales and summary scores. We assessed improvement (defined as ≥MCID) in 8 SF-36 scales and 2 summary scales. Independent variables included age, tophi (presence/absence), comorbidities (presence/absence), baseline joint involvement, baseline serum urate levels, change in serum urate level and number of flares from baseline to 12 months.

**Results:** Of 99 subjects, 96 were male, mean age was 57.1 years, disease duration was 8.2 years, 47% had associated comorbidities, 40% had tophi, and 64% had evidence of radiographic damage. Data was available for 77 patients at 1 year and 36 patients at 2 years. Patients were treated with urate lowering therapy (ULT) including allopurinol (N=64), benzbromarone (N=4), or combination therapy (N=1); only 7 patients were on oral colchicine. Baseline mean (SD) serum urate level was 8.9 (1.36) mg/dl and mean numbers of flares were 4.7 (4.5) over the last year. Patients with presence of tophi, polyarticular disease, and radiographic damage had lower SF-36 scores compared to patients without it. Urate-lowering therapies were associated with reduction in serum uric acid to 5.46 (1.1), -3.44 (1.73); p < 0.001) and number of flares (-4.00 (4.32); p<0.001) over 12 months; and associated with a statistically significant and clinically meaningful improvement in the SF-36 scales and summary scores at 12 months (Table). Reduction in flares independently predicted improvements in SF-36 scales (bodily pain, physical functioning, and role physical) at 1 year after adjusting for the covariates (p values= 0.001–0.06). Improvement in SF-36 scores was maintained at 2 years.

**Conclusion:** In this real-life observational cohort, appropriate gout specific-therapy was associated with statistical and clinically meaningful improvements in the number of flares and HRQOL at 1 year then maintained at 2 years. SF-36 is responsive to change in treatment in gout over time. Our data shows that SF-36 is responsive to change in chronic gout.

**Disclosure:** P. Khanna: ACR, 2, NIAMS-NIH, 2; F. Perez-Ruiz: None; P. Maranian: None; D. Khanna: NIAMS-NIH, 2.

Background: As part of developing administrative claims-based algorithms for identifying subtrochanteric and diaphyseal fractures of the femur (SFF and DFF), we assessed the accuracy of hospital and physician diagnosis codes for these fractures. Algorithms that combined hospital discharge with surgeon's diagnosis codes to identify cases of these fractures yielded relatively high positive predictive values (PPV) and will be useful in future population-based observational studies.

Methods: Candidates for study inclusion were all patients with an ICD-9 diagnosis code for femoral fracture, at a University hospital from 01/2004 to 12/2008. Individuals with hospital discharge diagnosis for open femoral fracture and distal end femoral fractures were excluded because these fractures are usually caused by major trauma and not associated with longer term hipshophosplonate use.

Based on the clinical history, radiology report, operative note, and discharge summary accounting for the fracture admission, patients were assigned to one of the following classifications: (1) SFF, defined as fracture at the region between the lesser trochanter and a point 5 centimeters distal; (2) DFF, defined as fracture at the region between subtrochanter and supracondylar areas; or (3) “typical” hip fracture, other than SFF and DFF. We classified suspected SFF and DFF cases according to several alternative algorithms based on ICD-9 diagnosis codes, with the goal of identifying the algorithm that maximized PPV.

Result: We identified 137 persons with a suspected SFF and randomly selected 50 persons each with a suspected SFF or typical hip fracture. The PPV of case algorithms, which were varied based on the position and source of the diagnosis codes on medical claims, ranged from 69–89% for SFF, from 89–98% for DFF and from 85–98% for typical hip fracture.

In a subgroup analysis, the PPVs of the various algorithms for SFF and typical hip fracture among patients age >55 years and among patients without major trauma ICD-9 codes were the same as those in the primary analysis. In contrast, the PPVs of algorithms for DFF were lower for these subgroups than those in primary analysis. However, the number of confirmed DFF cases in these subgroups was small.

Table 1. Characteristic of Validation Sample

<table>
<thead>
<tr>
<th>All patients (n=235)</th>
<th>Subtrochanteric Fracture (n=137)</th>
<th>Diaphyseal Fracture (n=55)</th>
<th>Typical Hip Fracture (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD)</td>
<td>71 (±15)</td>
<td>81 (±15)</td>
<td>87 (±15)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>36 (16)</td>
<td>32 (19)</td>
<td>38 (13)</td>
</tr>
<tr>
<td>Presence of major trauma code (%)</td>
<td>71 (30)</td>
<td>81 (30)</td>
<td>87 (30)</td>
</tr>
</tbody>
</table>

1 Subtrochanteric fracture (ICD-9: 820.22)
2 Diaphyseal fracture (ICD-9: 821.00 and 821.01)
3 Typical hip fracture (ICD-9: 820.00, 820.01, 820.02, 820.03, 820.20, 820.21, and 820.8)
4 Major trauma code (ICD-9: E800–E804, E808–E809, and E916–E928)

Table 2. Positive Predictive Value (PPV) of Various Case Identification Algorithms for Subtrochanteric, Diaphyseal, and Typical Hip Fractures

<table>
<thead>
<tr>
<th>Case Identification Algorithm</th>
<th>Subtrochanteric Fracture</th>
<th>Diaphyseal Fracture</th>
<th>Typical Hip Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients Number of identified cases by different (%)</td>
<td>PPV (%)*</td>
<td>PPV (%)*</td>
<td>PPV (%)*</td>
</tr>
<tr>
<td>Age ≥ 55 years</td>
<td>137 (100)</td>
<td>69 (51)</td>
<td>72 (54)</td>
</tr>
<tr>
<td>Primary hospital discharge</td>
<td>107 (79)</td>
<td>76 (56)</td>
<td>80 (62)</td>
</tr>
<tr>
<td>Surgeon’s diagnosis on administrative claim</td>
<td>87 (64)</td>
<td>82 (58)</td>
<td>85 (68)</td>
</tr>
<tr>
<td>Both primary discharge diagnosis AND surgeon’s diagnosis</td>
<td>62 (45)</td>
<td>69 (51)</td>
<td>76 (60)</td>
</tr>
<tr>
<td>Diaphyseal Fracture</td>
<td>55 (100)</td>
<td>60 (10)</td>
<td>70 (12)</td>
</tr>
<tr>
<td>Primary hospital discharge</td>
<td>50 (91)</td>
<td>60 (12)</td>
<td>70 (14)</td>
</tr>
<tr>
<td>Surgeon’s diagnosis on administrative claim</td>
<td>48 (88)</td>
<td>66 (11)</td>
<td>77 (15)</td>
</tr>
<tr>
<td>Both primary discharge diagnosis AND surgeon’s diagnosis</td>
<td>36 (66)</td>
<td>66 (11)</td>
<td>77 (15)</td>
</tr>
<tr>
<td>Typical Hip Fracture</td>
<td>51 (100)</td>
<td>76 (15)</td>
<td>80 (16)</td>
</tr>
<tr>
<td>Primary hospital discharge</td>
<td>48 (94)</td>
<td>76 (15)</td>
<td>80 (16)</td>
</tr>
<tr>
<td>Surgeon’s diagnosis on administrative claim</td>
<td>31 (61)</td>
<td>76 (15)</td>
<td>80 (16)</td>
</tr>
<tr>
<td>Both primary discharge diagnosis AND surgeon’s diagnosis</td>
<td>22 (43)</td>
<td>76 (15)</td>
<td>80 (16)</td>
</tr>
</tbody>
</table>

* One trial consisted of two distinct vitamin C intervention groups.

Conclusions: Administrative claims data-based algorithms that combined hospital discharge with surgeon’s diagnosis codes to identify cases of SFF, DFF, and typical hip fracture yielded high PPVs. These claims algorithms will be useful in future population-based observational studies to evaluate the association between osteoporosis medications and subtrochanteric and diaphyseal fractures.

Disclosure: P. Narongroeknawin: None; N. M. Patkar: None; B. Shakoory: None; A. Jain: None; J. R. Curtis: Amgen Inc., 2, 5, Centocor, Inc., 2, 5, Corostra, 5, Eli Lilly and Company, 2, 8, Merck Pharmaceuticals, 2, 8, Novartis Pharmaceuticals Corporation, 2, 5, 8, Proctor & Gamble Pharmaceuticals, 2, 5, 8, Roche, 2, 5, 8, UCB, Inc.; E. Delzell: Amgen Inc., 2, P. H. Lander: None; R. Lopez-Ben: None; M. J. Pitt: None; M. M. Safford: None; D. A. Volgas: Synthes, 2, K. G. Saag: Amgen Inc., 2, 5, Aventis Pharmaceuticals, 5, Eli Lilly and Company, 2, 5, GlaxoSmithKline, 2, Merck Pharmaceuticals, 2, 5, National Osteoporosis Foundation, 9, Novartis Pharmaceuticals Corporation, 2, 5, 8, Proctor & Gamble Pharm.

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Vitamin C Supplementation and Serum Uric Acid: A Meta-Analysis of Randomized Controlled Trials. Stephen P. Juraschek, Edgar R. Miller and Allan C. Gelber. Johns Hopkins Medical Institutions, Baltimore, MD

Background: Vitamin C is an essential micronutrient with uricosuric properties. Observational studies demonstrate an inverse association between levels of dietary or plasma vitamin C and serum uric acid (SUA). Thus far, clinical trials of vitamin C report inconsistent effects on SUA. The purpose of this meta-analysis was to determine the pooled effect of vitamin C on SUA called from prior reports.

Methods: We conducted a meta-analysis of randomized controlled trials of vitamin C supplementation on SUA. A total of 1,988 publications, identified in MEDLINE, EMBASE, and CENTRAL databases, were subjected to the following inclusion criteria: (1) randomized controlled trials conducted on human subjects; (2) end-trial serum uric acid means and variance were reported; (3) oral vitamin C supplementation and a concurrent control group; and, (4) trial duration of at least one week. Trials that enrolled children or patients on dialysis or where vitamin C supplements were combined with other uricosuric agents were excluded. SUA effects were pooled by random-effects models and weighted by inverse variance.

Summary of Results: Thirteen trials met our eligibility criteria, totaling 545 participants. The median dose of vitamin C was 500 mg/d, trial size ranged from 8 to 184 participants, and median study duration was 30 days. Eight trials examined vitamin C as the only active intervention, whereas 5 trials administered vitamin C together with other vitamins, minerals or pharmacologic agents. The aggregate weighted effect of the 13 trials showed a SUA reduction of −0.33 mg/dL (95% CI: −0.66, 0.00; P = 0.05). Trials with a mean pretreatment SUA level above 4.85 mg/dL, the median value for these 13 trials, had a significantly greater SUA reduction in comparison to trials with mean pretreatment values ≤4.85 mg/dL (P = 0.02 in subgroup comparison). Notably, the pooled effects of trials with larger doses of vitamin C and those with vitamin C as the sole intervention showed greater significant reductions in SUA levels (Table).

Table. Vitamin C supplementation effects on serum uric acid - overall and subgroup analyses.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Serum Uric Acid (mg/dL)</th>
<th>Mean (95% CI) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Trials (N = 13)</td>
<td>545</td>
<td>−0.33 (−0.66, 0.00)</td>
</tr>
<tr>
<td>Subgroup: Pretreatment Serum Uric Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials with mean UA ≤4.85 mg/dL (N = 51)</td>
<td>204</td>
<td>0.15 (−0.09, 0.39)</td>
</tr>
<tr>
<td>Trials with mean UA &gt;4.85 mg/dL (N = 51)</td>
<td>252</td>
<td>−0.83 (−1.62, −0.04)</td>
</tr>
<tr>
<td>Subgroup: Vitamin C Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials with dose ≤500 mg/dL (N = 35)</td>
<td>203</td>
<td>0.09 (−0.17, 0.34)</td>
</tr>
<tr>
<td>Trials with dose ≥500 mg/dL (N = 8*)</td>
<td>369*</td>
<td>−0.56 (−1.01, −0.11)</td>
</tr>
<tr>
<td>Subgroup: Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only Vitamin C (N = 9*)</td>
<td>372*</td>
<td>−0.52 (−0.93, −0.10)</td>
</tr>
<tr>
<td>Vitamin C and other agents (N = 5)</td>
<td>200</td>
<td>0.12 (−0.15, 0.39)</td>
</tr>
</tbody>
</table>

N = Number of trials; n = Number of trial participants.

* Total number does not equal 13 since 3 trials did not report mean pretreatment SUA.

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...
Conclusions: In this meta-analysis, vitamin C supplementation lowered SUA. Greater reductions in SUA occurred in trials that used high doses of vitamin C and in trials with subjects with higher pretreatment SUA levels. These data support consideration of vitamin C supplementation as a uricosuric agent in the prevention and control of gout.

Disclosure: S. P. Juraschek; None; E. R. Miller: NIH, 2; A. C. Gelber: Donald B. And Dorothy Stabler Foundation, 2, NIH, 2.

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What Kinds of Advice Do Health Food Store Employees and Pharmacists Provide to Consumers with Acute Low Back Pain? Jaya K. Rao1, Doo Kavalieratos1, Mary Roth1, Morris Weinberger2 and Timothy Carey1

Chapel Hill, NC, 1UNC Eshelman School of Pharmacy, Chapel Hill, NC

Background: Approximately 80% of adults experience at least 1 episode of acute low back pain (ALBP) during their lives. ALBP symptoms typically resolve in 4–6 weeks. Evidence-based guidelines recommend that physicians treat patients with ALBP conservatively with nonsteroidal anti-inflammatory drugs, avoid ordering imaging studies, and encourage usual activities as tolerated. Given that patients often use self-care strategies to treat pain, we examined the advice that health food store (HFS) employees and retail pharmacists provide for ALBP symptoms.

Methods: The study protocol was approved by the University of North Carolina Institutional Review Board. The actor, a 22-year-old Caucasian male, visited 10 retail pharmacies and 10 HFSs in North Carolina during October 2009. He interacted with the HFS employees and pharmacists using the following standardized script: 1) his symptoms began 2 days ago and he was able to see a primary care physician (PCP) earlier that day; 2) the PCP followed ALBP guidelines and recommended ibuprofen every 6 hours; and 3) he was dissatisfied with the PCP’s recommendations. He asked for general treatment recommendations, and specifically asked whether he needed to see a physician or other practitioner. He documented the recommendations on a data collection form following each encounter. We calculated the total monthly costs for each product recommended and examined whether the products had underlying evidence as a treatment for ALBP or potential side effects or interactions with prescribed medicines.

Results: Of the 6 pharmacists who recommended continuing ibuprofen, 2 reinforced a regular dosing schedule. Another 3 recommended changing to naproxen and 1 stated that the physician should have prescribed a muscle relaxant. Seven pharmacists suggested a physician visit but varied with respect to time frame; 4 recommended a visit if the symptoms lasted more than 2–3 days while 3 recommended a visit if the symptoms were not resolved within 1–2 weeks. Although 4 pharmacists said that imaging studies were not necessary, 3 recommended a radiographic study (1 specifically suggesting an MRI). Of the 10 HFS employees, 4 suggested continuing the ibuprofen; notably, 1 recommended increasing the dose to 800 mg every 6 hours. Nine HFS employees recommended various supplements and topical remedies with a total monthly cost ranging from $2 to $331. The recommendations included products that are safe but have no evidence to support their use for ALBP (e.g., glucosamine) and several that have known side effects (e.g., magnesium citrate) or could interact adversely with prescription medications (e.g., bromelain extract). Only 2 HFS employees suggested a physician visit, with one recommending having an MRI performed.

Conclusions: Pharmacists may inadvertently raise expectations regarding ALBP evaluation and symptom resolution while HFS employees may confer genetic predisposition to specific sub-phenotypes of SLE. IRF5

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Conclusions: Pharmacists may inadvertently raise expectations regarding ALBP evaluation and symptom resolution while HFS employees may confer genetic predisposition to specific sub-phenotypes of SLE.

Disclosure: J. K. Rao: None; D. Kavalieratos: None; M. Roth: None; M. Weinberger: None; T. Carey: None.

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Who Falls? A Decade of Experience at a Musculoskeletal Specialty Hospital, Lisa A. Mandl1, Michael Parks2, Patricia Quinlan3, Tina Bailey4, Jacklyn Katz1 and Steven Magid5

Hospital for Special Surgery, New York, NY, 1Hospital for Special Surgery

Summary: This study evaluates in-patients who fell at a musculoskeletal specialty hospital with no emergency room or trauma unit. Almost all admissions were for elective orthopedic procedures, a small percentage for trauma admissions were for elective orthopedic procedures, a small percentage for trauma

Methods: Our SLE case-control cohort consisted of 606 patients (mean age 43.4 years, 90.6% women) and 934 unrelated controls (mean age 52.6 years, 25.0% women), and they were all Japanese. We selected four single nucleotide polymorphisms (SNPs), rs13277113 (BLK), rs7574865 (STAT4), rs41298401 (IRF5) and rs2230926 (TINFAP3), which are established genetic risk factors for SLE shared between Caucasian and Asian populations. We genotyped the SNPs using TaqMan assays. The difference of the genotype frequency was tested with the Cochran-Armitage trend test, using PLINK.

Results: We found a significant association of rs13277113 (BLK) with renal involvement (OR 1.48, 95% CI 1.14–1.93, p = 0.0034) and a moderate association of rs41298401 (IRF5) with lupus anticoagulant (LAC) positivity.
None of the SNPs in SCUBE1 reached significance after correction for multiple testing. Extremely high heterogeneity in the distribution of haplotypes and patterns of LD were observed among different countries.

**Conclusions:** We not only replicated the association of BLK, ATG5 and PXK but also present an extensive mapping of these genes. We narrowed down the associated regions and performed functional studies in order to understand the role of potentially causal variants on gene function.

**Disclosure:** A. M. Delgado-Vega: None; S. Kozyrev: None; J. Frostegård: None; L. Truedsson: None; B. A. Pons-Estel: None; S. D’Alfonso: None; T. Witte: None; B. Lauwerys: None; E. Endreffy: None; L. Kovács: None; C. Vasconcelos: None; B. Martins da Silva: None; J. Martin: None; M. E. Alarcón-Riquelme: None.

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A Comprehensive Replication Study and Functional Analysis of SLE Associated Variants in BLK, ATG5, PXK and SCUBE1

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Background: The HapMap International project has provided an extensive catalogue of the common human genetic variation. It made possible the design of genome-wide association studies, which have radically contributed to the dissection of the genetic basis of SLE and multiple susceptibility variants have been identified. The 1000 genomes project, although not completed yet, is providing a deep source of newly identified variants that are ready to be used. In the present work, we have fine mapped four SLE-associated genes and imputed a handful of SNPs using these data, revealing novel potentially functional variants.

Methods: Fine mapping of BLK, ATG5, PXK and SCUBE1 was performed in the European multicenter collection “BIOLOUPUS”. Individuals with <90% of European ancestry identified by using PCA and STRUCTURE were removed as well as duplicated or related samples. Publicly available reference haplotypes and fine-scale recombination maps were downloaded from the 1000 genomes project (release August 2009) and HapMap phase 3 (CEU from the 1000 genomes project (release August 2009) and HapMap phase 3 reference panels and imputed the missing SNPs in our study data set. Stringent quality control criteria, adjustments for population stratification and standard GWA statistical methodologies were used to compare allele frequencies between cases and controls. A total of ~774,000 single nucleotide polymorphisms (SNPs) were tested for association to SS in our final GWA discovery cohort of 272 European-derived primary SS cases and 387 healthy controls. Stringent quality control criteria, adjustments for population stratification, and standard GWA statistical methodologies were used to compare allele frequencies between cases and controls. A total of ~774,000 single nucleotide polymorphisms (SNPs) were tested for association to SS in our final GWA dataset. For replication, we used a DNA pooling approach in an independent collection of cases and controls of European-decent also genotyped using the OMNI-Quad arrays. Weighted Z scores were used to determine meta p-values for combined discovery and replication data.

Results: The most significant region associated with risk of disease was the major histocompatibility complex (MHC) with 45 SNPs exceeding a genome-wide significance threshold of 5×10^-8, all of which replicated in our independent pool samples. With the MHC peak significance was observed at HLA-DRA for rs9268832 (p-value 1.65×10^-10, odds ratio 2.3, CI: 1.8–3.0). Analysis in the replication cohort for rs9268832 resulted in p-value 1.61×10^-4, and an overall combined p-value 2.56×10^-13. Additional results across the extended MHC support association with multiple loci throughout this region. Evidence for novel genetic associations outside of the MHC were also observed. For example, association of the SS with rs13282959 in both the discovery and replication cohorts was identified (meta p = 1.93×10^-6). This SNP is located in a region of high regulatory potential near the musculin (MSC) gene. MSC is a multi-functional transcription factor involved in signaling pathways following B cell receptor activation. We specifically evaluated our data for evidence of association with ~30 loci previously established in systemic lupus erythematosus (SLE), a closely

None of the SNPs in SCUBE1 reached significance after correction for multiple testing. Extremely high heterogeneity in the distribution of haplotypes and patterns of LD were observed among different countries.

**Conclusions:** We not only replicated the association of BLK, ATG5 and PXK but also present an extensive mapping of these genes. We narrowed down the associated regions and performed functional studies in order to understand the role of potentially causal variants on gene function.

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related autoimmune disease. Association of IRF5 and TNIP1 was observed in both our discovery and replication cohorts. Support for other associated genes in both SLE and SS was observed for BANK1, PRDM1, JAZZF1, STAT4, and IL12B.

Conclusions: This study represents the most comprehensive assessment of the genetic contribution to SS performed to date. We have identified and replicated numerous loci associated with disease, some of which have been previously associated with SLE and other related autoimmune diseases. Further characterization of these effects are warranted to precisely define causal variants and determine functional consequences that contribute to disease pathogenesis.

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An Immune Signature Based on Ex Vivo Responsiveness of Peripheral Blood Cells Is Associated with Radiographic Joint Damage in Rheumatoid Arthritis. John M. Davis III, Keith L. Knutson, Michael A. Strausbauch, Cynthia S. Crowson, Terry M. Therneau, Eric L. Matteson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN

Purpose: In rheumatoid arthritis (RA), joint damage may occur even in patients with minimal disease activity. Thus, new techniques for determining the potential for future immune-mediated joint injury may facilitate targeting high-risk patients for aggressive therapy. The objective was to identify immune signatures of RA damage by broadly assessing ex vivo cytokine release by PBMC in response to stimulation.

Methods: We studied patients with early RA of <3 yrs duration, positive for rheumatoid factor or anti-citrullinated peptide antibodies. Radiography of the hands, wrists and feet was performed, and modified van der Heijde-Spring (vdH-S) scores were determined. To establish immune signatures, we measured the release of 17 cytokines from PBMC in response to a panel of stimuli in or media alone using multiplexed immunoassays. The stimulation panel included anti-CD3/anti-CD28, CpG oligonucleotides (CpG), combined cytomegalovirus and Epstein Barr virus lysates (CMV/EBV), heat shock protein 60 (HSP60), phosphor myristate acetate with ionomycin (PMA/ionomycin), phytohemagglutinin, and combined Staphylococcal enterotoxins A and B (SEA/SEB). Mixed effects models were used to normalize the log-transformed cytokine data and adjust for assay effects. Gradient boosting models (GBM) were used to predict the vdH-S score using all of the 136 stimulated cytokine concentrations and thereby derive a multi-cytokine prediction score. Linear regression models were used to determine the associations of the score with validated disease activity measures, including the Disease Activity Score in 28 joints (DAS28), adjusting for clinical covariates.

Results: The study included 98 patients (63% female; mean age 56 yrs; mean RA duration 2.9 mo) with a total of 136 visits. In the factor analysis, pain levels influenced the PRO composite outcome most heavily. Among patients with high PRO composite scores, we observed that the release of T cell-derived cytokines, including IFN-γ, MIP-1β, IL-4, IL-5, IL-10, and TNF-α, was significantly decreased. In contrast, we observed that the release of several innate cell-derived cytokines, including IL-1β, IL-6, and TNF-α, was significantly increased in these patients. In the GBM analysis, the most influential cytokines were MIP-1β, IL-7, IL-5, IFN-γ, and IL-13, and the most influential stimuli were CMV/EBV, CpG, PMA/ionomycin, and anti-CD3/anti-CD28. The multi-cytokine prediction score was confirmed to be associated with the PROs used to train the score and also with established disease activity measures, demonstrating evidence of criterion validity. The score (0 – 100) was strongly associated with the DAS28 (β coefficient: 0.25 per 10 units; standard error: 0.063; p = 0.0002), independent of clinical covariates, including the use of methotrexate, biologics, and prednisone.

Conclusions: A PBMC-based immune signature, reflecting aberrant responsiveness of the innate and adaptive immune systems, is able to quantify the clinical activity of RA. If validated and standardized in future studies, this approach could enable more sensitive monitoring of RA activity, facilitating strategies of tight control and improved patient outcomes.

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An Immune Signature Based on the Ex Vivo Responsiveness of Peripheral Blood Cells for Monitoring Disease Activity in Rheumatoid Arthritis. John M. Davis III, Keith L. Knutson, Michael A. Strausbauch, Cynthia S. Crowson, Terry M. Therneau, Eric L. Matteson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN

Purpose: New techniques with enhanced capacity to detect systemic immune dysfunction are needed to enable tighter control of rheumatoid arthritis (RA). The objective was to identify an “immune signature” for predicting the level of disease activity in patients with RA by broadly assessing ex vivo cytokone release by PBMC in response to stimulation.

Methods: We conducted a correlative study of patients with early RA in an academic rheumatology practice. Data were collected for patient reported outcomes (PROs), including pain, morning stiffness, disability, and quality of life, using validated instruments. To establish immune signatures, we measured the release of 17 cytokines by PBMC in response to a panel of stimuli or in media alone using multiplexed immunoassays. The stimulant panel included anti-CD3/anti-CD28, CpG oligonucleotides (CpG), combined cytomegalovirus and Epstein Barr virus lysates (CMV/EBV), heat shock protein 60, phosphor myristate acetate with ionomycin (PMA/ionomycin), phytohemagglutinin, and combined Staphylococcal enterotoxins A and B. Mixed effects models were used to normalize the log-transformed cytokine data and adjust for assay effects. Factor analysis was used to identify multiple PROs into a composite outcome. A gradient boosting models (GBM) were used to predict the PRO composite outcome using all of the 136 stimulated cytokine concentrations and thereby derive a multi-cytokine prediction score. Linear regression models were used to determine the associations of the score with validated disease activity measures, including the Disease Activity Score in 28 joints (DAS28), adjusting for clinical covariates.

Results: The study included 98 patients (63% female; mean age 56 yrs; mean RA duration 2.9 mo) with a total of 136 visits. In the factor analysis, pain levels influenced the PRO composite outcome most heavily. Among patients with high PRO composite scores, we observed that the release of T cell-derived cytokines, including IFN-γ, MIP-1β, IL-4, IL-5, IL-10, and TNF-α, was significantly decreased. In contrast, we observed that the release of several innate cell-derived cytokines, including IL-1β, IL-6, and TNF-α, was significantly increased in these patients. In the GBM analysis, the most influential cytokines were MIP-1β, IL-7, IL-5, IFN-γ, and IL-13, and the most influential stimuli were CMV/EBV, CpG, PMA/ionomycin, and anti-CD3/anti-CD28. The multi-cytokine prediction score was confirmed to be associated with the PROs used to train the score and also with established disease activity measures, demonstrating evidence of criterion validity. The score (0 – 100) was strongly associated with the DAS28 (β coefficient: 0.25 per 10 units; standard error: 0.063; p = 0.0002), independent of clinical covariates, including the use of methotrexate, biologics, and prednisone.

Conclusions: A PBMC-based immune signature, reflecting aberrant responsiveness of the innate and adaptive immune systems, is able to quantify the clinical activity of RA. If validated and standardized in future studies, this approach could enable more sensitive monitoring of RA activity, facilitating strategies of tight control and improved patient outcomes.

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Objective: To evaluate the genetic relationship between the two functional polymorphism of CDA (22G>A) and TNF-α (-308G>A), gene, and PTPN22 R620W respectively, in Rheumatoid Arthritis (RA) and their possible association with B cell depletion gene.

Methods: One hundred and twenty three (82% female) RA patients who did not respond to previous DMARDs and/or TNFα blockers were enrolled in a multicenter Italian study to evaluate the efficacy of RTX therapy. All RA were seropositive for at least one (RF-IgM,RF-IgG,RF-IgA) autoantibody.

Results: All SNPs were in HWE except CDAK27Q (p=0.00011). Considering also the contribution of the Research Foundation, Arthritis and Immunology Program, Oklahoma Medical difference in genotype distribution nor in allele frequencies of PTPN22 R620W genotype K*/Q* (31.2%) in RA patients compared to controls (Q*/Q*: 29.9%; frequency of the genotype Q*/Q* (40.2%) and a decreased frequency of the (19.8%) in the RA cohort compared to controls (9.1%; OR (95% CIs): 2.23

Conclusion: Our study provides evidence that PTPCA2 represents a novel locus predisposing to SLE susceptibility in Asian, European and Native American populations. The common risk haplotype shared in these populations is likely to carry one or more underlying causal variant(s) that increase risk for the development of SLE.

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**Objectives:** Our previous study identified the G allele of an X-linked TLR7 SNP (rs8358383, located at 3'UTR) associated with increased expression levels of TLR7 and SPE susceptibility in 9,274 Eastern Asians ($p = 6.5 \times 10^{-10}$) that had a stronger male effect. In this study, we sought to further characterize and localize SLE-associated SNPs of TLR7 and its functionality related gene TLR8 (17kb downstream of rs8358383) in non-Aisan populations.

**Methods:** A total of 47 SNPs spanning ~5kb genomic region of TLR7-TLR8, were genotyped on a customized Illumina array in a collection of case-control samples including European Americans (EA, 3930 cases vs. 3477 controls), African Americans & Gullah (Aa&Gullah, 1674 cases vs. 1915 controls), and Hispanics & Native Americans (Hisp&NA, 1479 cases vs. 800 controls). Additionally, ~400 ancestry informative markers were genotyped to control population stratification and remove genetic outliers for analysis. Association analysis for each SNP was performed using the TSK program and controlling population structure. A trans-ethnic meta-analysis was conducted to distinguish independent signals from associated SNPs. We used Q statistic to test the heterogeneity of OR between males and females, and Mantel-Haenszel test to generate a trans-ethnic meta-analysis P value.

**Results:** Significant associations of SNPs ($p < 0.05$) with SLE in each ethnic group were observed at TLR7 region after Bonferroni correction, including 3 SNPs in EA, 1 SNP in Aa&Gullah and 1 SNP in Hisp&NA. The following conditional analysis revealed the previously identified TLR7 3'UTR SNP (rs8358383) as the only independent variant across all 3 populations, exhibiting the strongest association ($P = 1.5 \times 10^{-10}$ in EA, $1.4 \times 10^{-10}$ in Aa&Gullah and $2.8 \times 10^{-10}$ in Hisp&NA, Table 1). Trans-ethnic meta-analysis yielded a $P$ with genome-wide significance ($P = 1.05 \times 10^{-12}$; OR = 1.26), confirming our previous finding in Eastern Asians. However, unlike the same sample where both sexes showed association, the evidence for this SNP conferring risk to SLE was only observed in female non-Asian datasets.

**Conclusion:** We replicated the association between rs8358383 and SLE with genome-wide significance in EA, Aa&Gullah, and Hisp&NA populations, showing TLR7 as a common risk locus for SLE in multiple ethnic groups.

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Association of Variants in the TNFAIP3 Region with Systemic Lupus Erythematosus in Multiple Populations. Graham Wiley, Jennifer M. Henson, Mei Li, and Manuel Anaya.

**Objectives:** Systemic lupus erythematosus (SLE) is a complex autoimmune disease with varied and potentially severe clinical manifestations affecting multiple organs. Prevalence of this disease varies between genders and among age-groups and ethnicities. SLE affects women nine times greater than men and is more common in non-Caucasians than in Caucasians. Recent studies indicate that genetic variants in the region of tumor necrosis factor alpha-induced protein 3 (TNFAIP3) are associated with SLE in subjects of European and Asian ancestry. TNFAIP3 encodes a zinc-finger protein called A20, a critical regulator of inflammatory signaling pathways. To further characterize and localize the effect of TNFAIP3, we genotyped and imputed single-nucleotide polymorphisms (SNPs) within and flanking TNFAIP3 in multiple populations: European, African-American, Asian including Korean, Hispanic enriched for Amerindian-European admixture, and Gullah populations.

**Methods:** Using a custom designed SNP panel for the Illumina iSelect system, we genotyped 127 SNPs in and around TNFAIP3 and 343 ancestry informative markers (AIMs) in a total of 8922 SLE unrelated cases and 8077 controls. Then, using HapMap Phase III and 1000 Genomes Project data we imputed a minimum of 274 additional SNPs for each of the populations (the number varied based on linkage disequilibrium structure). We converted the posterior probabilities to the most likely genotypes with a threshold of 0.8 and removed imputed SNPs with less than 90% average certainty of the most probable genotypes. We assessed single marker association to SLE using logistic regression with sex, global and local ancestry adjustments under additive, dominant, and recessive models.

**Results:** Association analysis identified risk haplotypes in Europeans and Asians likely to harbor a causal variant. Further haplotype comparisons across populations revealed a variant that likely explains the majority of the genetic association between SLE and TNFAIP3 identified in our study populations with $OR = 1.41 - 2.04$ in Europeans, $P = 3.30 \times 10^{-9}$, 95% CI = 1.73 - 2.97 in Asians, and $P = 1.24 \times 10^{-9}$, OR = 2.53, 95% CI = 1.88 - 3.41 in Koreans. No significant association was found in other populations.

**Conclusion:** These results support genetic association with SLE in the region of TNFAIP3, unique to Europeans and Asians and further demonstrate the complexity of identifying associations across different populations. Sequencing and functional studies are necessary to validate this variant and determine the contribution of TNFAIP3 to SLE.

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Background: The transcription factor NF-kB is an important factor in inflammation and the immune response. Unrestrained NF-kB response has previously been associated with autoimmune disease, sepsis, and some cancers. It is therefore not surprising that NF-kB signaling is tightly regulated within the cell through a pathway of protein-protein interaction and post-translational protein modification. One key component of this pathway is the TNFAIP3 complex consisting of TNFAIP3, TNPI, TNP2, TAX1BP1, ITCH, and RNF11. This complex, along with the ubiquitin-conjugating enzyme UBE2L3, deactivates NF-kB pathway proteins through deubiquitination of K63 polyubiquitin chains and subsequently targets those proteins for degradation via K48 ubiquitination. Recent GWAS have revealed that genetic variants in the TNFAIP3, TNPI, and UBE2L3 regions are associated with systemic lupus erythematosus (SLE) in subjects of European and Asian ancestry. SLE is an autoimmune disease characterized by loss of tolerance to self-antigens and dysregulated interferon responses. To further characterize and localize the effect of the TNFAIP3 regulatory complex, we genotyped and imputed single-nucleotide polymorphisms (SNPs) within and flanking TNFAIP3 on 5q33, TNPI on 4p16, UBE2L3 on 22q11, TAX1BP1 on 7p15 in multiple populations: African-Americans (1,569 cases/1,893 controls), Asians (1,328 cases/1,348 controls), Europeans (4,248 cases/3,818 controls), Gullah (155 cases/131 controls), and Hispanics enriched for Amerindian-European admixture (1,622 cases/887 controls).

Methods: Using the Illumina iSelect system, we genotyped a total of 231 SNPs in and around those loci and 343 ancestry-informative markers (AIMs). We then imputed untyped SNPs at those loci using HapMap Phase III and 1000 Genomes Project data. We converted the posterior probability to the most likely genotypes with a threshold of 0.8 and removed imputed SNPs with less than 90% average certainty of the most probable genotypes. We assessed single marker association to SLE using logistic regression with sex and global ancestry adjustments under additive, dominant, and recessive genetic models.

Results: We observed strong associations between SLE and multiple SNPs within TNPI in Europeans, Hispanics, African-Americans, and Asians ($P_{combined} \leq 5 \times 10^{-8}$) with the strongest signal at rs708392 ($P_{combined}$ = 2.53 x 10^{-19}). We also identified strong associations within UBE2L3 in Europeans, Asians, African-Americans and Hispanics with the most significant association at rs4744 ($P_{combined}$ = 1.25 x 10^{-14}).

Conclusions: These results establish that variants within TNPI and UBE2L3 contribute to differential risk of SLE in multiple populations. Further functional studies will be required to determine the precise variant(s) influencing SLE risk.

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Association Study of the IL4RI Gene with Susceptibility to Systemic Lupus Erythematosus and Systemic Sclerosis.
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We explored whether single nucleotide polymorphisms (SNPs) in the Interleukin-1 receptor associated kinase (IRAK1) gene contribute to systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) susceptibility in the Japanese population. Two hundred forty-four patients with SLE, 180 patients with SSC and 268 healthy controls (HC) were enrolled in this study. Four SNPs (rs2239673, rs763737, rs7601789, and rs5945174) in the IRAK1 gene were determined by allelic discrimination with the use of a specific TaqMan probe and PCR restriction fragment length polymorphism (PCR-RFLP). Association measured using either χ2 or Fisher’s exact test at the allelic and genotypic levels. Because IRAK1 is located on chromosome Xq28, cases and controls were stratified by gender and measured for each stratum. In patients with SLE, the most common clinical manifestations in this study were nephritis (45%), cytopenia (32%), and neuropsychiatric manifestations (30%). The prevalence of butterfly rash was 17%, arthritis was 25%, serositis was 7%, and antiphospholipid antibody syndrome was 5%.

Both alleles and genotypes of all of the four SNPs in IRAK1 gene showed strong associations with SLE in female cohort (P < 0.0002; odds ratio = 1.9), although there were no associations between allelic and genotypes in the SSc cohort. Although SLE and SSC are both autoimmune diseases, in SLE, there were significant correlations between the allele of each SNP and nephritis. There were also significant differences in the frequencies of genotype of the SNPs between patients with butterfly rash or cytopenia and HC. In the frequency of genotype of rs945174, there was a significant difference between patients with nephritis and HC. In patients with SSc, there were no association in the alleles and genotypes of the four SNPs in the IL4RI gene.

In haplotype analyses, GOGG haplotype (defined as “G” at rs2239673, “G” at rs763737, “G” at rs5945174, “G” at rs7061789) was associated with susceptibility to Japanese patients with both SLE and SSc. The p value for association reached to 10^{-19} and 10^{-2} respectively. In this study, we confirmed the association between an SNP in the IRAK1 gene and susceptibility to SLE in female Japanese population. Several autoimmune disorders, including multiple sclerosis, rheumatoid arthritis, SLE and SSc are more common in women than men. Several mechanisms have been proposed as explanations for this gender bias. IRAK1, an X chromosome gene may have a critical role in the pathogenesis of SLE and SSc.

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Combining Genetic and Environmental Risk Factors To Model RA Susceptibility.
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Background: Cumulative genetic risk scores (GRSs) have shown promise in modeling rheumatoid arthritis (RA) susceptibility. In addition, many gene-environment interactions (GEIs) have been significant factors in RA risk. We combine a GRS and GEIs to develop the best model for RA risk.

Methods: We studied models of RA risk in two cohorts, the U.S. Nurses’ Health Studies (NHS) and the Swedish Epidemiologic Investigation of RA (EIRA). We created a weighted GRS using 31 non-HLA single nucleotide polymorphisms at validated RA risk loci, where the weight for each risk allele is the log of the odds ratio based on published GWAS or meta-analysis. In addition, we genotyped HLA-DRB1 locus with subjects coded as having 0, 1 or 2 copies of shared epitope (SE) alleles. Based on previously found significant interactions, we included two additional genotypes, GSTT1-null and HM0X1. Smoking was the main environmental factor for GEI (dichotomized as ≤ 10 pack-years vs. > 10 pack-years). Parallel analyses were performed among (1) 371 Caucasian seropositive (CCP+ and/or RF+) cases and 551 controls from NHS and (2) 987 Caucasian ACPA positive cases and 958 controls from EIRA to develop the best model in each dataset. We began with a base model including year of birth and smoking (plus sex and region of Sweden in EIRA). Hierarchical models adding the most significant factors were compared to the previous and base models using pseudo R² for parsimony and area under the ROC curve (AUC) and the Integrated Discrimination Improvement (IDI), which quantifies the overall improvement in sensitivity and specificity) for discrimination.

Results: The mean (SD) age of diagnosis of RA was 57 (10) in NHS and 50 (12) in EIRA. For NHS, the base model produced an AUC of 0.578. Adding the GRS and HLA to the model increased the AUC to 0.669. The IDI between the 2 models was 0.07 (0.05–0.08), indicating a significant improvement (null IDI = 0). Our best performing model contained the GRS and GEIs combining smoking and HLA, GSTT1-null and HM0X1 and had an AUC of 0.700 and IDI of 0.10 (0.07–0.12) compared to the base model and 0.03 (0.02–0.04) as compared to the model with GRS and HLA. For EIRA, the base model produced an AUC of 0.630. Adding the GRS and HLA to the model increased the AUC to 0.733. The IDI between the 2 models was 0.11
including base, genetic and environmental factors. The results emphasize the importance of developing models separately in different populations. However, further work to discover genetic, environmental and GEF factors is needed before these models are used in clinical settings.

### Table: Summary Measures for Selected Models in the US Nurses’ Health Study and Swedish Epidemiologic Investigation in RA

<table>
<thead>
<tr>
<th>Model</th>
<th>NHS1</th>
<th>EIRA2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IDI^4 (95% CI) compared to Base</td>
<td>IDI^4 (95% CI) compared to Base + GRS + HLA-SE</td>
</tr>
<tr>
<td>Base</td>
<td>0.578</td>
<td>N/A</td>
</tr>
<tr>
<td>Base + GRS</td>
<td>0.669</td>
<td>0.07*</td>
</tr>
<tr>
<td>+ HLA-SE</td>
<td>(0.05–0.08)</td>
<td>(0.10–0.13)</td>
</tr>
<tr>
<td>Base + GRS + GEF</td>
<td>0.700</td>
<td>0.10*</td>
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<tr>
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<td>(0.07–0.12)</td>
<td>(0.10–0.13)</td>
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<table>
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<td></td>
</tr>
<tr>
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<td>0.630</td>
</tr>
<tr>
<td>Base + GRS</td>
<td>N/A</td>
</tr>
<tr>
<td>+ HLA-SE</td>
<td>N/A</td>
</tr>
<tr>
<td>Base + GRS + GEF</td>
<td>N/A</td>
</tr>
</tbody>
</table>

1 NHS: Nurses’ Health Study; 2 EIRA: Epidemiologic Investigation in RA; 3 AUC: Area Under Receiver Operating Characteristic Curve; 4 IDI: Integrated Discrimination Improvement; 5 Baseline Model includes year of birth and heavy smoking in NHS and year of birth, heavy smoking, sex, and geographical region of Sweden for EIRA; 6 GRS: Genetic Risk Score; 7 HLA-SE: Human Leukocyte Antigen Shared Epitope; 8 GEF: Gene-Environment Interactions

**Disclosure:** L. B. Chibnik: None; B. Ding: None; B. T. Keenan: None; K. P. Liao: None; K. H. Costenbader: None; L. Klareskog: None; L. Alfredsson: None; E. W. Karlson: None.

### 1589

**Contribution of VpreB1 Gene Copy Number Variation to the Risk of Rheumatoid Arthritis.** Seung-Cheol Shim2, Mi-Kyoung Lim2, Dong-Hyuk Sheen2 and Yeun-Jun Chung1. 1Catholic University, Seoul, Korea, Republic of Korea; 2Eulji University, Daejeon, Korea, Republic of Korea.

**Background:** Copy number variation (CNV), especially in the genomic loci harboring dosage-sensitive genes, has been reported to affect susceptibility to diverse autoimmune diseases. In human, a copy number loss of 22q11.2, a region harboring pre-B cell receptor gene (VpreB1), has been suggested to be associated with chronic autoimmune arthritis. Recently, mice lacking surrogate light chain encoded by As5 and VpreB1 has been reported to harbor high levels of autoantibodies, and showed evidence of escape of pre-B cells expressing prototypic autoantibody heavy chains from negative selection, leading to mature autoantibody secreting CD21+CD23+ B cells in their serum.

**Objective:** To investigate whether CNV of the VpreB1 associates with susceptibility to rheumatoid arthritis (RA), and whether RA patients have a significantly higher frequency of CD21+CD23+ B cells in the peripheral blood than healthy controls.

**Methods:** We evaluated the copy numbers of the VpreB1 in an independent cohort of 229 cases and 233 controls using genomic quantitative real-time PCR. We also performed fluorescence in-situ hybridization analysis targeting VpreB1 locus (22q11.22) and diploid control locus of the same chromosome arm (22q13.1). Next, we explored the frequency of B cell subsets in the peripheral blood from RA patients and controls, and further characterized CD21+CD23+ B cells using FACS.

**Results:** The median gene dose of VpreB1 in the study population was two. The proportion of the individuals with <2 copy of VpreB1 was significantly higher in RA patients than in controls (10.9% vs 0.9%, p<0.0001), while that of the individuals with ≥2 copy was lower in RA patients (1.7% in RA vs 18.9% in controls, p<0.0001).

**Conclusion:** VpreB1 copy number < 2 was associated with an increased risk of RA in which the odds ratio (OR) was 11.5 (95% CI 2.7–49.3). The OR for RA in individuals with ≥2 copies was significantly lower than that with 2 copies (OR=0.1, 95% CI 0.03–0.3). We also found that the proportion of CD21+CD23+ cells was significantly lower in RA patients than in controls (26.2% vs 34.9%, p=0.005), while that of CD21+CD23− cells was significantly higher in RA (11.9% in RA vs 5.7% in controls, p=0.002).

**Disclosure:** S.-C. Shim: None; M.-K. Lim: None; D.-H. Sheen: None; Y.-J. Chung: None.
Early Disease Onset Is Predicted by a Higher Genetic Risk for Lupus and Is Associated with a More Severe Phenotype in Lupus Patients.

**Purpose:** Systemic lupus erythematosus (SLE) is a chronic, multi-organ, autoimmune disease that affects people of all ages and ethnicities. Herein, we explore the relationship between the age at disease onset and many of its diverse manifestations. We further determine the relationship between age of disease onset and genetic risk in SLE patients.

**Methods:** We explore the relationship between the age at disease onset and SLE manifestations in a multi-ethnic cohort of 1,317 patients. SLE patients were genotyped across 19 confirmed genetic susceptibility loci for SLE. Logistic regression was used to determine the relationships between the number of risk alleles present and age of disease onset.

**Results:** Childhood-onset SLE had higher odds of proteinuria, malar rash, anti-dsDNA antibody, hemolytic anemia, arthritis, and leukopenia (odds ratios = 3.03, 2.13, 2.08, 2.50, 1.89, 1.53, respectively, and p-values <0.0001, 0.0004, 0.0005, 0.0024, 0.011, and 0.045, respectively). In females, the odds of having cellular casts were 2.18 times higher in childhood-onset versus adult-onset SLE (p=0.0027). With age of onset >50, the odds of having proteinuria, cellular casts, anti-nRNP antibody, anti-Sm antibody, anti-dsDNA antibody, and seizures were reduced. Instead, late adult-onset SLE patients have higher odds of developing photosensitivity compared with early adult-onset patients (onset ≥18 and <50 yrs). Importantly, each SLE-susceptibility risk allele carried within the genome of SLE patients increased the odds of having a childhood-onset disease, in an ethnically-specific manner: each risk allele increased risk by an average of 48% in Gullah, and 25% in African-Americans, but this was not significant in Hispanic and European-American lupus patients.

**Conclusions:** We report and quantify for the first time the genetic contribution towards predicting early-onset disease in SLE patients. Furthermore, we report a more severe SLE phenotype in patients with an early-onset disease in a large multi-ethnic cohort, independent of gender, race, and disease duration.

**Disclosure:** R. Webb: None; J. A. Kelly: None; E. C. Somers: None; T. Hughes: None; K. M. Kaufman: None; E. Sanchez: None; S. K. Nath: None; G. Bruner: None; M. E. Alarcon-Riquelme: None; D. L. Kamen: None; B. C. Richardson: None; J. B. Harley: None; A. H. Salavah: None.

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Ethnic Specific Genetic Associations within the FCRL Gene Cluster in SLE.

**Purpose:** The FCRL gene cluster in humans on chromosome 1q23.1 encodes 5 proteins that share a common ancestor with the classical Ig-binding Fc receptors. Each of the FCRL1–5 gene products are expressed by B cells but vary in their distribution on different subpopulations while FCRL3 is also found on NK and T cell subsets. Despite the similarity to the classical FCR, no definitive data demonstrate binding of Ig but very recent studies suggest binding of MHC and MHC-like molecules. A functional promoter variant in the FCRL3 locus has been inconsistently associated with SLE.

**Methods:** We have performed a large case-control association study (n=1571967 [intronic SNP](p=3.6×10^{-4}, OR=0.61[0.47–0.80])). This SNP was replicated in an independent collection of Asian case/control samples from North America (n=625/520) (combined p=3.6×10^{-6}, OR=0.66 [0.54–0.80]).

**Results:** We also observed independent association at 2 non-synonymous SNPs in the FCRL5 gene in the Asian population (peak association at rs67679791, combined p=2.0×10^{-7}, OR=0.69 [0.57–0.84]). No evidence of association within FCRL3 (including the previously associated −169 promoter SNP, rs7528684) was observed. No significant associations (p<0.005) were detected in the FCRL1–5 genes in the EA, AA and Hisp populations.

**Conclusions:** Together, these results demonstrate an association in the FCRL5 gene with SLE in Asians. FCRL5 is known to bind a viral MHC class I-like molecule and is likely to be involved in regulating innate immunity. The identification of non-synonymous SNPs in FCRL5 that associate with SLE in Asian populations provides the opportunity to explore the impact of genetic variation in regulating immune responses in autoimmunity.

**Disclosure:** N. M. Pajewski: None; C. D. Langefeld: None; K. M. Kaufman: None; A. Williams: None; M. Comeau: None; G. S. Alarcon: None; M. A. Petri: None; R. Ramsey-Goldman: None; J. D. Reveille: None; L. M. Vila: None; M. E. Alarcon-Riquelme: None; J.-M. Anaya: None; S.-C. Bue: None; S. A. Boackle: None; B. I. Freedman: None; P. M. Gaffney: None; G. S. Gilkeson: None; P. K. Gregersen: None; J. B. Harley: None; C. O. Jacob: None; J. A. James: None; J. T. Merrill: None; K. L. Moser: None; T. B. Niewold: None; R. H. Scofield: None; A. M. Stevens: None; B. P. Tsao: None; T. J. Vyse: None; E. E. Brown: None; R. P. Kimberly: None; J. C. Edberg: None.
European Genetic Ancestry Protects Against the Development of Renal Disease in Systemic Lupus Erythematosus. Ilana B. Richman, Kimberly E. Taylor, Sharon A. Chung, Laura Trupin, Michelle A. Petri, Edward H. Yelin, Robert R. Graham, Annette T. Lee, Timothy W. Behrens, P. K. Gregersen, Michael F. Seldin and Lindsey A. Criswell. Feinstein Institute Med Resch, Manhasset, NY, 2Genentech Inc, South San Francisco, CA, 3Immunology Biomarkers Group, Genentech, South San Francisco, 4Johns Hopkins University School of Medicine, Timonium, MD, 5N Shore Univ Hosp Rach Ctr, Manhasset, NY, 6Rosalind Russell Medical Research Center for Arthritis, Division of Rheumatology, University of California, San Francisco, San Francisco, CA, 7Rosalind Russell Medical Research Center for Arthritis, Division of Rheumatology, University of California, San Francisco, 8UCSF-Box 0500, San Francisco, CA, 9University of California, Davis

Background: African Americans, Asians, and Hispanics with systemic lupus erythematosus (SLE) are at greater risk of developing renal disease than Caucasians. The extent to which genetic or environmental factors contribute to these disparities remains uncertain. We hypothesized that in a multiethnic SLE case series, European genetic ancestry would be protective against the development of renal disease. We further hypothesized that any protective effect of ancestry may be partially attributable to variation in specific genes associated with renal disease in SLE.

Methods: This was a cross-sectional study of 1,910 adults with SLE enrolled in two SLE case collections. Clinical data and confirmation of SLE diagnosis were obtained by chart review. Self-reported socioeconomic data were available for a subset of participants. All participants were genotyped for a set of 116 single nucleotide polymorphisms (SNPs) informative for continental ancestry. A subset of participants was also genotyped for 80 SNPs in 14 candidate genes for renal disease in SLE and had HLA typing available. Continental ancestry was estimated for each participant using the program STRUCTURE, assuming 5 populations. We used logistic regression to test the association between European ancestry and renal disease, adjusting for disease duration and sex. Subsequent analyses assessed whether also adjusting for other continental ancestries, educational attainment, or SNPs in genes associated with renal disease in SLE attenuated the relationship between European ancestry and renal disease.

Results: Genetic ancestry estimation for 1910 SLE cases demonstrated that participants had on average 62.4% European, 15.8% African, 11.5% East Asian, 6.5% Amerindian, and 3.8% South Asian ancestry. Among participants, 34.4% (n=656) had a history of renal disease. After adjustment for ancestry, SNPs in IRF5 (rs4728142), BLK (rs2736340), STAT4 (rs3024912), ITGAM (rs9937837) and HLA-DRB1*0301 and DRB1*1501 were associated with renal disease in SLE (p<0.05). In multivariable logistic regression, a 10% increase in European ancestry after adjustment for disease duration and sex (OR 0.85, 95% CI 0.82–0.87, p=1.9e–30). Adjusting for other genetic ancestries, educational attainment, or SNPs associated with renal disease did not substantively alter this relationship (Table).

Table. Association between European Ancestry and Renal Disease among SLE Cases

<table>
<thead>
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<th>Model</th>
<th>N</th>
<th>OR for 10%</th>
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<tr>
<td></td>
<td></td>
<td>in Euro Ancestry</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1820</td>
<td>0.85</td>
<td>0.82–0.87</td>
</tr>
<tr>
<td>Model 1 + other genetic ancestries</td>
<td>1820</td>
<td>0.82</td>
<td>0.77–0.87</td>
</tr>
<tr>
<td>Model 1 + educational attainment</td>
<td>1129</td>
<td>0.83</td>
<td>0.80–0.86</td>
</tr>
<tr>
<td>Model 1 + IRF5 (rs4728142), BLK (rs2736340), STAT4 (rs3024912), HLA-DRB1*0301, *1501, other genetic ancestry5</td>
<td>753</td>
<td>0.82</td>
<td>0.69–0.98</td>
</tr>
</tbody>
</table>

† Only SNPs with p < 0.05 in multivariable models were retained in the final model

Conclusions: European ancestry is protective against the development of renal disease in SLE, an effect independent of other genetic ancestries, common risk alleles, and socioeconomic status.

Disclosure: I. B. Richman: None; K. E. Taylor: None; S. A. Chung: None; L. Trupin: None; M. A. Petri: None; E. H. Yelin: None; R. R. Graham: Genentech and Biogen IDEC Inc; 3; A. T. Lee: None; T. W. Behrens: Genentech and Biogen IDEC Inc; 3; P. K. Gregersen: None; M. F. Seldin: None; L. A. Criswell: None.

Fine Mapping and Expression Studies Point to KIF5A as the Gene Responsible for Association of the 12q13 Locus with Rheumatoid Arthritis. Annie McClure, Steve Eyer, Wendy Thomson, Jane Worthington and Anne Barton. The University of Manchester, Manchester, United Kingdom

Background: A region on chromosome 12q13 was shown to have modest association with rheumatoid arthritis (RA) in the Wellcome Trust genome-wide association study (GWAS) of seven common diseases. Two parallel studies have since confirmed this as a RA susceptibility locus in UK and US populations (rs1678542 P=1.3×10−7 and P=5.4×10−7; respectively) and the same SNP has also been associated with type 1 diabetes (T1D). Variants mapping to nearby genes have also been associated with T1D and multiple sclerosis. The associated variant, rs1678542, is located in intron 15 of KIF5A. KIF5A is a microtubule motor protein involved in the transport of HLA-class II molecules. It was reported to be confined to neurons. However other ubiquitous kinesin family members have been shown to be involved in cell motility and intracellular transport of HLA-class II molecules.

Objectives: The aim of the current study was to investigate the 12q13 region further to identify the most likely RA susceptibility gene in the region.

Methods: A region of ~400kb surrounding the associated variant on 12q13 was selected for fine mapping. Tag SNPs were chosen to capture all the known variation across the region (r2 > 0.8). Any SNPs showing larger effect sizes than rs1678542 were then genotyped in a larger, independent validation cohort of 3633 RA cases and 2908 controls. To investigate the expression of KIF5A, RNA was extracted from the blood of 52 RA patients and cDNA was synthesised. Whole blood RNA samples were selected to represent the range of possible genotypes at rs1678542 (major allele homozygous n=20, heterozygous n=19, minor allele homozygous n=13). KIF5A is known to be expressed in the brain so RNA was extracted from mouse brain to act as a positive control. Primers were designed to amplify KIF5A in human and mouse transcriptomes. The expression of two housekeeping genes (GAPDH and ACTIN) was also measured in order to normalise KIF5A expression. QRT-PCR was carried out using the ABI 7500.

Results: In a fine-mapping cohort of 1,000 RA cases and 1,000 controls, 5 tag SNPs were identified that exhibited greater effect sizes than rs1678542. These 5 SNPs and rs1678542 were then genotyped in the larger validation cohort. Only rs1678542 remained significantly associated (p=0.004, OR 0.90 95% CI 0.84–0.97). QRT-PCR of KIF5A confirmed its expression in whole blood. Correlation of expression with genotype at rs1678542 by linear regression showed a significant trend in expression by genotype (1×10−7). Individuals homozygote for the protective major allele had reduced KIF5A expression when compared to individuals who were heterozygote or homozygote for the minor allele at rs1678542.

Conclusion: After fine mapping of the region, association remains strongest with the original SNP identified in the WTCCC GWAS mapping to the KIF5A gene. The demonstration of expression of KIF5A in whole blood improves its potential for involvement in RA pathogenesis. Furthermore we present the first evidence of a correlation between KIF5A expression and genotype at a SNP associated with RA. The next step will be to validate this correlation using allele specific expression.

Disclosure: A. McClure: None; S. Eyer: None; W. Thomson: None; J. Worthington: None; A. Barton: None.

Fine Mapping and Trans-Ethnicity Genotyping in IL2/IL21 Establish the Genetic Association between IL21 and Systemic Lupus Erythematosus. Travis Hughes, Xana Kim, Jennifer A. Kelley, Kenneth M. Kaufman, Carl D. Langefeld, Julie Ziegler, Robert P. Kimberly, Jeffrey C. Edberg, Rosalind Ramsey-Goldman, Michelle A. Petri, John D. Revillie, Javier Martin, Elizabeth E. Browi, Luis M. Vila, Judith A. James, Gary S. Gilkeson, Kately L. Moser, Patrick M. Gaffney, Joan T. Merrill, Timothy J. Vyse, Marta E. Alarcon-Riquelme, Swapan K. Nath, John B. Harley and Amr H. Savallia. 1Timonium, MD, 2Imperial College, Rheumatology Section, Hammarks Hospital, 3Instituto de Patologia and Biomedicina Lopez-Neyra, Consejo Superior de Investigaciones Científicas, 4Med Univ of South Carolina, Charleston, SC, 5Northwestern University, Chicago, IL, 6Oklahoma Med Research Foundation, Oklahoma City, OK, 7OMRF, 8OMRF, Center for Genomics and Oncological Research Pfizer, 9University of Granada, Junta de Andalucia, Uppsala, Sweden, 10OMRF, OUHSC, VAMC, 11Univ Alabama at Birmingham, Birmingham, AL, 12Univ of Oklahoma Health Sci Ctr, Oklahoma City, OK, 13Univ of PuertoRico Schl of Med, San Juan, PR, 14Univ Texas Health Sci Ctr, Houston, TX, 15University of Alabama at Birmingham, Birmingham, AL, 16University of Oklahoma Health Sciences Center, OMRF, VAMC, Oklahoma City, OK, 17Wake Forest University Health Sciences

Purpose: Genetic association of the IL2/IL21 region at q427 has been previously reported in lupus and a number of autoimmune and inflammatory diseases. Herein, using a very large cohort of lupus patients and controls, we localize this genetic effect to the IL21 gene.
Methods: We genotyped 45 tag SNPs across the IL2/IL21 locus in two independent lupus cohorts. We studied a European-derived cohort consisting of 4,248 lupus patients and 3,818 healthy controls, and an African-American cohort of 1,569 patients and 1,893 healthy controls. Genetic association between the genotyped markers was determined, and pair-wise conditional analysis was performed to localize the genetic effect in the IL2/IL21 locus in lupus.

Results: We establish and confirm the genetic association between IL2/IL21 and lupus in two independent lupus cohorts. Using conditional analysis and utilizing trans-ethnic genotyping, we localize the genetic effect for the first time in this locus to two SNPs; rs6835457 located in the lupus. Analysis was performed to localize the genetic effect in the IL2/IL21 locus in between the genotyped markers was determined, and pair-wise conditional rs2022013 in to other autoimmune and inflammatory disease with a reported association in the IL2/IL21 linkage disequilibrium block. This localization might be relevant P

Conclusion: Our data identify IL21 as a lupus susceptibility gene within the IL2/IL21 linkage disequilibrium block. This localization might be relevant to other autoimmune and inflammatory disease with a reported association in the IL2/IL21 genetic locus.

Disclosure: T. Hughes: None; X. Kim: None; J. A. Kelley: None; K. M. Kaufman: None; C. D. Langefeld: None; J. Ziegler: None; R. P. Kimberly: None; J. C. Edberg: None; R. Ramsey-Goldman: None; M. A. Petri: None; J. D. Revelle: None; J. Martin: None; E. E. Brown: None; L. M. Vila: None; J. A. James: None; G. S. Gilkeson: None; K. L. Moser: None; P. M. Gaffney: None; J. T. Merrill: None; T. J. Vyse: None; M. E. Alarcon-Riquelme: None; S. K. Nath: None; J. B. Harley: None; A. H. Savalha: None.

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Fine Mapping of NMNAT2 for Association with SLE Susceptibility: A Multiethnic Case-Control Study. Jian Zhao1, Carl D. Langefeld2,3, Kenneth M. Kaufman2, Jennifer A. Kelly1, Patrick M. Gaffney1, Kathy L. Moser1, Marta E. Alarcon-Riquelme on Behalf of the BIOLUPUS and GENES Networks2, Timothy J. Vyse3, Chaim O. Jacob4, Robert P. Kimberly3, Jeffrey C. Edberg5, Elizabeth E. Brown on Behalf of PROFILE investigators6, Lindsey A. Criswell7, John B. Harley5, Deh-Ming Chang8, Yeong Wook Song9, Chack-Yung Yu10, Bernardo Pons-Estel8, Jennifer M. Moser2, T. Hughes: None; X. Kim: None; J. A. Kelley: None; K. M. Kaufman: None; C. D. Langefeld: None; J. Ziegler: None; R. P. Kimberly: None; J. C. Edberg: None; R. Ramsey-Goldman: None; M. A. Petri: None; J. D. Revelle: None; J. Martin: None; E. E. Brown: None; L. M. Vila: None; J. A. James: None; G. S. Gilkeson: None; K. L. Moser: None; P. M. Gaffney: None; J. T. Merrill: None; T. J. Vyse: None; M. E. Alarcon-Riquelme: None; S. K. Nath: None; J. B. Harley: None; A. H. Savalha: None.

Background: NMNAT2, one of the three Nicotinamide mononucleotide adenyl transferases, is a central enzyme of the NAD biosynthesis pathway mainly expressed in Golgi-complex with a known function of delaying axon degeneration. In this study, we sought to replicate a putative association at rs2022013 in NMNAT2 from the SLEGEN genome-wide association study (GWAS) conducted in women of European ancestry (Harley et al, 2008) not yet exceeding the stringent threshold for genome-wide significance (typically P<5×10⁻⁷).

Methods: A total of 24 SNPs, spanning the genomic region of NMNAT2, were genotyped on a customized Illumina array. Additionally, ~400 ancestry informative markers were used to control population admixture and to eliminate genetic outliers. The association of NMNAT2 SNPs with SLE was tested in a collection of 15,424 case-control samples consisting of European Americans (EA), African Americans and Gullahs (AA&Gullah), Asians and Hispanic and Native Americans (Hisp&NA). We performed Chi-square test to compare the allelic difference between cases and controls, likelihood ratio test to distinguish independent signals from associated SNPs, and Mantel-Haenszel test to conduct the trans-ethnic meta-analysis.

Result: Among the 16 association signals observed in EA (3477 vs. 3470 case-control samples independent of SLEGEN GWAS), we replicated the association of rs2022013 (P=9.5×10⁻⁷, OR=0.84) and identified 4 independent SLE-associated SNPs located in intron 1 of NMNAT2 (long isofrom) with the strongest signal at rs12146097 (P=1.6×10⁻⁹, OR=1.34). Allelic association detected in EA was partially extended to Hisp&NA (5 SNPs with allelic P from 0.018 to 7.8×10⁻⁴, 1508 vs. 812) but not to AA&Gullah (1680 vs. 1953). Rs607332 (within intron 6) exhibited the strongest signal in AA&Gullah (P=0.0013, OR=0.9) and Hisp&NA (P=2.9×10⁻⁴, OR=0.8) but had no association in EA, which indicated specific associations of NMNAT2 SNPs in various populations. No SNP showed significant association with SLE in Asians (1272 vs. 1270). The most significant meta-analysis P value of 4 ethnic groups was detected at rs12146097 (P=1.25×10⁻⁹, OR=1.29).

Conclusion: We provided independent evidence that NMNAT2 predisposes to susceptibility to SLE with genome-wide significance. Trans-ethnic fine mapping showed NMNAT2 SNPs had different association patterns among multiple ethnic groups. Our data suggested the novel role of NAD biosynthesis in the pathogenesis of SLE.

Disclosure: J. Zhao: None; C. D. Langefeld: None; K. M. Kaufman: None; J. A. Kelley: None; P. M. Gaffney: None; K. L. Moser: None; M. E. Alarcon-Riquelme on Behalf of t None; T. J. Vyse: None; C. O. Jacob: None; R. P. Kimberly: None; J. C. Edberg: None; E. E. Brown on Behalf of PROFILE investigators None; L. A. Criswell: None; J. B. Harley: None; D.-M. Chang: None; Y. W. Song: None; C.-Y. Yu: None; B. Pons-Estel: None; J. M. Grossman: None; R. M. Cantor: None; B. H. Hahn: None; B. P. Tsao: None.

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Gene-Interactions Influence Methotrexate Efficacy in Rheumatoid Arthritis: Analysis of 62 SNPs Panel in a Monocentric Cohort of Rheumatoid Arthritis Affected Patients. Thomas Barnetche1, Caroline Rooyrick-Thambo2, Christophe Hubert1, Christophe Riches2, Benoit Arveiler4, Thierry Schaeverbeke2, 1Bordeaux University Hospital, Rheumatology Department, Bordeaux, France, 2Bordeaux University Hospital, Rheumatology Department, 3Genomics-Transcriptomics Facility, Bordeaux, 4Human Genetics Laboratory EA4137, University Victor Segalen Bordeaux 2

Purpose: Methotrexate (MTX) is one of the most widely used disease-modifying antirheumatic drugs (DMARDs) for the treatment of rheumatoid arthritis. No single genetic marker allows predicting response to the treatment. Here, we aimed to establish gene-gene epistatic interactions to predict MTX response therapy. SNPs were selected in proteins and enzymes that step in folate, purine and adenosine pathways, and also in several transporters that participate to MTX cellular absorption and elimination.

Method: A sample of 222 RA affected patients treated with low dose of MTX (7,5mg to 25mg with oral, intra-muscular or subcutaneous administration) was included in a monocentric study. Efficacy to MTX was assessed using EUCLAR response criteria and/or physician’s assessment. A panel of 62 SNPs was analyzed for each patient. Univariate analysis in genotypes and allele frequencies was performed. Then gene-gene interactions were studied using Multifactor Dimensionality Reduction (MDR). MDR is considered as a non-parametric approach to detect non-linear interactions between binary variables that influence a binary outcome. This method reduces the dimensionality of genotypes predictors from N-dimensions to one dimension in pooling multilocus genotypes into high-risk and low risks MTX response groups. The robustness and significance of the model were tested through cross validation consistency (CVC, 10-fold).

Results: The MDR method highlights that MTX response (about 67% in this sample) is related with epistatic interactions among variants in ABCB3 (ATP-binding cassette, sub-family C) efflux transporter (rs739921 [CG], rs4148412 [CT]), ABCC5 efflux transporter (rs4148575 [CT]) and adenosine monophosphate deaminase 1 (rs2286699 [A/C]). Testing accuracy was 0.635 and CVC was 10/10. Carriers of a predisposing genotype combination were 4 ethnic groups was detected at rs12146097 (P=1.25×10⁻⁹, OR=1.29).

Conclusion: We provided independent evidence that NMNAT2 predisposes to susceptibility to SLE with genome-wide significance. Trans-ethnic fine mapping showed NMNAT2 SNPs had different association patterns among multiple ethnic groups. Our data suggested the novel role of NAD biosynthesis in the pathogenesis of SLE.

Disclosure: T. Barnetche: None; C. Rooyrick-Thambo: None; C. Hubert: None; C. Riches: None; B. Arveiler: None; T. Schaeverbeke: None.
Genome-Wide Association Study for Rheumatoid Arthritis in the Korean Population Points to Population-Specific Candidate Loci as Well as Overlap with European Susceptibility Loci. Jan Freudenberg1, Hye-Soon Lee2, H. D. Shin3, B. D. Han4, Y. M. Kang5, S. C. Shim6, Y. K. Sung6, CB Choi7, Annette Lee8, Peter K. Gregersen9 and S. C. Bae9, 1Eulji University Hospital, 2Feinstein Institute for Medical Research, Manhasset, NY, 3Feinstein Institute for Medical Research, 4Hanyang University Hospital for Rheumatic Diseases, 5Korea National Institute of Health, 6Kyungpook National University School of Medicine, 7Sogang University

We have carried out a genome-wide association study (GWAS) in Korean individuals in order to identify susceptibility loci for Rheumatoid Arthritis (RA). We generated high quality genotypes for 441398 SNPs in 801 cases of RA and 757 controls. Genome-wide significance (p<5*10^(-8) was attained by markers from the MHC-region and from the Rheumatic Diseases, 5Korea National Institute of Health, 6Kyungpook National University School of Medicine, 7Sogang University

Genome-Wide Association Study (GWAS) has led to the discovery of several genetic associations with this disease. However, the replication data showed nominal association signals (p<5*10^(-2)) for markers from 11 out of the 46 replicated loci, greatly exceeding random expectation. Genes that were most significant in the replication stage and in the combined analysis included the known European RA loci BLK, AFF3 and CCL21. Thus, in addition to the previously associated STAT4 alleles, variants at these three loci may contribute to RA not only among Europeans, but also among Asians. In addition, we observed replication signals near the genes PTPN2, FLI1, ARHGFE3, LCP2, GPRRII, TRHD and CG41. Based on the excess of small P-values in the replication stage, we estimate that more than half of these loci are genuine RA susceptibility genes. Finally, we systematically analysed the presence of association signals in Koreans at established European RA loci. This showed a significant enrichment of European RA loci among Korean RA loci.

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Genome-Wide Copy-Number-Variation Study in Chinese Han Population Identifies Deletion of LCE3C_LCE3B as Susceptibility Factor for Rheumatoid Arthritis. Xiaolan Lu1, Jianping Gao2, Ru Li3, Xia Liu4, Zuowei Wu5, Jinxia Shi6, Xinyu Wu6, Yingli Li7, Yi Zhao8, Chun Li9, Sisi Pan1, Lei Zhu1, Jing He1, Xu Liu1, Wenjun Chen1, Baoli Zhu1 and Zhanguo Li1, 1Beijing Institute of Genomics, Chinese Academy of Sciences, 2Department of Rheumatology and Immunology, People’s Hospital Peking University, Beijing, China, 3Department of Rheumatology and Immunology, People’s Hospital Peking University, 4Institute of Microbiology, Chinese Academy of Sciences

Objective: To identify susceptibility genes concerning copy number variations (CNVs) in rheumatoid arthritis (RA) and to determine whether the RA risk CNVs are specifically associated with certain subsets of RA.

Methods: We first conducted a genome-wide CNV analyses by array comparative genomic hybridization (aCGH), and further characterized the association between the CNV of the late cornified envelope (LCE) genes, LCE3C_LCE3B and RA in a case-control cohort (518 RA patients and 507 controls). All samples were directly genotyped for the presence or absence of LCE3C_LCE3B alleles by PCR. The cases were classified based on their HLA–DRB1 genotypes, anti-citrullinated protein antibodies (ACPAs) and LCE3C_LCE3B alleles by PCR. The cases were classified based on their controls). All samples were directly genotyped for the presence or absence of variations (CNVs) in rheumatoid arthritis (RA) and to determine whether the RA risk CNVs are specifically associated with certain subsets of RA.

Results: In aCGH study, we identified LCE3C_LCE3B as a candidate risk factor for RA (Log2 ratio = 1.50 ± 0.92). In replication study, we further demonstrated that the deletion of LCE3C_LCE3B was associated with RA (allele analysis: p = 3.03×10^(-3); OR 1.30, 95%CI 1.09–1.56; genotype analysis: p = 2.02×10^(-3); OR 1.58, 95%CI 1.20–2.45), with the specificities in anti-cyclic citrullinated peptide antibody (anti-CCP) positive (p = 0.03; OR 1.40, 95%CI 1.01–1.94), RF negative (p = 0.04; OR 1.78, 95%CI 1.04–3.06), anti-keratin antibody (AKA) negative (p = 6.69×10^(-3); OR 1.51, 95%CI 1.01–2.26), and rheumatoid nodules (RNs) negative subsets (p = 0.01; OR 1.52, 95%CI 1.08–2.13).

Conclusion: Our study demonstrated that LCE3C_LCE3B-del was a novel susceptibility factor for RA in Chinese Han population, and the LCE3C_LCE3B-del association with RA was significantly relevant to HLA–DRB1 shared epitope (SE), anti-CCP, RF and AKA status.

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Genome-Wide Pathway Analysis Identifies Oxidative Stress Related Gene MSRA as Rheumatoid Arthritis Susceptibility Locus. Jose Ezequel Martin1, Behrooz Z. Alizadeh19, Miguel A. Gonzalez-Gay4, Alejandro Balsa2, Dora Pascual-Salcedo3, Benjamín Fernández-Gutiérrez2, Enrique Raya2, Lude Franke2, Ruben Van’t Slot1, Marieke J. H. Coenen2, Piet van Riel1, T. R. D. J. Radstake2, B. P. C. Koelman1 and Javier Martin2, 1Hospital Clinico San Carlos, Dept. of Rheumatology, Spain, 2Hospital La Paz, Dept. of Rheumatology, Spain, 3Hospital, 4Hospital Xeral-Calde, Dept. of Rheumatology, Lugo, Spain, 5Instituto de Parasitología y Biomedicina López-Neyra, CSIC, Armilla, Granada, Spain, 6Instituto de Parasitología y Biomedicina López-Neyra, CSIC, Spain, 7Radboud University Nijmegen Medical Center, Department of Human Genetics, The Netherlands, 8Radboud University Nijmegen Medical Center, Department of Rheumatology, The Netherlands, 9University Medical Center Groningen, Dept. Human Genetic, The Netherlands, 10University Medical Centre Groningen, Dept. of Epidemiology, 11University Medical Centre Utrecht, Dept. Medical Genetics, The Netherlands

Objective: Genome-wide association studies (GWAS) carried out in rheumatoid arthritis (RA) have led to the discovery of several genetic associations with this disease. However, the current associated genetic variations can explain only part of the genetic risk involved in RA, and it is well recognised that these GWASs are likely underpowered to detect all common disease variants. Therefore, we explored the genomic regions showing low-significance associations in previous GWASs of RA.

Methods: To reduce the false-positive signal fraction, we exploited pathway analysis to prioritise regions containing genes most likely to be implicated in RA. We hypothesised that true disease genes would be in a similar pathway. Therefore, genes from similar pathways but located in different regions were prioritised for replication using Prioritizer software. 384 genetic variants selected from previous RA GWASs were tested in a Spanish case/control discovery cohort comprising 376 RA patients and 478 healthy controls for replication. Statistically significant associations were further validated in replication cohorts from Spain and Netherlands, up to a total of 1,818 RA patients and 2,498 controls.

Results: We detected a novel genetic association between RA and the MSRA gene (rs10903323, P = 2.91×10^(-5); OR = 1.51) in the Spanish combined population. This association was further tested in our independent Dutch replication cohort. Combined analysis showed an overall association of MSRA with RA (P = 2.19×10^(-5); OR = 1.28).

Conclusion: Novel association in the MSRA gene area related to oxidative stress is described herein and support a major role for this process in RA.

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are recorded at inclusion and at yearly assessments thereafter. Serologic status (anti citrullinated protein antibodies (ACPA)) is determined at study entry. A subset of 372 patients was genotyped for 370,404 single nucleotide polymorphisms (SNPs) by genome-wide array (Illumina). The association of SNP markers with clinical and radiological markers of disease severity was investigated using the presence of erosions by 5 years as the primary outcome measure. Adjustment for the presence of ACFA, a known marker of disease severity, and for receiving disease modifying anti-rheumatic medications was incorporated into the analysis.

**Results:** At baseline 84% of the 372 genotyped patients satisfied the 1987 ACR criteria for RA; and 62% carried at least one copy of an HLA-DRB1 allele known to confer susceptibility to RA. 48% were erosive by 5 years. Genome-wide association studies revealed a number of SNPs with evidence for association with erosions by year 5 of follow-up (p-values < 5.9 x 10^{-8} for SNPs mapping to SLC15A4 (chr. 12), XIRP2 (chr. 2) and HLA-DQ (chr. 6)) or with the extent of radiological damage quantified by the Larsen score (5 SNPs mapping to MTMR7, p = 4.4 x 10^{-10}). Logistic regression analysis within the genotyped NOAR dataset confirmed the known strong association between positivity for ACPA and erosions, and showed a weaker but independent association between HLA-DRB1 susceptibility alleles and erosions.

**Discussion:** We have found a set of SNPs with strong evidence for association with radiological damage by 5 years. Genotyping of these candidate SNPs is currently underway in an independent cohort. The identification of genetic predictors of severity at presentation could be used to predict which patients are likely to develop erosive disease, and it may be possible to target these patients for more aggressive treatment earlier in their disease course. Identified, these genetic markers may improve the predictive value of ACPA in identifying patients likely to experience a severe disease course and pave the way for a more personalised approach to medicine.

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**1601 Identification of KIAA Proteins in Immune Complex Proteome from Juvenile Idiopathic Arthritis and Systemic Lupus Erythematosus.** Anil Chauhan1, Brooke Gilliam2, Catherine P. Riley2, Jiri Adamec1 and Terry L. Moore3. 1Purdue University, 2Saint Louis University, 3St Louis University.

**Purpose:** Biomarkers discovered by proteome analysis are not only useful for patient stratification but for monitoring therapeutic responses and understanding of disease pathogenesis. Biological fluids such as plasma although a good source of information, present a technical challenge due to at least ten orders of magnitude dynamic range of protein concentration. Protein and peptide immuno-affinity pre-fractionation coupled with mass spectrometry (MS)-based proteomics have been used for biomarker discovery; however a prior knowledge of the disease association is required. Thus we wanted to develop a proteomic approach that is capable of identifying low abundance disease associated proteins as a possible biomarker candidate. We achieved this by combining receptor affinity for isolation of immune complexes (ICs) with downstream coupling to nano-LC/MS-MS.

**Methods:** Fifteen IC samples from juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE) patients were purified using receptor affinity columns and then fractionated on a Criterion XT Bis Tris precast gel. Thereafter, each sample protein lane was cut into 5 equal pieces. Tryptic peptides from these samples were then deduced on a nanoLC-Chip system (1100 Series LC, Agilent) and separated on the on-chip C-18 reversed phase ZORBAX 300SB-C18 (0.075 µm x 150 mm, Agilent). The NanoLC-MS chromatograms were acquired in positive ion mode with a capillary voltage of 1850 V, an end plate offset of 500 V, dry gas at 300°C and 4 L/min. Spectra were acquired for 350–2000 m/z at a scan speed of 8,100 m/z/s with 0.15 s maximum accumulation time.

**Results:** We identified a total of 873 proteins from ICs purified from the fifteen samples. The ICs from the JIA patients showed more proteins associated with cell adhesion, proliferation, protein transport, and ATP biosynthetic process, while the SLE group with cytoskeleton organization, signal transduction, T cell activation, and intracellular and signaling cascade. A number of proteins that are known target of post translational modifications in autoimmune response were also identified. The common proteins present in these ICs were complement proteins, fibrinogen, apolipoprotein A-I, cartilage acidic protein, and S100 calcium-binding proteins. The SLE-ICs showed a large number of nuclear proteins such as zinc finger proteins including 652, 644, 133, and matrin type 5. In addition, ICs from JIA and SLE showed the presence of T cell receptor beta chains, suggesting an active role for T cells. KIAA proteins are proteins encoded by large cDNA identified by Kazusa cDNA project. They display multiple domains that suggest their involvement in interactions with other biological molecules. We observed two unique sets of KIAA proteins one associated to JIA and other with SLE. There are 2031 KIAA cDNA entries in HUGE database that are being characterized (http://www.jsp/huge/ppi).

**Conclusion:** We show a successful approach to identify low abundance antigens from ICs. The IC proteome shows more proteins unique to individuals rather than disease group. The presence of KIAA proteins in the ICs suggest their role in disease pathogenesis and as a new potential biomarker group.

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**1602 Major Histocompatibility Complex Associations with Thrombosis and Antiphospholipid Antibody Production in Systemic Lupus Erythematosus.** Rachel Kaiser1, Sharon A. Chung2, Kimberly E. Taylor2, Suzanne L. May2, Patricia P. Ramsay2, Hong L. Quach2, Diana L. Quach2, Julie A. Lane1, Janelle A. Noble3, Michael F. Seldin3, Lisa Barcellos2 and Lindsey A. Criswell2. 1Children’s Hospital Oakland Research Institute, 2UC Berkeley, 3UC Davis, UCSF, San Francisco, CA, 4UCSF-Box 0500, San Francisco, CA.

**Purpose:** Thrombosis occurs at a younger age and at an increased frequency in systemic lupus erythematosus (SLE) compared to the general population. Known risk factors such as antiphospholipid antibodies (aPL) incompletely explain outcomes in this complex phenotype. The major histocompatibility complex (MHC) has the strongest association with SLE but associations with subphenotypes are less well-established due to part in linkage disequilibrium in the region. Prior studies in Caucasians suggest that HLA-DRB1 allele frequencies differ between SLE patients with and without aPL, and that DR4 and DR7 may be associated with anticardiolipin autoantibodies (aCL). We investigated the association of HLA-DRB1 and other MHC loci (independent of HLA-DRB1) with thrombosis and aPL production in SLE.

**Methods:** We genotyped 909 SLE cases of European descent for 2360 single nucleotide polymorphisms (SNPs) across 4.9 Mb of the MHC using the Illumina Combined MHC panel. These cases were also genotyped for HLA-DRB1 and 384 ancestry informative markers. Thrombotic events (deep venous thrombosis, myocardial infarction, stroke, pulmonary embolism, retinal vein thrombosis, recurrent miscarriage) and aPL status (aCL IgG and IgM, lupus anticoagulant (LAC)) were obtained from medical record review. Associations with HLA-DRB1 alleles were identified using a relative predispositional effects (REP) method. SNPs associated with aPL and thrombosis were identified using forward selection with conditional logistic regression based on haplotypes implemented in WHAP.

**Results:** We genotyped 1974 SNPs and 640 SLE cases after stringent quality control criteria were applied and subjects with <90% northern European ancestry were removed. Five percent of the subjects were LAC positive, 33% were aCL positive, 35% were positive for at least one of these aPLs, and 24% experienced at least one thrombosis. HLA-DRB1*0701 was associated with thrombosis in a global $X^2$ test and in a multivariate model adjusting for age, gender, smoking history, disease duration, nephritis history, aPL, Northern European ancestry and medications (including immunomodulators and hydroxychloroquine) (OR 2.06, 95%CI: 1.09–3.90, $p=0.027$). No DRB1 associations were found with aPL (global $X^2 p>0.05$). Conditional logistic regression identified associations independent of HLA-DRB1 in or near the BAT3-MDC1-HCPS region with thrombosis (OR=2.53, haplotype specific $p=1.35 	imes 10^{-10}$) and in or near the BTNL2-HLA-E-HLA-B region with aPL (OR=4.50, haplotype specific $p=6.80 	imes 10^{-7}$). The presence of KIAA proteins in the ICs suggest their role in disease pathogenesis and as a new potential biomarker group.

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**1603**

**MMEL1 and CDK6 Are Associated with ACPA Positive and RF Positive Rheumatoid Arthritis.** Marthe Thoresen Mæhlen1, Tore K. Kvien2, Till Uhlig3 and Benedicte A. Lie4. 1Dept. of Rheumatology, Diakonhjemmet Hospital, 2 Institute of Immunology, Oslo University Hospital, Oslo, Oslo, Norway, 3Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, 4Institute of Immunology, Oslo University Hospital, Oslo, Norway

**Background:** Genes play an important role in the aetiology of rheumatoid arthritis (RA), and recent genome wide association studies have reported several new SNPs to be associated with RA. Some of these have been replicated. However, further studies are needed to establish whether these are true risk loci.

**Objective:** Investigate whether 11 candidate SNPs (in KIF5A, REL, CCL21, PRKCC, STAT4, CTLA4, MMEL1, CDK6, TRAF1, OLIG3, TNFAIP3 (2 SNPs)) are associated with RA and autoantibody production in the Norwegian population.

**Method:** DNA from 950 Norwegian RA patients and 1130 Norwegian controls were genotyped with TaqMan assays (Applied Biosystems). All 11 SNPs had >98% genotyping success rate and all genotypes were in Hardy-Weinberg equilibrium. χ² tests were used to test for associations. For the SNPs that were not associated with RA, we calculated the power in our dataset to detect an association using Power and Sample Size program, version PS 3.0.13. These calculations were based on odds ratios and minor allele frequencies published in a recent meta-analysis (Stahl, E.A. et al Nat. Genet. 2010).

**Results:** The major allele of MMEL1 and minor allele of CDK6 were both significantly associated with RA (table). The associations were restricted to ACPA positive and RF positive RA. The minor allele of STAT 4 was significantly associated with ACPA positive RA only. None of these 3 SNPs were associated with ACPA negative or RF negative RA. The remaining eight SNPs showed no significant association with RA in our Norwegian cohort.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Patients</th>
<th>Minor allele</th>
<th>MAF case</th>
<th>MAF control</th>
<th>Allele test</th>
<th>OR 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMEL1</td>
<td>ALL</td>
<td>C</td>
<td>0.298</td>
<td>0.334</td>
<td>T/C</td>
<td>1.18 (1.03–1.35)</td>
<td>0.01</td>
</tr>
<tr>
<td>MMEL1</td>
<td>ACPA+</td>
<td>C</td>
<td>0.276</td>
<td>0.334</td>
<td>T/C</td>
<td>1.30 (1.11–1.53)</td>
<td>0.001</td>
</tr>
<tr>
<td>MMEL1</td>
<td>RF+</td>
<td>C</td>
<td>0.251</td>
<td>0.334</td>
<td>T/C</td>
<td>1.45 (1.26–1.78)</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>CDK6</td>
<td>ALL</td>
<td>G</td>
<td>0.262</td>
<td>0.227</td>
<td>G/C</td>
<td>1.20 (1.04–1.39)</td>
<td>0.01</td>
</tr>
<tr>
<td>CDK6</td>
<td>ACPA+</td>
<td>G</td>
<td>0.274</td>
<td>0.227</td>
<td>G/C</td>
<td>1.26 (1.10–1.52)</td>
<td>0.003</td>
</tr>
<tr>
<td>CDK6</td>
<td>RF+</td>
<td>G</td>
<td>0.278</td>
<td>0.227</td>
<td>G/C</td>
<td>1.31 (1.10–1.56)</td>
<td>0.003</td>
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<tr>
<td>STAT4</td>
<td>ALL</td>
<td>T</td>
<td>0.239</td>
<td>0.223</td>
<td>T/G</td>
<td>1.10 (0.95–1.27)</td>
<td>0.22</td>
</tr>
<tr>
<td>STAT4</td>
<td>ACPA+</td>
<td>T</td>
<td>0.253</td>
<td>0.223</td>
<td>T/G</td>
<td>1.18 (1.01–1.40)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Conclusion:** We replicated the proposed associations between MMEL1 and CDK6 with RA. In addition we demonstrated that CDK6 and MMEL1 are associated to both ACPA positive and RF positive RA. Further we demonstrated that CDK6 and MMEL1 with RA. In addition we demonstrated that CDK6 and MMEL1 with RA. Furthermore, we found that expanded B-cell clones can be detected in inflamed synovial tissue (ST) of patients with longstanding RA. These clones were either absent or of very low frequency in peripheral blood (PB), suggesting local retention and/or proliferation in the synovium. Here we examined whether oligoclonal B-cell expansions can be detected in early stages of RA.

**Objectives:** Compare expanded B-cells in paired samples (ST and PB) during different stages of disease using novel high throughput sequencing technology.

**Methods:** We included 2 anti-CCP+ patients with active RA. Patient 1 (pt1) was DMARD naïve and had a disease duration less than 1 year. Patient 2 (pt2) had active disease despite methotrexate treatment and had a disease duration of more than 10 years (longstanding RA). mRNA was isolated from paired samples (ST biopsies from arthritic ankle/knee and PB, respectively). Linear amplification was performed with primers for all V(earable)-families of the receptor heavy-chain. The amplified products contain the Complementarity Determining Region 3 (CDR3), which can be used as a ‘fingerprint’ for each clone. The samples were analyzed using a Genome Sequencer (454/ Roche). The frequency of clones was determined by custom bioinformatics algorithms identifying the CDR3-region of each receptor (up to 1 million receptors at once). Clones with a frequency of ≥1% were arbitrarily considered as highly expanded.

**Results:** In the longstanding RA-patient 15 highly expanded B cell clones were detected in the ST. Of interest, we also detected 14 highly expanded clones in the ST of the early RA patient. In both patients the highest frequency observed was 7%, none of the highly expanded clones had a clearly higher frequency than the other clones. The oligoclonal pattern observed was defined by distinctly different CDR3 sequences and use of different gene segments in both patients. In the PB samples of both patients only few expanded clones were found (5 and 6 highly expanded clones, respectively). However, most clones that were highly expanded in ST could also be detected in the PB of both patients, albeit at very low frequencies (less than 0.05% in both patients). In contrast, highly expanded clones from the PB were not at all found in ST. Comparing both patients, the highly expanded clones were all different.

**Conclusion:** This is the first analysis of B-cell clones in ST and PB samples comparing RA patients with different disease duration, using novel HTS technology. Our data suggest that oligoclonal B-cell expansions can already be detected in early stages of RA. This suggests that multiple epitopes might already be involved in so-called early RA.

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1605

**New HLA-DRB1 Classifications in Association with Rheumatoid Arthritis for Global Application: Beyond the Conventional Shared Epitope Hypothesis.** So-Yong Bang3, Hye-Soon Lee3, Ji-Seon Lee3, Eun-Mi Kim1, Kyung Wha Lee2 and Sang-Cheol Bae1. 1Department of Rheumatology, Hanyang University Hospital for Rheumatic Disease, Korea, Republic of, 2Hallym Institute for Genome Application, Hallym University Sacred Heart Hospital, Korea, Republic of

**Objectives:** The HLA-DRB1 shared epitope (SE) hypothesis does not wholly explain HLA contribution to rheumatoid arthritis (RA) susceptibility. Different classification systems have been proposed, but few have been validated in non-Caucasians. Here, we investigated the relevance of recent HLA-DRB1 allele classifications of RA susceptibility and protection in a large Asian cohort of RA patients and controls.

**Methods:** All 2,601 unrelated Korean subjects including 1,482 patients with RA and 1,119 unaffected controls were genotyped. Four-digit level HLA-DRB1 typing was performed by direct DNA sequence analysis. HLA-DRB1 alleles were grouped according to the Tezenas du Montcel and Mattey classification systems.

**Results:** Based on Tezenas du Montcel classification, S_{2/3P} genotype was associated with the greatest risk for RA, with an OR (95% CI) of 15.30 (4.79–48.93). We confirmed our previous finding that DRB1*0901 was the second significant risk allele for RA in the Korean population (OR 1.83 (1.53–2.19), P = 4.37 × 10⁻¹²). The HLA-DRB1 alleles were realigned according to our modified classification system including DRB1*0901 [S_{2} (^{*}F^{6}RRRAE^{7}]). Interestingly, S_{2/3P} and S_{2/3P} genotypes were associated with the higher risk for RA compared with conventional classification. Additionally, the SE/D^{*} genotype was associated with lower risk for RA, compared with the SE/D^{*} genotype using the Mattey classification system.
RA risk for genotypes according to our modified HLA-DRB1 classification system

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No. (%) of controls (n=1,119)</th>
<th>No. (%) of RA cases (n=1,482)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>S&lt;sub&gt;4&lt;/sub&gt;/S&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4 (0.36)</td>
<td>26 (1.75)</td>
<td>21.96 (6.82–70.73)</td>
<td>3.87 × 10⁻⁷</td>
</tr>
<tr>
<td>S&lt;sub&gt;4&lt;/sub&gt;/S&lt;sub&gt;3&lt;/sub&gt;*</td>
<td>36 (3.22)</td>
<td>149 (10.05)</td>
<td>11.91 (7.59–18.68)</td>
<td>1.20 × 10⁻¹⁰</td>
</tr>
<tr>
<td>S&lt;sub&gt;4&lt;/sub&gt;/S&lt;sub&gt;1&lt;/sub&gt;*</td>
<td>3* (3.13)</td>
<td>190 (12.82)</td>
<td>11.90 (7.69–18.43)</td>
<td>1.20 × 10⁻¹⁰</td>
</tr>
<tr>
<td>S&lt;sub&gt;3&lt;/sub&gt;/S&lt;sub&gt;4&lt;/sub&gt;</td>
<td>11 (0.98)</td>
<td>31 (2.09)</td>
<td>6.46 (2.91–14.35)</td>
<td>4.44 × 10⁻⁴</td>
</tr>
<tr>
<td>S&lt;sub&gt;1&lt;/sub&gt;/L</td>
<td>311 (27.7%)</td>
<td>602 (40.62)</td>
<td>4.41 (3.47–5.60)</td>
<td>6.00 × 10⁻⁴</td>
</tr>
<tr>
<td>S&lt;sub&gt;3&lt;/sub&gt;/L</td>
<td>11 (0.98)</td>
<td>20 (1.35)</td>
<td>2.61 (1.09–6.24)</td>
<td>0.03</td>
</tr>
<tr>
<td>L/L</td>
<td>148 (13.23)</td>
<td>203 (13.70)</td>
<td>2.59 (1.91–3.51)</td>
<td>9.82 × 10⁻¹₀</td>
</tr>
</tbody>
</table>

Logistic regression analysis adjusted for age and sex. All odds ratios (OR) 95% confidence intervals (95% CI), and P values were calculated by comparing each group with the reference group. DRB1 alleles were divided into three susceptible genotypes (S<sub>4</sub>/S<sub>4</sub>, S<sub>4</sub>/S<sub>3</sub>* or S<sub>4</sub>/S<sub>1</sub>*). S<sub>2</sub>S<sub>2</sub> and S<sub>3</sub>S<sub>3</sub> genotypes were not observed in Korean populations.

Conclusions: All susceptible alleles, except *S0901, were classified as S<sub>2</sub> or S<sub>1</sub>, using the Tezenas du Montcel criteria. We propose that an appropriate HLA classification system including DRB1*0901 is required in populations with DRB1*0901 as an RA susceptibility allele. An appropriate HLA-DRB1 model should aid in clarifying the roles of these alleles in RA.

Disclosure: S.-Y. Bang: None; H.-S. Lee: None; J.-S. Lee: None; E.-M. Kim: None; K. W. Lee: None; S.-C. Bae: None.

1606

Pre Analytical Effects of Serum Collection and Handling in Quantitative Immunassays for Rheumatoid Arthritis. Ferhan Qureshi<sup>1</sup>, William Manning<sup>1</sup>, Scott Eastman<sup>1</sup>, Wayne Hu<sup>2</sup>, Michael Centola<sup>3</sup>, Mary Turner<sup>4</sup>, Craig W. Carson<sup>5</sup>, Ana A. Kumar<sup>4</sup>, Linda A. Zacharias<sup>2</sup>, Claire Alexander<sup>3</sup>, Doug Haney<sup>3</sup>, Guy Cavet<sup>5</sup> and Lyndal K. Hestergberg<sup>5</sup>. Crescendo Bioscience, Inc., 3, 5, 9, OMRF, 3, 5, 9; OK Arthritis Center, Edmond, OK, 5, Oklahoma Medical Research Foundation, Oklahoma City, OK, 5, Oklahoma Medical Research Foundation.

Background: Pre-analytical variables related to serum processing and handling can have significant influences on the results obtained in quantitative protein immunassays. Understanding the impact of these variables is critical for assay development, validation, and commercial testing. The effect of 2 routine serum collection methods (on the clot with ambient temperature shipping vs. centrifuged with cold chain shipping) and 2 serum handling methods (shipping vs. centrifuged with cold chain shipping) and 2 serum handling methods (shipping vs. centrifuged with cold chain shipping) were evaluated on biomarker levels. Additional proteins being evaluated as predictors of structural damage progression were assayed using Meso Scale Discovery immunoassays.

Method: To evaluate serum collection variables, multiple matched sets of sera were held at multiple temperatures (0°C, 4°C, 20°C, 80°C) and the effect of 2 handling methods (shipping vs. centrifuged with cold chain shipping) on biomarker levels was minimal. Additional studies, to characterize combinations of multiple pre-analytical variables are currently being designed.

Conclusion: Serum collection, processing and handling methods have a significant impact on the measurable serum protein levels. These results illustrate the importance of characterizing pre-analytical variability to ensure test accuracy and for using robust serum processing and handling procedures for development, validation, and clinical testing with biomarker assays including the DA Score.


1607

Serum TNFα and IL-6 Concentrations in Systemic Lupus Erythematosus, Rheumatoid Arthritis and Controls Associated with Polymorphisms in TPtp2, IRF5, INFg and NOD2. Joseph F. Solus<sup>1</sup>, Young Hee Rho<sup>2</sup>, Annette M. Oeser<sup>3</sup>, Cecilia P. Chung<sup>2</sup>, Chun Li<sup>2</sup>, Jeffrey R. Smith<sup>3</sup> and C. Michael Stein<sup>1</sup>. Vanderbilt University Medical Center, Nashville, TN, 2Vanderbilt University Medical Center, Baltimore, MD, 3Vanderbilt University Medical Center, 4VUMC 23rd Ave South Pierce, Nashville, TN.

Purpose: Elevated serum concentrations of inflammatory mediators are characteristic of autoimmune inflammatory disease. Genetic variation contributes to the regulation of inflammation. We examined the hypothesis that indicators of inflammation in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are associated with a subset of genetic polymorphisms previously implicated in the etiology and pathology of autoimmune disease.

Method: Serum TNFα and IL-6 concentrations were measured by multiplex ELISA (Millipore Corp.) in patients with SLE (n=148) or RA (n=166) and in control subjects without inflammatory rheumatic disease (n=177). Candidate genes were chosen from publications reporting association with autoimmune or inflammatory disease. Genotypes for 345 SNP markers from 75 genes were determined using Golden Gate assay (Illumina Inc.). Association was calculated by linear regression of log<sub>10</sub>-transformed data using an additive genetic model.

Results: TNFα concentrations were higher in patients with SLE (median 4.8, IQR [3.1–7.9] pg/ml) and RA (5.5 [2.8–11.0] pg/ml) than controls (2.8 [2.1–3.9] pg/ml). IL-6 concentrations were higher in patients with SLE (5.7 [2.3–22.4] pg/ml) and RA (13.8 [4.4–43.0] pg/ml) than controls (2.9 [1.0–11.5] pg/ml) and were higher in RA than SLE (p<0.001). Several genetic variants were associated with markers of inflammation. TNFα was associated with IRF5(rs10488631) in SLE (p=0.01) and controls (p=0.001) but not in RA, and with IFNG(rs2069727) in SLE (p=0.007) but not in RA and controls. TNFα was associated with TPTP2(rs2542151), DRB1(rs3021304) and NOD2(rs5743291) in RA (p=0.001, 0.001, 0.009), and in controls with NOD2 (p=0.01), but not in SLE. The top rank order for associations with IL-6 were TF2(rs280523) and IL10(rs1800890) in SLE (p=0.005 for each, DBR1(rs3021304) and NOD2(rs7488855) in RA (p=0.0005, 0.001), and MMP7(rs312258347, rs17098318) in controls (p=0.002, 0.009). Several other associations for IL-6 were of nominal significance (p<0.01). The analysis of all samples as a single group revealed TP2P2 as the top rank order association for both TNFα and IL-6 (p<0.0001, p=0.0006). A possible interaction between TP2P2 and disease status was observed for TNFα (p=0.03) but not for IL-6 (p=0.9).

Conclusion: An IRF5 polymorphism previously associated with susceptibility to lupus and other autoimmune disease was associated with serum TNFα concentrations in SLE patients and controls but not in RA, suggesting that the mechanism of regulation of TNFα through interferon regulatory factor 5 is retained in SLE but is disrupted or obscured by other factors in RA. An analogous situation may exist for regulation of TNFα and IL-6 in patients with RA or SLE and healthy controls through TP2P2, NOD2, and IFNG.

Disclosure: J. F. Solus: None; Y. H. Rho: None; A. M. Oeser: None; C. P. Chung: None; C. Li: None; J. R. Smith: None; C. M. Stein: None.
1608

SLE-Associated Genetic Variants Influence Gene Expression in Patients.
Hatrice Bilgic1, Thearth Koeuth2, Joseph C. Wilson2, Ward Ortmann2, Michelle Petri3, Peter Gregersen1, Timothy Behrens1 and Emily C. Baechele2.
1Genentech, Inc., 2Johns Hopkins School of Medicine, 3The Feinstein Institute for Medical Research, 4University of Minnesota, 5University of Minnesota.

Background: SLE is a complex disorder which is likely to be affected by multiple biological pathways. Mapping the genetic influences of individual genes and or/paths that contribute to disease may reduce complexity and increase the power to identify genetic risk factors that cause SLE. Recent genome-wide genetic association studies in SLE have identified numerous single nucleotide polymorphisms (SNPs) conferring risk to lupus. We hypothesized that some of these genetic variants will correlate with gene expression phenotypes in SLE. Uncovering these SNP/transcript associations may permit a better understanding of the genetic underpinnings of human SLE, and the identification of novel targets for therapy.

Methods: We studied 309 Caucasian SLE patients enrolled from the Hopkins Lupus Cohort via the Autoimmune Biomarkers Collaborative Network. Gene expression levels were quantified in peripheral blood cells of SLE patients with the Illumina WG-6 BeadChip expression arrays. Any gene that had a detection p-value >0.1 (not expressed) for >95% of samples was removed from analysis. For the remaining genes, the expression values in individual samples that had detection p>0.1 had been replaced with the minimum detectable (p<0.1) expression value for that gene. This resulted in 24,849 probes for further analyses. Type I interferon (IFN) gene signature scores were calculated from the expression of 70 IFN-inducible genes. DNA samples from the same subjects were genotyped on Illumina HumanHap 550K Genotyping BeadChip and subjected to standard data quality filters. We selected 34 SNPs previously shown to be associated with SLE and interrogated the correlation of genotype with gene expression using Pearson correlation and one-way ANOVA.

Results: In this discovery cohort, we identified putative cis-associations between blood cell gene expression levels and SNPs in or near 3 genes (BLK, KLK1, and UBEL2L3) for which there is a prior evidence of genetic association with disease. Two SNPs upstream of BLK (rs2736340, rs13277113) were significantly correlated with BLK transcript levels (r=-0.21, p=0.0002; ANOVA p<0.001). SNP rs266858 is in the kallikrein gene cluster on chromosome 19, near the SLE-associated KLK1 gene. This SNP was significantly correlated with KLK1 transcript levels (r=-0.16, p=0.006; ANOVA p<0.001). A SNP within the gene that encodes the ubiquitin-conjugating enzyme UBEL2L3 (rs5754217) was significantly correlated with UBEL2L3 gene expression (r=0.39, p<0.0001; ANOVA p<0.001). We also identified significant correlations between the type I IFN gene score and SLE-associated SNPs in/near 3 genes (BLK, KLK1, and UBE2L3) for which there is a priori evidence of genetic association between blood cell gene expression levels and SNPs in or near 3 genes (BLK, KLK1, and UBEL2L3) for which there is a prior evidence of genetic association with disease. Two SNPs upstream of BLK (rs2736340, rs13277113) were significantly correlated with BLK transcript levels (r=-0.21, p=0.0002; ANOVA p<0.001). SNP rs266858 is in the kallikrein gene cluster on chromosome 19, near the SLE-associated KLK1 gene. This SNP was significantly correlated with KLK1 transcript levels (r=-0.16, p=0.006; ANOVA p<0.001). A SNP within the gene that encodes the ubiquitin-conjugating enzyme UBEL2L3 (rs5754217) was significantly correlated with UBEL2L3 gene expression (r=0.39, p<0.0001; ANOVA p<0.001). We also identified significant correlations between the type I IFN gene score and SLE-associated SNPs in/near 3 genes (BLK, KLK1, and UBE2L3) for which there is a prior evidence of genetic association with disease.

Conclusions: Our initial findings suggest that several cis interactions between SLE-associated alleles and transcript levels, and that SLE SNPs may influence the type I IFN signature. A complete validation analysis is required to identify the most promising genetic effects for further studies.

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1609

Stratification of Rheumatoid Arthritis Patients into Disease Subtypes with Clinical Implications. Glynn Dennis, Cecile Holweg, Jason Hackney, Houston Gilber, Wei Yu Lin, Lauri Diehl, Judith Endres, David Fox, Mike Townsend and Flavious Martin. Genentech.

Purpose: The study aimed to identify molecular subtypes of rheumatoid arthritis (RA) that differ in their biological composition and response to therapy.

Methods: Genome-wide transcriptional profiles for 81 synovial tissue samples obtained by surgery from 50 active RA patients fulfilling the 1987 ACR criteria were stratified by bootstrapped hierarchical clustering. Statistically supported sample subtypes were further characterized by significance analysis of microarrays and pathway analysis. Platform independent validation of subtypes was performed by immunohistochemistry, fluorescence-based cell sorting and semi-quantitative polymerase chain reaction. Subtype-intrinsic gene signatures were tested for their ability to classify external data using linear discriminant analysis. Protein biomarker assays measured the association between serum proteins and response to rituximab.

Results: Multi-scale bootstrapped hierarchical clustering of 81 samples inferred four molecular subtypes of RA. Each subtype represented a discrete transcriptional program that reflected differences in tissue cellularity and biological composition. Differentially infiltrated tissues were assigned to one of two subtypes characterized by fibroblast-like transcriptional programs that differed slightly, but significantly, in their pathway composition. Tissues with substantial immune infiltration were assigned to one of two immunoregulatory subtypes distinguishable by either a potent B cell signature or a broad inflammatory signature reflecting various myeloid and T cell transcriptional programs. Predictive gene signatures for each subtype accurately classified institutionally independent microarray profiles of histologically similar samples. Protein-based assays of B cell signature genes in a large placebo-controlled study of rituximab in RA revealed a combinatorial relationship between low levels of certain B cell biomarkers in serum and a poor clinical response to B cell depleting therapy.

Conclusions: We reduced RA tissue heterogeneity down to 4 discrete molecular subtypes and provided subtype-intrinsic gene signatures that were able to accurately classify independently derived external data. The unique cellular and biological composition of each subtype suggests that molecular stratification of RA patients has the potential to improve clinical trial design and therapeutic intervention by identifying those patients that are most likely to benefit from a given therapy.

Disclosure: G. Dennis: Genentech and Biogen IDEC Inc, 3; C. Holweg: Genentech and Biogen IDEC Inc, 3; J. Hackney: Genentech and Biogen IDEC Inc, 3; H. Gilber: Genentech and Biogen IDEC Inc, 3; W. Y. Lin: Genentech and Biogen IDEC Inc, 3; L. Diehl: Genentech and Biogen IDEC Inc, 3; J. Endres: None; D. Fox: None; M. Townsend: Genentech and Biogen IDEC Inc, 3; F. Martin: Genentech and Biogen IDEC Inc, 3.

1610

The Associations between RA Genetic Risk Alleles and Seropositive but Non-Erosive Rheumatoid Arthritis. Katherine P. Lia, Jing Cui, Michael E. Weinblatt, Christine Iannaccone, Nancy Shadick, Robert M. Plenge, Daniel H. Solomon and Elizabeth W. Karlson. Brigham and Women’s Hospital, Boston, MA.

Background: Presently, little is known about the subgroup of subjects with seropositive rheumatoid arthritis (RA) who never develop bone erosions in contrast to those with erosions that remain stable or progress despite treatment. Our objective was to determine whether specific RA genetic risk alleles were associated with remaining erosion-free in a longitudinal RA cohort.

Methods: Our study was conducted in a prospective observational cohort of >1100 RA patients recruited from the outpatient practice of an academic medical center. We included patients with bilateral hand radiographs obtained at baseline and at 2 yr follow-up with formally assessed Sharp scores. The primary outcome was erosion-free status at recruitment and at 2 yr follow-up. We generated 31 validated B risk alleles in a seropositive (RF+ or anti-CCP+) subset of this cohort.

To assess whether individual risk alleles for seropositive RA were also associated with erosion-free status, we tested each polymorphism using a logistic regression adjusted for clinical predictors of erosion-free status. The significant clinical predictors were determined in a previous study. The younger age at RA onset, male gender, and shorter RA duration. We quantified the association between risk alleles and erosion-free status using odds ratios (OR), 95% confidence intervals (CI) and p-values from the logistic regression models.

Summary: Three hundred-three RA subjects in the cohort had Sharp scores and genotype information; 18% were erosion-free at recruitment and 2 year follow-up; 75% female, mean age at RA onset of 44.3 years (SD 10.1) and mean RA duration of 8 years (SD 8); 94.6% were anti-CCP+, 83.6% were RF+, and 76.6% had ≥ 1 copy of the HLA-shared epitope (HLA-SE). In the erosive group, 84% were female, with mean age at RA onset of 41.8 years (SD 14) and mean RA duration of 18 years (SD 12.3). There was no significant difference between anti-CCP status, methotrexate and anti-TNF use at baseline between the erosion-free group and those with erosions.

Two alleles were independently associated with erosion-free status after adjusting for clinical factors (age at RA onset, gender, RA duration): REL (rs13001237, T allele) with erosion-free status and KIF5A (rs775322, T allele) with not remaining erosion-free (Table 1). Neither allele reached statistical significance after Bonferroni correction. The HLA-SE was not associated with erosion-free status in this seropositive cohort.
TNIP2 is Associated with Joint Destruction in Patients with Rheumatoid Arthritis. Taku Suzuki2, Katsunori Ikari2, Koichiro Yano2, Yoshiaki Toyama1, Atsuo Taniguchi2, Hisashi Yamanaka3 and Shigeki Momohara4.1Department of Orthopaedic Surgery, Keio University, 2Institute of Rheumatology, Tokyo Woman’s Medical University, Japan

Background: Recently a large-scaled meta-analysis of genome-wide association studies (GWAS) and replication studies identified novel rheumatoid arthritis (RA) risk loci in European descent populations; CD2/CD58 association studies (GWAS) and replication studies identified novel rheumatology, Tokyo Woman’s Medical University, Japan

Materials and Methods: DNA samples from 1504 Japanese patients were collected from the IORRA (Institute of Rheumatology RA cohort) DNA collection (84% of the patients were female, 87% were anticyclic citrullinated peptides (ACPA) antibody positive, 88% were rheumatoid factor positive and the mean age of the patients was 59.3 years). Of the patients, Sharp/ van der Heijde score (SHS) of the hands at 5-year disease duration, which represents joint destruction, could be measured in 628 patients.

Tested SNPs on the genes were selected based on the published studies (1–3). Genotyping was performed using the TaqMan assay according to the manufacturer’s instructions (Applied Biosystems, Japan). Multiple regression analysis was performed with SHS (hands) as a dependent variable, and as independent variables, the number of HLA-DRB1 alleles encoding the shared epitope (SE), the number of the risk alleles of RA-susceptible genes, sex, ACPA, and age of onset. The analysis was performed using the R software package.

Results: Sex (female, $P = 1.3 \times 10^{-4}$), age of onset (younger, $P = 1.3 \times 10^{-4}$), the number of SE ($P = 0.034$), the risk allele of TNIP2 ($P = 0.0092$) had impact on radiographic joint damage in Japanese RA patients while the other RA-susceptible genes did not show any association with the joint destruction.

Conclusions: We identified TNIP2 as a genetic factor for the joint destruction in RA patients.

References:
2. REL, encoding a member of the NF-kappaB family of transcription factors, is a newly defined risk locus for rheumatoid arthritis. Nat Genet. (4):820–3.

Disclosure: K. P. Liao: None; J. Cui: None; M. E. Weinblatt: Biogen Idec, 2, 5, Crescendo Bioscience, 2, 5; C. Iannaccone: None; N. Shadick: Amgen Inc., 9, Biogen Idec, 2, Crescendo, 2; R. M. Plenge: None; D. H. Solomon: Abbott Immunology Pharmaceuticals, 2, Amgen Inc., 2, Bristol-Myers Squibb, 9; E. W. Karshon: None.

1611

Introduction: Systemic lupus erythematosus (SLE) is a highly heterogeneous disorder. SLE-associated autoantibodies and high serum interferon alpha (IFN-α) are important heritable phenotypes in SLE which are correlated with each other, and play a role in disease pathogenesis. We set out to detect genetic factors associated with autoantibody profiles and serum IFN-α in SLE.

Methods: SLE patients were stratified by extremes of phenotype in serology and serum IFN-α for a case-case-gene-wide association study. Single nucleotide polymorphisms (SNPs) in seven loci were selected for follow up in a large independent cohort of 450 SLE patients and 522 controls using a multi-step screening approach based on novel metrics and expert database review. The seven loci were: LRR2C, PPM1H, LPRAK1, AINSK1A, PTPRM, EFNA5, and VSIG2.

Results: SNPs in the LRR2C0, PPM1H, LPRAK1, AINSK1A, and VSIG2 loci each demonstrated strong association with a particular serologic profile (all OR ≥2.2 and p < 8 × 10^{-4}). Each of these serologic profiles was associated with increased serum IFN-α. SNPs in PTPRM and LRR2C were associated with increased serum IFN-α independent of serologic profile (p = 3.2 × 10^{-4} and p = 5.0 × 10^{-3} respectively). None of the SNPs were strongly associated with SLE in case-control analysis, suggesting that the major impact of these variants will be upon subphenotypes in SLE.

Conclusions: This study demonstrates the power of using serologic and cytokine subphenotypes to elucidate genetic factors involved in complex autoimmune disease. The distinct associations observed emphasize the heterogeneity of molecular pathogenesis in SLE, and the need for stratification by subphenotypes in genetic studies.

Disclosure: S. N. Karuki: None; B. S. Franek: None; A. A. Kumar: None; J. Arrington: None; A. A. Mikolaitis: None; T. O. Utset: Genentech and Biogen IDEC, 5; M. Jolly: None; M. K. Crow: None; A. D. Skol: None; T. B. Niewold: ALR, 2; ANRP, 2, Chicago/France Center, 2, LRI, 2, NIH, 2.

ACR Poster Session C

Imaging of Rheumatic Disease II: Ultrasound, PET, Capillary Microscopy and Molecular Imaging

Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1612

Trait-Stratified Genome-Wide Association Study Identifies Novel and Diverse Genetic Associations with Serologic and Cytokine Phenotypes in Systemic Lupus Erythematosus. Silvia N. Kariuki4, Beverly S. Franke2, Akash A. Kumar5, Jasmine Arrington4, Racheal A. Mikolaitis6, Tammy O. Utset6, Meenakshi Yano7, Mary K. Crow8, Andrew D. Skol8 and Timothy B. Niewold8.1Hospital for Special Surgery, Mary Kirkland Center for Lupus Research, New York, NY, 2Rush University, Section of Rheumatology, Chicago, IL, 3University of Chicago Prizker School of Medicine, Section of Genetic Medicine, Chicago, IL, 4University of Chicago Prizker School of Medicine, Section of Rheumatology and Gwen Knapp Center for Lupus and Immunology Research, Chicago, IL

Introduction: Systemic lupus erythematosus (SLE) is a highly heterogeneous disorder. SLE-associated autoantibodies and high serum interferon alpha (IFN-α) are important heritable phenotypes in SLE which are correlated with each other, and play a role in disease pathogenesis. We set out to detect genetic factors associated with autoantibody profiles and serum IFN-α in SLE.

Methods: SLE patients were stratified by extremes of phenotype in serology and serum IFN-α for a case-case-gene-wide association study. Single nucleotide polymorphisms (SNPs) in seven loci were selected for follow up in a large independent cohort of 450 SLE patients and 522 controls using a multi-step screening approach based on novel metrics and expert database review. The seven loci were: LRR2C, PPM1H, LPRAK1, AINSK1A, PTPRM, EFNA5, and VSIG2.

Results: SNPs in the LRR2C0, PPM1H, LPRAK1, AINSK1A, and VSIG2 loci each demonstrated strong association with a particular serologic profile (all OR ≥2.2 and p < 8 × 10^{-4}). Each of these serologic profiles was associated with increased serum IFN-α. SNPs in PTPRM and LRR2C were associated with increased serum IFN-α independent of serologic profile (p = 3.2 × 10^{-4} and p = 5.0 × 10^{-3} respectively). None of the SNPs were strongly associated with SLE in case-control analysis, suggesting that the major impact of these variants will be upon subphenotypes in SLE.

Conclusions: This study demonstrates the power of using serologic and cytokine subphenotypes to elucidate genetic factors involved in complex autoimmune disease. The distinct associations observed emphasize the heterogeneity of molecular pathogenesis in SLE, and the need for stratification by subphenotypes in genetic studies.

Disclosure: S. N. Karuki: None; B. S. Franek: None; A. A. Kumar: None; J. Arrington: None; A. A. Mikolaitis: None; T. O. Utset: Genentech and Biogen IDEC, 5; M. Jolly: None; M. K. Crow: None; A. D. Skol: None; T. B. Niewold: ALR, 2; ANRP, 2, Chicago/France Center, 2, LRI, 2, NIH, 2.

ACR Poster Session C

Imaging of Rheumatic Disease II: Ultrasound, PET, Capillary Microscopy and Molecular Imaging

Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1613

[18F]PEG-Folate: A New Potential Macrophage PET Tracer for Imaging of Arthritis. Conny J. van der Laken1, Inge de Greeuw2, Yoono Y. J. Gent3, Karin Weijers3, Alexandre E. Voskuyl4, Gerrit Jensen5, Ben A. C. Dijkmans6, Aadriaan A. Lammersma7, Phil S. Low7, Sumith Kularatne8, Albert D. Windhorst8 and Carla F. M. Molthoff8.1Dept. of Chemistry, Purdue University, 2Dept. of Nuclear Medicine & PET Research, VU Medical Center, Amsterdam, The Netherlands, 3Dept. of Rheumatology, Amsterdam, 4Dept. of Rheumatology, VU Medical Center, Amsterdam, The Netherlands, 2Dept. of Rheumatology, VU Medical Center

Background: Previous studies in rheumatoid arthritis (RA) patients have shown clear visualization of arthritis with Positron Emission Tomography (PET) and (18)F-fluorodeoxyglucose ([18F] FDG). We found more specific imaging of arthritis with macrophage targeting, using the PET tracer, [11C]PK111951. Due to the relatively high level of non-specific binding of [11C]PK11195 in surrounding tissues, we developed another macrophage PET tracer, [18F]PEG-folate, with potential superior imaging characteristics.

Our previous work has shown that the folate receptor (FR-β) on activated macrophages may be an attractive target for imaging of arthritis2.
Objective: Pilot study to investigate the potential of \[^{18}F\]PEG-folate PET to image arthritis in a rat model.

Methods: FR binding affinity for F-PEG-folate relative to folic acid and the circulating plasma folate [6S]-5-methyltetrahydrofolate was assessed by FACScan analysis and binding competition with Folate-FITC. Five Wistar rats were immunized with methylated bovine serum albumin (mBSA) and adjuvants. At day 21, arthritis was induced with an intra-articular injection (ia) of mBSA in the right knee. At day 30, 4 rats were injected with 20 MBq \[^{18}F\]PEG-folate and 1 rat with 10 MBq \[^{18}F\]FDG, followed by PET imaging during 2 hrs. Following imaging, rats were sacrificed to obtain ex vivo tissue biodistribution and (immuno)histopathological analysis.

Results: FR binding affinity for F-PEG folate was just 1.2-fold lower than for folic acid, but 5-fold higher than for [6S]-5-methyltetrahydrofolate. In all rats with induced arthritis, histopathology showed a macrophage-rich inflammation in the synovial tissue of the affected joint, resembling synovitis in RA patients. \[^{18}F\]PEG-folate cleared rapidly from the circulation, with levels decreasing from 2.1%ID/g at 1 min post-injection (p.i.) to 0.01 %ID/g at 1 hr p.i., 30 times lower than blood levels of \[^{18}F\]FDG at 1 hr p.i. On \[^{18}F\]PEG-folate PET images, the arthritic joints were clearly depicted. Inflamed-to-control knee ratios of \[^{18}F\]PEG-folate increased continuously up to 2.3 at 1 hr p.i. and 2.6 at 2 hr p.i. In contrast, ratios of \[^{18}F\]FDG declined over time to 1.3 at 1 hr. Ex vivo tissue biodistribution data also revealed uptake of \[^{18}F\]PEG-folate in spleen, skin, fat and lymph nodes, suggesting binding to locally present (activated) macrophages in these tissues. This finding was confirmed by in vivo blockade of folate receptors by injection of i.v. glucosamine-folate prior to injection of \[^{18}F\]PEG-folate which significantly reduced uptake of \[^{18}F\]PEG-folate in these tissues.

Conclusion: These first pilot data show that \[^{18}F\]PEG-folate may be a promising PET tracer for imaging arthritis by targeting of macrophages in synovial tissue. Further explorative rat studies, including comparison with \[^{11}C\]PK11195, are in progress and will be followed by investigation in humans.

References:

Disclosure: C. J. van der Laken: None; I. de Greeuw: None; Y. Y. J. Gent: None; K. Weijers: None; A. E. Voskuyl: None; G. Jansen: None; B. A. C. Dijkmans: None; N. A. A. Lammertmans: None; P. S. Low: Endocyte, S. S. Kularatne: None; A. D. Windhorst: None; C. F. M. Molthoff: None.

1614

Asymptomatic Hyperuricemia: Ultrasonographic Findings.
Carla Solano1, Pedro José Rodríguez-Hernández2, Fritz Hofmann1, Araceli Bernal1, Norma Marín-Ariagga3, Alberto Gabriel López-Reyes3, Luis Guirado1, Angelica Vargas-Guerrero1, Luis Amezquita-Guerra1, Marwin Gutierrez2, Cristina Hernández-Díaz2, Manuel Martínez-Lavin2 and Carlos Pineda2. 1Instituto de Neurología, 2Hospital General de México, 3Instituto Nacional de Rehabilitación, Mexico City, Mexico, 4Universidad Politécnica delle Marche Ospedale “A Murti”, Italy

Background: Musculoskeletal ultrasound (US) is a low-cost, widely accessible, non-invasive technique, which allows a multilayer, real-time evaluation of joints without the use of ionizing radiation. Its use has recently been expanded to the evaluation of inflammatory arthritides, including gout. Ultrasonographic characteristics of gout are already well described; however, the findings in asymptomatic patients have not been thoroughly described. US have shown to be superior in detecting changes in articular symptoms (control group) were recruited after informed consent. The findings in asymptomatic patients have not been defined; however, the findings in asymptomatic patients have not been thoroughly described. US scans of the femoral cartilage and tendons in the knee, tendons at the ankle, Achilles tendon and first metatarsophalangeal (1st MTP) joint were obtained. OMERACT definitions for US pathology were applied; tendinopathy: defined as a loss of the fibrilar pattern, intratendinous tophi and/or calcifications.

Results: Demographic: 97 subjects were enrolled; 45 hyperuricemic and 52 normouricemic control subjects with a median age of 56 and 47.3 years. The average uric acid level in the hyperuricemic group was 8.17mg/dL (±0.95), see Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hyperuricemia (n=45)</th>
<th>Normouricemia (n=52)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56 ± 17.2</td>
<td>47.3 ± 10.9</td>
<td>0.003*</td>
</tr>
<tr>
<td>Male</td>
<td>30</td>
<td>35</td>
<td>0.9**</td>
</tr>
<tr>
<td>Uric Acid, mg/dL</td>
<td>8.17 ± 0.95</td>
<td>5.47 ± 0.90</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

* Unpaired t test
** Chi-square test

In the hyperuricemic group tendinopathy was found in the posterior tibial tendon p < 0.05, as well as the presence of double contour sign in the 1st MTP joint p <0.0001.

Conclusion: Asymptomatic hyperuricemic patients show US morphostructural changes similar to those with established gout. Results confirm the notion that urate crystals are present in articular tissues before gout is clinically evident and may give further support for the use of urate-lowering therapy in asymptomatic hyperuricemic patients.

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1615

Capillary Microscopy—A Cross-Sectional Study in the Population. Oliver Sander1, Moritz Schroeder1, Benedikt Ostendorf1, Jutta Richter1, Matthias Reppel1, Hasan Acar2, Martina Blumenroth3 and Matthias K. Schneider1. 1Dept. Rheumatology, Heinrich-Heine University, Duesseldorf, Germany, 2Dept. Rheumatology, Heinrich-Heine University, 3Heinrich-Heine University Duesseldorf, 4Rheumazentrum Rhein-Ruhr

Objective: Application of capillary microscopy in the general population.

Method: Our mobile campaign for rheumatic diseases (Rheuma-Truck) visited 26 sites in the metropolitan region Rhine-Ruhr. The visitors could participate in different tests (including capillary microscopy of fingers III-V of both hands with standardized image documentation). Demographic data, self reported symptoms based on the connective tissue screening questionnaire (CSQ), and an ad hoc diagnosis by a rheumatologist were documented. 110 outpatient visitors of the rheumatologic department were documented the same way and served as controls. The capillary images were assessed by an experienced examiner semi quantitatively regarding density, edema, bleeding, hairpin shape, caliber equalization, enlargement, giant capillaries, ramification, bushy capillaries, elongation, torsion, flow properties and filling. The results were combined with the other collected data and analyzed statistically.

Results: 3196 visitors were counted. 754 visitors underwent capillary microscopy to availability of the device (mean age 54 years, 75% female, 10,000 images evaluable). Capillary microscopy and evaluation took 1 to 2 minutes each. The costs were restricted to the purchase of the device. 8% of the sample were not assessable. 68% of the capillaries showed the normal hairpin form, torsion (17%), ramification (3%), elongation (2%), enlargement (1%) was seen in the others. Hemorrhage was seen in 5% of subjects; 4 giant capillaries were detected. Hairpin shape was seen in only 52% of the rheumatologic outpatients and 31% of patients with known systemic sclerosis. Those had higher counts of divergences, esp. giant capillaries.
There are no gender differences in the capillary morphology. The number of normal capillaries decreases slightly with age (71% in the under-30s to 65% among 70–80 year olds). A previous described association of tortuous capillaries and psoriasis (in the personal and family medical history) could not be confirmed. A new diagnosis of systemic sclerosis was not identified. In fibromyalgia, the rate of normal hairpin shape capillaries was with a rate of 79% significant higher than the average for the visitors. Raynaud’s phenomenon was associated with altered blood flow and capillary filling, but no detectable differences in the morphology.

**Conclusion:** The expected high rate of inconspicuous findings in the visitors was confirmed, contrasting the observations in patients with rheumatic diseases. Raynaud’s phenomenon was detectable by altered fillings and blood flow. The capillary microscopy is suitable for the application in larger populations.

**Disclosures:** O. Sander: Actelion Pharmaceuticals Germany, 2; M. Schroeder: None; B. Ostendorf: None; J. Richter: None; M. Reppel: None; H. Acar: None; M. Blumenroth: None; M. K. Schneider: None.

**1616**

Concordance between Ultrasound Readers Determining Presence of Monosodium Urate Crystal Deposition in Knee and Toe Joints. Rennie N. G. Howard2, Michael H. Pillinger3, Soterios Gyftopoulos1, Ralf G. Thiele4, Christopher Swearingen1 and Jonathan Samuels1. 1New York University Hospital for Joint Disease, New York, NY, 2NYU Langone Medical Center, NYU Hospital for Joint Diseases, New York, NY, 3University of Arkansas for Medical Sciences, Little Rock, AR, 4University of Rochester, Rochester, NY

**Background:** Determination of monosodium urate (MSU) deposition in joints by musculoskeletal ultrasound (MSK-US) could have implications for uric acid (UA) management in patients with gout and possibly asymptomatic hyperuricemia (AH). Recently, criteria for sonographic diagnosis of MSU crystal deposition have been developed, but reproducibility of readings using these criteria has not been well established.

**Methods:** We consecutively recruited male patients ages 55–85 during primary care visits to an urban VA hospital. We assessed all patients for gout by ACR criteria, and obtained serum UA levels. Patients were divided into 3 groups: gout, AH (no gout, UA ≥ 6.9 mg/dL), and controls (no gout, UA ≤ 6.8 mg/dL). 50 patients (14 with gout, 17 with AH, and 19 controls) returned for subsequent evaluation which included MSK-US of knees and 1st metatarsalphalangeal (MTP) joints to evaluate for the double contour sign (knees) and tophi (MTPs). All images were read blindly by two observers trained in rheumatology and MSK-US. Kappa statistics were used to estimate the amount of agreement between ultrasound measures scored by the two raters. We also calculated the total percent of observations in agreement.

**Results:** Evidence of MSU crystal deposition was found in the same 10 patients by both observers (6 gout, 3 AH, 1 control), and in 3 additional patients by one of the observers (1 gout, 2 AH). These findings were further analyzed by site. MSU crystal deposition was identified in a total of 14 common joints by both observers, and in 4 additional joints by the first observer and 6 additional joints by the second observer. Percentage agreement and kappa statistics for our three primary ultrasound measures were as follows; total joints (n=200, 95% agreement, kappa 0.709), femoral articular cartilage (n=100, 95% agreement, kappa 0.679) and 1st MTPs (n=100, 95% agreement, kappa 0.734). Additional analyses by left and right side are shown in the table below. Ratings on only 10 out of 200 joints were in disagreement.

<table>
<thead>
<tr>
<th>Site</th>
<th># of Joints Assessed</th>
<th>Rater 1</th>
<th>Rater 2</th>
<th>% Agreement</th>
<th>Kappa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral Articular Cartilage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Right</td>
<td>100</td>
<td>8</td>
<td>9</td>
<td>95</td>
<td>0.679 (0.415, 0.943)</td>
</tr>
<tr>
<td>-Left</td>
<td>100</td>
<td>5</td>
<td>6</td>
<td>96</td>
<td>0.632 (0.649, 1.000)</td>
</tr>
<tr>
<td>First MTP</td>
<td>100</td>
<td>10</td>
<td>11</td>
<td>95</td>
<td>0.734 (0.512, 0.956)</td>
</tr>
<tr>
<td>-Right</td>
<td>50</td>
<td>5</td>
<td>6</td>
<td>98</td>
<td>0.890 (0.701, 1.000)</td>
</tr>
<tr>
<td>-Left</td>
<td>50</td>
<td>5</td>
<td>5</td>
<td>92</td>
<td>0.556 (0.168, 0.944)</td>
</tr>
<tr>
<td>Total Joints</td>
<td>200</td>
<td>18</td>
<td>20</td>
<td>95</td>
<td>0.709 (0.539, 0.880)</td>
</tr>
</tbody>
</table>

**Conclusions:** Both percentage agreement and agreement beyond chance between the raters (as estimated by kappa statistics) were very high for the three ultrasound measures. These findings support the use of MSK-US as a reliable modality for detecting MSU deposition. Since MSU deposition is an indication for urate lowering, this type of imaging could be performed noninvasively at the bedside or in the clinic to help direct therapy in gout patients, with possible implications for treatment in AH patients as well should these findings be reproducible in larger cohorts.

**Disclosure:** R. N. G. Howard: None; M. H. Pillinger: None; S. Gyftopoulos: None; R. G. Thiele: None; C. Swearingen: None; J. Samuels: None.

**1617**

Demonstrating Musculoskeletal Ultrasound Competency in a Valid and Reliable Way. Eugene Y. Kissin1, Jingbo Niu1, Ralf G. Thiele1,2,3, Midori Jane Nishito1, Jay B. Higgs1,3, Janak R. Goyal1,2, Daniel G. Malone1,2, David A. Bong1,2, Amy M. Evangelisto1, Wolfgang A. Schmidt1, Peter Balint1, Carlos Pineda1, and Gurjit S. Kaeley1. 1Lafayette, CA, 2Bruce, WI, 3Arthritis Rheumatic & Back Disease Association, Philadelphia, PA, 4Boston University, Boston, MA, 5Boston University, Boston, MA, 6Instituto Nacional de Rehab, Mexico City, Mexico, 7Medical Center for Rheumatology Berlin-Buch, Berlin, Germany, 8National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, 9University of Florida College of Medicine, Ponte Vedra Beach, FL, 10University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Perth Amboy, NJ, 11University of Rochester, Rochester, NY, 12University of Wisconsin, Madison, WI, 13William Hall Medical Center/Booke Army Medical Center, San Antonio, TX

**Purpose:** The amount of training needed to become competent in musculoskeletal ultrasound (MSUS) is debatable, and a valid exam to determine competency in MSUS is needed. While others have previously established training and testing procedures, none has yet documented MSUS test reliability or validity. We aim to develop a reliable and valid MSUS test.

**Methods:** USA rheumatology fellows who had participated in an 8-month standardized MSUS curriculum completed an exam of MSUS consisting of multiple choice questions (MCQs), and practical scanning (PrE) of normal anatomy.

10 faculty members (> 4 years of practical and teaching experience in MSUS courses) individually submitted 250 MCQs covering 8 peripheral joint regions and typical rheumatic conditions. As a group, the faculty excluded 143 MCQs that were unclear or irrelevant to rheumatology. Remaining MCQs were tested in 2 groups: 3 rheumatologists without MSUS training, to exclude MCQs answered correctly by all 3, and 5 rheumatologists expert in MSUS to exclude MCQs answered incorrectly by 3 of 5, resulting in 76 MCQs on the exam.

To validate the MCQ exam, 3 additional groups completed it: rheumatologists who finished an intermediate course of training through the Mexican School of Musculoskeletal Ultrasound (Intermediate Group (IG), n=7), rheumatologists with > 2 years of experience in MSUS from both Mexico and the USA (Advanced Group (AG), n=7), and USA fellows (Fellow Group (FG), n=19).

All fellows and 2 MSUS faculty members took an 8-station PrE for scanning technique in all 8 joint areas. Faculty graded images from the PrE, blinded to source, on a 5 point scale based on predefined quality measures.

**Results:** The MCQ exam was reliable (Cronbach’s a = 0.76) and discriminated between IG and AG (median score 63% vs. 79%, p = 0.003 Wilcoxon). The FG median MCQ test score exceeded that of the IG (72% vs. 63%, p = 0.02 Wilcoxon), but had the greatest range - from worse than the IG to better than the AG (Figure 1). Fellows and faculty median PrE scores were
not significantly different (2.4 vs 2.8, p=0.18), but 2 fellows scored significantly lower than the faculty members. PrE and MCQ results correlated well (Spearman r=0.63, p=0.004).

Conclusions: A written and practical exam proved moderately reliable and valid in a comparison of practitioners of varying levels of training. The correlation between results of the two exam parts adds further validity. Most fellows who completed an 8 month MSUS training program achieved similar essential MSUS knowledge to the advanced MSUS group (MCQ), and similar basic scanning technique to their mentors (PrE), thus demonstrating basic competence. However, fellow test results varied significantly despite completion of a standardized teaching program. Given the variability in achieving MSUS competency after uniform training, requisite MSUS experience should be based on outcome testing rather than a fixed time period of education.

Disclosure: E. Y. Kissin: None; J. Niu: None; R. G. Thiele: None; M. J. Nishio: None; J. P. Higgs: None; J. R. Goyal: None; D. G. Malone: None; A. D. Bong: None; A. M. Evangelista: None; W. A. Schmidt: None; P. Balint: None; C. Pineda: None; G. S. Kaelley: None.

Background: MSKUS is a sensitive and specific imaging modality with growing utilization in rheumatology. However, the impact that MSKUS examination may have on therapeutic decision making in the management of inflammatory arthritis is unknown.

Methods: Rheumatologists were presented with online survey including 4 standard clinical vignettes (3 RA and 1 PsA), and were asked to make management decisions before and after data from joint ultrasound was reported. Physician demographics, use and familiarity with MSKUS were also surveyed.

Results: Of the 332 respondents (mean age 53.7 yrs), who answered the survey, 30% reported performing MSKUS, 25% send patients to imaging centers, 34% reported being familiar, but not performing MSKUS themselves, and 29% were not familiar with/never using MSKUS. Confidence that MSKUS can detect active synovitis using power Doppler (PD) or visualization of synovial tissue/ fluid was expressed by 59% and 78%, respectively, and for detection of enthesitis by 56% of respondents.

When presented with 4 clinical scenarios, the addition of typical data to the MSKUS examination may have on therapeutic decision making in the early RA patient with early RA without x-ray erosions and low joint count after PD. Case 3: in polyarticular PsA on MTX 15 mg/wk and a TNF-inhibitor without clinically active peripheral synovitis, but tender unilateral Achilles, a finding of bilateral Achilles paratenonitis and enthesitis by MSKUS prompted respondents to escalate prednisone (3% pre-MSKUS vs 11% post, p < 0.0001), DMARD (22% pre, vs 50% post, p < 0.0001) or escalate/change a biologic (8% pre vs 34% post, p < 0.0001). Case 4: no significant changes in therapy (prednisone, p > 0.14, or biologic, p > 0.70) occurred when MSKUS results were similar to those of clinical examination in severe active RA.

Lack of training, followed by reimbursement uncertainty and time concerns were reported as major barriers for MSKUS utilization among rheumatologists.

Conclusions: In specific clinical settings, typical results from MSKUS, can significantly impact therapeutic decision making. The most pronounced influence of the MSKUS examination was seen on the decisions to use biologic agents. This data is being validated in an ongoing clinical study using real time MSKUS on actual RA patients in a clinic setting.

Disclosure: A. Ceponis: None; J. J. Cush: None; A. Kavanaugh: None.

Effect of Musculoskeletal Ultrasound (MSKUS) Examination on Therapeutic Decision Making in Inflammatory Arthritis

Effect of Musculoskeletal Ultrasound (MSKUS) Examination on Therapeutic Decision Making in Inflammatory Arthritis

A. M. Evangelisto: None; G. S. Kaeley: None; John J. Cush: None; Arthur Kavanaugh: None; 1Baylor Research Institute, Dallas, TX; 2Division of Rheumatology, Allergy and Immunology, University of California San Diego, San Diego, CA; 3University of California-San Diego, La Jolla, CA

Wednesday, November 10

Background: MSKUS is a sensitive and specific imaging modality with growing utilization in rheumatology. However, the impact that MSKUS examination may have on therapeutic decision making in the management of inflammatory arthritis is unknown.

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Disclosure: A. Ceponis: None; J. J. Cush: None; A. Kavanaugh: None.

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Enthesopathy Detected by 18-Fluorodeoxyglucose Positron Emission Tomography in Patients with Polymyalgia Rheumatica


1Department of Radiology, National Center for Global Health and Medicine, 2Division of Rheumatic Diseases, National Center for Global Health and Medicine, Shinjuku-ku, Tokyo, Japan, 3Division of Rheumatic Diseases, National Center for Global Health and Medicine

Background: Polymyalgia rheumatica (PMR) is characterised by acute-onset proximal muscle pain and stiffness in patients over 50 years of age, and is diagnosed by excluding other disorders that cause similar complaints. Although the exact pathology of PMR is unknown, synovitis and bursitis are also common in this disease. Magnetic resonance imaging (MRI) or ultrasonography frequently reveals inflammation of the tenosynovial sheaths on the patients’ hands or feet. A study of PMR using 18-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) documented involvement of the spinous processes. Here, we present additional PET/CT findings in PMR.

Patients and Methods: Thirteen consecutive patients with PMR admitted to our institute between August 2007 and April 2010 were enrolled in the study. The number of the patients and the mean age ± SD was 13 and 76.2±6.5 years (range, 66–87), respectively. The diagnosis was based on the criteria of PMR of Chuang et al.

Results and Discussion: A week before starting steroid therapy. One patient also had clinical symptoms of temporal arteritis. In additional, muscle-tendon attachment sites in 69% (9/13) of the patients were FDG-positive, i.e., a majority of our PMR patients had enthesopathy. Of the large joints, the shoulders (11/11), hips (11/11), and knees (7/11) were the main affected sites. The enthesopathy was predominantly detected in the ischial tuberosities (9/9) and greater trochanter of the femur (8/9). Some of the FDG-positive lesions were detected on MRI, and the ratio of positive results in patients examined was 4/4 in the large joints, 1/1 in enthesopathy, and 0/2 in the spinous processes. Large vessel involvement was detected in two patients as multiple FDG uptake lesions. Of these, one patient had clinical symptoms of temporal arteritis, while the other was completely asymptomatic for the vasculitis. Enthesopathy in the patients was difficult to detect on physical examination because of overlapping myalgias or arthralgias. PET/CT may be useful for evaluating organ involvement in PMR patients.

Conclusion: FDG-PET/CT shows that not only inflammation of the spinous processes and large joints but also enthesopathy may be common in polymyalgia rheumatica.

Disclosure: H. Yamashita: None; K. Kubota: None; Y. Takahashi: None; H. Kaneko: None; A. Mimori: None.
Erosive Osteoarthritis Is Not Associated with Invading Synovial Tissue: An Ultrasound Study.

Ralf G. Thiele, Laura A. Paxton, Bethany A. Marston, Darren Tabechian and Allen P. Anandarajah. University of Rochester, Rochester, NY; University of Rochester, Rochester, NY; University of Rochester, North Chili, NY; University of Rochester School of Medicine, Rochester, NY.

Background: In patients with osteoarthritis, bony defects in small joints of the hand can occasionally be seen with conventional radiography (CR). Such a condition may be called erosive osteoarthritis (EOA). Swelling may occur, and the term “inflammatory osteoarthritis” is occasionally used. The degree of actual synovial proliferation remains unclear. It also remains unclear if bony defects of EOA are associated with synovial proliferation, similar to rheumatoid arthritis (RA).

Objectives: To assess if synovial proliferation and synovial hyperemia can be detected sonographically in EOA.

Methods: 1091 US studies obtained over 16 months were reviewed. All US studies were performed by a rheumatologist certified in musculoskeletal US, with >15 years of US experience. Studies were performed using a Toshiba Xario US machine with an 18 MHz linear transducer with differential tissue harmonic imaging and high-sensitivity Doppler capability, and a SonoSite M-Turbo machine.

Patients with a CR diagnosis of EOA were identified. For the diagnosis of EOA, the radiologist’s final assessment was counted.

US studies of joints in which EOA had been described by CR were assessed for the following:

1. Effusion, defined as a distension of the hyperechoic, fibrinous joint capsule by anechoic synovial fluid; 2. Synovial proliferation, defined as hypo-echoic synovial tissue within the joint cavity and emanating from the hyperechoic, fibrinous capsule; 3. Synovial hyperemia, defined as a pulsatile Doppler signal within the joint capsule, associated with synovial tissue.

Doppler signals were graded as follows: 0 = no signal; 1 = single vessel dots; 2 = confluent Doppler signals occupying less than half of the identified synovial tissue; 3 = confluent Doppler signals occupying more than half of the identified synovial tissue.

US studies of 13 RA patients were randomly selected and scored as a comparison group.

Results: Results were available for 13 EOA patients and 21 joints: DIP, n = 15; PIP, n = 6 (13 RA patients: MCP, n = 104; PIP, n = 104). Effusions were seen in 4/21 (19%) joints in EOA and 67/208 (32%) joints in RA. When effusions in EOA patients were seen, they were seen over the volar aspects of DIP and PIP joints, or immediately adjacent to bone spurs, where the spurs mechanically distended the joint capsule. Synovial proliferation was seen in 2/21 (9.5%) joints in EOA and 120/208 (58%) in RA. The degree was minimal in all cases of EOA. Only a concentric proliferation of the synovial lining was seen, but no invading pannus tissue was appreciated in EOA. Doppler scoring was 0 in 19/21 (90.5%) or 1 in 2/21 (9.5%) in EOA and 3 in 28/208 (13.5%), 2 in 52/208 (25%), 1 in 30/208 (14%) and 0 in 98/208 (47%) in RA.

Conclusion: In this US study, synovial changes were found to be fundamentally different in EOA and RA. Increases in synovial fluid around bone spurs in EOA did not have an inflammatory character. Synovial proliferation in EOA was, in stark contrast to RA, minimal. Similarly, synovial hyperemia was rarely seen in EOA, while this is common feature of RA. Invading synovial tissue was not seen adjacent to bony defects in EOA. Using sensitive US technology, synovial proliferation and hyperemia were not characteristic of EOA.

Disclosure: R. G. Thiele: SonoSite, 8, 9; L. A. Paxton: None; B. A. Marston: None; D. Tabechian: None; A. P. Anandarajah: None.

Evaluation of the 7-Joint Ultrasound Score (US7) by Detailed Joint Region-Analysis of an Arthritis Patient Cohort over One Year.

Sarah Ohnndorf, Beatrice Halbauer, Lydia Naumann, Ekkhart Dietz, Gerd R. Burmester and Marina Backhaus. Charite-University Medicine, Berlin, Germany; Department of Medical Statistics Charte, Berlin, Germany; Department of Rheumatology and Clinical Immunology, University Hospital Charite, Berlin, Germany; University Medicine Berlin: Campus Charte Mitte, Berlin, Germany.

Purpose: To evaluate the 7-joint ultrasound score (US7) by joint region-analysis of a cohort of arthritis patients over one year.

Methods: US7 examines the clinically dominant wrist, MCP andPIP II and III, MTP II, and V joints for synovitis, tenosynovitis/paratenonitis and erosions. Synovial inflammation is scored semi-quantitatively (grade 0–3) by grey scale (GS) and vascularity by power Doppler (PD) ultrasound (US), respectively. Tenosynovitis/paratenonitis and erosions are scored qualitatively (grade 0–1) by GS US.

Forty-five patients with RA (84.4%), PsA (13.3%) and AS with peripheral joint involvement (2.2%) with a mean disease duration of 9.0 years (SD 7.9, range 7.5 months-47.6 years) were included and examined before (baseline) and after 3, 6 and 12 months (t3, t6 and t12) starting or changing therapy (DMARD±TNF inhib.).

A detailed US7 analysis was performed for the baseline examination, referring to each examined joint region.

Results: N=45 patients with longstanding arthritis were recruited from the rheumatology Outpatient Clinic of the Charite-University Hospital Berlin, Germany.

The initial joint region-analysis resulted in 95.6% involved wrists from dorsal, of which grade 2 was most often detected (48.9%). Furthermore, erosions in this joint region were detected in 68.9% of patients, respectively. Wrist joints from palmar also showed synovitis in 88.9% with nearly the same number each for grade 1 (40%) and grade 2 (37.8%). Here, erosions were detected in 57.8%. Tenosynovitis of the extensor carpi ulnaris tendon being considered as an early finding in RA, was just found in 40% with a PD activity in 6.6%.

GS synovitis was evaluated in 95.6% both in MCP joint II and III from palmar. Most erosions in the MCP joint II were detected from radial (68.9%) in comparison to palmar (44.4%) and dorsal (48.9%). In the MTP joint V 75.6% of erosions were seen as focal.

With regards to paratenonitis, MCP joint II showed changes in 4.4% of patients, and MCP joints II only in 2.2%.

Conclusion: Synovitis in GS US was more often detected in the wrist from dorsal than from palmar. Tenosynovitis of the extensor carpi ulnaris tendon is often involved in RA and could be presented by GS US in 40%, respectively. Most erosions were found in the lateral scan of the MTP joint V and the radial scan of the MCP joint II. The detailed joint region-analysis showed that paratenonitis was a rare finding with the consequence that paratenonitis might not be a necessary component in the US7.

Disclosure: S. Ohnndorf: None; B. Halbauer: None; L. Naumann: None; E. Dietz: None; G. R. Burmester: None; M. Backhaus: None.

Fluorescence Imaging of Articular Proteinase Activities and Osteoblast Activity Showed Treatment Response to Anti-Interleukin-1 Antibodies in a Mouse Model of Collagen-Induced Arthritis.

Fons A. J. van de Loo, Eline Vermeij, Onno J. Arntz, Marije Koenders and Wim B. van den Berg. Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Objective: To monitor the response of anti-IL-1αβ antibody treatment on collagen-induced arthritis (CIA) using cathepsin- and matrix metalloproteinase (MMP) cleavable near-infrared probes, and a probe of osteoblast activation.

Methods: CIA was induced in male DBA/1J mice by immunization with bovine collagen-type II. Mice received either anti-IL-1αβ sera (200 μl i.v.) or normal rabbit serum as a control at day 21. Ten days later, probes were injected i.v. and 6 hours later mice were imaged using the IVIS Lumina (Caliper Life Sciences). Thereafter, ankle and knee joints were dissected and processed for RNA, histology or X-ray. The ProSense 680 probe (VisEn Medical Inc, Bedford, USA) became activated upon enzymatic cleavage by cathepsins (B, K, L, S, D), collagen degrading lysosomal cysteine proteinases.

The MMPSense 680, can be activated by different MMPs (2,3,9,13), known to degrade collagen and proteoglycans during arthritis. OsteoSense 680 is a fluorescent biphosphonate that binds to hydroxyapatite, a biomarker for osteoblast activation. Gene expression profiling was done of synovial biopsies from (non)-inflamed knees of untreated mice (MOE430_2 oligonucleotide array, Affymetrix, CA). Ankle joints were X-ray photographed and analyzed using a stereo microscope and scored on a scale ranging from no damage (0) to complete bone destruction (5).

Results: Inflamed synovia of CIA showed enhanced expression of the extracellular matrix degrading enzymes cathepsin-K (13-fold, osteoclasts specific gene), cathepsin-S (9-fold, specific for monocyes), MMP-13 (50-fold), MMP-3 (22-fold), MMP-14 (9-fold), MMP9 and MMP-2 (4-fold).

Genes related to bone destruction as cathepsin K (13-fold), TGFB1 (5-fold), TRAP5 (9-fold) and RANKL (10-fold) were upregulated as were also the...
High Reliability of Nailfold Videocapillaroscopy—An Outcome Measure for Systemic Sclerosis-Related Microvascular Disease? Herman Hofstee1, Erik Serne2, Chris Roberts2, Roger Hesselstrand3, Agneta Scheja3, Tonia Moore3, Marie Wildt1, Joanne Manning2, Anton Vonk Noordegraaf4, Alexandre Voskuyl4 and Ariane Herrick2. 1Lund University, Sweden, 2The University of Manchester, United Kingdom, 3The University of Manchester, United Kingdom 4VU University Medical Center, Amsterdam, The Netherlands

Background: Systemic sclerosis (SSc)-related structural microvascular abnormalities can be directly visualised using the non-invasive technique of nailfold capillaroscopy. Computerised techniques combined with high magnification videocapillaroscopy bring the potential of capillaroscopy being not only a diagnostic tool but also an outcome measure in longitudinal studies of SSc-related microvascular disease, including studies of treatment response. Good reliability is a necessary prerequisite for a test to be a valid clinical or research tool. The aim of our study was to investigate the inter- and intra-observer reliability of both qualitative and quantitative nailfold capillaroscopic parameters.

Methods: Mosaic nailfold images were acquired from the non-dominant ring finger of 10 healthy controls, 10 patients with primary Raynaud’s phenomenon, and 30 with SSc using a computerised videocapillaroscopy system (magnification 300x). Each image was assessed ‘blindly’ by 6 observers (2 from each of 3 centres from 3 different countries). Images were graded for both qualitative (including capillary architecture, avascularity, haemorrhages, and tortuous, ramified, bushy and bizarre loops) and quantitative parameters (including number of mega- and giant capillaries, capillary density, and capillary dimensions). Inter- and intra-rater reproducibility were assessed for (a) ordered categorical scores (qualitative and quantitative) using a weighted kappa co-efficient with quadratic weights and (b) quantitative measurements using intra-class correlations.

Results: These are summarised in the table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Inter-observer reliability</th>
<th>Intra-observer reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architecture</td>
<td>0.72 (0.55, 0.82)</td>
<td>0.75 (0.64, 0.83)</td>
</tr>
<tr>
<td>Avascularity</td>
<td>0.61 (0.37, 0.75)</td>
<td>0.74 (0.62, 0.82)</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>0.56 (0.16, 0.79)</td>
<td>0.73 (0.57, 0.86)</td>
</tr>
<tr>
<td>Tortuous</td>
<td>0.39 (0.25, 0.50)</td>
<td>0.68 (0.60, 0.76)</td>
</tr>
<tr>
<td>Ramified</td>
<td>0.58 (0.30, 0.73)</td>
<td>0.73 (0.59, 0.84)</td>
</tr>
<tr>
<td>Bushy</td>
<td>0.73 (0.50, 0.90)</td>
<td>0.80 (0.58, 0.94)</td>
</tr>
<tr>
<td>Bizarre</td>
<td>0.21 (0.00, 0.32)</td>
<td>0.76 (0.55, 0.92)</td>
</tr>
<tr>
<td>Mega capillary</td>
<td>0.76 (0.64, 0.84)</td>
<td>0.87 (0.82, 0.91)</td>
</tr>
<tr>
<td>Giant capillary</td>
<td>0.84 (0.71, 0.92)</td>
<td>0.92 (0.87, 0.96)</td>
</tr>
<tr>
<td>Intra-class correlation coefficient of quantitative measurements (95% CI)</td>
<td>0.87 (0.88, 0.92)</td>
<td></td>
</tr>
</tbody>
</table>

Inter- and intra-observer reliability of quantitative parameters showed substantial to almost perfect agreement. Certain qualitative parameters (architecture, avascularity, haemorrhage, ramified, and bushy capillaries) showed moderate to substantial inter-observer agreement and substantial intra-observer agreement, whereas other parameters including tortuous and bizarre capillaries showed moderate to poor inter-observer agreement.

Conclusions:
1) All quantitative and some qualitative parameters are highly reliable in terms of inter- and intra-observer agreement.
2) Other qualitative parameters, including tortuosity, are less reliable.
3) Capillaroscopy is likely to be a useful diagnostic tool and an outcome measure in studies of SS-related microvascular disease, provided that parameters selected are those with high reliability.

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Hypodermal Compressibility as a Diagnostic Test for Eosinophilic Fasciitis. Eugene Y. Kissin1, Michael R. York2 and Robert W. Simms3. 1Boston University, Boston, MA, 2Boston University Medical Ctr, Boston, MA, 3Boston University School of Medicine, Boston, MA

Purpose: Eosinophilic fasciitis (EF) is an autoimmune, fibrotic disorder that presents with painful swollen extremities. Though there are clinical characteristics that may distinguish it from diffuse systemic sclerosis (dSSc), frequently a deep wedge biopsy of the skin and fascia is felt to be necessary to confirm the diagnosis. We sought to determine whether high resolution B-mode ultrasound could distinguish forearm involvement by EF from similar fibrotic diseases such as systemic sclerosis, and diabetic cheiroarthropathy (DMc), and from controls with normal skin and fascia.

Methods: Consecutive patients with clinically diagnosed EF, DMc, dSSc, and fibromyalgia (FM) (FM with normal skin and subcutaneous tissue) were recruited from a rheumatology clinic over a period of 2 years to undergo ultrasound evaluation of the forearm. A GE LOGIQ e ultrasound unit with an L12 probe was used to evaluate the more clinically affected mid-dorsal forearm. The hypodermal tissues between the deep dermal interface and the muscle edge at the groove formed between the extensor digitorum and extensor carpi radialis was evaluated in short axis for the following variables: tissue depth with no transducer pressure (gel layer used to “float” the transducer to avoid any pressure), tissue depth with maximal tissue compression by transducer, and tissue echogenicity measured by densitometry (NIH Image). Dermal thickness was also measured. Tissue compressibility was calculated as (non-compressed tissue depth–compressed tissue depth)/non-compressed tissue depth. Statistical analysis was by T-test.

Results: The following numbers of patients were studied in each group: EF–8, dSSc–23, DMc–8, FM–8. Hypodermal percent compressibility was significantly less in EF compared with the other groups (means ± SD): EF–9 ± 7, dSSc–30 ± 13 (p<0.004 vs. EF), DMc–29 ± 20 (p<0.02 vs. EF), and FM–29 ± 14 (p<0.003 vs. EF) (figure). Hypodermal atrophy, measuring less than 4mm in thickness, was apparent in patients with EF–3/8 (38%), dSSc–7/23 (30%), and DMc–4/8 (50%), but not FM–0/8 (0%). DMc or dSSc patients only had <20% hypodermal compressibility if they also had hypodermal atrophy, while all but one EF patient had compressibility of less than 20% regardless of hypodermal atrophy. Hypodermal tissue average echogenicity did not differ between the 4 groups (EF=155 ± 21 densitometry units (du), dSSc=145 ± 16 du, DMc=157 ± 12 du, FM=149 ± 17 du, p=NS). Dermal thickness also did not vary significantly between the 4 groups (EF=1.3mm ± 0.2, dSSc=1.4mm ± 0.3, DMc=1.4mm ± 0.3, FM 1.3mm ± 0.3, p=NS).
Conclusions: Ultrasound can easily measure hypodermal compressibility. Our data suggest that reduction in hypodermal compressibility to less than 20% in non-atrophied hypodermis can be used to distinguish EF from dSSc and DMc, potentially obviating the need for wedge biopsy.

Disclosure: E. Y. Kissin: None; M. R. York: None; R. W. Simms: None.

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Novel PET/MR Fusion Imaging and Quantification of Knee Synovitis in Rheumatoid Arthritis. John T. Ryan1, C. T. Ng1, Aisling Kennedy1, Robert G. Gibney1, Oliver Fitzgerald1, Patrick C. Brennan1, Eric Heffernan1, Jonathan McNulty1, Louise Rainford3, Ursula Fearon1 and Douglas Veale1.

1Dublin Academic Medical Centre, Dublin, Ireland, 2Dublin Academic Medical Centre, 3University College Dublin, 4University of Sydney, Lidcombe, NSW, Australia, 5University of Sydney

We recently identified hypoxia and altered blood vessel stability in the rheumatoid arthritis (RA) joint suggesting the vessels are dysfunctional, as they do not match metabolic demand. PET/CT imaging is recognized as an important advance in health care and research. In this study we aim to develop an innovative imaging approach to visualize and quantify synovial tissue (ST) blood flow and metabolic activity in inflamed joints of RA patients.

RA patients with an active knee joint synovitis were recruited and underwent clinical assessment prior to contiguous imaging initially with MR, then PET/CT followed by a needle videarthroscopy, ST biopsy and pO2 measurement (novel LICOX probe). The PET radiotracer - Fluorodeoxyglucose (18F) was used and image-data intensity resolution was optimised for ST. These images exhibit the qualities of MRI with higher intensity regions in the areas of ST inflammation with extra heat-map information from the PET imaging. Semi-quantitative scoring of the MRI datasets was performed using the RAMRIS score. ST biopsies were stained for CD3+ (T cells), CD68+ (macrophages), and Factor VIII/ SMA (Blood vessel maturity) and NCAM expression.

RA patients (n=9) have completed combined scanning/arthroscopy protocols. Proof-of-concept images and quantitative assessments have been developed (Fig. 1, 2). Fig. 1a and b show the CT and PET/CT scans, 1c shows MR and the PET/MR fusion image is shown in Fig 1d. Evaluation of disease activity, blood flow or metabolic activity is not possible in Fig 1a or 1c, while Fig. 1b only provides information of metabolic activity. Fig. 1c does illustrate areas of high signal representing inflammation. Fig. 1d shows the contrast of PET imaging of an inflamed knee compared to the uninfamed contralateral knee and good PET/MRI structural agreement. A region of interest (ROI) was evaluated (n=3) of the target and the opposite knee to calculate a ratio of affected/unaffected. A significant correlation was found between PET activity with MRI score (r = 0.9986, p < 0.0001), with low tpO2 in vivo levels (xyz), while an inverse relationship was found with blood vessel maturity and stability, reflected by factor VIII/ SMA and NCAM expression on ST immunohistology of the blood vessels (r = −0.99, p < 0.0001).
This is the first description of hybrid PET/MRI fusion imaging of inflamed joint in RA. The preliminary data suggest a close correlation between measures of inflammation, blood flow and metabolic activity. The potential correlation with cellular and molecular biomarkers suggests this novel imaging protocol may be extremely powerful in assessing response to therapies in vivo.

Disclosure: J. T. Ryan: None; C. T. Ng: None; A. Kennedy: None; R. G. Gibney: None; O. Fitzgerald: None; P. C. Brennan: None; E. Heffernan: None; J. McNulty: None; L. Rainford: None; D. Veale: Abbott Laboratories, 2, Amgen Inc., 8, Centocor, Inc., 2, GlaxoSmithKline, 2, Mundipharma, 2, 8, Opsona, 2, 8, Pfizer Inc, 8, Schering-Plough, 8, Wyeth Pharmaceuticals, 2, 8.

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Outcomes and Cost-Effectiveness of Carpal Tunnel Injections Using Sonographic Needle Guidance. Natalia R. Chavez-Chiang, Suzanne Delea, Wilmer L. Sibbitt, Arthur D. Bankhurst and Hillary Norton. 1University of New Mexico, Albuquerque, NM, 2University of New Mexico HSC, Albuquerque, NM, 3University of NM Med Ctr, Albuquerque, NM

Objective: This randomized controlled study addressed whether sonographic needle guidance affected the outcomes of corticosteroid injection for carpal tunnel syndrome.

Methods: 76 symptomatic carpal tunnels were randomized to injection by conventional palpation-guided or sonographic image-guided injection enhanced with a one-handed RPD (the reciprocating procedure device) syringe. A one needle, two-syringe technique was used where sonographic-guided hydrodissection with 1% lidocaine with a first syringe was performed followed by injection with 80 mg of triamcinolone acetonide.

Baseline pain, procedural pain, pain at outcome (2 weeks and 6 months), responders, therapeutic duration, reinjection rates, total cost, and cost per responder were determined.

Results: There were no complications in either treatment group. Relative to conventional palpation-guided methods, sonographic guidance for injection of the carpal tunnel resulted in 77.1% reduction in procedural pain (p<0.001), a 63.3% reduction in pain scores at outcome (p<0.002), 84.6% increase in the responder rate (p<0.001), 51.6% reduction in the non-responder rate (p<0.001), a 71.0% increase in therapeutic duration (p<0.001), a 59.3% ($150) reduction in cost/responder/year for a hospital outpatient (p<0.001) and a 20.8% reduction in cost/patient/year for a hospital outpatient (p<0.001).

Conclusion: Sonographic needle guidance improves the performance, clinical outcomes, and cost-effectiveness of injection of the carpal tunnel.

Disclosure: N. R. Chavez-Chiang: None; S. Delea: None; W. L. Sibbitt: Apple, 1, 2, 5, Avanca Inc, 1, 2, 5, Avanca Medical Devices, 1, 2, 5, Avasca Inc, 1, 2, 5, Avasca Medical, 1, 2, 5, Becton Dickinson, 5, Celgene, 1, Ferring Pharmaceuticals Inc, 5, Intelligence management solutions, 1, 2, 5; A. D. Bankhurst: None; H. Norton: None.

1627 WITHDRAWN
Potential Use of Matrix Metalloproteinase-13 Fluorogenic Probe for Imaging Osteoarthritis Development In Vivo. Sung Jae Choi1,2, Young Ho Lee2, Jong Dae Ji1 and Gwan Gyu Song3. 1Korea Univ College of Med, Seoul, Korea, Republic of, 2Korea Univ College of Medicine, Korea, Republic of

Objective: the early detection of osteoarthritis (OA) is currently a key challenge in the field of rheumatology. Biochemical studies of OA have indicated that matrix metalloproteinase-13 (MMP-13) plays a central role in cartilage degradation. In this study, we describe the potential use of a dark-quenched fluorogenic MMP-13 probe to image MMP-13 in both in Vitro and rat models in Vivo.

Method: the imaging technique involved using a MMP-13 peptide substrate, near-infrared (NIR) dye, and a NIR dark quencher. This compound is composed of (i) Cy5.5, which was used as the near-infrared (NIR) dye (ex/em; 675/695), (ii) a short peptide sequence, GPLGMBGLGK, which was used as the MMP-13 cleavable substrate, and (iii) black hole quencher-3 (BHQ-3), which was used as the NIR dark-quencher specific for Cy5.5 (abs. 650 nm). The quenching properties of the probe were analyzed and visualized using a spectrofluorometer with a fixed excitation wavelength of 675 nm and a Kodak Image Station 4000MM equipped with filter for Cy5.5.

Results: OA-induced cartilage produced strong NIR fluorescence signals that were clearly visualized in the fluorescent images (1.30.2, 3.3 0.7, and 7.4 1.4-fold vs normal side for 0, 6, and 8 weeks, respectively; n = 3). NIR fluorescence signals in the eight-week OA rat had a 2.2-fold increase relative to the six week OA rat. Furthermore, the histological section of the normal cartilage showed a smooth articular surface with clear demarcation between the cartilage and subchondral bone. The results from this study demonstrate that the use of a dark-quenched fluorogenic probe allows for the visual detection of MMP-13 in Vitro and in OA-induced rat models. In particular, by targeting this OA biomarker, the symptoms of the early and late stages of OA can be readily monitored, imaged, and analyzed in a rapid and efficient fashion.

Conclusion: we anticipate that this simple and highly efficient fluorogenic probe will assist in the clinical management of patients with OA, not only for early diagnosis but also to assess individual patient responses to new drug treatments.

Figure 1. In Vivo imaging of upregulated MMP-13 in OA-induced cartilages 1 hour after intracartilage-injection of probe 1.

Figure 2. In ViVo NIR fluorescence tomographic images of normal and OA cartilage after local injection of probe 1 with or without the addition of the MMP-13 inhibitor in eight week OA-induced rat model.

Disclosure: S J. Choi: None; Y. H. Lee: None; J. D. Ji: None; G. G. Song: None.

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Psychometric Properties of Synovitis Assessed in Rheumatoid Arthritis: Improved Intraobserver Reliability of Ultrasound vs. Clinical Evaluation in an Ancillary Study of the “Etanercept Versus DMARDs” Randomized, Prospective, Multicentre Study. Peter Mandl1, Peter V. Balint2, Yves Brault1, Marina Backhaus1, Maria Antonietta D’Agostino1, Walter Grassl1, Desiree M. Van Der Heijde3, Antonietta D’Agostino7, Walter Grassi1, Desiree M. Van Der Heijde3, Eugenio De Miguel8, Richard J. Wakefield6, Isabelle Logeart4 and Marina Dougdados2. 1Clinica Reumatologica, Università Politecnica delle Marche, Jesi, Ancona, Italy, 2Hospital Cochin, Paris, France, 3Leiden University Medical Center, Meerssen, The Netherlands, 4Pfizer, La Défense, Paris, France, 5Rheumatology Department III, National Institute of Rheumatology and Physiotherapy, Budapest, Pest, Hungary, 6Rheumatology Department, University of Leeds, Chapel Allerton Hospital, Leeds, United Kingdom, 7Rheumatology Department, Versailles-Saint Quentin en Yvelines University; APHP, Ambroise-Paré Hospital, Boulogne-Billancourt, France, 8Rheumatology Unit, La Paz University Hospital, Madrid, Spain, 9University Medicine Berlin: Campus Charité Mitte, Berlin, Germany

Objectives: To propose different global ultrasound (US) and Power Doppler ultrasound (PD) scoring systems for measuring synovitis in rheumatoid arthritis (RA), with regard to the optimal number of joints to be evaluated. To evaluate for each proposed scoring system intra-observer reliability, face validity and discriminant capacity of US and PD synovitis versus clinical synovitis.

Methods: This 52-week, prospective, open-label, randomized, parallel-group, multicenter, outpatient study was conducted in RA subjects with moderate disease receiving etanercept combined with methotrexate (ETN+MTX) or various DMARDs. Due to early termination of the study, analyses were restricted to data collected from screening to the week-12 visit period. To study selected global scoring systems for clinical, US and PDUS derived data, including both counts and scores. A total of 66 different scoring systems were evaluated consisting of 11 different joint combinations, clinical, US and PDUS derived data, including both counts and scores. Intra-observer reliability was calculated at several timepoints by intraclass correlation coefficient (ICC) and standard error of measurement. Face validity was evaluated as the degree of association between CRP or ESR and each scoring system; correlation was assessed at screening (Pearson’s). To calculate discriminant capacity of scoring systems, the ETN+MTX and the conventional DMARD groups were evaluated separately and the difference in SRM was calculated.
Results: 66 patients were randomized in the study; 62 patients (mean age 53.8 years, 80.6% female, mean disease duration: 8.8 years) were included in the modified intention to treat population with 30 patients receiving various DMARDS, and 32 receiving EN-T-MTX. Reliability was better for US and PD than for clinical evaluation of synovitis in stable subjects between baseline and screening visit ranging from 0.6–0.95 and 0.56–0.93 vs. 0.33–0.75 (respective ICC values of US, PD, clinical indices). Face clinical validity was similar between the techniques. Difference in discriminant capacity (difference of difference in SRR between treatment groups) of US and PD vs. clinical synovitis, was $-0.25 (-0.96/0.64) and 0.08 (-0.37/0.59) (median, range) respectively in the baseline to 12 weeks period. No relevant differences in psychometric properties were observed regarding the number and specific localizations of the evaluated joints between the different scoring systems but with a trend in favor of better performance while referring to PD indices.

Conclusions: This study suggests that US and PD have not only similar but better reliability than generally used clinical indices for evaluating synovitis in RA. PD was also found to have better discriminant capacity than clinical synovitis for distinguishing between treatment arms. Such findings were observed for the different tested scoring systems suggesting that a simplified scoring system referring to the PD findings might be sufficient; these findings require further evaluation in larger study populations.

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Sensitivity and Specificity of the Physical Examination Compared to Ultrasound in Identifying Knee and Ankle Arthritis in JIA.

Ginger L. Janow1, Vikash Panghaal2, Terry L. Levin3 and Norman T. Ilowite1. 1Children’s Hospital Montefiore, Bronx, NY, 2Department of Radiology, Montefiore Medical Center, 3Division of Pediatric Rheumatology, Children’s Hospital Montefiore, New York, NY

Background: JIA can be an extremely debilitating disease of childhood with significant physical, psychological and financial costs to affected children. Early identification of active arthritis and treatment are crucial to the prevention of long term joint damage and disability. There is significant inter-user variability in the physical exam, as well as limitations of clinical examination and has been shown to be a helpful tool in assessing joint involvement and has the capability to identify sub-clinical disease. Use of US in all children with JIA may not be justifiable because of the cost.

Objective: (1) To determine the sensitivity and specificity of physical examination for identifying synovitis in knee and ankle joints of children with juvenile idiopathic arthritis. (2) To identify patients who would benefit most from additional screening via ultrasound.

Methods: A total of 22 patients with JIA were referred for ultrasound. Bilateral knees and ankles were examined using US with and without power Doppler in a blinded manner. Active arthritis on physical examination was defined as non bony swelling (criteria 1) or limitation of motion with either pain on motion or tenderness (criteria 2). Active arthritis on ultrasound was defined as synovial hyperplasia, effusion or increased vascularity on power Doppler. Eighty-eight joint assessments were completed by both a pediatric rheumatologist and a radiologist. Rheumatologist assessments were collected via chart review.

Results: Physical exam had a sensitivity of 61%, a specificity of 75%, a positive predictive value of 71% and negative predictive value of 66% as compared to US. When the definition of clinical synovitis was restricted to include only joints that met both of the clinical criteria (1 and 2), the specificity improved to 90%, with a decrease in sensitivity to 50%. Overall, the physical exam was more specific for identifying synovitis in the ankle than knees (specificity of 81% and 58% respectively).

Discussion: These data support the use of US to assess joints that do not meet both of the clinical criteria. Additionally, the physical exam is less sensitive for identifying knee arthritis which could support further US screening of these joints. Prudent use of ultra-sound in situations where the physical exam is less reliable could help identify sub-clinical disease and improve long-term outcomes.

Disclosure: G. L. Janow: None; V. Panghaal: None; T. L. Levin: None; N. T. Ilowite: None.

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The Comparison of Ultrasound & Physical Findings (CUSP) Remission Study—Ultrasound Remission Is Attained in Only 20% of Patients on Anti-TNF Therapy.

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Background: Studies show persistent inflammation on imaging in a proportion of patients in clinical remission on traditional DMARDS. This study aimed to evaluate clinical remission in patients on anti-tumour necrosis factor alpha (anti-TNF) drugs using objective measurement with DAS scores & ultrasound scoring using gray scale (GS) & power Doppler (PD) imaging.

Methods: Patients with Rheumatoid (n=29) and Psoriatic arthritis (n=12) on anti-TNF therapy & deemed by their supervising clinician to be in remission were assessed. Patient joint counts were performed. C-reactive protein (CRP) was measured and DAS28CRP was calculated. Visual analogue scales (VAS) (pain, general wellbeing) & Health Assessment Questionnaires (HAQ) were completed. Ultrasound examination of the DAS28 joint set and of the ankles and metatarso-phalangeal joints was performed (GE Logiq 9) with a high frequency (15MHz) linear array transducer. GS and PD synovitis were graded using an established semi-quantitative scale (0–3).

Results: The mean disease duration was 9.9 years (range 2–30) & mean patient age was 56 years (range 33–75). Average duration of biologic therapy was 31.5 months (4–67) and 95% were on their first biologic. Mean DAS28CRP was 2.57 (1.35–4.85) while mean DAS28 was 2.74 (0.91–4.9), 21/41(51%) of patients were in DAS28CRP remission, 14 had low disease activity (DAS28CRP >2.6, <3.2) while 5 patients had active disease. Mean HAQ score was 0.58 (0–1.63), 34/41 (83%) had GS synovitis of at least Grade 2 in one joint, while the remainder (7/41, 17%) had Grade 3 synovitis in at least one joint. All patients had positive PD signal in at least one joint. Mean total score of PD was 19 (range 2–64), 22/41 (54%) patients had Grade 2 PD and 4/41 (10%) had grade 3 PD. If PD remission was defined as PD total score of 10 or less, 9/41 pts (22%, mean 6.4, range 2–10) fulfilled criteria. If PD remission was defined as PD total score of 0 or less, 4/41 pts (10%, mean 3.75, range 2-5) fulfilled criteria. GS and PD synovitis scores were significantly positively correlated with DAS28CRP (r=0.575 and r=0.793 respectively, p<0.01 for both).

Conclusion: Ninety percent (37/41) of patients in clinical remission & 81% (17/21) of patients in DAS remission on anti-TNF show persistent inflammation on GS & PD imaging. Standard clinical assessment alone is...
The Role of Ultrasound in B Mode and Power Doppler Sonography in the Diagnosis of Enthesitis in Children. Dana Toib1, Anthony R. French1, Nirvikar Dahiya2, William D. Middleton2, Richard Brasington1 and Andrew J. White1.

Purpose: Enthesitis is a distinctive feature of Juvenile Spa (JSpA). Recently, ultrasound in B mode and power Doppler sonography has been suggested to be a valuable tool in the assessment of enthesitis. The aim of this study was to compare the physical exam (PE) with ultrasonography (US) in the assessment of enthesitis in children.

Methods: 20 JSpA patients, 19 polyarticular/pauciarticular JIA patients, 8 adolescent patients with idiopathic arthralgias and 9 healthy pediatric controls underwent US exam of 16 peripheral entheses using Terason 13000 equipment with 12-MHz linear array transducer. The US images were interpreted independently by two radiologists and abnormalities were quantified using a modification of the Madrid sonographic enthesis index (MASEI). Enthesal PE was completed independently by two pediatric rheumatologists. Current treatment, inflammatory markers and CHAQ scores were recorded on all patients.

Results: Sonographic evidence of enthesitis was most common in the JSpA group (53% of patients; 6.9% of examined entheses), but was also found in all other study groups, including pauciarticular/pauciarticular JIA (37% of patients; 5.0% of entheses), idiopathic arthralgias (38% of patients; 2.7% of entheses) and healthy controls (28% of patients; 2.1% of entheses).

Disclosures: None.

The Power Doppler Ultrasonography Score from 24 Synovial Sites or 6 Simplified Synovial Sites, Including the Metacarpophalangeal (MCP) Joints, Reflects Well the Clinical Disease Activity and Serum Biomarkers in Patients with Rheumatoid Arthritis. Atsushi Kawakami1, Shin-ya Kawashiri1, Naoki Iwamoto1, Mami Tamai1, Hideki Nakamura1, Junko Kita2, Atsuhiko Koga3, Satoshi Yamasaki1, Tomoki Origuchi2 and Katsumi Eguchi2. 1Nagasaki University, Nagasaki, Japan, 2Sasebo City General Hospital, Sasebo, Nagasaki, Japan

Purpose of Study: We evaluated the significance of the Power Doppler ultrasonography (PDUS) score by comparing it with serum biomarkers and clinical disease activity.

Methods: We measured the PDUS scores of 24 synovial sites in 12 joints in 22 RA patients. For convenience, the PDUS scores of 6 synovial sites in 6 joints were also examined. Both PDUS scores included the metacarpophalangeal (MCP) joints. Each joint was scored for a power Doppler (PD) signal on a scale from 0 to 3. The PDUS scores are the sums of the PD signal scores for the 24 synovial sites or for a power Doppler (PD) signal on a scale from 0 to 3. The PDUS score was positively correlated with tender joints counts, swollen joint counts, DAS28, SDAI, CDAI and serum biomarkers including MMP-3, VEGF.

Results: The standard as well as the simplified PDUS scores well reflected clinical disease activity and serum variables, including angiogenic factors. Our data reaffirm the utility of ultrasonography for monitoring disease activity in patients with RA.

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Ultrasound Bone Erosions—Their Morphological Basis Obtained by High-Resolution Micro-Computed Tomography Imaging. Stephanie Finzel1, Sarah Ohrdorf1, Matthias Englbrecht2, Christian M. Stach3, Janin Messerschmidt1, Georg Schett1 and Marina Backhaus1. 1Charite University Hospital, Berlin, Germany, 2Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, 3Friedrich Alexander Univ, Erlangen, Germany, 4University Medicine Berlin: Campus Charité Mitte, Berlin, Germany

Objectives: To validate, whether bony lesions appearing in high-resolution ultrasound (HRUS) are true bone erosions.

Methods: In total, 26 individuals (14 with rheumatoid and 6 with psoriatic arthritis as well as 6 healthy controls) were assessed for bone erosions at the radial, palmar and dorsal side of the MCP2 and the palmar and dorsal sides of the MCP3 and MCP4 joint. All patients received a HRUS and for validation of results a micro-computed tomography scan (μCT). The prevalence (0/1) and severity of bone erosions obtained in HR US and μCT were recorded and compared.

Results: Overall there was a good correlation between the severity of US erosions and μCT erosions (r = 0.463, p < 0.0001).
A good correlation between the severity of bone erosions in the US and sensitivity of US for detecting bone erosions was high and there was US indeed based on true bone erosions with a cortical break. The true breaks in the cortical bone surface.

Conclusions: These data show that the majority of erosion in the US was indeed based on true bone erosions with a cortical break. The sensitivity of US for detecting bone erosions was high and there was a good correlation between the severity of bone erosions in the US and the μCT imaging. Specificity of US for bone erosions was substantially lower, suggesting that smaller US lesions do not always refer to true breaks in the cortical bone surface.

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increased vascularity and erosions. Retrospective review of this imaging data as well as clinical data including age, sex, serological status (RF & CCP antibody positivity), inflammatory markers (ESR & CRP) and final diagnosis was performed.

Results: Total Patients 80 Clinical Data Available 53 Male 65 Female 55 Age Median 50 (Median Age = 52) RF positive 6 CCP antibody positive 4 Elevated ESR Elevated CRP 9

There were 48 patients with synovial thickening and increased vascularity and 35 patients with erosions at one or more joints. Changes suggestive of inflammatory arthritis were most commonly seen at 2nd & 3rd MCP and wrist joints. Thirty patients were found to have synovial thickening, 25 increased vascularity and 13 erosions at one or more joints despite having negative RF & CCP antibodies and normal inflammatory markers (ESR & CRP). Fourteen patients were given final diagnosis of inflammatory arthritis primarily based on musculoskeletal ultrasound results and all 14 had synovial thickening and increased vascularity at one or more of 2nd & 3rd MCP and wrist joints.

Conclusions: 1. Musculoskeletal ultrasound is a very useful tool in diagnosis of early inflammatory arthritis in clinical practice.

2. Brief musculoskeletal ultrasound, restricted to just 6 joints (bilateral 2nd & 3rd MCP and wrist joints) instead of 22 joints, can be used to make the diagnosis of early inflammatory arthritis without significantly compromising diagnostic accuracy and thus reducing time required to perform the exam.

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1637

Utility of Ultrasound in the Diagnostic Assessment of Shoulder Pain in Polyarthritis Rheumatica: Results from an International, Prospective, Multi-Center Longitudinal Study. ACR-EULAR Study Group for Development of Classification Criteria for PMR. Wolfgang A. Schmidt1, Marco A. Cimmino1, Peter Mandl1, Peter V. Balint1, Annamaria Iagnocco2, Richard J. Wakefield3, Michael Schirmo2, Carlo Salvare1, Artur Bacht1, Maria C. Cid3, Christina Dufner1, Christian Dejaco2, Georgina Espigol-Frigole2, Pierluigi Macchioni2, Zouza Schmidt1, Novak P. Kaposi3, Gyula Pog1, Elisabeth Nordborg3, Haner Direskeneli11, Sibel Z. Aydin11, Colin Pease20, Khalid Ahmed13, Mehndad Mazlumzadeh1, Andy Abril1, Neil Gontner21, Hilal Maradit-Kremers1, Cynthia S. Crowson1, Bhaskar Dasgupta14 and Eric L. Matteson5.

2nd MCP Left Right 2nd MCP Left Right 2nd MCP Left Right 2nd MCP Left Right

Wrist 28 29 26 30 4 1

5th MCP 2 22 61 51 2 91 1

3rd MCP 4 04 33 53 32 52 5

2nd MCP 40 43 32 33 32 31 31

Elevated CRP 9

Increased Vascularity 10

Bilateral 28 29 26 30 4 1

Elevated CRP 9

Conclusions: In this largest and first multicenter study of US in PMR, most subjects with PMR have abnormal findings on shoulder US. US had limited value in distinguishing PMR from RA, but had value in discriminating PMR from other conditions associated with shoulder pain. US of the shoulders and hips may have added value for diagnosis of PMR.

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1638

A Comparison of the Presentation, Synovial Fluid Analysis, and Treatment Course in Children and Adults with Lyme Arthritis. Brian E. Dukl5, Fred Emerson1, F. Lee Lucas2, Robert Smith1 and Carol McCarthy1.

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In the northeastern United States, Lyme arthritis is an increasingly recognized form of monoarticular inflammatory arthritis in both the pediatric
and adult population. We have observed that some cases of pediatric Lyme arthritis may be confused with septic arthritis leading to unnecessary hospitalization and surgical drainage. We wondered how frequently this occurs in children and whether there are differences between the pediatric and adult population in the presentation and management of Lyme arthritis.

**Methods:** Charts of pediatric and adult patients evaluated for Lyme arthritis by rheumatologists and pediatric infectious disease specialists in Portland, ME between January 2002 and July 2008 were reviewed. Patients included for analysis had documented synovitis and positive Lyme serology. Data on clinical presentation, synovial fluid and peripheral blood results, treatment, and clinical course were extracted and subjected to statistical analysis.

**Results:** 29 adults and 50 children met inclusion criteria and were studied. Children were more likely than adults to present acutely (p = 0.01). They were less likely to be weight bearing (p = 0.04), had a higher mean synovial fluid WBC count (p = 0.00064), were more likely to be hospitalized (p = 0.02) and were more likely to have a suspected septic arthritis (p = 0.02), although there was no statistical difference between the two groups with respect to surgical intervention. In contrast, adults received more oral antibiotic courses (p = 0.006).

They were less likely to have normal function within four weeks of initiating antibiotic treatment (p = 0.0002), were more likely to have intravenous antibiotics in subsequent treatment courses (p = 0.01), and were more likely to be diagnosed with a persistent arthritis (p = 0.0007).

**Conclusions:** The presentation of Lyme arthritis in children and adults in our study population differed in the acuity of presentation and subsequent management. Children were more frequently hospitalized for suspected septic arthritis whereas adults were more often managed in the outpatient setting. Yet children tended to have more prompt resolution of their synovitis and received less treatment overall. The clinical spectrum of Lyme arthritis is variable, ranging from chronic indolent synovitis to acute monoarticular arthritis mimicking septic arthritis. In the appropriate geographic and clinical setting, Lyme arthritis should be considered in children presenting with acute monoarticular arthritis. Considering the diagnosis early may prevent hospitalization and needless intervention including surgical drainage.

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1639

**Autoantibodies to a Novel Cytoplasmic Rod/Ring Structure Targeted CTP/GTP Synthetic Pathway in HCV Infection After Interferon/Ribavirin Therapy.** Wendy C. Carcamo,1 Angela Ceribelli,1 Jason Y. F. Chan,1, Westley H. Reeves,2 Giovanni Covini, Carlos A. Von Muhlen,2 Liu Chen,3 Minoru Satoh,4 and Edward K. L. Chan2.

1Department of Medicine, Portland VA Health Care System, Portland, ME; 2University of Florida, Gainesville, FL, 3University of Florida

**Purpose:** Autoantibodies (aab) can be important disease markers and basic research tools in molecular and cell biology. Cytoplasmic antigentic structures identified by ANA screening consisting of rods and rings (RR) are novel subcellular structures. The current aim is to identify clinical occurrences associated with RR antibody, elucidate the antigenic targets and their biologic function.

**Methods:** Sera collected from multiple clinical centers were analyzed by IHC on HEp-2 slides as well as other mammalian cell lines for the presence of anti-RR. Positive samples were then analyzed by immunoprecipitation of 35S-labeled K562 cell extracts. Identity of candidate antigens associated with RR was validated by co-staining with established specific antibodies.

**Results:** Anti-RR recognized cytoplasmic rods of 3–10μm in length and rings with ~2–5μm in diameter in HEp-2 cells, distinct from all known aab reported to date. A total of 80 anti-RR samples were identified, clinically linked to Hepatitis C virus (HCV), mostly after interferon-alpha/ribavirin (IFN/R) therapy. Clinical data were available from 23 Italian anti-RR+ patients: 15 HCV+, 6 HCV−, and 2 unknown. Prevalence of anti-RR did not correlate with specific HCV genotypes: Type 1 (6/15), 2a (3/3), 3 (1/15), and 4 (4/15). 14/15 HCV+ were treated with IFN/R therapy, indicating a strong link of RR aab to this therapy. 75% (9/12) of HCV with anti-RR had no response to IFN/R therapy, suggesting anti-RR may be associated with poor response. The 6 HCV−(−)RR patients had no common diagnosis. However, prevalence of anti-RR in general hepatic disease population was low (3.5%, ~3/1000), indicating that HCV infection alone seldom induces anti-RR aab. In an autoimmune disease center setting, prevalence of anti-RR was also very low; only 2 SLE patients were identified among ~2,000 in database. Analysis of the 2 SLE patients over 3 yr span was available. Interestingly, patient #1 had HCV(3a) and anti-RR was detected within 4 mo after IFN/R treatment. This patient was unresponsive and treated again with IFN/R after 6 mo. Liver function then normalized and anti-RR disappeared. Patient #2 had anti-Sm/RNP, anti-phospholipid aab with lupus nephritis, but was apparently HCV- and had stable anti-RR for at least 2 yrs.

**Conclusion:** About a third of anti-RR+ sera immunoprecipitated 55kDa doublets. Candidate 55kDa antigens cytosine triphosphate synthase (CTPS1) and inosine monophosphate dehydrogenase 2 (IMPDH2) were identified to be highly enriched in RR. Multiple inhibitors of these enzymes were shown to be sensitive inducers of RR formation in all mammalian cell types analyzed.

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1640

**Chloroquine (CQN) Is Not Superior to Meloxicam (MCM) in the Treatment of Early Persistent ‘Musculoskeletal Pain and Polyarthralgias’ (MSK-P) Following Chikungunya (CHIKV): A Non Commercial Investigator Initiated Community Based Controlled Drug Study.** Arvind Chopra,1 Manjit Saluja1 and Anuradha Venugopalan,1, 2Center for Rheumatic Diseases, 2Center for Rheumatic Diseases, Pune, India, 3Center for Rheumatic Diseases

CHIKV is predominantly a self limiting short duration febrile severe arthralgia illness. Though experimentally demonstrated (Sourisseau. PLoS Pathog 2007; 3(6):e89). Therapeutic role for CQN is flimsy. A CQN trial (CuraChik: NCT00391313) was abandoned. CQN was used rampant in the recent India CHIKV epidemic.(Chopra. Arthritis Rheum 2008; 59(9): 2921). We carried out an exploratory study during the epidemic.

**Methods:** 509 cases of CHIKV were identified in a survey of 1450 population in village Bavi (Sholapur, West India). Acute cases received symptomatic measures. 70 consenting patients (62 women, median age 50 years) with persistent MSK-P (minimal duration 4 weeks, active painVAS > 40 mm) and seronegative anti-CHIKV IgM/IgG antibody were enrolled into randomized, single blind (doctor) parallel efficacy two arm (CQN=38, MCM=32) trial of 24 weeks duration; CQN phosphate (250 mg od) and meloxicam (MCM, 7.5 mg od). Rescue analgesic(paracetamol) was monitored. MSK-P could not be further classified. 43 patients showed minimal few site synovitis/tenosynovitis. We visited homes monthly, to complete trial procedures/assessments. Pain VAS (primary efficacy) and ACR efficacy measures (+ Indian version HAQ) were recorded. Besides routine laboratory investigations, selected cytokines (IL-6, -10, IFN-α, TNF-α, CXCL-10/IP-10, and IL-13) were assessed and geometric mean (fig 2) computed; pre-epidemic controls were used. X-rays were not taken.

An intention to treat analysis (last observation carried forward, ANOVA) was completed/significant p < 0.05 with CI (95% confidence interval). At baseline, the groups matched well.

**Results:** The mean change from baseline to completion for efficacy and cytokines did not differ significantly between the groups [Difference for pain VAS: CI ~ −0.8, 1.3]. Paracetamol consumption was almost similar.

**Figure 1.**
Fig. 1 shows mean painVAS and pain/tender joint count. Amongst completers, beyond 3 months study, pain was asymptomatic, mild and moderately severe in 37%, 52% and 11% trial patients respectively; corresponding 42%, 42% & 15% for CQN. Seven patients withdrew but none due to AE. Five patients reported mild AE (usually dyspepsia; none skin/eye).

Though decreased from baseline, cytokines remained elevated (above control) at 24 weeks endpoint.

Conclusion: This is the first ever truly community based drug intervention trial. CQN did not offer any therapeutic advantage over symptomatic NSAID in the long term treatment of early persistent MSK-P following CHIKV. Despite clinical relief, cytokines (especially IL-6) remained elevated and this may implicate long term prognosis.

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1641

Clinical Features of Acute Human Parvovirus B19 in Adults: What We Could Learn from It? Hideto Oshikawa1, Makiko Yamamoto2, Akira Jibatake2, Kiyoharu Muranaka2, Kazuki Yoshida2, Masako Utsunomiya2, Tatsuo Kobayashi2, Mitsumasa Kishimoto1 and Kazuki Matsui1, 2. 1Department of Rheumatology, Kameda Medical Center, 2St Luke's International Hospital, Japan

Background: Human parvovirus (HPV) B19 infection in adults often mimics rheumatic disease such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA).

Purpose: To investigate the clinical features of acute HPV B19 infection in adults and examine the rate of patients who fulfill the classification criteria for SLE or RA.

Methods: Retrospective chart review of adult patients with newly-diagnosed acute HPV B19 infection from April 2006 to April 2010 was performed in a community-based hospital in Japan. The diagnosis was made with the positive serum anti-HPV B19 IgM antibody.

Results: Of the thirty-five patients diagnosed as acute HPV B19 infection, 24 patients (68.5%) were female and the mean age was 38.6 years. Nearly half of the patients (48.5%) had a history of recent sickness and 24 patients (68.5%) were female and the mean age was 38.6 years. Half of the patients (48.5%) had a history of recent sickness and 24 patients (68.5%) were female and the mean age was 38.6 years.

The following abnormal laboratory findings were observed: positive anti-nuclear antibody (ANA) (95.2%), lymphocytopenia (81.2%), elevated lactate dehydrogenase (68.7%), hypocomplementemia (50%), and anemia (21.2%). Rheumatoid factor and anti-CCP antibody were not detected in patients who were tested (22 and 10 patients).

Four patients (11.4%) fulfilled the 1997 revised ACR SLE Criteria and 9 patients (25.7%) fulfilled the preliminary 2010 SLICC/ACR SLE Criteria. Of 11 patients with physician identified arthritis, none fulfilled the 1987 ACR RA Criteria, and 4 patients (36.3%) fulfilled the 2010 ACR/EULAR RA Criteria. Three patients fulfilled both new SLE and RA criteria.

During the mean follow-up of 5.6 weeks (range 0—42), the mean duration of arthritis was 22 days (range 11—36). As for treatment, NSAIDs were used in 11 patients (31.4%), and acetylsalicylic acid in 10 patients (28.5%).

Conclusion: HPV B19 infection in adults, often present with acute polyarthritis and skin rash accompanied with lymphocytopenia, hypo-complementemia, and positive ANA. About one-third of adult patients with acute HPV B19 infection fulfill the criteria for SLE or RA, or both. We should consider the possibility of HPV B19 infection in the differential diagnosis of SLE or early onset RA.

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1642

Cytokines in Chikungunya (CHIKV): Storm in a Teacup or Winds before the Storm. Arvind Chopra1 and Anuradha Venugopalan2, 1Center for Rheumatic Disease, Pune, India, 2Center for Rheumatic Diseases, Pune, India

CHIKV is an acute severe (polyarthralgias) self limiting arboviral illness. 10% cases develop chronic RMSK. We witnessed a wide spectrum of inflammatory arthritis following CHIKV in our referral practise (Chopra. Arthritis Rheum 2008;58(9):2921). During the epidemic (2006), we completed a cross section house to house 1192 rural population (West India) survey in 10 weeks and identified 509 clinical cases (86% symptomatic);225 cases (81% symptomatic) consented blood investigations and are the basis of current report.

Methods: Clinical, diagnosis was substantiated by serology (49% IgM and 62% IgG CHIKV antibodies; immunochromatographic and IIF). Persistent RMSK cases followed up to 18–21 months. Lab investigations (including RF, CRP, ANA, CCP) repeated at predetermined timepoints: malaria and dengue excluded. None showed thrombocytopenia. IL-6 (51.12 pg/ml), IL-13 (181.44 pg/ml), TNF-α (32.79 pg/ml), IFN-γ (3.12 pg/ml) and CXCL10/ IP-10 (3.16 pg/ml) assayed by standard ELISA; geometric means from healthy control (pre-epidemic) shown in parentheses.

Observations: Post onset, 65% cases recovered within one month. None died. Rest suffered from predominantly (86%) persisted non-specific polyarthritis (NSA). Overt synovitis/ tenosynovitis was mild and uncommon. 18% and 12% cases remained symptomatic at 6 and 12 months respectively. IgM response vanished by 6 months while IgG rising titer was demonstrated till study completion. Cytokine profile shown in the figures.
Figure 2.
The cytokine upsurge persisted irrespective of symptom resolution or the type of RMSK (NSA/OA/Inflammatory/soft tissue rheumatism).
An early robust IFN-\(\gamma\) response was often associated with early resolution. High IL-13 was often evident in patients with chronic RMSK. Though conjointly elevated in early illness, a disconnect was observed between IL-6 (remained high) and C-Reactive Protein (low levels) during follow up. The overall seropositivity of autoantibodies was low (~5%). 

Conclusions: This daunting community study of CHIKV epidemic demonstrates an intense proinflammatory cytokine milieu during early and persistent phase (RMSK) despite an overall benign clinical profile. It may be linked with persistence of RMSK. We continue to follow this story and hope to unravel the long term implication of this intriguing arbovirus.

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1643
Geographic Distribution of Endemic Fungal Infections among Older Americans. John W. Baddley\(^1\), Kevin L. Winthrop\(^1\), Nivedita M. Patkar\(^3\), Elizabeth Delzell\(^4\), Fenglong Xie\(^4\), Lang Chen\(^4\) and Jeffrey R. Curtis\(^2\).
\(^1\)Oregon Health Sciences University, \(^2\)University of Alabama-Birmingham, Birmingham, AL, \(^3\)University of Alabama at Birmingham, Birmingham, AL, \(^4\)University of Alabama at Birmingham, Birmingham, AL.

Background: Histoplasmosis (histo), blastomycosis (blasto) and coccidiodomycosis (cocci) are major endemic fungal infections in the U.S. and have been associated with use of biologics for arthritis. Data regarding the epidemiology and geographic distribution of endemic fungal infections in older adults are limited. Identifying geographic areas with a relatively high incidence of endemic fungal infection may impact diagnostic or prevention measures in older adults receiving biologics.

Methods: We evaluated a 5% sample of national Medicare data for years 1999–2008. Fungal infections were identified by ICD-9 codes (histo, 115.x; blasto, 116.0; cocci, 114.x). A case required one inpatient claim or at least two outpatient claims at least 7 days apart but within 90 days. Co-morbidities were identified by ICD-9 codes and defined as one physician claim within 6-months prior to the index case date. We calculated national, regional and state-based incidence rates (per 100,000 person-years) and determined mortality 90-days post diagnosis date.

Results: Five-hundred fifteen cases (241 histo; 218 cocci; 56 blasto) were identified. Mean age was 77.7 years and 53.8% were male. Regional variation was evident (Figures 1, 2), with histo and blasto incidence higher in southern and midwestern states; and cocci incidence was higher in the Southwest US. Of all histo cases, 3.8% had an underlying diagnosis of rheumatoid arthritis (RA); 5.2% of cocci cases had underlying RA. Ninety-day mortality was highest (12.5%) in histo patients.

Conclusion: Histoplasmosis is the most common endemic fungal infection among older Americans. Geographic distribution for these mycoses is evident; however, it is important to note that cases occur outside of endemic areas. Histo and blasto incidence rates were higher in southern and midwestern states; and cocci incidence was higher in the Southwest US. Knowledge of areas of increased risk may impact diagnostic or prevention measures in older adults with inflammatory conditions and those receiving biologics.

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1644

Background: Baggio-Yoshinari Syndrome (BYS) is a new tick-borne infection, similar to Lyme Disease (LD) described in the northern hemisphere, except for essential differences in epidemiological, clinical and laboratory findings. The difficulty in identifying the BYS causative agent has delayed the dissemination of knowledge about this emerging zoonosis. The purpose of this study was to identify the etiologic agent of BYS using a conserved gene that synthesizes the flagellar hook (flgE) of \textit{Borrelia burgdorferi} sensu lato by molecular typing method based on Polymerase Chain Reaction (PCR).

Background: HIV is a global pandemic. Since the advent of antiretroviral therapies (HAART), mortality has been dramatically reduced in the western world but HIV-infected adults are living longer to acquire comorbidities. This cross-sectional epidemiologic study investigated the prevalence of musculoskeletal pain among a large cohort of HIV-infected adults.

Methods: Outpatient attendees at an HIV Unit in the UK were surveyed over a 6-month period. A questionnaire enquiring about demography, regional and widespread pain, symptoms of musculoskeletal disease (e.g. pain, swelling, rashes, sicca symptoms, fracture) was administered by trained nurses.

Results: In total 1050 HIV-infected adults were approached from whom 859 (82%) useable replies were received. 90% of the respondents were male, mean age 42 years, mean duration HIV infection 6 years. 76% were current users of HAART. In total, 539 (63%) reported pain lasting >1 day in past month; 431 reported chronic musculoskeletal pain (>3 months). The mean duration of chronic pain was 4.5 years. Pain was significantly increased in older age groups (p=0.002). Women reported pain more frequently than men throughout the age range, had higher mean pain scores (p=0.022) and were significantly more likely to take painkillers most days (p<0.0001). HIV patients with pain were significantly more likely to be working (p=0.0001).

Conclusions: Musculoskeletal pain is common amongst HIV-infected adults, particularly women. As in uninfected patients, psychosocial factors are importantly associated but so are HIV factors including duration of infection and exposure to Protease Inhibitors. Musculoskeletal pain impacts significantly in this population causing disability and sickness absence and reduced quality of life.

Disclosure: K. Walker-Bone: None; E. Lawson: None; D. Churchill: None; Y. Gilleece: None; M. Fisher: None; C. Sabin: None.

1646 Surrogate Markers of B-Cell Non-Hodgkin Lymphoma in Patients with Hepatitis C Virus-Related Cryoglobulinemia Vasculitis. Guillaume Geri1, Benjamin Terrier2, Oren Semoun2, David Saadoun3, Damien Sène4, Hélène Merle-Beral5, Frédéric Charlotte6, Lucile Musset7, Mathieu Resche-Rigon8, Patrice Cacoub9. 1INSERM URMS 717, Paris 7, Paris, France, 2Pitié-Salpêtrière Hospital, Paris, France

Methods: Eight patients fulfilling the BYS diagnostic criteria were selected from November 2008 to October 2009. The patients had to present erythema migrans and positive epidemiologic history. Thirty healthy individuals, without history of tick bite or risk areas exposure, were included in the study. Partial sequences (flgE 470) of Borrelia burgdorferi flagellar hook protein (HfE) gene (L43849). All samples of the control group were negative for the primers used in this study.

Results: PCR targeting the gene flgE, which amplifies a fragment of ~470bp, showed positivity in 4 samples (50%). Sequences disclosed 99% of homology to B. burgdorferi flagellar hook protein generated in this study were deposited into GenBank and assigned nucleotide accession no. HM245929. Targeting the gene flgE followed by sequence analysis.

Conclusions: For the first time, we identified B. burgdorferi can cause two different clinical entities, Lyme disease in United States of America and Eurasia and Baggio-Yoshinari Syndrome in Brazil.

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1645 Prevalence, Impact and Risk Factors for Musculoskeletal Pain among HIV Infected Adults: An Epidemiologic Study. Karen Walker-Bone1, Edwina Lawson2, Duncan Churchill2, Yvonne Gilleece2, Martin Fisher2 and Caroline Sabin1. 1Brighton & Sussex Medical School, Brighton, United Kingdom, 2Brighton & Sussex University Hospitals NHS Trust, University College, London

Methods: We designed an internet survey that was sent to rheumatologists worldwide. The aims of this 26 question internet survey were twofold: to determine how often practicing rheumatologists diagnose ReA compared to other types of SpA and RA, and to uncover factors that might lead to this underdiagnosis. The survey was sent out to random rheumatologists who are registered with the American College of Rheumatology.

Results: The survey was delivered to 3,200 rheumatologists and 377 replied (11.8% response rate). Of the rheumatologists who replied 257/377 (68.2%) were male, 289/377 (76.7%) spend at least half time there in clinical care, 271/377 (71.9%) see at least 100 patients per month, 300/377 (79.6%) have been in clinical practice longer than 5 years since completion of their fellowship, and 256/377 (67.9%) practice in the U.S. In adult patients with new-onset diagnoses (disease duration <6 months), RA was the most common diagnosis followed by psoriatic arthritis (PsA), ankylosing spondylitis (AS), undifferentiated spondyloarthrtis (uSpA), ReA, and inflammatory bowel disease related SpA; in patients with a disease duration of > 6 months, the order in decreasing frequency was RA followed by PsA, AS, uSpA, BD related SpA, and ReA. PsA sine psoriasis was diagnosed only slightly less often than ReA in patients with disease duration of <6 months and at a nearly identical rate to ReA in patients >6 months disease duration. RA patients are more likely to have a monoarthritis or oligoarthritis if they are seronegative. Patients with inflammatory arthritis are queried about the possibility of preceding sexually transmitted diseases and dysentery, but they are more likely to be asked about the latter. Keratoderma blennorrhagicum is rarely diagnosed with 283/377 (75.1%) of respondents stating that they diagnose this in 0–10% of ReA patients; yet palmoplantarpustular psoriasis with arthritis is diagnosed nearly as often as ReA with an average of 4.4 vs. 6.13 cases per year respectively. Radiographic and advanced imaging work-up performed for ReA is the same as other types of SpA. There does not appear to be an

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1647 The Diagnosis of Reactive Arthritis in the Real World and Factors That Might Contribute to Its Under/Misdiagnosis. Jenny Lin1, Anjali G. Shetty1 and John D. Carter1. 1Univ of South Florida, Tampa, FL, 2University of South Florida

Purpose: Epidemiological data indicate that reactive arthritis (ReA) is under/misdiagnosed. Most epidemiologic studies demonstrate that ReA is the second most prevalent type of spondyloarthritis (SpA) with one study suggesting it is the most common. Other data demonstrate that the incidence of ReA should rival that of rheumatoid arthritis. A breadth of clinical experience, however, suggests that rheumatoid arthritis (RA) and other types of SpA are diagnosed far more often than ReA. The purpose of this study was to see how often rheumatologists diagnose ReA and determine factors that might contribute to this under/misdiagnosis.

Methods: Outpatient attendees at an HIV Unit in the UK were surveyed over a 6-month period. A questionnaire enquiring about demography, regional and widespread pain, symptoms of musculoskeletal disease (e.g. pain, swelling, rashes, sicca symptoms, fracture) was administered by trained nurses.

Results: In total 1050 HIV-infected adults were approached from whom 859 (82%) useable replies were received. 90% of the respondents were male, mean age 42 years, mean duration HIV infection 6 years. 76% were current users of HAART. In total, 539 (63%) reported pain lasting >1 day in past month; 431 reported chronic musculoskeletal pain (>3 months). The mean duration of chronic pain was 4.5 years. Pain was significantly increased in older age groups (p=0.002). Women reported pain more frequently than men throughout the age range, had higher mean pain scores (p=0.022) and were significantly more likely to take painkillers most days (p<0.0001). HIV patients with pain were significantly more likely to be working (p<0.0001).

Conclusions: Musculoskeletal pain is common amongst HIV-infected adults, particularly women. As in uninfected patients, psychosocial factors are importantly associated but so are HIV factors including duration of infection and exposure to Protease Inhibitors. Musculoskeletal pain impacts significantly in this population causing disability and sickness absence and reduced quality of life.

Disclosure: K. Walker-Bone: None; E. Lawson: None; D. Churchill: None; Y. Gilleece: None; M. Fisher: None; C. Sabin: None.

Background: Hepatitis C virus (HCV) is associated with mixed cryoglobulinemia (MC) vasculitis and B-cell non-Hodgkin lymphoma (B-NHL), with a risk for B-NHL 35-fold higher in HCV-MC patients than the general population. However, no surrogate markers associated with the presence of B-NHL are available in HCV-MC vasculitis patients in clinical daily practice.

Methods: 104 HCV-MC vasculitis patients (including 20 with B-NHL) were included. The main clinical and biological markers associated with the presence of B-NHL were evaluated.

Results: Main epidemiological and virologic features were similar between patients with and without B-NHL. Patients with B-NHL compared to those without showed higher rates of poor general status (40 vs 16.7%; p=0.032), purpura (90 vs 66.7%; p=0.05), renal involvement (50 vs 28.6%; p=0.11), and cardiac involvement (15 vs 0%; p=0.0006). Patients with B-NHL showed higher median cryoglobulin level (1.44 vs 0.67 g/L; p=0.0084), and lower median C4 (0.025 vs 0.06 g/L; p=0.001) and gammaglobulin levels (5.3 vs 13.3 g/L; p<0.0001) than patients without B-NHL. Free light chain kappa/lambda ratio was more frequently abnormal in patients with than those without B-NHL (64.3 vs 33.3%; p=0.10). In multivariate analysis, only gammaglobulin level was associated with the presence of B-NHL [OR 0.77 (95% CI -0.44; -0.13); p=0.0006]. Using receiving operating characteristics curves, the optimal cut-off value for gammaglobulin level was 9 g/L, with sensitivity, specificity, positive and negative predictive values for the presence of B-NHL of 75, 82, 50 and 93%, respectively.

Conclusion: In HCV-MC patients, low gammaglobulin level (<9g/L) is strongly associated with the presence of B-NHL.
overreliance on the HLA-B27 antigen or the complete triad of symptoms to make the diagnosis of ReA.

**Conclusion:** Rheumatologists diagnose RA far more often than any type of SpA. RA, specifically, is the second least commonly diagnosed type of SpA in acute patients and the most infrequent diagnosis in those with chronic SpA. RA patients could be misdiagnosed as seronegative RA, PsA sine psoriasis, or palmoplantar pustulosis with arthritis.

Disclosure: J. Lin: None; A. G. Shetty: None; J. D. Carter: NIH, 2.

1648

The Infectious Risk of the Lower Respiratory Tract Is Increased in Patients with Rheumatic Diseases Treated by Biologic DMARDs, in Particular in Case of Pre-Existing Colonisation. Guillaume Geri, Sabrina Dadoun, Simon Paternotte, Maxime Dougados and Laure Gossec. Cochin Hospital, Paris, France

**Introduction:** Bronchiectasis is frequently associated (up to 30%) with chronic inflammatory rheumatic diseases and leads to repeated infectious events of the lower respiratory tract. Objective: To evaluate the risk of infectious events lower respiratory tract in patients treated with biologic disease modifying anti-rheumatic drugs for chronic inflammatory rheumatic diseases.

**Methods:** Monocenter, retrospective systematic study of all patients with a chronic inflammatory rheumatic disease and with concomitant bronchiectasis, seen at least twice in the department between 2000 and July 2009. An episode of infection was defined as an infection necessitating prescription of antibiotics for pulmonary purposes. Pre-existing bacteriologic colonization of the lower respiratory tract was collected at each time point. Univariate and multivariate analyses were performed to pick up predictive factors of the number of infectious respiratory events.

**Results:** 47 patients were included (mean age 64.1 ± 9.1 years, 33 (70.2%) women), with a mean follow-up per patient of 43.3 ± 3.1 years, i.e., 194 patient-years of follow-up totaling 98 treatment periods. Rheumatoid arthritis was the main rheumatic disease (80.1%). The mean number of infectious events was 0.7 ± 1.0 event per patient-year. The factors predicting infections were the type of treatment (biologic vs synthetic disease-modifying treatments), with an odds ratio of 8.7 (95% confidence interval: 1.7–43.4) and bronchial colonization by any germ (odds ratio 7.4, 2.0–26.8). Five patients had previous colonization (by: Pseudomonas aeruginosa (60%), Staphylococcus aureus (20%) or Haemophilus influenza (20%)).

**Conclusion:** Infectious risk was much higher in patients treated with biologic DMARDs than in those with non-biologic DMARDs. Bronchial colonisation was an important and independent risk factor, including if the colonization was by usual germs. Physicians should regularly monitor for colonization during biologics treatment.

Disclosure: G. Geri: None; S. Dadoun: None; S. Paternotte: None; M. Dougados: None; L. Gossec: None.

1649

Usefulness of Procalcitonin Measurement in Differentiating between Activity of Systemic Autoimmune Disease and Bacterial Infection. Olga Sleglova1, Helena Dejmekova1, Jana Uhnova1 and Jaromir Belacek1. 1Department of Biostatistics, 1. Medical Faculty, Charles University, Prague, Czech Republic, 2Institute of Clinical Biochemistry, Prague, Czech Republic, 3Institute of Rheumatology, Prague, Czech Republic

**Objective:** To evaluate the usefulness of testing for serum procalcitonin (PCT) in the differential diagnosis of infectious complications and acute disease exacerbation in patients with systemic autoimmune diseases.

**Methods:** 125 patients with systemic autoimmune diseases who were admitted to the inpatient department for suspected acute infection or acute exacerbation of their disease were prospectively tested for PCT concentrations. Concurrently, the levels of C-reactive protein (CRP), white blood cell counts (WBC), C3 and C4 complement components were established. The group of patients with infection comprised of two subgroups: with systemic and localised infection. Control group included 87 ambulatory patients with autoimmune diseases without any signs of deterioration.

**Results:** The serum PCT levels were significantly higher in patients with infections than in patients with an active systemic disease (PCT mean ± SEM 4.560 ± 1.513 vs. 0.254 ± 0.029, p < 0.001). The levels of CRP and white blood cell counts were also higher in patients with infections; the differences between C3 and C4 complement component values were not statistically significant. PCT serum concentrations were not elevated in any of the patients included in control group, and they were not affected by the current corticosteroids or immunosuppressive treatment. The sensitivity of the PCT test for an infectious complication (cut-off value = 0.5 mg/ml) was 52.4%, specificity 94.0% and diagnostic accuracy 80.2%. The area under ROC curve for PCT was 73.21%.

**Conclusion:** The increased serum PCT levels demonstrate good specificity for the evidence of infection in patients with systemic diseases. The sensitivity of PCT serum values is lower, yet it is therefore suitable to complement the assessment with another high-sensitivity indicator, such as CRP.

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ACR Poster Session C
Miscellaneous Rheumatic and Inflammatory Diseases II

Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1650

Adalimumab Therapy in 18 Patients with Severe Hidradenitis Suppurativa. Orlando Pompei Fernandez1, Ricardo Blanco Alonso2, Ignacio Vila2, Marcos Gonzalez Lopez3, Hector Fernandez Llaca3, M. Del Carmen Gonzalez-Vela4, Mario Agudo Bilbao5, Cristina Martinez Dubois6, Victor M. Martinez-Taboada6, M. Enriqueta Peiro Callizo6, Jose Luis Pea Salgado6, Alfonso Fernandez Corrales Martinez7 and Miguel Angel Gonzalez Gay Mantecon1. 1Department of Dermatology, Hospital Universitario Marques de Valdecilla, Santander, Cantabria, 2Department of Immunology, Hospital de Liencres, Santander, Cantabria, 3Department of Pathology, Hospital Universitario Marques de Valdecilla, 4Department of Rheumatology, Hospital Universitario Marques de Valdecilla, Santander, Cantabria, Spain, 5Department of Rheumatology, Hospital Universitario Marques de Valdecilla, Santander, Cantabria, Department of Rheumatology, Hospital Universitario Marques de Valdecilla, Santander, Spain

**Objective:** Several case-reports describing successful response to TNF-α antagonists in patients with hidradenitis suppurativa (HS), especially with infliximab and etanercept, have been reported. However, most of them had a short follow-up, showed limited efficacy and/or unacceptable side effects. Our aim was to evaluate the efficacy and safety of adalimumab therapy in 18 patients with refractory HS.

**Methods:** All of them fulfilled the following criteria: (1) HS resistant to standard medical treatments; (2) lack of response to at least 1 systemic immunomodulating drug; (3) multifocal active HS. In all cases Adalimumab therapy (40 mg subcutaneously every-other-week) was started. If HS was not adequately controlled, adalimumab dosage was increased up to 40 mg/week. If persistent clinical remission was achieved adalimumab therapy was gradually decreased to a minimum dose of 40 mg every 3 weeks. Quality of life was assessed using the Dermatology Life Quality Index (DLQI).

**Results:** 18 patients (9W:9M) (mean age, 45.17 ± 15.8 years) with severe HS (mean disease duration, 19.83 ± 17.3 years) were studied. In 6 patients HS was associated with other conditions; SLE (2 cases), rheumatoid arthritis (2 cases), idiopathic monoarthitis (1 case), and psoriasis (1 case). Five patients had initially been treated with infliximab and 1 with etanercept. All these 5 patients were switched to adalimumab due to inefficacy. At 1st month 13, 4 and 1 patient achieved high, moderate and none improvement in suppurative symptoms, respectively. The 6 patients with associated diseases also experienced improvement of these conditions. After a mean follow-up of 92 ± 88 weeks adalimumab efficacy was maintained. Adalimumab was well-tolerated. The most frequent side-effect was mild to moderate pain at injection site, and only 1 patient developed a severe facial skin reaction.

**Conclusions:** Adalimumab seems to be an effective and safe treatment in refractory HS. These promising results warrant the need of prospective controlled study.

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1651


Disclosure: None; None; None; None; None.
Objectives: Histiocytes are a heterogeneous group of diseases that can be classified into either Langerhans cell histiocytosis (LCH) or non-Langerhans cell histiocytosis. The latter includes Erdheim-Chester disease (ECD). This study investigated the clinical association between LCH and ECD.

Methods: This retrospective study included 16 patients (10 males, 6 females, median age 41 years) treated at twelve different university hospitals between 1970 and 2010. Inclusion criteria were biopsy-proven LCH in association with two or more diagnostic signs of ECD.

Results: LCH and ECD were diagnosed simultaneously in 4/16 cases, whereas LCH preceded ECD in 12/16 cases. The median time interval was 7.5 years (range 2–22) in these cases. Major organs involved in LCH were the bones (n=12), skin (n=8) and lungs (n=3). ECD mainly affected the large vessels (n=11), bones (n=11) and retroperitoneum (n=9). Non-biopsy proven central nervous system (n=6) and pituitary gland (n=6) involvement also occurred. No specific histologic features were identified in the 65 biopsies studied, including platelet growth factor receptor β expression. Between one and four lines of treatment were required in nine patients diagnosed with LCH. Nine patients were treated with interferon α-2a after the diagnosis of ECD was made. A partial improvement occurred in all assessable patients concerning ECD (n=5) and/or LCH (n=2). These 16 patients were compared with a monocentric cohort of 48 ECD patients; the only difference between the groups was a lower frequency of bone involvement in ECD patients with concomitant LCH (9/13 vs 47/48, p<0.003).

Conclusions: This study suggests that a pathogenic link exists between LCH and ECD. Although the mechanisms responsible for both diseases remain unknown, the present association could argue for transitions between monocytic/macrophage and dendritic cell lineages. The patient characteristics of LCH in association with ECD were similar to those in patients with LCH alone, whereas bone involvement may have been less common in ECD when it was in association with LCH. Clinicians should be aware of this association and should consider the possibility of ECD in patients with LCH, especially in the case of treatment resistance.

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1652

Blinded Multi-Rater Evaluation of Diagnosis and Candidate Classification Criteria for Polymyalgia Rheumatica (PMR). ACR-EULAR Study Group for Development of Classification Criteria for PMR. Eric L. Matteson1, Marco A. Cimmino2, Hilal Maradit-Kremers2, Carlo Salvarani3, Michael S. Maria Nuova4, Reggio Emilia, Italy, 5Department of Rheumatology, Marmara University Medical School, Istanbul, Turkey, 6Department of Rheumatology, Mayo Clinic, Scottsdale, AZ, 7Department of Internal Medicine, Schirmer3, Wolfgang A. Schmidt13, Maria C. Cid12, Christian Dejaco10, Pierre Duhaut19, Zuzua Schmid14, Annamaria Iagnocco19, Artur Bachta1, Carlotta Nannini11, Fabrizio Cantini19, Victor Martinez-Taboada19, Hannu Dreskeneli7, Sibel Z. Aydin4, Raashid Lugmani13, Colin Pease16, Mehrdad Malmazudzhad19, Kenneth Calamia4, Clement J. Michet5, Andy Abril4, Neil Gonter17, Cynthia S. Crowson1, Rickey Carter1 and Bhaskar Dasgupta11. 1Department of Health Sciences Research, Mayo Clinic, Rochester, MN, 2Department of Rheumatology, Mayo Clinic, Rochester, MN, 3Department of Internal Medicine and Rheumatology, WIM CSK MON, Warszawa, Poland, 4Department of Internal Medicine I, Medical University Innsbruck, Innsbruck, Austria, 5Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Jacksonville, FL, 6Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Rochester, MN, 7Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Scottsdale, AZ, 8Department of Internal Medicine, University of Genova, Genova, Italy, 9Department of Rheumatology, Arc spindle S. Maria Nuova, Reggio Emilia, Italy, 10Department of Rheumatology, Marnara University Medical School, Istanbul, Turkey, 11Department of Rheumatology, Medical University, Graz, Graz, Austria, 12Department of Rheumatology, South end University Hospital, Essex, United Kingdom, 13Department of Systemic Autoimmune Hospital Clinic Provincial, Barcelona, Spain, 14Immanuel Krankenhaus Berlin; Medical Center for Rheumatology Berlin-Buch Berlin, Berlin, Germany, 15National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, 16Suffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford University, Oxford, UK, 17Rheumatology and Rehabilitation Research Unit, University of Leeds, Leeds, UK, 18Rheumatology Associates of North Jersey, Teaneck, NJ, 19Rheumatology Unit, Clinica e Terapia Medica Department, Sapienza Università di Roma, Policlinico Umberto I, Rome, Italy, 20Rheumatology Unit, Ospedale Misericordia e Dolce, Prato, Italy, 21Rheumatology and Reumatology, University Hospital de Cantabria, Cantabria, Spain, 22Rheumatology and Reumatology, University Hospital de Cantabria, Santander, Spain

Methods: A total of 23 investigators were asked to blindly rate 10 PMR cases and 20 controls derived from a large prospective study of candidate criteria for PMR. Investigators were asked to review the clinical features, examination findings (ie restricted shoulder/hip movement, synovitis), inflammatory markers (ESR/CRP), serology for RF and anti-CCP, the steroid response (categorized as rapid, complete, sustained). Each criteria was rated on a 5-point scale reflecting the degree of confidence of a PMR diagnosis (1=strongly influences diagnosis of PMR to 5=strongly influences the diagnosis was not PMR). After all criteria were rated, investigators were asked to provide a diagnosis of PMR or other condition and indicated whether they would enter such a subject in a clinical trial for PMR. To assess the diagnostic accuracy of each candidate criteria, the mean rating across all raters was taken. This composite score was then used to determine the areas under the ROC curve (AUC), denoted as the c-statistic. Patients were categorized into 3 groups based on raters’ classification rates. Group 1: greater than 50% misclassified; Group 2: 20–50% misclassified; Group 3: less than 20% misclassified.

Results: Misclassification proportion was ≥20% in 10 patients. Factors that contributed to misclassification in Group 1 (n=3, 1 case, 2 controls) were normal ESR and/or CRP, poor or ill- sustained steroid response and RF positivity without peripheral synovitis. In Group 2 (n=7; 4 cases, 3 controls), misclassification was related to persistent synovitis, no complete/sustained steroid response, RF or CCP positivity and low baseline ESR and/or CRP. The AUC c-statistic suggested that gender, duration of symptoms, systemic symptoms such as weight loss, neck pain, limitation of movement and serum electrophoresis were unique among PMR cases from controls in discriminating cases from controls (c-statistic < 0.8 in all). Bilateral hip pain, morning stiffness, ESR and CRP levels (pre and especially post steroid), steroid response were good discriminators of cases from controls (c-statistic > 0.8 in all, table).

Conclusions: The verification exercise showed the stepped diagnostic process and most candidate criteria items performed well in discriminating PMR cases from controls. However, a significant proportion of cases/controls were difficult to classify. Questions such as whether PMR may not always adequately respond to steroids and whether polymyalgic RF positive disease without peripheral synovitis can occur need further investigation.

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Bone Events in Type 1 Gaucher Disease before and during Treatment. Jerome Stirnemann2, Djazia Heraoui1, Corine Vincent3, Olivier Fain2, Bruno Bone Events in Type 1 Gaucher Disease before and during Treatment. Jerome Stirnemann2, Djazia Heraoui1, Corine Vincent3, Olivier Fain2, Bruno Stirnemann2, Djazia Heraoui1, Corine Vincent3, Olivier Fain2, Bruno Stirnemann2, Djazia Heraoui1, Corine Vincent3, Olivier Fain2, Bruno Stirnemann2, Djazia Heraoui1, Corine Vincent3, Olivier Fain2, Bruno Stirnemann2, Djazia Heraoui1, Corine Vincent3, Olivier Fain2, Bruno

Introduction: Gaucher disease (GD), a rare autosomal-recessive disorder, is due to a deficiency of a lysosomal enzyme (glucocerebrosidase) and is characterized by liver and spleen enlargement and severe bone complications. Enzyme replacement therapy (ERT), available since 1991 (algulcerase then imiglucerase), is the reference treatment. Bone complications generally decline after 2 years of ERT. However, no data are available on main bone events (BE) (avascular necrosis, bone infarcts, pathologic fractures) occurring during treatment. Several biomarkers (chitotriosidase, ferritin, angiotsin
converting enzyme and tartrate-resistant acid phosphatase) are elevated during GD evolution.

The aim of this study was to retrospectively evaluate the frequency of bone events (BE) during 2 periods, diagnosis to first treatment and the latter to the closing date.

**Methods:** BE of 62 treated patients followed at Beaujon Hospital, Clichy, France, were described with Kaplan–Meier curves and linear-mixed models were used to evaluate their biomarker changes.

**Results:** BE occurred before treatment (54 events in 21 patients) but also during treatment (12 events in 10 patients), with respective frequencies (95% confidence interval) at 10 years of 22.4% (13.3–36.3) and 20.0% (10.2–36.9)

Figure 1 represents the first BE in the 62 Gaucher-disease between diagnosis and first treatment during the first 30 years of follow-up; Figure 2 represents the first BE in these 62 patients receiving ERT between first treatment and closing date during 15 years of follow-up.

Figure 1. Bone events (BE) in the 62 Gaucher-disease patients between diagnosis and first treatment during the first 30 years of follow-up.

![Image](https://example.com/image1)

Figure 2. Bone events (BE) in the 62 Gaucher-disease patients between first treatment and closing date during 15 years of follow-up.

![Image](https://example.com/image2)

The 54 BE before treatment onset were [n (%)] 28 (52%) avascular necroses, 7 (13%) bone infarcts, 12 (22%) pathologic fractures and 5 (9%) vertebral compression fractures. The 12 BE that occurred during treatment were [n (%)] 3 (25%) avascular necrosis, 4 (33%) bone infarcts with clinical bone crises and 5 (42%) pathologic fractures. The probability of suffering an BE by 10 years (95% CI) was 22.4% (13.3–36.3) before treatment and 20.0% (10.2–36.9) under ERT.

High ferritin levels and low platelet counts at treatment onset were significantly associated with BE during treatment (P=0.019 and P=0.039, respectively).

**Conclusions:** Bone complications could occur without but also under ERT (about 20% at 10 years). Platelet counts and ferritin levels at treatment onset at start of treatment seem to predict BE during treatment.

**Disclosure:** J. Stirnemann: Genzyme Corporation, 9; D. Heraoui: None; C. Vincent: None; O. Fain: None; B. Fantin: None; F. Mentre: None; N. Belmatoug: Shire, 9.

1654

**Development of Classification Criteria for Polymyalgia Rheumatica (PMR):** Results from an International, Prospective, Multi-Center Longitudinal Study ACR—EULAR Study Group for Development of Classification Criteria for PMR. Bhaskar Dasgupta 1, Marco A. Cimmino 2, Hilal Mandir-Kremenza 3, Wolfgang A. Schlamann 4, Michael Schirmacher 5, Peter Mandl 6, Artur Bachta 7, Marta Cid 8, Haner Direskeneli 9, Pierluigi Macchioni 10, Peter V. Balint 11, Christina Dufner 12, Christian Dejaco 13, Hanna Slott Jensen 14, Zsuzsa Schmidt 15, Gyula Póor 16, Annamaria Iagnocco 17, Victor Martinez-Toraboa 18, Elisabeth Nordborg 19, Carlotta Namini 20, Pierre Duhaute 21, Nicola Pitipone 22, Georgina Espigol-Frigole 23, Sibel Z. Aydin 24, Khalid Ahmed 25, Raastad Luqmani 26, Brian Hazzelman 27, Colin Pease 28, Richard J. Wakefield 29, Neil Conter 30, Ralph Marcar 31, Clement J. Michel 32, Mehrdad Maimanadeh 33, Andy Abril 34, Cynthia S. Crowson 35, and Eric L. Matteson 36. 3rd Rheumatology Department, National Institute of Rheumatology and Physiotherapy, Budapest, 2Center for Diagnosis Imaging, Hospital Clinic, Montserrat del Amo, Barcelona, Spain, 1Department of Health Sciences Research, Mayo Clinic, Rochester, MN, 10Department of Internal Medicine and Rheumatology, WIM CSK MON, Warszawa, Poland, 1Department of Internal Medicine I, Medical University Innsbruck, Innsbruck, Austria, 1Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Jacksonville, FL, 1Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Rochester, MN, 9Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Scottsdale, AZ, 1Department of Internal Medicine, General Hospital of the Elisabethinen, Klagenfurt, Austria, 1Department of Internal Medicine, University of Genova, Genova, Italy, 1Department of Rheumatology, Arcispedale S. Maria Nuova, Reggio Emilia, Italy, 1Department of Rheumatology, Cambridge University, Cambridge, UK, 1Department of Rheumatology, Mamman School, Istanbul, Turkey, 1Department of Rheumatology, Medical University, Graz, Graz, Austria, 1Department of Rheumatology, Princess Alexandra Hospital, Harlow, United Kingdom, 1Department of Rheumatology, Southend University Hospital, Essex, United Kingdom, 1Department of Systemic Autoimmune Hospital Clinic Provincial, Barcelona, Spain, 1Gentofte Hospital, Rheumatology Division, Hellerup, Denmark, 1Immanuel Krankenhaus Berlin: Medical Center for Rheumatology Berlin-Buch Berlin, Berlin, Germany, 2National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, 1Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford University, Oxford, UK, 1Rheumatology and Rehabilitation Research Unit, University of Leeds, Leeds, UK, 1Rheumatology Associates of North Jersey, Teenack, NJ, 1Rheumatology Unit, Clinica e Terapia Medica Department, Sapienza Universita di Roma, Policlinico Umberto I, Rome, Italy, 1Rheumatology Unit, Ospedale Misericordia e Dolce, Prato, Italy, 1Sahlgren University Hospital, Department of Rheumatology, Göteborg, Sweden, 2Service de Medecine Interne, Amiens, France, 2Service de Reumatologia, Hospital Universitario Marques de Valdecilla, Facultad de Medicina, Universidad de Cantabria, Santander, Spain

**Objective:** To develop ACR/EULAR classification criteria for PMR by assessing the performance of candidate criteria in a prospective longitudinal study of patients presenting with new onset bilateral shoulder pain.

**Methods:** Candidate inclusion/exclusion criteria for classification of PMR and assessment of steroid response were defined through a consensus conference and a wider Delphi survey. These criteria were then evaluated in a 6-month prospective study of patients ≥50 years of age including subjects with a diagnosis of new onset PMR and controls with newly diagnosed conditions mimicking PMR (i.e. new onset rheumatoid arthritis (RA), connective tissue diseases, shoulder conditions, fibromyalgia, osteoarthritis, etc.) presenting with. Recent onset of bilateral shoulder pain. All subjects were evaluated at baseline and week 26 resulting in reclassification of 9 PMR subjects and 4 controls. Data collection included clinical signs and symptoms, lab results, treatment details, ultrasound (US) evaluation, MHAQ, SF36, and pain rating. The c-statistic (i.e. area under receiver operating characteristic curve) was used to assess the ability of each criterion to discriminate controls from PMR subjects (based on diagnosis at week 26).

**Results:** Disease features present in >80% of the 92 PMR subjects were ≥2 weeks duration of symptoms, bilateral shoulder pain, morning stiffness ≥45 min duration and elevated c-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). 73% of PMR subjects presented with all 3 features, while only 29% of the 131 controls had all 3. Features that best discriminated RA from PMR were peripheral synovitis, abnormal rheumatoid factor (RF) or anti-citullinated protein antibody (ACPA) and hip pain/limited range of motion (c-statistic ≥ 0.7). Features best discriminating shoulder conditions from PMR were hip pain/limited range of motion, morning stiffness and elevated CRP/ESR (c-statistic ≥ 0.7). A scoring algorithm was developed and included morning stiffness ≥45 min (2 points), abnormal CRP/ESR (2 points), hip pain/limited range of motion (1 point),
abnormal RF or ACPA (-2 points), and other joint pain (-1 point). A score ≥ 3 had 76% sensitivity and 77% specificity for discriminating all controls from PMR. The specificity was higher (91%) for discriminating shoulder conditions from PMR and lower (71%) for discriminating RA from PMR. US findings were somewhat useful in discriminating PMR from shoulder conditions, but not from RA.

Conclusions: Patients ≥50 yrs old presenting with bilateral shoulder pain can be classified as having PMR in the presence of morning stiffness >45 min, elevated CRP/ESR and new hip pain in the absence of peripheral synovitis or positive RA serology.

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1655

Different Diagnostic Criteria in the Diagnosis of Polymyalgia Rheumatica.

Samy Zakout and John R. Kirwan. University of Bristol, Bristol, United Kingdom

Background: Patients with polymyalgia rheumatica (PMR) are often treated in the community. General practitioners (GPs) may refer for rheumatological opinion in situations of diagnostic uncertainty or disease relapse, but PMR often presents a diagnostic dilemma as the differential diagnosis is wide. Published diagnostic criteria are primarily used for research or to distinguish between rheumatic diseases. Their sensitivity and specificity in a routine referral clinic are not known.

Objective: To explore how PMR diagnostic criteria perform when applied to patients with or without PMR, diagnosed on clinical grounds in a routine hospital outpatient department.

Methods: A hospital-based PMR rapid access clinic was established in our rheumatology department in July 2007. The aim of this clinic is to see new patients with suspected PMR within 2 weeks of referral. The diagnosis of PMR was made on clinical grounds. Published criteria were consulted at the time of this analysis.

Diagnostic criteria used are those of Bird’s, Hunder, Healey and Hazleman. Sensitivity and specificity of each of the diagnostic criteria were then calculated. The results of applying two criteria consecutively were also explored.

Results: 182 patients were referred over 28 months. 171 patients attended their hospital appointments. Patients with relapse were excluded from the analysis of the diagnostic criteria which were applied to 94 patients with a diagnosis of new PMR and 66 with an alternative diagnosis. Only half of the patients had new PMR (figure 1).

The ability of different criteria to identify PMR and non-PMR patients as well as sensitivity and specificity are shown in figure 2.

If patients are first classified as PMR using Bird criteria and are then rejected if they fail the Hazleman or Healey criteria, both high sensitivity (95.7%) and high specificity (98.5%) are achieved.

Conclusion: There is a clear potential for improving diagnostic accuracy using a rapid access PMR clinic where the diagnosis can be made or ruled out in most patients in one or two visits. No criteria have both high sensitivity and high specificity for identifying clinically diagnosed PMR in a routine referral clinic but a combination of criteria applied consecutively may offer an advantage.

References:

Disclosure: S. Zakout: None; J. R. Kirwan: None.

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Diseases Associated with Positive NOD2/CARD15 Gene Mutations: Blau’s Syndrome Versus an Intermediate Subset of Blau’s Syndrome and Crohn’s Disease. Qingping Yao, Lan Zhou, Philip Cusumano and Le-Chu Su. 1The Department of Gastroenterology, Cleveland Clinic, Cleveland, OH, 2The Department of Internal Medicine, Cleveland Clinic, Cleveland, OH, 3The Department of Neurology, Cleveland Clinic, Cleveland, OH, 4The Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, OH

Purpose: Blau’s syndrome is an autosomal dominant autoinflammatory disease, characterized by dermatitis, arthritis, and uveitis. Since the report in 1985, the clinical features of the disease have chiefly derived from studies of the pediatric population. Fevers, eruptions, and internal organ involvement have been reported as well. However, sporadic adult onset Blau’s syndrome has rarely been seen in the medical literature. NOD2/CARD15 gene mutations have been associated with both Crohn’s disease and Blau’s syndrome. It is hypothesized that an intermediate subset of Blau’s syndrome and Crohn’s disease could be present but no similar reports have appeared. A small case series are presented herein to expand the clinical spectrum of the diseases.

Method: Four adult patients were referred to the Department of Rheumatology at the Cleveland Clinic between January 2009 and April 2010 for unclear diagnoses. These patients were also seen by internists and consulted by other specialists. The medical records of the patients were reviewed and relevant clinical and laboratory data was excerpted and analyzed. The blood specimens of the patients were tested for NOD2/CARD15 gene mutations.

Results: We report 4 patients with clinical features of autoinflammatory diseases and positive NOD2/CARD15 gene mutations. The mean age was 45.5 (age 28 to 55), disease duration was 3.1 (0.5 to 7 yrs), with 3 female and 1 male, and 3 cases were Caucasian with 1 Jewish. Three of them presented with rash, 1 had subacute spongiform dermatitis with superficial perivascular lymphoplasmacytic infiltrate, 1 had palisaded neutrophilic and granulomatous
dermatitis, and had pigmented purpuric dermatitis and mesenteric granulomatous lymphadenitis. Three patients developed low to high grade fevers, 3 developed polyarthritis, with 1 patient with a history of bilateral total hip replacements, and 3 had ocular symptoms with a case of documented iritis. Of the 3 patients with abdominal pain and diarrhea, 2 carried the diagnosis of Crohn’s disease with reports of colonicoscopic evidence of cryptitis, and 1 had normal endoscopy. One case was found to have small fiber neuropathy. Therapeutically, 3 patients were treated with oral glucocorticoids, with response, 1 was treated with TNF blockers (infliximab and adalimumab) with some response, and 1 responded well to anakinra.

**Conclusion:** Adult onset patients with positive NOD2/CARD15 gene mutations may present with atypical clinical features of Blau’s syndrome, and some features may be shared by Crohn’s disease. Given the shared phenotype and genotype by Crohn’s disease and Blau’s syndrome, a subset of these two diseases, intermediate syndrome, may be entertained.

**Disclosure:** Q. Yao: None; L. Zhou: None; P. Cusumano: None; L.-C. Su: None.

### 1657

**Efficacy and Safety of Thalidomide on Mucocutaneous Symptoms: A Systematic Review and Meta-Analysis.** Juan A. Martinez Lopez1, Estibaliz Loza1, Jesús Maese2, María Rosario Rodriguez Moreno2, María Piedad Rosario Lozano3 and Loreto Camaño1. 1Fundación Española Reumatol, Madrid, Spain, 2Hospital Virgen de las Nieves, Granada, Spain, 3Sociedad Española de Reumatología, Madrid, Spain

**Background:** Adverse events lead to the suspension of thalidomide’s commercial use in many states. However, it has immunomodulatory properties for which thalidomide is being used to treat oral and genital ulcers, and it’s not yet held for multiple myeloma. Our objective was to analyze the efficacy and safety of thalidomide in mucocutaneous symptoms. Methods: A systematic literature review on the efficacy and safety of thalidomide on mucocutaneous symptoms in patients with Behçet disease, Human Immunodeficiency Virus (HIV) infection, discoid chronic lupus erythematosus or angiodysplasia was performed. A broad search strategy was run at the following databases (incorporation to January 2010): Medline, Embase, Cochrane Library, IME, IBVCS, Lilacs, Scielo, and The US National Institutes of Health Ongoing Trials Register databases. The abstracts of the ACR (2005–2009) and EULAR (2005–2009) annual scientific meetings were also searched. Additionally, we inquired manufactures of thalidomide about any published or unpublished trials, and we hand-searched the references of the included studies, and all the publications or other information provided by the manufactures. The selection criteria included: 1) randomized controlled trials (RCT), with a Jadad score ≥3, comparing thalidomide with placebo or with an active comparator—no dosage, route or frequency limits were applied; 2) patients had to be 18 or older, and present mucocutaneous symptoms due to a diagnosis of Behçet disease, discoid chronic lupus erythematosus, Human Immunodeficiency Virus (HIV) infection, prurigo or intestinal angiodysplasia; and 3) studies had to assess the efficacy of thalidomide—changes in the number, size and time needed for complete healing of lesions.

**Methods:** A systematic review on the efficacy and safety of thalidomide was carried out. Twenty-five eligible studies were included. The patients’ characteristics were: 56 years (29–77). The median follow-up was 18 months (6–60). The treatment was started because of: CNS involvement (n=5), heart involvement (n=4), association of CNS & heart involvement (n=5), severe exophthalmos (n=1) and other (n=5). High doses of IFNα were started as first line treatment (n=12) or after a low dose course of IFNα (n=8), which was insufficient.

**Results:** High doses of IFNα were efficient in 17 cases: incomplete remission (n=14, 70%) & stabilization (n=3, 15%). However, two patients did not respond to this treatment (10%) and another patient could not be evaluated (early treatment interruption). For these three patients the following treatments were inefficient (death, n=3).

**Conclusions:** High doses of IFNα were well-tolerated (n=14, 70%). However, six patients displayed side effects: severe anemia (n=3), depression (n=2), eczema (n=1) requiring an interrupted treatment course (n=2) and an early definitive interruption (n=1). One responder patient died under IFNα after 24 months of follow-up.

**Disclosure:** B. Hervier: None; L. Arnaud: None; B. Wechsler: None; Z. Amoura: None; J. Haroche: None.

### 1658

**Efficacy of High Doses of Interferon-a-2a (IFNα) in Erdheim-Chester Disease.** Baptiste Hervier, Laurent Arnaud, Bertrand Wechsler, Zahir Amoura and Julien Haroche. CHU Pitié-Salpêtrière, APHP, Paris France, French Reference Center for Lupus & Autoimmune Diseases

**Introduction:** Erdheim-Chester disease (ECD) is a rare non-langerhans form of histiocytosis, characterized by a foamy histiocyte tissue infiltration. Treatments are not standardized. Efficacy of low doses of Interferon-a-2a (IFNα) have been suggested in small series but with variation depending of the organs involved. Indeed, central nervous system (CNS) and perivascular infiltration were reported to be resistant to low doses of IFNα.

**Our aim is to report our single-center experience about the use of high doses of IFNα in ECD.**

**Methods:** Twenty patients with biopsy-proven ECD have received high doses of IFNα (IFNα ≥ 18 MIU/week or PEG-IFNα ≥ 180 μg/week).

IFNα efficiency was systematically evaluated both clinically and morphologically (CT-scan or MRI for vessels & CNS, cardiac MRI, bone scintigraphy or MRL 18F-FDG-PET).

**Results:** Sixteen men & four women were included (median age at diagnosis: 56 years (29–77). The median follow-up was 18 months (6–60). Treatments were IFNα 18 millions MIU/week (n=4), IFNα 27 MIU/week (n=8), PEG-IFNα 180 μg/week (n=8).

The treatment was started because of: CNS involvement (n=5), heart involvement (n=4), association of CNS & heart involvement (n=5), severe exophthalmos (n=1) and other (n=5). High doses of IFNα were started as first line treatment (n=12) or after a low dose course of IFNα (n=8), which was insufficient.

High doses of IFNα were efficient in 17 cases: incomplete remission (n=14, 70%) & stabilization (n=3, 15%). However, two patients did not respond to this treatment (10%) and another patient could not be evaluated (early treatment interruption). For these three patients the following treatments were inefficient (death, n=3).

**Conclusions:** High doses of IFNα may control severe ECD (85% of the cases) and are well tolerated (70%).

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### 1659

**Endothelial Anti-Inflammatory Effect of alpha2 Adrenergic Agonists.** Ada Herrera1, M. Jesús Domínguez2, Teresa Arce2, A. Díaz2, Manuel Feria1 and Federico Díaz2. 1Medical School, Spain, 2Rheumatology Service, Hospital Universitario de Canarias, Spain

Our group has observed that a2 adrenergic agonists are able to modulate the inflammatory response in animal models of inflammation. However, the mechanisms thought which a2 adrenergic receptors participate in the regulation of the inflammatory response have not been clarified.

**Objectives:** To study the mechanisms responsible for the antiinflammatory action of a2 agonists.

**Methods:** Surface expression of L-selectin, CD11b, ICAM-1 and VCAM-1 were assessed by flow cytometry. The a2 agonists, yaxilane and UK14304, and the a2 antagonist, RX821002 were used in this work. The presence of the a2 adrenergic receptor subunits: A, B and C were detected by western blot. The three subunits of a2 adrenergic receptor. However, only the presence of receptors a2A, in PMN and a2B, in HUVEC were detected by flow chamber. The endothelial intercellular junction was analyzed by the cell distribution of VE-Cadherin and CD31 by confocal microscopy. Wilcoxon signed-rank test (p<0.05) was used to evaluate the statistical significance.

**Results:** Both neuropehils and HUVEC expressed mRNA transcripts of the three subunits of a2 adrenergic receptor. However, only the presence of receptors a2A, in PMN and a2B, in HUVEC were detected by western blot.

**Disclosure:** J. A. Martinez Lopez: None; E. Loza: None; J. Maese: None; M. R. Rodriguez Moreno: None; M. P. Rosario Lozano: None; L. Camaño: None.
Basal expression of L-selectin and CD11b, in neutrophils and VCAM-1, in HUVEC were not modified by the presence of a2 agonists. However, ICAM-1 basal expression in TNF-a-activated HUVEC showed a significative dose-dependent reduction in the presence of UK 14304. When HUVEC where activated in the presence of UK14304, the basal migration of human neutrophils through activated HUVEC in static conditions was decreased up to 40-8%. This effect was reverted by RX821002. When neutrophils were incubated with UK14304 no effect on cell migration was observed. The presence of the agonist a, UK 14304 did not interfere with the ability of PMN rolling on activated vascular endothelium, but it reduced the transmigration ability of neutrophils by 60% under shear stress conditions. The endothelial intercellular surface positive for VE-Cadherin and CD31 staining was increased in a 50% by UK14.308 respect to the basal. 

Conclusions: The a2 adrenergic agonists are able to modulate the inflammatory response at endothelium level. These compounds seem to increase a2 adrenergic cell-cell interaction resulting in a reduction of the neutrophil movement across the endothelial barrier. This finding supports the endothelium as a therapeutic target for developing new anti-inflammatory agents potentially useful for inflammatory rheumatic diseases.

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1660
Erdheim-Chester Disease: Prospective Follow-Up of a Single-Center Cohort of 48 Patients Reveals Improved Survival in Patients Treated with Interferon-alpha. Laurent Arnaud, Julien Haroche, Baptiste Hervier, Bertrand Wechsler, Nathalie Cостодоаt-Chalumeau, Patrice Cabouc, David Saadoun and Zahir Amoura. Department of Internal Medicine, Groupe Hospitalier Pitié-Salpêtrière, UPMC Univ Paris 6, AP-HP, 47–83 bd de l’Hôpital, Paris, France

Background: Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis, with poor prognosis and non-codified therapeutic management. This study was undertaken to evaluate the impact of treatment with interferon alpha on survival in ECD patients.

Methods: Forty-eight patients (36 men and 12 women; median age: 59 years; median follow-up duration: 40.8 months) with biopsy-proven ECD were included in a single-center prospective cohort study, between Nov. 1981 and Jan. 2010. Five patients were excluded because of an overlap with another form of histiocytosis. Independent predictors of survival were identified using Cox proportional hazard model.

Results: Nine patients (18.8%) died after a median follow-up of 28.1 months (13.0–155.7 months). Univariate analysis revealed no difference in survival between gender (p=0.78), patients with and without biological inflammation (p=0.64), and treatment with or without corticosteroids (p=0.54). Comparison of patients treated with (n=40) and without (n=3) interferon-alpha and/or Pegylated interferon-alpha for at least 3 months (median duration of treatment: 23.4 months [3.2–148.2 months]) revealed an almost significant improvement (p=0.059) in patients treated with interferon (5 patients were excluded from this analysis because they received interferon for ≤ 3 months). Multivariate survival analysis using Cox proportional hazard model revealed that treatment with interferon alpha and/or Pegylated interferon-alpha for at least 3 months was the sole independent predictor of survival in our cohort (Hazard Ratio, HR: 0.10, IC95%: 0.01–0.82; p=0.03).

Conclusions: Although definitive confirmation would require a randomized controlled trial, our result strongly suggests that interferon-alpha improves survival in patients with ECD.

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Expression of Type 1 Interferon Related Proteins and Plasmacytoid Dendritic Cells in the Lesional Skin of Morphea Patients. Mehran Ghoreishi1, Cristian Vera Kellet2 and Jan Peter Dutz1. 1Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada. 2Department of Dermatology, Pontificia Universidad Católica de Chile, Santiago, Vancouver, BC, Canada

Background: Morphea is a sclerosing condition limited to the skin and subcutaneous tissue. The co-existence of morphea with other autoimmune diseases, the elevated levels of rheumatoid factor and other auto-antibodies and the activated state of infiltrating inflammatory cells all suggest that morphea is an autoimmune disease. Type 1 interferons have been shown to promote autoimmune diseases involving the skin such as cutaneous lupus erythematosus, lichen planus and psoriasis. Type 1 interferons have recently been implicated in the pathogenesis of systemic sclerosis. The role of type 1 interferons in morphea is unknown. A type 1 interferon “signature” can be detected in tissues by the presence of interferon-α induced myxovirus A protein (MxA). Type 1 interferons are mainly produced by plasmacytoid dendritic cells (pDC), which normally do not home to the skin.

Purpose: To study the expression of type 1 interferon-induced MxA and the presence of pDCs in lesional and non-lesional skin of morphea patients.

Methods: Skin samples from 11 generalized morphea patients were collected. Paraffin embedded sections of lesional and non-lesional skin of morphea patients were stained with anti-human antibodies against MxA, CD123 and BDCA-2 and were compared with positive controls (lichen planus and other sclerosing conditions [keloid]).

Results: MxA expression was detected in keratinocytes, dermal vascularization and fibroblasts in the dermis and subcutis of morphea samples (10/11 samples). pDC can be identified by their expression of CD123 and BDCA-2. CD123 and BDCA-2 positive cells were abundant in lesions of morphea in superficial and deep dermis as well as in the subcutis (10/11). In contrast, non-lesional morphea samples (2/2) did not show detectable MxA and demonstrated few pDCs. Minimal expression of MxA was detectable in the vascular endothelium of keloid samples. There was no evidence of epidermal MxA expression in keloid.

Conclusions: To our knowledge this is the first study to show that type 1 interferons and pDCs are increased in skin lesions of morphea. This finding suggests that morphea shares a type 1 interferon dependent inflammatory pattern detected in lichenoid skin diseases such as cutaneous lupus erythematosus and lichen planus. These compounds seem to increase the endothelial cell-cell interaction resulting in a reduction of the infiltrate, which normally do not home to the skin.

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1662
Idiopathic Retroperitoneal Fibrosis: Clinical Findings in 185 Patients. Tanaz A. Kermani1, Cynthia S. Crowson2 and Harvinder S. Luthra1. 1Mayo Clinic, Rochester, MN, “Mayo Clinic

Purpose: To describe the clinical manifestations, laboratory, imaging findings and treatment of 185 patients with retroperitoneal fibrosis (RF) from a single tertiary-care center.

Methods: In this retrospective study all patients with newly diagnosed RF between 1/1/1996 and 12/31/2006 were included. Diagnosis was based on compatible imaging findings. RF associated with malignancy/radiation therapy and inflammatory abdominal aortic aneurysms were excluded. Medical records were reviewed and clinical information was abstracted using standardized case report forms. Descriptive statistics were used.

Results: We identified 185 patients; 113 (61%) men, 72 (39%) women with RF, mean age at diagnosis 57.6 (±11.81) years. Diagnosis was confirmed by biopsy in 140 cases (76%). The most common presenting symptoms were back pain (37.3%) and/or abdominal pain (36.8%). At diagnosis, 33 patients (17.8%) had exposure to a medication reported as associated with RF including beta-blockers (29 patients), methysergide (2 patients), ergotamine (1 patient), methyldopa (1 patient) and pergolide (1 patient). Five patients (3%) reported asbestos exposure, and 128 patients (69%) were ever-smokers. Preceding or subsequent autoimmune diseases were present in 26 patients (15%); inflammatory bowel disease was the most common (6 patients). Eleven patients (6%) had other fibrosing conditions including mediastinal fibrosis in 3 patients.

Mean hemoglobin at diagnosis was 12.6 (±1.74) g/dL. Baseline ESR and/or CRP was elevated in 62.3% (151 patients tested). Mean creatinine (Cr) at diagnosis was 2.43 (±2.78) mg/dL. New renal insufficiency was present in 74 patients (40%); median Cr 2.3 (range 1.2–13.0) mg/dL. ANA was positive in 6/118 (5%) patients tested while rheumatoid factor was positive in 8/89 (9%) subjects tested.

Baseline imaging studies in 182 patients showed a soft tissue mass which was periaortic in 115 cases (63%), periureteric in 10 patients (6%) and periaortie and periureteric in 39 patients (21%). Hydrenephrosis and renal atrophy were present in 98 patients (53%) and 15 patients (8%) respectively.

Fifteen patients (8%) were treated with surgery alone, 57 patients (31%)
with medications alone and 106 patients (57%) received medical and surgical treatment. Corticosteroids were started in 116 patients. Tamoxifen was the most commonly used medication (120 patients) followed by methotrexate (51 patients).

Follow-up was available for 151 patients (82%), and 104 (69%) had normal Cr at last visit. There were 13 deaths. Nine patients developed cancer after RF diagnosis. Median duration from diagnosis of RF to cancer was 50 (range 4–112) months.

**Conclusions:** Idiopathic RF is a chronic inflammatory disorder of unknown etiology. This is the largest single-center study of RF with follow-up available in 82% cases. Additionally, 70% of patients were evaluated by one of us. In contrast to prior studies, we found only a slightly increased male predominance. Also, ANA was positive in only 5% patients.

**Follow-up Available in 82% Cases.** Additionally, 70% of patients were close observation and appropriate management, outcomes such as worsening renal dysfunction or death due to renal failure were uncommon.

**Disclosure:** R. M. Smith: None; C. S. Crowson: None; H. S. Luthra: None.

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**1663**

**IL-1 Blockade for Schnitzler’s Syndrome.** Rona M. Smith1, Helen J. Lachmann1 and David R. W. Jayne2,3. Addenbrooke’s Hospital, Cambridge, United Kingdom; 2UK National Amyloidosis Centre, London

**Introduction:** Urticarial vasculitis is a clinicopathological entity consisting of urticaria and a leucocytoclastic vasculitis on skin biopsy. It can be localised to the skin, or form part of a systemic condition, and tends to have a benign, self-limiting prognosis. A few patients, however, pursue a refractory course. Schnitzler’s Syndrome is a rare case of refractory urticarial vasculitis, characterised by the presence of a monoclonal IgM component.

**Methods:** We have a cohort of six patients with Schnitzler’s Syndrome. Detailed here are the complex courses of two patients (Patient A aged 60 and Patient B aged 35) who were diagnosed with the condition in 2009, selected to highlight the refractory nature of this condition, and the importance of making this rare diagnosis. They both presented with biopsy proven urticarial vasculitis to our clinic in 2005. Both had associated systemic symptoms, namely episodic fevers, sweats, arthralgias and significant weight loss in Patient A, and recurrent abdominal pain and distal limb paraesthesiae in Patient B.

**Investigations:** Both had marked elevations of ESR (>80mm/hr) and CRP; a persistent neutrophilia and an IgM paraprotein. Patient A had axillary lymphadenopathy and mesenteric lymphadenopathy on CT scan, but a lymph node biopsy revealed reactive cells only. Patient B had a bone marrow biopsy, which showed no evidence of lymphoproliferative disease. Both had normal PET scans, and angiograms which suggested the presence of renal and superior mesenteric artery aneurysms respectively.

**Treatments:** Both initially had good responses to high dose (>40mg/day) prednisolone, but relapsed on steroid taper. In light of the angiogram findings, both were treated as possible cases of polyarteritis nodosa with intravenous cyclophosphamide, but with only partial clinical effect. Multiple other immunosuppressive drugs including anti-TNF agents, calcineurin inhibitors, antimitobalites, rituximab, alemtuzumab and thalidomide were trialled over the years, but with minimal success.

**Diagnosis:** In view of the challenging nature of the cases, a second opinion was sought. A diagnosis of Schnitzler’s syndrome was made, and therapy with anakinra (Kineret, Biovitrum AB) (an IL-1 receptor antagonist) was commenced. Both patients’ clinical conditions dramatically improved within 48 hours of therapy, and their marked acute phase response completely subsided. Prednisolone doses are currently below 5mg/day—the lowest since presentation. After eight months therapy, both are tolerating anakinra well, and the transient neutropenia that occurred in Patient B has resolved.

**Conclusion:** IL-1 blockade should be considered as a potential treatment for cases of refractory urticarial vasculitis, and has been shown to be particularly effective in Schnitzler’s syndrome. Although extremely rare, with only about 100 reported cases in the literature, clinicians should be aware of the diagnosis of Schnitzler’s Syndrome, as it responds exquisitely well to therapy, transforming patients’ quality of life.

**Disclosure:** R. M. Smith: None; H. J. Lachmann: EU framework 7, 2, Novartis Pharmaceuticals Corporation, 5; D. R. W. Jayne: Merck Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 2, Roche, 2, 5, UCB, Inc., 5.

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**1664**

**IL-18 Binding Protein (IL-18BP) Dramatically Improves Liver Histological Lesions in an Animal Model of Macrophage Activation Syndrome (MAS).** Laura Chiossone1, Sandra Audonnet2, Karin Mazodier3, Marc Dalod4, Catherine Farnarier, Daniela Novick, Charles A. Dinarello5, Eric Vivier1 and Gilles Kaplanski6. 1Assistance Publique-Hôpitaux de Marseille, Marseille, France; 2Assistance Publique-Hôpitaux de Marseille, Marseille, France; 3CIML, Marseille, France; 4University of Colorado Health Science, Denver, CO, 5Weizmann Institute of Science, Rehovot, Israel

MAS is a severe complication of various infectious, inflammatory or neoplastic diseases. Severely impaired lymphocyte cytotoxicity and large excess of inflammatory cytokines, notably IFN-g, participate in its pathogenesis. In patients with MAS, concentrations of IL-18, a strong inducer of IFN-g, are largely increased, but not those of its natural inhibitor IL-18BP, favoring a severe IL-18/IL-18BP imbalance.

**Aim:** We asked whether IL-18BP may be an efficient treatment in an animal model of MAS consisting in perforin-KO mice infected with murine cytomegalovirus (MCMV), which has been previously reported to be IFN-g and TNF-a dependent.

**Results:** 7–12 days after infection, 100% KO mice died whereas all wild type (WT) mice survived. Injection of 10 microgram/mice/day IL-18BP starting at day 0 or day 4 post-infection did not improve KO mice survival, nor did anti-TNF-a treatment.

Liver showed very severe histological lesions in MCMV-infected KO mice which was almost completely abrogated by IL-18 BP, in a comparable way to anti-TNF-a treatment. Combination of both did not further improve the lesions.

Serum cytokine concentrations at day 6 post-infection showed very high concentrations of IFN-g (38 +/− 5 vs 1 +/− 1 ng/ml in WT) and TNF-a (13.8 +/− 2 vs 0.5 ng/ml in WT) in MCMV-infected KO mice, which were 50% reduced by IL-18BP treatment (20 +/− 10 ng/ml for IFN-g and 7.5 +/− 2 ng/ml for TNF-a, respectively). Combination of IL-18BP and anti-TNF-a treatment 100% inhibited IFN-G levels.

**Conclusions:** In this model of MAS which has been shown to be entirely IFN-g and TNF-a-mediated, IL-18BP appears to be as efficient as anti-TNF-a treatment in preventing liver damage through inhibition of both IFN-g and TNF-a, confirming the role of IL-18 in the pathogenesis of this disease.

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**1665**

Is Pamidronate Useful as Very Effective Therapeutic Intervention in Midtarsal Arthropathy? Mani Nallasivan1 and Tim Tait. 1Diana Princess of Wales Hospital Grimsby, Grimsby, Lincolnshire, United Kingdom; 2Diana Princess of Wales Hospital, Grimsby, Northern Lincolnshire and Goole Hospital NHS Trust, Hull, Yorkshire, United Kingdom

**Background:** Midtarsal Arthropathy is a recognised cause of Foot pain. It usually presents as pain with or without swelling of the midfoot, extending from the ankle to the metatarsal head and, rarely, to the forefoot. Midtarsal arthropathy is used in the UK for the management of Paget’s disease, tumour related hypercalcaemia, NSAID refractory AS, refractory SAPHO syndrome and in Charcot’s arthropathy. Bisphosphonates are known to inhibit osteoclasts, improve bone density measurements and prevent fractures, suppress pro-inflammatory cytokines such as interleukin (IL-1), TNF-a and IL-6, and show anti-inflammatory properties in arthritis.

**Objectives:** We have used Pamidronate for midtarsal arthropathy for the past five years and have previously reported our experience with six patients. We hereby report our further experience in 20 patients, which demonstrates good clinical resolution.

**Methods:** Retrospective case records of patients who had pamidronate infusion for midtarsal arthropathy were reviewed from 2005 until 2009. 20 patients had treatment of which 5 were male. Mean age was 64.6 years (37–79). All patients had pain in the midfoot and no history of trauma. Seven patients were having treatment for Rheumatoid arthritis but no active disease. Their Plain x-rays of the foot didn’t show erosive arthropathy or fracture. These patients had isotope bone scan which showed increased uptake in the...
midtarsal region. All had intravenous pamidronate infusion (60mgs) and some of them had 3–4 infusions over 2-year period.

Results: All patients reported significant improvement of pain after one infusion and became asymptomatic with five needing a second infusion. Median time interval before second infusion was 7 months. Follow up has been done for a maximum of three years.

Conclusion: Pamidronate is very effective in treating midtarsal arthropathy. This warrants further study. Our five years experience further explores our understanding on the versatile benefits of this bisphosphonate.

References:

Disclosure: M. Nallasivan: None; T. Tait: None.

1666
Nonalcoholic Steatohepatitis as a Complication of Collagen Disease. Kae Takagi, Yasushi Kawaguchi, Yuko Ota, Akiko Tochimoto, Chikako Fukazawa, Takahisa Gono, Yasuhiro Katsumata, Masako Hara and Hisashi Yamanaka. Tokyo Women’s Medical University, Tokyo, Japan

Background: Nonalcoholic fatty liver disease (NAFLD) is a silent disease, and is one of the most common causes of elevated liver enzymes. Nonalcoholic steatohepatitis (NASH) is distinguished from NAFLD by a liver biopsy revealing fatty change in the liver along with inflammation and damage. The development of NASH in collagen disease has been rarely reported. Our aims are to elucidate the frequency, clinical features, pathogenesis, and treatment of NASH associated with collagen disease.

Methods: A retrospective survey of collagen disease patients who were hospitalized and initially screened for NASH by identifying abnormalities in serum liver enzymes, and findings of severe fatty liver changes on abdominal computed tomography (CT) and ultrasound. NASH was confirmed by liver biopsy, and the clinical features of these patients before and after treatment were evaluated.

Results: Five patients were identified with NASH (3 patients with systemic lupus erythematosus and 2 patients with Weber-Christian disease). Mean age was 33.8 ± 15.6 years old. Three of five patients showed increased BMI and high HOMA-R. All patients showed the increase levels of serum aminotransferase (AST/ALT). Before diagnosis of NASH, 4 patients had been treated by small amount of corticosteroid against collagen diseases. Fatty change was revealed by CT and/or US in all patients. Three cases having ALT level higher than 150IU/L, showed more prominent fatty change in CT grading. The Liver/spleen (L/S) ratio measured by CT were observed around 0.8 higher than 0.4. Pathological examination using liver biopsy specimens showed NASI in all patients. Based on Brunt’s classification, pathological score of two patients were Grade 2 and Stage 2, whereas the score were 1 in other three patients.

Table 1. Clinical characteristic

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</tr>
<tr>
<td>AST (IU/l)</td>
<td>218</td>
<td>82</td>
<td>161</td>
<td>51</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
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<td>262</td>
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<td>LDH (IU/l)</td>
<td>958</td>
<td>594</td>
<td>720</td>
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<tr>
<td>gGT (IU/l)</td>
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<tr>
<td>ALP (IU/l)</td>
<td>308</td>
<td>234</td>
<td>159</td>
<td>146</td>
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<td>Tchol (mg/dl)</td>
<td>223</td>
<td>256</td>
<td>172</td>
<td>175</td>
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<tr>
<td>HDL (mg/dl)</td>
<td>19</td>
<td>51</td>
<td>12</td>
<td>NE</td>
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<tr>
<td>LDL (mg/dl)</td>
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<td>79</td>
<td>NE</td>
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<td>TG (mg/dl)</td>
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<td>104</td>
<td>405</td>
<td>220</td>
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<tr>
<td>Adiponectin (μg/ml)</td>
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<td>29.4</td>
<td>6.5</td>
<td>5</td>
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<tr>
<td>Leptin (μg/ml)</td>
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<td>24.4</td>
<td>14.7</td>
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<td>Insulin (μU/ml)</td>
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<td>72.5</td>
<td>175</td>
<td>85</td>
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<td>BS (mg/dl)</td>
<td>62</td>
<td>181</td>
<td>108</td>
<td>120</td>
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<tr>
<td>HbA1C (%)</td>
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<td>6.5</td>
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<td>NE</td>
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<tr>
<td>TNFα (pg/ml)</td>
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<td>3</td>
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<tr>
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<td>0.41</td>
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<td>NE</td>
</tr>
<tr>
<td>US (grade)</td>
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<td>1</td>
</tr>
<tr>
<td>Pathology (grade)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

In order to suppress the collagen disease activity, all patients were treated by higher amount of corticosteroid (prednisolone 20–40 mg/day) with and without immunosuppressive drugs such as cyclophosphamide, ciclosporin or mizoribine. In all patients, serum AST/ALT levels were remarkably turned to be normal in parallel with improvement of collagen disease activity within six months (AST: 117.4 ± 31.2 vs.26.0 ± 3.7, p < 0.05; ALT: 171.8 ± 29.1 vs.48.4 ± 16.7, p < 0.01). Furthermore, fatty liver change determined by CT and US were diminished. The average of L/S ratio before and after treatment was changed from 0.49 ± 0.26 to 1.22 ± 0.17 with statistically significant difference (p < 0.01). Although HOMA-R was improved in three cases, there were no significant changes in other risk factors including body weight and BMI before and after treatment.

Conclusions: NASH is relatively rare in collagen disease patients. Corticosteroid treatment with or without immunosuppressive drugs was effective for collagen disease as well as for NASH, suggesting that autoimmune factors are involved in the development of NASH associated with collagen disease.

Disclosure: K. Takagi: None; Y. Kawaguchi: None; Y. Ota: None; A. Tochimoto: None; C. Fukazawa: None; T. Gono: None; Y. Katsumata: None; M. Hara: None; H. Yamanaka: None.

1667
Prevalence of Atherosclerotic Risk Factors and the Metabolic Syndrome in Patients with Chronic Inflammatory Arthritis. Chi Chiu Mo1,2, Tin Chai Ko1,2, Ling Yin Ho1,2, Ka Lung Yu1,2, Pak To Chan1,2 and Chi Hung To1,2. Chinese University Hong Kong, Tuen Mun Hospital

Objectives: To evaluate the prevalence of atherosclerotic risk factors and the metabolic syndrome (MetS) in patients with rheumatoid arthritis(RA), ankylosing spondylitis(AS) and psoriatic arthritis(PSA).

Patients and Methods: Consecutive patients with RA, AS or PSA who attended our out-patient arthritis clinics between July and November 2009 were recruited for a study of the prevalence of atherosclerotic risk factors and the MetS, defined according to the 2009 Joint Statements using the Asian criteria for central obesity. Participants were screened for the presence of vascular risk factors. Waist and hip circumferences, body weight, body height and blood pressure were measured; and fasting blood was taken for glucose
and lipid levels. Medications being received by patients were also reviewed. The MetS was present when ≥3 of the following components were present: (1) Increased waist circumference to ≥90 cm in men or ≥80 cm in women; (2) Elevated blood pressure to ≥130/85 mmHg or requiring drug therapy; (3) Elevated serum triglyceride level to ≥1.7 mmol/L; (4) Reduced serum high density lipoprotein (HDL)-cholesterol to ≤1.0 mmol/L in men and ≤1.3 mmol/L in women; and (5) Elevated fasting glucose level to ≥5.6 mmol/L. The prevalence of vascular risk factors and MetS was compared among different inflammatory arthritis; and with age and gender-matched healthy controls in a 1:2 matching.

**Results:** 844 patients were studied (651 RA, 94 AS and 99 PSA; 72% women; age 51.7±12.6 years). The mean disease duration for patients with RA, AS and PSA was 5.1±5.4, 4.9±4.8, and 3.3±3.0 years, respectively. The prevalence of MetS was significantly higher in PSA (40%) than RA (20%) or AS (13%) (p<0.001). The odds ratios for the MetS compared to age- and gender-matched controls were 0.95 (0.75–1.19; p=0.68), 0.80 (0.39–1.65; p=0.60) and 3.27 (1.90–5.64; p<0.001), respectively, for RA, AS and PSA. Patients with PSA had significantly higher prevalence of impaired fasting glucose (33%; p<0.001), low HDL-cholesterol (34%; p<0.001), high triglyceride (22%; p=0.01) and central obesity (66%; p=0.009). In a logistic regression model, the odds ratio for the MetS in PSA was 2.64 (1.58–4.41) (p=0.001) compared to RA or AS. The adjusted odds ratios for central obesity, impaired fasting glucose, hypertriglyceridemia and low HDL-cholesterol were also significantly higher in patients with PSA. The prevalence of the MetS in all the three diseases studies was not significantly higher those patients with established (>2 years’ duration) than early disease (<2 years’ duration).

**Conclusions:** Patients with PSA, but not RA or AS, have a significantly higher prevalence of the MetS syndrome compared to the general population. Among the three diseases studied, PSA has the highest prevalence of the MetS and is associated with highest cardiovascular risk.

**Disclosure:** C. C. Mok: None; T. C. Ko: None; L. Y. Ho: None; K. L. Yu: None; P. T. Chan: None; C. H. YLie: None.

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**1668 Renal Dysfunction Is Associated with Increased Mortality in Adults with Macrophage Activation Syndrome.** Bita Shakoory1, W. Winn Chatham2, Graciela S. Alarcon1 and Randy Q. Cron3. 1Oakland, CA, 2Children’s Hospital of Alabama, Birmingham, AL, 3Univ of Alabama-Birmingham, Birmingham, AL

**Background:** Macrophage activation syndrome (MAS) remains a potentially fatal cause of multiorgan dysfunction (MOD) in adults, with an estimated mortality of 50%. This longitudinal study reports the short and long term outcomes in hospitalized adults with MAS due to various triggering factors from a single academic institution.

**Methods:** Patients diagnosed with MAS from April ’08 to May ’10 at a regional tertiary institution were identified from rheumatology consultation notes. A retrospective chart review was completed for all patients to identify the following: (1) Age, gender, ethnicity, the presence of two or more triggering factors, or the length of HS or CC stay between survivors and non-survivors (Table).

**Conclusions:** In adults, a diagnosis of MAS often results in prolonged and complicated hospital course with high mortality and should be investigated and treated in patients with early manifestations of MOD to prevent critical care interventions and associated morbidity and mortality.

**Disclosure:** B. Shakoory: None; W. W. Chatham: None; G. S. Alarcon: None; R. Q. Cron: None.

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**1669 Retrospective Analysis of Relapsing Polychondritis in the US Department of Defense Population.** Stephanie D. Mathew, Daniel F. Battafarano and Michael J. Morris. San Antonio Military Medical Consortium, Fort Sam Houston, TX

**Purpose:** Relapsing polychondritis (RPC) is a rare autoimmune disorder with an prevalence of 3.5 cases/million. RPC affects cartilaginous structures including the ear, nose, larynx, trachea, bronchi, joints, skin, heart valves and the aorta. Cardiopulmonary and vascular involvement can be life threatening. The objective of this study was to characterize the clinical features of RPC within our patient population and determine the utility of echocardiography, imaging studies and spirometry.

**Methods:** We performed a retrospective EMR chart review of all patients diagnosed with RPC within the Department of Defense between January 2004 and December 2009 from a beneficiary base of 9.5 million. Patients were included if they met McAdams diagnostic criteria for RPC or if they had recurrent chondritis with deformity plus vestibular dysfunction, ocular inflammation or inflammatory arthritis. Demographic information, along with disease duration, organ involvement, treatment history, imaging studies, echocardiography and pulmonary function tests (PFTs) were recorded.

**Results:** Thirty patients met McAdams diagnostic criteria and an additional 13 met our criteria as outlined above. Twenty-three of the patients (53%) were female; with a mean age of 51. The average age at diagnosis was 43 and disease duration of 7.1 years. Auricular chondritis was present in 38 (88%), inflammatory arthritis in 26 (60%), inflammatory eye disease in 23 (57%), pulmonary involvement in 16 (37%) sensorineural hearing loss in 16 (37%), nasal chondritis in 15 (35%) and keratoconjunctivitis in 7 (16%). Two patients had vasculitis and one presented with renal insufficiency and proteinuria. Twenty-one (49%) patients had concomitant connective tissue disease. Methylxate was used in 18 (42%), corticosteroids in 13 (21%), NSAIDs in 10 (23%), other DMARDs in 8 (18%), biologics in 7 (16%), and dapsone in 4 (9%). Twenty (47%) required multiple medications. Thirty (70%) patients had PFTs, 18 with reviewable flow volume loops. Flow volume loop abnormalities were observed in 6 of 18 (33%); all had upper respiratory symptoms. Imaging with chest CT was performed in 27 (63%) and in 5 of 6 patients with flow volume loop abnormalities. Pulmonary CT abnormalities in 13 of the 27 patients (48%) revealed parenchymal lung disease (9), tracheal abnormalities (4) and enlargement of the great vessels (2). Echocardiography was abnormal in 12 of 25 (48%) with valvular (aortic and mitral) regurgitation or stenosis (8), aortic root dilatation (3), and pericarditis (1).

**Conclusions:** Our RPC patients were similar to previous studies in incidence, demographic data and organ involvement. The diagnosis of RPC was primarily based on physical examination and symptom driven diagnostic testing. There was no observable pattern for monitoring progression of the disease.
Rituximab Therapy Is an Effective Approach in Treatment of IgG4-Related Systemic Disease. Arezou Khosroshahi1, Donald B. Bloch2, Vikram Deshpande1 and John H. Stone1. 1Massachusetts General Hospital, Sudbury, MA, 2Massachusetts General Hospital, Newton, MA, 3Massachusetts General Hospital, Boston, MA, and 4Massachusetts General Hospital

Patients with IgG4-related systemic disease (IgG4-RSD) often have strikingly elevated serum concentrations of IgG4 and typically share certain histopathological features regardless of the affected organ(s). The histopathological features of IgG4-RSD include diffuse lymphoplasmacytic infiltration, extensive deposition of IgG4-positive plasma cells, obliterative phlebitis, and tissue fibrosis. Patients with IgG4-RSD frequently require prolonged treatment with glucocorticoids and are often unable to taper these medications. Traditional disease-modifying antirheumatic drugs (DMARDs) are generally ineffective.

Objective: We assessed the clinical and serologic responses of patients with steroid- and DMARD-refractory IgG4-RSD to B lymphocyte depletion therapy.

Methods: Eight patients with IgG4-RSD were treated with rituximab (1000 mg times two). Clinical improvement was assessed by monitoring patients’ ability to taper/discontinue prednisone and DMARDs, and by measuring the serum concentrations of B lymphocytes, immunoglobulins, and IgG subclasses before and after rituximab therapy.

Results: The patients’ organ involvement included the pancreas, biliary tree, aorta, salivary glands (submandibular and parotid), eyes, lacrimal glands, lymph nodes, and retroperitoneum. Five patients had elevated serum IgG4 levels at baseline, with a mean concentration of 1547 mg/dl (normal: 8–140 mg/dl). Among these patients, the serum IgG4 concentrations declined by a mean of 65% within 2 months of rituximab administration. The decline in serum IgG4 concentrations was substantially steeper than that of the autoantibody concentrations in immune-mediated conditions in which rituximab is known to be effective, such as in rheumatoid arthritis. In addition, the reduction in IgG4-subclass levels was specific for IgG4.

All eight patients demonstrated striking clinical improvement within 1 month of the initiation of rituximab therapy. Tapering or discontinuation of both prednisone and DMARDs was achieved in all eight patients. Four patients had minor disease recurrences approximately six months after treatment, characterized by symptom recurrence or serum IgG4 elevations. These disease flares correlated with B cell cell in the peripheral blood. All four disease flares responded to second courses of rituximab. All eight patients are now off glucocorticoids and DMARDs entirely.

Conclusion: Treatment with rituximab led to prompt clinical and serologic improvement in refractory IgG4-RSD. The swift improvement of IgG4-RSD suggests that rituximab achieves its effects in IgG4-RSD by depleting the pool of B lymphocytes that replenish short-lived IgG4-secreting plasma cells, offering insights into the mechanism of action of this treatment approach.

Disclosure: A. Khosroshahi: None; D. B. Bloch: None; V. Deshpande: None; J. H. Stone: None.

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ACR Poster Session C
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Pediatric Rheumatic Diseases II
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1672
Anti-CADM-140/MDA5 Antibody Predicts Complication of Interstitial Lung Disease in Japanese Cases of Juvenile Dermatomyositis. Ichiro Kobayashi1, Yuka Okura1, Yasuhiro Yamazaki1, Shimichiro Takezaki1, Masafumi Yamada1, Masataka Kuwana1 and Tadashi Ariga1. 1Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan, 2Keto University School of Med, Tokyo, Japan

Background: Interstitial lung disease (ILD) is a life-threatening complication of both adult dermatomyositis (DM) and juvenile dermatomyositis (JDM). We have indicated that most of ILD develops at an early stage or at the time of relapse of JDM and is rapidly or moderately progressive (Kobayashi I, et al. Rheumatology 2003). Among ILD associated with DM, rapidly progressive interstitial pneumonia preferentially develops in clinically amyopathic DM (CADM) particularly in Asian races (Sontheimer RD. Arch Dermatol. 2010). Recently, anti-CADM-140/MDA5 antibody has been identified as a disease marker for ILD associated with adult CADM. In the present study, we examined the autoantibody in JDM complicated with or without ILD.

Materials and Methods: Thirteen cases of JDM including 6 cases with ILD were involved in this study. The diagnosis of JDM was made according to the diagnostic criteria by Bohan and Peters. Sera were obtained from the patients at the time of diagnosis of JDM and stored at −20°C until use. Anti-CADM-140/MDA5 antibody was measured by enzyme-linked immunosorbent assay using purified recombinant MDA-5 as an antigen as previously described (Sato S, et al., Arthritis Rheum 2009). The antibody units

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Rituximab Therapy Is an Effective Approach in Treatment of IgG4-Related Systemic Disease. Arezou Khosroshahi1, Donald B. Bloch2, Vikram Deshpande1 and John H. Stone1. 1Massachusetts General Hospital, Sudbury, MA, 2Massachusetts General Hospital, Newton, MA, 3Massachusetts General Hospital, Boston, MA, and 4Massachusetts General Hospital

Patients with IgG4-related systemic disease (IgG4-RSD) often have strikingly elevated serum concentrations of IgG4 and typically share certain histopathological features regardless of the affected organ(s). The histopathological features of IgG4-RSD include diffuse lymphoplasmacytic infiltration,
were calculated from the optical density at 450 nm results (normal range: <8.0 U).

**Results:** Although case 1 died of respiratory failure, the other four previously reported cases showed recovery following the commencement of cyclosporine A in combination with methylprednisolone pulse therapy and oral high-dose prednisolone, and are drug-free for at least four years without relapse of either JDM or ILD. In an additional case, ILD developed approximately two months after the diagnosis of JDM which was associated with elevation of a serum KL-6 level (2.376 U/ml). This case is now successfully treated with cyclosporine A in combination with prednisolone following methylprednisolone pulse therapy. All the cases with ILD showed clinically apparent myositis associated with elevated levels of serum muscle derived enzymes during the course. Among the seven cases without ILD, two cases lacked both clinical myopathy and elevation of muscle-derived enzymes.

Five of the six cases with ILD were positive for the anti-CADM-140/MDA5 antibody (9.5–902.3 U). Three cases with rapidly progressive ILD showed extremely high levels of the antibody (357.6–902.3 U). In two cases in which ILD developed more than 1 month after the diagnosis of JDM, the antibody was detected before the development of ILD. All of the 7 cases without ILD were negative for the antibody (1.3–3.5 U).

**Conclusion:** Anti-c-CDM140/MDA-5 autoantibody is not only a disease marker for ILD associated with JDM but also a predictive marker for the complication regardless of the muscle weakness. Our results suggest that common or similar mechanisms are involved in the development of ILD in both adult CADM and JDM.

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**1673**


Bayolor College of Medicine, Houston, TX, 2BC Children’s Hospital, Vancouver, BC, 3University of Louisville SOM, Med Ctr, Akron, OH, 4Children’s Hospital of Michigan, Huntington Woods, MI, 5Children’s Hospital of Pittsburgh, Pittsburgh, PA, 6Children’s Hospital LA, M60, Los Angeles, CA, 7Children’s Hospital Boston, Boston, MA, 8Children’s Hospital Medical Center, Cincinnati, OH, 9Children’s Hospital of NY, New York, NY, 10Childrens Med Ctr Med Schl GA, Augusta, GA, 11Childrens Hosp NW Univ, Chicago, IL, 12Corner Children’s Hospital, Chicago, IL, 13Duke University Medical Center, Durham, NC, 14IWK Health Centre, Halifax, NS, Canada, 15Joseph M Sanzari Children’s Hospital, Short Hills, NJ, 16Legacy Emanuel Children’s Hosp, Portland, OR, 17Mattel Children’s UCLA, Los Angeles, CA, 18Mayo Clinic Rochester, Rochester, MN, 19Montreal Children’s Hospital, Montreal, QC, Canada, 20Nationwide Childrens Hosp, Columbus, OH, 21OU Health Science Center, Oklahoma City, OK, 22Pediatrics, U. of Washington, Seattle, WA, 23Phoenix Children’s Hospital, Phoenix, AZ, 24Rainbow Babies and Children’s Hospital, Beachwood, OH, 25Riley Children’s Hospital, Nashville, TN, 26Robert Wood Johnson Medical School, Metuchen, NJ, 27Schneider Children’s Hospital, New Hyde Park, NY, 28St Louis Children’s Hosp, St Louis, MO, 29Stamford Univ Schl of Med, Stanford, CA, 30The Hospital for Sick Children, Toronto, ON, Canada, 31TSScottish Rite Hosp, Dallas, TX, 32UCSF, San Francisco, CA, 33University of Florida, Orlando, FL, 34University of Louisville SOM, Louisville, KY, 35University of Utah, Salt Lake City, UT, 36University of Vermont, Morrisville, VT

**Background:** Descriptions of MPA are limited by the inability of definitions (e.g. Chapel Hill Consensus Conference) to uniquely define patients and exclude another related vasculitis. Classification algorithms have been used to distinguish patients with related vasculitides by applying in a hierarchical sequence, from the most specific to the least specific, diagnostic criteria for each patient in a population.

**Aims:** To describe interval to diagnosis, presenting features and initial treatment for children uniquely classified as having MPA in ARCHiVe.

**Methods:** Time-of-diagnosis data on children with AAV diagnosed since 2004 by expert rheumatologists (MD-diagnosis) has been contributed to ARCHiVe from 37 US/Canadian sites. A pediatric modification of the European Medicines Agency (EMEA) for AAV and polyarteritis nodosa (PAN) classification algorithm was applied by computation to this cohort to uniquely classify patients with MPA. Descriptive data on these MPA patients were then extracted. Sensitivity and specificity of the algorithm classification of MPA were tested (MD-diagnosis reference standard). The recently validated EULAR/PRINTO/PRES pediatric Wegener’s granulomatosis (WG) criteria were applied to children with MPA to determine if there was diagnostic overlap.

**Results:** Of the 155 patients, 18 (12%) had MPA, 113 WG, 2 Churg-Strauss syndrome, 1 PAN, and 21 were unclassifiable. For the 18 children with MPA (67% female, 56% Caucasian) the median age at diagnosis was 13 (range 3–16) y, and the median interval from disease onset to diagnosis was 23 (range 2–50) mo. Presenting features are shown in Table and included: renal 95%, constitutional 89%, pulmonary 28% and sinus-upper respiratory 17%. Anti-MPO and anti-PR3 were present in 61% and 28% of patients respectively. Necrotizing pauci-immune glomerulonephritis was reported in 20% of 15 kidney biopsies. In 14 (78%) patients corticosteroids (CS) and cyclophosphamide (6 PO, 7 IV, 1 PO+IV) were the initial treatment; plasmapheresis (n=3), rituximab (n=2), and methotrexate (n=1) were also used in these 14. The remainder (n=4) received CS alone. Sensitivity and specificity of the EMEA algorithm for MPA were 22% and 92%. No MPA patients were concurrently classified by EULAR/PRINTO/PRES as WG.

**Table.** Frequency of presenting clinical features in pediatric patients with microscopic polyangiitis in the ARCHiVe cohort (n = 155)

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Affected patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSTITUTIONAL/GENERAL</td>
<td>58 (89)</td>
</tr>
<tr>
<td>Malaise</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Fever</td>
<td>7 (39)</td>
</tr>
<tr>
<td>RENAL</td>
<td></td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>13 (72)</td>
</tr>
<tr>
<td>Hematuria with proteinuria</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Hematuria with red blood cell casts</td>
<td>3 (6)</td>
</tr>
<tr>
<td>PULMONARY</td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Hemoptysis/alveolar hemorrhage</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Respiratory failure requiring ventilation</td>
<td>1 (6)</td>
</tr>
<tr>
<td>EAR, NOSE, THROAT</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>1 (6)</td>
</tr>
<tr>
<td>ANCA SEROLOGY</td>
<td></td>
</tr>
<tr>
<td>Immunofluorescence for cANCA/pANCA, positive</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Anti-MPO positive ELISA</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Anti-PR3 positive ELISA</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Negative ELISA</td>
<td>1 (6)</td>
</tr>
<tr>
<td>ELISA not done/not available</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

**Conclusion:** Pediatric patients uniquely classified with MPA had predominantly renal and constitutional manifestations and a positive ANCA. A minority had upper or lower respiratory tract disease. Initial therapy varied considerably. The protracted interval from symptom onset to diagnosis suggests MPA is a poorly recognized entity in children.

Disclosure: D. A. Cabral: None; A. G. Uribe: None; L. S. Abramson: None; M. D. Adams: None; S. M. Benseler: None; S. S. C. Campillo: None; P. Chira: None; B. A. Eberhard: None; K. C. Ede: None; A. O. Hersh: None; G. C. Higgins: None; A. Huber: None; L. F. Imundo: None; R. S. Jerath: None; S. Kim: None; D. J. Kingsbury: None; M. S. Klein-Gitelman: None; S. C. Li: None; D. J. Lovell: None; T. G. Mason: None; D. K. McCurdy: None; R. F. Medica: None; L. N. Moorthy: None; E. Muscal: None; K. Nanda: None; L. A. Nasses: None; K. M. O’Neill: None; E. C. Rabjohnich: None; A. O. Reiff: None; M. A. Rosenkrantz: None; K. N. Schilkner: None; A. M. Stevens: None; M. B. Toth: None; L. Wagner-Weiner: None; D. M. Wahezi: None; A. J. White: None; A. L. Woodward: None; A. S. Zelt: None; ARCHiVe Investigators of CARRA: None.
Clinical and Serological Factors Associated with Lupus Serositis in Children: Results from the 1000 Canadian Faces Multicohort Study. America G. Uribe, Jaime Guzman, Ross E. Petty, Lori B. Tucker, Laura Musyl, Earl D. Silverman, Gaele Cheveddie, Adam Huber, Suzanne E. Ramsey, and Christine A. Peschken. 1BC Childrens Hospital, 2BC Childrens Hospital, 3IWK Health Centre, Halifax, NS, Canada, 4IWK Health Ctr, Halifax, NS, Canada, 5Montreal Children’s Hospital, 6Univ of Manitoba, Winnipeg, MB, Canada

Background: Studies in adult patients with systemic lupus erythematosus (SLE) report serositis prevalence of 30–60%, and more common in patients with younger age SLE onset. In childhood-onset SLE, serositis prevalence ranges from 5%-60%; positive anti-Ro, La, Sm and Jo-1 antibodies are related factors. The association of ethnicity with serositis has not been explored in pediatric patients.

Aim: To determine the prevalence of serositis in a multiethnic Canadian cohort of children and adolescents with SLE, and sociodemographic, clinical and serological features associated with serositis.

Methods: Eligible patients in the 1000 Canadian Faces of Lupus cohort (a prospective multicentre observational study of incident and prevalent cases of childhood and adolescents with SLE), were those diagnosed with definite SLE at age ≤18 yrs (fulfilling >4 ACR criteria), regardless of disease duration. Selected baseline data included: socio-demographic information (age at diagnosis, ethnicity, gender); clinical characteristics [accrued SLE criteria, disease activity (SLEDAI, physician and patient global assessment on a 10-cm visual analogue scale), organ damage (SLICC damage index)]; and serology results (ANA, anti-dsDNA, -Sm, -RNP, -La, -Ro, IgG and IgM anticardiolipin antibodies, lupus anticoagulant). Serositis was defined as the presence of pleuritis, pericarditis and/or peritonitis as per the ACR criteria or SLEDAI definitions. Factors related to serositis were examined using univariable descriptive statistics, followed by multivariable analyses.

Results: 193 children were studied (154 female). Mean (SD) age at diagnosis was 12.3 (3.3) yrs. Mean (SD) total disease duration at study entry was 2.5 (2.6) yrs. Serositis was present in 35 (18.1%) children, 18 patients had pleuritis only, 5 had pericarditis, and 12 had both. Serositis was present at diagnosis in 48.6%. Sociodemographic and clinical characteristics associated with serositis are presented in Table. In multivariable analyses, Aboriginal (OR=18.5, 95% CI 1.8–188.6) and African Canadian (OR=5.7, 95% CI 2.1–15.7) ethnicity and accrual of 5 or more ACR criteria at study recruitment (OR=12.7, 95% CI 4.0–40.9) were positively associated with serositis; conversely, mucocutaneous involvement (OR=0.1, 95% CI 0.1–0.5) and positive result for any anti-phospholipid antibody (OR=0.3, 95% CI 0.1–0.8) were negatively associated with serositis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serositis No (n = 158)</th>
<th>Serositis Yes (n = 35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>80.3</td>
<td>91.4</td>
<td>0.118</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>12.4</td>
<td>11.6</td>
<td>0.213</td>
</tr>
<tr>
<td>African</td>
<td>25.0</td>
<td>75.0</td>
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</tr>
<tr>
<td>Asian</td>
<td>52.7</td>
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<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>81.7</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>87.0</td>
<td>13.0</td>
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<tr>
<td>Middle Eastern</td>
<td>100.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous involvement, %</td>
<td>72.5</td>
<td>45.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Arthritis, %</td>
<td>62.1</td>
<td>65.7</td>
<td>0.689</td>
</tr>
<tr>
<td>Neurologic involvement-T0, %</td>
<td>12.0</td>
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<tr>
<td>Renal involvement, %</td>
<td>38.6</td>
<td>40.0</td>
<td>0.875</td>
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<tr>
<td>Hematologic involvement, %</td>
<td>68.6</td>
<td>82.9</td>
<td>0.093</td>
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<tr>
<td>Fulfilled ⩾ 5 ACR criteria, %</td>
<td>28.1</td>
<td>62.9</td>
<td>&lt;0.001</td>
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<tr>
<td>SLEDAI score, mean (SD)</td>
<td>3.4 (4.4)</td>
<td>3.5 (3.8)</td>
<td>0.846</td>
</tr>
<tr>
<td>Physician global assessment, cm, mean (SD)</td>
<td>1.7</td>
<td>1.5</td>
<td>0.776</td>
</tr>
<tr>
<td>SLICC/ACR Damage Index, mean (SD)</td>
<td>0.3 (0.8)</td>
<td>0.4 (0.8)</td>
<td>0.660</td>
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</table>

<table>
<thead>
<tr>
<th>Autoantibodies, positive, %</th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Antinuclear</td>
<td>99.3</td>
<td>100.0</td>
<td>1.000</td>
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<tr>
<td>Anti-dsDNA</td>
<td>83.5</td>
<td>77.1</td>
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<tr>
<td>Anti-Sm</td>
<td>37.8</td>
<td>46.9</td>
<td>0.348</td>
</tr>
<tr>
<td>Any anti-phospholipid</td>
<td>60.0</td>
<td>40.6</td>
<td>0.080</td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>38.1</td>
<td>36.1</td>
<td>0.853</td>
</tr>
<tr>
<td>Anti-La</td>
<td>16.0</td>
<td>30.6</td>
<td>0.057</td>
</tr>
<tr>
<td>Anti-Ro</td>
<td>33.7</td>
<td>41.7</td>
<td>0.443</td>
</tr>
</tbody>
</table>

Conclusion: We found a lower than expected prevalence of serositis in this multiethnic Canadian pediatric lupus cohort. Serositis was more prevalent among Aboriginal and African Canadian patients. Positive anti-phospholipid antibodies or mucocutaneous involvement were less frequent among patients with serositis.

Disclosure: A. G. Uribe: None; J. Guzman: None; R. E. Petty: None; L. B. Tucker: None; L. Musyl: None; E. D. Silverman: None; G. Cheveddie: None; A. Huber: None; S. E. Ramsey: None; C. A. Peschken: None.

Cogan Syndrome: A Rare but Severe Vasculitis in Pediatric Age. Ilaria Pagnini, Maria Elisabetta Zannin, Marianna Sari, Gabriele Simonini, Rolando Cimaz and Francesco Zulian. 1Anna Meyer Children’s Hospital, Florence, Italy, 2Department of Medical and Surgical Specialties, Section of Otolaryngology, University of Padua, Italy, 3Department of Pediatrics, University of Padua, Italy, 4Department of Medical and Surgical Specialties, Section of Otolaryngology, University of Padua, Italy, 5Universita Di Padova, Padova, Italy, 6University of Firenze, Firenze, Italy

Background: Cogan syndrome (CS) is a vasculitis characterized by systemic, ocular and vestibulolabyrinthary symptoms. Only a few pediatric patients have been reported in literature so far and few information is available as far as disease course and outcome.

Methods and Materials: We describe three caucasian children (1M, 2F) with CS and compare them with the data of the literature. We reviewed the clinical records of patients with defined diagnosis of CS followed at two Pediatric Rheumatology Institutions and patients with pediatric-onset CS from a database search in Medline. Data collected included clinical features, ocular and ENT evaluations at onset and during the disease course, laboratory variables, treatment and outcome.

Summary of the Results: During the period 1990–2009, three patients with definite diagnosis of CS have been followed in our units and 20 more patients have been reported in 16 publications. In the whole cohort of 23 cases, the mean age at onset was 11.6 years (range 4–18) and the F:M ratio was 2:1. Half of the patients had systemic symptoms at onset such as fever (30%), or musculoskeletal pain (26%), 78% had ocular symptoms such as red eye, often with photophobia (57%), as presenting signs of interstitial keratitis (26%), episcleritis (9%) or uveitis (4%), conjunctivitis (17%), and visual loss (4%). Oudiovestibular symptoms were present in 74% of the patients, most of them (65%) had sensory neural hearing loss (SNHL) and 35% vestibular dysfunction such as vertigo, vomiting or ataxia. Cardiac involvement, mainly aortic insufficiency, and skin rash were found in 22% and 13% of the patients, respectively. Treatment consisted in corticosteroids (83%), methotrexate (30%), cyclophosphamide or MMF (4%). After a mean 4 year follow-up, 35% of the patients were in complete remission with no organ damage, the remaining reported residual deafness or SNHL (35%), irreversible cardiac complications (13%), vestibular dysfunction (4%), ocular damage (4%), or chronic hepatitis (4%). Only one patient died one year after disease onset for subarachnoid hemorrhage.

Conclusions: Cogan syndrome is a rare, severe and, probably, under diagnosed vasculitis of the pediatric age. In older children with systemic symptoms, red eye, vertigo and/or hearing loss CS should be always considered in the differential diagnosis since a prompt treatment may prevent irreversible organ damage.

Disclosure: I. Pagnini: None; M. E. Zannin: None; M. Sari: None; G. Simonini: None; R. Cimaz: None; F. Zulian: None.

Decreased Vitamin D Levels in Children and Adolescents with Systemic Lupus Erythematosus. Octavio Augusto Bedin Peracchi, Regina Viviane Munekata, Maria Teresa Ramos Ascensão Terreri, Roseli Oselka Sacardo Sari, Marise Lazaretti and Maria Odete Esteves Hilario. 1Universidade Federal de São Paulo, São Paulo, Brazil, 2Universidade Federal de São Paulo, Brazil

Background: The vitamin D deficiency has been related to the development of autoimmune diseases. There are only a few studies in the literature evaluating the nutritional status related to vitamin D in pediatric patients with rheumatic diseases.

Objectives: To evaluate the levels of 25(OH)D3 and to correlate them with disease activity, use of medications (chloroquine and glucocorticoids),
calcium and vitamin D intake, bone mineral density and parathormone (PTH) levels.

Methods: Determination of 25(OH)D3 and PTH was performed during the spring in 30 children and adolescents with Systemic Lupus Erythematosus according to the Hochberg classification criteria (1997). The patients with or without disease activity, with any clinical manifestation, in use of any medication, and with minimal disease follow-up of 6 months were compared to 30 healthy individuals age and gender matched. Controls (n=50) were not on any medication and had no calcium metabolism impairment. Vitamin D normal levels were considered between 20–32 ng/mL. Bone mineral densitometry was also performed in the patients.

Results: We found significant different levels of 25(OH)D3 between patients and controls (mean 18.79 ng/mL and 27.18 ng/mL respectively—p<0.01). Fifteen (50%) patients and 6 (20%) controls had low levels of 25(OH)D3 (< 20 ng/mL). There was no association between PTH and vitamin D levels in patients and controls (mean of 35.86 pg/mL and 31.26 pg/mL respectively; p=0.268). Only one patient with low level of vitamin D presented with hyperparathyroidism. We found no association between disease activity when studied SLEDAI > 1 or SLEDAI = 4 and low levels of vitamin D. Eleven (37%) patients were taking vitamin D supplementation and 5 of them (17%) had low levels of vitamin D. Seven patients (23%) presented a bone mineral density under –2.0 SD and mean levels of 25(OH)D3 of 14.70 ng/mL (9.61–19.88) with no significant association between them (p=0.456).

Conclusion: Children and adolescents with lupus may present lower serum levels of vitamin D, however with no association with disease activity, higher levels of PTH and bone mineral density alterations.

References:


Disclosure: O. A. B. Peracchi; None; R. V. Munekata; None; M. T. R. A. Terreri; None; R. O. S. Sarini; None; M. Lazaretti; None; M. O. E. Hilaria; None.

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Does Atorvastatin Reduce Progression of Carotid Intimal Media Thickness (CIMT) in Childhood SLE? Results from the Atherosclerosis Prevention in Pediatric Lupus (APPLE) Trial: A Multicenter, Randomized, Double-Blind Placebo-Controlled Study

Background: SLE patients are at markedly elevated risk for premature cardiovascular events. Given lifelong exposure to increased atherogenic potential, children and adolescents with SLE are ideal targets for prevention. Statins reduce cardiovascular morbidity and mortality in the general population, but their efficacy in preventing atherosclerosis progression in pediatric SLE is unknown.

Methods: Children and adolescents with SLE, aged 10–21y, from 21 CARRA sites were randomized to receive atorvastatin (10–20 mg based on weight) or placebo and followed for 3 years. All subjects met 1997 ACR criteria for SLE. Exclusion criteria included nephrotic syndrome, cholesterol >350, creatinine >2.5, CPK >15X, liver function >2X normal, Background therapy included hydroxychloroquine, aspirin, folate, risk factor counseling, the AHA Therapeutic Lifestyle Changes diet, and routine SLE management. The primary endpoint was rate of progression of mean common CIMT, a surrogate marker for atherosclerosis, using a standardized ultrasound protocol read by a central core. Secondary endpoints included progression of mean maximal CIMT and lipid levels. The total sample size of 220 provided 83–98% power to detect a 0.0045mm/y difference in mean-common CIMT progression rates between groups with an overall 0.05 type I error for several scenarios based on the estimated parameters for mean-mean common CIMT correlation of 0.6 between time points and SD (0.038–0.047mm), dropout (11.6–23.1%), and compliance rate (71–84%).

Results: A total of 221 subjects were randomized between 9/03–11/06 with 183 (83%) of them completing the trial. See table for baseline characteristics.

There were 138 SAEs with 7 considered related to study drug. Rhabdomyolysis was not reported. Database was locked on 6/21/10 and the final results of primary and secondary endpoints will be presented.

Conclusions: APPLE is an RCT designed to assess the safety and efficacy of atorvastatin in preventing progression of CIMT in pediatric SLE. APPLE represents the first RCT in pediatric SLE, the first CARRA clinical trial, and the longest study of statins in a pediatric cohort. Preliminary data demonstrate successful enrollment of the target population and completion of trial within study parameters. The data quality indicates that study results will determine whether use of statins in children and adolescents with SLE decreases CIMT progression and the risk of premature atherosclerosis.

Disclosure: L. E. Schanberg; Pfizer Inc; 2, 5; C. I. Sandborg; Pfizer Inc; 2, H. X. Barnhart; None; S. P. Ardon; None; E. Yow; None; G. W. Evans; Pfizer Inc; 5; K. L. Mieszalski; None; N. T. Ilowite; None; A. Eberhard; None; L. F. Imundo; None; K. Kimura; None; E. Von Scheven; None; E. Silverman; None; S. L. Bowyer; None; L. Munaro; None; N. G. Singer; Pfizer Inc; 9; D. D. Sherry; None; D. McCurdy; None; M. Klein-Gittelman; None; C. A. Wallace; None; R. Silver; None; L. Wagner-Weiner; None; G. C. Higgins; None; H. I. Brunner; None; L. Jung; None; J. B. Soep; None; A. Reed; None; G. Teegler; None; APPLE Investigators; None.

1678

Environmental Factors Preceding Illness Onset Differ in Phenotypes of the Juvenile Idiopathic Inflammatory Myopathies

Background: JIIMs are rare diseases with substantial variability in clinical presentation and disease course. Environmental factors have been postulated to play a role in disease onset in JIIMs, but the specific factors associated with the onset of JIIM in each clinical phenotype remain largely unknown. The aim of the present study was to determine the specific environmental factors that may precede the onset of JIIMs in select clinical phenotypes.

Methods: Using a case-control design, questions regarding documented events preceding illness onset were asked in 2X normal.

Disclosure:Lisa G. Rider; None; L. Wu; None; Guhnara Mamyrova; None; David D. Sherry; None; Maria D. Perez; None; Carol A. Wallace; None; Lisa F. Imundo; None; Catherine A. Bingham; None; Lawrence S. Zemel; None; Carol B. Lindsay; None; Rafael F. Rivas-Chacon; None; Patience H. White; None; Robert Rennebohm; 3; Michael Henrickson; 3; Ira N. Targoff; 3; Frederick W. Miller; 3; and Childhood Myositis Heterogeneity Study Group; 3; Connecticut Childrens Med Ctr, Hartford, CT, 2 National Institute of Environmental Health Sciences, NIH, Kennesington, MD, 3 NIH, NIH, Washington, DC, 4 NEIHS, NIH, Oklahoma City, OK, 5 NEIHS, NIH, New York, NY, 6 NEIHS, NIH, Miami, FL, 7 NEIHS, NIH, Kansas City, KS, 8 NEIHS, NIH, Houston, TX, 9 NEIHS, NIH, Cincinnati, OH, 10 NEIHS, NIH, Bethesda, MD, 11 NieHS, NIH, The Children’s Hospital of Philadelphia, Philadelphia, PA, 12 University of Washington and Seattle Childrens Hospital, Seattle, WA.

Purpose: We examined whether certain environmental factors are temporally associated with the onset of juvenile idiopathic inflammatory myopathies (JIIM) and differ among age, ethnic, disease course and autoantibody phenotypes.

Method: Physicians completed questionnaires regarding documented infections, medications, immunizations, and an open-ended question about other noted exposures within six months before illness onset for 285 patients with probable or definite JIIM. Medical records were available and reviewed
for 81% of cases to confirm the exposure. Myositis autoantibodies were identified by validated immunoprecipitation methods.

**Results:** Sixty percent of JIIM patients had a reported exposure within six months before illness onset. Most patients (62%) had one recorded exposure, 26% had two, and 12% had 3–5 exposures. Patients older than the median age at diagnosis, those with a longer delay to diagnosis and those with anti-signal recognition particle autoantibody had a higher frequency of documented exposures (OR 3.4–31). Infections were the most common exposure and represented 44% of the total number of reported exposures, with respiratory infections being the most common (66%). Pharyngitis was the most frequent specific infection (22%) and was more frequent in older patients (OR 2.7). Noninfectious exposures included medications (18%), immunizations (11%), stressful life events (11%), unusual sun exposure (7%), and others including, chemicals, animal contact, weight training, and dietary supplement use (<5% each). Exposures varied by age at diagnosis, delay to diagnosis, race, disease course, and the presence of certain myositis autoantibodies. Children younger than the median age at diagnosis, those with ≤4 months delay to diagnosis, or with a polyyclic illness course were more likely to have an infection within six months of diagnosis (OR 1.8–4.3), whereas older children had a higher frequency of stressful life events prior to illness onset (OR 3.5). Caucasian patients and those without a myositis autoantibody had a higher frequency of infections in the six months prior to illness onset (OR 2.7–3.9). Older children were more likely to have two drug exposures prior to illness onset (OR 18.9), and 36% of these were potentially myopathic or photosensitizing agents.

**Conclusion:** While infections were the most common exposure temporally associated with the onset of JIIM, supporting prior findings, many other exposures, including non-infectious agents, were also documented within six months before disease onset. The JIIM may be related to multiple exposures, and these exposures appear to vary among illness phenotypes. This exploratory study has identified 3–4 number of environmental exposures, which are potential risk factors and suggests that controlled investigations of independent populations be performed to confirm and expand upon these findings.

**Disclosure:** L. G. Rider: None; L. Wu: None; G. Mamynova: None; D. D. Sherry: None; M. D. Anderson: None; C. A. Wallace: None; L. F. Imundt: None; C. A. Bingham: None; L. S. Zemel: None; C. B. Lindsey: None; R. F. Rivas-Chacon: None; P. H. White: None; R. Rennebohm: None; M. Henrikson: None; L. N. Targoff: None; F. W. Miller: None; Childhood Myositis Heterogeneity Study Grou None.

**1679**

**High Prevalence of Inflammatory Myositis in Patients with Pediatric Systemic Lupus Erythematosus in a Southeastern US State.** Jessica L. Record⁴, Timothy Beukelman² and Randy Q. Cron¹. ¹Children’s Hospital of Alabama, Birmingham, AL, ²University of Alabama-Birmingham, Birmingham, AL, ³University of Alabama-Birmingham, Birmingham, AL.

**Background:** Inflammatory myositis has traditionally been recognized as a feature in 5–11% of adult systemic lupus erythematosus (SLE) patients. The aims of this study were to determine the prevalence of myositis in a cohort of pediatric SLE patients from a single center in a southeastern US state, to compare this rate with the reported prevalence in the medical literature, and to evaluate clinical factors for possible association with myositis.

**Methods:** Records of 55 patients with the diagnosis of SLE who had been evaluated by the Division of Pediatric Rheumatology and satisfied at least 4 out of 11 ACR criteria for the classification of SLE were identified at an academic children’s hospital in the southeastern US. Their electronic medical records were reviewed and information was collected regarding general demographics, complement levels, muscle enzymes, musculoskeletal exam, and clinical and serological manifestations. For the purpose of this study, patients were defined as having inflammatory myositis if they satisfied one of the following categories: 1) Proximal muscle weakness on physical exam with evidence of muscle edema on MRI (T2 or STIR image) of the lower extremity; 2) Proximal muscle weakness on physical exam with an elevation in one of the following muscle enzymes: CK, AST, aldolase, or LDH; 3) Patient reported muscle weakness or muscle pain (without weakness noted on physical exam) and an elevated CK. The prevalence rate of myositis in our cohort was compared to previously reported rates using the chi-square test. Fisher’s exact test and one-way ANOVA were used to determine possible associations between myositis and clinical and laboratory factors.

**Results:** The mean age of our cohort at the time of this study was 16.4 years. The mean age of onset of initial SLE symptoms was 13.2 years. 87.3% were female and 74.5% were African-American. Inflammatory myositis was present as a feature of SLE in 31% (n=17) with a 95% confidence interval of 19 to 45%, which is statistically different from the reported rates of 5–11% (p<0.0001). Myositis was shown to be positively associated with anti-ribonucleoprotein (RNP) antibodies (p=0.009) and anti-Smith (Sm) antibodies (p=0.06). Negative associations with myositis were the presence of anti-double stranded DNA antibodies (p=0.02) and hematological disorders (p=0.02).

**Conclusions:** In this southeastern US state, pediatric SLE myositis is present at a statistically higher rate than previously published values of adult SLE myositis. The association of myositis with anti-RNP antibodies is consistent with the medical literature. The presence of myositis can serve as a warning sign for a potential SLE flare and a marker of the effectiveness of a treatment regimen. The presence of both anti-RNP and anti-Sm antibodies further highlights the significant overlap SLE has with other autoimmune diseases such as mixed-connective tissue disease and the challenges that come with appropriately classifying and treating these overlap patients.

**Disclosure:** J. L. Record: None; T. Beukelman: None; R. Q. Cron: None.

**1680**

**Infliximab for the Treatment of Intravenous Immunoglobulin Resistant Kawasaki Disease in Chinese Children.** F. Q. Wu¹, X. M. Hu², Y. L. Zhang³ and L. P. Yang². ¹Capital Institute of Pediatrics, Beijing, China, ²Capital Institute of Pediatrics

**Objectives:** Evaluate the efficacy and safety of Infliximab in patients with Kawasaki disease (KD) who were unresponsive to intravenous gamma globulin (IVIG) treatment.

**Methods:** The diagnosis of KD was made according to the diagnostic guidelines for Kawasaki disease (5th revised edition) of the Kawasaki Disease Committee in Japan and APP/AHA diagnostic guidelines for Kawasaki disease, published in 2004. Pediatric subjects diagnosed with KD with coronary artery lesions, and who failed treatment with IVIG, were enrolled in the study. Subjects were given a single infusion of Infliximab of 5–6mg/kg. The patients were followed up for 21 weeks. The persistence time of fever, CRP, ESR, ultrascan cardiomgram and infusion reaction were observed.

**Results:** A total of 12 subjects were enrolled in the study from May 2009 to Jan 2010 in Department of Rheumatology of Capital institute of Pediatrics, including seven boys and five girls. The mean age was 23.3 months and the mean duration of the symptoms was 6.6 days. Seven of the subjects were <1 year. All 12 subjects were treated with IVIG 2–3 times. Injectable dexamethasone was used in 4 subjects for fever. All subjects had taken aspirin (30mg/kg) orally before treatment with Infliximab. The clinical and laboratory recovery times are listed in the table below. The subjects’ temperature decreased within 12 hours after treatment with Infliximab. The CRP, ESR, blood cell counts and mild-to-moderate coronary artery lesions recovered within 8 weeks. No infusion reactions were observed.

**Conclusion:** Infliximab appears to have good efficacy and safety in the treatment of Kawasaki syndrome in patients who were unresponsive to treatment with IVIG.

<table>
<thead>
<tr>
<th>Infliximab for the Treatment of Intravenous Immunoglobulin Resistant Kawasaki Disease in Chinese Children</th>
<th>Patients (n)</th>
<th>Recover time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical manifestation</td>
<td>Fever</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Erythra</td>
<td>10</td>
</tr>
<tr>
<td>Laboratory examination</td>
<td>Increase of white cell count</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Increase of platelet</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Increase of CRP</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Increase of ESR</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Decrease of serum albumin</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Increase of ALT</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Increase of AST</td>
<td>5</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>T wave change</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>*= atrioventricular block</td>
<td>4</td>
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<tr>
<td>Echocardiography</td>
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<tr>
<td></td>
<td>Left anterior descending distension</td>
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**Disclosure:** F. Q. Wu: None; X.M. Hu: None; Y. L. Zhang: None; L. P. Yang: None.
Juvenile Fibromyalgia: Responsiveness of Tools, Greatest Areas of Impairment, and Impact of an Aerobic Exercise Program. Nadia J. C. Luca1, Brian M. Feldman1, Larisa Tshantshapanyan2, Lusine Abrahamyan3, Samantha Stephens4, Nicolette Bradley5, Jane Schneiderman6, Virginia Wright6 and Shirley M. L. Te7. 1Bloorview Kids Rehab, Bloorview Research Institute, 2Hospital for Sick Children, Toronto, ON, Canada, 3The Hospital for Sick Children, Toronto, ON, Canada, 4The Hospital for Sick Children, 5University of Tennessee Medical Center, Nashville, TN, USA, 6The Hospital for Sick Children, Toronto, ON, Canada, 7University of Padua.

Background: Patients with juvenile fibromyalgia (FM) have generalized MSK pain, fatigue, and poor sleep, as well as high rates of school absence and functional disability.

Objectives: This study determines which areas of functioning are most impaired in children with FM, as well as the effect of an aerobic exercise program on ability to do specific activities. Also, the responsiveness of various evaluation tools in juvenile FM was evaluated.

Methods: FM patients aged 8–18 were asked to complete the FM Impact Questionnaire and Functional Status and Symptom Questionnaire (FSSQ), as well as other questionnaires, while participating in a randomized, 12-week trial of either aerobic exercise or control (qigong). Data were collected before and after the intervention. A repeated measures analysis of variance was used to compare the rates of change in ability between the groups after the exercise intervention.

Results: Thirty patients participated in the study, and 24 patients completed the program (12 in aerobic and 12 in qigong group). At baseline, a minority of patients reported difficulties with daily function (homework 11%, chores 23%) and social function (31%), whereas, on average, 56% reported difficulty with physical function. Specific activities associated with great difficulty or inability included playing sports after school (43%), running long distances (35%), and participating in gym class (25%). The most prominent symptom during physical activities was pain. Subjects also reported difficulty with waking up for school and attending overnight camp (37% and 26% respectively), mostly due to fatigue and sleep difficulties.

After the exercise intervention, subjects in both groups showed improvement in function. However, when compared with subjects in the qigong group, those in the aerobic group demonstrated a significantly greater improvement in ability to run long distances (P = 0.023), attend school every day (P = 0.036), and complete homework (P = 0.003).

Greatest responsiveness, as measured by effect size, was associated with PedsQLpain2, HR QOL, C-HAQ (total score), and the FSSQ questionnaires.

Conclusions: Juvenile FM causes significant difficulties in function, mostly seen in physical activities and activities affected by poor sleep. Daily and social activities tend to be relatively spared. The most prominent symptoms experienced are pain, fatigue and sleep difficulties. Aerobic exercise was found to have greatest impact in improving physical and daily functions but, in our sample, did not affect social function. The FSSQ, as well as other evaluation tools for juvenile FM, has a strong responsiveness.

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1682

Juvenile Localized Scleroderma of the Face: A Neuro-Cutaneous Disease? Francesco Zulian1, Mattia Parolin2, Fabio Vittadello1, Milena Calderone1, Giorgia Martini3 and Susanne Ullman1. 1Bispebjerg Hospital, Copenhagen, Denmark, 2University of Padua, Padova, Italy, 3University of Padua.

Background: Neurological involvement has been reported in few case reports of patients with juvenile localized scleroderma of the face (JLS-F). Aim of the study was to systematically investigate frequency, clinical and radiological features of CNS involvement in JLS-F.

Methods: A cohort of consecutive patients with JLS-F (including en coup de sabre (ECDS) and Parry Romberg syndrome (PRS)) underwent a comprehensive clinical examination, EEG and brain MRI. All radiographic films were analyzed by 2 neuroradiologists who were blinded to the patients’ identity and clinical records. Parenchymal lesions were assessed by a standardized protocol (1) and classified by number, laterality, gray or white matter involvement and concordance with the skin lesion.

Results: 34 patients with JLS-F entered the study. F:M ratio was 1.4:1, mean age at disease onset 8.6 years. Twenty nine patients (85.3%) had linear scleroderma of the face, 5 (14.7%) presented a mixed subtype, 23 patients (67.6%) had ECDS, 11 (32.4%) PRS. CNS involvement was found 21 (61.8%) patients, 11 (32.4%) had neurological symptoms such as chronic headache (5), seizures (3), hemiparesis (1), behavioural abnormalities (1) and cranial nerve palsy (1). Ten patients (29.4%) presented MRI abnormalities without symptoms. EEG was abnormal in 5 patients (14,7%), all symptomatic and/or with MRI changes. Cerebral MRI resulted abnormal in 17/34 patients (50%). Twelve patients underwent more than one brain MRI which worsened in 5 patients (41.7%), unchanged in 5 (41.7%) and persisted normal in 2 (16.6%). Eight patients had a single brain lesion, 9 a multiple pattern. In 88,2% the site of skin and neurologic lesions were concordant. White matter involvement was present in 10/17 (58,8%), lesions extended to the grey matter in 7 (41,2%).

Four group of patients have been identified: group 1 patients with neurological symptoms and organic brain lesions (mainly multiple with white and grey matter involvement) concomitant or following the onset of the scleroderma skin lesion (no.7), group 2 (no.10) patients with just organic brain lesions following the skin lesions by 1–18 years, mainly single white matter lesions concordant with the site of skin lesion, group 3 (no. 4) patients with neurological symptoms but no organic brain lesions and group 4 (no.13) patients with no neurological involvement.

Conclusion: The high prevalence of neurological involvement in JLS-F reinforces the hypothesis of a possible pathogenetic link CNS-skin in localized scleroderma and confirms the need for a careful clinical and radiological monitoring of every patient since the disease onset.


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1683

Localized Scleroderma Therapy: When Would Be a Good Time To Stop? Thaschawee Arkachaisri1 and Kathryn S. Torok2. 1KK Women’s and Children’s Hosp, Singapore, Singapore, 2Univ of Pittsburgh Med Ctr, Pittsburgh, PA

Background: Localized Scleroderma (LS) is the most common form of juvenile scleroderma. Its long-term physical and psychological impact continues to cause significant disability. Different therapy options were reported with inconsistent results. Longterm followup (FU) data after the disease is under control is unknown. Combined high dose SC methotrexate and a weaning dose of oral corticosteroids have been shown to be effective in our pediatric LS cohort.

Purpose: We report a prospective data on the longterm outcome of a single center treatment protocol in a pediatric LS cohort and propose the duration of therapy for LS.

Methods: LS patients were recruited from the Sclerodema Clinic at the Children’s Hospital of Pittsburgh. Patients with active disease, defined as those with erythematous lesions, and/or new lesions, or expansion of existing lesions; were started on oral prednisone 2 mg/kg/day (max 60mg/day) and SC methotrexate (MTX) at 1 mg/kg/week. Prednisone was weaned to reach 1 mg/kg/day by the end of 6–8 weeks, and then further weaned to 0.25 mg/kg/day to complete 12 months of steroid therapy. MTX was continued for a full 24 months of SC therapy with subsequent oral therapy for 12 more months. The disease outcome parameters used to assess effectiveness of therapy were the modified LS Skin Severity Index.
(mLoSsI) and the physician global assessment of disease activity (PGA).
All patients were followed every 4–8 weeks with appropriate therapy adverse reaction monitoring. Flare was defined by the reoccurrence of erythematous lesions, and/or new lesions, or expansion of existing lesions. Kaplan-Meier analysis was used to analyzed recurrence rate and survival-time data.

Results: Thirty-nine patients were included (70% female, 95% Cau-
casians). LS Subtypes are–4 plaque morphea, 14 linear scleroderma (Li), 6 en plaques, 3 subcutaneous morphea (Sqm), 5 generalized morphea and 7 mixed LS. Median age at onset was 7.9 years (IQR 4.5–11.6). Median duration of FU was 36.9 mo (range 8.7–105.8). Clinical improvement (mLoSsI and PGA) was demonstrated at the median of 1.1 mo (IQR 0.5–1.9). No patients developed flare during therapy. During FU period, 4 patients flared (3 Li and mixed LS and 1 SqM; 3 females) after discontinued therapy after completed 36 mo and in remission.

Median duration to flare was 4.7 mo (range 0.99–10.1). This gives the flare incidence 0.0034 person-months. Cumulative probability risk of recurrence is estimated from our cohort that about 25% and 50% of flare within 46 and 54 mo, respectively. Over the study period (up to 78 mo), the probability of flare does not reach 75%. There was no major complication noted.

Conclusion: The uniform treatment protocol given to all LS patients who required systemic therapy in our center enables us to assess the longterm outcome of the regimen more accurately. The therapy is effective in controlling the disease, however, after discontinuing therapy, 10% flare within 6 months. We proposed to continue the therapy longer, at least 48–54 months in order to decrease the rate of flare.

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1684

Longitudinal Study on Growth Failure and Height Deflection in Juvenile Systemic Lupus Erythematosus (JSLE): The Result of a Prospective Multicentre PRINTO Study, Marite Rygg1, Angela Pistorio1, Angelo Ravelli1, Mohamad Maghnie1, Natascia Di Iorgi2, Erkan Demirkaya3, Srdjan Pasic3, Huri Ozdogan4, Brigitte Bader-Meunier5, Carlos Henrique M. Da Silva5, Ljora Harel5, Maria Rosa Roldan Molina4, Helena Canhao6, Johannes Roth7, Carine Wouters8, Judith Barash9, Rym Hajri Ben Ammar10, Christina Dracou11, Sylvie Gandon-Laloumi11, Alberto Martini12 and Nicoletto Ruperto12, 1IRCCS G. Gaslini/Universita` degli Studi di Genova, Genova, Italy, 2IRCCS G. Gaslini/ Universita` degli Studi di Genova, Genova, Italy, 3IRCCS G. Gaslini/Universita` degli Studi di Genova, Genova, Italy, 4PRINTO

Background: Growth failure is a unique feature of JSLE, caused by long-term disease activity, side effects of drugs, and/or co-morbid conditions.

Objective: The goal of the study was to obtain longitudinal data on growth in a large-scale, multi-national cohort of patients with JSLE followed for 26 months.

Materials and Methods: This prospective, multi-centric study on JSLE was carried out in 39 countries from Northern and Southern Europe, Latin America, US and Asia between 2001 and 2004. Patients seen at the participating centers were diagnosed of JSLE, at active phase, and age younger than 18 years at enrollment were included.

Results: Data was collected from 557 patients with JSLE. There was a significant reduction in parent-adjusted height z score with time in females and males (p<0.0001) with a significant gender difference (p<0.0001), male height being most affected. Median BMI z score peaked at 6 months and was still significantly above baseline after 26 months (p<0.01) with no gender difference. Standardized height reduction was inversely related to age at disease onset in females, especially pronounced at onset age <8 years. Females with onset age <12 years had a median parent-adjusted height z score of −0.87 with no catch-up growth. At the end of the study, growth failure was seen in 14.7% of the females and 24.5% of the males. Height deflection (less than−0.25/year) was found in 20.7% of the females and 45.5% of the males.

Conclusions: The longitudinal effect on height is modest in JSLE females with age at onset ≥12 years. In spite of all our knowledge and careful treatment, females <12 years at onset and males are still at risk of experiencing a considerable height loss during the course of the disease.

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1685

Long-Term Follow Up of Hyper IgD Syndrome: A National Multi-
centre Study, Silvia Federici1, Alberto Tommasini2, Antonella Meini3, Giuseppina Calca`gno4, Francesco Zulian5, Rita Consolini5, Martina Finetti1, Luciana Breda6, Roberta Caorsi7, Romina Gallizzi8, Maria Alesso9, Alberto Martini10 and Marco Gattorno10, 1Clinica Pediatrica, Divisione Reumatologica Pediatrica, Ospedale Policlinico di Chieti, 2Dipartimento A.I. di Pediatria, Universit`a` di Padova, 3Dipartimento di Medicina della Procreazione e dell’E`ta` Evolutiva, Università di Pisa, Italy, 4Dipartimento di Pediatria, Universita` Federico II, Napoli, Italy, 5Dipartimento di Scienze Pediatriche, AO`U “G. Martin`, Messina, 6IRCCS Burlo Garofolo, Trieste, 7Unit`a` di Immunologia e Reumatologica Pediatrica, Spedali Civili, Brescia, 8IO Pediatria II Istituto G. Gaslini, Genova, Italy

Purpose: Hyper-IgD syndrome (HIDS) is an autosomal recessive disease caused by mutation in the MVK gene. Aim of the study was to analyze the long term follow-up of a group of children and young adults affected by HIDS.

Patients & Methods: The first 10 exons of MVK genes were analyzed in 720 consecutive patients with periodic fever by means of denaturing high-performance liquid chromatography (DHPLC) and DNA sequencing. 40 patients carried 2 mutations of the MVK gene. Detailed clinical information were collected at the time of molecular analysis and last follow up through a standardized questionnaire. Spontaneous disease course was classified as follows: i) resolution (no episodes in the last 6 months), ii) improvement (reduction of more than 30% of fever episodes) iii) stationarity iv) worsening (increase frequency of fever episodes or appearance of new major clinical manifestation). The Child Health Questionnaire (CHQ-PF 50) was used to assess the health related quality of life.

Results: the mean age of disease onset was 0.7 yrs (range 1 months-3 yrs). At baseline, mean duration of fever episode was 4.7 days. The clinical features associated to fever episodes were abdominal pain (97.5%), cervical lymphadenopathy (97.5%) with pain (80%), diarrhea (77.5%), erythematous pharingitis (75%), vomiting (65%) and aphtous stomatitis (57.5%). So far, data on follow up are available for 24 patients. The mean follow up time was 13.8 yrs (range 2.3–38.2 yrs). Steroid on demand was effective in treating fever episodes. Ten patients showed a significant spontaneous reduction of the frequency of fever episodes. In the remaining 14 patients the frequency of fever episodes was stable (7 patients) or increased (7 patients). Complete resolution was achieved after introduction of Anakinra (2 patients) and tonsillectomy (1 patient). One patients improved after Anakinra, 2 after tonsillectomy. Two patient did not respond to Etanercept.

Health–related quality of life at follow up was generally affected when compared to a cohort of healthy age-matched individuals.

Conclusions: even if a relevant percentage of HIDS patient show a spontaneous amelioration of the disease, most of them display a tendency towards a persistence of fever episodes that affect their quality of life.

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1686

Measuring Changes in Calcifications in Juvenile Dermatomyositis (JDM) Using Single Slice Computerized Tomography (CT), Maria F. Ibara1, Cynthia Rigsby1, Gabrielle Morgan2, Deli Wang3 and Lauren M. Pachman1, 1Children’s Memorial Research Center’s Biostatistics Core, Chicago, IL, 2Clinical Immunology, Children’s Memorial Research Center (CMRC), Chicago, IL, 3Division of Radiology, Children’s Memorial Hospital (CMH), Feinberg School of Medicine, Northwestern University, Chicago, IL, 4Division of Rheumatology and Clinical Immunology, Children’s Memorial Research Center (CMRC), Feinberg School of Medicine, Northwestern University, Chicago, IL, 5Division of Rheumatology, Children’s Memorial Hospital (CMH), Feinberg School of Medicine, Northwestern University, Chicago, IL.
**Objectives:** To determine the utility of single slice CT to measure change in the volume of calcifications in patients with JDM over time.

**Methods:** Children with definite/possible JDM and severe calcifications had at least two CT scans over a 2 year period. Severe calcifications were defined as a deep sheet-like deposits within intramuscular fascia, and were identified by physical examination and/or previous x rays. The limited four slice CT study focused on the area of greatest calcium burden. The area enclosing the calcification was calculated from the CT images, using a CT post processing workstation. Demographic and baseline characteristics were assessed by descriptive statistics. Generalized linear models were applied to analyze changes in the volume of calcifications and their association between clinical variables including DAS (Disease activity score) skin, DAS muscle, and the number of nailfold ERL (end row capillary loops). Data analysis used SAS 9.2.

**Results:** 11 children with JDM and severe calcifications were recruited. 8 patients were female; 8 were Caucasian. The average age was 13.84 years (+/- 4.9 years). The average duration of untreated disease at JDM diagnosis was 7.57 (+/- 7.2) months, and they all had active disease for an average = 100 months +/- 65. The volume of calcifications changed significantly over time (p<0.0001). Decrease in calcification volume was significantly associated with decrease in DAS skin (p=0.0002) and improvement in the number of nailfold ERL (p=0.0025) but not with change in DAS muscle.

**Conclusion:** This limited CT technique provides objective measurement of the volume of calcifications over time that may be helpful as a research tool to monitor progression and regression of dystrophic deposits in JDM and other rheumatic diseases.

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**1687**

**Odontostomatologic Involvement in Juvenile Localized Scleroderma of the Face.** Sabina Trainito¹, Troels Herlin², Thomas Klit Pedersen², Giorgia Martini, Chiara Scibetta², Giuseppe Fioretti, Vittorio Favero, Stefano Puggina³, Lorenzo Favero and Francesco Zulian ¹. Padova, Italy, ²Department of Dentistry, Gnatology Unit, University of Padova, Italy, ³Department of Orthodontics and Radiology, University of Aarhus, Denmark, ⁴Department of Pediatrics, Rheumatology Unit, University of Aarhus, Denmark, ⁵Department of Pediatrics, Rheumatology Unit, University of Padova, Padova, Italy, ⁶Radiology Institute, University of Padova, Italy

**Background:** Juvenile Localized scleroderma (JLS) is the most frequent form of scleroderma in childhood. The linear facial subtype (known also as scleroderma en coup de sabre and Parry-Romberg syndrome) can lead to significant aesthetic and functional abnormalities. Despite their quite frequent clinical observation, the odontostomatologic complications are not thoroughly described in the literature and their management is challenging because of the lack of specific indicators of disease activity and progression. Aim of the study was to describe the clinical features and prevalence of the most frequent odontostomatologic abnormalities of JLS of the face and to propose clinical and radiologic criteria for the assessment and follow up of these complications. The most suitable to measure JLS odontostomatologic involvement is a comprehensive rheumatologic evaluation, including dental examination (intraoral and gnathologic examination, orthodontic casts, photographs), conventional radiology (orthopantomography, frontal and lateral skull teleradiography) and Cone Beam Computed Tomography (CBCT). Odontostomatologic complications are not thoroughly described in the literature and their management is challenging because of the lack of specific indicators of disease activity and progression. Aim of the study was to describe the clinical features and prevalence of the most frequent odontostomatologic abnormalities of JLS of the face and to propose clinical and radiologic criteria for the assessment and follow up of these complications. Supported by NIAMS R01 AR48289- and the Cure-JM Foundation

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**1688**

**Preliminary Criteria for Global Disease Flares in Juvenile Systemic Lupus Erythematosus (JSL).** Rina Mina, Michael Beresford, B. Anne Eberhard, Edward H. Giannini, Deborah M. Levy, Clarissa Pilkington, Marilyn G. Punaro, Angelo Ravelli, Andrea O. Reiff, Claudia Saad-Magalhaes, Laura E. Schanberg, Lori B. Tucker, Marisa S. Klein-Gitelman, Shannen L. Nelson, Jamie Eaton, Jun Ying and Hermine J. Brunner. ¹BC Children’s Hospital, Vancouver, BC, Canada, ²Children’s Hosp LA MS60, Los Angeles, CA, ³Children’s Hosp Med Ctr, Cincinnati, OH, ⁴Childrens Mem Hosp/NW Univ, Chicago, IL, ⁵Cincinnati Children’s Hospital, ⁶Cincinnati Children’s Hospital, Cincinnati, OH, ⁷Cincinnati Children’s Hospital Medical Ctr, Cincinnati, OH, ⁸Children’s Med Ctr, Cincinnati, OH, ⁹Duke Univ Medical Center, Durham, NC, ¹⁰Great Ormond Street and University College London Hospitals, ¹¹IRCCS G Gaslini, ¹²Royal Liverpool Children’s Hospital, ¹³Schneider Children’s Hospital, New Hyde Park, NY, ¹⁴Texas Scottish Rite Hospital for Children, Dallas, TX, ¹⁵The Hospital for Sick Children, Toronto, ON, Canada, ¹⁶UNESP, ¹⁷University of Cincinnati

**Background:** Widely accepted valid, reliable and feasible flare criteria to assess the effects of new medications and the benefits of current treatments in jSLE are lacking.

**Objectives:** Develop accurate flare criteria for jSLE by employing consensus formation methodology and statistical approaches.

**Methods:** As part of a consensus formation process, an international group of pediatric rheumatologists (n=138) were randomized to rate a total of 400 different patient profiles that were abstracted from prospective jSLE cohorts. jSLE flare descriptors deemed important, as per previous Delphi surveys (patient global assessment, physician global assessment, disease activity score, health status, proteinuria, anti-dsDNA antibody titer, ESR, complement C3 and C4), were considered when generating candidate flare algorithms, using various percentage changes of the flare descriptors, examination of flare criteria used in adult SLE, multinomial logistic regression, and Classification and Regression Tree (CART). For each candidate flare algorithm derived by multinomial logistic regression or CART analysis, the area under the ROC curve was calculated, using the consensus of the profile raters (minor flare, moderate flare, major flare, no flare) as criterion standard. An international consensus conference was held to rank the generated candidate flare algorithms following the process previously suggested by the ACR Criteria Subcommittee (consensus level 75%).

**Results:** A total of 2,995 expert ratings were available for analysis (survey response rate 70%). Consensus was reached that jSLE flare criteria derived by multinomial logistic regression or CART analysis are most suitable to measure jSLE flares. The highest ranked such candidate flare criteria consider absolute changes in the score of a disease activity index (SLEDAI or BILAG), the physician global assessment, spot urine protein/creatinine (P/C) ratio, and ESR when calculating a jSLE flare score. This score is then used to determine the presence of a global flare and to discriminate among categories of flare severity (minor,
moderate and major). The highest ranked preliminary jSLE flare criteria have excellent to outstanding accuracy as measured by the area under the Receiver Operating Characteristic Curve (AUC) (see Table).

<table>
<thead>
<tr>
<th>Preliminary Criteria for Global Flares</th>
<th>Accuracy (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(All algorithms use change in variables between follow up-baseline visit)</td>
<td>Minor Flare</td>
</tr>
<tr>
<td>A. 0.5 x SLEDAI + 0.3 x P/C ratio + 0.5 x PGA + 0.02 x ESR</td>
<td>0.90</td>
</tr>
<tr>
<td>B. 0.4 x BILAG + 0.65 x P/C ratio + 0.5 x PGA + 0.02 x ESR</td>
<td>0.89</td>
</tr>
<tr>
<td>C. 0.4 x SLEDAI + 0.33 x P/C ratio + 0.6 x PGA</td>
<td>0.87</td>
</tr>
<tr>
<td>D. 0.4 x BILAG + 0.55 x P/C ratio + 0.5 x PGA</td>
<td>0.88</td>
</tr>
<tr>
<td>E. CART analysis (patient is categorized by highest flare level)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

**Major Flare:** SLEDAI ≥ 10 OR PGA ≥ 6
**Moderate Flare:** 7 ≤ SLEDAI ≤ 9 OR P/C ratio ≥ 2.3 OR ESR ≥ 13
**Minor Flare:** 3 ≤ SLEDAI ≤ 6 OR 2 ≤ PGA < 6 OR 0.7 ≤ P/C ratio ≤ 2.2

**Conclusions:** Consensus has been reached on the preliminary criteria for global flares in jSLE. Prospective validation of these criteria is needed to assess their usefulness as outcomes for clinical trials and other research settings.

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### 1689

**Preliminary Findings of Functional Magnetic Resonance Imaging (fMRI) Assessments of Specific Cognitive Domains in Childhood-Onset Systemic Lupus Erythematosus (cSLE) Patients and Best-Friend Controls.**

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**Purpose:** 1) To use fMRI to identify brain regions and associated networks that support visuoconstructional ability (VCA), working memory and attention, which are cognitive domains often affected in cSLE. 2) To characterize both behavioral and neuro-functional differences in VCA, working memory, and attention in cSLE patients and matched best-friend controls using fMRI and formal neuropsychological (NP) testing.

**Methods:** 36 subjects (F:M = 28:8; age 10–17 years; 50% African-American, 50% Caucasian; 11% Hispanic), 18 with cSLE and 18 controls matched for age, sex, and race, performed the square completion (SC) task, N-Back, and continuous performance (CPT) tasks to probe VCA, working memory, and attention, respectively during fMRI. Functional data, acquired at 3 Tesla, consisted of T2*-weighted echo-planar images with TR=3s, 64x64 matrix, 256 mm FOV, and 44 axial 3 mm slices. A high resolution T1-weighted anatomic reference images were acquired for each subject. Average responses were calculated (p=0.001 uncorrected) for both cSLE and control groups and analyzed per anatomic regions of interest (ROI). 

**Results:** Activation was observed in expected brain regions for each task (Figure 1). Performance of the SC task activated both dorsal (“where”) and ventral (“what”) visual pathways, as expected for a task measuring VCA. The attention task, CPT, produced a similar pattern plus frontal and insular activations. The N-Back task, which probes working memory, activated the dorsolateral prefrontal, parietal, insular and anterior cingulate cortices (ACC). ROI analyses revealed differences between cSLE and control groups. Controls activated more strongly for SC in the insula, ACC and dorsal visual stream. CPT resulted in greater activation for controls in the insula as well as the ventral visual pathway. The ACC activated more in the controls than in the cSLE group for the N-Back task. Group analysis resulted in deactivated in some ROI. Particularly, the hippocampus deactivated more strongly for cSLE than it did for controls when doing the NBack task. Select Z-scores attained from formal NP testing were found to correlate with ROI activation by subject in the cSLE group. A positive correlation was found between the ventral stream ROI activation for the SC task and an NP test for VCA. Activation in the same ROI for the CPT task correlated negatively with an NP test for attention.

**Conclusions:** In this ongoing study, cSLE patients and their best-friend controls differed regarding the extent of fMRI activation in anatomic regions of interest (ROI) relevant to specific cognitive domains. Some ROIs activated per subject with correlation to performance in corresponding formal NP testing. The observed trends await confirmation as the sample size is augmented.

**Disclosure:** B. Dina: None; A. Baker: None; A. C. Sagdal-Gironella: None; M. Klein-Gitelman: None; F. Zelko: None; D. Myones: None; D. Gitelman: None; M. Di Francese: None; H. Brunner: NIAMS-NIH, 2.

### 1690

**Pre-Pubertal Onset Systemic Lupus Erythematosus in Girls: Clinical and Serologic Manifestations Differ from Post-Pubertal Onset SLE.**

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**Objective:** Children with pre-pubertal onset systemic lupus erythematosus (SLE) represent a small minority of children with the disease. To better understand this subset of children with lupus, and to define the role of specific hormones in SLE expression, we enrolled a cohort of girls with early onset disease in a longitudinal prospective observational study spanning the period of physiologic puberty.

**Methods:** The study was approved by CARRA and the institutional review boards of each participating CARRA site. Girls with 4 or more ACR diagnostic criteria of SLE between the ages of 8 and 13 years who had achieved only Tanner I or II stage of sexual development were evaluated with medical history, review of systems, physical examinations and laboratory studies every 3 months until 2 years after menarche. Clinical and laboratory evaluations of the first 28 girls enrolled were compared to 23 girls with disease onset after menarche. Abnormalities present or absent were compared as categorical variables using the chi square statistic.

**Results:** The two groups differed (p<0.05) in several clinical characteristics. The girls with pre-pubertal onset SLE had more frequent thrombocytopenia (32% vs 4%, p=0.013), anemia (57% vs 30%, p=0.05), GI complaints (46% vs 4%, p=0.0008) and depression (43% vs 4%, p=0.0017) than the girls with older onset disease. The older girls, in contrast, had more frequent morning stiffness (78% vs 43%, p=0.011), pleuritis (65% vs 18%, p=0.038), pericarditis (39% vs 7%, p=0.0016), fatigue (96% vs 39%, p=0.0003), and weight loss (39% vs 18%, p=0.001) than the girls with prepubertal SLE. In contrast, the pre-pubertal cohort had more frequent autoantibodies: anti-cardiolipin (50% vs 22%, p=0.038), dsDNA (100% vs 57%, p=0.0001), SSA (3% vs 13%, p=0.037) and SS-B (39% vs 8%, p=0.13) compared to the teens. The occurrence of malar or discoid rash, arthrites, myositis, hematuria, fever, Raynaud phenomenon, oral/nasal ulcers, alopecia, hypertension, headache, and peripheral vasculitis did not differ between the two groups. The presence of Sm and RNP antibodies, likewise, was similar in both groups.

**Conclusions:** Girls with pre-pubertal onset SLE have different clinical manifestations and autoantibody profiles than girls with teen-onset SLE. In particular, the younger girls have more autoantibodies, more hematologic abnormalities, and more GI complaints; the older girls have more serositis, fatigue and morning stiffness. Further study of this large prospective cohort of children with prepubertal SLE is important to understanding the role sexual maturity and hormone changes of puberty play in SLE.

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Background: The European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) classification criteria for Wegener’s Granulomatosis (WG), proposed to be more applicable to children than American College of Rheumatology (ACR) criteria, were recently validated in adults. The current study aimed to uniquely classify all patients. However, even when using the EMEA algorithm many children diagnosed with AAV remained unclassified.

Results: The European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) classification criteria for Wegener’s Granulomatosis (WG), proposed to be more applicable to children than American College of Rheumatology (ACR) criteria, were recently validated in adults. The current study aimed to uniquely classify all patients. However, even when using the EMEA algorithm many children diagnosed with AAV remained unclassified.

Conclusion: The EULAR/PRINTO/PRES criteria are more sensitive than the ACR criteria in classifying pediatric WG. Performance of both criteria were limited when applied to a cohort that includes patients with MPA for which neither classification systems have established criteria, unlike the most sensitive EMEA classification algorithm which specifically aims to uniquely classify all patients. However, even when using the EMEA algorithm many children diagnosed with AAV remained unclassified.

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Background: Antiphospholipid antibody syndrome (APS) is the most common acquired autoimmune thrombotic state in children. The underlying mechanism(s) by which aPL antibodies result in thrombosis remains poorly understood. Annexin A5, a potent anti-coagulant protein, shields anionic phospholipids, and disruption of this shield by aPL antibodies plays a role in the pathogenesis of APS in adults. In this study, we investigated the association between aPL antibodies and annexin A5 resistance in children with rheumatic diseases.

Methods: Clinical and laboratory data were collected from children with rheumatic diseases (n = 90), including systemic lupus erythematosus (SLE) (n = 49), juvenile idiopathic arthritis (JIA) (n = 21), juvenile dermatomyositis (JDM) (n = 8), primary APS (n = 6), Sjogren’s syndrome (SS) (n = 3), mixed connective tissue disease (MCTD) (n = 1), systemic sclerosis (n = 1), and systemic vasculitis (n = 1). For children with persistently positive aPL antibodies, we performed annexin A5 resistance assays in serum and correlated with clinical characteristics. A total of 12 laboratories measured annexin A5 resistance using the 2013 ACR/APS criteria.

Results: In the total cohort, 11 children (9%) had persistently positive aPL antibodies. Resistance to annexin A5 was higher in children with persistently positive aPL antibodies compared to children with negative aPL antibodies (p = 0.0032). There was a significant correlation between annexin A5 resistance and the presence of antiphospholipid antibodies (aPL) (p = 0.0032). Children with persistently positive aPL antibodies had higher annexin A5 resistance compared to children with negative aPL antibodies (p = 0.0032).

Conclusion: Annexin A5 resistance is significantly higher in children with persistently positive aPL antibodies compared to children with negative aPL antibodies. This finding supports the role of annexin A5 in the pathogenesis of APS in children with rheumatic diseases.
Conclusions: The ASR assay is the first mechanistic assay targeted at the underlying pathogenesis of APLS. This is the first report demonstrating significantly lower mean ASR levels in children with rheumatic diseases and persistent aPL antibodies. Furthermore, patients with prior history of thrombosis were shown to have reduced ASR levels as compared to patients with no history of thrombosis. We plan to expand these findings into a larger, multi-center cohort of children with SLE to determine if ASR is highly associated with thrombosis or other aPL related manifestations.

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1693 Safety and Efficiency of Rituximab in Juvenile Dermatomyositis: A Series of Eight Cases from the French AIR Registry, Brigitte Bader-Meunier1, Helene Decaluwe2, Pierre Quarterier1, Albert Faye3, Vincent Guigoni5, Anne Pagnier5, Christine Barnerias3, Jacques E. Gottenberg6 and Isabelle Ferriani2. 1Evandro Chagas Institute (WHO National Influenza Center), 2Igando, Brazil, 3School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

Background: Juvenile dermatomyositis (JDM) is a rare vasculopathic condition of presumably autoimmune etiology. No data are available regarding the safety and efficacy of anti-CD20 treatment in patients with JDM refractory to conventional treatments except for six case reports with conflicting results.

Aim: To describe the efficacy and safety of rituximab (RTX) in JDM patients.

Methods: French multicenter retrospective study of patients with JDM diagnosed according to the criteria of Bohan and Peter treated with RTX and included in the French Autoimmunity and Rituximab (AIR) registry. Complete remission was defined by the normalization of muscle mass and strength (MMT) and child myositis assessment scale (CMAS) for muscular involvement and by the disappearance of active skin lesions and abdominal pain for the treatment of abdominal complications.

Results: Eight patients (7 girls and 1 boy) were included. Age at diagnosis of JDM ranged from 2.5 to 10 years, and JDM duration at onset of rituximab therapy from 0.15 to 11 years. All the patients had been previously treated with immunosuppressive agents, and received rituximab because of the lack of efficacy of these treatments. The main indication for rituximab treatment was refractory muscle, skin and/or gastrointestinal involvement (6 patients) (group 1) and chronic complications consisting of severe calcinosis and severe abdominal pain associated with abdominal lipomatosis (2 patients) (group 2). The number of rituximab infusions (375–500 mg/m² infusion) ranged from 2 to 5. RTX was associated with corticosteroids and with immunosuppressive drugs in 8/8 and 4/8 patients respectively. The first RTX infusion had to be stopped in 1 patient (group 1) because of an infusion-related event. Clinical muscular, cutaneous and abdominal remission was achieved in 3/5 evaluable patients in group 1, including one patient with severe JDM who received plasmapheresis before and during the RTX course; MMT and CMAS returned to normal values within 3 to 12 months; normal values of serum CPK level were observed before and after RTX. In these responders steroid therapy was stopped in 1 patient 1,5 years after the first infusion of RTX, and was tapered at 10 and 15% of the baseline dosage respectively in the two others; the mean follow-up was 1,5 to 4 years, and complete remission lasted in 2 patients, while 1 patient has a relapse occurring 16 months after the start of the first course, successfully retreated with a second course of rituximab. RTX was ineffective in four patients (2 patients in each group). Calcinosis did not improve in two responders as well as in one non responder. Two patients presented localized bacterial infection of the calcinosis sites 2 and 11 months after RTX, and 1 patient died from non-related DM cause. Effective depletion of peripheral blood B cells was observed in all the patients and lasted more than 7 months in all patients except in one non responder.

Conclusion: This small series suggests that rituximab may be an effective and safe co-therapy for treating muscular and skin involvement in a subset of children with refractory JDM, but had no effect on calcinosis.

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1694 Safety and Immunogenicity of Influenza Vaccine (FluVac) in Patients with Juvenile Systemic Lupus Erythematosus (JSLE), Luciana M. de Carvalho2, Rodrigo V. D. Silvestre3, Wyller A. Mello3 and Virginia P. L. Ferriani. 1Evandro Chagas Institute (WHO National Influenza Center), Ananindeua, Brazil, 2School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

Background: The FluVac is highly effective in general population. However there have been concerns about safety and immunogenicity of this vaccine in patients with SLE.

Objective: To evaluate safety and immunogenicity of FluVac in JSLE.

Patients and Methods: Twenty-six JSLE patients (10–18 years; mean SLEDAI score of 5.8), were immunized with trivalent split FluVac (A/Solomon Islands/3/2006, A/Brasilie/10/2007, B/Florida/2006), licensed for the 2008 Winter season in the South Hemisphere (Sanofi Pasteur SA/Butantan Institute Brazil). All but one patient were receiving prednisone (mean dose 12.2mg/day), and 17 were also receiving other drugs (methotrexate/leflunomide; azathioprine; mycophenolate mofetil). Influenza antibodies were measured before and 4–6 weeks after vaccination using hemagglutination inhibition (HAI) test according to standard World Health Organization procedure. Immune response (seroconversion) was defined as a 4-fold or greater rise in HAI antibodies and seroprotection rate was considered when HAI titers were at least 1:40. Local symptoms at the injection site and systemic symptoms were assessed by diary. The SLEDAI score, erythrocyte sedimentation rate (ESR), anti-dsDNA and anti-cardiolipin antibodies were evaluated before and 4–6 weeks after vaccination.

Results: All patients responded to at least 2 FluVac strains. Seroprotection rates after vaccination were 92% to A/H1N1, 73% to A/H3N2 and 100% to B-strain. Seroconversion rates were 91% to A/H1N1, 60% to A/H3N2 and 45% to B-strain. Use of medications did not interfere in seroprotection or seroconversion rates. No significant differences were found in SLEDAI score, ESR, or antibody titers against dsDNA and cardiolipin 4–6 weeks after vaccination. Local symptoms at the injection site (tenderness and/or redness) were described in 5/26 patients; 1 patient had a quickly reversible arthralgia five minutes after receiving the vaccine and 2 patients developed cough and rhinorrhea without fever, one and nine days after receiving the vaccine.

Conclusion: Trivalent split influenza vaccine seems to be safe and immunogenic in patients with JSLE.

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1695 Serum Tumor Necrosis Factor alfa (TNFα) Is Associated with Disease Activity in Juvenil Systemic Lupus Erythematosus (JSLE), Mariana Postal, Karina Pereira, Karina Pelic¸ari, Bárbara Longhi, Roberto Marini, Lilian T. L. Costallat and Simone Appenzeller. State University of Campinas

Objective: To compare serum TNFα concentrations in JSLE patients, first-degree relatives and healthy volunteers. To determine clinical, laboratory and treatment features associated with TNFα in JSLE.

Methods: We included consecutive SLE patients with disease onset before the age of 16 (JSLE), first-degree relatives and age and healthy age and
sex matched controls. SLE patients were assessed for the number of non-renal and renal American College of Rheumatology (ACR) criteria ever present, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Mood disorders were determined through Becks Depression and Becks Anxiety Inventory (BDI and BAI). TNFα levels were measured by enzyme-linked immunosorbent assay using commercial kits from RD Systems (London, UK). Analysis of variance was used to compare TNFα concentrations between groups. We assessed the effects of various demographic and clinical factors and TNFα concentrations in jSLE using univariate analyses. Multivariate analysis was performed including sex, age, SLE duration, disease activity, damage, number of non-renal and renal ACR criteria ever present, and current drug exposures.

**Results:** We included 50 jSLE (mean age 17.8 ± 3.9), 45 first-degree relatives (mean age 40.2 ± 6.3) and 49 controls (mean age 20.8 ± 4.6). The mean level of serum TNFα was 4.6 ± 9.6 pg/ml in jSLE, compared to 2.5 ± 2.7 pg/ml (p = 0.15) in first-degree relatives and 1.8 ± 1.9 pg/ml in healthy controls (p = 0.04). No difference between first-degree relatives and healthy controls was observed (p = 0.13). TNFα concentrations correlated directly with SLEDAI scores (r = 0.41; p = 0.003), renal ACR criteria (r = 0.3; p = 0.05), and anxiety (r = 0.3; p = 0.03). No association between TNFα and SDI scores, depression, current use and dose of corticosteroids, hydroxychloroquine and immunosuppressants was observed. In adjusted analysis, TNFα levels was independently associated with SLEDAI scores (OR = 3.1; 95% CI = 1.6–6.5). When analyzing individual SLEDAI items, TNFα was associated with the presence of vasculitis (OR = 3.9; 95% CI = 1.3–4.9).

**Conclusions:** TNFα was significantly higher in jSLE patients when compared to healthy controls and was associated independently with disease activity in adjusted analysis. TNFα may be a useful marker for disease activity in jSLE; however longitudinal studies are necessary to determine if TNFα may predict flares in jSLE. The heterogeneity of clinical manifestations observed in jSLE may be explained by different cytokine profile. Since TNFα was associated with the presence of vasculitis, anti-TNF treatment may be a treatment option for this manifestation.

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**1696**

**Study of the Growth and Body Mass Index (BMI) of 86 Children with Familial Mediterranean Fever (FMF): Results of the French Referral Centre for Auto-Inflammatory Diseases (CeReMAI).** Aurelie Klein1, Alexia Letierce1, Anuela Kondi1, Veronique Hentgen2, Isabelle Kone-Paut1 and Severine Guillaume-Czitrom1. 1Bicetre University Hospital, Le Kremlin-Bicetre, France; 2Versailles University Hospital, Versailles, France.

**Background:** Little is known on growth and BMI in FMF children.

**Objective:** To study the growth and BMI of FMF children, and evaluate the impact of disease severity and mutation load.

**Methods:** FMF children selected from the CeReMAI with available measures of height and weight were included. These measures were recorded at disease onset, genetic diagnosis, Colchicine start, and last visit, and Z-scores of growth and BMI matched for age and gender, calculated; Z-scores of heights were compared with the paired Wilcoxon test to Z-scores of target heights. Likewise, the BMI Z-scores were compared to the general population. Differences were analysed according to the severity of FMF evaluated with the modified Pras score and to the mutation load.

**Results:** 86 children were included, 49 girls and 37 boys, of whom 77 were under Colchicine therapy (90%). The mean age at first visit was 14.2 ± 1.9 years, the mean age at appearance of first symptom 10.9 ± 3.1 years, and the mean age at ISG fulfilment 13.1 ± 2.6 years. At the time of first visit, patients had oral ulcers (100%; 166/166), genital ulcers (68%; 113/166), pathergy positivity (63%; 104/166), papulopustular lesions (57%; 94/166), erythema nodosum (42%; 69/166), arthritis (20%; 33/166), eye disease (48%; 80/166), venular disease (13%; 22/166) and neurological disease (8%; 13/166). The clinical manifestations at first visit such as genital ulcer, papulopustular lesions, erythema nodosum and arthritis were less frequent compared to the adult population (1). The dural sinus thrombosis type of neurological involvement was the most common type of involvement (58%; 11/166). Familial history of BS was present in 41 (25%) patients. Information on the onset of piberty was available only in 94 patients. The onset was prepubertal in 39 and postpubertal in the remaining 55. While erythema nodosum was more common among those with prepubertal onset (24/39 vs 16/55), genital ulcer was more common among those with postpubertal onset (18/39 vs 44/55). A total of 13 (8%) were lost to follow-up after a single visit. Six (4%) (all males) had died. The median follow-up time in the remaining was median 10 years [4–17]. Causes of death in 6 males were pulmonary artery aneurysms (n = 2), hepatic failure due to Budd-Chiari syndrome (n = 1), suicide (n = 2) and pneumonia (n = 1). At the end of follow-up 18 patients (22.5%) had lost useful vision (bilateral: 8, unilateral: 10). The visual acuity in either eye was between 0.6–1.0 in 44 (56%) and between 0.5–0.1 in the remaining 18 (22.5%). Two patients (all males) with neurological involvement had severe neurological deficit (hemiplegia and optic atrophy. As seen adults, skin-mucosa lesions and joint involvement stopped occurring during the follow-up. Among 77 patients (50 M/27 F) in whom a final evaluation was available after a median of 9 [4–18] years, we observed that oral ulcer (90%) and papulopustular lesions (55%) were more frequent compared to genital ulcers (18%), erythema nodosum (29%) and arthritis (14%).

**Conclusions:** Pediatric cases made up around 0.2% of all Behcet patients. As in the adult, BS runs a severe course among the boys considering overall mortality in addition to the vascular and neurological involvement.

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**1698**

**The Role of Montelukast in the Management of Hyperimmunoglobulinemia D with Periodic Fever Syndrome (HIDS).** Donald P. Goldsmith2, Karyl S. Barron3, Anne Jones1, Dawn Chapelle1, Beverly Bartham1, Robert Lenbro1, Eric Hanson1, Amanda Ombrello1, Deborah Stone1 and Daniel L. Kastner1. 1National Institutes of Health, Bethesda, MD; 2National Institutes of Health, Drexel University College of Medicine, Philadelphia, PA; 3NIAMS, NIH, Bethesda, MD.

**Introduction:** In 2001 Freinkel et al reported elevated urinary levels of leukotriene E4 in 7 patients with HIDS and suggested that cysteinyi leuko-
tienes might play a role in its pathogenesis (Arch Dis Child 85:158). There is anecdotal evidence of benefits from treatment with the leukotriene receptor antagonist, montelukast.

**Aim:** To assess the therapeutic response of a pediatric HIDS cohort to montelukast.

**Methods:** This study is a retrospective chart review of 21 children with HIDS followed at the NIH Periodic Fever Program. Seventeen of 21 patients, ages 2–16 (mean 7.2y) were treated with montelukast. All were started on once daily standard doses of montelukast based on age (2–9y: 4mg; 6–14y 5mg; >15y: 10mg). Daily dosage was increased up to 8–12mg in 3 children; 6 patients were also treated with one additional similar dose on the first day of each febrile episode. Clinical response was assessed at each outpatient visit by the same attending physician by interview, clinical examination, and patient score cards.

**Results:** In 7 children there was no clinical response. In 2 the frequency of febrile episodes decreased slightly but each episode was more severe (not considered to be clinically beneficial). In 3 children, febrile episodes were judged to be less frequent and of reduced severity but montelukast was stopped because of behavioral side effects (one of these being parental fear [but not actual] of suicidal ideation). Similar improvement was noted in 4 additional children, but in all of these patients, benefit was judged to have dissipated after 6–8 months and montelukast was then stopped. Only 1 child still remains on montelukast. One child was lost to follow-up after starting montelukast.

**Conclusions:** Therapeutic benefit from montelukast is seen only in 7 (41%) of children and is not enduring. Significant side effects are not uncommon. In our experience montelukast is not likely to favorably alter the long term clinical course of pediatric HIDS. It seems improbable that leukotriene activation is primarily involved in the pathogenesis of HIDS but is more likely a secondary phenomenon associated with generalized immune stimulation.

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**1700**

**Therapeutic Approaches for the Treatment of Active Juvenile Dermatomyositis: An International Multicenter Study.** Rachana Hasija1, Angela Pistorio1, Angelo Ravelli1, Erkan Demirkaya1, Raju Khubchandani1, Dinara Gusemova1, Clara Malattia1, Carmen De Cunto1, Thomas Brent Graham1, Kathleen Haines1, Christian Huemer1, Yukiko Kimura2, Harald Mangge2, Silvana Martino2, Carlo Minetti3, Ellen Berit Nordal4, Pierre Philippet5, Manuel Salgado6, Alberto Martini6 and Nicolina Ruperto6, 1IRCCS G. Gaslini/Università degli Studi di Genova, Genova, Italy, 2IRCSS G. Gaslini/Università degli Studi di Genova, 3PRINTO

**Background:** Recently published articles have documented a marked improvement in long-term outcome and survival of juvenile dermatomyositis (JDM) patients but little information is available on standardized evaluations of response to therapy based on current treatment options.

**Objective:** Our aim was to evaluate in large prospective cohort of JDM patients the response to therapy over a 24 months period, according to the PRINTO JDM response criteria.

**Patients & Methods:** Clinical, laboratory and therapeutic modalities were collected prospectively between 2001 and 2004 in JDM patients by PRINTO/PRCGS members from 36 countries. Patients with probable or definite JDM, age ≤ 18 years, in an active phase of their disease, at 4 time points (baseline, 6, 12 and 24 months), were included. The validated core set variables were the global assessment by the physician and parent, muscle strength, functional ability, quality of life and disease activity tool. Patients were defined as improved if able to demonstrate at least 20% (50, 70, or 90) improvement from baseline in 3 or any 6 core set variables. Remission was defined as at least 50% improvement over 2 months.

**Results:** The analysis data set included 275/294 (94%) patients. Patients median ages at onset and disease duration visit were 7.2 and 6 months respectively with 168 (61%) being female. The greatest improvement in clinical and laboratory measures was observed in the first 6 months of therapy and maintained thereafter. At baseline treatment options included steroids in 269 (97.8%), metotrexate (MTX) in 134 (48.7%) with 91 newly started, cyclosporine A in 44 (16%), hydroxychloroquine in 37 (13.5%), and IVIG in 38 (13.8%). Oral steroids dose at baseline and 6 months were 1 and 0.3 mg/kg/day respectively, at 24 months 91 patients (52.3%) were still on steroids at 0.21 mg/kg/day; steroids pulses were used in 100 (36.4%) at baseline. Figure shows the 20, 50, 70, 90 response and remission over time.
A substantial improvement was observed in the initial 6 months (PRINTO 20 criteria 84%) and maintained thereafter.

**Conclusions:** Six months of therapy lead to a significant improvement in JDM core set measures and response criteria, that was maintained up to 2 years follow-ups. These data provided standardized response to therapy data in patients with JDM treated according to the current available options.

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**1701**

**Towards Defining Clinical Remission in Juvenile Systemic Lupus Erythematosus (jSLE).** Rina Mina1, Laura E. Schanberg2, B. Anne Eberhard1,12, Marisa S. Klein-Gitelman1, Gloria C. Higgins12, Karen One12, Nora G. Singer13, Kathleen M. O’Neil13, Lori B. Tucker1, Lisa F. Imundo2, Emily Von Scheven15, Shannen L. Nelson1, Frank Dressler15, Ruben Cuttica10, Claudia Saad Magalhaes10, Angelo Raveli9, Alberto Martini8 and Hermine I. Brunner5. 1BC Children’s Hospital, Vancouver, BC, Canada, 2Children’s Hospital of NY, New York, NY, 3Children’s Hospital of Philadelphia, Philadelphia, PA, 4Ohio State University, Columbus, OH, 5Stanford University, Stanford, CA, 6Texas Scottish Rite Hospital for Children, Dallas, TX, 7Duke Medical Center, Durham, NC, 8La Rabida Children’s Hospital, Chicago, Chicago, IL, 9University of Oklahoma, Oklahoma City, OK, 10University of California San Francisco, San Francisco, CA, 11Robert W Johnson University, Metuchen, NJ, 12Schneider Children’s Hospital, New Hyde Park, NY, 13Stanford University, Stanford, CA, 14Texas Scottish Rite Hospital for Children, Dallas, TX, 15Univ of Calif San Francisco, San Francisco, CA, 16University of Washington and Seattle Childrens’s Hospital, Seattle, WA.

**Background:** There is no established definition for global clinical remission in jSLE and to identify candidate criteria for measuring jSLE clinical remission.

**Methods:** Pediatric rheumatologists from all over the world (n=137) were surveyed about issues pertaining to defining and measuring clinical remission in jSLE. Consensus for the Delphi survey was set at 70%. Survey-responses were compared to prospective clinical data from a cohort of jSLE (n=33) considered to be in clinical remission by their treating physician.

**Results:** Survey response rate was 65%. There was consensus that ‘clinical remission’ is different from ‘minimal disease activity’ in jSLE. There was consensus that a jSLE patient in clinical remission (a) may have some subjective symptoms (i.e. fatigue, joint pains, headaches) but should not have any objective physical signs of disease activity; (b) may have a persistently positive ANA but should not have abnormal ESR, C3 level, complete blood count and urine sediment; and thus (c) may have disease activity scores > 0. No consensus was reached as to whether remission constitutes a time point or a period of time and whether medication use is important in its definition. Clinical data of jSLE patients considered to be in remission supported the survey responses (see Table).

<table>
<thead>
<tr>
<th>Outcome measure</th>
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<td>SLEDAI</td>
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<td>0-3</td>
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<tr>
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<td>0-5</td>
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<tr>
<td>BILAG</td>
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</tr>
<tr>
<td>Physician Global Assessment</td>
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<tr>
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<td>6-9</td>
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</table>

**Conclusions:** Consensus has been reached on preliminary variables useful to define and measure clinical remission in jSLE. Further studies are in progress.

**Disclosure:** R. Mina: NIH, 2; L. E. Schanberg: None; B. A. Eberhard: None; M. S. Klein-Gitelman: None; G. C. Higgins: None; K. One: None; N. G. singer: None; K. M. O’Neil: None; L. B. Tucker: None; L. F. Imundo: None; E. Von Scheven: None; S. L. Nelson: None; F. Dressler: None; R. Cuttica: None; C. Saad Magalhaes: None; A. Raveli: None; A. Martin: None; H. I. Brunner: NIAMS-NIH, 2.

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**1702**

**Towards the Development of Standardized Treatment Protocols for Proliferative Nephritis in Juvenile Systemic Lupus Erythematosus (jSLE).** Rina Mina1, Hermine Brunner2, B. Anne Eberhard3, Marilyn G. Punaro4, Stacy P. Ardoin5, Marisa S. Klein-Gitelman2, Joyce J. Hsu3, Lakshmi N. Moorthy4, Linda Wagner-Weiner6, Eyal Muscal1, Suhais M. Radhakrishna7, Jenny Palter8, Laura Schanberg2, Carol A. Wallace9, Norman T. Ilowite10, Emily Von Scheven11 and for the CARRA Lupus Disease-Specific Group. 1Baylor College of Medicine, Houston, TX, 2Children’s Hospital Los Angeles, Los Angeles, CA, 3Children’s Hospital Montefiore, Bronx, NY, 4Childrens Mem Hosp/UNW Univ, Chicago, IL, 5Cincinnati Child Hosp Med Ctr, Cincinnati, OH, 6Cincinnati Children’s Med Ctr, Cincinnati, OH, 7Duke Medical Center, Durham, NC, 8La Rabida Children’s Hospital, Chicago, IL, 9Lupus Foundation, 10Ohio State University, Columbus, OH, 11Robert W Johnson University, Metuchen, NJ, 12Schneider Children’s Hospital, New Hyde Park, NY, 13Stanford University, Stanford, CA, 14Texas Scottish Rite Hospital for Children, Dallas, TX, 15Univ of Calif San Francisco, San Francisco, CA, 16University of Washington and Seattle Childrens’s Hospital, Seattle, WA.

**Background:** There is a paucity of clinical trials (RCTs) to help guide treatment of proliferative lupus nephritis (LN) in jSLE. Comparison of outcomes resulting from standardized treatment protocols may offer an alternative to expensive RCTs for elucidating the best therapy in this population.

**Objectives:** Describe current clinical practice patterns and patient-specific features that influence the management of proliferative LN in jSLE as a first step towards the development of standardized treatment protocols for LN in children.

**Methods:** Based on literature review, a Delphi survey pertaining to issues in LN induction and maintenance therapy was sent to 103 members of the SLE Subcommittee of the Childhood Arthritis and Rheumatology Research Alliance. Consensus was set at 80%.

**Results:** Survey response rate was 80%; most of the respondents had at least 6 years of clinical experience. The majority (79%) use cyclophosphamide according to the NIH protocol as induction therapy for Class IV LN. Mycophenolate mofetil (MMF) is less commonly used (17%) and rituximab and azathioprine were rarely prescribed for induction. The choice for induction agent is influenced by co-existent cerebritis and risk for non-adherence but not patient age, race or gender. MMF is the medication of choice for maintenance therapy. Although corticosteroids are almost universally utilized for LN therapy, there is a striking variability in the regimen (dose, route, and duration) employed. There was consensus that definitions of flare and response based on ACR/EULAR renal outcomes criteria are useful to guide treatment decisions. No consensus was reached about duration of induction or maintenance therapy; treatment adjustment for LN relapse; treatment-effects of nephrosis or persistent proteinuria, and strategies for prevention of medication side-effects. LN is typically monitored with C3/C4 levels, spot urine protein to creatinine ratio, anti-dsDNA antibody titers, GFR, and urine sediment while repeat kidney biopsy is not routine.

**Conclusions:** While there is a marked variation in practice patterns among pediatric rheumatologists in the treatment of Class IV LN in jSLE, cyclophosphamide is often the preferred induction medication, and MMF is the maintenance therapy of choice. These survey responses will help guide the development of standardized treatment protocols. Based on the experience from other chronic diseases, this will allow for comparative effectiveness studies to determine the optimal therapy for LN in children, thereby leading to improved outcomes.

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**1703**

**Background:** The incidence of complex regional pain syndrome (CRPS) in hospitalized pediatric patients has been incompletely characterized and optimal treatment is debated.

**Methods:** We conducted a retrospective observational study using Pediatric Health Information Systems (PHIS), an administrative database from 40 freestanding US children’s hospitals. We determined admission temporal trends, patient characteristics, and drug therapy of children with a discharge diagnosis of CRPS between 1 January 2004 and 31 December 2009.

**Results:** During this 6-year study, there were 848 hospitalizations for CRPS, of which 644 were an initial admission. The median age was 14 (IQR: 11–16 years), and three-quarters of the patients were females. Seventy-five percent were white, 9% black, 2% Asian, 5% other, 9% unknown. Overall time, there was a significant increase in cases of CRPS (from 18.6 cases per 100,000 admissions in 2004 to 49.2 cases per 100,000 admission in 2009; P = 0.03, by test for trend). The median length of stay for all 848 admissions was 5 days (IQR: 3–9 days). Pharmacologic drug therapy during the initial admission included narcotics (490 patients, 78.4%), non-narcotic analgesics (214 patients, 33.3%), sedative hypnotics (149 patients, 23.8%), and anesthetics such as ketamine (178 patients, 28.5%).

**Conclusions:** The number of hospitalized children with CRPS has increased significantly over the last 6 years, due to either increasing incidence of this chronic pain syndrome, improved recognition and diagnosis, a shift in diagnostic coding, or some combination of these mechanisms. Regardless, the treatments received by these patients are diverse and warrant study regarding short and long term effectiveness.

Figure: Annual hospital admissions for children with CRPS.

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**1705**

**Validation of Birmingham Vasculitis Activity Score in Childhood Vasculitis**

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**Background:** Unlike for adults patients with systemic vasculitis, there are no validated tools to measure disease activity status in childhood (c-) systemic vasculitis.

**Objectives:** Our aim was to validate the last version of Birmingham Vasculitis Activity Score (BVAS v 3) and the Disease Extend Index (DEI) for comprehensive assessment of paediatric primary c-systemic vasculitis.

**Methods:** We extracted from the PRINTO database all patients who fulfilled the Henoch-Schoenlein (HSP), childhood (c) polyarteritis nodosa (c-PAN), c-Wegener (c-WG) and c-Takayasu (c-TA) EULAR/PRINTO/PRES c-vasculitis classification criteria and whose disease duration at the time of diagnosis was ≤3 months. Data were also available for follow-up evaluation ≥3 months after diagnosis. The validation of the BVAS and DEI were examined by assessing discriminant ability among the 4 c-vasculitis, correlation validity by Spearman correlation coefficient with physician’s global assessment of disease activity (MD global), indexes of inflammation (ESR/CRP), responsiveness to change over time through the standardizes response mean (SRM); A SRM value <0.5 is considered small, ≥0.5 and <0.8 moderate, and values ≥ 0.8 represent large effect.

**Results:** The analysis data set included 796/1124 (71%) patients (M:F 669 (%): there were 669 HSP, 80 c-PAN, 25 c-WG and 22 c-TA. The median age of the diagnosis was 6.99-year (6.6–11.96) and median delay for the diagnosis from the onset of signs or symptoms was 0.01 (0.003–0.027) years. In the table 1 are reported the 9 subscore of the BVAS, the total BVAS score, the DEI, the MD global and indexes of inflammation. The BVAS was able to discriminate between the 4 c-vasculitides with total BVAS scores equal to 9 (6.0–14.0), 17.5 (11.5–24.5), 23 (19–29), 15 (11–20) in HSP, c-PAN, c-WG and c-TA respectively.

**Table 1.** Discriminant ability of the BVAS total scores and the other tools: data are medians (1*-3* quartiles).

<table>
<thead>
<tr>
<th>All patients n = 796</th>
<th>HSP n = 669 (%)</th>
<th>c-PAN n = 80 (%)</th>
<th>c-WG n = 25 (%)</th>
<th>c-TA n = 22 (%)</th>
<th>P values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BVAS 10 (8.0–16.0)</td>
<td>9 (6.0–14.0)</td>
<td>15 (11.5–24.5)</td>
<td>23 (19–29)</td>
<td>15 (11–20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DEI 5 (4.0–6.0)</td>
<td>5 (4.0–6.0)</td>
<td>5 (4.0–6.0)</td>
<td>5 (4.0–6.0)</td>
<td>5 (4.0–6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MD global 9 (3.7–7)</td>
<td>9 (3.7–7)</td>
<td>9 (3.7–7)</td>
<td>9 (3.7–7)</td>
<td>9 (3.7–7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP 1.38 (0.5–4.33)</td>
<td>1.38 (0.5–4.33)</td>
<td>1.38 (0.5–4.33)</td>
<td>1.38 (0.5–4.33)</td>
<td>1.38 (0.5–4.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESR 29 (14.0–51.5)</td>
<td>29 (14.0–51.5)</td>
<td>29 (14.0–51.5)</td>
<td>29 (14.0–51.5)</td>
<td>29 (14.0–51.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P values refers to ANOVA with Dunn text as a post hoc.
The cutaneous and cardiovascular sub-score are able to distinguish TA patients from the others; the ENT sub-score shows a significant ability to discriminate the c-WG patients from the others. A strong correlation was found between the BVAS and DEI (r = 0.80) while correlation with MD global were moderate (r = 0.49) and poor with CRP and ESR (r = 0.34, r = 0.31). Responsiveness was large for BVAS total score (SRM = 1.38), DEI (SRM = 1.9), MD global (SRM = 1.3) and ESR (SRM = 0.85).

Conclusion: BVAS and DEI showed adequate discriminant ability and sensitivity to change but, poor to moderate convergent validity. Further work is needed in order to improve activity measurement in c-vasculitides.

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1706

Validation of the Newly Developed Pediatric Criteria for the Diagnosis of Familial Mediterranean Fever in a Large Pediatric Cohort of Western European Children with Periodic Fever.
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Purpose: FMF belong to the group of the periodic fever and is caused by mutations in the MEFV gene. Despite the possibility of a molecular characterization the diagnosis of the disease is mainly based on clinical criteria. Several diagnostic criteria have been developed, but none of them are specific for the pediatric age. A new set of criteria for the diagnosis of FMF in children were recently proposed (Yalcinkaya et al., Rheumatology 2009; 48(4):395). Aim of the study was to verify in a pediatric cohort of Caucasian patients with periodic fever the sensitivity and specificity of the new pediatric criteria in comparison to classical adult criteria (Livneh et al A&R 1997; 40(10):1879).

Patients & Methods: Detailed clinical information on 389 pediatric patients (mean age 8.5 y; SD:±8.3) with periodic fever were collected. All patients were screened for mutations of MEFV, TNFRSF1A and MEFV genes. For each patient adult FMF criteria and new pediatric FMF criteria were applied.

Results: 106 children carried mutations of MEFV gene (40 were homozygous or compound heterozygous, 66 with a single mutation), 38 patients displayed two mutations of MVK gene. Structural mutations of TNFRSF1A gene were found in 12 patients, whereas 18 patients displayed low-penetrance (R92Q or P46L) TNFRSF1A mutations. 215 patients were negative to all three genes. All patients (100%) carrying two mutations of MEFV gene and 49 heterozygous individuals (74%) were positive for adult FMF criteria. The same criteria were also positive in 135 (63%) of genetically negative and 71 % of individuals affected by other monogenic periodic fevers, with an overall specificity of 33.2%. Conversely, the new pediatric criteria were positive in 33/40 (82.5%) patients carrying two MEFV mutations and in 27/66 (41%) heterozygous patients, whereas its overall specificity was 76 %.Six out of the 7 patients carrying two MEFV mutations that did not satisfied the new pediatric criteria carried low penetration mutations and generally displayed a mild phenotype.

Conclusions: Pediatric FMF criteria show a higher specificity when compared to classical adult FMF criteria.

Disclosure: S. Federici: None; G. Calcagno: None; M. Finetti: None; A. Meini: None; A. Vitale: None; M. Cattalini: None; R. Caorsi: None; F. Zulian: None; A. Tommasinini: None; M. Baldi: None; J. Frenkel: None; I. Ceccherini: None; A. Martini: None; M. Gattorno: None.

1707

(22–52)adenosinomudrin Shifts Cytokine Balance from Th1 to Th2, Reduces IL-17A Expressions and Modulates Treg Cells in Collagen-Induced Arthritis. Marie-Dominique Ah Kioon1, Carine Asensio2, Kenj Koyama3, Sandrine Rulle4, Geraldo de Almeida Palogore3, Corinne Collet5, Jean-Marie Launay6 and Frederic P. Liote7.

1 Central Institute for Experimental Animals, Kawasaki, Japan, 2 Department of Virology, Division of Medical Science, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan, 3 Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine, Itabashi Tokyo, Japan, 4 Department of Infectious Diseases, National Research Institute for Child Health and Development, Tokyo, Japan, 5 Department of Microbiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, 6 Department of Virology, Division of Medical Science, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan, 7 Central Institute for Experimental Animals, Kawasaki, Japan.

Purpose: Rheumatoid arthritis is an inflammatory disease characterized by an increase in pro-inflammatory cytokine production due to activated Th1 and Th17 cells, and Treg dysregulation. Depending on cell types, adrenomedullin (AM) acts as a pro- or anti-inflammatory peptide in vitro. It exerts anti-inflammatory effects in vivo: AM reduces IL-1, IL-6 and TNF-α in septic mice and reduces collagen-induced arthritis (CIA) by up-regulating Treg cells. (22–52)AM, a fragment peptide which binds to AM receptors, acts also as an antagonist or agonist of ADM in vitro but its in vivo effects are unknown. Our aim was to evaluate effects of (22–52)AM on arthritis score, seric and articular cytokines expression in CIA.

Methods: CIA DBA/1 mice were treated with 1.2 μg/kg (22–52)AM or saline (control). Arthritis was scored as arthritis occurrence, intensity and duration and scored at day 45 (D45). Joints were processed for histology and protein studies and spleens for Treg expression. Expression of cytokines (ELISA) was studied in joint tissues and in sera.

Results: At D24 post-immunization, control CIA saline-treated mice started to develop arthritis as shown by arthritis score (ranging from 2 to 11 from 0 to 22). At sacrifice, (22–52)AM had decreased arthritis score compared to saline treated mice (5.8±2 vs 11±3, respectively; p<0.05). Incidence of arthritis was reduced by 25 % with (22–52)AM. Histological scores were decreased with (22–52)AM control to (0.56±0.04 vs 3.78±0.26, p<0.05). Compared to naive mice, saline-treated CIA mice had significantly higher serum levels of the pro-inflammatory cytokines TNF-α, IL-6, IL-17A). (22–52)AM completely abrogated this increase The broad systemic antiinflammatory activity of AM and (22–52)AM was accompanied by down-regulation of Th1 (TNF-α, IL-6) and Th17 (IL-17A) cytokine expression in knee extracts and up-regulation of anti-inflammatory cytokines (IL-10, IL-4). Furthermore, the number of Treg cells expressing CD4+CD25+Foxp3 was decreased in control CIA mice vs naive mice. (22–52)AM had no effect on number of Treg cells as compared to CIA control mice but, (22–52)AM treatment significantly increased serum IL-2 level in CIA mice.

Conclusions: (22–52)AM, along with reduced clinical and histological arthritis score in CIA, dramatically decreased serum and articular pro-inflammatory cytokines and triggered a robust increase in anti-inflammatory cytokines in CIA mice. (22–52)AM did not modulate the number of CD4+CD25+Foxp3 Treg cells but, increased Treg functions, as evidenced by increased IL-2 production, a marker of Treg activity.

Disclosure: M.-D. Ah Kioon: None; C. Asensio: None; K. Koyama: None; S. Rulle: None; G. Palogore: None; C. Collet: None; J.-M. Launay: None; F. P. Liote: None.
**Purpose:** Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology characterized by destructive synovitis and systemic immunologic abnormalities. In this study, whether Epstein-Barr virus (EBV) infection could result in erosive arthritis that resembles RA in NOD/Shi-scid/IL-2Rnull (NOD) mice was examined.

**Methods:** NOG mice, a highly immunodeficient mouse strain, in which the functional human immune system is reconstituted when they receive hematopoietic stem cell (HSC) transplants, were used. Human CD34+ HSCs were obtained from cord blood using a magnetic-activated cell sorting (MACS) direct CD34 Progenitor Cell Isolation Kit. These CD3+ cells (1×10^6 to 1.2×10^5 cells/mouse) were injected intravenously into 6–10-week-old, female, NOG mice. The NOG mice were inoculated intravenously through the tail vein with EBV (10^6 to 10^7 ITD-50) on days 106 to 180 after stem cell transplantation. EBV DNA in peripheral blood was quantified by a real-time quantitative polymerase chain reaction (PCR) assay based on the TagMan Assay (Applied Biosystems) 1 to 4 months after inoculation. One, two, six, and twelve months after being inoculated with EBV, the humanized NOG mice were sacrificed, and their joints were examined pathologically. The joint tissues were stained with hematoxylin-eosin (H-E) stain, and immunostaining and EBV in situ hybridization were performed.

**Results:** The joint tissues of the mice revealed pannus invading bone tissue, synovial membrane proliferation, and inflammatory tissues infiltrating the bone marrow (BM) space. Human CD4+ T cells were seen proliferating to the synovium and the BM near joints. Migration of large multinuclear giant cells, thought to be osteoclasts, was also evident in the pannus site. EBV-infected cells were mainly conformed within the BM of the EBV-giant cells, thought to be osteoclasts, was also evident in the pannus site. Migration of large multinuclear giant cells, thought to be osteoclasts, was also evident in the pannus site.

**Conclusions:** In this study, bone erosion accompanied by pannus and synovial membrane proliferation was confirmed at the joints of EBV-infected NOG mice. Furthermore, some EBV-infected NOG mice revealed BM erosion as a result of the inflammatory cell infiltration. The results of this study suggest that EBV-inoculated NOG mice develop erosive arthritis that resembles RA.

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**1709**

ASC Plays a Role in the Priming Phase of the Immune Response to Type II Collagen in Collagen-Induced Arthritis. Hideshi Yamazaki1, Michiko Takeoka1, Masato Kitazawa1, Takashi Ehara1, Naoki Iino1, Hiroyuki Kato2, and Shu-Chiyo Taniguchi2. Shinshu University Graduate School of Medicine, Matsumoto, Japan, 2Shinshu University School of Medicine, Matsumoto, Japan

**Background:** Although rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology, the role of TNF-α, IL-1β, IL-18, and IL-6 in the pathogenesis of RA has been well established. IL-1β and IL-18 are generated via cleavage of their pro-forms in the presence of the apoptosis-associated speck-like protein containing a caspase recruit domain (ASC), which is an adaptor protein that activates procaspase-1. We therefore investigated the involvement of ASC in RA progression and assessed the phase at which ASC exerts effects using ASC-deficient mice models of collagen-induced arthritis (CIA) and collagen antibody-induced arthritis (CAIA).

**Method:** CIA was developed in ASC-deficient (ASC-) and wild-type (ASC+/+) mice by four back-crosses to the DBA/1J background. CAIA was induced in ASC-deficient (ASC-null) and ASC+/+ mice using a mouse monoclonal anti-type II collagen five clone antibody cocktail. Histological findings and expression of pro-inflammatory cytokines in knee joints were then compared and disease severity in joint sections was graded using a scoring system. Analysis of IL-1β and IL-18 expression was also performed by immunohistochemistry.

**Results:** Histological examination and scoring of arthritis knee joints from ASC-/− mice and ASC-/−/ASC+/+ mice revealed that infiltration of inflammatory cells and cartilage/bone destruction were significantly decreased in ASC-/− mice compared with ASC+/+ mice. Conversely, no differences were observed between ASC-deficient mice and controls for CAIA. In CIA knee joints, IL-1β and IL-18 expression were lower in ASC-/− mice compared with ASC+/+ mice, whereas these cytokines were expressed at similar levels in the knee joints of ASC- and ASC+/+ CAIA mice.

**Conclusion:** We demonstrated that ASC-deficient mice were comparably susceptible to CAIA as normal mice, but were protected from disease severity in CIA. Thus, ASC is believed to be involved in early CIA development and may play a role in the priming phase of the immune response to type II collagen.

**Disclosure:** H. Yamazaki: None; M. Takeoka: None; M. Kitazawa: None; T. Ehara: None; N. Iino: None; H. Kato: None; S. Taniguchi: None.

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**1710**

Asymmetric Arthritic Flare in the Knees of TNF-Tg Mice Is Mediated by Expansion of CD23+/CD21hi B Cells and Ipsilateral Collapse of Lymph Nodes in Series. Jie Li, Igor Kuzin, Christopher Ritchlin, Ignacio Sanz, Andrea Bottaro, Liangping Xing and Edward Schwarz. University of Rochester

**Purpose:** The efficacy of TNF antagonists and anti-CD20 therapy has demonstrated a critical role for TNF and B cells in the pathogenesis of rheumatoid arthritis (RA). However, the mechanism underlying arthritic flare and asymmetric arthritis in particular joints is still unknown.

**Methods:** 5–7 month old TNF-Tg mice with expanding or collapsed PLNs were identified by longitudinal CE-MRI, and their knees were phenotyped for arthritic flare (defined as synovial volume >3mm³). PLNs (n=10) and ILNs (n=10) were harvested from the TNF-Tg mice, and their WT littermate controls, for flow cytometry or immunohistochemistry (IHC) to quantify Bin and their location within the node. Lymphatic drainage function of PLN and ILN were measured by NIR of ICG injected into the footpad or knee cavity, respectively.

**Results:** Flow cytometry of PLNs revealed a significant (p<0.05) 2.8-fold expansion of the Bin population from 7.2% in WT to 19.8% in TNF-Tg, which was consistent with the significant (p<0.05) 3.3-fold increase from 10% to 33.2% observed in WT and TNF-Tg PLN respectively. While Bin numbers were similar in both expanding and collapsed PLNs, IHC revealed that ILN ipsilateral to collapsed PLN have similar lymphoid architecture in which Bin are depleted from the follicular region, and reside in paracortical areas. Controls, for flow cytometry of ILNs revealed a significant (p<0.05) 3.3-fold expansion of the Bin population from 7.2% in WT to 19.8% in TNF-Tg, which was consistent with the significant (p<0.05) 3.3-fold increase from 10% to 33.2% observed in WT and TNF-Tg PLN respectively. While Bin numbers were similar in both expanding and collapsed PLNs, IHC revealed that ILN ipsilateral to collapsed PLN have similar lymphoid architecture in which Bin are depleted from the follicular region, and reside in paracortical areas.

**Conclusion:** Our results showed that ipsilateral ILN and PLN function in series. The decrease of lymphatic flow from the lower limb and Bin translocation from the follicles into lymphatic sinuses of draining LNs occur simultaneously. This finding supports a novel mechanism of the asymmetric arthritic flare that is triggered by Bin translocation in draining LN, which results in decreased afferent lymph flow from the inflamed joint. Future studies aimed establish this Bin “clogging” phenomena in mice and RA patients will be discussed.

**Disclosure:** J. Li: None; I. Kuzin: None; C. Ritchlin: None; I. Sanz: None; A. Bottaro: None; L. Xing: None; E. Schwarz: None.

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**1711**

CD44 Involvement in Arthritis: The Role of cd44-Splice Variants in Development of Collagen-Induced Arthritis in Mice. Celia Menckeberg1, Marjolein van Maanen1, Ronald van der Neut2, Steven T. Pals2, Margriet Vervoordeldonk2 and Paul P. Tak1. 1Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, 2Department of Pathology, Amsterdam, The Netherlands, 3Division of Clinical Immunology and Rheumatology, Amsterdam, The Netherlands, 4Division of Clinical Immunology, Amsterdam, The Netherlands
Objective: CD44 comprises a family of type I transmembrane glycoproteins with a wide tissue distribution including expression on leukocytes, fibroblasts, as well as epithelial and endothelial cells, and is capable of binding to several ligands, its preferred ligand being hyaluronic acid (HA). There have been several reports suggesting a role for CD44 and HA in rheumatoid arthritis (RA). Interestingly, it is now clear that alternative splicing and selective tissue distribution of CD44 variants confer specific functions to the CD44 molecule. Specifically, it has been shown that distinct CD44 splice variants differ in their ability to interact with extracellular matrix molecules (ECM) and with cytokines/growth factors. The role of these molecules in rheumatic diseases has been rarely studied so far, although it has for example been shown that CD44v3 is overexpressed on synovial fibroblasts, which carry an increased invasive capacity in vitro. In contrast, overexpression of CD44v8-9 was described to correlate negatively with the invasive capacity of fibroblast-like synoviocytes. Therefore, we explored the role of CD44 splice variants in an animal model of RA by using a unique series of CD44 knock-out-knock-in mice that selectively express CD44 variants, differing in their capacity to interact with hyaluronan, chemokines/cytokines, and growth factors.

Methods: In C57Bl6 mice collagen-induced arthritis (CIA) was induced at day 0 by an intradermal injection with chicken type II collagen at the base of the tail followed by the same injection on day 20. CIA was induced in wild-type (WT) mice, CD44 knock-out mice (KO), expressing none of the isoforms, and knock-out-knock-in strains CD44v4/s (able to bind HA but not growth factors, chemokines), CD44v3-v10 (carrying the heparan sulphate (HS) side chains), and CD44v4-v10 mice (similar to CD44v3-v10 but missing the HS attachment site). All mice were viable and did not show any detectable disease. Paw size was measured on day 56 after induction of disease. Disease progression was monitored by visual clinical scoring and measurement of paw swelling. In addition, inflammation and joint destruction were examined by histology and radiology. Serum levels of anti-collagen type II antibodies were measured by enzyme-linked immunosorbent assay.

Results: There was a significant decrease in the incidence and severity of arthritis in KO, CD44v4/s, KO, and CD44v4-v10 mouse strains (P<0.05), accompanied by reduced synovial inflammation (P< 0.05) and bone destruction, compared to WT mice. In contrast, the CD44v3-v10 mice showed a delayed onset of disease but the clinical scores reached similar levels as those in WT. Moreover, we found a specific decrease in the collagen-specific ‘Th1-associated’ IgG2a response (P<0.01) in mice with reduced arthritis activity, but not in CD44v3-v10 mice.

Conclusion: The results suggest the involvement of the CD44 v3 region in the development and expression of arthritis.

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1712

Counter-Regulatory Role of Interferon Regulatory Factor 7 in Serum Transfer K/BxN Inflammatory Arthritis. Susan E. Sweeney1 and Trevor B. Kimbler. 1University of California San Diego, La Jolla, CA, 2University of California San Diego

Purpose: Innate immune response pathways play a role in synovial activation and cell recruitment into the rheumatoid joint. Viral-stress inducible proteins such as type I interferon (IFNα and IFNβ), IP-10, and RANTES are produced through the activation of NF-κB, MAP kinases, and IFN-regulatory factors (IRF) as a result of innate sensor recognition of dsDNA. The IRF family members include the IRF response factor, also cell differentiation, cell cycle, and apoptosis. This study examines the effect of genetic deficiency of IRF7 in regulation of the type I IFN response in murine synoviocytes, macrophages, and a passive K/BxN serum transfer model of arthritis.

Methods: Fibroblast-like synoviocytes (FLS) and peritoneal macrophages isolated from IRF7−/− mice were stimulated overnight with poly (I-C) followed by Q-PCR to evaluate gene expression. Passive K/BxN serum transfer arthritis was induced in IRF7−/− mice and additional groups were treated with IFNβ or poly (I-C). Clinical arthritis scores were measured and synovial tissue Q-PCR was performed. Mouse serum was analyzed for IFNβ, IL-10, and IL-1RA by ELISA.

Results: Poly (I-C) stimulation of murine IRF7−/− FLS resulted in increased induction of pro-inflammatory gene expression of RANTES (5.2-fold, p<0.01), MIP1α (1.8-fold, p<0.05), and MMP-3 (2.7-fold, p<0.05) compared with C57BL/6 wild type FLS. In contrast, IRF7−/− macrophages stimulated with poly (I-C) showed significantly less induction of inflammatory cytokine gene expression, including IFNβ, IP-10, MIP1α and IL-6 (8.8-fold, p<0.01; 11.2-fold, p<0.01; 5.3-fold, p<0.05; 21.7-fold, p<0.005 respectively). In the K/BxN passive in vivo model, arthritis severity in IRF7−/− mice was significantly increased (day 12 score 8.8 vs. 3.9; p<0.01) compared with wild type K/BxN. Gene expression of IFNβ, RANTES, MIP1α, and IL-6 was decreased in IRF7−/− synovial tissue compared with K/BxN control synovium (3.9-fold, p<0.05; 2.2-fold, p<0.05; 2.4-fold, p<0.04; 1.7-fold, p<0.05 respectively). The serum IFNβ level in IRF7−/− mice was also significantly decreased compared with control K/BxN serum (2.8-fold, p<0.04). IRF7−/− mice injected with IFNβ had a decrease in paw score (ΔPaw = 1.8) similar to wild type mice (ΔPaw score = 2.9), suggesting that the increased arthritis might be partially due to decreased IFNβ. Poly (I-C) treatment diminished arthritis severity (17% change, p<0.05) in IRF7−/− mice and increased serum IFNβ levels (1.6-fold, p<0.05).

Conclusion: These data suggest that IRF7 contributes to regulation of the type I IFN response and cytokine production in cell-specific manner in macrophages (pro-inflammatory) and synoviocytes (anti-inflammatory). IRF7 plays an anti-inflammatory role in passive transfer K/BxN arthritis possibly through regulation of IFNβ. IRF7 also partially contributes to poly (I-C)-mediated inhibition of arthritis in this model. Our data suggest that TLR agonists that induce IRF7 might represent a novel therapeutic approach in the treatment of inflammatory arthritis.

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1713

Dectin-1 and NOD2 Mediate Zymosan-Induced Arthritis in Mice. Holly L. Rosenzweig1, Jenna S. Clowers2, Gabriel Nunez3, Janne T. Rosenbaum1 and Michael P. Davey4. 1Oregon Health & Science University/VA Medical Ctr, Portland, OR, 2Oregon Health Science Univ, Portland, OR, 3University of Michigan Medical School, Ann Arbor, MI, 4VA Medical Ctr, VA Medical Ctr/Oregon Health & Science University, Portland, OR

Purpose: Rheumatoid arthritis (RA) remains a disease of unknown etiology. Genetics, the environment and specific features of diarthroidal joints are presumed to play contributory roles. Receptors of the innate immune system within diarthroidal joints may contribute to arthritis by detecting components of infectious agents, a hypothesis often implicated in the etiology of RA. We sought to elucidate the role of innate immune receptors within the Toll-like receptor (TLR), NOD-like receptor (NLR) and C-type lectin receptor (CLR) families in the well-established murine model of zymosan-induced arthritis (ZIA).

Methods: Arthritis was elicited by intra-articular injections of zymosan or fungal cell wall components: curdlan, laminarin and mannan. The extent of disease within the joint was assessed by NIR-fluorescence imaging and histology. The contribution of individual immune receptors or a signaling molecule (CR3, TLR2, MyD88, Dectin-1, Dectin-2, NOD1, or NOD2) was assessed using knock-out mice or blocking antibodies. For fungal infection, mice were infected with Candida albicans and the presence of fungi and joint inflammation were assessed by PAS/green staining and NIR imaging.

Results: Systemic fungal infection caused mild arthritis in mice that coincided with the presence of fungi within the joint. As previously demonstrated, intra-articular injection of zymosan triggered arthritis in mice at 3 days following injection. This response was dependent on Dectin-1, a member of the CLR family. Dectin-2 also contributed to ZIA, but to a lesser extent than Dectin-1. However, deficiency in TLR2, MyD88 or CR3 did not significantly alter ZIA. Injection of curdlan, laminarin or mannan (the individual components of zymosan) showed that curdlan alone was the arthritogenic component of zymosan and the effect was dependent on Dectin-1. Somewhat surprisingly, we found that ZIA was dependent on NOD2 as NOD2 KO mice were resistant to disease. In contrast to NOD2, we found that NOD1 deficiency did not alter arthritis.

Conclusion: The present study elucidates the receptors involved in mediating ZIA. Together, Dectin-1 and NOD2 are essential receptors of the innate immune system in the arthritogenic effects of zymosan. This is the first association of NOD2 with innate immune responses to fungal components and points to a regulatory role for NOD2 in the normal physiology of diarthroidal joints. Given that mutations in NOD2 cause of an inherited form of arthritis (Blau syndrome), our findings further implicate NOD2 as an important protein within diarthroidal joints contributing to inflammatory arthritis.

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Dendritic Cell-Based Immunotherapy Combined with Low-Dose Methotrexate is Effective in the Treatment of Advanced Collagen-Induced Arthritis in Mice. Mi-Sun Kang1, Jung-Wook Lee1, Hyun-Soo Lee2, Chan-Bum Choi1, Hye-Soon Lee3, Sang-Cheol Bae3 and Yong-Soo Bae3. 1Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Republic of Korea, 2Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea, Republic of Korea, 3Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases.

Disclosure: M.-S. Kang:

Arthritis in Mice. Dendritic Cell-Based Immunotherapy Combined with Low-Dose Methotrexate (MTX) in advanced stage of CIA mice.

Methods: CIA mice in arthritis score 2-3 (5-6 weeks after primary CIA inoculation) were treated with MTX and collagen-loaded sDCs (CII-sDC) in three consecutive therapeutic cycles. Each therapeutic cycle was completed by administration of MTX three times on days 2, 4 and 6, followed by administration of CII-sDC on day 7. Footpad thickness and the disease severity of each mouse were measured once or twice a week for 90 days after completion of three therapeutic cycles. Fosp-3-positive regulatory T cell (Treg) populations, Th1/Th2 immune response, and cytokine profiles were assessed in the spleen and lymph nodes.

Results: Combination therapy with low-dose (0.5mg/kg) MTX and CII-sDC alone was more effective than high or low dose MTX alone or combination of high dose MTX and CII-sDC in inhibiting disease progression. Treatment with CII-sDC alone also showed comparable effect. CD4+ Fosp-3+ Treg populations were markedly increased in mice treated with the combination therapy compared to mice treated with CII-sDC alone as well as the proportion of Foxp3+ CD4+ T cells. IL-10 secretion also increased in proportion to the level of induced Treg. The combination therapy reduced the secretion of interferon gamma (IFN-γ), but did not affect or slightly increased the IL-4 secretion in the mixed lymphocyte reaction with spleen or lymph node T cells. Treg induced by combination therapy were effective in inhibiting CII-specific T cell proliferation. However, total CD4+ T cell populations were not significantly changed by the combination therapy.

Conclusion: Combination therapy with low-dose MTX and CII-sDC, or CII-sDC alone, was efficacious in the treatment of advanced arthritis mice by inducing antigen-specific Treg population, rather than changing Th1/Th2 immune deviation, followed by blocking autoreactive T cell proliferation, resulting in disease control.


Histone Deacetylase Inhibitor (HDAl) Ameliorates Chronic Arthritis in SKG Mice by Altering Conventional Dendritic Cells (cDCs) Phenotype into Tolerogenic DCs. Kenta Misaki1, Akio Mornobu2, Jun Saegusa3, Yoshiaki Miyamoto4, Shinpei Kasagi2, Shinichi Kumagai1. 1Clinical Immunology and Pathology, Kobe University, Kobe, Japan, 2Clinical Immunology and Pathology, Kobe University, Kobe, Japan, 3Clinical Immunology and Pathology, Kobe University, Kobe, Japan

Background & Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory polyarthritis, leading to joint destruction. cDCs contribute to pathogenesis of RA by triggering the immune responses. HDAI plays a significant role of controlling gene transcription, and has been reported to regulate immune responses. Here we examined the therapeutic effects of HDAl (Trichostatin A: TSA) on the RA model mice and cDCs.

Methods: SKG mice were injected with Zymosan A (ZyA) to induce chronic arthritis. DMSO or TSA was daily administered to SKG mice. Cell surface molecules and cytokine production in splenic cDCs, clinical arthritis scores, histological arthritis scores were evaluated in each group. The effects of TSA on bone marrow cells-derived cDCs treated with ZyA (BMDCs-ZyA) were assessed by flow cytometry, ELISA, real-time PCR (RT-PCR) and the allo-mixed lymphocyte reaction (allo-MLR) in vitro.

Results: Clinical arthritis scores and histological arthritis scores in SKG mice treated with TSA were significantly lower than those with DMSO. CD80 and CD86 expression of splenic cDCs in TSA group were notably down-regulated compared to those in DMSO group. IL-17A production in CD4 positive splenocytes was also decreased in TSA group. In vitro, IL-12p70, IL-12p40, IL-6 secretions and CD80, CD86 levels of BMDCs-ZyA were reduced in BMDCs-ZyA with TSA by flow cytometry and ELISA, respectively. Indoleamine 2,3-dioxygenase (IDO) expression in BMDCs-ZyA with TSA was much higher than those in BM-cDC-ZyA determined by immunohistochemistry. Pretreatment of BM-cDCs with ZyA + TSA resulted in significantly reduced naïve CD4 positive T cell proliferation compared to that with BMDCs-ZyA in allo-MLR.

Conclusions: TSA has notable anti-arthritis effects on SKG mice by modulating functions of cDCs. TSA alters DC function into tolerogenic DC, such as decreased expression of co-stimulatory molecules and pro-inflammatory cytokines, increased IDO expression, and reduced T cell proliferation. This is the first report that HDAl ameliorates the disease activity of SKG mice.

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IDO Expressed CD11c+CD11b+ Dendritic Cells Enhance the Differentiation of Ag Inducible CD4+CD25+ Regulatory T Cells in Induction of Oral Tolerance under the Inflammatory State. Min Jung Park1, Yong-Geun Jung1, Su-Jin Moon2, Jin-Min Kim3, Seung-Ki Kwok2, Ji-Hyeon Ju4, Kyung-Su Park5, Hyun Sil Park2, Mi-La Cho2, Sung-Hwan Park2 and Ho-Yoon Kim1. 1Kang Nam St Marys Hospital, Seoul, Korea, Republic of Korea, 2Kang Nam St Marys Hospital, Seoul, Korea, Republic of Korea, 3Kang Nam St Marys Hospital, Seoul, Korea, Republic of Korea, 4Kang Nam St Marys Hospital, Seoul, Republic of Korea, 5Kang Nam St Marys Hospital, Seoul, Republic of Korea.

Repeated oral administration of an antigen is known to induce immunological hypo-responsiveness to that specific antigen, which is called oral tolerance. The mechanism of oral tolerance is believed to involve regulatory T cells (Tregs), tolerogenic dendritic cells (DCs) and several immunoregulatory molecules. Indoleamine 2,3-dioxygenase (IDO) which is expressed by DCs suppress T cell responses by catabolizing tryptophan and generating Tregs. In this experiment, we tried to identify which DC subsets in spleen express IDO and are involved in the generation of CD4+CD25+ Tregs during oral tolerance induction in murine collagen-induced arthritis (CIA) model.

We separated CD11c+ CD11b+ DCs from CIA mice after repeated oral administration of type II collagen (CII). The splenic CD11c+CD11b+ DCs produced IL-10 and TGFB-β which are preferentially involved in the oral tolerance induction. In addition, splenic CD11c+CD11b+ DCs from CIA mice expressed higher level of IDO than those from PBS fed CIA mice did. We compared the CIA oral tolerance-induced IDO expression by and Treg inducing effect of CD11b+ DCs from CIA-illuminized CIA mice with those from un-immunized control mice. IDO expression in CD11b+ DCs as well as the proportion of Foxp3+ T cells in spleen and Peyer’s Patch was significantly higher in CIA-illuminized CIA mice (inflammatory state) than in CIA-illuminized mice. Our data suggest that the immunoregulatory effect of CIA-illuminized CD11b+ DCs is more prominent in CIA-illuminized CIA mice (inflammation condition). CD11c+CD11b+ DCs from tolerized mice suppressed CIA-specific T cell response and down-regulated proinflammatory cytokine production in an IDO-dependent manner. Notably, IDO-expressing CD11c+CD11b+ DCs from CIA-illuminized mice converted CD4+CD25+T cell into CD4+CD25+Foxp3+ regulatory T cells with regulatory property.

Our results demonstrated that after repeated CIA administration the specialized, tolerogenic DC subset, such as CD11b+ DCs can induce the peripheral differentiation of Tregs, prominently in inflammatory condition. Our data suggest that IDO-expressing CD11c+CD11b+ DCs play a crucial role in oral tolerance through an IDO-dependent pathway in inflammatory state and may be a candidate cell population for therapeutic modality in the treatment of autoimmune arthritis.

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Immunisation with Citrullinated Human and Porphyromonas Gingivalis Envelope Induces Rapid Onset Arthritis in IL-10 Deficient Genetically Engineered Mice. Andrew J. Kinloch1, William Brindnell2, David Yue3, Lilian Barra3, Natalia Wegner4, Karin Lundberg1, David A. Bell1, Ewa Cairns and Patrick J. Venables. 1Imperial College London, 2Imperial College London, London, United Kingdom, 3SJHC, London, ON, Canada, 4Univ Western Ontario, London, ON, Canada, 5University of Western Ontario.
Background: Antibodies to citrullinated (cit) proteins/peptides are specific for RA, and predict more severe disease. Well-documented specific cit protein antigens include cit-fibrinogen and, more recently, cit-a-enolase. HLA DR4 alleles are genetic risk factors for antibodies to both antigens, with a preferential link with antibodies to an immunodominant peptide (CEP-1) of cit-a-enolase (Mahl et al, Nature Genetics, 2009). The CEP-1 sequence is conserved in the enolase orthologue of Parvynomonas gingivalis, a bacterium which also expresses an active deiminase, which can citrullinate both cit-fibrinogen and cit-a-enolase. This suggests that antigens generated by this bacterium could breach immunological tolerance. Hill et al (J Exp Med, 2008) demonstrated that mice expressing the human 0401 gene (DR4-IE transgenic mice) immunised with cit-fibrinogen developed chronic arthritis after 40 days and that this arthritis was dependent on the 0401 transgene. Given that the link with 0401 is particularly strong for anti-CEP-1 in human disease, the purpose of this study was to examine the arthritogenicity of cit-a-enolase in the same DR4-IE transgenic mouse model.

Methods: Recombinant human and P. gingivalis citroenase were citrallinated in vitro with rabbit PAD2 and used to immunise DR4-IE mice and control mice (MHC class II knockout and C57BL/6). Arthritis was quantified by measuring ankle swelling in the hind paws. The joints were examined by histopathology. Serum IgG reactivity with enolase and cit- enolase was assayed by Western blotting and ELISA. IgG antibodies to CEP1 and the arginine methylesterase control (REPI) were measured by ELISA.

Results: All DR4-IE mice immunised with cit-enolase, both from human and P. gingivalis, developed significant ankle swelling (mean 0.98 +/- 0.05 mm) in both hind paws, which peaked at day 20 whereas none of the other groups developed arthritis (swelling < 0.20 mm) p<0.0001 (Student’s t-Test). Pathology of arthritic joints showed synovial hyperplasia, but a relative paucity of leukocyte infiltration. IgG antibodies reacting with both cit- and non-cit-enolase, and also CEP1 and REPI were detectable in all groups apart from those treated with the REPI control. In contrast, the MHC class II knockout group.

Conclusions: Both human and P. gingivalis cit-enolase induce arthritis in DR4-IE mice. The arthritis was restricted to the group with the 0401 transgene, whereas the antibody response to both cit and non-cit antigens was not MHC-dependent. These data support recent epidemiologic evidence in humans that cit-enolase is an antigen of etiologic importance in RA in the context of DR4 risk alleles, and provides a novel model for investigating an etiologic role for P. gingivalis in RA.

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Loss of Integrin alpha2beta1 Suppresses Joint Inflammation and Cartilage Destruction in Mouse Models of Rheumatoid Arthritis.

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Background: Integrins are the main receptors for cell-matrix interactions, and integrin signaling is critical for a variety of cellular functions such as adhesion, cell spreading and inflammatory responses. Alpha2beta1 integrin acts as major receptor for type I collagen on a number of different cells, including inflammatory cells and fibroblasts. Although alpha2-deficient mice appear normal apart from mild platelet dysfunction, it was shown that alpha2 contributes to the induction and activation of MMPs in tissue remodeling. Based on the hypothesis that under stress conditions such as chronic inflammation alpha2beta1 integrin is more involved in the activation of synovial cells, we investigated its role in inflammatory arthritis.

Methods: The role of alpha2 was examined in two different murine models of arthritis, (i) alpha2-deficiency during antigen-induced arthritis (AIA), and (ii) alpha2-deficient mice crossed with arthritic human TNFalpha transgenic (hTNFtg) mice. Clinical signs of arthritis, weight and histological scores of synovitis and cartilage destruction were investigated using standard clinical evaluation and histomorphometric analysis. In addition, we analyzed MMP expression in tissue sections, serum and fibroblast-like synoviocytes (FSL) from all genotypes and analyzed changes in proliferation and ERK phosphorylation. The role of the alpha2 subunit in the attachment of FLS to healthy and IL-1 damaged articular cartilage was analyzed using an established in vitro assay.

Results: At day 5 after AIA induction, alpha2(-/-) mice showed a decrease of joint inflammation (75%) and proteoglycan loss (54%) compared to wildtype mice. In addition, MMP3 levels were significantly lower in tissue sections of alpha2(-/-) mice. In hTNFtg mice, the loss of alpha2 integrin resulted in improved clinical signs and symptoms. hTNFtg/alpha2(-/-) mice had less paw swelling (1.80 vs. 2.38), increased grip strength (4.2 vs. 1.71), and a decreased cartilage erosion (8.55% vs. 48.5%) and significantly reduced attachment of FLS to cartilage (55.5%). MMP-3 expression was reduced in the serum and in FLS of alpha2(-/-) mice. Additionally, the proliferation of alpha2(-/-) FLS was reduced, particularly after induction of proteoglycan loss in IL-1 treated articular cartilage in vitro.

Conclusions: The results support the hypothesis that alpha2 deficiency is an important factor in inflammatory cartilage destruction by interfering with fibroblast attachment and proliferation as well as by modulating MMP expression.

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Lung Inflammation and Pulmonary Function Alterations in Collagen-Induced Arthritis and in the Absence of Interferon-gamma Signaling.

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Wednesday, November 10
Background: Rheumatoid arthritis (RA), a systemic inflammatory disease affecting the joints, is regularly associated with extra-articular symptoms. Lung complications are one of these manifestations and have a profound impact on patient well-being and survival. There are no reports on pulmonary complications in collagen-induced arthritis (CIA), a widely used animal model for RA. We investigated potential lung inflammation and changes in pulmonary functions during CIA, using both wild type and interferon-gamma (IFN-γ) receptor knock-out (IFN-γR KO) mice, which develop a more severe form of arthritis.

Methods: CIA was induced in mice by a subcutaneous injection of collagen type II in Freund’s adjuvant. At various time points after induction, cytokine and chemokine expression in the lungs and in synovial tissues were analysed by qPCR. Cell influx in the airways and inflammation in lung tissue were determined by bronchoalveolar lavage (BAL) and histology, respectively. To analyse the impact of arthritis on lung physiology, lung function measurements were assessed via the invasive forced oscillation technique of the flexiVent system. Resistance and elastance of the whole lung and more specific, the large airways and the alveoli were measured.

Results: Upon induction of CIA, the onset of arthritic symptoms was accompanied by induction of interleukin-1β (IL-1β) and the neutrophil chemokine Granulocyte Chemotactic Protein 2 (GCP-2) in the synovial tissues of both wild type and IFN-γR KO mice. In the lungs of wild type mice, IL-1β levels became detectable at day 10, before the onset of arthritis. In arthritic IFN-γR KO mice, lungs expressed GCP-2 and other chemokines such as KC and Monocyte Chemotactic Protein 1 (MCP-1). BAL fluid of arthritic wild type and IFN-γR KO mice contained elevated numbers of cells as compared to their respective naïve counterparts. The increase in cell numbers was caused by influx of macrophages and lymphocytes. BAL fluid of immunized IFN-γR KO mice showed an additional influx of neutrophils. On histological examination, lungs of arthritic IFN-γR KO mice demonstrated a perivascular lymphocytic infiltration into the lung tissue which was absent in arthritic wild type mice and in naïve animals. When lung function measurements were performed, tissue elasticity (H) and resistance (Rn) of the lungs were significantly elevated in arthritic IFN-γR KO mice as compared to naïve mice. No such effects could be observed in wild type mice.

Conclusions: Lung manifestations, as evident from expression of pro-inflammatory cytokines and chemokines in lung tissue and from cell influx in BAL, were detectable in both wild type and IFN-γR KO mice. In the lungs of wild type mice, IL-1β levels became detectable at day 10, before the onset of arthritis. In arthritic IFN-γR KO mice, lungs expressed GCP-2 and other chemokines such as KC and Monocyte Chemotactic Protein 1 (MCP-1). BAL fluid of arthritic wild type and IFN-γR KO mice contained elevated numbers of cells as compared to their respective naïve counterparts. The increase in cell numbers was caused by influx of macrophages and lymphocytes. BAL fluid of immunized IFN-γR KO mice showed an additional influx of neutrophils. On histological examination, lungs of arthritic IFN-γR KO mice demonstrated a perivascular lymphocytic infiltration into the lung tissue which was absent in arthritic wild type mice and in naïve animals. When lung function measurements were performed, tissue elasticity (H) and resistance (Rn) of the lungs were significantly elevated in arthritic IFN-γR KO mice as compared to naïve mice. No such effects could be observed in wild type mice.

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1721 Macrophage Migration Inhibitory Factor Plays an Important Role in Inflammatory Arthritis. Mohammad A. Amin, Jeffrey H. Ruth, Bradley J. Rabquer, Phillip L. Campbell, Solhee Lee, John R. David and Alisa E. Koch. 1Harvard School of Public Health, 2University of Michigan, 3VA Medical Service and University of Michigan Medical School, Ann Arbor, MI

Purpose: Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine which plays an important role in an inflammatory poisson of rheumatoid arthritis (RA). We have previously shown that MIF mediates angiogenesis via phosphatidylinositol 3 kinase (PI3K) and mitogen activated protein kinase, and upregulates the expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in monocytes via Src, PI3K, and NF-κB. In this study, we examined the contribution of MIF to experimental inflammatory arthritis using K/BxN serum induced arthritis by employing MIF null and wild type (wt) mice.

Methods: We induced serum transfer K/BxN arthritis in MIF null and wt mice to examine the role of MIF in mouse inflammatory arthritis. We injected 150 µl of pooled K/BxN serum on days 0 and 2. Mice were scored clinically and ankle circumference was measured with a caliper before the induction of arthritis and then every day by an observer blinded to the experimental groups. We used enzyme linked immunosorbent (ELISA) assays to determine cytokine levels in arthritic MIF null ankle homogenates compared to wt mouse ankle homogenates. We also performed immunohistochemistry (IHC) to determine the inflammatory response in MIF null and wt mouse ankle sections. To further elucidate the contribution of MIF in an animal model of arthritis, we subjected MIF null and wt mice to sublethal total body irradiation. We performed bone marrow transfer experiments. In these experiments, irradiated MIF null mice received wt bone marrow cells (106 cells in 100 µl of PBS) and vice versa. After 12 weeks of bone marrow transplant, we induced K/BxN arthritis in these mice and collected ankles.

Results: MIF null mice had significantly less arthritis, showing a significant decrease in ankle circumference and articular index compared to wt mice. Mouse ankles were harvested on day 9 (day of maximal arthritis). Some of ankles were snap frozen for homogenization and cytokine analysis, while others were frozen in OCT for histology. While there was no difference in interleukin-1β in mouse ankle joint homogenates, monocyte chemotactic protein-1 (MCP-1/CCL2) was significantly decreased in MIF null mouse arthritic ankle homogenates compared to wt mouse arthritic ankles. This decrease was ~2 fold, suggesting an important role of MIF in the regulation of MCP-1/CCL2. IHC of MIF null ankle sections revealed reduced inflammation compared to wt mice. There was a marked decrease in MCP-1/CCL2 levels in irradiated wt mice injected with bone marrow harvested from MIF null mice compared to irradiated MIF null mice which received wt bone marrow, further confirming the significance of MIF in inflammatory arthritis.

Conclusions: These data suggest an important role for MIF in induction of MCP-1/CCL2 in mouse inflammatory arthritis. MIF may be a potential therapeutic target for the treatment of chronic inflammatory diseases like RA.

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1722 Matrix Components Influence the Aggressive Behavior of Rheumatoid Arthritis Synovial Fibroblasts. Stephanie Lefevre, Birgit Zimmermann, Matthias Geyer, Angela Lehr, Henning Stürz, Stefan Rehak, Ulf Müller-Ladner and Elena Neumann. 1Dept Experimental Orthopedics, Justus-Liebig-University Giessen, 2Dept Internal Medicine and Rheumatology, Justus-Liebig University Giessen, Bad Nauheim, Germany, 3Dept Internal Medicine and Rheumatology, Justus-Liebig University Giessen, 4Dept Orthopedics and Orthopedic Surgery, Justus-Liebig-University Giessen, 5Dept Orthopedics and Trauma Surgery, Markus-Hospital, Frankfurt

Background: Central mediators in joint destruction in rheumatoid arthritis (RA) are activated synovial fibroblasts (SFs). They adhere to and invade into human cartilage but the molecular details of this disease-specific behavior are known only to a limited extent. As we could show the migratory potential of RASFs in the SCID mouse model of RA, in the present study we addressed the role of extracellular matrix (ECM) regarding RASF adhesion and migration.

Methods: Chemotactic effects of finely ground cartilage were analyzed in vitro. After (membrane-) coating with Matrigel, growth factor-reduced Matrigel or collagen type II and adding RASFs, adhesion (after 30min) and transmigration (after 16h) of RASFs were analyzed. Isolated RASFs or whole synovial RA tissue were implanted with healthy human cartilage (ipsilateral; 1 subcutaneously into SCID mice. Cartilage without RASFs was included contralaterally. To analyze potential effects of the ECM, bovine or murine cartilage or cartilage without vital chondrocytes was implanted. ECM components were analyzed in vivo by coating the carrier matrices in various combinations (either the ipsilateral or the contralateral carrier matrix or both) with the following factors: Matrigel, fibronectin, aggregan, growth factor-reduced Matrigel, collagen type II, PuraMatrix Peptide Hydrogel. Histological analyses of implants followed after 60 days.

Results: RASFs invaded the coimplanted cartilage directly and migrated to and invaded into the cartilage thereby contralaterally independently of the species background and the source of RASFs (isolated or whole RA synovium). Cartilage inserted into carrier matrices coated with growth factor-reduced Matrigel showed a reduced invasion (invasion score 1 (non-coated carrier-matrix): 1.7±0.5, Co (coated carrier matrix): 0.2±0.3; 1 coated carrier matrix): 0.9±0.6, Co (non-coated carrier matrix): 2.0±0.0) compared to cartilage in uncoated matrices (control; I: 2.1±0.6; Co: 1.5±0.4). A concentration-dependent increase of the chemotactic effect of finely ground cartilage regarding RASF migration was demonstrated in vitro. Transmigration and adhesion of RASFs were decreased in vivo after coating with growth factor-reduced Matrigel compared to coating with Matrigel or collagen type II (up to 80% or 90% resp.).

Conclusion: The ECM as well as matrix associated components such as growth factors influence RASF migration from the ipsilaterally to the contralaterally implanted cartilage. Accordingly, adhesion of RASFs to growth factor-reduced Matrigel was decreased compared to other coatings. In contrast, chondrocyte vitality and species background of the cartilage appear
not to be crucial for RASF migration. Taken together, matrix components play a central role in RASF migration, transmigration, adhesion to cartilage and following joint destruction.

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1723
Monocytes Are Required for Progression but Not for Initiation of Arthritis in Mouse Model of Autoantibody-Mediated Arthritis. Alexander Misharin1, Evan Weber1 and Harris R. Perlman1. 1Division of Rheumatology, Northwestern University, Chicago, IL, 2Northwestern University, Chicago, IL.

Background: Monocytes and macrophages play essential role in pathogenesis of rheumatoid arthritis. However their role in initiation vs. perpetuation of inflammatory arthritis in rodent models is unclear. K/BxN serum-transfer model is a commonly used model for studying the effector phase of arthritis in mice. Role of the neutrophils and mast cells in this model has been studied in details and it is now clear that these cells are essential for initiation of arthritis. Thought there are no doubts that monocytes and macrophages play very important role arthritis, it is less well studied. Previous studies have shown that mice depleted of macrophages by clodronate liposome treatment are completely resistant to K/BxN serum-induced arthritis and that reconstitution of these mice with macrophages from naive animals reverses this resistance. However effect of clodronate is long-term and irreversible and it does not allow assessing role of monocytes and macrophages in different steps of effector phase of arthritis. Therefore we decided to take advantage of a conditional ablation system mediated by diphtheria toxin (DT) receptor (human hβEGF) expressed under CD11b promoter to study the effects of monocytes and macrophages depletion on the course of serum transfer arthritis.

Methods: Bone marrow from transgenic mice (C57Bl/6) expressing DTR under CD11b promoter was transferred into irradiated hosts. Six weeks after reconstitution all mice received injection of K/BxN serum and the severity of arthritis was assessed by measuring ankle width and clinical score for each limb on day 0, 2, 4, 7, 9, 11 and 14. Additionally mice were divided into three groups: arthritis only or control group – did not receive DT treatment; initial monocytes depletion—received DT on days −1 and 0; and continuous monocytes depletion—received DT on days −1, 0 and every 48 hours till the end of experiment (days 2, 4, 6, 8, 10 and 12). To assess the effects of DT peripheral blood was obtained on day −6, day 0 and day 14 and analyzed by flow cytometry.

Results: Single injection of DT did not affect T and B cells populations, but induced profound decrease of monocytes in peripheral blood (from 10.7% to 1.4% and from 13.2% to 1% for initially and continuously depleted mice, respectively). At the end of study levels of monocytes in mice that received only two injections of DT returned to baseline values and did not differ from control group (11.0% and 15.7%, correspondingly), while in mice that received continuous treatment with DT levels were significantly lower (3.8%). There was no decrease in neutrophils in DT-treated mice. All mice developed arthritis initially, however only mice continuously treated with DT failed to display progression of arthritis.

Conclusions: Continuous depletion of monocytes and macrophages prevents further progression of arthritis but not of initiation of K/BxN serum transfer arthritis. Taken together with recent findings about role of neutrophils in the effector phase of inflammatory arthritis, our work suggest that monocytes are necessary for its progression and bone damage while neutrophils are required for initiation of arthritis.

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1724
Overexpression of RORγt Attenuated Collagen Induced Arthritis (CIA). Zhaojin Yao2, Yuva Kondo2, Masahiro Tahara2, Satoru Takahashi1, Isao Matsumoto2 and Takayuki Sumida1. 1Department of Anatomy and Embryology, Biomolecular, and Integrated Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 2Division of Clinical Immunology, Major of Advanced Biochemical Applications, Graduate School of Comprehensive Human Science, University of Tsukuba, Ibaraki, Japan, 3Univ of Tsukuba/Inst Clin Med, Tsukuba City, Japan.

Background: IL-17 producing CD4+ T cells such as Th17 cells play a crucial role in the generation of collagen induced arthritis (CIA). However, it is unclear how Th17 specific master regulator RORγt contributes to the development of arthritis. The purpose of the present study is to determine the role of RORγt overexpression on T cells in the generation of subpopulation with CIA.

Methods: 1) RORγt transgenic (RORγt Tg) mice were generated in C57BL/6 (B6) mice background under the promoter of CD2 gene. RORγt Tg and B6 mice were immunized with type II collagen (CII) emulsified with complete Freund’s adjuvant (CFA).
2) Cells in draining lymph nodes were harvested on day 10 after immunization of CII and they were analyzed for the proportion and number of T cell subsets by flow cytometry.
3) After these cells were cultured in vitro with CII for 72 h, the expression of RORγt and Foxp3 in CD4+ cells was analyzed by intracellular staining method.
4) Cytokine production (IL-17, IFN-γ, IL-21, IL-6, and IL-4) by CD4+ T cells was analyzed by intracellular cytokine staining method, and levels in supernatants were measured by enzyme-linked immunosorbent assay (ELISA).
5) CII specific IgG antibodies (Abs) in sera on day 56 after immunization were measured by ELISA.

Results:
1) The incidence and severity of arthritis was significantly suppressed in RORγt Tg mice.
2) The number of total T cells in the draining lymph node after immunizations was not significantly different between RORγt Tg mice and B6 mice.
3) The RORγt expression in CD4+ T cells in RORgt mice was increased compared to B6 mice. Whereas, foxp3 expression was not changed.
4) Flow cytometry analyses shows that the number of IL-17 producing cells increased in RORγt Tg mice. ELISA assay also revealed the increase of IL-17 in supernatants.
5) CII specific IgG Abs production was significantly suppressed in RORγt Tg mice.

Conclusion: Overexpression of RORγt in T cells suppresses the development of autoimmune arthritis, in spite of the induction of antigen-specific Th17 responses. Low level of antigen specific IgG Ab production might be one of the factors for reduction of CIA in RORγt Tg mice.

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1725
Paradoxical Decrease in Collagen Induced Arthritis Severity in Gadd45β Deficient Mice. Yubin Luo2, David L. Boyle1 and Gary S. Firestein1. 1UCSD School of Medicine, La Jolla, CA, 2UCSD School of Medicine.

Purpose: Growth arrest and DNA damage inducible 45b (Gadd45β) is involved in stress responses, cell cycle regulation, and oncogenesis. The mechanism of action for many functions relates to the ability of Gadd45β to block c-Jun amino terminal kinase (JNK) activity by binding to its upstream kinase MKK7. Gadd45β−/− mice have increase JNK activation and greater disease severity in models of innate immunity (passive K/BxN arthritis) and adaptive immunity (experimental allergic encephalomyelitis). We examined the role of Gadd45β in collagen-induced arthritis, which is a more complex model that includes an initial adaptive immune response to an autoantigen followed by an immune complex mediated effector phase.

Methods: CIA was induced in wild type DBA/1 (WT) and Gadd45β−/− DBA/1 mice by immunizing with type II collagen in complete Freund’s adjuvant. Arthritis severity was assessed by clinical arthritis scores (maximum score =16) and histological evaluation of synovitis, bone erosion, extra-articular inflammation and proteoglycan damage (max score =16). Serum anti-collagen antibodies were measured by ELISA. Cytokine and matrix metalloproteinase (MMP) expression in joint and spleen extracts was determined by quantitative PCR. Phospho-JNK (p-JNK) in the joints was measured by Western blot analysis.

Results: The initiation onset and peak arthritis severity were similar in Gadd45β−/− and WT mice (Day 34 WT=13±2; Gadd45β−/−=12±2; P>0.5) Unexpectedly, the resolution phase was accelerated in Gadd45β−/− mice (Day 55 clinical scores: WT=11±2; Gadd45β−/−=6±2; P=0.03). Histology scores and joint damage were also significantly lower in the Gadd45β−/− mice (Day 55 WT=9±2; Gadd45β−/−=5±2; P=0.04).

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However, serum anti-collagen antibody levels were similar in the two groups. Consistent with histologic evidence of joint damage, MMP3 and MMP13 expression was 4-fold higher in WT mice compared with Gadd45β−/− mice (P<0.01). Despite higher synovial MMP expression in JNK-deficient mice, Gadd45β−/− and WT were similar (P>0.1). mRNA levels for synovial IL-1, IL-6, and TNFα were similar in WT and Gadd45β−/− mice. Spleen gPCR demonstrated 2-fold higher levels of IFNγ and IL-10 mRNA in Gadd45β−/− with WT (P<0.05).

Conclusions: Gadd45β deficiency is usually associated with increase JNK activation and disease severity in murine inflammation models. Surprisingly, Gadd45β−/− mice had normal onset and peak severity of CIA but had accelerated resolution of arthritis. Adaptive immune responses were normal, as judged by autoantibody production. These data suggest that Gadd45β plays a complex role in immune responses. Enhanced resolution of arthritis could be due to altered cytokine balance in central lymphoid organs, such as increased IL-10 production.

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1726

Protection from Collagen-Induced Arthritis in a CX3CR1-Deficient Mouse Strain. Grainne Murphy1, Arun Kumar2, Fergus Shanahan1, Sinead Harney1, Michael Molloy1 and Noel Caplice2. 1Cork University Hospital, Cork, Ireland, 2University College Cork, Cork, Ireland

Background: Fractalkine(FKN), is up-regulated in RA and has been implicated in the immunological dysfunction associated with this disease. FKN interacts specifically with its receptor, CX3CR1 and lacks the redundancy characteristic of many other chemokine partnerships. The role of the FKN-CX3CR1 interaction in the initiation of RA is however unknown.

Objective: To compare the incidence and severity of collagen-induced arthritis(CIA) in a CX3CR1 homozygote deficient transgenic mouse strain with that of wild-type and competent heterozygote mice.

Methods: We used a transgenic mouse model, on a C57/B6 background, where one or both copies of the CX3CR1 gene were replaced by enhanced Green Fluorescent Protein (eGFP), generating the homozygote functionally deficient or competent heterozygote state. The incorporated GFP construct facilitated the direct tracking of peripheral and bone marrow (BM) derived CX3CR1+ cells. CIA was induced in homozygotes (11), heterozygotes (9) and wild-type mice (9) using 2 intra-dermal injections of a 1:1 ratio of chick collagen and Freund’s adjuvant (5mg/ml Mycobacterium TB). Circulating and bone marrow derived CX3CR1+ cells were analysed by flow cytometry. Following sacrifice, joints were analysed by H&E and immunohistochemistry to characterize the inflammatory infiltrate. Serum was collected on Day 40 for analysis of the IgG2a and IgG2b anti-collagen antibody responses.

Results: Homozygote mice had a significantly delayed onset of a very mild clinical phenotype in 18% compared with 77% in both the heterozygote and wild-type strains (p<0.001). Histologically, homozygotes had significantly milder synovial hyperplasia (p=0.01) with no evidence of bone or cartilage destruction. In contrast, CX3CR1-/- mice displayed a significant accumulation of F4/80+ macrophages, 95% of which co-expressed CX3CR1. BM and peripheral CX3CR1+ cells were expanded in both the hetero- and homozygotes. Moreover although strains were comparable in IgG2a responses, IgG2b was significantly higher in hetero- than homo-zoogtes, an isoform characteristic of many other chemokine partnerships. The role of the FKN-CX3CR1 interaction in the initiation of RA is however unknown.

Conclusion: To compare the incidence and severity of collagen-induced arthritis(CIA) in a CX3CR1 homozygote deficient transgenic mouse strain with that of wild-type and competent heterozygote mice.

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1727

Role of the Central Nervous System (CNS) in Peripheral Inflammation: Sympathetic Innervation of the Spleen Regulates Inflammatory Arthritis. David L. Boyle1, Meghan Edgar2, Linda Sorkin3 and Gary S. Firestein4. 1UCSD School of Medicine, La Jolla, CA, 2UCSD School of Medicine

Purpose: The CNS has been identified as a key regulator of peripheral inflammatory and immune responses, especially spinal reflexes and the vagus nerve. However, the sympathetic nervous system can also modulate inflammation in animal models of arthritis, with counter-balancing pro-inflammatory and anti-inflammatory effects at different times during the course of the model. The mechanism of sympathetic influence on immune regulation in arthritis is unknown. Because the spleen is a secondary lymphoid organ exclusively innervated by sympathetic fibers, we explored the role of splenic denervation on adjuvant arthritis in the rat.

Methods: Surgical splenic denervation of male Lewis rats was performed by dual transection and removal of the intervening segment of the splenic nerve and confirmed by norepinephrine assay of the spleen. Adjuvant arthritis was induced by injecting 1mg complete Freund’s adjuvant at the base of the tail. Arthritis severity was measured by hind-limb plethysmometry. Hind-limb radiographs were scored on a 0–6 point scale. Splenic mRNA expression was determined by QPCR and expressed as relative expression units (REU).

Results: Splenic denervation (SD) decreased paw swelling by 48% compared with controls (C) (SD 0.65±0.2ml versus C 1.34±0.1ml; p<0.0001). Radiographic analysis showed that SD significantly decreased bone destruction (SD 1.1±0.4; C 2.20±0.2; p<0.03).

Splenic norepinephrine levels in C animals were 3.1±0.4ng/mg tissue at baseline (day 0) and trended to higher levels in active arthritis (day 12, 4.8±1.1ng/mg), and decreased to below baseline levels at the end of the model (day 21, 0.9±0.1mg; p<0.0001 compared to baseline). Denervation reduced splenic norepinephrine to 0.48±0.34 ng/mg at all time points. TNF expression in arthritic animals was also reduced in denervated spleens (0.258±0.03 REU in SD vs 0.48±0.12 REU in SH; p<0.02). IL-1, GRO/CINQ1, IFNγ, IL-2 and TGF-β were not affected. Spleen mass was indistinguishable between SD and C groups in the presence or absence of arthritis, although spleen mass was doubled in arthritic animals compared with non-arthritic.

Conclusion: The sympathetic nervous system regulates the immune response in acute and chronic inflammation. Surprisingly, sympathetic innervation of the spleen is a key mechanism for neuro-regulation of inflammatory arthritis and is required for full expression of synovitis and matrix destruction. The mechanisms might include direct effects of neurotransmitters on immune cells via β adrenergic receptors, such as macrophages, with reduced splenic TNF production.

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SapC-DOPS Agents in Imaging Arthritis. Sherry Thornton1, Malinda Pinkerton2, Monica DeLa2, Tristan Bourdeau2, Rachel Mason2, Zhengtao Chu2, Matthew Flick2 and Xiaoyang Qi1. 1Cincinnati Children’s Research Foundation, Cincinnati, OH, 2Cincinnati Children’s Research Foundation

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects about 1% of the population worldwide. The devastating endpoint of RA pathology is the destruction of cartilage and bone ultimately leading to loss of joint function. Early detection and intervention of disease represents the best hope for successful treatment and preservation of joint.
mobility and function. To date, reliable and non-invasive techniques that accurately measure arthritis onset and progression are largely lacking. Here we investigate a novel method of disease assessment that has the advantages of (i) non-invasive, (ii) highly sensitive, and (iii) both qualitative and quantitative. We recently developed an agent, composed of the membrane-associated lysosomal protein Saponin C incorporated into 1,2-Dioleoyl-sn-Glycero-3-Phospho-L-Serine lipid nanovesicles (SapC-DOPS). SapC-DOPS has a high affinity for phosphatidylserine (PS)-rich domains on cellular surfaces, and fuses with PS-rich membranes on targeting. SapC-DOPS is tracked by labeling with a CellVue Maroon fluorophore (CVM). Since PS is normally present only on the inner leaflet of plasma membranes but is “flipped” to the outer leaflet upon cell damage, we hypothesized that the SapC-DOPS-CVM could be used to detect local tissue damage in inflammatory arthritis. To test this concept, two animal models of arthritis, K/BxN and collagen-induced arthritis (CIA) were utilized. Both of these models exhibit histological changes similar to RA including mononuclear cell infiltration, pannus development, fibrin deposition, and cartilage and bone erosion. SapC-DOPS-CVM was administered to arthritic and non-arthritic mice and detected by in vivo optical imaging (IVIS®). Our data indicate localization of SapC-DOPS-CVM to arthritic paws with 100% penetrance in both animal models; however, SapC-DOPS-CVM was not observed in non-arthritic paws. Flow cytometry analyses of total cells harvested from paws demonstrate that SapC-DOPS-CVM localized to approximately 20% of the joint cells from arthritic mice while less than 2% of cells from non-arthritic paws were CVM-positive. Preliminary studies indicated that in K/BxN arthritis, SapC-DOPS localized primarily to CD11b+ cells that are CD11c- and CD8-, with additional studies being performed to further characterize the cell types that are targeted by SapC-DOPS in each arthritis model. Results from the current studies provide support for the use of SapC-DOPS-CVM in imaging arthritis onset and progression in live subjects. Furthermore, this imaging strategy provides a novel method for tracking cells involved in inflammatory processes during arthritis.

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1729

Systemic, Lentiviral Gene Delivery of the Stress Protein BiP (Binding Immunoglobulin Protein) Improves Clinical, Histological and Immunological Parameters of Collagen-Induced Arthritis Via Suppression of IL-17, IL-18, and Histological Analysis. This study investigated the therapeutic potential of lentiviral gene therapy using BiP in the murine collagen-induced arthritis (CIA) model.

Methods: The murine BiP gene was manipulated to facilitate efficient protein secretion from transduced cells and cloned into a 3rd generation, self-inactivating HIV-1 lentiviral vector backbone containing a CMV responsive promoter. An equivalent vector containing the GFP gene was produced as a control (Lenti-GFP). CIA was established in DBA/1 mice and lentiviral vectors were administered intraperitoneally at arthritis onset. Clinical, histological and immunological parameters of disease were studied.

Results: 2×10^5 infectious viral particles encoding the murine BiP gene significantly suppressed clinical disease scores compared to Lenti-GFP treated animals when delivered at disease onset (Fig. 1) (day 55: Lenti-GFP - 8.6±0.6 vs. Lenti BiP – 5.1±0.7, p<0.001).

Conclusion: Lentiviral delivery of the murine BiP gene modulates clinical, histological and immunological parameters of CIA. Further experiments are underway to examine the mechanism of Lenti-BiP-mediated suppression and to target anti-inflammatory gene expression using stress-responsive promoters.

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1730

Targets of Innate and Adaptive Immunity in a Humanized Arthritis Model: Research Value of the RA Synovium SCID Mouse Model. Marije I. Koenders¹, Shahla Abdollahi-Roodsaz², Renoud J. Marijnissen³, Franco E. Di Padova⁴, John Dulos⁵, Annemieke M. H. Boots⁶ and Wim B. van den Berg⁷, ¹MSD, Oss, The Netherlands, ²Novartis Pharma AG, Switzerland, ³Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, ⁴Radboud University Nijmegen Medical Centre, The Netherlands

Target discovery and drug development is a very time consuming and expensive process, which is partly due to the fact that preclinical findings from animal models cannot always be translated to the clinical situation. To provide an intermediate step between classical arthritis models and clinical trials, the RA synovium SCID mouse model could be a valuable tool during preclinical research. In this study, the validity of this humanized mouse model was investigated.

SCID.CB17 mice were engrafted with two standardized pieces of human RA synovial tissue subcutaneously on the back, and subsequently the therapeutic effect of various biologicals on these grafts was assessed. After an engraftment period of seven days, mice were systemically treated with anti-TNF (Abalimumab), anti-IL-1, CTLA4-Ig (Abatacept), anti-CD20 (Rituximab), or isotype control antibodies at an excess dose of 10 mg/kg. In addition, this RA SCID model was used to study two new potential therapeutic targets, using theTLR4 antagonist B. quintana LPS, and anti-HL-17A antibodies. As readout, serum levels of human cytokines and chemokines were analyzed by Lumixen, and the synovial grafts were isolated for histological analysis.

Anti-TNF treatment significantly reduced serum levels of IL-6 and IL-8, and histological analysis demonstrated that this coincided with a clear reduction in the inflammation scores of the grafts and suppressed expression of TNF and IL-1 in the synovium as demonstrated by immunohistochemistry. In contrast, anti-IL-1 therapy did not show any effect. Since Adalimumab also
shows great efficacy in the clinics, anti-TNF antibodies were used as positive control throughout our further SCID studies.

The potential of the RA SCID model for T and B cell-related therapies was investigated using CTLA4-Ig and anti-CD20 respectively. Abatacept treatment was not effective in this RA SCID model, despite pre-screening of the synovial tissue for the presence of CD3+ T cells and the B7 molecules CD80/86 that provide costimulatory signals for T cell activation. In contrast, anti-CD20 treatment did reduce serum cytokines and histological scores, suggesting that this model is more sensitive to B cell than T cell-related therapies.

Our recent studies in IL-1Ra-deficient mice and collagen-induced arthritis suggested an important role for TLR4 in recognition of both exogenous and endogenous ligands that contribute to the pathological process during arthritis. Also for anti-IL-17 treatment great therapeutic potential was observed in mice, but additional proof was needed in more translational models. While our IL-17A/IL-17F inhibition studies could hint to a possible anti-IL-17 treatment, IL-17 blocking seemed to be selectively effective in cases where high numbers of CD3+ T cells were present in the synovium.

In conclusion, the human RA synovium SCID mouse model seems a powerful tool in preclinical research. Using this model, further evidence was obtained that TLR4 and IL-17 might indeed be interesting therapeutic targets in RA. Further characterization of the RA patients’ individual synovial profile is of great importance to achieve tailor-made therapy.

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**1731**

**The Role for TIM-2 in Collagen-Induced Arthritis.** Toshiro Kawamoto, Hitaya Akiba, Yoshiyuki Abe, Shinnji Morimoto, Ken Yamaji, Naoto Tamura and Yoshinari Takasaki. 1Department of Immunology, Juntendo University School of Medicine, 2Department of Rheumatology, Juntendo University School of Medicine

Introduction: T cell Ig and mucin domain-2 (TIM-2) has been shown to regulate CD4 T cell activation. TIM-2-deficient mice developed more severe airway inflammation under Th2-polarizing condition. Thus, it seems likely that TIM-2 is a negative regulator of Th2 immune responses. However, the immunological function of TIM-2 under Th1-polarizing condition is still unclear. This study therefore examined the contribution of TIM-2 to the development of collagen type II (CII)-induced arthritis (CIA), which is a Th1-polarized disease model, by administering a newly generated anti-TIM-2 mAb.

Methods: In this study, we investigated the effects of anti-TIM-2 monoclonal antibodies in a collagen-induced arthritis (CIA), which is a mouse model of rheumatoid arthritis, to determine whether TIM-2 contributes to the development of pathogenic Th1 or Th17 cells and joint inflammation. A murine model of CIA can be induced by injection of CII emulsified with adjuvant in genetically susceptible DBA/1 mice. Mice were examined daily for the onset of CIA. The swelling of four paws was graded from 0 to 4, each paw was graded, and the four scores were totaled so that the maximal score per mouse was 16. Spleen and draining lymph node cells were isolated and pooled, and cultured in the presence or absence of indicated dose of denatured bovine CII. All cultures were pulsed with [3H]-thymidine for the last 6h of a 72h or 96h culture and harvested. To determine the production of cytokines, cell-free supernatants were collected at 72h or 120h and assayed for INF-γ or IL-17 were measured by ELISA. Serums were collected and titers of anti-CII IgG Abs were measured by ELISA.

Results: Administration of anti-TIM-2 mAbs in early phase, but not late phase, significantly exacerbated the development of CIA. Although anti-TIM-2 mAbs treatment did not affect the development of Th1 or Th17 cells in the draining lymph node, the serum levels of anti-type II collagen Abs were significantly increased in the anti-TIM-2 mice. TIM-2 expression was found on splenic B cells and further up-regulated by anti-IgM, anti-CD40, and IL-4 stimulation. In contrast, CD4 T cells did not express TIM-2 even when stimulated with both anti-CD30 and anti-CD28 mAbs. Interestingly, anti-TIM-2 mAbs enhanced proliferation and Ig production of activated B cells in vitro.

Conclusions: These results suggest that the exacerbation of CIA by anti-TIM-2 mAbs is caused by enhancement of B cell activation and Ab production.

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**1732**

The TNF-Ligand APRIL Can Control CIA by Regulating Antibody-Production and Stimulating Anti-Inflammatory IL-10 Producing B Cells. Leticia Fernandez, Cecilia Rocha, Carla Carvalho-Pinto, Jan Paul Medema, Bernard G. Combe, Dominique Baeten, Jacques Morel and Michael Hahne. 1Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, 2Academic Medical Center, University of Amsterdam, 3Hopital Lapeyronie, Montpellier, France, 4Hopital Lapeyronie, 5Institut de Gene´tique Mole´culaire de Montpellier, 6Universidade Federal Fluminense/UFF, Niteroi

Background: TNF family members are frequently implicated in inflammation and autoimmune disease, and APRIL (A Proliferation Inducing Ligand) were found in synovial fluid and serum of patients with inflammatory arthritis pointing to a pro-inflammatory role of APRIL. APRIL can bind to BCMA and TACI, two receptors of the TNF family, which can also bind the B cell activating factor (BAFF). In the collagen-induced arthritis (CIA), administration of TACI-Ig was found to prevent disease progression and to lower disease scores, compared with controls. As TACI binds both APRIL and BAFF, it remained to be determined, whether this effect was due to the capacity of TACI to block just one or both ligands.

Methods: CIA was induced in APRIL-transgenic (Tg) DBA/1 mice and littersmates. Severity of disease was measured for each paw using a scale 0–4. In addition, mice were analyzed for histological signs of arthritis. Anti-collagen antibody titers were determined by ELISA. Lymphocyte populations in draining lymph nodes, spleen and peritoneum were analyzed by FACS. In another experimental setting mice were exposed to the collagen antibodies induced arthritis (CAIA). In addition, we employed the contact hypersensitivity model (CHS). For this, APRIL Tg and control mice were sensitized and challenged at the ear with oxazolone. Ear swelling and histological alterations were monitored.

Results: APRIL Tg (n=14) mice displayed in contrast to littersmates (n=16) a lower disease score (maximal score at day 38 after first immunization: 4.9±0.9 versus 1.0±0.5), a lower incidence of arthritis (p<0.01), and also produced less collagen specific antibodies (p<0.001, at day 41 after first immunization). Joints of littersmates had higher IgG levels. One of the main effector mechanisms of anti-collagen antibodies in arthritis is the activation of mast cells by immune-complexes. Indeed we detected decreased number of degranulating, thus activated, mast cells in the joints of Tg mice. To confirm that the decreased IgG levels developed in the CIA model in APRIL Tg mice are directly linked to the less severe disease development, we employed the model of CAIA. In fact, disease development in CAIA was similar in APRIL Tg and control mice. In addition, we detected a significantly increased IL-10 production of peritoneal B cells in APRIL Tg mice in the CIA model (n=8 for each group, p<0.05). Evidence is accumulating that IL-10 producing B cells can regulate autoimmune diseases including arthritis. The regulatory role of APRIL by modulating activity of mast cells and IL-10-producing B was confirmed in the CHS model.

Conclusion: Our results show that APRIL can control inflammation in two disease models, i.e. arthritis and CHS. This suggests a therapeutic potential of APRIL agonists to down-regulate inflammatory diseases such as rheumatoid arthritis.

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**1733**

Towards Personalized Arthritis Gene Therapy: Screening of Computationally-Designed Promoters in an In Vivo Mouse Model and in Human Synovial Fibroblasts. Fons A. J. van de Loo, Eline Vermeij, Onno J. Arntz, Miranda B. Bennink, Jeroen Geurts and Wim B. van der Berg. Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Introduction: Chronic synovial inflammation is a hallmark of the autoimmune disease rheumatoid arthritis (RA). The synovial membrane is regarded as the primary target tissue for local gene therapeutic treatment of arthritic joints. RA is a truly heterogeneous disease, which is supported by gene expression analyses of RA tissues that have revealed molecularly distinct inflammatory subtypes. Therefore, personalized gene therapy using
rheumatoid synovial tissue of varying inflammatory subtypes. Saa3, Cxcl1, Cxcl5 and Ifnb promoters could be induced by stimulation of RA synovial fibroblasts with pro-inflammatory stimuli. Uniquely, relative Saa3 promoter responses to cytokines and a TLR4 agonist were significantly higher in fibroblasts with an inflammatory genetic imprint both as a group as in individual samples. Relative Cxcl1 promoter responses did not discriminate between inflammatory synovial fibroblast subtypes.

Conclusion: These data demonstrate that computational design of promoters is of great value for the development of disease-regulated gene therapy. Towards personalized arthritis gene therapy, the Saa3 promoter appears an excellent candidate for sensing the extent of joint inflammation and responding differentially in human arthritic synovium according to their inflammatory phenotype.

Disclosure: F. A. J. van de Loo: None; E. Vermeij: None; O. J. Arutz: None; M. B. Bennink: None; J. Geurts: None; W. B. van den Berg: None.

ACR Poster Session C
Rheumatoid Arthritis - Clinical Aspects: Classification, Biomarkers, Predictors of Response, Disease Activity, Severity III Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1734
A Longitudinal Trivariate Model of Disease Activity Score, Physical Function and Radiographic Damage: Results from SONORA Study
Maggie Chen1, Xiuying Li1, Poornima Akhavan1 and Claire Bombardier1. 1University Health Network, 2University of Toronto, University Health Network, 3University of Toronto, University Health Network, Mount Sinai Hospital, Toronto, ON, Canada

Purpose: Rheumatoid arthritis (RA) affects approximately 1% of adults in North America. Active disease leads to radiographic damage and poor physical function. The purpose of this study is to demonstrate the use of a novel longitudinal trivariate model to identify simultaneously common significant predictors for three important outcomes in RA: Disease Activity Score (DAS); physical function measured with the Health Assessment Questionnaire (HAQ) and radiographic damage (Sharp Score).

Method: 994 Patients diagnosed as having new onset RA (symptoms ≥3 but ≤12 months) by a board-certified rheumatologist were recruited from 98 rheumatology practices. Clinical, laboratory, X-ray and health questionnaire data were collected by the enrolling rheumatologist at baseline, year 1 and year 2. A trivariate longitudinal model of DAS28, HAQ and sharp score was constructed and estimated using pooled cross sections for two years period, adjusting the significant predictors from the univariate analysis at the same time allowing for the latent individual-level effect. Different covariance structures were tested for the assumptions among these three outcomes in the model.

Results: The mean age of patients was 53 years (SD, 14.8), with 72% female and 90% Caucasian. The mean RA symptom duration was 170 days (180). The DAS28, HAQ and Sharp score were 4.4(1.32), 1.0(1.73) and 5.01 (7.28) at baseline, 3.4(1.38), 0.82(0.71) and 6.19(8.73) at year 1, 3.2(1.34), 0.77(0.72) and 6.39(9.25) at year 2, respectively. Partial correlation analysis showed that baseline DAS, HAQ and Sharp score are significantly correlated (all p-values <0.001). The longitudinal trivariate model showed that only higher baseline DAS, HAQ or Sharp Score value (P<0.0001), higher 28 swollen joint count (P<0.0001), longer disease duration (P=0.002) and lower house hold income (P=0.015) were significant predictors for these three combined outcomes.

Conclusion: This innovative method identified the significant common predictors for three outcomes which related to the different aspects of RA patients. This method can help us better understand the longitudinally complex relationship between different aspects from a broader view of the disease. These identified factors can help rheumatologists to identify the patients who are at greater risk of worsen disease, physical function and radiographic damage and make treatment decisions for RA patients at the early stage.

Disclosure: M. Chen: None; X. Li: None; P. Akhavan: None; C. Bombardier: None.
**Table:** Between within Groups Differences for Intervention and Control Groups: Changes in Practice (Performing Measurements and Making Treatment Changes)

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen Joint Count</td>
<td>Pre 96%</td>
<td>Pre 94%</td>
</tr>
<tr>
<td>Post 98%</td>
<td>Post 93%</td>
<td></td>
</tr>
<tr>
<td>Tender Joint Count</td>
<td>Pre 80%</td>
<td>Pre 93%</td>
</tr>
<tr>
<td>Post 79%</td>
<td>Post 92%</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>Pre 69%</td>
<td>Pre 69%</td>
</tr>
<tr>
<td>Post 74%</td>
<td>Post 73%</td>
<td></td>
</tr>
<tr>
<td>HAQ</td>
<td>Pre 37%</td>
<td>Pre 42%</td>
</tr>
<tr>
<td>Post 42%</td>
<td>Post 44%</td>
<td></td>
</tr>
<tr>
<td>Patient global frequency</td>
<td>Pre 55% &lt; 0.05</td>
<td>Pre 66% &lt; 0.05</td>
</tr>
<tr>
<td>Post 62%</td>
<td>Post 59%</td>
<td></td>
</tr>
<tr>
<td>MD global frequency</td>
<td>Pre 50% p &lt; 0.01</td>
<td>Pre 71% p = 0.17</td>
</tr>
<tr>
<td>Post 60%</td>
<td>Post 66%</td>
<td></td>
</tr>
</tbody>
</table>

**Results:**
- CDAI > 2.8 but < 4 receiving joint injection or DMARD change
- SDAI > 3.3 but < 11 receiving joint injection or DMARD change
- DAS28 > 2.4 but < 3.6 receiving joint injection or DMARD change

**Conclusions:** Despite a good baseline systematic assessment and many patients in a low disease state, there was improvement in the intervention group that surpassed the control group in both the frequency of performing assessments and the number of treatment changes when patients were not in remission. This is the first RCT of RA rheumatologist education where a change in behavior has been linked directly to an intervention (comparative practice and education) as the control group did not change behavior. Small group learning with feedback from practice audits is an inexpensive way to improve outcomes in RA.

**Disclosure:** J. E. Pope: Abbott Laboratories, 2; J. C. Thorne: Abbott Laboratories, 2; A. A. Cividino: Abbott Laboratories, 2; K. Lucas: Abbott Laboratories, 2.

**1736**

A Simple Fatigue Severity Scale Predicts Poor Health Outcomes, Frailty and Death in the Long-Term Follow-Up of Patients with Rheumatoid Arthritis. Gisela Westhoff and Angela Zink. German Rheumatism Research Centre Berlin, Berlin, Germany

**Background:** Rheumatoid arthritis (RA) patients highlighted fatigue as permeating every sphere of life. The EULAR/ACR task force recommended that fatigue should be included in an RA outcome measure core set. We investigated the association between baseline fatigue severity and 8-year outcomes in an early RA inception cohort.

**Methods:** Data from 1,057 RA patients with a disease duration <24 months at inclusion were used. Self-reports of functional capacity, pain, global health (GH) and fatigue, measured by 11-point numerical rating scales (NRS 0–10), were collected for up to 8 years. Reasons for drop out were investigated thoroughly. Clinical and self-reported baseline parameters were compared between patients who attained the 8th year in favorable GH (0–6) and those who did not meet favorable outcomes, i.e. they attained the 8th year in poor GH (7–10), had stopped participation without specifying reasons, or had dropped out due to frailty or had died. Multivariate logistic regression analyses were performed to identify baseline predictors of adverse outcomes.

**Results:** At inclusion, 42.6% of the patients reported no or mild fatigue, 36.2% reported moderate fatigue and 21.2% reported severe fatigue. At 8 years, 12.7% of the patients had died, 7.0% had terminated participation due to frailty, 6.2% had withdrawn without specifying reasons, 3.2% were lost to follow-up and 13.2% reported poor GH (7–10). Three baseline parameters were significantly associated with unfavorable outcomes in the multivariate analyses. Besides higher age and substantial functional limitations, severe fatigue almost doubled the risk for adverse outcomes (adjusted OR 1.82; 95% CI 1.21–2.73). Furthermore, severe fatigue at inclusion was the only parameter predicting each individual type of drop-out, i.e. drop-out without specifying reasons (OR 2.8; CI 1.4–5.3), drop-out due to frailty (OR 2.3; CI 1.2–4.5) or death (OR 2.3; CI 1.3–4.2). Acute phase reactants, DAS28, erosiveness, rheumatoid factor and pain were not predictive of unfavorable outcomes.

**Conclusions:** Severe fatigue in early RA is indicative of poor long-term outcomes; it outranges all other baseline parameters taken into consideration.

Therefore, fatigue should be implemented in an RA outcome measure core set, and, equally important, high attention should be paid to RA patients suffering from substantial fatigue.

**Disclosure:** G. Westhoff: None; A. Zink: None.

**1737**

Age, Sex, RF Antibodies, Baseline HAQ and DAS28 Score—But Not the Type of Initial Treatment—are Predictive of Clinical Remission at 1 Year in Early Inflammatory Arthritis. Bindee Kuriya1,2, Boulos Harroui3, Gilles Boire4, Carol A. Hitchon5, Janet E. Pope6, J. Carter Thorne7, Diane S. Ferland8, Ed C. Keystone8 and Vivian P. Bykerk9. 1Brigham and Women’s Hospital, Toronto, ON, Canada, 2CHUS-Sherbrooke University, Sherbrooke, QC, Canada, 3Hospital Maisonneuve Rosemont, LaSalle, QC, Canada, 4Institut de Rhumatologie, Montreal, QC, Canada, 5Southlake Regional Health Care, Newmarket, ON, Canada, 6St Joseph Health Care London, London, ON, Canada, 7University of Manitoba, Winnipeg, MB, Canada, 8University of Toronto, Toronto, ON, Canada, 9University of Toronto, Brookline, MA

**Background:** Aggressive DMARD therapy is more effective when given early in the disease course and the goal of treatment is remission. Factors associated with remission have been inconsistently reported in studies of early inflammatory arthritis (EIA). In Canada, access to biologics is reserved for those who have failed ≥ 2 DMARDs. Identifying those who will achieve remission can facilitate decisions to prevent over-under-treatment with limited resources. Our aim was to identify baseline and early treatment predictors of DAS28 remission at 1 year.

**Methods:** As of November 2009, 893 subjects were recruited to the Canadian Arthritis CoHort (CATCH). Patients are ≥16 years old; have symptoms between 6 weeks–12 months; have ≥ 2 swollen joints or 1 swollen MCP or PIP joint and ≥1 of: positive RF, anti-CCP, morning stiffness, response to NSAID or painful MTP squeeze test. Patients are assessed every 3 months and therapy is adjusted to minimize disease activity. Baseline demographic and clinical characteristics were analyzed via logistic regression.

**Results:** 363 subjects had ≥ 1 year of follow-up. Over this time, 288 (79%) patients met criteria for RA and 75 (21%) remained undifferentiated or fulfilled other diagnoses. Overall, 147 (41%) achieved DAS28 remission at 1 year. In univariate analyses, patients who experienced remission were younger, male, had lower HAQ scores, lower ESR and lower disease activity at baseline. Physical examination findings and radiographic erosions did not discriminate between the two groups. The presence of RF antibodies was less frequent among those who experienced remission but anti-CCP antibodies did not differ. The use of DMARDs early in the disease course was variable; methotrexate monotherapy was used less, while combination DMARD therapy was used more frequently in patients achieving remission. No patients were commenced on biologics during the first 3 months. After adjusting for significant univariate predictors (p < 0.10), the multivariate model revealed 5 factors to be associated with remission: age, sex, RF, HAQ score and DAS28 score (Table, p < 0.05).

**Conclusion:** Clinical remission was achievable in 41% of EIA patients. Predictors that favorably impacted this response included younger age, male sex, absent RF, low HAQ, and low disease activity at baseline. While sustained treatment with DMARDs has favorable long-term outcomes, DMARD use during the first 3 months alone or in combination did not accurately predict remission at 1 year.

**Table:** Multivariate analysis of baseline predictors for DAS28 remission at 1 year.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* years</td>
<td>0.98 (0.9–1.01)</td>
<td>0.03</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.44 (0.25–0.78)</td>
<td>0.01</td>
</tr>
<tr>
<td>RF positive</td>
<td>0.78 (0.47–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>HAQ score*</td>
<td>0.66 (0.44–0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>DAS28 score</td>
<td>0.06 (0.44–0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>ESR*, mm/hr</td>
<td>0.99 (0.98–1.01)</td>
<td>0.77</td>
</tr>
<tr>
<td>MTX monotherapy</td>
<td>0.59 (0.29–1.21)</td>
<td>0.15</td>
</tr>
<tr>
<td>Combination DMARD therapy</td>
<td>1.52 (0.84–2.75)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*Treated as continuous variables.

**Disclosure:** B. Kuriya: Amgen Inc., 2; Pfizer Inc, 2; B. Harroui: Amgen Inc., 2; Pfizer Inc, 2; G. Boire: Amgen Inc., 2; Pfizer Inc, 2; C. A. Hitchon: Amgen Inc, 2; Pfizer Inc, 2; J. E. Pope: Amgen Inc., 2; Pfizer Inc, 2; J. C. Thorne: Amgen Inc., 2; Pfizer Inc, 2; D. S. Ferland: Amgen Inc., 2; Pfizer Inc, 2; E. C. Keystone: Amgen Inc, 2; Pfizer Inc, 2; V. P. Bykerk: Amgen Inc., 2; Pfizer Inc, 2.
Algorithm Using Genome-Wide SNP Analysis for Prediction of Progres-

sion of Joint Destruction in RA Patients from Multiple Medical Cohorts.

Tsukasa Matsubara2, Satoru Koyano1, Yoshitada Sakai1, Keiko Funahashi3,
Takahumi Haygawa2, Takako Miura4, Kosuke Okuda5, Akira Sagawa6,
Takumi Sakurai1, Hiroaki Matsuno1, Tomomaro Izumihara1 and Eiuke
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Takasaki, Japan, 3Izumihara Rheumatic and Medical Clinic, Kagoshima,
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Hospital, Kato, Japan, 6Matsuno Clinic for Rheumatic Diseases, Toyama,
Japan, 7Research Institute of Joint Diseases, Kobe, Japan, 8Sagawa Akira
Rheumatology Clinic, Sapporo, Japan, 9Shono Rheumatology Clinic,
Fukuoka, Japan

Purpose: Although not yet fully possible, ideally, the prediction of progres-

sion of joint destruction would be pivotal in establishing a strategy of treatment for

individual RA patient since patients with rapidly progressing joint destruction need tight initial control. We have developed an SNP algorithm with the aim of enabling the prediction of progression of joint destruction with genome-wide SNP analysis by using multiple medical cohorts.

Patients and Methods: One-hundred and twenty-seven RA patients whose disease duration was within 5 years were enrolled in this study from 6 hospitals in different regions of Japan. All patients were treated with biologics after the failure of DMARDs therapy. RA joint destruction was estimated by Sharp score. Forty-five patients had a Sharp score of >100 (severe joint destruction), 30 had a score of 100-50 (intermediate joint destruction) and 52 had a score of <50 (mild joint destruction). Genome-wide SNP genotyping was performed by Illumina HumanHap500K chip. Case-control analyses between 278,347 SNPs and joint destruction (severe vs. mild) were examined by Fisher’s exact tests. We selected 10 SNPs associated with joint destruction (p < 0.0001). We then scored relationship between each SNP and progress of joint destruction, the estimated total score of 10 SNPs (estimated scoring in each SNP) was as follows: homo allele in the majority in severe joint destruction group: 1 point, hetero allele: 0 point, and homo allele in the majority of mild joint destruction group: –1 point, and examined relationships between the severe and mild group, and the total score.

Results: Accuracy (true positive+true negative)/total), specificity (true negative/false positive+true negative) and sensitivity (true positive/false positive+false negative) of the algorithm for distinguishing the severe destruction group from the mild destruction group ranged from 92–97%. It is therefore suggested that the SNP algorithm may enable the prediction of rapidly progressing severe joint destruction.

Conclusion: This highly accurate algorithm using SNP analysis may be useful in initially distinguishing severe joint destruction, and, in this way, may contribute to establishing a strategy of treatment for individual RA patients.

Disclosure: T. Matsubara: None; S. Koyano: None; Y. Sakai: None; K. Funahashi: None; T. Haygawa: None; T. Miura: None; K. Okuda: None; A. Sagawa: None; T. Sakurai: None; H. Matsuno: None; T. Izumihara: None; E. Shono: None.

Anticyclic Citrullinated Protein Antibodies Are Detected in a Significant Proportion of Patients with Anti-CCP-Negative, Early RA: Implications for Improved RA Diagnosis and Guided Therapy. Reuven Bromberg1, Jeremy Sokolove2, Piyanka Chandra3, Aarat Patel4, Stacy Cofield7, Theresa McVie5, S. Louis Bridges6, Larry W. Moreland7 and William Robinson3.

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mingham, AL, 5Univ of Alabama-Birmingham, 6Univ of Pittsburgh Med Ctr,
Pittsburgh, PA, 7University of Alabama-Birmingham, University of Pitts-
burgh, Pittsburgh, PA

Purpose: The presence of anti-cyclic citrullinated peptide (CCP) antibod-
ies, as detected by the anti-CCP2 test, is highly specific for the diagnosis of rheumatoid arthritis (RA). However, anti-citrullinated protein antibodies (ACPAs)—only some of which recognize CCP—collectively target many different antigens, and the anti-CCP2 test may therefore fail to detect the entire population of patients with anti-citrulline reactivity. We profiled ACPA reactivity in a cohort of patients with early RA by using a novel multiplex autoantigen array and compared our array results with those obtained using the commercial anti-CCP2 ELISA.

Methods: We performed multiplex autoantibody profiling using the Bio-Plex System to evaluate the presence of 16 ACPA specificities in serum from untreated patients with early RA who were enrolled in the Treatment of Early Aggressive RA (TEAR) trial and in serum from 80 non-RA controls. Bead arrays were used to profile antibodies targeting citrullinated epitopes derived from fibrinogen, vimentin, histone 2B, clusterin, biglycan and other candidate synovial antigens. Values that were 3 SD above the median value in controls were considered positive. Diagnostic sensitivity and specificity, as well as negative and positive predictive values, were calculated for seropositivity for 2, 3, or 4 different ACPAs, and the results were compared to those obtained using the commercial anti-CCP2 ELISA.

Results: Of 360 patients with early RA, 270 (75%) were positive for

anti-CCP antibodies. Of the 90 anti-CCP-negative patients, 30 (33.3%), 30 (17.8%), and 11 (1.2%) had 2, 3, or 4 ACPAs, respectively. Diagnostic specificity of anti-CCP2 was 75%, whereas sensitivity of >/= 2, 3, or 4 ACPAs was 81.1%, 73.9%, and 67.2%, respectively. Diagnostic specificity was maintained even when the presence of only a small number of ACPAs was used for diagnosis: specificity was 91.3%, 97.6%, and 97.6% when using a threshold of 2, 3, or 4 ACPAs, respectively. Combining detection of ACPAs and anti-CCP improved diagnostic sensitivity over that achieved with anti-CCP alone with minimal decrease in diagnostic specificity.

Conclusion: We demonstrate the presence of >/= 2 ACPA in 33.3% of patients designated seronegative by the commercial anti-CCP2 ELISA. Given that anti-CCP positivity has been shown to be a marker of more aggressive disease and potentially an indication for the need for earlier and more
aggressive intervention, our data suggest that an additional subpopulation may benefit from the use of a broader panel of ACPA biomarkers in the diagnosis and treatment of RA. Profiling of other ACPAs in addition to those detected by the current anti-CCP assay could yield greater sensitivity in the diagnosis of RA.

Disclosure: R. Bromberg: None; J. Sokolove: None; P. Chandra: None; A. Patel: None; S. Cofield: None; T. McVie: None; S. L. Bridges: None; L. W. Moreland: None; W. Robinson: None.

1741

Anti-Cyclic Citrullinated Peptide Antibodies: Beyond Rheumatoid Arthritis, Dolors Grados, Melanie Martinez-Morillo, Susana Holgado, Sonia Minguez, Anna Moltó, Beatriz Tejera, Lourdes Mateo, Xavier Tena, Anna Marín, Ituki Salvador, Eva Martinez-Caceres, Estibaliz Ruiz and Alejandro Olivé. Hospital Universitari Germans Trias i Pujol

Background: The determination of anti-cyclic citrullinated peptide antibodies has diagnostic and prognostic value in rheumatoid arthritis, with a sensitivity similar to that of the rheumatoid factor and of greater specificity.

Objectives: To describe the clinical characteristics of a cohort of patients with positive anti-cyclic citrullinated peptide antibodies.

Methods: The retrospective study was done at the university hospital with a reference population of 700,000 between 2007 and 2009. We reviewed the medical records of patients with anti-cyclic citrullinated peptide antibodies (citrullinated vimentin peptides) greater than or equal to 20 U/ml excluding those cases without clinical information. Technique used: ELISA anti-cCMV

Results: We carried out 1222 determinations, of which 418 (34%) were positive. We analyzed 320 patients: 103 men (32%) and 217 women (68%). In 234 cases (73%) patients had an associated rheumatic disease.

Table 1.

<table>
<thead>
<tr>
<th>Category</th>
<th>20–50 U/ml</th>
<th>51–100 U/ml</th>
<th>101–500 U/ml</th>
<th>&gt;500 U/ml</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>21</td>
<td>19</td>
<td>36</td>
<td>51</td>
<td>127</td>
</tr>
<tr>
<td>Elderly-onset arthritis</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Non-titrated arthritis</td>
<td>18</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Connective vasculitis</td>
<td>30</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>Still's disease</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Palindromic rheumatism</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>15</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>

64.5% of patients with rheumatoid arthritis, who had values above 100 U/ml, where seropositive and erosive forms. In the cases of vasculitis and connective tissue disease the values were between 20 and 50 U/ml. They were above 50 U/ml only in six patients: 3 with SLE and 3 with Sjogren syndrome. The distribution in Still’s disease, palindromic rheumatism and elderly-onset arthritis was similar for all values. 72% of the non-filitated arthritis had values between 20 and 50 U/ml. In the miscellaneous group (psoriatic arthritis, microcrystalline arthritis, polymyalgia rheumatica, sarcoidosis, arthritis associated with inflammatory bowel disease and postinfectious arthritis), 75% had values less than 50 U/ml. The value of 100 U/ml was only exceeded in a case of polymyalgia rheumatica and a case of chondrocalcinosis.

In 86 cases (27%) the patients did not have any associated rheumatic disease.

Table 2.

<table>
<thead>
<tr>
<th>Category</th>
<th>20–50 U/ml</th>
<th>51–100 U/ml</th>
<th>101–500 U/ml</th>
<th>&gt;500 U/ml</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrinology and nephropathy</td>
<td>16</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Lung disease</td>
<td>16</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Hematology and infections</td>
<td>16</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>28</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>31</td>
</tr>
</tbody>
</table>

Fifteen patients (17%), two of whom were smokers, had values above 50 U/ml. In six cases the values were greater than 100; 2 with nephropathy, 2 with lung disease (pulmonary hypertension and idiopathic pulmonary fibrosis), 1 with autoimmune hemolytic anemia and 1 case of dracopneumony.

Conclusion: Although anti-cyclic citrullinated peptide antibodies are highly specific for rheumatoid arthritis, they have also been described in other rheumatic diseases. Values above 100 U/ml usually relate to rheumatoid arthritis. Values between 20–50 U/ml without articular symptoms, must be considered negative, so this determination must be valued only in the context of rheumatic disease.

Disclosure: D. Grados: None; M. Martinez-Morillo: None; S. Holgado: None; S. Minguez: None; A. Moltó: None; B. Tejera: None; L. Mateo: None; X. Tena: None; A. Marín: None; I. Salvador: None; E. Martinez-Caceres: None; E. Ruiz: None; A. Olivé: None.

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Assessment of Nontraditional Prognostic Markers in Patients with Rheumatoid Arthritis, Bozena Targonska-Stepniak and Maria Majdan. Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Lublin, Poland

Background: Rheumatoid arthritis (RA) is associated with patients' shortened life expectancy. Premature deaths are mostly due to accelerated cardiovascular disease (CVD) which cannot only be explained by the prevalent traditional CV risk factors. The search for new markers of poor prognosis seems to be crucial. N-terminal pro-BNP (NT-proBNP) concentrations are increased in CVD and predict the risk of CV events. Renal involvement worsens both the course of RA and CVD. Cystatin C (Cys-C) is used as an endogenous, precise marker for glomerular filtration rate. Carotid intima-media thickness (cIMT) assessed by ultrasound reflects early stages of atherosclerosis and is a strong predictor of CV events.

The purpose of the study was to assess the value of chosen prognostic markers in patients with RA in association with markers of disease activity.

Methods: The study population consisted of 140 RA patients (111 women and 29 men); with the mean (SD): age 50.3 (10.9) years and disease duration 120.6 (89.8) months. Disease Activity Score in 28 joints (DAS28) was calculated as a primary outcome measure. High disease activity (DAS28>5.1) was observed in 42 patients (30%), erosive form of RA in 117 (83.6%). Plasma NT-proBNP concentration was assessed in patients and 20 healthy controls with chemiluminescent immunometric method. Serum Cys-C concentration was assessed with quantitative enhanced immunonephelometry method (normal range 0.53– 0.95 mg/l). cIMT was measured in patients and 31 healthy controls using high-resolution B-mode ultrasonography.

Results: The mean (SD) concentration of NT-proBNP was significantly higher in RA patients than in controls [120.1 (212.3) pg/ml vs 30.8 (30.0) pg/ml; p< 0.0001], as well as cIMT [0.75 (0.17) mm vs 0.59 (0.12) mm (p< 0.0001)]. The mean (SD) serum Cys-C concentration was 0.78 (0.3) mg/l (range 0.42–3.37).

The three markers correlated positively with each other (NT-proBNP and cIMT: R = 0.29; p=0.0005; NT-proBNP and Cys-C: R= 0.34; p=0.00003; Cys-C and cIMT: R= 0.44; p=0.00001). There were significant associations with metabolic variables: between cIMT and cholesterol (total and LDL), atherogenic index, glucose, body mass index; between Cys-C concentration and triglycerides, atherogenic index.

The value of cIMT, Cys-C, NT-proBNP correlated positively with the patients’ age and inflammatory markers (ESR, fibrinogen). Both NT-proBNP and Cys-C were also significantly associated with markers of RA: immunological (ACPA) and functional (HAQ). Only Cys-C concentration showed significant correlation with markers of disease activity (DAS28, CRP, mornning stiffness, VAS patient’s global assessment of disease activity).

Conclusions: The values of Cys-C, NT-proBNP and cIMT in RA patients were associated with the age and metabolic parameters, but also with markers of the disease activity. These nontraditional prognostic markers may be helpful in early diagnosis of complications associated with the course of RA.

Disclosure: B. Targonska-Stepniak: None; M. Majdan: None.

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Baseline ADAMTS5 Expression Could Sort the Prediction of Response to Infliximab or Adalimumab in Patients with Rheumatoid Arthritis, Kensei Tsuzaka1, Yuka Itami1, Naoshi Shinozaki1 and Tetsuo Morishita2. Tokyo Dental College Ichikawa General Hospital, Ichikawa, Chiba, Japan, 1Tokyo Dental College Ichikawa General Hospital, Ichikawa, Chiba, Japan

Objective: We have reported a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) as a candidate marker for predicting the efficacy of infliximab (IFX) in RA patients in the last ACR meeting. In this paper, we investigate ADAMTS5 as a predicting marker for the
adalimumab (ADA) treatment in RA to certify the sorting of ADA or IFX by baseline ADAMTS5 expression.

**Methods:** Forty-eight and one hundred active RA patients were treated with ADA and IFX, respectively. Peripheral blood samples were collected at baseline and ADAMTS5 mRNA was quantified using real-time PCR.

**Results:** Baseline ADAMTS5 mRNA levels (× 10^{-4}) in the ADA good responder (GR) (3.54 ± 2.18) were significantly (p=0.003) higher than that in the ADA moderate and non-responder (NGR) (2.02 ± 1.23) at 12 weeks’ ADA treatment. The DAS28 at 12 weeks’ ADA treatment was significantly lower in the baseline High-ADAMTS5 (≥ 4.90 × 10^{-4}) groups than in the Low-ADAMTS5 groups, respectively (Fig.1). We observed high positive predictive value (PPV) of the baseline High-ADAMTS5 (≥ 4.90 × 10^{-4}) for predicting ADA GR and ADA remission (DAS28<2.6 at 12 weeks) as shown in Table 1.

On the other hand, baseline ADAMTS5 mRNA level (× 10^{-4}) in the IFX GR (1.82 ± 1.31) was significantly (p=0.004) lower than that in the IFX NGR (2.78 ± 1.77) at 14 weeks’ IFX treatment. The DAS28 at 14 weeks’ IFX treatment was significantly lower in the baseline Low-ADAMTS5 (<1.12 × 10^{-4}) group than in the High-ADAMTS5 group (Fig.1). We observed high positive predictive value (PPV) of the baseline Low-ADAMTS5 (<1.12 × 10^{-4}) for predicting IFX GR and IFX remission (DAS28<2.6 at 14 weeks) as shown in Table 1.

68% of the patients that fulfilled the 1987-criteria during the first year of the disease but not at baseline did fulfill the 2010 criteria at baseline. This indicates that the 2010 criteria indeed classify RA in an earlier stage of the disease. The sensitivity and the specificity were 0.90 and 0.56 with initiation of methotrexate therapy as outcome and 0.83 and 0.74 respectively with use of any DMARD as outcome. When taking arthritis persistency over 5 years as outcome, the sensitivity and specificity were 0.70 and 0.63.

**Conclusion:** Compared to the 1987 criteria, the 2010 criteria classify more patients with RA and in an earlier phase of RA. The discriminative ability of the 2010 criteria is reasonable.

**Disclosure:** M. P. M. van der Linden: None; R. Knevel: None; T. W. J. Huizinga: None; A. H. M. van der Helm-van Mil: None.

**Clinical Utility and Validity of Self Assessed Joint Involvement in Rheumatoid Arthritis (RA) Patients with Low Active Disease**

**Background:** Joint swelling and tenderness are essential clinical manifestations of RA disease activity. Especially in patients in low disease activity states without significant joint involvement regular performance routine visit are usually less frequent. In these patients, self assessment of joints, and potentially, the use of a purely patient derived disease activity score might be an acceptable alternative. As a first step, we evaluated the validity of patient self assessed joint counts and a composite disease activity scores calculated from patient derived scores.

**Methods:** 212 patients with established RA were instructed to perform self-assessment of joint counts regarding swelling and tenderness on the 28 joint count (SJC28, TJC28) before an independent routine assessment by a trained evaluator. A randomly chosen subgroup of patients (n=79) received short training of joint assessment by a physician.

Based on patient derived joint counts a composite index of disease activity was calculated (patient clinical disease activity index CDAI_p = TJC28 patient + SJC28 patient + patient global assessment (PGA) in cm) and correlated with the standard CDAI (CDAIe) via Spearman Correlation. Furthermore we calculated the concordance of CDAI states and differences in swollen and tender joint counts between the two different assessors using Wilcoxon test. Subsequently patients were divided into their level of disease activity defined by CDAIe and agreement was analyzed in the 4 subgroups.

**Disclosure:** None; R. Knevel: None; T. W. J. Huizinga: None; A. H. M. van der Helm-van Mil: None.

**Classification of Rheumatoid Arthritis—Comparison of the 1987 ACR and 2010 ACR/EULAR Criteria**

**Objective:** New criteria to classify RA have been derived in order to increase the specificity and sensitivity for early RA compared to the 1987 criteria. This study evaluated differences in classification between the 1987 ACR criteria and 2010 ACR/EULAR criteria and determined the test characteristics of the 2010 ACR/EULAR criteria.

**Methods:** 2258 early arthritis patients included in the Leiden Early Arthritis Clinic cohort between 1993 and February 2009 were studied. Fulfillment of the 1987 and 2010 criteria for RA was determined at baseline. Also the diagnosis at the 1 year visit was assessed. The sensitivity and specificity of the 2010 criteria were determined using three outcome measures: initiation of methotrexate therapy or any DMARD therapy during the first year of followup and having persistent arthritis over 5 years. Persistent arthritis was defined as the absence of remission, which was defined by the absence of arthritis for at least one year after the cessation of eventual DMARD-therapy.

**Results:** At first presentation, 1090 patients fulfilled the 2010 criteria and 726 patients fulfilled the 1987 criteria for RA. 85 of the 726 patients (12%) that fulfilled the 1987 criteria did not fulfill the 2010 criteria at the same time point.

**Conclusion:** Compared to the 1987 criteria, the 2010 criteria classify more patients with RA and in an earlier phase of RA. The discriminative ability of the 2010 criteria is reasonable.

**Disclosure:** None; M. P. M. van der Linden: None; R. Knevel: None; T. W. J. Huizinga: None; A. H. M. van der Helm-van Mil: None.
Last, differences of agreement for trained and untrained subgroups were calculated separately to investigate the effect of training.

### Table 1

Wilcoxon test comparing patient and evaluator derived swollen and tender joint counts (SJC28p, TJC28p; SJC28e, TJC28e) as well as the clinical disease activity index calculated by patient derived values (CDAIp) compared to the standard one (CDAle) in the total cohort and subgroups defined by CDAI.

<table>
<thead>
<tr>
<th>Wilcoxon Test</th>
<th>TOTAL</th>
<th>REM</th>
<th>LDA</th>
<th>MDA</th>
<th>HAD</th>
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<tbody>
<tr>
<td>SJC28p&gt;SJC28e</td>
<td>76</td>
<td>7</td>
<td>39</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>SJC28p&lt;SJC28e</td>
<td>75</td>
<td>4</td>
<td>39</td>
<td>25</td>
<td>77</td>
</tr>
<tr>
<td>ties</td>
<td>61</td>
<td>26</td>
<td>26</td>
<td>72</td>
<td>2</td>
</tr>
<tr>
<td>TJC28p&gt;TJC28e</td>
<td>86</td>
<td>10</td>
<td>45</td>
<td>26</td>
<td>5</td>
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<tr>
<td>TJC28p&lt;TJC28e</td>
<td>45</td>
<td>3</td>
<td>22</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>ties</td>
<td>81</td>
<td>24</td>
<td>37</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>CDAIp&gt;CDAle</td>
<td>36</td>
<td>7</td>
<td>22</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>CDAIp&lt;CDAle</td>
<td>47</td>
<td>0</td>
<td>23</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>ties</td>
<td>129</td>
<td>30</td>
<td>59</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>total</td>
<td>212</td>
<td>37</td>
<td>104</td>
<td>53</td>
<td>18</td>
</tr>
</tbody>
</table>

**Results:**

We found a significant correlation (p < 0.01) of patient and assessor derived SJC28 (r = 0.42), TJC28 (r = 0.71) and CDAI (r = 0.79). Wilcoxon test showed good accordance of CDAI level between CDAIp and CDAle (ties = 129 of 212) and slightly lower agreement of SJC28 (ties = 61) and TJC28 (ties = 81). In different subgroups of CDAI-level we found a high concordance of patient and evaluator derived values using Wilcoxon test (see table) and significant (p < 0.01) correlation of CDAI in all subgroups of disease activity except HDA (REM r = 0.61; LDA r = 0.50; MDA r = 0.38; HDA r = 0.36 p = 0.13).

Comparing trained and untrained patients we found no significant differences between these two subgroups regarding Spearman correlation of CDAIp and CDAle (trained r = 0.74; untrained r = 0.83) or Wilcoxon test (ties CDAI level trained = 48 of 79, untrained = 81 of 133).

**Conclusion:** Patients self assessment of joints show good correlation with those performed by specialists, regardless of training. To improve effective follow-up, especially in patients with REM or LDA, a purely patient derived disease activity index seems valid and might be a helpful tool in daily clinical practice.

**Disclosure:** R. Radner: None; T. A. Stamm: None; J. Griser: None; J. S. Smolen: None; D. L. Ateh: None.

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**Comparing the Validity of the EuroQol-5D, Short Form-6D and the Well-Being Preference-Based Scores Using the Mean Short Form-36 Health Dimension Scores in Patients with Rheumatoid Arthritis and in Healthy Controls.** Fausto Salafi1, Marina Carotti2, Stefania Gasparini1, Alessandro Ciapetti1 and Walter Grassi1. 1Department of Molecular Pathology and Innovative Therapies, Division of Rheumatology, University of Ancona (Politecnica delle Marche), Italy, 2Department of Radiology, University of Ancona (Politecnica delle Marche), Italy

**Background:** Over the years, the interest of the preference-based generic instruments, used to measure the health-related quality of life in a general population or in rheumatoid arthritis (RA) patients, have been increased. However, the several instruments have several discrepancies in terms of utility of results.

**Objective:** To compare the validity of the EuroQol-5D (EQ-5D), Short Form-6D (SF-6D) and the well-being preference-based scores (RS) using the mean Short Form-36 health dimension scores in patients with rheumatoid arthritis and in healthy controls.

**Methods:** A cross-sectional study was carried out among 511 patients with RA (364 women, 127 men) who were attending at Rheumatology Department. Each patient was asked to complete EQ-5D, SF-6D and the RS questionnaires. The SF-6D was derived from the Short-Form 36 health dimension (SF-36) questionnaire. SF-6D utility scores were calculated using the eight mean SF-36 scores by algorithms developed from the UK general population. Agreement between the utility instruments was assessed by Bland-Altman plot, showing proportional error, and wide limits of agreement. The instrument correlated equally with disease activity and demographic characteristics. The EQ-5D and SF-6D yield incomparable scores in patients with RA Moreover, measures of damage were weakly correlated with these instruments, suggesting that HRQL is an important complementary source of information about patients with RA. Further research is required to fully understand the respective roles of the above mentioned instruments and to examine their implications for estimates of the impact of health care interventions in RA.


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**Computer Assisted Patient Reported (PR) Versus Physician Generated (PG) Joint Count (JC) and DAS28 Scores for Rheumatoid Arthritis (RA) Patients.** Norman B. Gaylis1, Jeffrey Scott2, Sue North3, Marty True1, Guss Savoff4 and Barry W. Forget5. 1Rheumatology and Arthritis, 2Rheumatic Disease Specialties, 3Arthritis & Rheumatic Disease Specialties, Aventura, FL, 4P4 Healthcare, 5UCB, Inc. 1747

**Objective:** The purpose of this study was to evaluate the similarity and difference between JCs and corresponding DAS28 scores generated by computer assisted patient self-report or through clinical interview.

**Methods:** An electronic hemocumulus was created allowing RA patients to rate the severity of tenderness (TEN) and swelling (SW) for indicated joints through touch screen computer tablets. PG JC斯 were generated through normal clinical interview. A clinician interface allowed the same JC information to be recorded electronically by medical staff. JCs were combined with erythrocyte sedimentation rate (ESR) to calculate DAS28 scores using PR and PG data respectively using accepted scoring methodology. The clinician was not formally blinded to the PR scores and the order of completion was determined by clinical circumstance. The analysis design was PRTENJC, PRSWJC, PGTENJC, PGSWJC, and RAPID4. Component 2 (Inflammation) was characterized by ESR PRTENJC, PRSWJC, and PGSWJC. Component 2 (Inflammation) was characterized by ESR PRDAS28, PRJCS and DAS28 scores would be similar to and not different from PG JCS and DAS28 scores.

**Results:** At the time of this report, 51 RA patients (M[SD] age = 59.3 [11.2]; 86% female) had available PR and PG JCs and DAS28 scores on the same day. PR and PG SWJCs were significantly correlated (R = 0.52, p < 0.001) and were not significantly different (M[SD] PRJCs = 3.2 [6.0], M[SD] PGJCs = 4.5 [5.1], paired samples t-test, t(df) = 1.1 [48], p > 0.1), PR and PG TENJCs were significantly correlated (R = 0.56, p < 0.001) and trended toward being higher when PG (M[SD] PRJC = 2.8 [5.2], M[SD] PGJC = 4.4 [6.7], paired samples t-test, t(df) = 1.9 [48], p = 0.07), PRDAS28 scores PGDAS28 scores were significantly correlated (R = 0.75, p < 0.001) and not significantly different (M[SD] PRDAS28 = 3.6 [1.6], M[SD] PGDAS28 = 3.7 [1.8], paired samples t-test, t(df) = 0.8 [50], p = 0.4). As shown in the table, PRDAS28, PRJCS and PRDAS28 scores were significantly correlated with Rapid3, Rapid4, and PGDAS28. An exploratory principal components factor analysis was performed on PRJCS, PRJCS, PGJCS, PGJCS, PGJCS, Rapid4, and ESR. Two components were extracted (Eigenvalues > 1) accounting for > 73% of the variance. Component 1 (Symptomology) was characterized by PRJCS, PRJCS, PGJCS, and PGJCS. Component 2 (Inflammation) was characterized by ESR PRDAS28, PGDAS28, and PGJCS.

**Conclusions:** This study suggests that a computer assisted PR JCs are valid and may be used to produce DAS28 scores comparable to PGDAS28 scores. Initial evaluation suggests the PRJCs are related to both RA symptomatology and inflammation. Future evaluations will also compare PR JCs.
and DAS scores to other available RA measures, such as radiologic indices, and will examine test-retest reliability. The primary study limitations are that PR and PG JCs were blinded and the post hoc nature of the hypothesis.

Disclosure: N. B. Gaylis; P4 Healthcare; S. J. Scott; P4 Healthcare; S. North; P4 Healthcare; M. True; P4 Healthcare; G. Savloff; None; B. V. Fortner; P4 Healthcare; S. North; P4 Healthcare; S. Momohara; None.

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Concurrent Depressive or Anxiety Disorders Significantly Worsen the Health-Related Quality of Life of Patients with Rheumatoid Arthritis. Eugenio Y. C. Lok1, Chi Chi Mok2, Fak Chi Cheung3 and Chi Wai Cheng4. 1Castle Peak Hospital, 2Tuen Mun Hospital

Objectives: To study the effects of depressive or anxiety disorders on the health-related quality of life (HRQOL) of patients with rheumatoid arthritis (RA).

Methods: Consecutive Chinese patients who fulfilled the ACR criteria for RA were recruited from an outpatient rheumatology clinic. Written consent was obtained from these patients who were interviewed by a psychiatrist for the presence of depressive or anxiety disorders using the Chinese-bilingual Structured Clinical Interview for DSM-IV Axis I disorders, Patient research version (CB-SCID-I-P). HRQOL was measured by the validated Chinese version of the MOS 36-item Short Form Health Survey (SF-36) questionnaire. Sociodemographic and clinical data (age, gender, duration of RA, disease activity scores (DAS28), family income, education level) at the time of interview were also collected.

Results: Between July 2007 and June 2008, 200 patients with RA were studied (79% women, mean age 51.4±10.5 years; median RA duration 4.0 years [IQR 2.0–9.0]). 47 (23.5%) patients were diagnosed to have a current psychiatric disorder (depressive disorders 14.5%, anxiety disorders 13.0%). There were no statistically differences in the age, sex distribution, education level, marital status, disease activity scores and duration of RA in patients who had either depressive or anxiety disorders compared to those without any psychiatric disorders (univariate analysis). However, RA patients with either depressive (p = 0.002) or anxiety disorders (p = 0.02) had significantly lower family income than those without psychiatric disorders. The mean scores (out of 100) of the eight subscales of SF-36 of RA patients with depressive disorders were 34.8±21.7 (physical functioning), 11.2±22.7 (role physical), 26.2±16.9 (bodily pain), 17.8±15.0 (general health), 22.1±17.5 (vitality), 34.6±24.5 (social functioning), 3.4±18.6 (role emotional) and 34.5±16.4 (mental health), respectively. The mean scores of each of the eight subscales of SF-36 of RA patients with anxiety disorders were 45.2±16.2 (physical functioning), 11.5±25.7 (bodily pain), 34.0±15.9 (general health), 25.6±27.4 (role emotional) and 45.7±15.4 (mental health), respectively. The scores of each of the eight subscales of SF-36 of patients with either depressive or anxiety disorders were significantly lower than those of RA patients who did not have any psychiatric disorders (p < 0.001 in both cases). In linear regression models, the depressive disorders and anxiety disorders were independently and inversely associated with the total SF-36 scores after adjustment for socioeconomic and demographic variables (p < 0.001 in both models). A lower family income was another independent factor for lower SF-36 scores.

Conclusion: The presence of concomitant depressive or anxiety disorders in patients with rheumatoid arthritis is associated with a significant worsening of the HRQOL, which is independent of demographic and socioeconomic factors.

Disclosure: E. Y. C. Lok: None; C. C. Mok: None; F. C. Cheung: None; C. W. Cheng: None.

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Construct Validity and Reliability of the Quick Disability of the Arm, Shoulder and Hand Questionnaire in Rheumatoid Arthritis Based on IORRA Cohort Study. Asami Tokita1, Takuji Iwamoto2, Ryo Hiroshima2, Asami Tokita1, Takuji Iwamoto2, Ryo Hiroshima2, Koichi Yano3, Kosei Kawakami4, Katsunori Ikari5, Atsuo Taniguchi6, Hisashi Yamakawa7 and Shigeki Momohara8. 1Institute of Rheumatology, Tokyo Women’s Medical University, Kawada-cho, Shinjuku-ku, Tokyo, Japan; 2Institute of Rheumatology, Tokyo Women’s Medical University, Japan

Background: The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire and the QuickDASH, which is a shorter version, are used for clinical research involving upper extremity musculoskeletal disorders. The purpose of this study is to test the reliability and validity of the Japanese

Society for Surgery of the Hand Version of the QuickDASH in patients with rheumatoid arthritis (RA).

Methods: For the validation, we examined the correlation between DASH and Quick DASH was examined in RA patients who have the upper extremity disorders. The correlation between DASH, QuickDASH and Cooney’s wrist score were also examined in patients with wrist disorders. Reliability was tested by a test-retest method for an average of 9.9 days interval in other patients. Moreover, the correlation between QuickDASH and Japan Health Assessment Questionnaire (J-HAQ), Visual analog scale (VAS), Disease Activity Score (DAS28) were investigated on 5,191 patients who participated in the Japanese RA cohort project (Institute of Rheumatology RA cohort: IORRA). Validity was tested using a Pearson correlation analysis.

Results: The QuickDASH was calculated for 85 out of 94 patients (90.4%). The mean of QuickDASH score was 36.25 (0–89). DASH and QuickDASH showed extremely high correlation (r = 0.97).

Fig. 1. DASH—QuickDASH.

The Cooney’s wrist score correlated strongly with the DASH (r = 0.79) and the QuickDASH (r = 0.7). Reliability of the DASH and QuickDASH was excellent. The intraclass correlation of DASH was 0.96, and QuickDASH was 0.95. In the IORRA cohort study, the QuickDASH could be calculated for 4,946 out of 5,192 patients (95.3%). The mean of QuickDASH score was 19.9 (0–97.7). The QuickDASH and J-HAQ also showed high correlation (r = 0.88).

Fig. 2. QuickDASH—J-HAQ.
Conclusions: The QuickDASH is a valid and reliable instrument for measuring the functional status of RA patients, and it is useful for large cohort study because of its high response rate.

Disclosure: A. Tokita: Mitsubishi Tanabe; 8, T. Iwamoto: Abbott Japan, 8, Mitsubishi Tanabe Pharma, 8, R. Hiroshima: None; 9, Y. Sakuma: None; 8, K. Yano: None; 8, K. Kawakami: None; 8, K. Ikari: Abbott Japan, 8, Eisai, 8, Mitsubishi Tanabe Pharma, 8; A. Taniguchi: None; 8, H. Yamakawa: Abbott Japan, 2, 5, Astellas Pharma, 2, 5, Banyu Pharmaceutical Company of Japan, 2, 5, Daiichi Sankyo, 2, 5, Hoffmann-La Roche Inc., 5, Janssen Pharmaceutical Product, L.P., 2, 5, Kissei Pharmaceutical, 2, 5, Mitsubishi, 5, S. Momohara: Abbott Japan, 8, Astellas Pharma, 8, Chugai, 8, Dainippon Sumitomo Pharma, 8, Eisai, 8, Kaken Pharmaceutical, 8, Mitsubishi Tanabe Pharma, 8, Nippon shiyaku, 8, sanofi-aventis, 8, Santen Pharmaceutical, 8, Takeda Pharmaceutical.

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Contribution of the Rheumatoid Arthritis Impact of Disease (RAID) on Disease Activity in Rheumatoid Arthritis (RA). Till Uhlig1, Turid Heiberg2, Cathrine Austad3 and Tore K. Kvien1. 1Diakonhjemmet Hospital, Oslo, Norway, 2Diakonhjemmet Hospital, Oslo, Norway, 3Oslo University Hospital, Oslo, Norway

Purpose: The RAID score is a new patient reported outcome developed through a EULAR task force (1). The OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) group recently put on its research agenda a need to explore how RAID relates to disease activity in RA. Currently, patient global assessment of disease activity (PatGlob) is the current gold standard and it is also a parameter already included in the OMERACT RA disease activity Index (RAID). However, Patient Global Assessment of Disease Activity (PatGlob) may not be comprehensive enough to reflect disease activity in RA. Therefore, we assessed the relationship between RAID and other commonly used measures of disease activity in RA. The RAID score was compared to other commonly used measures of disease activity in RA using Pearson correlation coefficients.

Methods: In a population based RA registry in Oslo, Norway, 868 patients aged 20–79 years (mean (SD) age 59.9 (12.3) years, disease duration 13.0 (10.8) years, 77.1% females, 57.0 % RF positive) responded in 2009 to a mailed questionnaire (response rate 60.6%). RAID score (0–10) is calculated from seven domains, perceived by patients to be particularly important: pain, functional disability, fatigue, sleep problems, emotional and physical well-being, coping. The Rheumatoid Arthritis Disease Activity Index (0–10) was used to assess disease activity. Other patient reported outcomes separately assessed included pain, fatigue and PatGlob on 100 mm visual analogue scales, modified HAQ, SF-36 with physical (PCS) and mental component summary (MCS) (low scores=poor health), and SF-6D derived utility.

Pearson correlation coefficients are reported between RAID and measures of disease activity. We further used linear regression analysis to calculate the explained variance of RAID and of PatGlob for disease activity in RA.

Results: RAID mean 3.35 (SD 2.16), disease activity (RAID) was 3.20 (SD 1.71) and both were strongly correlated (r=0.82). RAID was also highly or substantially correlated to other core measures of disease activity: pain (r=0.81), patients global (r=0.84), for physical function HAQ (r=0.67) and PCS (r=0.72), and also to fatigue (r=0.68), mental health (MCS (r=0.52) and SF-6D derived utility (r=0.78).

RAID explained 67% of the variance in disease activity, PatGlob explained 71%, and both together explained 77%.

Conclusion: RAID was highly and substantially related to core measures and to an index (RAADI) of disease activity. PatGlob explained only slightly more than RAID of the variation in disease activity. These results support that RAID as a global composite of disease is closely related to disease activity in RA.

References:

Disclosure: T. Uhlig: None; T. Heiberg: None; C. Austad: None; T. K. Kvien: None.

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CXCL2 as a Potential Biomarker of Disease Activity in Rheumatoid Arthritis. Kichul Shin1, Ji Ah Park2, Jun Wan Kim3, Hong Hee Kim1, Eun Bong Park1, Dong Wook Song1, 1Department of Cell and Developmental Biology, BK21 and DRI, Seoul National University School of Dentistry, Seoul, Korea, 2Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, Republic of, 3Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

Background: The diverse role of chemokines in rheumatoid arthritis (RA) includes enhancement of leukocyte migration, angiogenesis, and osteoclastogenesis in the synovium. CXCL2 is a chemokine produced by activated macrophages and acts as a mediator for chemotaxis of neutrophils, regulation of transmigration and extravascular tissue accumulation of leukocytes. We recently demonstrated that CXCL2 contributes in osteoclastogenesis and bone erosion in vivo. We investigated the relationship between serum CXCL2 concentration and clinical and radiological parameters in RA patients.

Methods: Eighty-one RA patients who visited the rheumatology outpatient clinic participated in this study. All patients fulfilled the 1987 ACR classification criteria for RA. Serum CXCL2, CRP levels and blood ESR were measured. Clinical parameters including DAS28, visual analog scale (VAS) of physician’s and patient’s global assessment, pain, fatigue, and health assessment questionnaire (HAQ) score as well as simple erosion narrowing score (SENS) were evaluated at the time point obtaining the samples. In addition, 19 patients treated with infliximab, sera at pre- and post-treatment (5 infusions) were obtained.

Results: Demographic data of 81 RA patients (female ratio 79 %) included mean age of 51 years, mean disease duration of 9.7 years, and DAS28(ESR) of 4.8 ± 1.8 (mean ± standard deviation). The serum level of CXCL2 in RA patients and healthy controls were 963.3 ± 42.1 vs. 505.0 ± 40.7 pg/ml (p= 0.002) respectively. Among the clinical parameters, a positive correlation was shown between DAS28(ESR) and CXCL2 levels (r= 0.235, p= 0.035). ESR and CRP levels also showed positive correlation with CXCL2 (r= 0.310, p= 0.005 and r= 0.540, p<0.001, respectively). SENS did not correlate with CXCL2 levels. Serum CXCL2 levels tended to decrease compared with baseline in 19 RA patients after receiving 5 infusions of infliximab (p=0.055).

Conclusion: Serum CXCL2 levels correlated well with DAS28(ESR), and ESR, CRP levels in RA patients. CXCL2 may be a potential biomarker of disease activity of RA.

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Development by the STPR Group of the Flare Instrument, a New Tool To Identify Flare in Rheumatoid Arthritis (RA) in Clinical Practice. Jean-Marie Berthelot1, Michel De Bandt2, Jacques Morel1, Arnaud Constantin3, Thao Pham, Alain Saraux, Elisabeth Solau-Gervais, Daniel Wendling, Elisabeth Spitro, Bruno Faucet and Francis Guillemin. 1Montpellier, France, 2Aulnay Sous Bois, France, 3Rheumatology Unit CHU Nantes, Nantes, France

Introduction: Rheumatoid arthritis (RA) patients may have stable disease activity at two determinations but flares may occur between two scheduled evaluations, not captured by any activity score. There is no measure for such flares in RA patients, although they could impact on radiographic and functional outcome.

Objectives: To explore the concept of flare (transient or lasting exacerbation of disease activity) in clinical practice in RA, from both patient’s and rheumatologist’s perspectives, and to develop a self-administered questionnaire enabling the prospective or retrospective detection of flare(s) in the timeframe between two medical visits.

Methods: To capture the patient perspective, 105 established RA patients from 12 rheumatology centres were proposed to participate in an individual, semi-structured interview scheduled to record their feeling about flare. Content analysis was used to identify verbatim and derive candidate items. The most representative and frequently reported items were selected. To explore the physician perspective, 13 RA-experienced physicians from the STPR (Strategy of Treatment in Patients with Rheumatoid arthritis) panel, participated to a Delphi exercise. They were asked to list the signs or symptoms best reflecting RA flare(s) from their point of view. The items listed were reduced in a 5-round Delphi process in which all items cited by at least 75% were definitively selected and those cited by less than 25% of the respondents were excluded.

Results: In the patient perspective, 10 items were selected: swollen joints, fatigue, unbearable pain, pain-killer intake, night awakening, being restricted to inaction, need for help, wish to be alone, drop in mood, irritability. They were integrated in a self-administered questionnaire presenting items with Likert scale-type response frame. In the physician perspective, 9 items were identified: morning stiffness, night awakening, joint swelling, raise in ESR or CRP, worsening of nightly or morning pain, deterioration in arthritis, increase in corticosteroid intake, increase in pain-killer intake, feeling of a flare. They
were presented with discrete answers. Four dimensions were common to physicians and patients: joint swelling, pain, sleep disturbance, increase in pain killer intakes.

Conclusion: The study enabled the identification of 15 different items and will allow the construction of a self-administered questionnaire potentially able to detect flares between two medical evaluations in clinical practice, regardless any disease activity index.

Disclosure: J.-M. Berthelot: None; M. De Bandt: None; J. Morel: None; A. Constantin: None; P. Gaudin: None; X. Le Loit: None; J.-F. Maillefer: None; O. Meyer: None; T. Pham: None; A. Sarau: None; E. Solau-Gervais: None; D. Wendling: None; E. Spitz: None; F. Faulret: None; F. Guillemin: None.

1753 Development of a Multi-Biomarker Test for Rheumatoid Arthritis (RA) Disease Activity (Vectra™ DA).

Methods: 25 serum protein biomarkers were previously selected from 137 candidates based on their relationship with disease activity in previous studies: SAA, IL-6, TFN-RI, VEGF-A, PYD, MMP-1, ICAM-1, calprotectin, YKL-40, MMP-3, EGF, IL-1RA, VCAM-1, leptin, resistin, CRP, IL-8, ApoAI, ApoCIII, CCL22, IL-1B, IL-6R, IL-18, keratan and ICTP. Biomarker assays were systematically optimized for analytical performance. Biomarkers were trained to derive a single clinical disease activity measure with concentrations of the 25 biomarkers and algorithm to combine them into a single, easy-to-interpret score. Results: Concentrations of the 25 biomarkers were cross-sectionally measured in 512 patient samples from InFoRM. Associations between scores between 1 and 100; models were developed using ordinary least squares regression.

Results: Concentrations of the 25 biomarkers were cross-sectionally measured in 512 patient samples from InFoRM. Associations between concentrations and multiple measures of disease activity were used to prioritize 15 top biomarkers which were subsequently measured in 167 patients. The combined set of 679 patients was diverse in geographic location, ethnicity, age, and RA disease activity. Multiple algorithms were developed; the algorithm with the best performance included 12 biomarkers and used an algorithm similar to the DAS calculation, with different subsets of the biomarkers used to estimate SJC28, TJC28 and patient disease activity. The 12-biomarker algorithm (DA Test) was assessed in the CAMERA cohort, an independent test set, where it achieved r of 0.73 with 70% sensitivity and auroc of 0.87. The DA Test score decreased significantly between the baseline and 6 month study visits, reflecting patients’ clinical response to therapy. The DA Test was advanced into independent validation in other cohorts.

Conclusion: An objective test (DA Test) integrating multiple serum biomarkers representing diverse RA pathophysiology has been derived and tested; it can quantify RA disease activity. Once validated in an independent cohort to confirm its performance and additional value, this test has the potential to enhance clinical assessment of RA patients.


1754 Evaluation of Patients with Rheumatoid Arthritis in Clinical Remission with 12 Joints Ultrasonography. Preliminary Results.

The current study assessed the ability of eight ultrasonography (US) parameters to discriminate RA patients in clinical remission (DAS28-ESR and / or DAS28-CRP <2.6).

Objective: To assess whether gray scale and power Doppler (PD) ultrasound of 12 joints can detect disease activity in rheumatoid arthritis (RA) patients classified as clinical remission by DAS28-ESR and / or DAS28-CRP <2.6.

Material and Methods: We included prospectively RA patients in clinical remission (DAS28-ESR and / or DAS28-CRP <2.6) from the Rheumatology Clinic of the Hospital Mariona Baixa and within 30 days of clinical evaluation a gray scale and PD ultrasound scan (Esaote, MyLab25 Gold) was performed, by the same rheumatologist who was unaware of the clinical data. We evaluated the presence of joint effusion and PD signal: elbows (anterior and posterior), wrists, 2nd and 3rd MCPs joints (dorsal and palmar aspects), knees (suprapatellar, medial and lateral recesses) and ankle (anterior). The effusion was scored from 0 to 3 points (OMERACT) and the patients were classified into 2 groups (> or <10 points) under the joint global sumation.

Results: We analyzed 33 consecutive RA patients in clinical remission, 73 % were women and the mean age was 60 ± 16 years. The average time course of RA was 88 ± 80 months (median 60). PD signal was detected in any joint in 52% of patients. Some degree of joint effusion was detected in 88% of patients. 22% of patients were in group A with effusion > 10 points and 78% in group B with effusion < 10 points. The mean time since diagnosis of AR was 81 in group B vs 114 months in the group A. Presence of erosions was 27% in group B vs 57% in group A. No significance was detected in the statistical analysis.

Conclusions: —Ultrasonographic inflammatory activity (presence of PD) was detected in 52% of RA patients (in clinical remission). 2—22% of patients were in group A with effusion > 10 points. 3—In this group a greater percentage of erosions was detected (57% vs 27%).
Background: Monitoring functional ability is important to assess efficacy of treatment in rheumatoid arthritis (RA), however implementation of routine assessment of functional ability in daily practice remains difficult.

Purpose: To assess the feasibility of and patients’ opinion about automated online health assessment questionnaire (HAQ) registrations by RA patients in our out patient clinic

Methods: RA patients visiting the out patient department were given an oral instruction and asked to fill in a computerized HAQ in METEOR, a freely used program designed for an automated functional ability test and daily disease activity. The time needed to fill in the HAQ and any problems arising were noted. Next, patients answered questions on computer access, the usefulness of the HAQ and the METEOR program. Answers were filled in on a 5 point Likert scale with a high score representing a positive answer and a low score a negative one.

Results: Of 111 consecutive patients, 92 agreed to participate, and 78 patients completed the whole evaluation, while 14 patients stopped early because of time constraints. Seventy-seven percent of the participants were female, and the average age was 58.4 years (range 25–78). Mean (SD) disease duration was 10.4 (8.7) years and mean (SD) HAQ score at the time of assessment was 1.01 (0.72). Of all participants, 84% had personal computer access and 73% reported frequent (daily or weekly) computer use. The mean time patients needed to fill in their own HAQ was 6 minutes, which 99% of patients reported as reasonable or good. Patients felt they had not needed much assistance when filling in the HAQ, although the investigator had noted that some assistance (mainly concerning technical computer problems) was needed in 78% of all patients. Average scores on questionnaire items are presented in table 1. Ninety-five percent of patients said they would be willing to fill in the computerized HAQ at the next visit and 83% was prepared to come to the hospital earlier to fill in the HAQ there. 73% of patients would like the option of filling in the HAQ at home and 72% of patients felt there were missing subjects in the HAQ, in particular work-related activities, social activities and sports, as well as registration of fatigue and psychological problems. Ninety-four percent reported that the subjects included in the HAQ were all relevant. According to patients discussing problems in daily functioning is important, however it is not always part of the out patients visit to the rheumatologist (table1).

Table 1. Results of patients survey questions.

<table>
<thead>
<tr>
<th>Question</th>
<th>Mean</th>
<th>Sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What was your opinion about filling in the HAQ on the computer?</td>
<td>4.5</td>
<td>1.1</td>
</tr>
<tr>
<td>(1=very difficult 5=very easy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Would you be capable of filling in the HAQ independently the next visit?</td>
<td>4.2</td>
<td>1.3</td>
</tr>
<tr>
<td>(1=definitely not 5=definitely)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Did you appreciate filling in the HAQ on the computer in the waiting room?</td>
<td>4.0</td>
<td>1.2</td>
</tr>
<tr>
<td>(1=no, not at all 5=yes, very much)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. How important is it discuss about problems in daily functioning with you rheumatologist?</td>
<td>4.0</td>
<td>1.1</td>
</tr>
<tr>
<td>(1=not important at all 5=very important)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. How often are problems in daily functioning discussed with the rheumatologist?</td>
<td>3.5</td>
<td>1.3</td>
</tr>
<tr>
<td>(1=never 5=always)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Do the questions in the HAQ give an accurate representation of your abilities and limitations in daily functioning?</td>
<td>3.9</td>
<td>1.2</td>
</tr>
<tr>
<td>(1=not at all 5=very much)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Independent computerized registration of physical functioning by RA patients in the out patient clinic is feasible and is appreciated by patients. Filling in the HAQ in the METEOR tool before seeing the rheumatologist may stimulate to discuss functional (dis)ability during the consultation, which patients find important, but is not always done.

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1757

Improvement of Serological Rheumatoid Arthritis Diagnostics by Autoantibody Profiling, Karsten Conrad1, Dirk Roggenbuck1 and Kirsten Lüthke1.1Generic Assays GmbH, Dahlowitz, Germany, Germany, 2Institute of Immunology, Medical Faculty of the Technical University of Dresden, Germany, 3Rheumatological Practice, Dresden, Germany, Germany

Appropriate treatment at a sufficiently early stage can have a favourable effect on progression and serious clinical complications of rheumatoid arthritis (RA). CCP antibodies are used as specific markers for RA but are detectable in less than 80%. Therefore, a multiparametric analysis of RA-associated autoantibodies (RA-ABB) may increase the diagnostic sensitivity.

Sera of 349 patients with definite rheumatoid arthritis (RA) and 535 patients with various diseases other than RA were tested for rheumatoid factors (IgM and IgA-RF) and antibodies to RA33 (HUman GmbH, Germany), CCP (GA Generic Assays GmbH, Germany), mutated citrullinated vimentin (MCV) (OR- GENTEC Diagnostika GmbH, Germany), and citrullinated protein (CPA) (HU- man GmbH, Germany). The diagnostic sensitivity and specificity as well as the receiver operating characteristics were analyzed for these autoantibodies. The cut-off values were determined, at which the diagnostic specificity reaches ≥95% (optimized cut-off). 76.8% of RA patients were positive for CCP antibodies. In 22% of the CCP antibody negative RA patients, at least one of the other RA-ABB could be found at the optimized cut-off. Hence, the diagnostic sensitivity for RA can be increased to 83.7% by parallel or sequential determination of RA-ABB without loss of diagnostic specificity.

Conclusion: The serological diagnosis of RA can be improved by varying cut-off values to increase diagnostic specificity of certain RA-ABB and by determination of RA-ABB profiles to increase diagnostic sensitivity. A further improvement depends on the discovery of novel RA-ABB with high specificity and high predictive values as well as on methodological aspects (e.g., multiplex analyses).

Disclosure: K. Conrad: None; D. Roggenbuck: Generic Assays GmbH, 2; K. Lüthke: None.

1758

In Patients with Rheumatoid Arthritis Who Are in a Low Disease Activity State or Remission, Does Lack of Fatigue Relate to Better Function and Damage Scores. George A. Wells1, Tracy Li1 and Maarten Boers1.1Bristol-Myers Squibb, Princeton, NJ, 2Univ of Ottawa Faculty of Med, Ottawa, ON, Canada, 3VU University Medical Center, Amsterdam, The Netherlands

Purpose: With current treatment options for patients with rheumatoid arthritis (RA), low disease activity (LDA) and remission are reasonable treatment goals. Most criteria for LDA and remission are based on physician-reported measures and traditional patient-reported outcomes (PRO). The Outcome Measures in Rheumatology (OMERACT) initiative has recently recommended fatigue be assessed in all clinical trials. The importance of fatigue in relation to response and disease activity criteria on function and damage scores needs to be evaluated. To evaluate the added effect of fatigue on function and radiography in patients with RA meeting response, LDA and remission criteria.

Methods: The active RA patients under study were from a 12-month,
randomized, double-blind, placebo controlled trial (AIM trial) comparing abatacept (n=433) to placebo (n=219) on a background of MTX. Assessments at 12 months included: function (HAQ), radiography (erosions, joint space narrowing, total), fatigue (100mm visual analog scale) and core set measures used to derive response (ACR20, ACR50, ACR70), LDA (DAS28v3.2, SDAIv11, CDAIv10) and remission (DAS28v2.6, SDAIv3.3, CDAIv2.8) criteria at 6 months. The following patient groups are of interest at 1 year: criteria not met (NC) and criteria met (C), and within the latter, those with high (>10; C-IoF) and low fatigue levels (<10; C-IoF). These 4 groups will be compared on their function and radiography.

**Results:** The results for function (HAQ) are given in the table. Except for SDAI remission criteria, the HAQ is significantly lower in the patients that met the criteria and fatigue was low (<10) compared to patients that met the criteria and fatigue was high (>10). For NC vs C and for NC vs C-IoF, p<0.001 for all criteria. For radiography, there was no significant difference between low and high fatigue patients meeting the criteria.

**Table.** HAQ-functional progression (mean ± SD)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Criteria Met Only</th>
<th>Criteria Met + Fatigue &gt;10</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 1</td>
<td>1.50 ± 0.65</td>
<td>1.05 ± 0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACR 10</td>
<td>3.60 ± 0.59</td>
<td>3.60 ± 0.38</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACR 70</td>
<td>1.23 ± 0.52</td>
<td>0.74 ± 0.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DAS28v2.6</td>
<td>1.14 ± 0.49</td>
<td>0.65 ± 0.48</td>
<td>0.0043</td>
</tr>
<tr>
<td>DAS28v3.2</td>
<td>1.17 ± 0.53</td>
<td>0.76 ± 0.54</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Conclusions:** For patients meeting various response and remission criteria, there is a significantly better function among patients with low fatigue, but no effect on radiography. As it relates to function, fatigue is an important factor to be considered in clinical practice and treatment evaluation.

Disclosures: G. A. Wells: Bristol-Myers Squibb, 2; T. Li: Bristol-Myers Squibb, 1, 3; M. Boers: None.

1759

Is Exclusion of Joints of the Feet in a Disease Activity Index like DAS28 a Clinical Problem When Assessing the Individual RA Patient? M. F. Bakker1, J. W. G. Jacobs2, P. M. J. Welsing3, F. P. J. G. Lafeber2 and J. W. J. Bijlsma1. 1Rheumatology & Clinical Immunology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands; 2Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

**Background:** The disease activity of RA patients is often assessed with the DAS28, in clinical trials as well as in daily practice. However, the DAS28 has not been validated for use in individual patients and joints of feet are not included. The aim of this investigation was to study whether this last drawback could be a clinical problem.

**Methods:** Patients within the CAMERA trial were divided into 3 ‘damage progression’ groups according to local radiographic progression rates: 1) primarily progression of the feet, 2) similar progression of hands and feet, and 3) primarily hand progression. This was done for radiographic progression within the first 2 years, between 2 and 5 years and from 5 until 5 years. Time-averaged DAS28, its individual components (TJC, SJC, ESR, and VAS-GH), and tender and swollen joints of feet were compared between the 3 groups within the first 2 time periods. The longitudinal relation of DAS28 with radiographic damage (total SHS score) over the 5 year period was investigated within the 3 ‘damage progression’ groups with RF-status, baseline joint damage as well as the SJC and TJC of the feet as covariates using longitudinal regression analysis (mixed model analysis).

**Results:** After 2 and 5 years of treatment, respectively 145 (55%) and 66 (33%) patients had no radiographic progression, 30 (11%) and 33 (16%) primarily feet progression, 60 (23%) and 69 (35%) similar progression and 30 (11%) and 32 (16%) primarily hand progression. Over the first two years the primarily feet and hand progression groups (group 1 and 3) had a similar mean (SD) DAS28: 4.0 (1.0) vs. 3.9 (0.9), respectively. However, compared to the primarily hand group, the primarily feet group had more tender and swollen joints of the feet: 3.4 (2.2) vs. 1.5 (1.3), p<0.001 and 2.8 (1.9) vs. 1.1 (1.2), p<0.001, respectively. This statistically significant difference was not present in the 2 until 5 year period. In both time periods, the ‘similar progression’ group (group 2) had lower disease activity scores and involvement of the feet in between those of groups 1 and 3.

On group level there was a longitudinal relation between the DAS28 and radiographic progression. The ‘damage progression’ groups modified the relation between the DAS28 and radiographic progression, with the ‘primarily foot progressors’ (group 3) showing more (change in) radiographic progression with the same (change in) the DAS28 as compared to the other groups (interaction term DAS28*primarily foot progressors: β=1.2, 95%CI: 0.6–1.9, p<0.001). In other words, the ‘primarily foot progressors’ the disease activity when assessed by the DAS28 seems to be underestimated. In the primarily foot progressors the joint counts for the feet were also longitudinally related to radiographic progression.

**Conclusions:** In a subgroup of RA patients the DAS28 underestimates the total joints involved (especially during the first 2 years of the disease) and the expected joint damage. This could particularly be a problem in tight control, using the DAS28 remission or low disease activity definition. For follow-up of individual patients, assessment of all for RA relevant joints seems indicated.

References:

Disclosure: M. F. Bakker: None; J. W. G. Jacobs: None; P. M. J. Welsing: None; F. P. J. G. Lafeber: None; J. W. J. Bijlsma: None.

1760

Level of Agreement of 1987 ACR and 2010 ACR/EULAR Classification Criteria: An Analysis Based on the ESPoir Cohort Data. Bruno Faure1, Nathalie Rincheval2, Bernard G. Cambé3, Maxime Douagos2 and ESPoir Scientific Committee. 1Hospital Lapeyronie, Montpellier, France; 2Hospital Cochin, Paris, France; 3Pitié Salpêtrière Hospital, Paris, France; 4UIRC Montpellier

New rheumatoid arthritis (RA) classification criteria have been developed conjointly by the ACR and EULAR in 2010 to replace the 1987 ACR ones. However, information is lacking to determine in what extent the “old” and “new” sets identify similar patients as having RA.

**Objective:** To assess the agreement between 1987 ACR and 2010 ACR/EULAR criteria and the source of potential disagreement of the 2 sets, based on the ESPoir cohort data.

**Patients and Methods:** 813 patients with early arthritis (EA) were included into the cohort between 2002 and 2005 and followed every 6 months during the first 2 years. Inclusion criteria were: 18 to 70 years old, more than 2 swollen joints for more than 6 weeks and less than 6 months; with suspected RA diagnosis. The agreement between the 2 criteria sets was based on Kappa coefficient calculation.

**Results:** On data on 811 patients were available with main characteristics as follows: female 77%; mean age 48 ±13 years; mean HAQ 1.0 ± 0.7; swollen joint count 7.2 ± 5; tender joint count 8.4 ± 7; DAS28 5.2 ± 1.5; ESR 29 ± 25 mm/1 hr; CRP 22 ± 34 mg/L, IgM RF +47 %, anti-CCP +39 % structural damage on X-ray 22.2%, 579 (71.4%) patients met the 1987 ACR criteria and 641 (79.0 %) the 2010 ACR/EULAR ones at baseline. 168 patients were discordant, 115 only satisfying the 2010 criteria and 53 only the 1987 ones. The concordance between the 2 sets was fair with a Kappa coefficient of 0.45 [95% CI: 0.38; 0.52]. Main sources of disagreement are indicated in the table below.

**Table.** Patients meeting both sets

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Both sets (n=556)</th>
<th>Only 2010 set (n=115)</th>
<th>Only 1987 set (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender joints, mean ± sd</td>
<td>10.4 ± 7.2</td>
<td>7.2 ± 6.2</td>
<td>3.8 ± 2.7</td>
</tr>
<tr>
<td>4 to 10 involved small joints, n(%)</td>
<td>91 (17.3)</td>
<td>31 (27.0)</td>
<td>38 (71.7)</td>
</tr>
<tr>
<td>≥10 involved joints, n (%)</td>
<td>421 (80.0)</td>
<td>61 (53.1)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Swollen joints, mean ± sd</td>
<td>9.1 ± 5.5</td>
<td>3.9 ± 3.2</td>
<td>5 ± 2.6</td>
</tr>
<tr>
<td>≥3 synovitis, n (%)</td>
<td>503 (95.6)</td>
<td>52 (45.2)</td>
<td>51 (96.2)</td>
</tr>
<tr>
<td>Symmetrical arthritis, n (%)</td>
<td>486 (92.4)</td>
<td>42 (36.5)</td>
<td>52 (98.1)</td>
</tr>
<tr>
<td>Morning stiffness ≥60 min, n (%)</td>
<td>497 (94.5)</td>
<td>74 (64.4)</td>
<td>53 (100)</td>
</tr>
<tr>
<td>RF +, n (%)</td>
<td>309 (58.7)</td>
<td>58 (50.4)</td>
<td>5 (5.7)</td>
</tr>
<tr>
<td>ACR 1987 (n %)</td>
<td>274 (52.1)</td>
<td>39 (33.9)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>RA diagnosis certainty at inclusion on a 0–10 VAS</td>
<td>7.9 ± 1.8</td>
<td>5.0 ± 2.4</td>
<td>6.2 ± 2.1</td>
</tr>
<tr>
<td>RA diagnosis certainty at 2 years on a 0–10 VAS</td>
<td>8.1 ± 2.7</td>
<td>6.3 ± 3.6</td>
<td>6.4 ± 3.5</td>
</tr>
</tbody>
</table>
Liver Injury in Patients with Rheumatic Diseases and Inflammatory Syndrome: A Case-Control Prospective Analysis Using Biomarkers (FibroTest, ActiTest and SteatoTest)


1 Paris 6 - Pierre et Marie Curie University; Hepatology, Pitié-Salpêtrière Hospital, Paris, France, 2 Paris 6 – Pierre et Marie Curie University; Rheumatology, Pitié-Salpêtrière Hospital, Paris, France

Background: Several drugs used in chronic rheumatic diseases (RHU) can induce liver damage. Few studies on consecutive cohorts are available because of the limitations of liver biopsy.

The aim was 1) to use validated biomarkers to evaluate the presence of fibrosis (Fibrotest), necroinflammatory activity (Actitest), and steatosis (Steato-test) and associated risk factors among RHU subjects hospitalized in a rheumatology department 2) to evaluate the impact of inflammatory syndrome estimated by C-reactive protein (CRP) on FibroTest parameters.

Methods: 211 prospective RHU were compared to 211 healthy controls without known liver disease (CTR), matched for age, gender, self-declared alcohol intake (SDA) and body mass index. Standard thresholds were: Fibrotest<0.27 for no/minimal fibrosis (METAVIR F0) and Fibrotest>0.48 for advanced fibrosis (AF, METAVIR F2); Actitest<0.29 for no/minimal activity (METAVIR A0); Steato-test<0.38 for no steatosis.

Results: Among RHU (36.4% male, age 48 years, median [range] CRP 4g/L [1.4-72]), 96 had rheumatoid arthritis (RA), 57 ankylosing spondylitis (AS), 14 psoriatic arthritis (PsA) and 50 other diagnoses; 36.5% were treated with methotrexate (MTX), 22.7% with corticosteroids, 22.8% with non-steroid anti-inflammatory, 8.1% with infliximab (IFX), 29.4% with paracetamol. Median [range] number of treatments per subject was 3[0-11]. The mean (SE) SDA in PsA compared with others was 12g/d (7.7) vs. 5g/d (0.7) (p=0.02).

The prevalence of presumed lesions in RHU versus CTR in overall population and according to etiology was presented in the table.

<table>
<thead>
<tr>
<th>RHU</th>
<th>CTR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis %</td>
<td>10.9</td>
<td>7.2</td>
</tr>
<tr>
<td>- RA</td>
<td>7.3</td>
<td>5.2</td>
</tr>
<tr>
<td>- AS</td>
<td>8.8</td>
<td>5.3</td>
</tr>
<tr>
<td>- PsA</td>
<td>21.4</td>
<td>7.1</td>
</tr>
<tr>
<td>AF</td>
<td>2.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Activity %</td>
<td>10.4</td>
<td>4.3</td>
</tr>
<tr>
<td>OR=2.61 [1.17-5.82]</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>OR=4.012 [1.08-14.88]</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>- RA</td>
<td>8.8</td>
<td>1.8</td>
</tr>
<tr>
<td>- AS</td>
<td>21.4</td>
<td>14.3</td>
</tr>
<tr>
<td>Steatosis%</td>
<td>38.5</td>
<td>30.2</td>
</tr>
<tr>
<td>OR=1.44 [0.95-2.17]</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>- RA</td>
<td>41.2</td>
<td>33.7</td>
</tr>
<tr>
<td>- AS</td>
<td>30.2</td>
<td>34</td>
</tr>
<tr>
<td>- PsA</td>
<td>64.3</td>
<td>28.6</td>
</tr>
</tbody>
</table>

Steatosis was more prevalent in patients treated with MTX or IFX than in CTR (40.3% vs 29.9%, p<0.0001; 52.9%vs17.6%, p=0.031 respectively).

The prevalence of other lesions was not different according to treatment regimen.

CRP was not correlated [Spearman correlation coefficient (SCC)] with alpha2-macroglobulin (SCC= 0.01, p=0.89) and was correlated only with haptoglobin (SCC= 0.71, p<0.0001) without impact on FibroTest results (SCC= −0.07, p=0.36).

Conclusions: Compared with CTR, RHU had a higher prevalence of necroinflammatory activity and steatosis presumed with biomarkers. The subjects with RA had greater presumed activity, and subjects with PsA more frequent steatosis. The presumed steatosis was associated with treatments with MTX and IFX. Haptoglobin and not alpha2macroglobulin was correlated with inflammatory syndrome without impact on final FibroTest results.

Disclosure: C. Gaujoux-Viala: None; M. Benhamou: None; M. Munteanu: None; Y. Ngo: None; D. Messous: None; F. Imbert-Bismut: None; V. Ratziu: None; P. Bourgeois: None; T. Poynard: None; B. Faurel: None; SAFE-T DILI-GHPS Study Group: None.
New 2010 ACR-EULAR Rheumatoid Arthritis Classification Criteria Are Highly Sensitive in Patients with Early Rheumatoid Arthritis. Sarang Chitale1, Nicola J. Goodson2, David W. Sharpley2, Robert N. Thompson1, Robert J. Moots3 and Cristina Estrach2. 1Academic Rheumatology Department, University Hospital Aintree, Liverpool, Merseyside, United Kingdom, 2Academic Rheumatology Department, University of Liverpool, Liverpool, Merseyside, United Kingdom.

Background: Rheumatoid Arthritis (RA) requires early recognition & treatment with disease modifying anti-rheumatic drugs (DMARD) to prevent erosive damage and long-term disability. Many patients with early RA (eRA) do not satisfy the 1987 ACR classification criteria [1] at initial presentation. Other revised criteria have been proposed to improve the identification of such patients [2]. ACR and EULAR have jointly formulated new RA classification criteria to facilitate early recognition of patients likely to have persistent and progressive disease and require DMARD therapy [3].

Aims: To explore whether a cohort of patients with symptom duration ≥12 months, diagnosed with eRA (based on the opinion of the rheumatologist) and started on DMARDS, met ACR-EULAR criteria at the initial assessment.

And to compare the percentage of patients diagnosed with RA at baseline by using 4 sets of criteria [1–3].

Methods: Baseline data on patients with eRA attending between May 2006 and March 2010 were examined & included symptom duration, joint involvement (small & large), symmetry, early morning stiffness in minutes, swollen and tender joint counts out of 44 joints, radiographic changes, anti-CCP & rheumatoid factor (RF) status and titre and ESR & CRP at initial presentation. All patients had at least 1 clinically swollen joint at baseline.

1987 ACR criteria, ACR tree criteria [1], anti-CCP revised criteria and the new ACR-EULAR 2010 RA classification criteria were applied. A score of ≥6 out of 10 by the ACR-EULAR criteria equals definite RA. Analysis was repeated for patients presenting with very early RA (veRA: defined as symptom duration ≤3 months).

Results: 208 patients with eRA were identified, with mean age 58.7 years (SD 15.7 years) and median symptom duration of 16 weeks, IQR [9.5, 28 weeks]. 130 (62.5 %) were female, 123 (59%) tested positive for both RF & anti-CCP and 28 (13%) had radiographic erosive disease at baseline. 91 (44%) presented with veRA.

171 (82%) with eRA & 74 (81%) with veRA had definite RA by the ACR-EULAR RA classification criteria. Proportion of eRA & veRA patients satisfying each of the four sets of RA classification criteria at their initial rheumatology assessment is shown in Table 1.

Table 1. Number of eRA & veRA patients satisfying RA criteria at baseline rheumatology assessment

<table>
<thead>
<tr>
<th>Criteria</th>
<th>eRA Patients n=208</th>
<th>veRA Patients n=91</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 1987 criteria</td>
<td>121</td>
<td>58</td>
</tr>
<tr>
<td>ACR Tree format</td>
<td>142</td>
<td>68</td>
</tr>
<tr>
<td>Anti-CCP revised criteria (CCP-6)</td>
<td>166</td>
<td>80</td>
</tr>
<tr>
<td>ACR-EULAR Definite RA (≥6 points)</td>
<td>171</td>
<td>82</td>
</tr>
</tbody>
</table>

Conclusion: This study demonstrates that the ACR-EULAR criteria are more sensitive for identifying RA at the initial rheumatology assessment than the other RA and eRA classification criteria in this EAC cohort. This difference was most marked in those patients presenting with veRA, with the highest sensitivity for ACR-EULAR criteria. Applying these criteria in the EAC setting should facilitate more rapid initiation of DMARD therapy with the highest sensitivity for ACR-EULAR criteria. Applying these criteria or an array-based assay using a novel multiplex technology described herein will develop a highly reproducible, automated, multiplex biomarker assay that can reliably distinguish between RA patients and healthy individuals or patients with other inflammatory arthritides. Multiplex measurement of a subset of the differentiating biomarkers provides high sensitivity and specificity for the diagnostic discrimination of RA. Identification of distinct biomarker signatures enabled molecular stratification of early-stage RA into clinically relevant subtypes.

Conclusions: The multiplex biomarker assay described herein has the potential to diagnose RA with greater sensitivity and specificity than do current clinical tests. Its ability to stratify RA patients in an automated and reproducible manner paves the way for the development of assays that can guide RA therapy.

Table 1. Performance characteristics of multiplex-assay autoantibody profiles in the diagnosis of rheumatoid arthritis.

<table>
<thead>
<tr>
<th>Biomarker panel</th>
<th>PPV</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 + markers</td>
<td>79.5%</td>
<td>92.6%</td>
<td>96.7%</td>
<td>62.5%</td>
</tr>
<tr>
<td>2 + markers</td>
<td>91.8%</td>
<td>89.7%</td>
<td>93.3%</td>
<td>87.5%</td>
</tr>
<tr>
<td>3 + markers</td>
<td>95.3%</td>
<td>79.8%</td>
<td>84.2%</td>
<td>93.8%</td>
</tr>
<tr>
<td>4 + markers</td>
<td>95.9%</td>
<td>61.1%</td>
<td>59.2%</td>
<td>96.3%</td>
</tr>
</tbody>
</table>

Disclosure: P. E. Chandra: None; J. Sokolove: None; B. G. Hipp: Roche Diagnostics, 3; H. Ebert: Roche Diagnostics, 3; U. Klause: Roche Diagnostics, 3; W. Robinson: Roche Diagnostics, 2.

1765

Patient Questionnaire Scores for Physical Function and Pain Are More Likely Than Erythrocyte Sedimentation Rate (ESR) To Document a Quantitative Abnormality in New Patients with Rheumatoid Arthritis (RA). Theodore Pincus1 and Christopher J. Swearingen2. 1New York University Hospital for Joint Disease, Hastings-on-Hudson, NY, 2University of Arkansas for Medical Sciences, Little Rock, AR

Purpose: To analyze the capacity of 3 quantitative measures—erythrocyte sedimentation rate (ESR), physical function on a multidimensional health assessment questionnaire (MDHAQ-FN) and pain (PAIN) on a 0–10 visual analog scale (VAS)—to document an abnormality at presentation of 413 new patients with RA seen between 1982 and 2006, by comparing the proportions with normal versus abnormal results.

Methods: All new patients seen at a weekly academic rheumatology clinic complete an MDHAQ with scores for MDHAQ-FN and PAIN. Patients with RA also had assessment of ESR. Complete data for ESR, MDHAQ-FN and PAIN scores were available for 413 new patients with RA seen between 1982 and 2006. Abnormal values were ESR ≥28 mm/h (clinical trial inclusion criterion), MDHAQ-FN ≥2 on a 0–10 scale (>2.0 on a 0–3 scale), and PAIN >2 on a 0–10 VAS. The proportions of patients with abnormal and normal values at presentation were compared, using descriptive statistics.

Results: Of the 413 patients, 192 (46%) had normal ESR <28 mm/h (54% had ESR ≥28), 122 (30%) had normal MDHAQ-FN scores ≤2 (70% had MDHAQ-FN >2), and 44 (11%) had normal PAIN scores <2 (89% had PAIN >2). Patients with ESR <28 were more likely to have MDHAQ-FN or
PAIN score ≤2. Nonetheless, among the 192 patients with a normal ESR of <28, 112 (58%) had an abnormal MDHAQ-FN score of ≥2.8, and 161 (84%) had an abnormal PAIN score of ≥2. A normal score for MDHAQ-FN, PAIN, and ESR was seen in only 26 patients, 14% of those with ESR <28, and 6% of all patients.

**Conclusion:** Among new patients with RA, 54% had an abnormal ESR, while 94% had at least one of three abnormal measures: ESR, MDHAQ-FN or PAIN. Patient self-report questionnaire scores for physical function and pain are more likely than ESR to document an abnormality in patients with RA at presentation. An abnormal quantitative baseline measure is desirable to assess changes over time. Scores for physical function and pain can be collected easily in the infrastructure of usual clinical care to improve quality and document quantitatively responses to therapies.

**Disclosure:** T. Pincus: None; C. J. Swearingen: None.

**1766**

**Preliminary Rheumatoid Arthritis (RA) Flare Assessment for Randomized Clinical Trials (RCTs): An Outcome Measures in Rheumatology (OMERACT) Data-Driven, Patient-Centered, and Consensus-Based Initiative.**

Clifton O. Bingham1, Ernest Choy2, Rieke Aalten3, Maarten Boers4, Peter Brooks5, Vivian Bykerk6, Robin Christensen7, Dan Furst8, Sarah Hewlett9, Amy Leong10, James May11, Tessa Sanderson10, Christof Pohl12, Tessa Sanderson10, Hewlett: None; Amye Leong: None; James May: None; C. Pohl: None; T. Sanderson: None; V. Strand: None; T. Woodward: None.

**Background:** Individuals with rheumatoid arthritis (RA) often experience a decreased ability to participate in valued life activities, such as working, traveling, gardening and attending social events. Many will make accommodations in order to continue participating in these activities. Such accommodations may be associated with the progression of disability in RA. To assess this important domain, including the need for accommodations, a short form of the Valued Life Activities Questionnaire (VLA) was developed and its initial reliability and validity demonstrated using item response analysis1. The short form of the VLA (S-VLA) is a 14-item self-report questionnaire with scores that range from 0 to 4, with higher scores indicating greater disability.

**Methods:** We conducted a series of questionnaires, the S-VLA, Rheumatoid Arthritis Disease Activity Index (RADAJ), Health Assessment Questionnaire-Disability (HAQ-D), Short Form-36 (SF-36) Health Survey, Satisfaction with Activities and Well-being Scale (SAWS) and the Activity Participation Questionnaire (APaqQ). Data from the first 100 patients were analyzed using Cronbach’s alpha for internal consistency reliability. Test–retest reliability was also calculated for a randomly selected subset of patients. Next, item statistics were calculated to assess the correlations between individual items and the total score on the S-VLA, while also correcting for overlap and scale redundancy. Lastly, correlations between the S-VLA and the other measures were used to evaluate convergent and discriminant validity.

**Results:** 100 of 150 patients have been enrolled. Mean (standard deviation) age was 55.01 (14.8) years, duration of RA was 12.5 (10.0) years and 71.0% were female. Test–retest reliability was 0.92 based on the responses of a random subset of 25 patients. Cronbach’s alpha for the S-VLA was 0.93, and none of the 14 items were associated with improved alpha coefficients when omitted. All items were strongly correlated with the S-VLA total score. item-total correlations ranged from 0.59 to 0.79. As anticipated, the total score for the S-VLA was highly positively correlated with patient-reported disease activity (RADAJ r=0.71; p≤0.001), the HAQ-D [r=0.77; p≤0.001], SAWs total score [r=0.77; p<0.001], SAWs satisfaction with activities subscale [r=0.77; p<0.001] and APaqQ days with activity limitations [r=0.61; p<0.001]. As hypothesized, the S-VLA was significantly inversely correlated with SF-36 Physical Component Summary score (r=-0.76; p<0.001) and the SF-36 subscales: Physical Functioning (r=-0.75; p<0.001), Role Physical (r=-0.68; p<0.001) and Social Functioning (r=-0.71; p<0.001).

**Disclosures:** The S-VLA is a new instrument for the measurement of valued life activities in RA. Data from the initial cohort of 100 patients from the larger validation trial lend support to its reliability and validity.


Background: Functional outcomes of Hispanics (H) with RA in the US have been under-reported and their predictors remain largely unknown. Prior works suggest worse function, pain, and global assessment scores in H despite a seemingly appropriate control of disease measures. We address self-reported outcomes, their relationships and determinants in a recently established cohort of H with RA from a single center in the US.

Methods: We describe the first 193 of 349 H fulfilling 1987 ACR criteria for RA and with regular follow-up. Demographic, serologic (RF, a-cyclic citrullinated peptide Ab-ACPA), radiographic parameters and treatments were recorded. Irreversible articular damage (IAD: ankylosis, subluxation, arthrodesis, prosthesis) and joint replacement surgeries (JRS) were tracked. Patients (pts) were evaluated quarterly and Disease Activity Score (DAS28-v-ESR), disability (HAQ-DI), pt-reported pain by visual analogue scale (pain-VAS: 0–3), and depression scores (PHQ-9 scales) were collected. Exploratory linear regressions with forward selection were performed followed by hierarchical multivariate regression to identify independent predictors of disability as reported by HAQ-DI. Data was analyzed with STATA 10.

Results: Median (IQR) DAS28 was 3.28 (2.5–4.1) and low disease activity (DAS28≤3.2-LDAS) was present in 46%. RF was seen in 93% and ACPA in 85%. Overall, 51% had HAQ-DI≥1.5 and 67% ≥1. In the DAS28 group in particular, 42% had HAQ-DI≥1.5 and 58% had DI≥1. Generally, 36% of pts had PHQ-9≥10, consistent with clinical depression. Pain-VAS, JRS, disease activity, depression, age and IAD were univariate determinants of disability (table). RF or ACPA status, erosions, biologics and number of DMARDs did not predict disability. In a multivariate model, pain-VAS was the most robust predictor of disability (standardized regression coefficient =0.4), followed by DAS28 (0.22), JR (0.21), depression (0.17) and age (0.12).

Conclusion: The majority of H report poor functional outcomes and high level of disability despite well controlled disease by physician standards. Pt-reported pain is the cardinal independent predictor of this disability, followed by disease activity, JR, and depression. The directionality for these relationships is being explored with a focus on future intervention.

Table 1. Determinants of disability

<table>
<thead>
<tr>
<th>categorical</th>
<th>b</th>
<th>SE</th>
<th>p</th>
<th>R²</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Female</td>
<td>0.42</td>
<td>0.18</td>
<td>0.02</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.12</td>
<td>0.06</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAD</td>
<td>0.11</td>
<td>0.04</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>JR</td>
<td>0.16</td>
<td>0.10</td>
<td>0.01</td>
<td></td>
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</tr>
<tr>
<td>Fibromyalgia</td>
<td>0.17</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>continuous</td>
<td>Age</td>
<td>0.02</td>
<td>0.01</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>duration</td>
<td>0.01</td>
<td>0.004</td>
<td>0.008</td>
<td>0.1</td>
<td></td>
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<tr>
<td>DAS28-3v</td>
<td>0.3</td>
<td>0.05</td>
<td>0.01</td>
<td></td>
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</tr>
<tr>
<td>ESR</td>
<td>0.005</td>
<td>0.003</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>0.03</td>
<td>0.04</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-VAS</td>
<td>0.57</td>
<td>0.07</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHQ-9</td>
<td>0.05</td>
<td>0.01</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disclosure: M. Chen: None; X. Li: None; P. Akhavan: None; C. Bombardier: None.

Conclusion: The majority of the early RA subjects in routine practice do not have radiographic progression within the first two years of the disease. Very few subjects continuously progressed within 2-year period. Baseline sharp score is the best indicator of whether the subject will progress or not followed by anti-CCP positive, CRP and swollen joint count. These identified indicators can help clinicians to identify the subjects who are at high risk of continuous radiographic progression.

Disclosures: M. Chen: None; X. Li: None; P. Akhavan: None; C. Bombardier: None.

1770
Quantification of Periarticular Osteopenia in Rheumatoid Arthritis. Inhye E. Ahn, Ji Hyeon Ju, Kwi Young Kang, Seung-Ki Kwok, Kyung-su Park, Sung-Hwan Park and Ho-Youn Kim. 1Department of Internal Medicine, Division of Rheumatology, Catholic University of Korea, Seoul, Korea, Republic of; 2Department of Internal Medicine, Division of Rheumatology, Chungbuk University, Cheongui, Korea, Republic of; 3Department of Internal Medicine, The Methodist Hospital, Houston, TX.

Objectives: By quantifying localized hand bone mineral density (BMD), we aimed to validate a new diagnostic method for evaluating the periarticular bone damage in rheumatoid arthritis (RA).

Methods: The study enrolled 195 patients with polyarthritis and was conducted in three steps.

Table 1. No progression N=567 Progression at year 2 only N=18 Progression at year 1 only N=40 Progression at year 1 and 2 N=14 P-value

| Age | 52 (13.79) | 60 (14.45) | 53 (14.15) | 57 (18.33) | 0.05 |
| Baseline swollen joint count | 4.89 (6.09) | 2.61 (3.32) | 6.75 (7.49) | 8.29 (6.66) | 0.02 |
| Baseline tender joint count | 4.88 (6.38) | 3.89 (5.22) | 5.90 (7.17) | 6.35 (6.50) | 0.55 |
| Baseline DAS | 3.85 (1.14) | 2.64 (1.14) | 4.17 (1.14) | 4.83 (1.06) | 0.05 |
| Baseline HAQ | 1.38 (0.74) | 0.83 (0.66) | 1.46 (0.83) | 1.36 (0.47) | 0.06 |
| Baseline Sharp score | 4.06 (5.7) | 3.93 (11.17) | 8.28 (8.47) | 14.0 (9.19) | 0.0001 |
| Baseline CRP | 3.78 (6.7) | 4.3 (3.69) | 3.91 (9.4) | 4.36 (7.79) | 0.09 |
| Disease duration (days) | 160 (213) | 124 (82) | 146 (93) | 148 (82) | 0.55 |
| Anti-CCP positive | 49.72 | 61.54 | 80.77 | 81.82 | 0.0003 |
| Male | 23.41% | 11.11% | 32.50% | 21.43% | 0.57 |
| Rheumatoid factor positive | 58.72% | 66.67% | 50% | 58.57% | 0.04 |
| Ever smoking | 57.74% | 41.18% | 58.82% | 50% | 0.57 |

Conclusion: The majority of the early RA subjects in routine practice do not have radiographic progression within the first two years of the disease. Very few subjects continuously progressed within 2-year period. Baseline sharp score is the best indicator of whether the subject will progress or not followed by anti-CCP positive, CRP and swollen joint count. These identified indicators can help clinicians to identify the subjects who are at high risk of continuous radiographic progression.

Disclosures: M. Chen: None; X. Li: None; P. Akhavan: None; C. Bombardier: None.
Abbreviations: SD: standard deviation. BMI: body mass index

First, inter-observer agreement of periarticular osteopenia in the conventional hand x-ray was evaluated. Second, BMDs of periarticular and non-periarticular regions were quantified by digital x-ray radiography (DXR). BMD ratios were calculated out of eight designated areas on proximal phalanges and compared between RA (n=45) versus non-RA (n=149) groups. Third, medical records of RA patients were retrospectively reviewed to identify clinical conditions predisposing to the loss of juxta-articular bone minerals.

Results: The interpretation of periarticular osteopenia on x-ray reached a moderate degree of inter-observer agreement among four physicians (kappa 0.47, p<0.001). On DXR-assisted BMD quantification, we designed three types of mathematical formulæ; the ratio of non-periarticular BMD, the mean of ratios, and the ratio of sums.

Cut-off values were within 2.10–2.15 (sensitivity 36.67–80.64%, specificity 52.17–86.42%). In bivariate analysis, body mass index, the duration of steroids and c-telopeptide showed correlation with BMD ratios (p<0.05).

Conclusion: In DXR-assisted localized quantification and proportional calculation, periarticular osteopenia is a distinctive feature of RA under 10 years of duration.

Clinical Trial Registration Number: KC090ISI0258

Disclosure: L. E. Ahn: None; J. H. Ju: None; K. Y. Kang: None; S.-K. Kwok: None; K.-s. Park: None; S.-H. Park: None; H.-Y. Kim: None.

1771

Radiological Progression in Very Early Rheumatoid Arthritis, Results of the DREAM Remission Induction Cohort. Marloes Vermeer1, Ina H. Kuper2, Monique Hoekstra3, Hein J. Bernelot Moens1, Piet L. C. M. van Riel2 and Mart A. F. J. van de Laar3. 1Isala Klinieken, Zwolle, The Netherlands, 2Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, 3University of Twente and Medisch Spectrum Twente, Enschede, The Netherlands, ‘Ziekenhuissgroep Twente, Almelo/Hengelo, The Netherlands

Background: Previous studies suggest that disease activity at baseline and even stronger disease activity over time are related to radiological progression in rheumatoid arthritis (RA) (1, 2). This emphasizes the importance of controlling inflammatory activity and inducing remission rapidly. The objective of this study was to assess the relationship between disease activity and radiographic progression after 1 year in a remission induction cohort of patients with very early RA.

Methods: Data of the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort were used. Inclusion criteria were: a clinical diagnosis of RA, age ≥ 18 years, duration of symptoms ≤ 1 year and no previous treatment with DMARDs and/or prednisolone. DMARD medication was adjusted based on 4–8 weekly DAS28 measurements, aiming at remission (DAS28 ≤ 2.6). The treatment protocol started with methotrexate (MTX), addition of sulfasalazine in case of inefficacy, followed by MTX + anti-TNF. Radiographs of hands and feet were obtained at baseline, after 6 and 12 months and evaluated in chronological order by two observers (consensus score) according to the Sharp-van der Heijde Score (SHS). An increase in SHS ≥ 5 U/year was regarded as clinically relevant radiological progression (3). Primary outcome was the association of the area under the curve (AUC) of the DAS28 (0, 3, 6, 9 and 12 months) and radiological progression after one year. This was analyzed in a logistic regression model with correction for confounders, in case of missing values the principle of last observation carried forward was applied. Secondary outcome was the percentage of patients without radiological progression after one year.

Results: One year radiological data were available for 143 patients. After one year, observed DAS28 levels were: 0.5% (88/143) remission (DAS28 < 2.6), 16.1% (23/143) low (2.6 ≤ DAS28 < 3.2), 19.6% (28/143) moderate (3.2 ≤ DAS28 ≤ 5.1) and 2.8% (4/143) high (DAS28 > 5.1). Median (IQR) SHS was 5.0 (2.0–10.0) and median (IQR) progression of SHS was 2.0 (1.0–5.0). Hundred of the 143 patients did not show radiological progression in the group with active disease (DAS28 > 3.2): 72.7%

Table 1. Clinical and demographic features of patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>Non-RA</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (total=195)</td>
<td>45</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>40/5</td>
<td>113/37</td>
<td>0.881</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>47.95 (16.36)</td>
<td>48.24 (15.69)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.06 (3.93)</td>
<td>23.94 (3.28)</td>
<td>0.262</td>
</tr>
<tr>
<td>L-spine T-score</td>
<td>-1.22 (1.23)</td>
<td>-0.80 (1.39)</td>
<td>0.415</td>
</tr>
<tr>
<td>L-spine Z-score</td>
<td>-0.23 (0.93)</td>
<td>0.02 (1.23)</td>
<td>0.099</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Medications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>86.67%</td>
</tr>
<tr>
<td>Calcium and/or Vitamin D supplements</td>
<td>60.00%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Morbidities &amp; Comorbidities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>3</td>
</tr>
<tr>
<td>Crystal-induced arthropathy (eg. Gout)</td>
<td>0</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>1</td>
</tr>
<tr>
<td>Sjogren’s disease</td>
<td>0</td>
</tr>
<tr>
<td>Dermatomyositis/Polyomyositis</td>
<td>1</td>
</tr>
<tr>
<td>Ankylosing Spondylitis</td>
<td>1</td>
</tr>
<tr>
<td>Behcet’s disease</td>
<td>9</td>
</tr>
</tbody>
</table>

Abbreviations: SD: standard deviation. BMI: body mass index

* Mann-Whitney rank sum test for unpaired differences p under 0.05 was considered statistically significant.

Table 2. Periarticular osteopenia in RA versus non-RA patients

<table>
<thead>
<tr>
<th></th>
<th>Non-RA mean (SD)</th>
<th>Total RA mean (SD)</th>
<th>p</th>
<th>RA&lt;10Y mean (SD)</th>
<th>p</th>
<th>RA≥10Y mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (total=195)</td>
<td>150</td>
<td></td>
<td></td>
<td>11</td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Digits of left hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index: L1/L1</td>
<td>1.85 (0.27)</td>
<td>1.98 (0.47)*</td>
<td>0.018</td>
<td>2.10 (0.24)*</td>
<td>&lt;0.01</td>
<td>1.65 (0.44)*</td>
<td>0.028</td>
</tr>
<tr>
<td>MIddle: L2/L2</td>
<td>1.90 (0.33)</td>
<td>1.97 (0.38)</td>
<td>0.249</td>
<td>2.07 (0.35)*</td>
<td>0.012</td>
<td>1.72 (0.37)</td>
<td>0.079</td>
</tr>
<tr>
<td>Ring: L3/L3</td>
<td>2.03 (0.35)</td>
<td>2.17 (0.59)*</td>
<td>0.041</td>
<td>2.25 (0.40)*</td>
<td>0.021</td>
<td>2.05 (0.78)</td>
<td>0.249</td>
</tr>
<tr>
<td>Small: L4/L4</td>
<td>1.91 (0.37)</td>
<td>2.06 (0.59)*</td>
<td>0.031</td>
<td>2.07 (0.40)</td>
<td>0.058</td>
<td>2.09 (0.92)</td>
<td>0.144</td>
</tr>
</tbody>
</table>

| Digits of right hand |                  |                    |       |                  |       |                  |       |
| Index: R1/R1        | 1.84 (0.31)      | 1.93 (0.50)        | 0.119 | 2.04 (0.46)*     | <0.01 | 1.66 (0.53)      | 0.099 |
| MIddle: R2/R2       | 1.85 (0.30)      | 1.96 (0.44)        | 0.051 | 2.05 (0.40)*     | <0.01 | 1.64 (0.37)      | 0.034 |
| Ring: R3/R3         | 2.00 (0.33)      | 2.08 (0.40)        | 0.227 | 2.19 (0.31)*     | <0.01 | 1.87 (0.48)      | 0.187 |
| Small: R4/R4        | 1.94 (0.36)      | 2.04 (0.52)        | 0.221 | 2.04 (0.49)      | 0.200 | 2.06 (0.64)      | 0.233 |

Formulae

Left: mean of mid-to-p  
Peri BMD ratio

Right: mean of mid-to-p   
BMD ratio

Both: mean of mid-to-p BMD ratio

Left: sum of mid BMD/sum of peri BMD

Right: sum of mid BMD/sum of peri BMD

Both: sum of mid BMD/sum of peri BMD

*Independent t-test to compare means of non-RA patients versus one of the three groups; all RA patients, RA under 10 years, RA for and over 10 years. An asterisk (*) indicates a statistically significant difference with p value under 0.05 when compared to the non-RA group. Other undefined values were not significant. Values are the mean (SD) in g/cm².

These values were significantly higher in patients with RA for less than 10 years than in non-RA group (p<0.05). RA for 10 years or longer blunted the BMD ratios, and the disease duration was inversely correlated to the ratio (correlation coefficient – 0.35).
(64/88) vs. 59.4% (19/32). The majority of patients achieved remission on conventional DMARD therapy. A higher AUC of DAS28 over the first year was associated with radiological progression (p=0.054, corrected for baseline SHS).

Conclusion: In very early RA, disease activity over time is associated with radiological progression. In this very early RA cohort, radiological progression was limited. Patients in remission showed less radiological progression than patients with persistent disease activity.

References:

Disclosure: M. Vermeer: None; I. H. Kuper: None; M. Hoekstra: None; H. J. Bernelet Moens: None; P. L. C. M. van Riel: None; M. A. F. J. van de Laar: None.

1772

Retinal Vascular Caliber Is Altered in Patients with Rheumatoid Arthritis: A Biomarker of Disease Activity and Cardiovascular Risk? Sharon Van Doornum1, Gemma Strickland2, Ryo Kawasaki3, Jing Xie3, Lauren Hodgson1, Ian Wicks2 and Tien Wong1. 1Royal Melbourne Hospital, Melbourne, Australia, 2Royal Melbourne Hospital, University of Melbourne

Introduction: Examination of the retinal vasculature is a novel method for assessing cardiovascular (CV) risk. Changes in retinal vascular caliber (narrowing of arteriolar caliber and/or widening of venular caliber) have been independently associated with CV risk factors and also with an increased risk of CV events. Retinal venular dilatation has also been associated with elevated biomarkers of inflammation.

Methods: 51 RA patients and 51 age and gender matched population controls had retinal photographs taken according to a standardized protocol. The digital images of all subjects were analysed by a single trained assessor using a validated computer program. The caliber of arterioles and venules were summarised as central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) respectively. Disease activity in RA patients was classified according to the 28 joint Disease Activity Score (DAS).

Results: Demographic characteristics and mean CRVE and CRAE of the RA patients and controls are shown in Table 1.

Table 1. Demographic and clinical details and retinal vascular caliber measurements in RA and control patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>RA (n=51)</th>
<th>Controls (n=51)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>34 (67)</td>
<td>34 (67)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.5 ± 12.5</td>
<td>59.5 ± 12.5</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131 ± 19</td>
<td>132 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77 ± 11</td>
<td>69 ± 11</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (9.8)</td>
<td>6 (11.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>7 (13.7)</td>
<td>2 (3.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>8 (15.7)</td>
<td>14 (27.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Never smoker</td>
<td>36 (70.6)</td>
<td>35 (68.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
<td>29.7 ± 5.6</td>
<td>29.2 ± 5.3</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.2 ± 1.2</td>
<td>5.3 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.6 ± 1.0</td>
<td>1.3 ± 0.4</td>
<td>0.012</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.9 ± 0.9</td>
<td>3.3 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.4 ± 0.6</td>
<td>1.5 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>RA disease duration in years (median (range))</td>
<td>9.4 (0.3–55)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>DAS (median (range))</td>
<td>3.4 (1.2–7.9)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>No. of DMARDs (median (range))</td>
<td>2 (0–4)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Central retinal arteriolar equivalent (µm)</td>
<td>152.3 ± 153</td>
<td>143.7 ± 13.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Central retinal venular equivalent (µm)</td>
<td>235.9 ± 24.6</td>
<td>211.6 ± 21.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
| Data are n (%) or mean±SD unless otherwise indicated. HDL high density lipoprotein, LDL low density lipoprotein, DAS disease activity score, DMARD disease modifying anti-rheumatic drug

Table 2 shows the relative difference in CRAE and CRVE between RA patients and controls in an unadjusted comparison and after adjustment for relevant clinical variables. In the unadjusted analysis both CRAE and CRVE were significantly wider in the RA group compared with controls. After adjustment for all relevant variables the CRVE remained significantly larger in the RA patients (mean CRVE 20.3 mm greater in RA vs controls, 95% CI 10.4–30.3) whereas CRAE was not different between the groups.

Table 2. Difference in CRAE and CRVE in RA patients as compared with matched Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted analysis (mean, 95% CI)</th>
<th>Adjusted analysis* (mean, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRAE in RA relative to controls, µm</td>
<td>8.6 (2.8–14.4)</td>
<td>2.4 (–4.3–9.1)</td>
</tr>
<tr>
<td>CRVE in RA relative to controls, µm</td>
<td>24.3 (15.2–33.2)</td>
<td>20.3 (10.4–30.3)</td>
</tr>
</tbody>
</table>

CRAE central retinal arteriolar equivalent CRVE central retinal venular equivalent

*Adjusted for age, gender, body mass index, systolic and diastolic blood pressure, lipid levels, diabetes status, smoking status and companion vessel calibre.

We also investigated the relationship between CRVE and inflammation. Figure 1 compares CRVE in controls and in the RA patients grouped according to disease activity. CRVE in the RA patients with high disease activity was greater than the controls and remaining RA patients, and this difference remained significant after adjusting for potential confounders.

Figure 1. Central retinal venular equivalent in controls and RA patients.

Conclusion: To our knowledge this is the first report of retinal vascular caliber measurement in patients with RA. We have demonstrated increased CRVE in RA patients and a relationship between RA disease activity and CRVE. Longitudinal studies correlating CRVE with subsequent CV events will be required to further evaluate this relationship and to examine the predictive role of CRVE measurement in this patient group.

Disclosure: S. Van Doornum: None; G. Strickland: None; R. Kawasaki: None; J. Xie: None; L. Hodgson: None; I. Wicks: None; T. Wong: None.

1773

Serum Undercarboxylated Osteocalcin Levels in Patients with Rheumatoid Arthritis. Kuninobu Wakabayashi, Kuniko Otsuka, Michihito Sato, Ryo Takahashi, Tsuyoshi Odai, Takeo Isosaki, Nobuyuki Yamina, Yusuke Miwa and Tsuyoshi Kasama. Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Purpose: Elevated serum levels of undercarboxylated osteocalcin (ucOC) is indicative of vitamin K (VK) deficiency in bone and increased risk of osteoporotic fracture. We assessed serum ucOC levels in patients with rheumatoid arthritis (RA).

Methods: Serum ucOC levels were measured in 100 RA patients, and the relationships between ucOC levels and age, sex, C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR) and prednisolone (PRL) dosage, with or without bisphosphonate (BP), were assessed. Patients whose ucOC levels were above a cut-off value of 4.5 ng/ml were treated with menatetrenone and the ucOC-positivity rate was higher among female patients than among male patients (p<0.05). We observed a significant negative correlation between serum ucOC levels and PRL dosage (p<0.001).

Figure 1. Serum ucOC levels in RA patients.

RA patients: DAS28 > 5.1 = high disease activity

RA rheumatoid arthritis; DAS28 > 5.1 = high disease activity

Table 2. Serum ucOC levels in RA patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serum ucOC levels (ng/ml)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA patients</td>
<td>4.3–9.1</td>
<td>NS</td>
</tr>
<tr>
<td>Controls</td>
<td>2.4–5.3</td>
<td>NS</td>
</tr>
<tr>
<td>RA patients</td>
<td>4.3–9.1</td>
<td>NS</td>
</tr>
<tr>
<td>Controls</td>
<td>2.4–5.3</td>
<td>NS</td>
</tr>
</tbody>
</table>
Thus ucOC levels were significantly lower in RA patients treated with PSL 5–10 mg/day than in patients treated with PSL <5 mg/day (p<0.01) or in untreated patients (p<0.001).

Moreover, those also receiving BP showed lower ucOC levels than those not receiving BP (p<0.02). Twenty-four patients with high ucOC levels were treated with menatetrenone (vitamin K2), which significantly reduced ucOC levels after 3 months of treatment (p<0.001). There was no correlation between serum ucOC levels and age, CRP or ESR.

Conclusion: PSL is known to inhibit bone formation and osteocalcin production. We suggest that levels of vitamin K, which is necessary for γ-carboxylation of the glutamate residues in osteocalcin, are reduced in RA patients treated with PSL 5 mg/day and whose serum ucOC levels are above a cut-off value of 4.5 ng/ml, menatetrenone (vitamin K2) treatment is effective against osteoporosis.

Disclosure: K. Wakabayashi: Eisai; 2; K. Otsuka: None; M. Sato: None; R. Takahashi: None; T. Odaï: None; T. Isozaki: None; N. Yajima: None; Y. Miwa: None; T. Kasama: None.

Background: The new ACR/EULAR criteria for rheumatoid arthritis (RA) were designed to predict risk of RA development at an early stage. The algorithm yields a score from 0–10 points where a patient needs ≥ 6 points to be classified as RA. The criteria need validation in cohorts of early arthritis patients.

Methods: Patients in the Norwegian Very Early Arthritis Clinic (NOR-VEAC) (swelling in ≥1 joint with duration ≤16 weeks, 18–75 years) were followed for 6 months and assessed for development of RA (clinical diagnosis). Only patients that did not contribute with data to Phase 1 of the criteria development were included to minimize overfitting of data. Sensitivity, specificity and likelihood ratios (LR) for different cut-offs were calculated and overall discriminatory ability was assessed with a receiver operating characteristics (ROC) curve.

Results: 298 patients (50 % females, median age 46.6 years, median duration of joint swelling 39 days, anti-CCP/IgM rheumatoid factor positives 18.5 %/14.2 %) were included in the analyses. After 6 months, 72 (24.2 %) patients had RA by the judgement of a rheumatologist (seropositive RA 45 (62.5 %)). Median (range) ACR/EULAR score at inclusion in RA/non-RA patients was 7(3–10)/3(0–9). Area under the ROC curve (95% CI) was 0.93 (0.90–0.96). The proposed cut-off of 6 points for RA classification showed a good combination of sensitivity, specificity and likelihood ratios (LR) for different cut-offs were calculated and overall discriminatory ability was assessed with a receiver operating characteristics (ROC) curve.

Conclusion: The new ACR/EULAR RA classification criteria performed well for prediction of clinical RA diagnosis in a cohort of very early arthritis patients. This validation supports the use of these criteria in clinical practice.

Table. Sensitivity, specificity and likelihood ratios for clinical RA diagnosis for different cut-offs for the 2010 ACR/EULAR RA criteria.

<table>
<thead>
<tr>
<th>Cut-off (points)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>LR+</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>100</td>
<td>36.3</td>
<td>1.57</td>
<td>0.00</td>
</tr>
<tr>
<td>4</td>
<td>98.6</td>
<td>58.8</td>
<td>2.39</td>
<td>0.02</td>
</tr>
<tr>
<td>5</td>
<td>91.7</td>
<td>76.5</td>
<td>3.90</td>
<td>0.11</td>
</tr>
<tr>
<td>6</td>
<td>88.9</td>
<td>83.2</td>
<td>5.29</td>
<td>0.13</td>
</tr>
<tr>
<td>7</td>
<td>63.9</td>
<td>93.4</td>
<td>9.68</td>
<td>0.39</td>
</tr>
<tr>
<td>8</td>
<td>47.2</td>
<td>99.4</td>
<td>78.67</td>
<td>0.53</td>
</tr>
</tbody>
</table>

LR+: positive likelihood ratio; LR−: negative likelihood ratio.
The ACR/EULAR 2010 Criteria as Well as Other Predictive Algorithms for Rheumatoid Arthritis Show Good Diagnostic Performance.

**Background:** The ACR/EULAR devised new diagnostic criteria to improve early diagnosis of rheumatoid arthritis. The criteria were developed as a diagnostic algorithm for persistent and/or erosive disease, what was previously considered to be rheumatoid arthritis. Several other diagnostic algorithms already exist [1,2].

**Objectives:** To evaluate the diagnostic performance of the ACR/EULAR 2010 criteria, van der Helm algorithm [1] and Visser algorithm [2] to identify persistent arthritis at 1 year using different patient sets and 2 outcomes.

**Methods:** Eligible patients in the Rotterdam Early Arthritis Cohort presented with inflammatory arthritis or ≥ 2 inflammatory tender joints and symptom duration less than 12 months. Diagnostic algorithms were tested on discrimination using ROC-curves and calibration by calibration plots. Robustness was tested using different (sub) sets of patients: (i) all patients (n=736) (ii) classified and unclassified arthritis (n=532), and (iii) undifferentiated arthritis (n=301). Two outcomes evaluated were: (a) persistence, defined as arthritis or the need for DMARDs and (b) the 1987 ACR criteria for rheumatoid arthritis.

**Results:** Patients (n=736) had mean age 51 yr (sd 14), median ESR 15 (0–121), RF+ 21%, Anti-CCP+ 20%, median SJC 2 (0–44), median TJC 6 (0–38), erosions 5% at baseline. Table 1 shows discrimination performance for each algorithm per patient set (i;ii;iii) and for outcome (a) and (b). The algorithms had comparable performance on discrimination and calibration, with better performance the ACR/EULAR 2010 and van der Helm algorithm on discrimination. The ACR/EULAR 2010 criteria and van der Helm algorithm performed best in sample (i). Figure 1 shows ROC-curves and calibration plots for the algorithms in patient set (i).

**Conclusion:** The algorithms had comparable performance. However, on discrimination the ACR/EULAR and the van der Helm algorithm performed best in the full patient set. The well performing algorithms enable use in different settings (e.g. primary and specialized care) and suggests that any of these models will improve early diagnosis of patients at risk for rheumatoid arthritis.

**Disclosure:** C. Alves: None; J. Luime: None; J. van Zeben: None; M. Huismans: None; A. Weel: None; P. Barendregt: None; J. Hazes: None.

**1776**

**The Diagnostic Performance of the ACR/EULAR 2010 Criteria If One of Its Parameters Is Not Available. Results from the Rotterdam Early Arthritis Cohort (REACH).** Celina Alves1, Jolanda Luime1, Jendé van Zeben3, Margriet Huism4, Angelique Weel3, Pieternella Barendregt3 and Johanna Hazes1. 1Erasmus MC, 2Erasmus MC, Rotterdam, The Netherlands, 3Maasstad Ziekenhuis, 4St Franciscus Gasthuis.

Recent criteria were developed for the diagnosis of RA to improve early diagnosis of RA, devised as a predictive algorithm for persistent and/or erosive arthritis. They contain 4 domains: joints, serology, acute phase reactants (APRs) and duration. However, in daily clinical practice components may not be available due to various reasons. Therefore we set out to evaluate the diagnostic value of the ACR/EULAR criteria if one of its parameters is not available.

**Methods:** Eligible patients for REACH presented with synovitis or ≥ 2 tender joints and symptom duration less than 12 months. The outcome used was persistent disease, defined as synovitis or the need for DMARDs at 1 year. Statistical analysis was done using ROC-curves for discriminative power and sensitivity and specificity when using the proposed cut off of 6 or higher. Data were analysed for the full model and 9 models with a missing or modified parameter: (i) use of swollen joint count (SJC) instead of SJC and tender joint count (TJC) for joints, (ii) missing RF, (iii) anti-CCP, (iv) ESR or (v) CRP and (vi, vii, viii) serology low or high values were replaced by a binary result attaching a count (TJC) for joints, (ii) missing RF, (iii) anti-CCP, (iv) ESR or (v) CRP and (vi, vii, viii) serology low or high values were replaced by a binary result attaching a count (TJC) for joints.

**Results:** Patients (n=736) had mean age 51 yr (sd 14), median ESR 15 (0–121), RF+ 21%, Anti-CCP+ 20%, median SJC 2 (0–44), median TJC 6 (0–42), erosions 5% at baseline. Complete information was not obtained for 36 patients. Figure 1 shows the ROC-curves for the full criteria set and all modified criteria sets. The model with only SJC provided the best AUC was 0.82 (95%CI 0.79–0.85) while the lack of anti-CCP provided the poorest model (AUC 0.71 (95%CI 0.68–0.75)). Table 1 shows sensitivity and specificity for identifying those who were ill (sensitivity).

**Conclusion:** The ACR/EULAR 2010 criteria are robust against missing values shown by a consistent diagnostic performance. However, the model with all 4 variables available but only swollen joints taken into account performed better than the original criteria including tender joints.

**Disclosure:** C. Alves: None; J. Luime: None; J. van Zeben: None; M. Huismans: None; A. Weel: None; P. Barendregt: None; J. Hazes: None.
The Performance of the Hospital Anxiety and Depression Scale for Screening of Depressive and Anxiety Disorders in Patients with Rheumatoid Arthritis (RA). Eun gia Y. C. Lok1, Chi Chiu Mok1, Fuk Chi Cheung1 and Chi Wai Cheng1. Castle Peak Hospital, 2Tuen Mun Hospital

Objectives: To evaluate the performance of the Hospital Anxiety and Depression Scale (HADS) for screening of depressive and anxiety disorders in patients with rheumatoid arthritis.

Methods: 200 consecutive Chinese patients who fulfilled the ACR criteria for RA were recruited from the outpatient rheumatology clinic. Written consent was obtained from these patients who were then interviewed by a psychiatrist for the presence of depressive disorders and anxiety disorders using the Chinese-bilingual Structured Clinical Interview for DSM-IV Axis I disorders, Patient research version (CB-SCID-I-P). Patients were invited to complete a validated Chinese version of the HADS questionnaire (depression sub-score 0–21; anxiety sub-score 0–21) before the psychiatric interview. Socio-demographic and clinical data including age, gender, duration of RA, disease activity scores (DAS28), pain, income and education level at the time of interview were also collected. The sensitivity and specificity of the cut-off scores of the HADS depression and anxiety subscales for the clinical diagnosis of depression or anxiety disorders was evaluated by the receiver operating curve (ROC) analysis.

Results: Between July 2007 and June 2008, 200 patients with RA were studied (79% women, mean age 51.4±10.5 years; median RA duration 4.0 years [IQR 2.0–9.0]). 47 (23.5%) patients were diagnosed to have a current psychiatric disorder (depressive disorders 14.5%, anxiety disorders 13%). Major depressive disorder was the most common current mood disorder whereas generalized anxiety disorder was the most common current anxiety disorder. The mean depression sub-score of HADS in patients who were diagnosed to have depressive disorders was 13.1±3.1, which was significantly higher than that in patients without depressive disorders (5.7±3.5; p<0.001). On the other hand, the mean anxiety sub-score of the HADS in patients with anxiety disorders was also significantly higher than those without anxiety disorders (11.2±3.4 vs 5.4±3.9; p<0.001). Using ROC analysis, the optimal cut-off score of the HADS depression subscale was 10 for the presence of depressive disorders, yielding a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 90%, 85%, 50% and 98%, respectively (area under the ROC: 93%). The optimal cut-off score of the anxiety subscale of HADS was 8 for the presence of anxiety disorders, with a sensitivity, specificity, PPV of 74%, NPV of 34% and NPV of 98% (area under the ROC: 87%).

Conclusion: As a screening tool, the HADS perform better for depressive disorders than anxiety disorders in patients with RA. A cut-off of 10 points in the HADS depression subscale yields a good sensitivity and specificity for picking up depressive disorders.

Disclosure: E. Y. C. Lok: None; C. C. Mok: None; F. C. Cheung: None; C. W. Cheng: None.

The Role of Objective Measures vs. Patient Reported Outcomes (PROs) as a Reflection of Flares in Patients with RA: Results from the Brigham RA Sequential Study (BRASS). Vivian Bykerk1, Daniel Hal Solomon2, Clifton O. Bingham3, Michelle Frits4, Christina Iannaccone5, Michael E. Weinblatt6 and Nancy A. Shadick5. 1Brigham & Women’s Hospital, Boston, MA, 2Brigham and Women’s Hospital, Jamaica Plain, MA, 3Brigham and Women’s Hospital, Boston, MA, 4Brigham and Women’s Hospital, MA, 5Johns Hopkins University, Baltimore, MD

Background: Worsening of disease activity or RA flare can be severe enough to warrant a change of therapy. Little is known about how frequently flares occur in RA or which measures best reflect a flare of RA.

Objective: To describe the frequency of self-reported flares in a population of patients with RA and determine which variables best relate to patients’ recall of flare in the prior 6 months.

Methods: Data were collected in a prospective, observational, single-academic center cohort of RA patients treated according to preference of their rheumatologist. Patients were questioned every 6 months if they’d had a flare of their disease, what the duration was and how they’d treated it. Variables analyzed included patient reported outcomes, composite indices of disease activity and laboratory measures. Univariate logistic regression analyses using generalized estimating equations (GEE) were performed to determine possible predictors of flare. Disease measures with a p ≤ 0.10 were included in a multiple logistic regression model using GEE. Additional multiple logistic regression models were performed, with patient reported measures and with objective measures.

Results: Of 1095 RA patients, 567 with ≥ 3 yrs follow-up reporting on flares were included for this analysis. Baseline characteristics included mean age: 57±13 yrs; 85% female, 93% Caucasian, mean disease duration 14.0 years. 75% reported flares at baseline, 59% at 6 months and 55 % reported flares every 6-months thereafter. 30% reported flares lasting > 2 weeks, 27% lasting 1–2 weeks & < 43% lasting ≤ 3 days. Variables significantly associated with current flare in the multivariate analysis overall, were pain, physician global, tender joint count (TJC), and age (figure 1). The TJC dropped out in the model containing only objective measures (figure 1). For predicting a flare within the next 6 months, pain, emotional distress, physician global, AM stiffness, and age were statistically significant (figure 2). Patients reported treatment during a flare included increases or changes in: prednisone by 35%, DMARDs by 32%, NSAIDs by 27%, biologics by 6%, narcotics by 5%, other pain meds by 15%.

Current flare analyses indicates variables that are associated with a recent flare as reported by the patient. (Odds Ratios from GEE)

Variables significantly associated with a current flare (Multivariate Regression)
Conclusions: Patient self-reported flares are frequent in RA; 50% last ≥ 1 week. Patient pain VAS, physician global and TJC best reflect flare in patients with RA. When considering PROs, only pain independently reflects flare at baseline.

Disclosure: V. Bykerk: Abbott Laboratories, 2, Agen Inc., 2, Roche, 5, Wyeth Pharmaceuticals, 2, D. H. Solomon: Abbott Immunology Pharmaceuticals, 2, Agen Inc., 2, Bristol-Myers Squobb, 9; C. O. Bingham: None; M. Frits: None; C. Iannaccone: None; M. E. Weimblt: Biogen Idec, 2, 5, Crescendo Bioscience, 2, 5; N. A. Shadick: Biogen Idec, 2, Crescendo Bioscience, 2.

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Total MRI Inflammatory Score Correlates with Disease Activity Measures after Aggressive Treatment of Rheumatoid Arthritis. Vegas K. Ranganath1, David A. Elashoff2, Paul Maranian3, Kambiz Motamed4, Espen Haavardsholm5, Fiona M. McQueen6, Theresa McVie7, Stacey S. Cofield8, Larry W. Moreland9, Weiling Chen10 and Harold E. Paulus1. 1Escino, CA; 2Diakonhjemmet Hospital, 1, UCLA, Los Angeles, CA, 3UCLA, 4Univ of Auckland Sch of Med, Auckland, New Zealand, 5Univ of Pittsburgh Med Ctr, Pittsburgh, PA, 6University of Birmingham

Purpose: MRI is a sensitive imaging modality to investigate “inflammation” in rheumatoid arthritis (RA) joints. T enosynovitis, synovitis, and bone edema independently correlate with disease activity measures in RA and suggest radiographic progression. The purpose of this study was to evaluate the relationship of clinical disease activity measures with two composite total MRI inflammatory score measures and their components, after 2 or more years of aggressive treatment of RA.

Methods: MRI with gadolinium contrast (1.5 Tesla) of the dominant wrist was obtained in 118 RA patients (RA duration 4.1 ± 10.8 months) seropositive or erosive RA patients after completing the TEAR 2-year controlled clinical trial comparing various combinations of MTX, etanercept, HCQ, and SSZ. Clinical erosive RA patients after completing the TEAR 2-year controlled clinical trial.

Conclusions: The weighted total MRI inflammatory score than with the individual components of the MRI scores did not improve the correlations. There was no single correlation coefficient that was greater than 0.4. All the clinical core set measures correlated significantly with the weighted and unweighted MRI inflammatory score and their components, with CDAI, physician global, patient global, ESR, pain, stiffness, and arthritis severity.

Table 1.

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>[mean (SD)]</th>
<th>N</th>
<th>mean</th>
<th>SD</th>
<th>TJC, (I.5, L.5)</th>
<th>SJC, (I.5, L.5)</th>
<th>BME, (I.5, L.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age, yrs [50.5(13)]</td>
<td>113</td>
<td>58.53</td>
<td>12.99</td>
<td>&lt;0.01</td>
<td>0.03</td>
<td>0.21*</td>
<td>0.07</td>
</tr>
<tr>
<td>RA duration, yrs [0.10(10.3)]</td>
<td>118</td>
<td>0.34</td>
<td>0.89</td>
<td>0.02</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>DAS28 [2.9(1.6)]</td>
<td>113</td>
<td>2.94</td>
<td>1.37</td>
<td>0.15</td>
<td>0.18</td>
<td>0.06</td>
<td>0.23*</td>
</tr>
<tr>
<td>CDAI [19.11(13)]</td>
<td>113</td>
<td>9.23</td>
<td>11.12</td>
<td>0.18</td>
<td>0.20*</td>
<td>0.20*</td>
<td>0.20*</td>
</tr>
<tr>
<td>Physician Global VAS [5.11(6.5)]</td>
<td>117</td>
<td>1.54</td>
<td>1.81</td>
<td>0.24*</td>
<td>0.31*</td>
<td>0.24*</td>
<td>0.40*</td>
</tr>
<tr>
<td>ESR [19.03(28)]</td>
<td>115</td>
<td>9.02</td>
<td>20.23</td>
<td>0.13</td>
<td>0.20*</td>
<td>0.01</td>
<td>0.33*</td>
</tr>
<tr>
<td>Pt Global VAS [9.23(15)]</td>
<td>113</td>
<td>2.25</td>
<td>2.08</td>
<td>0.20*</td>
<td>0.16</td>
<td>0.22*</td>
<td></td>
</tr>
<tr>
<td>Pain VAS [2.82(13)]</td>
<td>113</td>
<td>2.88</td>
<td>2.56</td>
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<td>0.20*</td>
<td>0.16</td>
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<tr>
<td>Fatigue VAS [7.25(11)]</td>
<td>113</td>
<td>2.96</td>
<td>2.64</td>
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<td>0.09</td>
<td>0.08</td>
<td>0.09</td>
</tr>
<tr>
<td>Stiffness VAS [6.25(9)]</td>
<td>113</td>
<td>2.4</td>
<td>2.12</td>
<td>0.12</td>
<td>0.34*</td>
<td>0.24*</td>
<td>0.34*</td>
</tr>
<tr>
<td>DAS28 [2.03(2.4)]</td>
<td>113</td>
<td>2.41</td>
<td>2.38</td>
<td>0.08</td>
<td>0.15*</td>
<td>0.17</td>
<td>0.20*</td>
</tr>
<tr>
<td>HAG-QL [0.64(1.4)]</td>
<td>115</td>
<td>0.66</td>
<td>0.85</td>
<td>0.11</td>
<td>0.18</td>
<td>0.12</td>
<td>0.20*</td>
</tr>
<tr>
<td>TJC [2.94(8.5)]</td>
<td>117</td>
<td>2.91</td>
<td>4.77</td>
<td>0.14</td>
<td>0.11</td>
<td>0.11</td>
<td>0.17</td>
</tr>
<tr>
<td>SJC [2.84(4.4)]</td>
<td>117</td>
<td>2.78</td>
<td>4.37</td>
<td>0.18*</td>
<td>0.16</td>
<td>0.20*</td>
<td>0.25*</td>
</tr>
</tbody>
</table>

Disclosure: V. K. Ranganath; None; D. A. Elashoff; None; P. Maranian; None; K. Motamed; None; E. Haavardsholm; None; F. M. McQueen; None; T. McVie; None; S. S. Cofield; None; L. W. Moreland; None; W. Chen; None; H. E. Paulus; None.

1780

Towards a Data-Driven Evaluation of the 2010 ACR/EULAR Criteria for Rheumatoid Arthritis: Is It Sensible To Look at Levels of Rheumatoid Factor? M. P. M. van der Linden1, M. R. Batstra2, L. E. Bakker-Jonges3, J. Detert4, H. Bastian5, H. U. Scherer5, G. R. Burmester6, M. D. Mijaavatten7, T. K. Kvien7, R. E. M. Toes8, T. W. J. Huizinga9 and A. H. M. van der Helm-van Mil1. 1Department of Medical Laboratories, Reinier de Graaf Group, Delft, The Netherlands, on Behalf of SKML-HIM (WGHAS), 2Department of Rheumatology and Clinical Immunology, Charité University Medicine Berlin, Berlin, Germany, 3Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, 4Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

Objective: The classification criteria for Rheumatoid Arthritis (RA) have been recently updated. The diagnosis of RA requires achieving ≥6 points; anti-citrullinated protein/peptides antibodies (ACPA) or Rheumatoid Factor (RF) presence yields 2 points and high levels 3 points. High RF level has an increased specificity for RA compared to RF-positivity, however the same holds for ACPA-positivity. This study evaluated the prognostic performance of high RF levels compared to the presence of ACPA (as determined by anti-CPAP antibodies) for the development of RA. The predictive ability for the severity of RA was also assessed.

Methods: Three independent cohorts with a total of 972 undifferentiated arthritis patients were studied for RA-development (according to the 1987 ACR criteria) and arthritis persistence. Positive and negative predictive values (PPV, NPV) and likelihood ratios (LR) were compared for different levels of RF with the presence of anti-CCP antibodies. A similar comparison was made in 686 RA-patients for the rate of joint destruction during 7 years of follow-up and achievement of sustained DMDAR-free remission. The variation in RF levels obtained by different measurement methods in the same RF-positive sera was explored.

Results: Presence of anti-CCP had a better balance between LR+ (LR+ and PPV/NPV) than high RF levels for RA-development. The additive value of anti-CCP assessment after high level RF-testing was higher than vice versa. High level RF was less strongly associated with RA severity than anti-CCP antibodies. The RF level obtained by different methods in the same patients sera varied considerably.

Conclusion: Level determination of RF is subject to large variation; high level RF has limited additive prognostic value compared to anti-CPAP-positivity.

Disclosure: M. P. M. van der Linden; None; M. R. Batstra; None; L. E. Bakker-Jonges; None; J. Detert; None; H. Bastian; None; H. U. Scherer; None; G. R. Burmester; None; M. D. Mijaavatten; None; T. K. Kvien; None; R. E. M. Toes; None; T. W. J. Huizinga; None; A. H. M. van der Helm-van Mil; None.

1781

Ultrasound Evaluation Reveals the Reason for High Interrater Variability in Joints of the 66/68 Joint Count. Matthias Nikolaus Witt, Monika Ronneberger1, Amelie Schnez2, Ruediger Laubender3, Matthias Engelbrecht4, Arthur Kavanau5, Hendrik Schulze-Koops6 and Mathias Grunke7. 1Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, 2Division of Rheumatology, Ludwig-Maximilians-University, Munich, Germany, 3Division of Rheumatology, Ludwig-Maximilians-University, Munich, Germany, 4Institute of Medical Informatics, Biometry and Epidemiology (IBE), Ludwig-Maximilians-University, Munich, Germany, 5Ludwig-Maximilians-University, Munich, Germany, 6University of California-San Diego, La Jolla, CA

Background: In patients with rheumatoid arthritis, joint counts are the key outcome parameter in clinical trials as well as in daily clinical practice. It has been shown, however, that there is a huge variability between different assessors of the same patient. In a previous paper we have shown, that this can be reduced by a standardised training of the EULAR examination technique. We have also shown, however, that the effect of standardisation is worse for the 68/68 than for the 28 joint count.

Objectives: To evaluate the reason for the higher interrater disagreement in the assessment of the 68/66 in contrast to the 28 joint count. Is it the greater difficulty in assessing the joints of the lower extremity and can this be ruled out by ultrasonography?
Methods: Participants of joint examination seminars evaluated a given RA patient before and after they were made familiar with the EULAR examination technique. Joints were rated positive or negative for tenderness and swelling without gradation. The amount of tender and swollen joints as well as the variability between the examiners (groups of 4–6 trainees per patient) before and after the training were compared. For every single joint, the degree of agreement was calculated using the Fleiss-Kappa test. In a subgroup of 40 patients, the clinical results were compared to an independent ultrasound examination of the MTP joints.

Results: 340 health professionals participating in standardised joint assessment trainings were evaluated. 256 were instructed in the 68/66, 84 in the 28 joint count. For both joint counts, the disagreement between different examiners was higher for the dimension of joint swelling than for tenderness. After the training of the EULAR examination technique, there was a significant reduction of interrater variability, which was more pronounced in the 28 than in the 68/66 joint count. Comparisons between manual and ultrasound assessment revealed, that concerning the dimension of swelling manual examination has a very low sensitivity and high variability in the joints of the feet.

Conclusion: Standardisation of the joint examination technique significantly reduces variability. The relatively better performance of the 28 joint count is partly due to the higher number of examined joints in the 68/66 joint count. Another reason is, that the joints of the feet, although they are more often rated negative by manual than by ultrasound evaluation, tend to imply a higher disagreement between different assessors.

Disclosure: M. N. Witt: None; M. Ronneberger: None; A. Schne: None; R. Laubender: None; M. Engelbrecht: None; A. Kavanagh: None; H. Schulze-Koops: None; M. Grunke: None.

Validation of a Multi-Biomarker Test for Rheumatoid Arthritis (RA) Disease Activity (Vectra [DA]) in a Multi-Cohort Study

Background: Regular measurement of disease activity enables more effective management of rheumatoid arthritis (RA). DAS28CRP is a validated tool for assessment of disease activity, but it requires enumeration of tender and swollen joints, which are subject to significant inter- and intra- assessor variability, and is not routinely performed by all physicians. A test based on serum protein biomarkers involved in RA pathophysiology has the potential to provide quantitative, objective, and reproducible information that has not previously been available to clinicians. A 12-biomarker test of RA Disease Activity (DA Test) has recently been developed in a series of clinical studies. Here we show in a prospectively-designed study that the biomarker-based DA Test validly quantifies RA disease activity as compared to the DAS28CRP.

Methods: 230 RF+ and/or anti-CCP+ patients were selected from participants in the Index for Rheumatoid Arthritis Measurement (InfoRM), Brigham and Women’s Hospital Rheumatoid Arthritis Sequential Study (BRASS), and Leiden Early Arthritis Clinic studies. To test validity across a wide range of disease activity, patients representing all levels of disease severity were selected. The concentrations of 12 serum biomarkers (IL-6, EGF, VEGF-A, Leptin, SAA, CRP, VCAM-1, MMP-1, MMP-3, Resistin, YKL-40, and TNF-RI) were measured and combined in a pre-specified algorithm to generate DA Test scores ranging from 1 to 100. The DA Test score was calculated from an equation similar to that for DAS28CRP where scores for TJC28, SJC28, and Patient Global were individually modeled using serum biomarkers. To calculate area under the ROC curve (AUROC), a DAS28CRP cutoff of 2.67 [1] was used to assign cases to low vs moderate/high disease activity. A separate, longitudinal analysis of patients from the InfoRM study with significant changes in DAS28CRP was undertaken to understand whether changes in DA Test score were associated with changes in DAS28CRP.

Results: The AUROC for DA relative to the DAS28CRP cutoff of 2.67 was 0.77 (CI: 0.70 – 0.83; p < 0.001); the correlation between DA and DAS28CRP was 0.56 (CI: 0.46 – 0.64; p < 0.001). Decomposition of the DA Test into a non-CRP DA Test score and a CRP term demonstrated that the non-CRP DA Test score was an independent predictor of DAS28CRP (p < 0.001) in multivariate analysis (after controlling for CRP). In longitudinal analysis, there was a significant association between change in DA Test score and change in DAS28CRP (p < 0.01). Exploratory analysis suggests the DA Test may more accurately detect low disease activity than CRP (Fig. 1).

Fig. 1. Proportion of patients with joint counts below a threshold for those with low CRP or DA test score.

Conclusion: The DA Test has been validated as a quantitative, objective, biomarker-based test of RA disease activity. It could be used to optimize clinical care and provide an objective measure of treatment response in observational analyses or randomized trials.


Validation of New Classification Criteria for Rheumatoid Arthritis in Japanese Population

Background: The Classification Criteria of Rheumatoid Arthritis has been revised by ACR/EULAR joint committee in 2009. The new criteria is aimed to establish the diagnosis earlier to initiate appropriate disease modifying anti-rheumatic drugs without delay in the current era when complete remission before joint damage becomes a realistic goal with the advance of medical treatment.

Objectives: We performed retrospective validation of the new criteria in patients with undifferentiated arthritis who were later diagnosed as rheumatoid arthritis based on 1987 ACR classification criteria.

Methods: We reviewed electronic medical records of all the patients who were referred to St. Luke’s International Hospital-Tokyo from October 2007 to November 2009 as undifferentiated arthritis before institution of any disease modifying anti-rheumatic drugs (DMARDs). We applied the new ACR/EULAR criteria for all the patients to determine in which points they could be diagnosed as rheumatoid arthritis if the new criteria was utilized instead. We also compare patients who had delayed diagnoses based on the old criteria to patients whose time of the diagnoses did not differ, to analyze the clinical characteristics and also prognosis of the joints.
Results: There were two hundreds six patients who were referred to our institution without definitive diagnoses of rheumatoid arthritis over the period. We excluded all the patients who had been prescribed any DMARD for any purpose in other institution. There were eighteen patients without definitive diagnoses at the time of chart review and none of them was classified as rheumatoid arthritis even with the new criteria.

For the rest of fifty eight patients who were later diagnosed as definitive rheumatoid arthritis based on 1987 ACR classification criteria, we applied the new ACR/EULAR criteria. The average age was 54.0, and 50 of them were female and 8 were male. Rheumatoid factor were positive in 39 (67%), and anti-CCP antibody (second generation) was significantly elevated in 46 patients (79%). Bone erosions were already detectable in 11 patients at their first visits. In seventeen patients (group 1), the definitive diagnoses could be established significantly earlier with the new criteria and the average difference was 63.1 days. In forty one patients (groups 2), the diagnoses was not delayed even with the old criteria. Overall, the durations of days from the first visits to diagnoses were 36.2 days and 17.7 days with the old and new criteria, respectively. Biologics were eventually prescribed in two of seventeen patients (group 1) and eight of forty one patients (group 2).

Conclusion: The new ACR/EULAR Classification Criteria was effective to establish the diagnoses of rheumatoid arthritis significantly earlier in substantial percentage of patients, who eventually require intensive medical treatment such as biologics.

Table 1. Baseline characteristics of patients who were diagnosed as definitive rheumatoid arthritis based on 1987 ACR classification criteria (n=58)

<table>
<thead>
<tr>
<th>Age</th>
<th>54.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n. (%)</td>
<td>50 (86)</td>
</tr>
<tr>
<td>No. of joint involvement*</td>
<td></td>
</tr>
<tr>
<td>- Total joints</td>
<td>7.3</td>
</tr>
<tr>
<td>- Small joints</td>
<td>5.1</td>
</tr>
<tr>
<td>DAS-CRP (ESR)*</td>
<td>4.22 (4.90)</td>
</tr>
<tr>
<td>RF positive, no. (%)</td>
<td>39 (67)</td>
</tr>
<tr>
<td>Anti-CCP positive, no. (%)</td>
<td>46 (79)</td>
</tr>
<tr>
<td>Duration of synovitis (≥5 weeks), no. (%)</td>
<td>55 (95)</td>
</tr>
<tr>
<td>Bone erosions, no. (%)</td>
<td>11 (19)</td>
</tr>
<tr>
<td>No. of days from the first visit to the diagnosis</td>
<td>36.0</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>- DMARDs alone, no (%)</td>
<td>30 (52)</td>
</tr>
<tr>
<td>- MTX, no. (%)</td>
<td>23 (40)</td>
</tr>
<tr>
<td>- Biologics, no (%)</td>
<td>10 (17)</td>
</tr>
</tbody>
</table>

*Evaluated at the diagnosis of RA based on new criteria

Disclosure: H. Shimizu: None; H. Tamaki: None; E. Uechi: None; M. Kishimoto: None; K.-I. Yamaguchi: None; M. Okada: None.

1784

Validity of Clinical Associations of Biomarkers in Translational Research Studies: The Case of Systemic Autoimmune Diseases. Maria Tektonidou1 and Michael Ward1. 1National Institute of Arthritis and Musculoskeletal and Skin Diseases, National University of Athens

Objective: Validity of biomarkers may be impacted if studies do not include certain features in their design. We evaluated if translational research studies of potential biomarkers incorporated design features important for valid clinical associations.

Methods: We searched 10 journals for translational studies in 6 systemic autoimmune diseases published in 2004–2009. We included studies that reported associations between laboratory markers and the presence of disease, measures of disease activity, or prognosis. We examined the following design features: age-, sex-, and race-matching; control for effects of treatment on expression of the biomarker; inclusion of both patients with early and late disease; or both active and inactive disease; longitudinal or cross-sectional design; and use of validated activity and damage measures.

Results: Among 170 articles, 156 articles examined potential biomarkers for diagnosis, 37 for disease activity assessment and 9 for prognosis; 67 were studies of rheumatoid arthritis (RA), 48 of systemic lupus erythematosus, and 41 of other diseases. Gene expression profiles were the most commonly examined potential biomarkers (N = 51). Less than one-half of studies incorporated study design features important for valid clinical associations. Only 47.4% of studies of biomarkers for diagnosis had groups that were age-matched, 45.5% were sex-matched, and 35.3% controlled for treatment. Studies that examined biomarkers in histological samples and studies of RA were less likely to include important design features.

Conclusion: Less than one-half of translational studies of potential biomarkers incorporated design features needed for valid interpretation of clinical associations. Attention to these features could reduce false-positive and false-negative associations.

Disclosure: M. Tektonidou: None; M. Ward: None.

1785

Validity of the Revised ACR/EULAR Classification Criteria for Rheumatoid Arthritis: Predicting Persistent Arthritis and Joint Erosions after 2 Years in Patients with Early Undifferentiated Arthritis. Jaap Fransen1, Mieke Hazes2 and Henk Visser1. 1Alysis Hospital, Arnhem, The Netherlands, 2Erasmus Medical Centre, Rotterdam, The Netherlands, 3Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Background: The revised ACR/EULAR criteria for the classification of RA were developed to enable a more timely diagnosis. With the criteria the probability of developing persistent inflammatory or erosive arthritis that is considered to be ‘RA’ is calculated. However, the revised criteria were not validated against these two outcomes.

Objective: To study the revised ACR/EULAR criteria for the ability to correctly predict persistent arthritis and joint erosions after 2 years in patients with early undifferentiated arthritis.

Methods: Data were used from an existing cohort of patients with early arthritis (N=566) [1]. Patients with undifferentiated arthritis were included for the current analysis if at baseline they had: synovitis in at least 1 joint (N=561/566), arthritis not explained by another diagnosis (N=396/561), no joint erosions on X-ray (N=322/396), completed 2 year follow-up (N=286/322). Patients had been clinically assessed at baseline, including joint involvement, RF and ACPA, symptom duration, ESR and CRP. Scoring for joint involvement was slightly modified because small joint swelling was registered in Ritchie units. The ‘risk’ score (0–10) of the revised classification criteria was applied to the baseline data, persistent arthritis and joint erosions on X-ray at year 2 were the outcomes.

Results: At year 2, 45% (129/286) had persistent arthritis and 48% (62/129) of them had erosions. At baseline, the median (P25-P75) number of swollen joints was 2 (1–4), 23% were RF positive and 18% ACPA positive, median symptom duration was 13 weeks, median (P25-P75) ESR was 26 (13–44). Height of the ‘risk’ score (0–10) was significantly associated with persistent arthritis, OR (95%CI) 1.6 (1.4–1.8), and erosions, OR (95%CI) 1.8 (1.5–2.3), with areas under the ROC curve of 0.79 and 0.81, respectively. Patients with a ‘risk’ score of ≥6 at baseline had a 7.4% probability to develop persistent arthritis after 2 years and given persistence there was a 68% probability to develop erosions. The proposed cut point for ‘definite RA’ may be held at ≥6, while ≥3 may be an appropriate cut point for ‘probable RA’. The diagnostic criteria of Visser et al. [1] performed slightly better, the list version of the 1987 ACR classification criteria was outperformed by the other criteria.


Disclosure: J. Fransen: None; M. Hazes: None; H. Visser: None.
Introduction: Evidence supports vitamin D deficiency as a potential risk factor for autoimmune disease. Small studies have yielded controversial data with regard to an association between vitamin D and disease activity measures among patients with RA.

Methods: Vitamin D levels were performed at baseline on 500 randomly selected patients with rheumatoid arthritis from the golimumab RCT. Participants met ACR criteria for the diagnosis, had active disease, and were naïve to both methotrexate and to other biologic therapies. Spearman correlations and multivariable linear regression were performed to assess associations between vitamin D levels and demographic and disease activity measures.

Results: 83% of patients had vitamin D levels <30 ng/mL, while 48% had levels <20 ng/mL. Vitamin D level did not correlate with the DAS28 score, ESR, CRP, or erosion score at baseline (Table 1). Vitamin D levels correlated with age (p=0.005), sex (p=0.009), BMI (p=0.02), HAQ scores (p=0.02), and patient reported health (p=0.03) (Table 1). The 6 black patients also had significantly lower vitamin D levels (p=0.03). Disease activity was similar across quartiles of vitamin D in a multivariable linear regression model. Age was the most important confounder of the non-significant trend between vitamin D and disease activity in the unadjusted model (Table 2). Disease activity was significantly decreased in the 22 patients with a vitamin D level >40 ng/mL. Age, race, BMI, and disease duration alone helped significantly to predict vitamin D levels in a predictive regression model.

Conclusions: Vitamin D levels do not correlate cross-sectionally with disease activity measures, erosion scores, or inflammatory markers in a large sample of patients with RA. Overall, vitamin D correlated with HAQ scores and patient reported health, but these were not independent predictors of vitamin D level in a predictive model including age, race, and BMI. Limitations include unknown geographic area and a study population that was selected for high disease activity. Overall, these data do not support a contribution of vitamin D in the activity of rheumatoid arthritis.

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spearman’s Rho</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28 Score (with ESR)</td>
<td>-0.08</td>
<td>0.09</td>
</tr>
<tr>
<td>ESR</td>
<td>-0.04</td>
<td>0.4</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.01</td>
<td>0.8</td>
</tr>
<tr>
<td>Tender Joint Count</td>
<td>-0.03</td>
<td>0.5</td>
</tr>
<tr>
<td>Swollen Joint Count</td>
<td>-0.03</td>
<td>0.6</td>
</tr>
<tr>
<td>Erosion Score</td>
<td>-0.02</td>
<td>0.97</td>
</tr>
<tr>
<td>HAQ Score</td>
<td>-0.10</td>
<td>0.02</td>
</tr>
<tr>
<td>Patient Reported Health</td>
<td>-0.10</td>
<td>0.03</td>
</tr>
<tr>
<td>Patient Reported Pain</td>
<td>-0.08</td>
<td>0.07</td>
</tr>
<tr>
<td>Age</td>
<td>-0.17</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.11</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coeff. (Δ DAS28)</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D 20–30</td>
<td>0.18</td>
<td>0.24</td>
<td>(-0.12–0.48)</td>
</tr>
<tr>
<td>Vitamin D 15–20</td>
<td>0.22</td>
<td>0.21</td>
<td>(-0.12–0.55)</td>
</tr>
<tr>
<td>Vitamin D &lt;15</td>
<td>0.27</td>
<td>0.096</td>
<td>(-0.046–0.59)</td>
</tr>
<tr>
<td>Adjusted*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D 20–30</td>
<td>0.087</td>
<td>0.55</td>
<td>(-0.20–0.37)</td>
</tr>
<tr>
<td>Vitamin D 15–20</td>
<td>0.088</td>
<td>0.59</td>
<td>(-0.23–0.41)</td>
</tr>
<tr>
<td>Vitamin D &lt;15</td>
<td>0.091</td>
<td>0.55</td>
<td>(-0.21–0.39)</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, sex, BMI, disease duration, elevated HAQ score, and winter month.

Disclosure: J. Baker: None; D. G. Baker: None; G. Toedter: None; J. Shults: None; M. B. Leonard: None.

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ACR Poster Session C
Rheumatoid Arthritis Treatment - Small Molecules, Biologies and Gene Therapy: Biologic DMARDs III

A Study To Evaluate the Effectiveness and Safety of the Interleukin-6 (IL-6) Receptor Antagonist Tocilizumab (TCZ) after 4 and 24 Weeks in Patients with Active Rheumatoid Arthritis (RA)—Final Effectiveness Results of the TAMARA Study. Eugen Feist1, Andrea Rubbert-Roth2, Jürgen Braun3, Jörg Kaufmann4, Herbert L. Kellner5, Reiner Kurthen6, Jürgen Wollenhaupt7 and Gerd R. Burmester7. 1Campus Charité Mitte, Med. Klinik Abt. Rheumatologie u. Klin. Immunologie, Berlin, Germany, 2Klinik für Innere Medizin, Uniklinik Cologne, Cologne, Germany, 3Praxis für Innere Medizin und Rheumatologie, Aachen, Germany, 4Praxis für Innere Medizin und Rheumatologie, Ludwigsfelde, Germany, 5Rheumatologikum Hamburg, Schön-Klinik Hamburg-Elbeck, Hamburg, Germany, 6Rheumazentrum Ruhrgebiet, St. Jospehs-Krankenhaus, Herne, Germany, 7Schwerpunktpraxis fuer Rheumatologie und Gastroenterologie, Munich, Germany
Additional analyses considered several subgroups, e.g. based on rheumatoid markers, and patient-reported outcomes such as HAQ-DI and FACIT-F (fatigue). Effectiveness variables included ACR responses, CDAI, SDAI, inflammatory pts. achieving DAS28 "low disease" (LDAS, DAS28 difference by characteristics. Subgroup analyses showed numerically better outcomes (i.e., tently observed in all applied outcome measures independent of the measure.

**Conclusions:** In a clinical setting close to usual care the treatment with TCZ led to rapid and sustained improvement of RA symptoms, thereby indicating the therapeutic benefits of TCZ. This improvement was consistently observed in all applied outcome measures independent of the measured characteristics. Subgroup analyses showed numerically better outcomes (i.e., difference by >10.0 percentage points in both LDAS and DAS remission when compared with the complementary group) in cDMARD-IR vs. TNF-α-IR pts. or pts. with baseline DAS28 4.1=5.1 vs. >5.1, whereas no such differences were seen between RF⁺ vs. RF⁻ pts., thereby suggesting that RF seemed not to relevantly predict the outcome at Wk 24.

**Disclosure:** E. Feist: Roche, 2, 5; 6; A. Rubbert-Roth: Roche, 5; 8; J. Braun: None; J. Kaufmann: None; H. L. Kellner: None; R. Kurchen: None; J. Wollenhaupt: Chugai, 5; 8; Roche, 5; 8; G. R. Burneuet: Roche, 2, 5; 8.

**Table 1.** Results (continuous data) of the Week 24 effectiveness analyses (ITT, LOCF)

<table>
<thead>
<tr>
<th>Single variables</th>
<th>Mean Change mean ± SD (N obs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJC (n)</td>
<td>9.6 ± 5.4 (286)</td>
</tr>
<tr>
<td>TJC (n)</td>
<td>12.6 ± 6.9 (286)</td>
</tr>
<tr>
<td>VAS-Disease Activity (mm)</td>
<td>62.2 ± 20.2 (286)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>37.4 ± 22.1 (274)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>23.1 ± 30.7 (274)</td>
</tr>
</tbody>
</table>

**Composite measures**

- **DAS28**: 6.0 ± 1.2 (274)
- **CDAI**: 34.7 ± 12.5 (284)
- **SDAI**: 37.2 ± 13.1 (272)

**Patient-reported outcome (PRO) measures**

- **HAQ-DI**: 1.48 ± 0.65 (258)
- **FACIT-F (fatigue)**: 28.8 ± 11.2 (283)

**Table 2.** Baseline Characteristics (n=100.0%) and DAS28 remission in several subgroups at Week 24

<table>
<thead>
<tr>
<th>Rheumatoid factor</th>
<th>N (n=100.0%)</th>
<th>LDAS n (%)</th>
<th>DAS28-Remission n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>184</td>
<td>105 (57.1)</td>
<td>85 (46.2)</td>
</tr>
<tr>
<td>Negative</td>
<td>81</td>
<td>48 (59.3)</td>
<td>41 (50.6)</td>
</tr>
</tbody>
</table>

**Previous RA treatment**

- **Conventional DMMARD-IR**: 163
- **Baseline DAS28**: 4.1 < DAS28 ≤5.1: 47
- **DAS28 >5.1**: 217

<table>
<thead>
<tr>
<th>Change in HAQ</th>
<th>Change in CDAI</th>
<th>CDAI Low Disease Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Coeff (SE)</td>
<td>p-value</td>
<td>Beta-Coeff (SE)</td>
</tr>
</tbody>
</table>

**Age at onset of RA**

- **Positive**:
  - Baseline CDAI/HAQ: 0.01 (0.00) <0.0001
  - Baseline CDAI/HAQ: -0.29 (0.02) <0.0001
  - Baseline Off Prednisone: 0.02 (0.02) 0.5222
  - Baseline Negative RF: 0.08 (0.03) 0.0095
  - Disease Duration: 0.00 (0.00) <0.0001
  - Gender (Female): 0.08 (0.03) 0.0083
  - Race (Non-White): 0.00 (0.03) 0.8985

**Conclusion:** In a large prospective cohort of RA patients who received at least 6 months of ETN therapy, younger age of onset and fewer comorbidities were associated with HAQ/CDAI improvement and with CDAI low disease activity after adjusting for other clinically relevant variables. These results confirm the importance of the number of reported comorbidities and age of onset in impacting RA response to anti-TNF treatment, and suggest that physicians should consider these factors when initiating therapy.

**Disclosure:** M. R. Shim: None; H. L. Kellner: None; J. S. Chaudhari: Amgen Inc., 9; Kforce Clinical Research, 3; J. Feng: Amgen Inc., 3; D. A. Elashoff: None; V. K. Ranganath: Genentech and Biogen IDEC Inc, 2; UCB, Inc., 2.
1790
Assessment of Real Life Efficacy of Rituximab in Rheumatoid Arthritis: Predicting Factors of the Therapeutic Maintenance and Demonstration of a Corticosteroid Sparing Effect in the Autoimmunity and Rituximab Registry, Jacques-Eric Gottenberg1, Philippe Ravaud2, Thomas Bardin3, Patricia Cacoub4, Alain Cantagrel1, Bernard Combo5, Maxime Dougdos6, René-Marc Filip7, Bertrand Godeau1, Loic Guilleuin8, Eric Hachulla9, Xavier Le Loei, Thierry Schaeverbeke1, Jean Sibilia10, Gabriel Baron9 and Xavier Mariette. 1Bordeaux Hospital, 2Cochin Hospital, 3Henri Mondor Hospital, 4Hotel Dieu Hospital, 5La Pitie Hospital, 6Lariboisie Hospital, 7Lille Hospital, 8Montpellier Hospital, 9Rouen Hospital, 10Strasbourg Hospital, 11Toulouse Hospital

Objectives: Registries might provide useful information on efficacy of biological agents, provided that the selected outcome criteria take into account the variability of the follow-up of hundreds of patients among a large number of centers. We therefore evaluated the real life efficacy of rituximab (RTX) in rheumatoid arthritis (RA) by analyzing its maintenance and its corticosteroid sparing effect.

Patients and Methods: The French Society of Rheumatology has developed an independent registry, named AutoImmunity and Rituximab (AIR), available on-line (www.air-cri.org), in which data of tolerance and efficacy of RTX in refractory RA and also other refractory autoimmune diseases are prospectively collected every 6 months during 5 years.

Results:
- Predicting factors of retreatment with RTX
  Among the 2005 patients with RA included in AIR registry (median age: 58 years, median RA duration: 13 years), 1057 patients (52.9%) have been retreated by RTX (2 cycles: 570, 3 cycles: 273, 4 cycles: 141, 5 cycles or more: 73).
  570 patients have a follow-up of at least 18 months, including 459 patients (80.5%) who were retreated by subsequent cycles of RTX and 111 patients (19.5%) who received only one cycle before RTX discontinuation, as indicated in the crf and/or by the initiation of a new biological DMARD. RTX was discontinued because of absence of efficacy (n = 92) or problem of safety (n = 19). On univariate analysis, a higher proportion of retreated patients had not received any previous TNF antagonists (22% versus 13.7% in patients who received a single cycle, P = 0.05), were RF-positive (82.1 vs 66.3%, P = 0.001) or anti-CCP positive (80.2% vs 61.7%, P < 0.0001) or were RF or anti-CCP positive (91.9% vs 77.4%, P = 0.04). In multivariate analysis, retreatment with RTX was significantly associated with anti-CCP positivity.
- Corticosteroid sparing effect
  The proportion of patients treated with oral corticosteroids decreased from 31.2% (P = 0.0001) or anti-CCP positive (80.2% vs 61.7%, P < 0.0001) or were RF or anti-CCP positive (91.9% vs 77.4%, P = 0.04). In multivariate analysis, retreatment with RTX was significantly associated with anti-CCP positivity.

Disclosure: J.-E. Gottenberg: None; P. Ravaud: None; T. Bardin: None; P. Cacoub: None; A. Cantagrel: None; B. Combo: None; M. Dougdos: None; R.-M. Filip: None; B. Godeau: None; L. Guilleuin: None; E. Hachulla: None; X. Le Loei: None; T. Schaeverbeke: None; J. Sibilia: None; G. Baron: None; X. Mariette: None.

1791
Clinical and Functional Improvements in Early RA Following Treatment with Adalimumab Plus Methotrexate Compared with Methotrexate Monotherapy: 26-Week Results of the OPTIMA Trial, Arthur Kavanaugh1, Roy Fleischmann2, Paul Emery3, Benoit Guerette4, Laura Reiden5, Kaushik Patra6 and Josef S. Smolen7. 1Abbott Laboratories, 2, 3P. Emery: Abbott Laboratories, 2, 5Bristol-Myers Squibb, 2, 5Merck Pharmaceuticals, 2, 5Pfizer Inc, 2, 5Roche, 2, 5B. Guerette: Abbott Laboratories, 1, 3, L. Reiden: Abbott Laboratories, 1, 3, K. Patra: Abbott Laboratories, 1, 3, J. S. Smolen: Abbott Laboratories, 2, 5Bristol-Myers Squibb, 2, 5Centocor, Inc., 2, 5Roche, 2, 5Schering-Plough, 2, 5UCB, Inc., 2, 5Wyeth Pharmaceuticals, 2, 5

In the MRI sub-study, PBO+MTX (N=32) and ADA+MTX (N=27) subjects, respectively, had mean changes from baseline to week 26 in synovitis of −2.0 and −3.6 (P = 0.003), in erosion of 1.4 and −0.8 (P = 0.004), and in osteitis of 0.0 and −1.9 (P = 0.006), suggesting more improvement of joint inflammation and damage in the ADA+MTX group. Serious adverse events occurred in 31 (6%) PBO+MTX and 36 (7%) ADA+MTX subjects.

Conclusion: Treatment of early RA with ADA+MTX resulted in rapid, enhanced clinical and functional responses and improved MRI profiles, compared with MTX monotherapy through 26 weeks.


1792
Clinical Response during Sequential Anti-Tumor Necrosis Factor Therapy in US Veterans Enrolled in the Veterans Affairs Rheumatoid Arthritis (VARA) Registry, Grant W. Cannon1, Brian C. Sauer2, Candace L. Hayden3, Liron Caplan4, Gill S. Kerr5, J. Steuart Richards6, Dannette S. Johnson3, Ted R. Mikuls6 and Andreas M. Reimold1. 1Dallas VA and University of Texas Southwestern, Dallas, TX, 2Denver VA and University of Colorado, Aurora, CO, 3Jackson VA and University of Mississippi, Jackson, MS, 4Salt Lake City VA and University of Utah, Salt Lake City, UT, 5Salt Lake City VA and University of Colorado, Aurora, CO, 6University of Nebraska Med Ctr, Omaha, NE, 7Washington VA and Georgetown and Howard Universities, Washington, DC

Purpose: The linkage of pharmacy databases with objective clinical outcome measures provides an opportunity to evaluate rheumatoid arthritis (RA) therapies
in “real-world” clinical settings. Merging of data from the Veterans Affairs RA (VARA) registry, initiated in 2003, and the VA Pharmacy Benefits Management (PBM) database dating back to 1998 allowed the investigation of disease activity score (DAS28) in patients receiving anti-tumor necrosis factor (TNF) therapy with adalimumab (ADA), etanercept (ETA), and infliximab (INF).

Methods: VARA routinely collects DAS28 on RA patients in this prospective cohort study. For each anti-TNF prescription, PBM data was used to estimate duration of the prescription, total dose dispensed, and anticipated refill date. A treatment course duration was defined as time from the initial prescription until the expected refill date or the last treatment course if less than 90 days gap or discontinuation. The average DAS28 and ESR was calculated during each course of therapy greater than 90 days during the observation period from 90 days after initial prescription to the end of the course.

Patients with sequential treatment courses with either the same anti-TNF (no switch) or a different anti-TNF therapy (switch) were evaluated. EULAR response criteria were evaluated using average DAS28 in comparing the sequential therapies and reported as better (if good or moderate response criteria fulfilled), worse (if a reverse of the sequence fulfilled EULAR good or moderate response criteria), and no change if neither better or worse.

Results: Of the 1382 patients in the VARA cohort, 601 (44%) had received anti-TNF therapy in 1258 courses. Of these courses, 530 (42%) were of greater than 90 days in duration with at least one DAS28 recorded during the clinical observation period. Comparison of no switch patients (n=56) and switch patients (n=46) showed that the initial DAS28 score during the initial (first) and subsequent (second) evaluable courses were higher in switch patients (p<0.001) but no difference in ESR (p=0.10) was discernable. Compared to initial values, the sequential DAS28 scores and ESR measurements were not statistically significant by pair-t test. EULAR response measures for better, worse, and no change response also did not achieve statistical significance (p=0.168). Evaluations of the different combinations for switching or not switching for each anti-TNF were also not statistically significantly different.

Table 1. Use of Anti-TNF agents in the VARA cohort

<table>
<thead>
<tr>
<th>Initial anti-TNF</th>
<th>Patients with any exposure (n=601)</th>
<th>Number of courses</th>
<th>Courses &gt;90 days</th>
<th>Courses &gt;90 days with DAS28</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA 170 (28%)</td>
<td>309 (51%)</td>
<td>425</td>
<td>327</td>
<td>195</td>
</tr>
<tr>
<td>ETA 311 (52%)</td>
<td>349 (55%)</td>
<td>533</td>
<td>294</td>
<td>221</td>
</tr>
<tr>
<td>INF 120 (20%)</td>
<td>175 (29%)</td>
<td>300</td>
<td>159</td>
<td>122</td>
</tr>
</tbody>
</table>

Table 2. Patients switching and not switching anti-TNF therapy. Clinical outcome during initial (first) and subsequent (second) course

<table>
<thead>
<tr>
<th>Anti-TNF therapy</th>
<th>EULAR response</th>
<th>DAS28 during:</th>
<th>ESR during:</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Switch (n=56)</td>
<td>Better</td>
<td>No change</td>
<td>Worse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switch Rx (n=46)</td>
<td>14 (25%)</td>
<td>31 (55%)</td>
<td>11 (20%)</td>
</tr>
<tr>
<td></td>
<td>18 (39%)</td>
<td>17 (40%)</td>
<td>11 (23%)</td>
</tr>
</tbody>
</table>

Conclusions: RA patients in the VARA registry who were switched to a second anti-TNF agent were more likely to have higher DAS28 scores than patients who were not switched. However, there was no evidence that a switch in anti-TNF therapy was associated with greater clinical improvement in patients who switched than patients who did not switch anti-TNF therapies, nor did any particular anti-TNF show superior efficacy.

Disclosure: G. W. Cannon: None; B. C. Sauer: None; C. L. Hayden: None; L. Caplan: None; G. S. Kerr: None; J. S. Richards: None; D. S. Johnson: None; T. R. Mikuls: None; A. M. Reimold: None.

1793

Clinical, Structural and Functional Remission in the Treatment of Rheumatoid Arthritis with Tocilizumab in Daily Clinical Practice—REACTION-2 Study. Tsutomu Takeuchi1, Yoshiya Tanaka2, Kouichi Amano1, Eri Sato1, Masao Nawata2, Hayato Nagasawa1, Daisuke Hoshi3, Masayoshi Saito3, Syunsuke Fukuyo4, Kentarou Hamada5, Hideto Kameda5, Takahiko Kurasawa6 and Hisashi Yamamura6. 1Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, Saitama, Japan, 2Division of Rheumatology, School of Medicine, Keio University, Tokyo, Japan, 3Division of Rheumatology, School of Medicine, Keio University, Tokyo, Japan, 4Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan, 5The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Kitakyusyu, Japan, 6The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Kitakyusyu, Japan.

Purpose: Anti-IL-6 receptor monoclonal antibody, tocilizumab (TCZ), is increasingly recognized as a powerful biological agent for the treatment of rheumatoid arthritis (RA). Comprehensive effectiveness of TCZ in daily clinical practice, in which the patients are advanced and even refractory to TNF inhibitors, is not fully understood. In this report, we evaluated the effectiveness of TCZ in the three major rheumatology centers as judged by clinical, structural and functional remission at 52 weeks in the advanced RA patients.

Patients and Methods: From May 2008 to March 2009, a total of 255 RA patients were enrolled and received 8 mg/kg every four weeks of TCZ treatment. Disease activity was assessed using DAS28-ESR, joint damage using the van der Heijde modified total Sharp score (mTSS), and functional disability using the health assessment questionnaire (HAQ) score. Safety was assessed by identifying adverse events for which a causal relationship with TCZ could not be ruled out. The last-observation-carried-forward method was used in each of the analyses.

Results: The mean (± SD) of each parameter at baseline were as indicated below, age; 59.1 ± 13.3 years, duration of RA; 12.4 ± 11.1 years, mTSS; 140 ± 101, prior biologics user; 62.8%, concomitant methotrexate (MTX) user; 55.6% (the mean dose was 5.31 ± 4.8 mg/week), and concomitant corticosteroid user; 67.0% (the mean dose was 3.9 mg/day).

With the 52 weeks TCZ treatment, the mean DAS28-ESR was significantly improved from 5.72 at baseline to 3.2 at week 52, and clinical remission was achieved in 42% of patients, and 55% of the patients reached low disease activity criteria. The individual parameters of DAS28-ESR decreased significantly until 24 weeks after starting treatment with TCZ, and this efficacy was maintained until 52 weeks. The estimated yearly progression of mTSS was also significantly improved from 26.0 at baseline to 1.1 at week 52 (p<0.0001). Cumulative probability analysis showed that progression of joint damage was inhibited in 61.7% of patients. Similarly, erosion was inhibited in 75.8% and joint space narrowing was inhibited in 71.1% of patients.

Based on the HAQ scores, extremely severe functional disability was evident before treatment, with a mean score of 1.56. After treatment with TCZ for 52 weeks, the HAQ score decreased to 1.29 with a gradual decline. Defined as HAQ score ≤ 0.5, functional remission was achieved by 26.4% of patients.

The 52-week retention rate was approximately 72%, independent of history of prior therapy with biologics. In contrast, the patients taking MTX achieved the higher continuation rate, compared to those without MTX.

Conclusions: This study showed that clinical remission was achieved in 42% of the patients with 12.4 years of disease duration and progression of joint damage is inhibited appreciably by treatment with TCZ in daily clinical practice. Given the results that functional remission was obtained among one fourth of the patients, which is apparently lower than that of clinical remission, early treatment with TCZ before irreversible and progressed disability by structural damage is important to achieve higher rate for all three remission criteria.

Disclosure: T. Takeuchi: Chugai, 2, 5; Y. Tanaka: Chugai, 2, 5; K. Amano: Chugai, 2, E. Sato: None; M. Nawata: None; H. Nagasawa: None; D. Hoshi: None; M. Saito: None; S. Fukuyo: None; K. Hanami: None; H. Kameda: None; T. Kurasawa: None; H. Yamamura: Chugai, 2, 5.

1794

Comparable Persistency and Effectiveness of Abatacept Versus Anti-TNF Agents in the Treatment of Biologic-Naïve Rheumatoid Arthritis Patients Using the CORRONA Registry. Leslie Harrold1, George Reed2, Lisa C. Rosenblatt1, Monica Mody1, Diane Moniz Reed1 and Jeffrey Greenberg2. 1Bristol-Myers Squibb, Princeton, NJ, 2NYU Hospital of Joint Diseases, New York, NY, 3University of Massachusetts Medical School, Worcester, MA.

Background: For RA patients who are new candidates for biologic treatment, there is limited observational data to guide physician decision making with respect to the relative merits of an anti-TNF as compared to a non-anti-TNF biologic, such as abatacept (ABA).

Objective: To examine the persistency and effectiveness of ABA versus anti-TNF agents among biologic-naïve RA patients in a multi-centered observational registry within the United States.

Methods: Using data from the Consortium of Rheumatology Researchers of North America (CORRONA) from 2/20/02–12/31/09, RA patients who initiated ABA or an anti-TNF and were not in remission (based on Clinical Disease Activity Index; CDAI) at the time of initiation were identified. Anti-TNF to ABA initiators (3 to 41) were matched based on age, RA
Comparative Effectiveness of Biological Treatment Options Following Tumor Necrosis Factor α Inhibitor Failure in Rheumatoid Arthritis: Systematic Review and Indirect Pairwise Meta-Analysis. Monika Schoels1, John B. Wong2, Daniel Aletaha3 and Josef S. Smolen4. 12nd Internal Medicine, Hietzing Hospital, Vienna, Austria

After one TNFi, diminished the clinical response when compared to the efficacy of biologicals sub-analyses, we investigated whether multiple previous TNFi failures (RD) for adverse events, serious adverse events and infection rates. In derived odds ratios (OR) for ACR response and ascertained risk differences concomitant methotrexate (MTX) for 24 weeks to match the other trials. We TOC to perform the analyses; for golimumab (GOL), we obtained ACR20, clinical trial data on abatacept (ABA), rituximab (RTX), and tocilizumab of drug efficacy and safety using a random effects model. We used published baseline, we performed an indirect meta-analysis with pairwise comparisons enced TNFi failure. After assessing the heterogeneity of trial populations at following inadequate response to TNFi. Additionally, we investigated the comparative effectiveness and safety of biologic agents with each other and reveals similar effects of all biologics.

Conclusions: In this small sample of RA patients in a real world setting, treatment with ABA was comparable in persistency or effectiveness to anti-TNFs. This study suggests similar effectiveness of ABA and anti-TNFs in biologic-naive RA patients, and further research with a larger sample size should be undertaken to confirm these findings.

Disclosure: L. Harrold: Bristol-Myers Squibb, 5; G. Reed: Corrona, 5; L. C. Rosenblatt: Bristol-Myers Squibb, 1, 3; M. Modi: Bristol-Myers Squibb, 1, 3, Eli Lilly and Company, 1, 3; D. Moniz Reed: Bristol-Myers Squibb, 1, 3, J. Greenberg: None.

1795

Comparative Effectiveness of Biological Treatment Options Following Tumor Necrosis Factor α Inhibitor Failure in Rheumatoid Arthritis: Systematic Review and Indirect Pairwise Meta-Analysis. Monika Schoels1, John B. Wong2, Daniel Aletaha3 and Josef S. Smolen4. 12nd Internal Medicine, Hietzing Hospital, Vienna, Austria

Conclusions: In patients refractory to one or more TNFi, new biological agents provide significant improvement with good safety. In the absence of head-to-head trials, adjusted indirect meta-analysis enables evaluation of the comparative effectiveness and safety of biologics with each other and reveals similar effects of all biologics.


1796

Comparative Effectiveness of Rituximab in Combination with Either Methotrexate or Leflunomide in the Treatment of Rheumatoid Arthritis. Javier Narvaez4, César Díaz Torne2, José Miguel Ruiz5, María Victoria Hernández1, Vicens Torrente2 and Sergio Ros3. 1Department of Rheumatology, Hospital Clinic, Barcelona, Spain, 2Department of Rheumatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, 3Department of Rheumatology, Hospital de Valladolid, Barcelona, Spain, 4Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain

Background: Rituximab (RTX) has only been approved in combination with methotrexate (MTX) for patients with rheumatoid arthritis (RA) who have not responded to treatment with tumour necrosis factor (TNF) blocking agents. When MTX is contraindicated, RTX in combination with other DMARDs is increasingly used, despite a lack of specifically-designed, randomised clinical trials assessing these alternative combination therapies. In this context, real-world data on the effectiveness and safety of treatment combinations arising from observational cohort studies are the second-best source of evidence. One treatment option lacking sufficient supporting data is the combination of RTX with leflunomide (LEF). To date, only a small retrospective case series of ten patients has been published, with promising results.
Purpose: To compare the effectiveness of a combination of RTX with either MTX or LEF in the treatment of patients with active RA and inadequate response to anti-TNF agents or traditional DMARDs in a real-world setting.

Methods: Data from 77 consecutive unselected patients with active RA and treated with at least one cycle of RTX (1 g x 2 weeks) plus MTX or LEF were retrospectively collected. The primary endpoint of this retrospective analysis was the DAS28 response rate at month 6, according to the EULAR improvement criteria. Secondary efficacy endpoints included the percentage of patients in remission (DAS28 < 2.6) and with low disease activity (defined as DAS28 ≤ 3.2), the percentage of patients that fulfilled the ACR50 and ACR70 response criteria, and the variations in level of disability as established by the HAQ score. The ACR and EULAR response considered for the analysis was the maximal clinical response obtained between the end of month 4 and the end of month 6 of follow-up after the first cycle of RTX.

Results: Of the 77 patients, 45 received RTX+MTX and 32 RTX+LEF. At baseline there were no significant differences between the groups in terms of the main clinical and laboratory data, or in the number of previous DMARDs and anti-TNF agents used. The responses at six months are presented in the following table:

<table>
<thead>
<tr>
<th></th>
<th>RTX+MTX (N=45)</th>
<th>RTX+LEF (N=32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28</td>
<td>4.24 (1.52)</td>
<td>3.85 (1.61)</td>
<td>0.2826</td>
</tr>
<tr>
<td>Change in DAS28</td>
<td>−1.68 (1.38)</td>
<td>−1.72 (1.43)</td>
<td>0.3105</td>
</tr>
<tr>
<td>Change≥ in DAS28</td>
<td>−28.85 (−7.3)</td>
<td>−26.41 (−9.2)</td>
<td>0.7158</td>
</tr>
<tr>
<td>EULAR response moderate</td>
<td>34 (75.5%)</td>
<td>25 (78.1%)</td>
<td>d=−2.6 CI (0.02, 17.2) (P&lt;0.05)</td>
</tr>
<tr>
<td>Good</td>
<td>10 (22.2%)</td>
<td>8 (25%)</td>
<td>d=−2.6 CI (−22, 15.5) (P&lt;0.05)</td>
</tr>
<tr>
<td>Moderate</td>
<td>24 (53.3%)</td>
<td>17 (53.1%)</td>
<td>d=−0.2 CI (−12, 21.8) (P&lt;0.05)</td>
</tr>
<tr>
<td>None</td>
<td>11 (24.8%)</td>
<td>7 (21.8%)</td>
<td>d=−2.6 CI (−17, 20.5) (P&lt;0.05)</td>
</tr>
<tr>
<td>DAS28 ≤ 3.2 (%)</td>
<td>11 (24.8%)</td>
<td>11 (33.7%)</td>
<td>0.3415</td>
</tr>
<tr>
<td>DAS28 ≤ 2.6 (%)</td>
<td>4 (8.8%)</td>
<td>6 (18.7%)</td>
<td>0.3038</td>
</tr>
<tr>
<td>ACR50 responders (%)</td>
<td>6 (13.3%)</td>
<td>7 (21.8%)</td>
<td>0.3241</td>
</tr>
<tr>
<td>ACR70 responders (%)</td>
<td>1 (2.2%)</td>
<td>2 (6.2%)</td>
<td>0.3803</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.5 (0.3)</td>
<td>0.75 (0.3)</td>
<td>0.4612</td>
</tr>
<tr>
<td>Change in HAQ</td>
<td>−0.68 (−3.1)</td>
<td>−0.64 (−2.2)</td>
<td>0.9149</td>
</tr>
<tr>
<td>Change≥ in HAQ</td>
<td>−60.00 (−100, 100)</td>
<td>−50.00 (−94, 700)</td>
<td>0.2488</td>
</tr>
</tbody>
</table>

Results are presented as mean (standard deviation), median (minimum, maximum) and counts and percentages. *P*<0.05.

Minor adverse events occurred in 8.8% (4/45) of RTX+MTX patients and in 9.3% (3/32) of RTX+LEF patients. None of the patients had serious adverse events and none discontinued the treatment.

Conclusion: Current clinical practice is to use MTX as a first choice for combination with RTX. However, in a number of patients MTX has to be replaced by another DMARD. Our preliminary data support the view that LEF is a useful alternative if MTX is contraindicated, since its effectiveness and safety seem similar.

Disclosure: J. NAVARRE: None; C. DIAZ TORNÉ: None; J. M. RUIZ: None; M. V. HERNÁNDEZ: None; V. TORRENTE: None; S. ROC: None.

1797

Comparison of Tocilizumab and Infliximab Treatment for RA for a Duration of 12 Weeks, Based on MMP-3: Preliminary Report. Isamu Yokoe, Hitomi Kobayashi, Hiroshi Sato and Shinya Nishio, Isahachi Chu Medical Center, Tokyo, Japan, "Isahachi Chu Medical Center"

Purpose: MMP-3, an enzyme produced by synoviocytes, is a marker of synovitis, providing a more direct indication of actual joint destruction than CRP or ESR. It is potentially useful to detect synovitis at an early stage. A synergistic effect of IL-6 and either TNF or IL-1 induces MMP-3 production, and in 9.3% (3/32) of RTX patients, MMP-3 was replaced by another DMARD. Our preliminary data support the view that LEF is a useful alternative if MTX is contraindicated, since its effectiveness and safety seem similar.

Conclusion: Current clinical practice is to use MTX as a first choice for combination with RTX. However, in a number of patients MTX has to be replaced by another DMARD. Our preliminary data support the view that LEF is a useful alternative if MTX is contraindicated, since its effectiveness and safety seem similar.

Disclosure: I. Yokoe: None; H. Kobayashi: None; H. Sato: None; S. Nishio: None.

1798

CTLA-4-Ig Fusion Protein (Abatacept) Modulate Inflammatory Activity of Cultured Synovial Macrophages from Rheumatoid Arthritis Patients. Maurizio E. Cutolo, Stefano Soldano, Paola Montagna, Alberto Sulili, Bruno Seriolo, Barbara Villaggio, Pier Franco Triolo, Paolo Clerico, Lamberto Felli, Luigi Molfetta and Renata Brizzolara, 1Academic Orthopedic Department, University of Genova, Italy, 2Orthopedic Unit, San Martino Hospital, Genova, Italy, "Research Laboratories and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Italy, 3Research Laboratory of Nephrology, Department of Internal Medicine - University of Genova, Genova, Italy, 4Rheumatoid Arthritis Unit – Orthopedic Surgery Department. CTO Hospital, Turin, Italy, 5University of Genova, Italy"
Our previous data in vitro demonstrated that CTLA-4-Ig blockade, in RA synovial macrophages/T cells co-cultures, resulted to induce anti-inflammatory effects [4].

The aim of this study was to investigate in vitro if CTLA-4-Ig directly affect the inflammatory activation of the cells of the monocytic lineage in monocultures of RA SM, in the absence of T cells.

**Methods:** RA SM were obtained from patients (5 females, 1 male; mean age 50±2 years; DAS28≥5.2) who underwent therapeutic arthroscopic synovectomy, after informed consent and in accordance with the local Ethical Committee. After 24 hours of culture, in the absence, as well as in the presence of CTLA-4-Ig at different in vitro concentrations (100, 500 μg/ml), RA SM were harvested and the expression of inflammatory cytokines (IL-6, TNFα, IL-1β) and TGFβ were evaluated by immunochemistry (ICC) (all mAbs diluted 1:100, Santa Cruz Biotechnology, Santa Cruz, CA, USA), with relative image analysis (Leica Q-Win image analysis system, Leica, Cambridge, UK) and western blot (WB) analysis. In addition, quantitative real-time PCR (qRT-PCR) analysis of mRNA was performed for IL-6, TNFα and IL-1β. Experiments were performed in triplicate.

**Results:** ICC image analysis revealed that the addition of CTLA-4-Ig 500 μg/ml in cultures of RA SM was able to significantly downregulate the cytokine expression (p<0.001 for IL-6 and TGFβ, p<0.01 for TNFα and IL-1β), compared to untreated RA SM. Moreover, the treatment with CTLA-4-Ig 100 μg/ml already showed a significant decrease for IL-6 (p<0.001) and IL-1β (p=0.05) and only TGFβ expression showed a significant variation for CTLA-4-Ig 100 μg/ml treatment compared to CTLA-4-Ig 500 μg/ml (p<0.01).

WB and qRT-PCR analysis confirmed these results and revealed a mild decrease in the amount of inflammatory cytokine production after CTLA-4-Ig 500 μg/ml treatment compared to untreated RA SM.

**Conclusions:** We provide evidence for a CTLA-4-Ig dose-dependent anti-inflammatory effect in vitro, in RA SM cultures. The addition of CTLA-4-Ig resulted in downregulating IL-6, TNFα, IL-1β and TGFβ production. Therefore, even if the best-defined mechanism of action of CTLA-4-Ig is the inhibition of the T cell co-stimulatory pathway, this study identifies the SM as further possible target cells of CTLA-4-Ig treatment in RA.

**References:**

**Disclosure:** M. E. Cutolo: None; S. Soldano: None; P. Montagna: None; A. Sulli: None; B. Seriolo: None; B. Villaggio: None; P. F. Trilo: None; P. Clerio: None; L. Felli: None; L. Molletta: None; R. Brizzolara: None.

**1799**

**Dosing of Anti-Tumor Necrosis Factor Biologics (Anti-TNFs) for Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA) in Clinical Practice in the United States. J. Timothy Harrington1, Dimitrios A. Pappas2, Susan Messing3, Xin Tu4, Rui Chen5, Kimberly Kaukeinen6, Timothy Pietras7, Jeffrey D. Greenberg8 and Joel M. Kremer9.

1Millburn, NJ, 2Johns Hopkins University, Baltimore, MD, 3The Center for Rheumatology, Albany, NY, 4University of Rochester Medical Center, 5University of Wisconsin, Madison, WI

**Background:** RA and PsA patients experience variable responses to biologics, and recommended doses and frequency of administration vary among the alternative anti-TNFs. Accelerated dosing is approved for infliximab (INFIL) infusions, but varies for the other individual anti-TNFs. Switching among anti-TNFs and to biologics with alternative therapeutic targets has also not been well studied in a US population. Insurers often deny higher dosing of anti-TNFs as experimental treatment, while at the same time, therapeutic acceleration is being recommended to achieve optimal disease control and long term outcomes, as for example in the Treat to Target initiative.

**Objective:** To study rheumatologists’ current choices of biologic agents in clinical practice, and the dosing of anti-TNFs in patients with RA and PsA enrolled in the CORRONA observational registry (Consortium of Rheumatology Researchers of North America, Inc.)

**Methods:** Biologic drug use is collected during routine office visits for the CORRONA enrolled RA and PsA patient populations. Food and Drug Administration (FDA) approved doses and frequencies are specified on the questionnaires, and space to indicate other dosing is also provided. Golimumab was not specified previously. Other doses, and/or frequencies of anti-TNF administration were pooled for this abstract into lower or higher than the specified categories. These were obtained from the most recent visit report for all enrolled patients.

**Results:** Current biologic treatments were reported for 8706 of 22973 RA enrollees (38%) and 1742 of 3604 PsA enrollees (48%). For RA, these included: INFIL (2733/8706, 31%), ETAN (2819, 32%), ADAL (1935, 22%), and all other biologics (1219, 14%). For PsA, these included: INFIL (460/1742, 26%), ETAN (768, 44%), ADAL (495, 28%), and all other biologics (19, 1%). Anti-TNFs account for 86% of biologic use for RA, and 99% for PsA. Anti-TNF dosing for INFIL, ETAN, and ADAL is shown in Table 1. Higher doses and/or frequencies of administration than those recommended are commonly reported.

**Table 1.** Dosing of Anti-TNFs (Number RA/Number PsA)

<table>
<thead>
<tr>
<th>Infliximab (mg)</th>
<th>&lt;300</th>
<th>3−&lt;500</th>
<th>5−&lt;900</th>
<th>9−&lt;1200</th>
<th>≥1200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses</td>
<td>332/34</td>
<td>1806/261</td>
<td>508/133</td>
<td>68/24</td>
<td></td>
</tr>
<tr>
<td>Enetancept (mg)</td>
<td>Lower</td>
<td>25/wk*</td>
<td>25 2x/wk*</td>
<td>50/wk*</td>
<td></td>
</tr>
<tr>
<td>Doses</td>
<td>26/17</td>
<td>119/23</td>
<td>410/121</td>
<td>1839/48</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: 1. Choices and dosing of biologic drugs vary greatly across these RA and PsA populations. 2. Higher doses of anti-TNFs are commonly prescribed, suggesting that dosage acceleration is being considered for patients who experience a partial response to initial doses. 3. Further studies are needed regarding clinical outcomes, relative safety, and cost effectiveness of higher dose biologic treatment. 4. The results of these studies will likely differ in the US and other countries where biologic drugs are less commonly prescribed.

**Disclosure:** J. T. Harrington: Corrona, 5; D. A. Pappas: Corrona, 5, 9; S. Messing: None; X. Tu: None; R. Chen: None; K. Kaukeinen: None; T. Pietras: None; J. D. Greenberg: Corrona, 9; J. M. Kremer: Abbott Laboratories, 2, 5, Ajen Inc., 2, 5; Corrona, 9, Ortho Biotech Products L.P., 2, 5, UCB, Inc., 2, 5

**1800**

**Drug Free REMission after Cessation of Tocilizumab (Actemra) Monotherapy (DREAM Study).** Norhiro Nishimoto. Wakayama Medical University, Ibaraki-City, Japan

**Purpose:** Tocilizumab (TCZ) has been demonstrated to frequently induce remission according to the DAS28 in patients with rheumatoid arthritis (RA). With long-term TCZ treatment reduced serum IL-6 levels have been observed in some patients, although TCZ does not directly act on IL-6, but inhibits the IL-6 receptor. It may be possible to discontinue TCZ in such patients without causing acute flare of the disease. We have previously reported that the serum IL-6 level correlates with actual in vivo IL-6 production and disease activity in patients with RA. Here we aimed to determine the rate of efficacy continuation at 52 weeks after cessation of TCZ treatment, and explore the factors that contribute to the duration of efficacy.

**Methods:** Patients who achieved DAS28≤2.6 at the last observation of the previous Japanese TCZ clinical trials were enrolled and monitored for their disease activities without DMARDs. Patients with DAS28≤3.2 were additionally enrolled to know if the disease activity at TCZ discontinuation might influence the efficacy duration. The loss of efficacy was defined as either DAS28>3.2 at 2 consecutive visits, initiation of additional RA treatments including increase in corticosteroid dose, or patient’s request for retreatment. We estimated the efficacy continuation rate from Kaplan-Meier curves.

**Results:** A total of 187 patients were enrolled. Baseline characteristics of the patients were as follows: median disease duration, 7.8 years; median previous TCZ treatment for 4.0 years; median DAS28, 1.5 (remission rate 90%); 34.2% received corticosteroid and mean dose was 2.8 mg/day in these patients. The efficacy continuation rate was 35.1% at 24 weeks and 13.4% at 52 weeks. Efficacy continued in 24 patients as long as 52 weeks. Furthermore 19 patients were completely free from any drug. Multivariate Cox regression analysis revealed that baseline disease duration of the patients did not influence efficacy duration after cessation of TCZ. However low serum IL-6 (<35 pg/mL) and normalization of MMP-3 level at TCZ discontinuation were identified as independent predictive markers for the longer efficacy duration. The estimated efficacy continuation rates in the patients both with serum IL-6 ≤12.9 pg/mL, which was calculated from receiver operating characteristic (ROC) curve, and with normal MMP-3 level was 70.6% at 24 weeks and 38.0% at 52 weeks, respectively. On the other hand, loss of efficacy among those with an IL-6 level higher than 35pg/mL was seen in 68.6% of patients within 12 weeks.
Effect of Rituximab Treatment on IL-15 and T Cell Subpopulations in Rheumatoid Arthritis Patients. Cesar Diaz-Torne1, Maria A. Ortiz1, Carme Geli1, Josep M. Llobet1, Elisabeth Cantó1, Elena Perez2, Hector Corominas3, Candido Juarez3, Cesar R. Diaz-Lopez3 and Silvia Vidal1. 1Hospital de la Santa Creu i Sant Pau, 2Hospital Moises Broggi

Rituximab is a therapeutic anti-CD20 antibody used for in vivo depletion of B cells. However, the mechanisms of action are not fully understood because clinical responses do not always correlate with the extent and duration of B cell depletion. This study was conducted to examine the effect of B cell depletion on peripheral T cells from rheumatoid arthritis patients after the first infusion and to compare the results with consecutive infusions.

Methods: 26 active RA patients received rituximab (1000 mg) on days 1 and 15. Following infusions were done depending clinical evolution (Never before 6 months) Peripheral blood samples were collected at baseline and at 30, 90 and 180 days postinfusion. The phenotype of T cell subsets of peripheral blood from RA patients were examined by cytometry and cytokine production was determined by ELISA and flow cytometry. Results from four consecutive infusions were compared and correlated with DAS28 activity index. Linear regression analysis was used to associate cellular changes and disease activity.

Results: Mean age was 61.5±11.5 years. 92.3% were women. Mean RA evolution was of 18.2±11.9 years. Previous DMRADs and biological therapies were used in 31.3% and 11.9% respectively. 95.9% were treated just with a rituximab and the other 50% on combination with a DMARD. 96.2% were also using glucocorticoids. 96.2% had a positive anti-CCP and/or rheumatoid factor. 89.5% had an erosive arthritis and 42.1% had a history of rheumatoid nodules. Patients previous DAS28 to treatment was 5.64±0.98.

According to our previous results, peripheral B cell depletion was fully effective by 30 days. No changes in the percentage of CD3+, CD4+, CD8+ and NK cells were found in the first as well as in the following infusions. Similarly to our observations in the first infusion, there was a comparative progressive diminution of CD8+CD45RO+ cells with the recovery starting at 180 days. DAS28 significantly correlated with CD8+CD45RO+ cells in the first and subsequent rituximab infusions. Since CD8+CD45RO+ diminution was coincident with the clinical response measured as DAS28, we investigated whether IL-15 could be responsible for this population changes in rheumatoid arthritis patients. As expected there was significant levels of IL-15 in the serum RA patients (192±31 pg/ml) compared to healthy donors (31 pg/ml) compared to healthy donors (31 pg/ml). A significant diminution was coincedent with the clinical response measured as DAS28, we investigated whether IL-15 could be responsible for this population changes in rheumatoid arthritis patients. As expected there was significant levels of IL-15 in the serum RA patients (192±31 pg/ml) compared to healthy donors (31 pg/ml). A significant diminution was measured as DAS28, we investigated whether IL-15 could be responsible for this population changes in rheumatoid arthritis patients. As expected there was significant levels of IL-15 in the serum RA patients (192±31 pg/ml) compared to healthy donors (31 pg/ml) compared to healthy donors (31 pg/ml). A significant diminution was measured as DAS28, we investigated whether IL-15 could be responsible for this population changes in rheumatoid arthritis patients. As expected there was significant levels of IL-15 in the serum RA patients (192±31 pg/ml) compared to healthy donors (31 pg/ml). A significant diminution was measured as DAS28, we investigated whether IL-15 could be responsible for this population changes in rheumatoid arthritis patients. As expected there was significant levels of IL-15 in the serum RA patients (192±31 pg/ml) compared to healthy donors (31 pg/ml). A significant diminution was measured as DAS28, we investigated whether IL-15 could be responsible for this population changes in rheumatoid arthritis patients. As expected there was significant levels of IL-15 in the serum RA patients (192±31 pg/ml) compared to healthy donors (31 pg/ml). A significant diminution was measured as DAS28, we investigated whether IL-15 could be responsible for this population changes in rheumatoid arthritis patients. As expected there was significant levels of IL-15 in the serum RA patients (192±31 pg/ml) compared to healthy donors (31 pg/ml). A significant diminution was measured as DAS28, we investigated whether IL-15 could be responsible for this population changes in rheumatoid arthritis patients. As expected there was significant levels of IL-15 in the serum RA patients (192±31 pg/ml) compared to healthy donors (31 pg/ml). A significant diminution was measured as DAS28, we investigated whether IL-15 could be responsible for this population changes in rheumatoid arthritis patients. As expected there was significant levels of IL-15 in the serum RA patients (192±31 pg/ml) compared to healthy donors (31 pg/ml). A significant diminution was measured as DAS28, we investigated whether IL-15 could be responsible for this population changes in rheumatoid arthritis patients. As expected there was significant levels of IL-15 in the serum RA patients (192±31 pg/ml) compared to healthy donors (31 pg/ml). A significant diminution was measured as DAS28, we investigated whether IL-15 could be responsible for this population changes in rheumatoid arthritis patients. As expected there was significant levels of IL-15 in the serum RA patients (192±31 pg/ml) compared to healthy donors (31 pg/ml). A significant diminution was
Methods: Forty RA patients (F/M:33/7) were enrolled to the study. Inflximb (n=9), etanercept (n=12) and adalimumab (n=19) were started according to current guidelines in Turkey. The rate of concomitant metotrexate usage was 70%. Disease activity was assessed by DAS28. HRCT, pulmonary function test (PFT) and diffusing capacity of the lung for carbon monoxide (DLCO) were performed in all patients before and after 6 months of anti-TNF therapy. Serum cytokines were measured by multiple ELISA assay (IL1, IL6, MCP, TNF, VEGF, IFN gamma, IL10, IL12, IL13) at baseline and at 6 months’ visit.

Results: Mean(SD) age was 48.8(11.8) and mean disease duration was 8.4(9.9) years. Anti-CCP and RF positivity were 55.6% and 80% respectively. Mean DAS28(SD) score was 5.5(1.1) and PPT (35.3% vs 30.6%, p = 0.03) at 6 months’ visit, however without a significant change in DLCO findings (14.7% vs 19.2%, p = 0.3). At both evaluations bronchiectasis and interstitial lung disease were the most common pulmonary complications. When compared to the baseline findings, the number of patients with bronchiectasis and ILD also decreased (n=16/9 vs 10/6, respectively) at 6 months’ visit. When the relationship of interstitial pulmonary involvement with the baseline HRCT, serum cytokine levels and serologic findings (RF, CCP) were analyzed, higher levels of IL10 (p = 0.025), IL1beta (p = 0.03) and MMP (p = 0.027) were found to be associated with interstitial lung disease in RA.

Conclusion: Our results suggest that HRCT is sensitive for monitoring pleuropulmonary changes in RA patients. Anti-TNF agents seem to improve the chances of recovery in interstitial lung disease.

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1804 Effects of Subcutaneous and Intravenous Golimumab on Markers of Inflammation in Patients with Rheumatoid Arthritis. Mittie K. Doyle1, Mahboob U. Rahman2, Bart Frederick3, Charles A. Birbara4, Dick de Vries5, Gary Toedter6, Xiaoying Wu7, Dione Chen8, Mark Westerman3 and Daniel E. Furst3.

1Centocor Research and Development, Inc., 2Malvern, PA, 3Centocor Research and Development, Inc., Philadelphia, PA, 4Centocor Research and Development, Inc., 5Leiden University Medical Center, Leiden, The Netherlands, 6Centocor Research and Development, Inc., Malvern, PA, 7Centocor Research and Development, Inc., 8Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, 9Intrinsic Life Sciences, 10Univ. of Massachusetts Bay Medical Campus, Worcester, MA, 11University of California Los Angeles School of Medicine, Los Angeles, CA.

Background: Treatment with the human anti-TNFα mAb golimumab, plus methotrexate, is effective in reducing the signs and symptoms of rheumatoid arthritis (RA). Elevated serum IL-6 and hepcidin have been associated with anemia of inflammation, common in RA pts, but the effects of golimumab on serum markers of inflammation and iron homeostasis are unknown.

Objectives: Assess early changes in inflammatory biomarkers, including CRP, IL-6, and hepcidin, in RA pts treated with golimumab (SC and IV).

Methods: In this phase 1, open-label study, pts ≥ 18 yrs with active RA for ≥ 3 months were randomized to receive SC injections of golimumab 100mg q4w through wk 20 or IV golimumab 2mg/kg at wks 0, 12. At wk 24, the proportion of patients achieving ACR20/50/70 responses was determined. Blood samples for measuring serum levels of CRP, IL-6, SAA, TNFα, MMP-3, hyaluronic acid, ferritin, Hgb, and haptoglobin were collected at baseline, wk 4, 24, and 52 hrs, and at wks 1, 2, 4, and 8. Urine hepcidin levels were measured at baseline, 48 hrs, and at wks 2, 4, and 8.

Results: 49 pts were randomized to receive SC golimumab (n=33) or IV golimumab (n=16). Most patients were iron replete at baseline with mean ferritin >97ng/mL and mean transferrin saturations >22%. 5 pts (SC group) had mild anemia at baseline (Hgb=10.3–11.1 g/dL). For all pts, mean baseline CRP level was mildly elevated (1.1mg/dL), while mean hepcidin levels started and remained within normal ranges (17–286 ng/mL) throughout the study. Urine and serum hepcidin were positively correlated at all times. Overall, Hgb levels were maintained or increased. Mean serum CRP, IL-6, SAA, TNFα, MMP-3, haptoglobin, ferritin and hepcidin decreased rapidly within 2 wks after the first golimumab administration and remained below baseline through wk8. Spearman’s correlations showed decreases in serum hepcidin correlated with decreases in CRP and ferritin at most timepoints. At wk24, 62% of pts in SC group and 56% in IV group achieved ACR20, 31% and 25%, respectively, achieved ACR50, and 21% and 19%, respectively, achieved ACR70. Golimumab was generally well tolerated. Infections were
event rates were comparable between CZP and control groups (65.1% vs 59.3%, and 5.4% vs 6.2%), with no new safety signals and no cases of TB observed.

**Conclusion:** In a diverse group of RA pts reflecting those seen in daily clinical practice (including those with prior TNF-inhibitor use), addition of CZP to current therapy was associated with a rapid clinical response consistent in all strata, improved function and reduced disease activity with a favorable risk benefit profile.

**References:**
4. Disclosures: M. Weinblatt: Abbott Laboratories, 2, 5; Amgen Inc, 5; Biogen Idec, 2, 5; Bristol-Myers Squibb, 5; Centocor, Inc, 5; Crescendo, 2, 5; Pfizer Inc, 5; Roche, 5; UCB, Inc, 5; Pfizer, Inc, 5; R. Fleischmann: Abbott Laboratories, 2, 5; Amgen Inc, 5; Biogen Idec, 2, 5; Bristol-Myers Squibb, 2, 5; Centocor, Inc, 5; Eli Lilly and Company, 2, Genentech and Biogen IDEC Inc, 2, 5; Lexicon, 2, 5; Pfizer Inc, 2, 5; Regeneron Pharmaceuticals; P. Emery: UCB, Inc, 2, 5; N. Goel: UCB, Inc, 1, 3; C. O. Bingham: UCB, Inc, 2, 5; J. Pope: UCB Inc, 2, 5; E. Massarotti: American College of Rheumatology, 5, 9; Bristol-Myers Squibb, 5; G. Merck-Medco, 5; Pfizer Inc, 5; Roche, 5; UCB, Inc, 5; R. van Vollenhoven: UCB Inc, 2, 5; T. W. J. Huizinga: Abbott Laboratories, 5; Axis-Shield, 5; Biotest AG, 2, 5; Bristol-Myers Squibb, 5, 8; EU & Dutch Arthritis Foundation, 2, 5, 6; Meteor Board, 2, 5, 6; Novartis Pharmaceuticals Corporation, 5; Pfizer Inc, 3, 5; Roche, 5; B. Duncan: UCB, Inc, 3; M. Dougados: Abbott Laboratories, 2, 5; Bristol-Myers Squibb, 2, 5; Pfizer Inc, 2, 5; Pfizer, Inc, 5; Roche, 5; UCB, Inc, 2, 5.

**1806 Efficacy and Safety of Certolizumab Pegol Plus Methotrexate in Patients with Rheumatoid Arthritis (RA): 3-Year Data from the RAPID 2 Study.** Josef S. Smolen1, Ronald F. van Vollenhoven2, Arthur Kavagnaugh3, Niti Goel4, Andreas Fichtner4, Vibeke Strand5, Jiri Vencovsky2 and Desiree van der Heijide6.

**Background:** Certolizumab pegol (CZP) every other week (EOW) + methotrexate (MTX) has maintained high efficacy and acceptable tolerability profile over 2 years (yrs) in patients (pts) with active RA despite MTX.1–3 Here we evaluate the sustainability of improvements in RA signs and symptoms, inhibition of joint damage progression and tolerability of CZP + MTX over 3 yrs in pts who completed 24 weeks (wks) of double-blind treatment with CZP 200 or 400 mg EOW + MTX (completers) in RAPID 2, and entered an open-label extension (OLE) of CZP 400 mg EOW + MTX (MTX over 3 yrs in RA pts are shown over 2.5 yrs (128 wks). Pts who withdrew from the OLE for any reason or took rescue medication in the OLE had data imputed from that time point.

**Methods:** ACR responses, DAS28(ESR), HAQ-DI, pain VAS (0–100 mm scale) are shown over 3 yrs (148 wks) from RAPID 2 baseline (BL) for CZP completers who entered the OLE; modified Total Sharp Scores (mTSS) are shown over 2.5 yrs (128 wks). Pts who withdrew from the OLE for any reason or took rescue medication in the OLE had data imputed from that time point.

**Results:** Of 494 pts treated with CZP + MTX, 355 completed RAPID 2; of these, 342 (96%) entered the OLE. Completers entering the OLE had high disease activity at RAPID 2 BL (mean: DAS28: 6.8; HAQ-DI: 1.6; pain VAS: 60.7); mean mTSS at RAPID 2 BL was 33.6. After 3 yrs, 79% of CZP completers continued to receive OL CZP; only 2 pts withdrew due to lack of efficacy. ACR responses and improvements in DAS28, HAQ-DI and pain from BL were sustained in the OLE to 3 yrs in CZP completers (Table). Inhibition of progression of structural damage observed during the placebo-controlled phase was sustained up to the last x-ray evaluation at 2.5 yrs. The incidence of AEs by Wk 148 was 108.17 cases/100 pt-yrs, and SAEs 13.35 cases/100 pt-yrs. Most AEs were mild to moderate; no new safety signals were identified. Serious infections were reported at a rate of 5.46 cases/100 pt-yrs, and malignancies at 0.64 cases/100 pt-yrs.

**Table. Efficacy of CZP+MTX over 3 yrs in RA pts**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wk 24</th>
<th>Wk 100</th>
<th>Wk 148</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR50 % responders</td>
<td>46.6</td>
<td>51.3</td>
<td>44.9</td>
</tr>
<tr>
<td>ACR70 % responders</td>
<td>19.1</td>
<td>21.0</td>
<td>22.9</td>
</tr>
<tr>
<td>DAS28</td>
<td>4.0 (2.0)</td>
<td>3.8 (2.0)</td>
<td>3.8 (1.2)</td>
</tr>
<tr>
<td>HAQ-DI change from BL, mean (SD)</td>
<td>-0.06 (0.9)</td>
<td>-0.06 (0.9)</td>
<td>-0.06 (0.5)</td>
</tr>
<tr>
<td>Pain VAS change from BL, mean (SD)</td>
<td>206.0 (82.4)</td>
<td>206.0 (82.4)</td>
<td>206.0 (82.4)</td>
</tr>
<tr>
<td>mTSS change from BL, mean (95% CI)</td>
<td>0.61 (0.13)</td>
<td>0.58 (0.11)</td>
<td>0.75 (0.23)</td>
</tr>
</tbody>
</table>

**Conclusion:** In pts with active RA despite MTX, the addition of CZP provides clinical improvements that are sustained over 3 yrs, inhibits joint damage progression, and is well tolerated.

**References:**

**1807 Efficacy and Safety of Rituximab Treatment in Clinical Practice: Data from the CERERRA Collaboration.** Katerina Chatzidiomou1, Elisabeth Lie2, Galina Lukina3, Merete L. Hetland4, Ulrik Tarp5, Cem Gabay6, Piet L. Van Riel7, Dan C. Nordström8, Juan J. Gomez-Reino9, Karel Pavelka10, Tore K. Kvien11, Ronald Van Vollenhoven12, Jiri Vencovsky2 and Desiree van der Heijide6.

**Background:** The optimal regimen for treatment of RTX in RA has not yet been established. The purpose of this study was to analyze the efficacy of treatment and retreatment with RTX within 12 months after the first treatment and to identify predictors of response.

**Methods:** Ten European registries submitted anonymized datasets with baseline characteristics.

**Results:** Baseline data were available for 2265 patients. The mean (SD) age/disease duration of patients was 53.4 (13.2)/12.1 (9.1) years. 80.4% of them were female, 77.3% RF positive and 75.5% (574 out of 760 patients) were ACPA positive. Significant reduction of DAS28 was observed at 6 [DAS28 = 1.92 (1.5)] and 12 months [DAS28 = 1.82 (1.5)]. HAQ was reduced from 1.63 (0.7) at baseline to 1.22 (0.7) and 1.27 (0.7) at 6 and 12 months, respectively. At 6
months. 21.1% and 42.6% of patients were EULAR good and moderate responders, respectively; at 12 months the respective proportions were 20.8% and 40.6%. Seropositivity was associated with better response at 6 and 12 months (Table 1).

Table 1. Mean ± SD reductions in DAS28 at 6 and 12 months by serology.

<table>
<thead>
<tr>
<th>DAS28 improvement</th>
<th>DAS28 improvement at 12 months (n=539)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>RF</td>
<td>1.95 ± 1.50</td>
</tr>
<tr>
<td>ACPA</td>
<td>2.02 ± 1.52</td>
</tr>
<tr>
<td>DOUBLE</td>
<td>2.02 ± 1.56</td>
</tr>
</tbody>
</table>

531 patients received retreatment by the end of 12 months. These patients achieved even higher DAS28 reductions at 12 months (ΔDAS28 = 2.25 (1.4)) while for non-retreated patients a loss of effectiveness was observed (ΔDAS28 = 1.46 (1.5)). A similar trend was observed in HAQ. 321 patients had an adverse event (AE) during the first year of treatment. The majority of the AE was infections and allergic reactions. 8 deaths occurred during the first year, 1 of them related to treatment (aspiration pneumonia). 193 patients discontinued RTX by the end of 12 months, 12 because of an AE, 92 because of inefficacy and the rest of the patients for other reasons. Retreatment was not associated with higher AE rate. Predictors of EULAR Good Response at 12 months positive anti-CCP (p=0.002) and lower DAS28 at baseline (p=0.03).

Conclusions: RTX was effective and well tolerated for the majority of patients. Retreatment before 12 months lead to sustained efficacy and is generally safe. Anti-CCP positivity was associated with good response to treatment with RTX.

Efficacy and Safety of Tocilizumab in Patients with Moderate to Severe Active RA and a Previous Inadequate Response to DMARDs: The ROSE Study, Yusuf Yazici1, Jeffrey R. Curtis2, Alkgun Ince3, Herbert Baraf4, Raymond L. Malamet5, Carol Y. Chung6 and Arthur Kavanaugh7. 1Genentech, a Member of the Roche Group, South San Francisco, South San Francisco, CA, 2Genentech, a Member of the Roche Group, South San Francisco, CA, 3NYU Hospital for Joint Diseases, New York, NY, 4St. Louis University School of Medicine, St. Louis, MO, 5The Center for Rheumatology and Bone Research, Wheaton, Wheaton, MD, 6University of Alabama at Birmingham, Birmingham, AL, 7University of California at San Diego, La Jolla, CA

Purpose: Early and aggressive treatment of RA has been associated with improved outcomes. The objective of the Rapid Onset and Systemic Efficacy (ROSE) study was to assess the efficacy of tocilizumab (TCZ) versus placebo in combination with DMARDs in reducing signs and symptoms during 24 weeks of treatment in patients with moderate to severe RA who have had inadequate clinical response to DMARDs.

Methods: 619 patients were randomly assigned to TCZ 8 mg/kg + DMARDs (TCZ, n=412) or placebo + DMARDs (control, n=207). The primary efficacy end point was ACR50 response at week 24. Efficacy parameters were assessed every 4 weeks through week 24. Disease activity was also assessed at 1 week for a subset of 62 patients. Safety and laboratory parameters were assessed throughout the study.

Results: Most patients were female (81%) and Caucasian (81%); mean age was 55 y, mean disease duration was 8.6 y, mean number of previous DMARDs was 1.2, and mean DAS28 was 6.5. At week 24, there was a significantly higher percentage of ACR50 responders (primary end point) in the TCZ group than in the control group (30.1% vs 11.2%; p<0.0001). Significantly higher percentages of patients in the TCZ group than in the control group achieved ACR20 and ACR50 responses from week 4 through week 24 and ACR70 responses from week 8 through week 24 (Table). Patients in the TCZ group had significant improvement in RAPID3 scores from week 4 through week 24 and in FACIT-Fatigue scores from week 8 through week 24 compared with control (Table). In the TCZ group, improvements in CRP and Hb levels occurred early (week 4) and were sustained throughout (week 24). CRP improvement was significant at all time points (p<0.0001). In the subset, DAS28 and patients’ pain and global assessment scores significantly improved, and CRP levels normalized 1 week after TCZ treatment (p<0.01 vs control). SAE rates/100 PY (95% CI) were 24 (17, 33) and 19 (11, 31) for the TCZ and control groups, respectively. Serious infections were reported in 2.9% and 0.5% of patients in the TCZ and control groups, respectively. Malignancies were reported in 0.7% and 1.5% of patients in the TCZ and control groups, respectively. ALT shifts from normal at baseline to >3× ULN occurred in 3.2% of TCZ patients and in 1.1% of control patients. Clinically significant (grade 3/4) decreases in neutrophil counts were reported in 2.9%/0% of TCZ patients; no grade 3/4 decreases were reported in control patients. There were no occurrences of decreased platelet counts to clinically significant values (grade 3/4).

Conclusions: TCZ led to significant improvements in disease activity, ACR responses, and CRP and Hb levels as early as week 4 and in DAS28 response as early as week 1; responses persisted through week 24. Safety findings were consistent with the known safety profile of TCZ. With early and sustained efficacy, TCZ is an effective treatment option for patients with RA who have failed DMARDs.

Disclosures: Y. Yazici: Bristol-Myers Squibb, 5, 8, Celgene, 5, Centocor, Inc., 2, 5, Genentech, a member of the Roche Group, 5, 8, Pfizer Inc, 8, Roche, 4, UCB, Inc., 5, 8, J. R. Curtis: Amgen Inc., 2, Centocor, Inc., 2, 5, Corrona, 2, 5, Corrona, Roche, 2, 5, 8, UCB, Inc., 5, 8, A. Ince: Abbott Laboratories, 8, Amgen Inc., 8, Wyeth Pharmaceuticals, 8; H. Baraf: Roche, 2, L. R. Malamet: Genentech, a member of the Roche Group, 3, C. Y. Chung: Genentech, a member of the Roche Group, 3, A. Kavanaugh: Roche, 5, 9.

Efficacy of Abatacept and Tocilizumab in Rheumatoid Arthritis Patients Treated in Clinical Practice. Results from the Nationwide Danish DANBIO Registry, Henrik C. Leffers1, Mikkel Ostergaard2, Bente Glinborg3, Niels Steen Krogh4, Heidi Foged5, Ulrik Tarp6, Tove Lorenzen7, Annette Hansen8, Michael S. Hansen9, Martin S. Jacobsen10 and Merete L. Hetland11. 1Aarhus University Hospital, Denmark, 2Copenhagen University Hospital Gentofte, Denmark, 3DANBIO Registry, and Copenhagen University Hospital Gentofte, Denmark, 4DANBIO Registry, and Copenhagen University Hospital Gentofte, Hvidovre and Glostrup, Hvidovre, Denmark, 5DANBIO Registry, and Copenhagen University Hospital Hvidovre and Glostrup, Denmark, 6Frederiksborg Hospital, Denmark, 7Holbæk Hospital, Denmark, 8Randers Hospital, Denmark, 9Vejle Hospital, Denmark, 10Randers Hospital, Denmark, 11Zitelab Aps, Denmark

Background: Abatacept (a selective T-cell costimulation modulator) and tocilizumab (an interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody) have recently been approved for the treatment of rheumatoid arthritis (RA) based on their efficacy and safety in randomized controlled clinical trials. However, reports on their efficacy in clinical practice are scarce.

The aim of this study was to describe the disease activity, clinical response and drug survival in RA patients treated with abatacept or tocilizumab for the first time, based on prospectively registered data from the nationwide Danish DANBIO registry.

Methods: In the DANBIO registry we identified 150 and 178 RA patients treated with abatacept or tocilizumab, respectively. The clinical efficacy was assessed by changes in the 28 joints Disease Activity Score (DAS28), European League Against Rheumatism (EULAR) response rates after 24 and 48 weeks and drug survival. No imputation of missing values was done.

Results: Of the patients receiving abatacept and tocilizumab, respectively, 34%/42% (abatacept/tocilizumab) were male, median (interquartile range, IQR) age 54 (43–62)/56 (43–68) years, disease duration 8.5 (3–14)/9 (3–12) years and number of previous biological drugs 2 (2–3)/2 (2–3). Nearly all patients (95%/95%) had previously received ≥1 Tumor Necrosis Factor inhibitor (TNFi).

In the abatacept group, DAS28 was 5.3 (4.7–6.1). 3.4 (2.7–4.9) and 3.3 (2.5–4.3) at baseline, weeks 24 and 48, respectively, while 5.4 (4.7–6.2), 2.9 (2.3–4.0) and 2.5 (1.9–4.5) in the tocilizumab group. Changes in DAS28 variables over time seemed numerically very similar, except for C-Reactive Protein (CRP), which declined more rapidly in tocilizumab treated patients.
Efficacy of Rituximab on Pulmonary Rheumatoid Nodules: Data of 10 Patients from the French AIR/PR Registry.

**Objectives:** To assess the outcomes of patients with PRN from the French autoimmunity and RTX registry (AIR).

**Method:** AIR is an independent registry under the aegis of the French society of Rheumatology. Standardized information was gathered every 6 months for 5 years by trained clinical nurses in each centre taking part. RA patients with pulmonary nodules observed on CT-scan at baseline and at follow up were included. Scanner readings were centralized (AR). The nodules were assessed according to their number and size (long axis).

**Results:** Of the 2573 patients from 85 centres reviewed, 30 had PRN. 10 of these patients fitted the inclusion criteria: 8 women with a mean age of 66.5 ± 59/79 years and 2 men with a mean age of 56 ± 51/61 years. All the patients had erosive, seropositive, anti-CCP positive RA. Nine patients had sub-cutaneous nodules. The nodules were found while the patients were undergoing treatment with methotrexate (MTX) (n=3), MTX in combination with etanercept (n=3) or adalimumab (n=1), adalimumab alone (n=1) and leflunomide in combination with etanercept (n=2). RTX was administered with MTX (n=4), leflunomide (n=2), salazopyrine and hydroxychloroquine (n=1) or alone (n=3). Nine patients were receiving corticosteroids (prednisolone) with a mean dose of 10.8 ± (5.20) mg. With a mean follow-up of 11.5 ± 8.2 months, twenty one out of the 27 nodules studied improved (78%) and the mean long axis decreased from 14.4 ± 7.8 mm to 8.5 ± 9.9 mm (p = 0.001). Fourteen nodules had improved after a mean follow-up of 8.3 ± 2.7 months (mean long axis from 14.4 ± 9 mm to 11.3 ± 8.9 mm). Seven nodules had disappeared after a mean follow-up of 19.5 ± 17.6 months (mean long axis at baseline: 15.2 ± 5.5 mm). Six nodules worsened after a mean follow-up of 14.8 ± 0.7 months (mean long axis from 14.8 ± 10 mm to 17.8 ± 9 mm).

**Conclusion:** RTX seems to be effective in treating pulmonary rheumatoid nodules.

**References:**

(n=2), heart failure (n=2), nausea and dizziness (n=2), pneumonia (n=2) and asthma (n=1).

Conclusions: Etanar® can effectively control disease activity in real-life patients with active RA and poor responses to MTX but also other DMARDs. Safety and tolerability assessment indicates Etanar to be well tolerated.

Disclosure: F. Rondon: Lafrancol, 2; A. Bautista: Lafrancol, 2; J. C. Salazar: Lafrancol, 2; N. Casas: Lafrancol, 2; P. Santos: Lafrancol, 2; F. Vargas: Lafrancol, 2; J. Márquez: Lafrancol, 2; F. Pumarejo: Lafrancol, 2; F. Fernández: Lafrancol, 2; A. Fernández: Lafrancol, 2; R. Mejia: Lafrancol, 2; O. Ruiz: Lafrancol, 2; A. Torrenegra: Lafrancol, 2; J. B. Martinez: Lafrancol, 2; R. D. Mantilla: Lafrancol, 2.

1812

Etanercept (ETN) Plus Methotrexate (MTX) Combination Therapy Resulted in a Better Radiographic Outcome Than ETN Monotherapy Even in Patients with Active Rheumatoid Arthritis Despite MTX Treatment: 104-Week Results from the JESMR Study. Hideto Kameda1, Katsuaki Kanbe7, Eri Sato2, Yukitaka Ueki5, Kazuyoshi Saitoh8, Shouhei Nagaoka9, Toshihiko Hidaka10, Tsuyoshi Atsama7, Michishii Tsakano9, Tatsuya Kasaama9, Shunichi Shiowaza3, Yoshiya Tanaka9, Hisashi Yamanaka7 and Tsutomu Takeuchi2.

1Hokkaido University Graduate School of Medicine, 2Keio University, 3Kobe University Hospital, 4Kumamoto Orthopaedic Hospital, 5Sasebo Chao Hospital, 6Showa University School of Medicine, 7Tokyo Women’s Medical University Medical Center, 8University of Occupational and Environmental Health, 9Yokohama Minami Kyoai Hospital, 10Zenjinkai Shinmin-No-Mori Hospital

Background: The radiographic superiority of the combination of methotrexate (MTX) to its discontinuation at the commencement of etanercept (ETN) in patients with active rheumatoid arthritis (RA) despite MTX therapy has not been clarified.

Objectives: An important aim of the JESMR study is to compare the radiographic efficacy of continuation versus discontinuation of MTX at the commencement of ETN for two years in patients with active RA despite MTX therapy.

Methods: In total, 151 patients with active RA despite treatment with MTX were randomized to either ETN 25 mg twice a week with 6–8 mg/week of MTX (the E+M group), or ETN alone (the E group). The radiographic progression was assessed by van der Heijde-modified Sharp score at baseline, weeks 24, 52 and 104. The last observation carried forward and linear imputation were used for the analysis of clinical and radiographic efficacy, respectively, for missing data.

Results: Demographic and clinical features between groups at baseline were similar. The cumulative probability plot of ACR-N at week 104 clearly demonstrated the superior response in the E+M group to that in the E group. The ACR 20, 50 and 70 response rates at week 52 were 82.2%, 68.5% and 46.6%, respectively, in the E+M group, all of which were significantly greater than 59.4% (p=0.003), 39.1% (p=0.001) and 23.2% (p=0.005), respectively, in the E group. The mean progression in total score (ΔTSS) tended to be smaller in the E+M group than in the E group (1.2 versus 6.6, p=0.09), and a significant difference was observed in the erosion score change at week 104 (~0.5 versus ~3.1, respectively, p=0.045). Furthermore, ACR-N < 50 predicted a risk for radiographic progression only in the E group.

Conclusion: The continuation of MTX at the commencement of ETN therapy is clinically and radiographically beneficial even in RA patients who had shown an inappropriate response to MTX.

Disclosure: H. Kameda: Pfizer Inc, 8; K. Kanbe: Pfizer Inc, 8; E. Sato: None; Y. Ueki: None; K. Saitoh: None; S. Nagaoka: Pfizer Inc, 2, 8; T. Hidaka: Pfizer Inc, 8; T. Atsumi: Pfizer Inc, 2; M. Tsukano: Pfizer Inc, 2, 8; T. Kasaama: Pfizer Inc, 2, 8; S. Shiowaza: Pfizer Inc, 2; Y. Tanaka: Pfizer Inc, 8; H. Yamanaka: Pfizer Inc, 2; T. Takeuchi: Pfizer Inc, 2, 8.

1813

Etanercept Normalizes Systemic Bone Metabolism in Rheumatoid Arthritis Patients. Won Park2, Mie Jin Lim3, Seong Ryal Kwon1, Ji Yeol Yoon1, Chang Gi Moon1 and Go Eun Ju1.

1Inha University Hospital, Incheon, Republic of Korea, 2Inha University Hospital, Choong-Gu Incheon, Korea, Republic of Korea

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease accompanied by bone loss. Etanercept is soluble TNF-α receptor which is effective in suppressing RA activity.

Objective: Our aim is to assess bone metabolism in TNF naïve RA patients and to figure out effects of etanercept on bone turnover markers and inflammatory mediators.

Methods: Twenty-one RA patients (19 women and 2 men; age 46.29 ± 11.6 years) were included. They were required to be active RA, thus meeting the criteria of DAS28 ≥ 3.2 and either ESR ≥ 28 mm/hr or CRP ≥ 2.0 mg/dL and morning stiffness ≥ 45 minutes.

Results: Venous blood was drawn at baseline in both groups and at week 14–16 after etanercept use, both serum CTX and sclerostin markedly increased (Table 1). Furthermore, ACR-N < 50 predicted a risk for radiographic progression only in the E group.

Table 1. Bone metabolism in TNF naïve RA patients and changes observed after etanercept use

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 14–16 after etanercept use</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (mm/hr)</td>
<td>39 ± 31.2</td>
<td>26 ± 25</td>
<td>0.013</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.98 ± 0.866</td>
<td>0.43 ± 1.118</td>
<td>0.013</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>3.58 ± 3.371</td>
<td>0.77 ± 0.726</td>
<td>0.001</td>
</tr>
<tr>
<td>OPG (pmol/L)</td>
<td>2.36 ± 1.081</td>
<td>2.2 ± 0.786</td>
<td>0.619</td>
</tr>
<tr>
<td>BSAP (U/L)</td>
<td>20 ± 6.97</td>
<td>20.3 ± 7.45</td>
<td>0.887</td>
</tr>
<tr>
<td>RANKL (pmol/L)</td>
<td>0.25 ± 0.37</td>
<td>0.22 ± 0.422</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Table 2. Bone turnover markers and inflammatory mediators after etanercept administration in RA patients

<table>
<thead>
<tr>
<th>Age and sex matched control</th>
<th>RA patients baseline</th>
<th>Intervention</th>
<th>Week 14–16</th>
<th>p-value</th>
<th>Assessment</th>
<th>PBO</th>
<th>GLM 50 mg</th>
<th>GLM 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (control vs. RA patients baseline)</td>
<td>(control vs. RA patients baseline)</td>
<td>vs. etanercept</td>
<td>(control vs. RA patients baseline)</td>
<td>of</td>
<td>week 14–16</td>
<td>(control vs. RA patients baseline)</td>
<td>(control vs. RA patients baseline)</td>
<td>(control vs. RA patients baseline)</td>
</tr>
<tr>
<td>Sclerostin (pg/mL)</td>
<td>2.2 ± 1.61</td>
<td>1.63 ± 2.26</td>
<td>0.03</td>
<td>2.95 ± 4.18</td>
<td>0.046</td>
<td>20 (19.0)</td>
<td>51 (50.5)*</td>
<td>60 (58.8%)*</td>
</tr>
<tr>
<td>Serum CTX (ng/mL)</td>
<td>0.38 ± 0.18</td>
<td>0.28 ± 0.13</td>
<td>0.114</td>
<td>0.34 ± 0.17</td>
<td>0.048</td>
<td>26 (27.7%)</td>
<td>69 (71.1%)*</td>
<td>74 (74.0%)*</td>
</tr>
</tbody>
</table>

Conclusion: Our study showed lower level of serum CTX and sclerostin in RA patients than in control group, which suggested slow bone resorption rate coupled with low bone production. However after etanercept use, bone turnover markers rose while inflammation was decreasing. Therefore we conclude that etanercept stimulates depressed bone metabolism in RA patients as it suppresses inflammation.

Disclosure: W. Park: None; M. J. Lim: None; S. B. Kwon: None; J. Y. Yoon: None; C. G. Moon: None; E. G. Ju: None.

1814
cantly inhibited progression of structural damage compared with PBO. Injection site reactions were mild and not increased compared with PBO. GLM monotherapy was well-tolerated with safety profile similar to other anti-TNF agents.

Table: Efficacy at Wk 14 and Wk 24

<table>
<thead>
<tr>
<th>Assessment</th>
<th>PBO</th>
<th>GLM 50 mg</th>
<th>GLM 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated</td>
<td>105</td>
<td>101</td>
<td>102</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>ACR 20 at Wk 14</td>
<td>20 (19.0)</td>
<td>51 (50.5)*</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>Wk 14</td>
<td>ACR 50</td>
<td>6 (5.7%)</td>
</tr>
<tr>
<td></td>
<td>ACR 70</td>
<td>1 (1.0%)</td>
<td>13 (12.9%)*</td>
</tr>
<tr>
<td></td>
<td>DAS28 (ESR) moderate responders</td>
<td>26 (27.7%)</td>
<td>69 (71.1%)*</td>
</tr>
<tr>
<td></td>
<td>Improvement from baseline in HAQ (mean [SD])</td>
<td>-0.042 (0.546)</td>
<td>0.255 (0.507)*</td>
</tr>
<tr>
<td></td>
<td>Median (IQR) range</td>
<td>(-1.88, 1.75)</td>
<td>(-1.88, 1.38)</td>
</tr>
<tr>
<td>Wk 24</td>
<td>Change from baseline in vDHS (TSS)</td>
<td>2.26 (0.046)</td>
<td>2.13 (10.42)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR) range</td>
<td>(-2.5, 10.25)</td>
<td>0.00 (0.0, 0.50)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.0043</td>
<td>0.0832</td>
</tr>
</tbody>
</table>

Conclusion: ACR 20 at Wk 14 was significantly better than PBO in improving signs and symptoms of RA and physical function (Table). At wk 24, the GLM 100mg groups were significantly better than PBO in improving signs and symptoms of RA and physical function (Table). At wk 24, the GLM 100mg groups were significantly better than PBO in improving signs and symptoms of RA and physical function (Table).
Objective: To assess the efficacy and safety of golimumab (GLM) in Japanese pts with active RA despite MTX therapy.

Methods: In this multicenter, randomized, double-blind, placebo-controlled study, pts with active RA despite MTX therapy with ≥4 swollen and ≥4 tender joints (SJC/TJC) were randomized to receive subcutaneous injections of PBO, GLM 50mg, and GLM100mg administered q4wks. All pts received MTX 6-8 mg orally/wk. Pts with <20% improvement in SJC/TJC entered early escape at wk16 in a blinded manner, as follows: PBO → GLM50mg+MTX, GLM50mg+MTX → GLM100mg+MTX. Pts receiving GLM100mg+MTX remained on the same dose. The primary endpoint was the proportion of pts achieving ACR20 at wk14. Secondary endpoints were the proportion of pts achieving ACR20 at wk24, ACR50, ACR70 response at wks14 and 24, and change from baseline in DAS28 (ESR) scores and improvement in Health Assessment Questionnaire (HAQ) at wk4 and 24, and change from baseline in Full Analysis Set (modified Intent-To-Treat) at all pts receiving one dose of study treatment included population.

The results of the non-parametric analysis using van der Waerden method is reported.

Results: 261 pts received treatment (88 PBO+MTX, 86 GLM50mg+MTX, and 87 GLM100mg+MTX). Treatment groups were balanced for baseline demographic and disease characteristics [mean(SD) values for all pts: CRP 1.86(2.29) mg/dL, ESR 44.3(29.94) mm/hr, SJC 11.56(60), TJC 13.17(9.2), DAS28 (ESR) 5.52(1.05), vdH-S/TSS 55.10 (58.09)]. Both doses of GLM+MTX were significantly better than PBO+MTX in improving signs and symptoms/physical function and in inhibiting radiographic progression (Table). Through wk24, 80.7%, 81.4%, and 82.8% of pts had ≥1 adverse event (AE) in the PBO + MTX, GLM 50mg + MTX, and GLM 100mg + MTX groups, respectively. Serious AEs occurred in 1.1%, 2.3%, and 3.4% of pts, respectively. Serious infections occurred in 0.0%, 0.0%, and 1.1% of pts, in the PBO + MTX, GLM50mg+MTX, and GLM100mg+MTX groups respectively. Injection site reactions occurred in 9.1%, 9.3%, and 11.5% of pts, respectively. One pt in the GLM50mg+MTX group had a bone neoplasm (thoracic vertebra tumor; hemangoendothelioma, of low malignancy potential). There were no reports of tuberculosis or deaths.

Conclusions: Both GLM + MTX doses had significantly greater improvement in signs and symptoms and physical function, as well as significantly better inhibition of progression of structural damage compared with PBO+MTX in pts with RA. Injection site reactions were mild and not increased compared with PBO+MTX. GLM+MTX was well-tolerated with safety profile similar to other anti-TNF agents.

Table: Efficacy results through Wk 14 and Wk 24

<table>
<thead>
<tr>
<th>Assessment</th>
<th>PBO + MTX</th>
<th>GLM 50 mg</th>
<th>GLM 100 mg</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts treated (n)</td>
<td>88</td>
<td>86</td>
<td>87</td>
<td>173</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>ACR 20</td>
<td>ACR 20</td>
<td>ACR 20</td>
<td>ACR 20</td>
</tr>
<tr>
<td>wk 14</td>
<td>24 (27.3%)</td>
<td>62 (72.1*)</td>
<td>55 (67.4*)</td>
<td>127 (73.6*)</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>ACR 50</td>
<td>ACR 50</td>
<td>ACR 50</td>
<td>ACR 50</td>
</tr>
<tr>
<td>wk 4</td>
<td>8 (9.1%)</td>
<td>37 (43.0*)</td>
<td>36 (41.9*)</td>
<td>78 (45.1*)</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>DAS28 (ESR)</td>
<td>DAS28 (ESR)</td>
<td>DAS28 (ESR)</td>
<td>DAS28 (ESR)</td>
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<tr>
<td>Moderate response</td>
<td>32 (37.8%)</td>
<td>66 (78.5*)</td>
<td>71 (85.5%)</td>
<td>157 (87.2*)</td>
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</table>

Methods: Circulating DCs, including myeloid DCs (mDCs) and plasmacytoid DCs (pDCs), and different T-cell subsets were longitudinally evaluated (M0, M3 and M6) by flow cytometry. Wilcoxon’s signed-rank test was used for the analyses of matched pairs. Correlation between cells numbers and activity markers were assessed using Spearman’s rank. P < 0.05 was considered statistically significant.

Results: Seventeen RA patients with inadequate response or intolerance to TNF-alpha blockers. Emile Shipley1, Christophe Richez2, Thomas Barnetche3, Cecile Contin-Bordes3, Patrick Blanco4 and Thierry Schaeverbeke1. Hôpital Pellegrin, Bordeaux, France, Metropolitan,1 Hôpital Pellegrin, France, Metropolitan.

Objectives: To assess the variation of circulating dendritic cells (DCs) and T cell subsets, including regulatory T cells (Treg), in rheumatoid arthritis (RA) patients with inadequate response (IR) or intolerance to TNF blockers receiving abatacept and methotrexate for at least 6 months. To evaluate whether these variations correlate with EULAR response criteria and to identify predictive factors of response to abatacept.

Results: Twenty-six RA patients with inadequate response or intolerance to TNF blockers initiated with abatacept + MTX were assessed at baseline, 3 and 6 months. 86% were female. These patients had mean age 61 years, disease duration 13 years, DAS28 4.9 (+/-1.4) and CRP 1.4 mg/dl (+/- 0.7). 75% were rheumatoid factor positive and 62.5% were anti-CCP positive. RA patients were classified as either good or moderate EULAR responders (11pts, 65%) or non-responders (6pts, 35%) at 3 months. At baseline, no correlation was found in the total population between disease activity and levels of different immune cells, whereas in the responders group, DAS28 negatively correlated with the absolute number of circulating T cells (r = -0.90, p = 0.0003, CD4+ T cells (r = -0.88, p = 0.0008, Tregs (r = -0.68, p = 0.03), mDCs (r = -0.79, p = 0.006) and activated mDCs (r = -0.82, p = 0.02).

Between M0 and M3, blood CD4+ T cells (959 +/- 362 x10^3 cells/ml at M0 vs. 743 +/- 523 x10^3 cells/ml at M3, p=0.04) and plasmacytoid DCs (3177 +/- 1036 x10^3 cells/ml at M0 vs. 2621 cells/ml at M3, p=0.02) levels increased substantially in RA patients treated with abatacept. Interestingly, EULAR responders showed a significant increase at M3 in their numbers of circulating CD3+ T cells (865 +/- 336 x10^3 cells/ml at M0 vs. 1045 +/- 428 x10^3 cells/ml at M3, p=0.02) and myeloid DCs (3177 +/- 2621 cells/ml at M0 vs. 9867 +/- 1145 cells/ml at M3, p=0.03).

Conclusion: Our data suggest that patients with active RA and responding to abatacept are characterized by a decrease at baseline in circulating DCs and T cells including Tregs, which are probably recruited in the target tissues. Efficient abatacept therapy restores levels of these immune cells. Inclusion of additional patients in this ongoing study and analysis of immune cells levels at M3 and M6 should precisely the impact of abatacept on DCs/T cells and eventually define predictive factors.


Disclosure: E. Shipley: None; C. Richez: Wyeth Pharmaceuticals, 5; T. Barnetche: None; C. Contin-Bordes: None; P. Blanco: None; T. Schaeeverbeke: Abbott Laboratoires, 5, Bristol-Myers Squibb, 2, 5, Merck Pharmaceuticals, 5, Pfizer Inc, 5, Roche, 5.
Impact of Abatacept on Synovitis and Structural Damage in Methotrexate (MTX)—Inadequate Responders with Active Rheumatoid Arthritis (RA): A Randomized, Controlled Magnetic Resonance Imaging (MRI) Exploratory Study

Philip G. Conaghan1, Patrick Durez2, Riske Ahlen3, Gerd Burmester4, Paul P. Tak5, Lars Klareskog6, Corine Gailliez7, Manuela Le Bars2, Xianhuang Zhou1 and Charles Peterfy7.1 Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, 2Bristol-Myers Squibb, Rueil-Malmaison, France, 3Bristol-Myers Squibb, Princeton, NJ, 4Charité-Universitätsmedizin Berlin, Berlin, Germany, 5Karolinska University Hospital, Stockholm, Sweden, 6Schlosspark-Klinik, University Medicine Berlin, Germany, 7Sparc Science LLC, San Francisco, CA. 8Université Catholique de Louvain, Brussels, Belgium, 9University of Leeds, Leeds, UK

Background: X-ray can detect erosions in established RA, but is less sensitive for early changes. MRI has the potential to study synovial inflammation and measure bone damage at an earlier stage and with greater sensitivity than X-ray.

Objective: Evaluate the impact of abatacept or placebo, + MTX, on MRI changes in wrist synovitis, osteitis and bone erosion in patients with RA and an inadequate response to MTX.

Methods: In this double-blind, randomized, Phase Illb study of abatacept (~10 mg/kg) versus placebo, + MTX, patients had active RA despite MTX, defined as either DAS28 (CRP) >3.2, or ≥8 tender and swollen joints and CRP above the upper limit of normal. Patients had clinically detectable synovitis of ≥1 wrist, and had ≥1 X-ray erosion or were positive for anti-CCP or RF. Patients had 1.5T MRI (coronal fat-suppressed 3D gradient-echo ± IV gadolinium-contrast) of one wrist at baseline and Month 4. The primary endpoint was mean change at Month 4 in MRI synovitis score (OMERACT-RAMRIS method). Wrist and hand osteitis and erosion scores were secondary endpoints. Exploratory efficacy analyses included DAS28 (CRP), LDAS (<3.2) and remission (<2.6). Comparisons in wrist synovitis change between groups were based on non-parametric ANCOVA. Efficacy was reported for the intent-to-treat population. Safety was reported for patients who received ≥1 abatacept dose.

Results: Of 27 and 23 patients randomized to abatacept + MTX or placebo + MTX, 26 and 23 completed 4 months. Baseline characteristics were generally similar between groups: mean (SD) RA duration was 25.7 (18.0) and 22.3 (15.3) months, and DAS28 scores were 5.3 (1.1) and 5.4 (1.0) for abatacept and placebo, respectively. However, 55.6 and 48.1% of patients in the abatacept and placebo group were RF and anti-CCP positive, respectively. Mean change from baseline to Month 4 in synovitis score was −0.44 for abatacept and 0.42 for placebo (p=0.015). For osteitis and erosion scores, mean changes were −1.94 and 0.45 for abatacept versus 1.54 and 0.95 for placebo (treatment difference [95% CI]: −0.50 [−1.77, 0.76] and −3.48 [−6.00, −0.96], respectively). The percentage of patients with newly involved joints at Month 4, by synovitis, osteitis and erosion scores was 8, 28 and 20% for abatacept versus 13, 30 and 30% for placebo. At Month 4, mean (95% CI) change from baseline in DAS28 was −1.68 (−2.15, −1.21) for abatacept and −0.55 (−0.95, −0.16) for placebo. Percentages (95% CI) of patients with LDAS and remission were 50.0 (30.8, 69.2) and 15.4% (1.5, 29.3) in the abatacept and 13.6 (0.0, 28.0) and 0.0% (0.0, 0.0) in the placebo group. Safety events were similar to previously reported abatacept trials.

Conclusions: The sensitivity of MRI is again demonstrated, in that even with small patient numbers and wrist-only assessments, abatacept + MTX treatment was associated with reductions in osteitis and erosion scores, and a trend toward reduced MRI synovitis scores versus placebo + MTX. The beneficial clinical outcomes were consistent with those in other large-scale abatacept clinical trials.

References:

Disclosure: P. G. Conaghan: AstraZeneca, 8, Bioiberica, 8, Bristol-Myers Squibb, 8, Centocor, Inc., 8, Merck Pharmaceuticals, 8, Novartis Pharmaceuticals Corporation, 8, Pfizer Inc, 8, 2, 8, Roche, 8, 8, Schering-Plough, 8, Wyeth Pharmaceuticals, 8, R. Allen: Bristol-Myers Squibb, 2, 8, G. Burmester: Bristol-Myers Squibb, 2, 8, P. P. Tak: Bristol-Myers Squibb, 2, 8, L. Klareskog: None; C. Gailliez: Bristol-Myers Squibb, 3, M. Le Bars: Bristol-Myers Squibb, 1; Z. Zhou: Bristol-Myers Squibb, 3; C. Peterfy: Sparc Sciences LLC, 3.

1818

Key Pharmacological Parameters Support Monthly Dosing for Golimumab (GLM)—Comparing Efficacy and Safety inPatients with Active Rheumatoid Arthritis (RA)

Hannah U. Rahman1, Ann Cai, Elyn Lacy, Jonathan Kay2, Ed C. Keystone3, Eric L. Matteson3, Chunhua Hu1, Honghui Zhou1 and Dave Shealy1.1Centocor Research and Development, Inc., 2Centocor Research and Development, Inc./University of Pennsylvania School of Medicine, Malvern, PA, 3Mayo Clinic, Rochester, MN, 4UMass Memorial Medical Center, Worcester, MA, 5University of Toronto, Toronto, ON, Canada

Purpose: To compare the molecular characteristics and clinical pharmacology of SC golimumab (GLM) and adalimumab (ADA), two human anti-TNFα antibodies with similar half-lives but different dosing frequencies.

Methods: Affinity to soluble TNFα was measured by surface plasmon resonance. Evaluation of in vitro neutralization efficiency (NE) was accomplished using bioassays for TNFα-induced cytotoxicity on a human rhabdomyosarcoma cell line (KYM-ID4) and E-selectin expression by human primary umbilical vein endothelial cells. A PK/PD model was developed using serum GLM concentrations (conc) and ACR20/50/70 results from GO-FORWARD (Ph 3 trial) using the MTX + PBO, MTX + GLM 50 mg, and MTX + GLM 100 mg grps. Mixed-effect logistic regression was used with a latent variable approach, in conjunction with an inhibitory indirect effect model, to model ACR20/50/70 results simultaneously. The PK/PD model linked time profiles of GLM conc and ACR20/50/70. Results from a Ph 2 dose-ranging study evaluating efficacy of GLM 50 or 100 mg SC q2 or q4 wk in pts with active RA despite MTX are presented. The GLM 50 and 100 mg q2 wk grps are combined into a (q2 wk) grp; GLM 50 and 100 mg q4 wk grps are combined into another (q4 wk) grp to assess the relative clinical efficacy of q2 and q4 wk dosing.

Conclusions: Compared with ADA, GLM demonstrates greater affinity to TNFα and capacity to neutralize TNFα, in vitro assays, and lower EC50 in PK/PD modeling. These data suggest that similar conc of GLM would maintain efficacy for longer duration than those of ADA and allow less frequent dosing, despite similar half-lives. A Ph2 dose ranging study also supports monthly dosing of GLM by demonstrating comparable clinical efficacy with q2 wk and q4 wk dosing.

LITHE: Tocilizumab (TCZ) Inhibits Radiographic Progression and Improves Physical Function in Rheumatoid Arthritis (RA) Patients (pts) at 3 Years with Maintenance of Clinical Efficacy over Time. Joel M. Kremer1, Daniel E. Furst2, Ruben Burgos-Vargas3, Jean Dudler2, Christopher M. Meinerz4, Emma Vernon5 and Roy M. Fleischmann6. 1Albany Medical College, Albany, NY, 2Hopital Orthopédique, Epalinges, Switzerland, 3Hospital General de México and Universidad Nacional Autónoma de México, Mexico City, México, Mexico, 4Metroplex Clinical Research Center, Dallas, TX, 5Roche, Welwyn, United Kingdom, 6UCLA Medical Center, Los Angeles, CA

Purpose: To report 3-yr data from the extension of a 3-arm, randomized, double-blind, placebo-controlled, phase 3 trial of TCZ in pts with moderate to severe RA who were MTX inadequate responders.

Methods: A total of 1190 pts were randomly assigned (1:1:1) to receive TCZ (4 mg/kg [TCZ4] or 8 mg/kg [TCZ8]) or placebo (control) every 4 wks plus MTX (10-25 mg/wk). After wk 52, pts switched to open-label treatment with TCZ8, an option chosen by the majority of pts (62%-68% across all 3 treatment groups). Radiographs of hands and feet were analyzed by Genant-modified Total Sharp Score (GmTSS) for any pt who had a baseline, wk 52, wk 104, and at least 1 post-wk 104 assessment. If a patient had a post-wk 104 but not a wk 152 value, linear extrapolation was used to impute to wk 152. Signs and symptoms data and safety data are reported as pooled data (All TCZ) in all pts who received at least 1 dose of TCZ; data are presented from the first dose of TCZ to August 28, 2009 (mean duration, 2.43 yrs). LOCF was used for missing tender and swollen joint counts; no imputation was used for missing HAQ score, CRP, ESR, and VAS assessments.

Results: The radiographic population consisted of 704 pts, accounting for approximately 80% of the pts who ultimately would have a post-wk 104 assessments: 244, 241, and 219 pts had been initially assigned to TCZ8, TCZ4, and control, respectively. The majority of pts had received open-label TCZ8 for at least 2 of 3 yrs of the study; 9% of placebo and 19% of TCZ4 pts had remained on original blinded treatment at 1 yr. The mean change in GmTSS from baseline to yr 3 was 60% lower in pts who were randomly assigned to TCZ compared with those initially receiving control, demonstrating inhibition of joint damage by TCZ (Table). The majority of radiographic progression in pts randomly assigned to control was observed in the first yr before switching to TCZ. By yr 3, no radiographic progression was observed in a greater proportion of pts initially assigned to TCZ8 and TCZ4 than to control.

The All TCZ group included 1149 pts with 2790 pt-yrs (PY) of exposure. ACR response and DAS28 remission rates were high, demonstrating continued clinical benefit (Table). At wk 104, 34% (257/768) of pts had HAQ scores <0.5; the proportion of pts with HAQ scores <0.5 was maintained through wk 152.

Overall rates/100 PY of serious adverse events and serious infections were 11.0 and 3.2; overall rates/100 PY of deaths and deaths from infections were 0.39 and 0.14. Malignancies occurred at an overall rate of 0.7/100 PY, including solid cancers (0.6/100 PY) and nonmelanoma skin cancers (n = 1; 0.01/100 PY).

<table>
<thead>
<tr>
<th>Table. Outcomes at Week 152</th>
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<tr>
<td><strong>GmTSS</strong></td>
</tr>
<tr>
<td>Mean (SD) change from baseline</td>
</tr>
<tr>
<td>Pts with no progression (GmTSS change from baseline ≤0), % (n)</td>
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<tr>
<td>Signs and Symptoms</td>
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<tr>
<td>ACR20, % (n/n)</td>
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<tr>
<td>ACR50, % (n/n)</td>
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<tr>
<td>ACR70, % (n/n)</td>
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<tr>
<td>DAS28 remission, % (n/n)</td>
</tr>
<tr>
<td>TJC and SJC= 0, % (n/n)</td>
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<tr>
<td>HAQ &lt;0.5, % (n/n)</td>
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<tr>
<td>n/n=no, patients achieving end point/no, patients reaching time point with valid assessments.</td>
</tr>
<tr>
<td>a,b,c p &lt;0.0001 vs control.</td>
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<tr>
<td>d e,f,p =0.0002 vs control.</td>
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<tr>
<td>g,h,j p calculated by logistic regression analysis adjusted for region.</td>
</tr>
</tbody>
</table>

Conclusions: During long-term treatment, TCZ + MTX continued to inhibit radiographic progression. Improvements in physical function and other clinical benefits were maintained at high levels. The safety profile did not change compared with the 2-yr analysis.

Disclosure: J. M. Kremer: Genentech, 2, 5, 8, Roche, 2, 5; D. E. Furst: Abbott Laboratories, 2, 5, Actelion Pharmaceuticals US, 2, 5, Amgen Inc., 2, Amgen, 2, 5, Biogen Idec, 5, Bristol-Myers Squibb, 2, 5, Centocor, Inc., 5, Corona, 3, Genentech, 2, 5, Gilead Sciences, Inc., 2, Gilead, 2, 5, GlaxoSmithKline, 2, 5, IBCU Medical Center, Los Angeles, CA, 7University Clinic General de México and Universidad Nacional Autónoma de México, Mexico City, México, Mexico, 8Metroplex Clinical Research Center, Dallas, TX, 9Roche, Welwyn, United Kingdom, 4UCLA Medical Center, Los Angeles, CA

1820

Long-Term Efficacy of Tocilizumab (TCZ) in Patients (Pts) with Rheumatoid Arthritis (RA) Treated up to 3.7 Years. Majed Khrasil1, Rieke Allen1, Juan J. Gomez-Reino2, Warren Rizzo3, Joy Scheichtman3, Andre Kahan1, Emma Vernon5, Monet Taylor4 and Josef Smolen1.

1Advanced Arthritis Care, Scottsdale, AZ, 2Hospital Clinico U. de Santiago, Santiago, Spain, 3Memorial University of Newfoundland, St. John’s, NL, Canada, 4Paris Descartes University, Paris, France, 5Roche, Welwyn, UK, 6SunValley Arthritis Center, Peoria, AZ, 7University Clinic for Internal Medicine, Vienna, Austria, 8University of Berlin, Berlin, Germany

Background: Efficacy and safety of TCZ have been shown in RA pts in phase 3 trials for up to 2 y. Efficacy data from ongoing extension studies for up to 3.7 y (wk 192) are presented for pts treated with TCZ ≤ MTX/other DMARDs.

Methods: This analysis was in 2 populations from long-term extensions (GROWTH95, GROWTH96, open-label phase of LITHE) of phase 3 trials. One population comprised pts who were previous inadequate responders to DMARDs (DMARD-IR: OPTION, TOWARD, LITHE), and the other comprised pts who were never exposed to or who had never failed MTX (AMBITION). Pts received at least 1 dose of TCZ + DMARDs/MTX in the phase 3 or extension trials except pts in AMBITION, who received TCZ monotherapy. Pts from AMBITION with <50% reduction from baseline in tender and swollen joint counts (TJC, SJC) could receive DMARDs/MTX in the extension. Outcomes were assessed every 4 wks in the original studies and, in the extensions, every 8 (LITHE) or 12 (GROWTH95/96) wks from initial TCZ exposure to Aug 28, 2009; data were assigned to the nearest 12-wk point for pooling. Numbers of pts with assessments decreased over time because some pts had not yet reached later assessments or withdrew. Results include pts who had assessments at each visit; no imputation was performed for missing data. Data were included until <10% of the baseline pt number was reached.

Results: The analysis was in 2904 DMARD-IR pts and 618 pts who were never exposed to or had never failed MTX. By the cutoff date, 27.7% of DMARD-IR pts and 24.6% of never exposed/never failed MTX pts had withdrawn. In DMARD-IR pts, TCZ efficacy was shown by continuously increasing absolute numbers achieving ACR50, LDA (DAS28 ≤3.2), and DAS28 remission (DAS28 ≤2.6) through wk 96 and ACR70 through wk 120 (Table). In never exposed/never failed MTX pts, efficacy was shown by sustained absolute numbers achieving ACR50/70, LDA, and DAS28 remission to wk 96 (Table). While proportions who achieved ACR50/70, LDA, and DAS28 remission were maintained to wks 168 and 192, data must be interpreted with caution due to lower absolute numbers reaching these visits in the extensions (Table). By wk 144, 20% (396/1980) of assessed pts had achieved the major clinical response of ACR70 maintained for 24 consecutive wks. At wk 120, 52.3% (1118/2139) and 38.4% (821/2139) of assessed DMARD-IR pts and 59.5% (278/467) and 38.3% (179/467) of assessed never exposed/never failed MTX pts, respectively, had ≤1 SJC and ≤1 TJC; 38.4% (772/2008) of DMARD-IR pts and 48.4% (216/446) of never exposed/never failed MTX pts had HAQ-DI scores ≤0.5.

S760
Table.

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<th>72</th>
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Never exposed or to failed MIK [n=618], % (n/n)

ACR90 NA 40 44 53 54 56 56 56 62 N/A
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1821

Mechanism of Inhibition of Joint Destruction by Rituximab in Rheumatoid Arthritis. Maria J. H. Boumans2, Rogier M. Thurlings3, Koen Vos4, Danielle M. Gerlag5 and Paul P. Tak1. 1Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, 2Academic Medical Center/University of Amsterdam, Amsterdam, Noord-Holland, The Netherlands, 3Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, 4Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, 5Millennium Pharmaceuticals, Inc, Department of Research and Development, Cambridge, MA

Methods: We used a novel technique to analyze the migration of labeled autologous monocytes using scintigraphy. CD14+ monocytes were isolated from patients with RA, using a positive selection procedure with magnetic-activated cell sorting, and labeled with 99mTc-HMPAO. Scintigraphic scans were made 1 hour, 2 hours and 3 hours after re-infusion. This procedure was performed at three time points with a two weeks interval. Adalimumab treatment was started after the second set of scans.

Results: Re-infusion lead to a stable number of monocytes in the joint of interest after 1, 2 and 3 hours on all days. Already 14 days after the start of treatment with adalimumab a significant decrease in DAS28 was shown. There was no significant change in monocyte influx 1, 2 and 3 hours after re-infusion from day -1 to day 1, which was before the start of adalimumab treatment (p=0.33, p=0.67, p=0.21, respectively). Of interest, the influx of monocytes did not decrease after re-infusion of monocytes comparing day 14 to baseline, indicating that adalimumab treatment did not affect the influx of monocytes early after initiation of treatment.

Conclusions: The results of this mechanistic study indicate that CD14+ monocyte influx into the synovium is not altered two weeks after the start of adalimumab treatment. As previous studies showed a rapid decrease in macrophage infiltration after anti-TNF-α antibody therapy, which could not be explained by increased cell death, this points to an important role for enhanced efflux of inflammatory cells from the synovium. These data are in line with the recent observation that monocytes migrate towards the inflamed RA synovium at a slow macrophage-replacement rate and with the recently shown increase in lymphatic vessels in the synovium after TNF-α blockade.

Disclosure: M. Herenius: None; R. Thurlings: None; C. Wijbrands: None; R. Bennink: None; S. Dohmen: None; C. Voerman: None; D. Wouters: None; E. Izmailova: Millennium Pharmaceuticals, 3; B. Gerlag: None; B. van Eck-Smit: None; P. P. Tak: None.

1822

Monocyte Migration to the Synovium in Rheumatoid Arthritis Patients Treated with Adalimumab. Marieke Herenius1, Roger Thurlings2, Carla Wijbrands3, Roelof Bennink3, Sergei Dohmen3, Carlijn Voerman3, Diana Wouters4, Elena Izmailova5, Danielle Gerlag6, Berthe van Eck-Smit7 and Paul P. Tak1. 1Department of Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, 2Department of Immunopathology, Sanquin Research, Amsterdam, Noord Holland, The Netherlands, 3Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, 4Division of Nuclear Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, 5Cardiovascular Laboratory, Department of Experimental Immunohematology, Sanquin Research, Amsterdam, The Netherlands, 6Millennium Pharmaceuticals, Inc, Department of Research and Development, Cambridge, MA

Background: The mechanism of action of treatment with tumor necrosis factor–α (TNF-α) blockers in rheumatoid arthritis (RA) is still not completely understood. Since the recognition of synovial tissue as the primary site of inflammation, studying the synovium has provided insight into the pathogenesis of the disease and the mechanism of action of different therapies. Anti-TNF antibody treatment has been shown to result in marked reduction of synovial inflammation in both RA and psoriatic arthritis early after initiation of therapy. This early reduction in synovial inflammation could not be explained by apoptosis induction at the site of inflammation. This leaves either reduced cell influx or enhanced cell efflux to explain this process. Therefore, the aim of this study is to test if adalimumab treatment could affect the influx of monocytes into the synovium.

Methods: We used a novel technique to analyze the migration of labeled autologous monocytes using scintigraphy. CD14+ monocytes were isolated from patients with RA, using a positive selection procedure with magnetic-activated cell sorting, and labeled with 99mTc-HMPAO. Scintigraphic scans were made 1 hour, 2 hours and 3 hours after re-infusion. This procedure was performed at three time points with a two weeks interval. Adalimumab treatment was started after the second set of scans.

Results: Re-infusion lead to a stable number of monocytes in the joint of interest after 1, 2 and 3 hours on all days. Already 14 days after the start of treatment with adalimumab a significant decrease in DAS28 was shown. There was no significant change in monocyte influx 1, 2 and 3 hours after re-infusion from day -1 to day 1, which was before the start of adalimumab treatment (p=0.33, p=0.67, p=0.21, respectively). Of interest, the influx of monocytes did not decrease after re-infusion of monocytes comparing day 14 to baseline, indicating that adalimumab treatment did not affect the influx of monocytes early after initiation of treatment.

Conclusions: The results of this mechanistic study indicate that CD14+ monocyte influx into the synovium is not altered two weeks after the start of adalimumab treatment. As previous studies showed a rapid decrease in macrophage infiltration after anti-TNF-α antibody therapy, which could not be explained by increased cell death, this points to an important role for enhanced efflux of inflammatory cells from the synovium. These data are in line with the recent observation that monocytes migrate towards the inflamed RA synovium at a slow macrophage-replacement rate and with the recently shown increase in lymphatic vessels in the synovium after TNF-α blockade.

Disclosure: M. Herenius: None; R. Thurlings: None; C. Wijbrands: None; R. Bennink: None; S. Dohmen: None; C. Voerman: None; D. Wouters: None; E. Izmailova: Millennium Pharmaceuticals, 3; B. Gerlag: None; B. van Eck-Smit: None; P. P. Tak: None.
Purpose: In order to identify the baseline clinical parameters associated with remission in RA patients treated with anti-IL-6 receptor monoclonal, tocilizumab (TCZ), we attempt to analyze clinical, laboratory and radiographic date set of REACTION-2 study by multiple logistic regression analysis.

Patients and Methods: In REACTION-2 study, a total of 255 RA patients were treated with TCZ 8 mg/kg every four weeks in three major rheumatic centers as daily clinical practice. In the assessment of disease activity, DAS28-ESR score <2.6 was defined as clinical remission, and non-responder imputation was used for missing data. For joint damage, modified TSS ≤0.5 was defined as structural remission, and for functional disability, HAQ score ≤0.5 was defined as functional remission. The associations with each type of remission were analyzed by multiple logistic regression analysis. The last-observation-carried-forward method was used in each of the analyses.

Results: Baseline characteristics of 255 patients showed that the mean age was 59.1 ± 13.3 years, the mean duration of RA was 12.4 ± 11.1 years, Methotrexate was used by 55.6% of patients, with the mean dose 3.31 ± 4.8 mg/day, and the mean steroid dose was 3.9 mg/day. Although a large proportion of patients, 62.8%, had been previously treated with biologics, the mean DAS28-ESR was 5.72.

Logistic regression analysis of baseline clinical parameters and clinical remission at 52 weeks demonstrated that clinical remission was significantly associated with younger age, lower DAS28-ESR, lower HAQ score, higher MTX dose and lower steroid dose at baseline. Multiple regression analysis of these associations confirmed that all the above factors independently influenced the achievement of clinical remission.

Similarly, multiple regression analysis revealed that HAQ score at baseline independently influenced the achievement of structural remission, while logistic regression analysis identified two significant parameters such as HAQ score and steroid dose at baseline.

Finally, multiple regression analysis demonstrated that only HAQ score at baseline independently influenced the achievement of functional remission, while logistic regression analysis showed six significant parameters including age, duration of RA, DAS28-ESR, HAQ score, mTSS score and MTX dose at baseline.

Conclusions: In this analysis, we identified the baseline clinical parameters influencing the various types of remission at 52 weeks by treatment with TCZ in clinical practice. It appears that baseline HAQ score before TCZ treatment is an important factor that influences clinical, structural and functional remission.

Disclosure: T. Takeuchi: Chugai, 2, 5; Y. Tanaka: Chugai, 2, 5; K. Amano: Chugai, 2; E. Saito: None; M. Nawata: None; H. Nagasawa: None; D. Hoshi: None; K. Saito: None; S. Fukuyo: None; K. Hanami: None; T. Kurasawa: None; H. Kameda: None; H. Yamanaka: Chugai, 2, 5.

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Patients Not Responding to Etanercept Obtain Lower Trough Etanercept Concentrations Compared to Responding Patients.

Anna Janni2, Michael T. Nurmohamed1, Margreet M. Hart2, Ben A. Dijkmans3, Lucien Aarden2 and Gerrit Jan Wolbink1. 1Jan van Breemen Institute, Sanquin Research, 3VU Medical Center

Purpose: A substantial proportion of the patients with rheumatoid arthritis (RA) failed to respond on treatment with etanercept. Previous research has shown that etanercept appeared to be less immunogenic compared to adalimumab and infliximab. The goal of this study is to investigate the relationship between etanercept levels and clinical response in a large cohort of RA patients.

Methods: Between 2004 and 2008, 292 consecutive patients with active RA (DAS28 > 3.2) and a new etanercept prescription were included in an observational cohort at the Jan van Breemen Institute, Amsterdam. Clinical response variables and etanercept levels were collected at baseline and after 1, 4 and 6 months of etanercept treatment. Trough serum etanercept levels were measured by ELISA (Sanquin research, The Netherlands). Last observation carried forward (LOCF) data was used for patients who discontinued the treatment with etanercept before 28 weeks. Differences between EULAR responders and non responders were evaluated by using an independent t-test, confounding analyses were performed using multiple regression analysis.

Results: After 6 months of etanercept treatment 103 patients were good, 115 were moderate and 74 were non responders according to EULAR response criteria. Etanercept levels were undetectable at baseline (<0.001 mg/l). Patients with good EULAR response had significantly higher trough etanercept concentrations than EULAR non responders, p= 0.009 at 1 month and p=0.001 at both 4 and 6 months. To know, 3.40 (2.22 – 4.62) at 1 month, 3.98 (2.72 – 5.35) at 4 months and 3.78 (2.53 – 5.17) at 6 months in EULAR responders compared to 2.64 (1.20 – 3.89) at 1 month, 2.54 (1.12 – 3.94) at 4 months, and 2.80 (1.27 – 3.93) at 6 months in EULAR non responders. No antibodies were detected against etanercept.
Prevalence and Persistence of Low Infliximab Serum Trough Levels in RA Patients with Low Disease Activity in Daily Clinical Practice. Aatke van der Maass, Alfons A. Den Broeder, Frank H. J. van den Hoogen, Piet L. C. M. van Riel and Bart J. F. van den Bemt. Department of Immunopathology, Sanquin Research, Amsterdam, The Netherlands, Department of Pharmacy, St. Maartenskliniek, Nijmegen, The Netherlands, Department of Rheumatology, St. Maartenskliniek, Nijmegen, The Netherlands, Department of Rheumatology, St. Maartenskliniek, Nijmegen, The Netherlands, Department of Rheumatology, St. Radboud UMCN, Nijmegen, The Netherlands.

Treatment of RA with infliximab requires optimal dosing to balance maximum effect and minimal dose related side effects and costs. DAS driven dose de-escalation can be used in patients with low disease activity, but costs time and can lead to flaring. Since infliximab serum trough levels and presence of HACA’s (Human Anti-Chimeric Antibodies) demonstrated a correlation with clinical effect in cross-sectional studies, they could be used as predictors for successful de-escalation. There is however not much data on prevalence and persistence of serum trough levels and HACA’s in RA patients with low disease activity. This prospective observational study aims to study prevalence and longitudinal course of serum trough levels and HACA’s and their persistence within patients treated in daily clinical practice, focussing on patients with low disease activity.

Methods: All RA patients treated with infliximab at the Sint Maartenskliniek Nijmegen for at least 6 months were included and followed in a 1.5 year period. At every visit DAS28, serum trough levels and HACA’s were measured. Cross sectional analysis of the prevalence of low serum trough levels (<1.0 μg/ml) and/or HACA’s was done in all patients and in a subgroup with stable low DAS28 ≤3.2 for at least 3 consecutive visits. Persistence at 2 consecutive visits in patients with stable DAS28 and infliximab dosing was analysed by means of a Spearman correlation coefficient and Wilcoxon test for serum trough levels, and with kappa analysis for HACA’s presence.

Results: 147 RA patients were included, 65 and 40 patients had a DAS28 < 3.2 and 2.6 respectively. In 35% of the patients with a DAS28<2.6 and in 31% with a DAS28≤3.2 non-measurable/low serum trough levels were found. 30% was associated with presence of HACA’s (see table 1). The longitudinally analysis showed that, in patients with stable low DAS28, 38% had low to non measurable serum trough levels, with nearly 50% showing HACA’s. There was no statistical difference between trough levels at 2 consecutive visits in patients with stable DAS28 and infliximab dosing was analysed by means of a Spearman correlation coefficient and Wilcoxon test for serum trough levels, and with kappa analysis for HACA’s presence.

Discussion: Among patients with sustained low disease activity low to non measurable serum trough levels are prevalent both in cross sectional and longitudinal analyses. In patients with stable treatment and DAS28 there is a high persistence between two consecutive measurements of trough levels and HACA’s. Therefore, infliximab serum trough levels and HACA are promising candidates to be tested for their predictive value for successful dose de-escalation.

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Regulatory T Cells from Patients with Rheumatoid Arthritis Are Not Affected by Adalimumab and Etanercept. Thierry Lequerre, Céline Bouche, Marine Beuteux, Amand Roucheux, Ingrid Dedreux, Serge Jacquot, Xavier Le Loët, Olivier Boyer and Olivier Vittecoq. Department of Immunology, Inserm905, Rouen University Hospital, University of Rouen, Inserm905, University of Rouen, Rheumatology Department, Inserm905, Rouen University Hospital, University of Rouen, Rheumatology Department, Inserm905, Rouen University Hospital, University of Rouen.

Background: Despite the overall benefits of TNFα blocking agents [adalimumab (ADA), etanercept (ETA)], their immune effects on CD4+CD25+ regulatory T cells (Tregs) in rheumatoid arthritis (RA) patients have not been fully characterized and is still controversial. It was suggested that INF increased significantly the number of Tregs in RA patients responding to INF. To our knowledge, any study compared the TNFα blocking agent effects’ differentiating antibodies and soluble receptor on the number of Tregs cells. The objective is to analyse the ETA and ADA treatment effects’ on the Tregs population in RA patients.

Material and Methods: RA patients (n = 48) were treated with either ADA (n = 28) or ETA (n = 20) associated with stable dose of methotrexate or leflunomide. Demographic and clinical data were collected at baseline, after 6 and 12 weeks of treatment. The disease activity score 28 (DAS28) criteria for response to these drugs were applied to assess clinical efficacy after 12 weeks of treatment, that led us to compare the Tregs population in responders [including good responders (GR) and moderate responders (MR)] and no responders (NR). Human blood mononuclear cells were isolated from whole venous blood by Ficoll–Hypaque centrifugation and samples were used fresh to perform flow cytometry analysis. Tregs were defined by different gating strategies (CD4+ CD25+g, CD4+ FoxP3+, CD4+ CD25+ CD127−). For all the statistical analyses, values less than 0.05 were considered significant.

Results: The overall mean (± SD) disease duration was 9.54 ± 9.8 years and the DAS28 score indicated that all these patients had highly active RA (5.46 ± 0.9) at baseline. Prior to treatment, all variables were similar for ADA and ETA subsets. The majority of RA patients (57.1% in ADA group and 65% in ETA group) received corticosteroids. After 12 weeks of treatment, the percentages of GR, MR and NR were respectively 46.5, 35.7 and 17.8% in ADA group and 30, 20 and 50% in the ETA group. The percentage of Tregs was 5 ± 0.04% for ADA group and 4.95 ± 0.02% for ETA group before treatment. Stratifying our RA patients based on corticosteroids status did not reveal any differences in Tregs frequencies before treatment. Overall, and also when stratifying RA patients according to the drug, the TNFα blocking agent had no effect on the percentage and on the absolute number of CD4+CD25+ cells in these patients after 6 weeks or 12 weeks of treatment. Moreover, the percentage of Tregs did not change at 6 and 12 weeks in RA patients responding to ADA or ETA as compared to RA patients nonresponding. Furthermore, the CD4+CD25+ CD45RA−, CD4+CD25+CD45RO+ and CD4+CD25+CD62L+ cells populations were unaffected by TNFα blocking agents whatever the response to these drugs.

Discussion: This is the first study analyzing the impact of ADA and ETA on the Tregs compartment of a substantial number of RA patients. None of these two molecules modified the phenotype and the percentage or the absolute number of blood Tregs after 6 and 12 weeks of treatment whatever the phenotype used to assay these Tregs. However, we cannot exclude that ADA and ETA may have more subtle effects such as on the functional capacity of tregs to regulate cytokines production.

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Relationship between Rituximab Serum Levels and Progression of Structural Damage in Rheumatoid Arthritis Patients.

Maria J. H. Boumans1, Y. K. O. Teng1, Rogier M. Thurlings1, Koen Vos1, Steven O. Stapel1, Gertjan Wolbink3, Janneke Tekstra4 and Paul P. Tak3.

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Background: Treatment with rituximab reduces disease activity in patients with rheumatoid arthritis (RA). The current dosing schedule of rituximab has been shown to induce and maintain a clinical response, and is also protective against progression of joint destruction. Studies on the relationship between serum levels of rituximab and its effects on structural damage may provide insights that may facilitate further optimisation of dosing regimens.

Objective: To determine whether low rituximab serum levels are associated with progression of structural damage in RA patients.

Method: Sixty-three RA patients were treated with two infusions of 1000 mg rituximab (days 1 and 15) in three different centres. The change in total Sharp score (TSS) after 1 year was used as radiographic endpoint and patients were divided into progressors (increase in TSS ≥ 5) versus non-progressors. Rituximab serum levels were measured by sandwich ELISA after 4 and 12 weeks (LUMC and UMCU) or 4 and 16 weeks (AMC). Differences were analyzed using the Mann-Whitney test.

Results: There was no (trend towards a) difference in rituximab levels between progressors versus non-progressors 4 weeks and 12/16 weeks after treatment in the different cohorts (week 4: LUMC: P = 0.8, UMCU: P = 0.38 and AMC: P = 0.5; week 12: LUMC: P = 0.47, UMCU: P = 0.14; week 16: AMC: P = 0.46). There was also no difference in rituximab levels between progressors and non-progressors when the data of the cohorts were pooled (week 4: P = 0.58 (all 3 cohorts); week 12: P = 0.64 (LUMC and UMCU)) (Table 1).

Table 1. Rituximab serum levels 4, 12 and 16 weeks after initiation of treatment.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Progressors</td>
<td>Non-progressors</td>
<td>P-value</td>
</tr>
<tr>
<td>LUMC</td>
<td>125 (57–149)</td>
<td>81 (118–153)</td>
<td>0.8</td>
</tr>
<tr>
<td>UMCU</td>
<td>188 (81–194)</td>
<td>152 (64–179)</td>
<td>0.38</td>
</tr>
<tr>
<td>AMC</td>
<td>112 (45–172)</td>
<td>128 (103–160)</td>
<td>0.5</td>
</tr>
<tr>
<td>3 cohorts pooled</td>
<td>126 (63–187)</td>
<td>128 (99–161)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Values represent the median and the interquartile range.

Conclusion: The rituximab serum levels between 4 and 16 weeks after initiation of treatment were similar between progressors and non-progressors. The results do not support the use of higher dosages of rituximab to inhibit progression of joint destruction.

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Response, Remission, and Flare during Early Treatment of Rheumatoid Arthritis with Infliximab.


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Background: For RA patients who are treated with infliximab (IFX), increases in dose and/or frequency can maximize benefit. Our objective was to investigate response patterns during first 14 weeks of treatment with IFX to identify patients who may be candidates for dose optimization.

Methods: This was a phase-IV, multicenter, observational study conducted in Europe. Enrollees were IFX–naive adults with RA for whom treatment with IFX 3 mg/kg had not been given per label. The relationship between patient characteristics and baseline DAS28 was explored using descriptive statistics. The efficacy-evaluable population, subjects were retrospectively classified into 3 groups: disease duration < 3 yr/anti-TNF naïve (group 1); disease duration ≥ 3 yr/anti-TNF naïve (group 2); failed/ did not tolerate prior anti-TNF (group 3). EULAR criteria for response and remission and inverse EULAR criteria for flare were used to describe change in disease activity during induction (infusions weeks 0, 2 and 6) and the first 8-week infusion interval (week 14).

Results: 728 patients were enrolled—78.4% female, mean age 54.1 years (SD 13.1), mean disease duration 9 years (SD 9.0). Weak correlations with baseline DAS28 were found for age (r = 0.1402, P < 0.005) and weight (r = 0.1152, P < 0.005), but not for gender and disease duration. Of 662 patients evaluable for efficacy, 76 (11.5%) were in group 1, 447 (67.5%) were in group 2, and 123 (18.6%) were in group 3, with 2.4% unclassified. The mean baseline DAS28 was 5.2 (SD 1.2) and core DAS28 components were similar among groups, with the exception of mean CRP, which was higher in group 1 than in 2 and 3 (33.6, 21.4, and 22.0 mg/L, respectively).

EULAR response (moderate/good) was achieved in 74% of all patients by week 6, and by week 14 this proportion had increased to 81.8% in group 1, remained stable in group 2, and decreased to 67.3% in group 3 (differences not significant). Remission was achieved in 25% of patients in group 1, 25% in group 2, and 15.7% in group 3 at week 6; by week 14, 23% of all patients remained in remission with no significant differences between groups. Of the 463 patients who had EULAR response at week 6, 75 (16.2%) had disease flare at week 14 (13.5% group 1, 15.1% group 2, 20.5% group 3). Of core DAS28 components, CRP showed an increase from 9.0 mg/L at week 2 to 18.3 mg/L at week 14, whereas others remained stable or continued to improve. Interestingly, the proportional contribution of global health VAS to the total DAS28 score increased from 35.7% at baseline to 43.4% at week 14 (P < 0.01). The most common adverse event (AE) was infections (13.2%). Serious AEs were reported by 5.5% of patients, and 6.8% discontinued IFX because of AEs.

Conclusion: Most patients treated with IFX achieve moderate/good EULAR response early in treatment. Response rates at 16 weeks are highest in patients naïve to anti-TNF agents. Early disease flare is uncommon and may be more frequent in prior anti-TNF users. Close monitoring with DAS28 during IFX treatment may help identify candidates for dose optimization.

Disclosure: R. F. Van Vollenhoven: Abbott Immunology Pharmaceuticals, 2, 5, 9, Merck Pharmaceuticals, 3; D. Boumpas: None; R. Westhovens: Bristol-Myers Squibb, 5, 8, Roche, 2, 5, UCB, Inc., 2; M. Brzosko: None; K. E. Svensson: None; O. Bjorneboe: None; C. Meeuwisse: Merck Pharmaceuticals, 3; S. Srinivasan: Merck Pharmaceuticals, 3; N. Vastesaeger: Merck Pharmaceuticals, 1; P. Gaudin: None.

Rituximab (RTX) Is More Effective in Active Sero-Positive RA Than Sero-Negative RA. Abdul Khan1, Taher Mahmoud2, Tony Hammond3, Mike Batley4 and Alison Leak5.

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Background: In patients naïve to anti-TNF agents, early disease flare is uncommon and may be more frequent in prior anti-TNF agents. Early disease flare is uncommon and may be more frequent in prior anti-TNF agents. Early disease flare is uncommon and may be more frequent in prior anti-TNF agents. Early disease flare is uncommon and may be more frequent in prior anti-TNF agents.
Introduction: The efficacy of Rituximab (RTX) was established in an open label study of 161 patients with sero-positive RA (Edwards J et al 2004). Evidence is now accumulating from clinical trials that patients with sero-positive RA respond better to RTX than those with sero-negative disease (Isaacs J et al EULAR 2009, Tak P et al EULAR 2009). NICE guidance in the UK states that RTX is indicated for severe active RA (usually DAS28 > 5.1) when patient has had inadequate response to DMARDs, and also failed anti-TNF therapy. NICE defines an adequate response to RTX as improvement in DAS28 in all 139 RA patients treated within Kent & Medway Rheumatology Network, comparing sero-positive to sero-negative patients.

Methods: All 10 rheumatologists in the K&M Network treating RA patients with RTX agreed to submit data for audit purposes to define local practice. This abstract is based on a review of the hospital notes of all 139 patients known to have had at least 6 months follow-up after their first course of RTX (dosage 1000mg on day 1 and 15) for active RA. Data was analysed for age, sex, disease duration, prior DMARD and anti-TNF treatment, positivity of Rheumatoid factor and anti-CCP antibodies, and response to RTX (with current DMARDs).

Categorical variables were compared using Fisher’s exact test; normally distributed continuous measures were compared using unpaired t-test and variables not normally distributed were compared using Mann-Whitney test.

Results: There were 85 patients with sero-positive RA (RF+CCP+ 28, RF-CCP+ 36, RF+CCP not done 7, CCP+RF- 14), and 54 patients with sero-negative RA (all RF negative, 50 CCP negative, 4 CCP not done). There were no differences between groups for age, sex, disease duration or number of prior anti-TNF drugs, nor current DMARD treatment with RTX, but sero-negative RA had more DMARDs prior to RTX than sero-positive RA (52 vs. 15) (p = 0.03).

Prior to treatment with RTX seropositive RA had a significant higher DAS28 score, mean 6.1, compared to 5.8 for sero-negatives (p = 0.02). However, post treatment with RTX seropositive RA had lower DAS (3.9) than sero-negatives (5.1), and reduction in DAS was significant greater in sero-positive RA (mean 2.2), compared to mean 0.6 in sero-negatives (both p < 0.001).

81% of sero-positive RA had a good EULAR response, compared to only 22% for sero-negative RA (p < 0.001). 67% of sero-positive RA reached low DAS (< 3.2) and 15% remission (DAS < 2.6), compared to 4% sero-negative RA (p < 0.001), and none remission (p = 0.002).

RTX Response

<table>
<thead>
<tr>
<th>Category</th>
<th>Sero-negative Number (%)</th>
<th>Sero-positive Number (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28 pre treatment</td>
<td>&lt;5.1</td>
<td>11 (20%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td></td>
<td>5.1 - 6.5</td>
<td>35 (65%)</td>
<td>54 (64%)</td>
</tr>
<tr>
<td></td>
<td>&gt;6.5</td>
<td>8 (15%)</td>
<td>22 (26%)</td>
</tr>
<tr>
<td>Below 5.1 post treatment</td>
<td>Yes</td>
<td>22 (41%)</td>
<td>73 (86%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>32 (59%)</td>
<td>12 (14%)</td>
</tr>
<tr>
<td>Low disease state post treatment</td>
<td>Yes</td>
<td>2 (4%)</td>
<td>57 (67%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>52 (96%)</td>
<td>28 (33%)</td>
</tr>
<tr>
<td>Remission post treatment</td>
<td>Yes</td>
<td>0 (0%)</td>
<td>13 (15%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>54 (100%)</td>
<td>72 (85%)</td>
</tr>
<tr>
<td>EULAR response</td>
<td>No response</td>
<td>32 (68%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td></td>
<td>Moderate response</td>
<td>10 (19%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td></td>
<td>Good response</td>
<td>12 (22%)</td>
<td>69 (81%)</td>
</tr>
<tr>
<td>EULAR outcome</td>
<td>None</td>
<td>38 (70%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>14 (26%)</td>
<td>49 (58%)</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>54 (4%)</td>
<td>85 (32%)</td>
</tr>
</tbody>
</table>

Conclusions: In this UK cohort, sero-positive RA patients respond more effectively to RTX than sero-negative RA, even when well matched for disease activity, disease duration and prior treatment.

Disclosures: A. Khan: None; T. Mahmud: None; T. Hammond: None; M. Bailey: None; A. Lead: None.

Methods: Open label treatment of refractory AOSD patients with IL-1 Trap resulted in meaningful clinical improvements in 3/5 patients. 2/3 patients achieved a response after one year of treatment and dose adjustments suggesting that longer term treatment may be necessary to optimally control disease. Patients showed increased levels of IL-6, IL-18, and TNFα at baseline compared to healthy controls. The reduction in IL-6 and TNFα but not IL-18 at 24 weeks tended to be higher in the responders. Patients responding to IL-1 Trap had higher levels of IL-18 at baseline than non-responders (344 ± 3). Adverse events included macrophage activation syndrome in one patient and mycobacterial infections in two patients; one with bursitis and one with a skin infection.

Disclosure: C. Henderson: None; M. Wilson: None; T.-H. Pham: None; G. Dolan: None; A. Gobbo: None; C. Snyder: None; E. Joyal: None; R. Goldbach-Mansky: None.

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Safety, Efficacy, and Sustained Improvements in Household Productivity and Daily Activities with Certolizumab Pegol (CZP) Monotherapy over 2 Years in Patients with Active Rheumatoid Arthritis (RA), Roy M. Fleischmann5, Ernest Cho2, Ronald van Vollenhoven1, Nita Goel1, Oana Purcaru2, Kristel Luijten1 and Vibeke Strand1. Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, CA, 1Karolinska Institute, Stockholm, Sweden, 2Kings College Hospital, London, United Kingdom, 3MRC, University of Texas, Dallas, TX, 4UCB, Brussels, Belgium, 5UCB, Smyrna, GA

Background: CZP was effective and well tolerated as monotherapy vs placebo over 24 months in patients with treatment refractory AOSD. The objective of this study was to evaluate long-term safety and efficacy of IL-1 Trap in rheumatoid arthritis (RA) previously failing on DMARDs. 2 We present 2-yr data on safety (primary), efficacy (secondary), and effects on household work and daily activities from an open-label extension (OLE).

Methods: Pts who completed FAST4WARD or withdrew on/after Wk 12 were eligible for CZP 400 mg Q4W in the OLE. The majority of pts (75%)
enrolled were from the USA. Adverse event (AE) and serious AE (SAE) cases per 100 pt-yrs were analyzed according to original DB randomization and through Wk 112 for all those receiving ≥1 CZP dose during the DB phase or OLE. Efficacy, including ACR response rates (NRI) and components (LOCF), was assessed over 112 wks from FAST4WARD baseline (BL) in CZP completers entering the OLE and for the ITT (NRI/LOCF). Household productivity and impact on family/social/leisure activities were assessed from BL (Q4W for 6 months, then Q12W) using the Work Productivity Survey (WPS-R). \(^1\) FAST4WARD: NCT00348834; \(^2\) FAST4WARD OLE: NCT01016093.

**Results:** Of 220 randomized pts (111 CZP, 109 P), 104 completed and 116 withdrew (35 CZP, 81 P). 32 were excluded for methotrexate use. Of 188 pts included in this safety analysis, 170 received CZP in the DB phase or OLE. Total mean CZP exposure at Wk 112 was 17.4 months (Table). No evidence of an increased incidence of AEs following longer-term CZP exposure and no new safety signals were observed. The majority of AEs were mild or moderate in intensity (Table). Infections (Table) and cardiovascular events were the most frequently reported SAEs. AEs led to withdrawal in 26 CZP-treated pts. 3 pts died during the OLE: 1 each from acute MI, cardiac arrest, and metastatic lung cancer. No cases of tuberculosis were reported. In 69 CZP completers entering the OLE, ACR20 and 50 response rates (70.3% and 34.4%, respectively, at Wk 112), and individual ACR subcomponent improvements, were sustained throughout. ITT analysis yielded similar ACR20 and 50 response rates (56.3% and 25.2%). The CZP completers also had on average fewer 1) household days lost, 2) days with reduced household productivity, and 3) missed days of family/social/leisure activities per month at Wk 112 compared with BL (1.0 vs 10.1; 1.1 vs 12.1 and 0.3 vs 5.0, respectively). Improvements seen as early as Wk 4 were sustained to Wk 100.

**Table.** Treatment-emergent AEs (safety population)

<table>
<thead>
<tr>
<th></th>
<th>DB phase</th>
<th>DB+OLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>297.1</td>
<td>387.5</td>
</tr>
<tr>
<td>Mild AE</td>
<td>156.7</td>
<td>218.0</td>
</tr>
<tr>
<td>Moderate AE</td>
<td>163.0</td>
<td>165.4</td>
</tr>
<tr>
<td>Severe AE</td>
<td>28.0</td>
<td>17.0</td>
</tr>
<tr>
<td>SAEs</td>
<td>10.1</td>
<td>19.6</td>
</tr>
<tr>
<td>Serious infection</td>
<td>0</td>
<td>4.8</td>
</tr>
</tbody>
</table>

**Conclusion:** There was no evidence of increased incidence of AEs with longer-term exposure to CZP 400 mg monotherapy Q4W in the OLE. This treatment regimen conferred sustained improvements in RA signs, symptoms and productivity in the home, and was associated with increased participation in family/social/leisure activities over 2 yrs.

References:


1833

**Statins Inhibit the Anti-Rheumatic Effects of Rituximab in Rheumatoid Arthritis—Results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) Registry,** Elke Arts, Tim Jansen, Alfons Den Broeder, Harald E. Vonkeman, Ellen Dutmer, Mart A. F. J. Van de Laar, Piet L. C. M. Van Riel and Jaap Fransen. Gelderse Vallei Hospital Ede, Medical Centre Leeuwarden, Medisch Spectrum Twente & University of Twente, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, Radboud University Nijmegen Medical Centre, Sint Maarten-skliniek

**Objective:** Rituximab (RTX) is used in the treatment of lymphomas and Rheumatoid Arthritis (RA). In lymphoma studies, it has been suggested that statins may inhibit the efficacy of RTX by impairing its binding to CD20. However, evidence is ambiguous. This study aims to investigate whether in RA, the combination of statins and RTX, compared with RTX alone, reduces its effect on disease activity at 6 months.

**Methods:** All (N=187) RA patients who started on RTX in the DREAM registry were included in this prospective cohort study. 23 patients were exposed to the combination of statins and RTX. The primary outcome was disease activity (DAS28) at 6 months, analyzed using ANCOVA. Power was calculated in advance and exceeded 0.80, α=0.05. The secondary outcome was drug survival of the first RTX course, analyzed using Cox-proportional hazards regression.

**Results:** Patients exposed to statins were older and more frequently male. Disease duration, ESR, DAS28, rheumatoid factor, previous DMARDS, use of glucocorticoids, and concomitant MTX use did not differ (p>0.05) at baseline. At 6 months DAS28 scores differed significantly (p=0.023) between patients exposed (mean 4.8, SD 1.5) and unexposed (mean 4.3, SD 1.1) to statins. RTX survival was significantly shorter in the exposed group, HR (95%CI) of 2.3 (1.4–3.9). Baseline DAS28 and rheumatoid factor were included as covariates in all models.

**Conclusion:** In RA, concomitant use of statins significantly reduces the effect of RTX on disease activity. This lends support to the hypothesis that statins can reduce the clinical effects of RTX, possibly through cholesterol depletion.

**Figure 1.**

**Figure 2.**

Disclosure: E. Arts: None; T. J. Jansen: None; A. Den Broeder: None; H. E. Vonkeman: None; E. Dutmer: None; M. A. F. J. Van de Laar: None; P. L. C. M. Van Riel: None; J. Fransen: None.

Background: In clinical practice, patients (pts) may temporarily interrupt their RA biologic therapy leading to reduced drug concentrations and immunogenicity, which can impact safety and efficacy, particularly during re-administration. We examine the impact of withdrawal and re-introduction of SC abatacept on safety, immunogenicity and efficacy in pts with RA receiving background methotrexate (MTX).

Methods: Pts with mild-to-moderate RA (receiving MTX for ≥3 mths) were enrolled in this randomized, double-blind, Phase III withdrawal trial. During a 12-wk, open-label (OL) period (I) pts received weekly SC abatacept 125 mg. On Day 1, pts also received an intravenous (IV) loading dose (≈10 mg/kg according to weight range). Period I responders (DAS28 [CRP] reduction from baseline of ≥0.6) were randomized (1:2) in Period II to either continue SC abatacept (Group 1) or to receive placebo (PBO; Group 2) for 12 wks. All Period II-treated pts could enter the 12-wk, OL, Period III; Group 1 pts continued SC abatacept, while Group 2 pts re-initiated SC abatacept with or without an IV loading dose (Group 2a and 2b, respectively). Pts who received ≥1 dose of abatacept were monitored for safety, and events are presented by Period. Immunogenicity (pts with ELISA-detected anti-abatacept antibodies) and disease activity (DAS28) data are presented for pts who entered Period II (as-observed).

Results: Of 167 pts who entered Period I, 106 (6%) discontinued, 37 (22%) were non-responders, and 120 (72%) entered Period II (Group 1 n=40; Group 2 n=80); 40 from Group 1 and 79 from Group 2 entered Period III, of whom 40 and 77 completed Period III. At baseline (Period II population), mean age was 49.0 (SD: ± 13.2) yrs, disease duration was 6.6 (± 6.5) yrs, DAS28 was 4.8 (± 0.8). Serious adverse events (SAEs) were infrequent during Periods I–III (<2.5% of pts across groups), with no change in trend over time. Local injection-site reactions were reported in two pts in Period I. One serious infection (cellulitis, considered unrelated) was reported in Period I. No autoimmune disorders or malignancies were reported. Immunogenicity was low throughout, with a non-significant numerical increase upon drug withdrawal in Group 2; 0/38 and 7/73 pts in Groups 1 and 2, respectively, were seropositive at the end of Period II (p=0.119). At the end of Period III, seropositivity was observed in 1/38 and 2/73 of pts in Groups 1 and 2; immunogenicity was comparable between Groups 2a and 2b. At the end of Period III, reductions from baseline in DAS28 were comparable for both groups (Figure).

Conclusions: Three-month interruption and subsequent re-introduction of SC abatacept is well-tolerated and does not negatively impact efficacy and safety. Furthermore, immunogenicity was consistent with the IV experience, and was not significantly affected by this stop-start schedule, an important consideration for the clinical use of SC abatacept.

Sustained and Clinically Meaningful Improvements in Both Day- and Night-Time Aspects of HRQoL Are Observed with Abatacept Treatment in Patients with Rheumatoid Arthritis (RA) and Previous Inadequate Response to MTX: 5-Year Data from the AIMP Trial. Joel Kremer1, Anthony S. Russell1, Rene Westhovens2, Julie Teng1, Lisa Rosenblatt1 and Paul Emery4. 1Bristol-Myers Squibb, Princeton, NJ, 2Center for Rheumatology, Albany Medical College, Albany, NY, 3University of Alberta Hospital, Edmonton, AB, Canada, 4University of Leeds, Leeds, United Kingdom, 5UZ Gasthuisberg, Leuven, Belgium

Background: RA significantly impairs patients’ quality of life and limits their ability to participate in daily activities. Long-term, sustainable improvements in HRQoL are important treatment goals for this chronic disease, and capturing this information is key to improving patient care. Here we report 5-year data from the AIMP trial, examining the long-term impact of abatacept across multiple day- and night-time aspects of HRQoL in patients with established RA.

Methods: In the double-blind (DB), placebo-controlled AIMP trial, patients were randomized to abatacept (~10 mg/kg) or placebo, plus methotrexate (MTX), for 1 year; patients who completed the 1-year period were eligible to enter an open-label (OL) long-term extension (LTE), during which all patients received abatacept (~10 mg/kg) plus MTX. Sleep quality (Medical Outcomes Study Sleep-Problem Index [SPI] scored 0–100) and fatigue (visual analog scale [0–100 mm]) were assessed up to Year 5 (1 year DB + 4 years OL), and activity (Activity Limitations Score, 0–30 days) up to Year 4 (1 year DB + 3 years OL). Minimal clinically important (MCI) changes in fatigue and activity were evaluated at ~6 units, 10 units and 4 days respectively.2,3 Data are summarized over time by original randomization group using point estimates for patients who received ≥1 dose of abatacept in the LTE (as-observed data).

Results: 433 and 219 patients were randomized and treated with abatacept or placebo in the 1-year DB period; 378 and 161, respectively, entered and were treated in the LTE, of which 390 (72.4%) have completed 5 years. At baseline, the mean age of patients entering the LTE was 50.8 years, mean duration of RA was 8.5 years, and mean tender and swollen joint counts were 31.6 and 21.9, respectively; mean baseline values for sleep, fatigue, and activity were similar between groups (Table). Initial improvements in HRQoL over 1-year DB treatment were greater for abatacept versus placebo (Table). Over 4–5 years’ treatment, patients initially treated with abatacept sustained clinically important improvements, i.e. above the MCI threshold, in all HRQoL domains. Over time, patients who switched to abatacept plus MTX after 1 year of MTX plus placebo showed similar sustained HRQoL improvements as those seen in patients continuously treated with abatacept.

Table. Mean changes from baseline over time in sleep problems, fatigue, and activity limitations

<table>
<thead>
<tr>
<th>Year</th>
<th>Sleep problem index (0–1000)</th>
<th>Fatigue, VAS (0–100 mm)</th>
<th>Activity limitation, number of days of limitation (0–30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>4.2 11.9 -11.7 -11.2 -10.6</td>
<td>65.8 29.7 12.6 12.0 11.3</td>
<td>11.3 31.1 30.0 30.6 31.3 31.2 32.6 32.3 32.0</td>
</tr>
<tr>
<td>1</td>
<td>4.9 8.9 9.4 9.1 9.0 8.9 9.6 9.4 10.1 10.0 9.7 9.7 9.7 9.7 9.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5.6 7.4 8.2 8.9 9.2 9.8 9.4 9.1 10.0 10.0 9.7 9.7 9.7 9.7 9.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6.4 8.2 9.0 9.9 9.6 9.4 9.1 10.0 10.0 9.7 9.7 9.7 9.7 9.7 9.7</td>
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</tr>
<tr>
<td>4</td>
<td>7.2 8.1 9.0 9.9 9.6 9.4 9.1 10.0 10.0 9.7 9.7 9.7 9.7 9.7 9.7</td>
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</tr>
<tr>
<td>5</td>
<td>8.0 9.0 9.9 9.6 9.4 9.1 10.0 10.0 9.7 9.7 9.7 9.7 9.7 9.7 9.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: In patients with RA and an inadequate response to MTX, abatacept provides sustained, long-term, MCI improvements across both day- and night-time measures of HRQoL, and reduces the limitation of patients usual daily activities caused by their disease. These improvements represent tangible benefits to patients.

References:

outcomes in Yr 2 after addition of abatacept at Yr 1. These data support the early use of abatacept to provide meaningful improvements in QoL and daily functioning in MTX-naive pts with early RA and poor prognostic factors.


Disclosure: R. Westhovens: Bristol-Myers Squibb, 5, 8, Centocor, Inc., 5, Roche, 5, Schering-Plough, 5, UCB, Inc., 2; J. Wollenhaupt: Bristol-Myers Squibb, 5; B. Harauvi: Abbott Laboratories, 2, 5, 8, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Roche, 2, 5, 8, Schering-Plough, 2, 5, 8, UCB, Inc., 2, 5, 8, Wyeth Pharmaceuticals, 2, 5, 8, J.-C. Becker: Bristol-Myers Squibb, 1, 3; A. Covucci: Bristol-Myers Squibb, 3; L. Rosenblatt: Bristol-Myers Squibb, 1, 3; J. Bathon: Amgen Inc., 2, Biogen Idec, 2, Bristol-Myers Squibb, 2, Centocor, Inc., 5, Riley, 5.

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TNF-alpha Antagonist Therapy Leads to an Expansion of IL-17 Expressing CD4+ T Cells Both In Vitro and In Vivo. Hayley G. Evans1, Nicola J. Gullick2, Bruce W. Kirkham1 and Leonie S. Taams2. 1Guy’s & St Thomas’ NHS Foundation Trust, 2Kings College London, London, United Kingdom, 3Kings College London

Purpose: TNF-alpha is a highly pro-inflammatory cytokine, which contributes to inflammation and joint damage progression in patients with Rheumatoid Arthritis (RA). Use of TNF-alpha antagonists has had considerable success in the clinic, by reducing disease activity and inhibiting joint damage progression. We have previously demonstrated that TNF-alpha can induce IL-17 expression and secretion from CD4+ T cells when produced in combination with IL-1 beta by in vitro activated monocytes. IL-17 has also been shown to induce tissue inflammation and bone destruction in RA. In the present study we investigated how the presence of IL-17-producing CD4+ T cells is affected by TNF-alpha antagonist therapy.

Methods: PBMC and CD4+ T cells from healthy controls (n=13) or patients with RA (n=34) were stimulated ex vivo with PMA/ionomycin and analysed via intracellular flow cytometry and ELISA for their production of IL-17 and IFN-gamma. PBMC (0.5×10^6 in a 48 well plate) and CD4+ T cell/monocyte (0.5×10^6:0.5×10^6), in a 24 well plate) co-cultures were also cultured in the absence or presence of Infliximab, Etanercept or Adalimumab followed by stimulation and analysis via flow cytometry and ELISA.

Results: The percentage of IL-17+ CD4+ T cells is significantly enriched in the blood of RA patients when compared to healthy controls (0.6±0.6% vs. 1.4±1.2%, p=0.003). When separated by treatment regimes, we observed a further enrichment of IL-17+ CD4+ T cells in patients treated with TNF-alpha antagonists compared to those on DMARD therapy (1.1±0.8% vs. 2.3±1.7%, p=0.02). This enrichment could not be explained by the method of stimulation, naive/memory cell ratio, the age, sex, and disease duration or disease activity of the patients. Instead this may be a direct drug effect since in vitro experiments demonstrated that the presence of TNF-alpha antagonists can stimulate the expression of IL-17 by CD4+ T cells (63±41%, n=6). Finally, preliminary data indicate a rise in the percentage CD4+IL-17+ expressing T cells in the blood when measured ex vivo pre and post anti-TNF-alpha therapy.

Conclusions: Treatment of RA patients with TNF-alpha antagonists leads to an increase of Th17 cells in the peripheral blood. In vitro experiments suggest this may not simply be the result of re-distribution of joint Th17 cells. We propose that the presence of this primed pool of pro-inflammatory T cells may contribute to relapse of disease when anti-TNF-alpha therapy is ceased.

The authors acknowledge financial support from the Department of Health via the NIHR comprehensive Biomedical Research Centre at GKT NHS Foundation Trust and King’s College London.

Disclosure: H. G. Evans: None; N. J. Gullick: None; B. W. Kirkham: Bristol-Myers Squibb, 9, Merck Pharmaceuticals, 9, Pfizer Inc, 2, Roche, 9, UCB, Inc., 2; L. S. Taams: None.

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Tocilizumab Monotherapy Improves Arterial Stiffness Compared with Other Biologies Monotherapy in Rheumatoid Arthritis. Kensuke Kume1, Kanzo Amano1, Susumu Yamada1 and Hiroyuki Ohta2. 1Hiroshima Clinic, Hiroshima, Japan, 2G8L School, Hiroshima, Japan

Background: Methotrexate (MTX) plus TNF inhibitor is very effective in rheumatoid arthritis (RA). But sometimes we choice biologics monotherapy, when it is difficult to use MTX. By the way, patients with RA have an increased cardiovascular (CV) risk. We should have strategies for prevent CV primary in RA patients. And some biologies reduce arterial stiffness and may improve CV morbidity in RA patients.

Objective: to examine the effect of tocilizumab (TCZ) alone, etanercept (ETN) alone, and Adalimumab (ADA) alone, compared respectively on arterial stiffness in RA patients in an open label randomized study design.

Methods: RA patients were eligible if they had active disease and no prior treatment with MTX or a TNF inhibitor. All patients have no previous history of CV. 32 RA patients with moderate to severe active disease (DAS 28>3.2) were randomly assigned to receive TCZ alone (n=11), ETN alone (n=11), or ADA alone (n=10). Arterial stiffness was assessed with augmentation index corrected for a heart rate of 75 beats per minute (AIX@75) and caro-ankle vascular index (CAVI) at baseline, 3 months, and 6 months follow-up. Clinical data was collected at regular visits. CAVI measures arterial stiffness independent of blood pressure and it is superior to brachial ankle pulse wave velocity as an index of arterial stiffness.

Results: Each groups of characteristics (DAS 28, CRP, diastolic blood pressure, age, gender, disease duration, class) at baseline are no significantly different. Treatment with TCZ (36.3 ± 11, 33.8 ± 3 and 33.9 ± 3%; P = 0.032), ETN (36.4 ± 3, 33.8 ± 5 and 33.5 ± 6%; P = 0.038), ADA (37.1 ± 8, 33.0 ± 5 and 34.1 ± 7%; P = 0.047) attenuated the AIX@75 significantly from baseline to 3 months and 6 months follow-up. Treatment with TCZ (10.82 ± 1.58, 9.62 ± 0.94 and 9.55 ± 1.42%; P = 0.028), ETN (10.92 ± 1.38, 10.29 ± 0.53 and 10.28 ± 1.31%; P = 0.035), ADA (10.74 ± 1.78, 10.38 ± 0.75 and 10.35 ± 0.98%; P = 0.025) attenuated the CAVI significantly from baseline to 3 months and 6 months follow-up. And the CAVI of the TCZ group has most significantly decreased in comparison with the CAVI of ETN or IFX group in 3 and 6 months follow-up.

Conclusions: Monotherapy of TCZ, ETN, and ADA reduces arterial stiffness in RA patients. TCZ monotherapy improves arterial stiffness more significantly compared with other biologies monotherapy in RA patients.

Disclosure: K. Kume: None; K. Amano: None; S. Yamada: None; H. Ohta: None.

1840

Tocilizumab Treatment in Patients with Rheumatoid Arthritis and an Inadequate Response to DMARDs and/or TNF Inhibitors: ACT-SURE Preliminary Results. Vivian P. Bykerk1, Jose Alvaro-Graça2, Jose Andres Roman Ivorra3, Michael T. Nuru Mohamed1, Karel Pavelka1, Corrado Bernasconi, Andrea Stancati8, Jean Sibilia2 and Andrew Östör and the ACT-SURE Study Group1. 1Addenbrookes Hospital, Cambridge, United Kingdom, 2Haupteipierre Service de Rhumatologie, Strasbourg, France, 3Hospital Universitario de La Princesa, IIS Princesa, Madrid, Spain, 4Hospital Universitario Dr. Peset, Valencia, Spain, 5Institute of Rheumatology, Prague, Czech Republic, 6Jan van Bremen Institute, Amsterdam, The Netherlands, 7Mount Sinai Hospital, Toronto, ON, Canada, 8Roche, Basel, Switzerland
Background: Safety and efficacy of TCZ have been demonstrated in 7 phase 3 controlled studies in pts with RA and DMARD-IR or TNFi-IR but not in pts who switched to TCZ without TNFi washout. The ACT-SURE study evaluated TCZ safety and efficacy in pts who were DMARD-IR or TNFi-IR, treated in tertiary academic and non academic centers as well as in private practice setting.

Methods: ACT-SURE was a phase 3b, open-label, single-arm, 6-mo study of DMARD-IR/TNFi-IR pts with active RA treated with TCZ 8 mg/kg Q4W alone or in combination with DMARDs. Safety endpoints included adverse events (AEs) and serious AEs (SAEs). Efficacy endpoints included ACR and DAS28 responses. Analyses were stratified by prestudy TNFi use: TNFi-naive (DMARD-IR) pts, previous TNFi users (>2 mos since TNFi use) or recent TNFi users (≤2 mos since TNFi use). Subanalysis of pts who received TCZ monotherapy was also performed.

Results: Of 1681 evaluable pts, 58% were DMARD-IR, 18% were previous TNFi users and 24% were recent TNFi users. Mean age of pts was 54 years; 81% were women. Mean RA duration was 8.2 years in DMARD-IR pts and 11.2±11.7 years in previous/recent TNFi users. Baseline DAS28 was similar among groups (5.9–6.2). Overall, 12.8% pts withdrew, 4.8% for safety-related reasons; infections were the primary safety-related cause of withdrawal (1.1% of pts or 1.8/100 patient-years [PY]). Rates/100 PY AEs/SAEs and serious infections were slightly lower in TNFi-naive pts than in those with previous TNFi exposure (Table). ALT shifts from normal at baseline to >3 ULN occurred in <3% of pts (Table). Onset of efficacy was rapid and increased over time: among the groups, DAS28 remission was achieved by 24%–38% of pts at wk 8 and 49%–62% of pts at wk 24. Clinical response tended to be higher in DMARD-IR pts, with little difference between recent and previous annual use (Table). At wk 24, mean DAS28 values were 2.34, 2.83 and 2.76 in DMARD-IR pts, previous TNFi users and recent TNFi users. Improvement in physical function was similar across groups: 74.1%, 71.1% and 70.2% of DMARD-IR pts, previous TNFi users and recent TNFi users achieved ≥0.22 point change from baseline in HAQ-DI. In the subgroup of pts who received TCZ monotherapy, 66.9%, 43.5% and 23.8% achieved ACR20/50/70 response at wk 24; 49.8% achieved DAS28 remission.

Conclusions: ACT-SURE was performed in a setting closer to clinical practice than is typical of phase 3 studies and confirmed the safety profile of TCZ shown in previous phase 3 trials. TCZ is effective when used in RA patients in clinical practice.

Real-life data from a large nationwide observational cohort showed that use of TNF inhibitors in RA patients treated for ≥2 years in

**Table. Safety and Efficacy Outcomes at Wk 24**

<table>
<thead>
<tr>
<th>AE Rate/100PY</th>
<th>ACR20 % (n)</th>
<th>ACR50 % (n)</th>
<th>ACR70 % (n)</th>
<th>ACR90 % (n)</th>
<th>ALT Shift From Baseline to &gt;3ULN % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMARD-IR</td>
<td>551.1</td>
<td>18.6</td>
<td>4.2</td>
<td>6.8 (66)</td>
<td>2.4 (23)</td>
</tr>
<tr>
<td>TNFi-IR, previous use</td>
<td>654.4</td>
<td>28.7</td>
<td>7.6</td>
<td>7.4 (22)</td>
<td>3.0 (9)</td>
</tr>
<tr>
<td>TNFi-IR, recent use</td>
<td>652.6</td>
<td>18.0</td>
<td>6.0</td>
<td>6.1 (25)</td>
<td>0.7 (3)</td>
</tr>
</tbody>
</table>

**Disclosure:**

V. P. Bykerk: Roche, 5; J. Álvarez-Gracia: Roche, 5; UCB, Inc., 5; J. R. I. Ivorra: Actelion Pharmaceuticals US, 2, 5; Merck Sharp & Dohme, 2, Pfizer Inc, 2, Roche, 2; M. T. Nurmodahem: Abbott Immunology Pharmaceuticals, 2, 8; Bristol-Myers Squibb, 2, 8, Roche, 2; sanofi-aventis, 2, Schering-Plough, 2, Wyeth Pharmaceuticals, 2; K. Pavelka: Roche, 5; C. Bernasconi: Roche, 5; A. Stancati: Roche, 3; J. Sibilia: None; A. Östör, and the ACT-SURE Study Group: Abbott Laboratories, 5, 8, AsahiKASEI, 5, 8, Bristol-Myers Squibb, 5, 8, Chugai, 8, GlaxoSmithKline, 5, MerckSoroion, 5, 8, Roche, 5, Schering-Plough, 5, 8, UCB, Inc., 5, 8, Wyeth Pharmaceuticals, 5.

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**In Table.**

**Table.** Radiographic progression during treatment with DMARDs and subsequent treatment with TNF-I in RA patients in clinical practice.

<table>
<thead>
<tr>
<th>A DMARD</th>
<th>B TNF-I start</th>
<th>Follow-up Delta A-B/Cyr</th>
<th>Delta B-Cyr</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSS mean(SD)</td>
<td>21.0 (29.8)</td>
<td>25.7 (33.6)</td>
<td>27.0 (32.0)</td>
<td>2.1 (3.4)</td>
</tr>
<tr>
<td>ES mean(SD)</td>
<td>7.1 (10.3)</td>
<td>14.3 (14.2)</td>
<td>13.0 (20.9)</td>
<td>0.3 (3.9)</td>
</tr>
<tr>
<td>ES mean(SD)</td>
<td>13.1 (19.9)</td>
<td>15.5 (21.3)</td>
<td>16.2 (21.7)</td>
<td>1.0 (4.0)</td>
</tr>
<tr>
<td>ES median (IQR)</td>
<td>4.0 (6.6)</td>
<td>6.0 (8.3)</td>
<td>6.1 (7.4)</td>
<td>0.2 (0.4)</td>
</tr>
<tr>
<td>JSM median (IQR)</td>
<td>7.0 (11.5)</td>
<td>10.2 (18.5)</td>
<td>9.6 (13.2)</td>
<td>1.6 (2.6)</td>
</tr>
<tr>
<td>JSM median (IQR)</td>
<td>2.0 (12.0)</td>
<td>5.0 (16.0)</td>
<td>6.1 (21.7)</td>
<td>0.0 (1.4)</td>
</tr>
<tr>
<td>Progressing patients (%)</td>
<td>59</td>
<td>31</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(1) Paired T-test (2) Paired Wilcoxon-test (3) Chi-square test. A: 2 years before TNF-I treatment start; B: TNF-I treatment start; C: 2 years total TNF-I treatment; D: AR, total; E: remission; F: DAS28 remission; G: joint space narrowing; H: standard deviation; IQR, inter quartile range; Delta A-B/Cyr, annual progression rate (A B/Cyr); Delta B-Cyr, annual progression rate (B-Cyr).

**Conclusion:**

Real-life data from a large nationwide observational cohort showed that use of TNF inhibitors in RA patients treated for ≥2 years in
routine care significantly reduces the rate of joint damage progression when compared to the previous ~2 years on conventional treatment.

Disclosure: L. M. Ornbjerg: None; M. Østergaard: Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, GlaxoSmithKline, 5, Pfizer Inc, 5, Roche, 5, Schering-Plough, 5, UCBC, Inc., 5, Wyeth Pharmaceuticals, 5; E. Bøhme: None; D. Dencker: None; H. Lindegaard: Abbott Laboratories, 5, Merck Pharmaceuticals, 5, Roche, 5; U. Poulsen: None; A. Hansen: Abbott Laboratories, 2, 5, Schering-Plough, 2, 5; V. Rüschendorf: None; A. Schlemmer: Schering-Plough, K. N. Grandahl: None; A. R. Andersen: None; J. Espeisen: None; G. Kollerup: Abbott Laboratories, 5; T. G. Christensen: None; R. Pelc: None; B. Glinthborg: None; O. R. Madsen: None; D. V. Jensen: None; O. Maigaard: None; M. L. Hetland: Abbott Laboratories, 5, Centocor, Inc.; 5, Roche; 5, Schering-Plough, 5, UCBC, Inc.; 5, Wyeth Pharmaceuticals, 5.

ACR Poster Session C
Systemic Lupus Erythematosus - Clinical Aspects and Treatment - Epidemiology and Health Services III

Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1842
Accumulation of Traditional Risk Factors for Coronary Heart Disease in Patients with Systemic Lupus Erythematosus.

Rosa W. Tellers1, Cristina C. D. Lanna2, Fabricia F. Simil1, Luana G. Machado1, Fabiana L. Sousa1, Luciana A. Rodrigues1 and Antonio L. Ribeiro1. Hospital das Clínicas, 2School of Medicine, School of Medicine-Universidade Federal de Minas Gerais-Brazil

Objective: to examine the accumulation of traditional risk factors for Coronary Heart Disease (CHD) in patients with SLE.

Patients and Methods: 157 patients included in a prospective study of atherosclerosis in lupus patients were followed during 39(37–42) months. Traditional risk factors for CHD were collected at entry (T0), throughout the atherosclerosis in lupus patients were followed during 39(37–42) months.

Gerias-Brazil (96.2%: female gender; 75.8%: non-white). Median (IR) duration of lupus was 45.2%; p = 0.006) and abdominal obesity (42% vs. 22.9%; p = 0.001). The number of current smokers did not differ (14% vs. 12.1%; p = 0.250). Although the prevalence of LDL≥130mg/dl (16.6% vs. 22.9%; p = 0.036) and the total cholesterol≥200mg/dl (17.8% vs. 28.7%; p = 0.024) increased, the prevalence of HDL<40mg/dl did not change (26.8% vs. 20.4%; p = 0.268). The number of traditional risk factors (age and sex, hypertension, diabetes mellitus, dyslipidemia, hypertiglyceridemia, family history for CHD and smoking habit) per patient also increased during the study interval [1(0–2) vs. 2(1–3); p = 0.015]. The annual mean incidence of the traditional risk factors were: hypertension 4%, diabetes mellitus 0.8%, dyslipidemia 10%, triglycerides≥150mg/dl 5.1%, obesity (BMI≥30kg/m²) 5.1% and abdominal obesity (abdominal circumference ≥102cm in men and ≥88cm in women) 11.5%.

Conclusion: the prevalence of traditional risk factors for CHD increased in a short-period in young patients with SLE. Some of these risk factors have been already associated with clinical and subclinical atherosclerosis in lupus. Lupus patients should be monitored for cardiovascular risk factors in a regular basis and appropriate treatment instituted.

Disclosure: R. W. Telles: None; C. C. D. Lanna: None; F. F. Simil: None; L. G. Machado: None; F. L. Sousa: None; L. A. Rodrigues: None; A. L. Ribeiro: None.

1843
Analysis of the Level of Agreement between Different Measures of Disease Flare in an Exploratory Study of Abatacept in Systemic Lupus Erythematosus (SLE).

Caroline Gordon1, Jean-Claude Becker2, Sheila Kelly1, Yun Peng2, Michael Kiniasczuk2 and Joan T. Merrill3. 1Bristol-Myers Squibb, Princeton, NJ; 2Bristol-Myers Squibb, Pennington, NJ; 3University of Birmingham, Birmingham, United Kingdom; 4University of Oklahoma, Oklahoma City, OK

Background: This Phase II exploratory trial of abatacept used BILAG A/B flare (adjudicated per protocol) as the primary endpoint. Post-hoc analyses examined other BILAG and physician-defined flare measures.

Methods: This was a double-blind, Phase II study in which SLE patients with active polyarthritis, serositis and/or discoid lesions were randomized to abatacept (~10 mg/kg) or placebo (PLC) for 1 year. Prednisone (30 mg/day or equivalent) was given for 1 month, then tapered by protocol. The primary outcome was adjudicated BILAG A/B flare (classic BILAG index) over 1 year after the start of steroid taper. Post-hoc assessments included BILAG A only flare (adjudicated), or physician-defined flare in response to the question “Since the last visit, does the patient exhibit symptoms of an acute SLE flare?” (yes/no). Treatment modifications were recorded on visits when physician-defined flares occurred. Analyses are based on data for all randomized and treated patients.

Results: 118 abatacept and 57 PLC patients were assessed. Proportions of patients with ≥1 BILAG A/B flare, BILAG A only flare or physician-assessed flare, respectively, were 79.7, 40.7 and 63.6% for abatacept versus 82.5, 54.4 and 82.5% for PLC. In the abatacept group, physician’s assessment agreed with BILAG A/B flare in 71/165 (43%) cases: when the flare definition was restricted to BILAG A only, agreement occurred in 23/33 (70%) cases (Table).

Cross-tabulation of the presence/absence of flare according to BILAG and physician-defined measures

<table>
<thead>
<tr>
<th></th>
<th>Total n=118</th>
<th>Abatacept (n=118)</th>
<th>Placebo (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No (%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Adjudicated BILAG A or B flare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician assessment of flare</td>
<td>Yes</td>
<td>131</td>
<td>71 (54.2)</td>
</tr>
<tr>
<td>No</td>
<td>1178</td>
<td>94* (8.0)</td>
<td>1048 (92.0)</td>
</tr>
<tr>
<td>Adjudicated BILAG A flare</td>
<td>Yes</td>
<td>131</td>
<td>23 (17.6)</td>
</tr>
<tr>
<td>No</td>
<td>1178</td>
<td>10 (0.8)</td>
<td>1168 (99.2)</td>
</tr>
</tbody>
</table>

*10 were A flares; the remaining 84 were B flares.

Conclusions: These data demonstrate some discordance between BILAG adjudication- and physician-defined flares. This may be due to: a) BILAG flare rules being based on an item worsening after improving at 2 prior visits (to avoid recording non-significant fluctuations in disease severity), whereas physicians may have recorded worsening irrespective of prior visits; b) physicians recording flare when items were the same over 4 prior weeks (not just when new, or worse after improving); c) the classic BILAG index may fail to capture some flare features detected by physicians. Some BILAG A/B flares occurred when no physician-defined flares were recorded; BILAG flares were more likely to be confirmed by the physician when restricted to BILAG A, suggesting increased ability of BILAG A to define events that physicians considered significant. These data provide valuable insight into issues encountered when assessing flare in clinical trials of SLE, and may help inform future trial design.


Disclosure: C. Gordon: Biogen Idec, 5, Bristol-Myers Squibb, 5, Genentech and Biogen IDEC Inc; 5, Roche, 5, UCB, Inc., 5, Wyeth Pharmaceuticals, 5; J. C. Becker: Bristol-Myers Squibb, 1, 3; S. Kelly: Bristol-Myers Squibb, 3; Y. Peng: Bristol-Myers Squibb, 3; M. Kinaszczuk: Bristol-Myers Squibb, 1, 3, Johnson & Johnson, 1; J. T. Merrill: Bristol-Myers Squibb, 5, 9.

1844
Anti-NR2A Antibody as a Predictor for Neuropsychiatric Systemic Lupus Erythematosus.

Masanori Hanaoka1, Takahisa Gono2, Yasushi Kawaguchi1, Hirotake Kaneko2, Katsujir Nishimura, Yasushi Katsumata, Yuko Okamoto2, Sayumi Baba2, Sayuri Kataoka2 and Hisashi Yamanaka4. 1Tokyo Women’s Medical Univ, Tokyo, Japan; 2Tokyo Women’s Medical Univ, Tokyo, Japan; 3Tokyo Women’s Medical Univ, Tokyo, Japan; 4Tokyo Women’s Medical University, Tokyo, Japan; 5Tokyo Women’s Medical Univ, Shinjuku-ku, Tokyo, Japan

Purpose: N-methyl-D-aspartate receptors (NMDAR) are ligand-gated ion channels with crucial roles in synaptic transmission and plasticity of central...
nervous system (CNS). Additionally, NMDAR are located on non-neuronal tissues, such as bone, skin, pancreas and megakaryocyte. Anti-NMDAR subunit 2A/2B (NR2A/2B) antibody has been reported to react against the peptide DWEYSVWLSN in systemic lupus erythematosus (SLE). Although DWEYS was reported as residues 283–287 in NR2A, the actual sequence of residues 283–287 is DWDYS in NR2A and DEWDY in NR2B. This will make DWDYS-peptide more specific than DWEYS-peptide in NR2A, even though most reports that have measured anti-NR2A antibody by enzyme-linked immunosorbent assay (ELISA) have used DWEYS-peptide. The aim of the present study is to establish a method to detect serum anti-NR2A antibody by ELISA and to evaluate the relationship between anti-NR2A antibody and various tissue damages in SLE.

Methods: Measurement of anti-NR2A antibody in sera was performed by ELISA using either DWEYS- or DWDYS-peptide as autoantigen. Clinical characteristics were compared between anti-NR2A antibody-positive 27 patients (P group) and -negative 80 patients (N group) in SLE, using DWDYS-peptide.

Results: The optical density (OD) value using DWDYS-peptide correlated significantly (r = 0.94, P < 0.0001) with the one using DWEYS-peptide in SLE patients. The median OD value was significantly higher (P < 0.0001) in DWDYS-peptide than DWEYS-peptide. The median OD value [interquartile range] using DWDYS-peptide were 0.449 [0.327–0.622] and 0.197 [0.14–0.29] in 107 SLE patients and 74 non-SLE patients, respectively. There was a strikingly significant difference between two subsets (P < 0.0001). Additionally, SLE Disease Activity Index (SLEDAI) was significantly higher (P = 0.023) in P group. The frequency of serositis, nephritis and neuropsychiatric SLE (NP-SLE) was significantly higher (P = 0.039, 0.015 and 0.0002, respectively) in P group. The frequency of diffuse CNS form and focal CNS form was significantly higher (P = 0.036 and 0.01, and odds ratios 3.5 and 5.3, respectively) in P group. The leukocyte count and hemoglobin was significantly decreasing (P = 0.021 and 0.0008, respectively) in P group. Although no correlation were found between anti-NR2A antibody and the titer of anti-DNA antibody, significant correlations were found between anti-NR2A antibody and leukocyte count (r = 0.31, P = 0.001) and hemoglobin (r = −0.42, P < 0.0001). NP SLE was a most significant independent variable (P = 0.0008), associated with anti-NR2A antibody-positivity, estimated by multiple liner regression analysis. The leukocyte count and hemoglobin were also significant variables (P = 0.0095 and 0.013, respectively) associated with anti-NR2A antibody-positivity.

Conclusion: Serum anti-NR2A antibody can be a predictor for NP SLE and may damage also non-nervous tissues. The usage of peptide including DWDYS is more preferable for detecting anti-NR2A antibody in ELISA.

Disclosure: M. Hanaoka: None; T. Gono: None; Y. Kawaguchi: None; H. Kaneko: None; K. Nishimura: None; Y. Katsumata: None; Y. Okamoto: None; S. Baba: None; S. Katouka: None; H. Yamanaka: None.

1845
Assessing the ANA Test as a Screening Tool: Utility or Futility? Areyh M. Abeles and Michä Abeles. University of Connecticut Health Center

Introduction: Current ANA testing may be overly sensitive, resulting in frequent false positives as well as unnecessary follow-up testing and misdiagnosis. Several studies have focused on ANA prevalence and predictive value, but the purpose of this investigation was to establish the clinical utility of a positive ANA test in a real-world setting, by reviewing the outcomes of patients referred to a tertiary rheumatology clinic for evaluation of a positive ANA test. No prior study has directly addressed this question.

Method: We reviewed records for all consultation patients presenting to the authors at the UCHC rheumatology clinic between July 2007 and July 2009. Patients were included in the evaluation if they had been referred for a positive ANA. Patients presenting with an already-diagnosed ANA-associated rheumatic disease (AARD) were excluded. All ANA tests and all referrals had been ordered by non-rheumatologists. A complete review of systems and physical examination was performed on each patient. 91 out of 101 patients with ANA titers ≥1:320 had the following labs drawn: antibody (Ab) panel (Anti-dsDNA, SSA/SSB, Sm, RNP), C3, C4, CH50, CBC, and ESR. Of 67 patients with ANA ≥1:640, 64 had lab evaluations performed as above. Referring physician reasons for ordering ANA testing were also collected.

Results: Of 1,306 initial consultation visits to our clinic, 232 were referrals for a positive ANA, with titers ranging from 1:40 to greater than 1:5120. Initial ANA testing had been performed at several different laboratories (the majority at UCHC). 98% of all initial ANA tests had been run using immunofluorescence assay with Hep-2 cells. 9.1% of patients evaluated (21/232) had an AARD (5 SLE, 12 Sjögren’s syndrome, 3 scleroderma, 1 MCTD). The remainder of patients had no AARD, of whom twenty-one (9.1%) had isolated autoimmune thyroid Ab present. No patient with an ANA ≤1:80, and only 1 patient with ANA =1:160, had a rheumatic disease. There was no correlation between the highest ANA titers with a specific rheumatic illness. The most common reason for ordering ANA testing was widespread pain and tenderness (54/232, 23.2%) but also included, among others, chronic lower back pain, episodic chronic rhinitis, palpitations, unilateral heel pain, and lateral buttck pain. The positive predictive value of an ANA test in our cohort of patients was 2.2% for lupus and 9.1% for any AARD.

Conclusion: In this retrospective study, over 90% of patients referred to a tertiary rheumatology clinic for positive ANA testing had no evidence of an AARD. The poor predictive value of a positive ANA test may in part be attributable to poor patient selection with concomitant low pretax probabilities. The extremely low positive predictive value of ANA tests at titers below or equal to 1:160 suggests that the cutoff of a “positive” ANA may need to be re-evaluated by testing laboratories. Even at high titers, however, many patients referred for a positive ANA had no discernable AARD, corroborating previously noted lack of predictive value of ANA testing.

Disclosure: A. M. Abeles: None; M. Abeles: None.

1846
Atherosclerosis in SLE: a Cross Sectional Study of 223 Patients with 223 Individually Matched Population Controls. Johanna T. Gustafsson1, Kerstin Utrustd Jensen1, Marie Herlitz-Lindberg1, Sonia Möller1, Susanne Petersson1, Iva Gunnarsson2 and Elisabet Svennsson3.1 Department of Clinical Physiology, Södersjukhuset, Karolinska Institute, Stockholm, Sweden, 2Department of Medicine Solna, Karolinska Institute. Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, 3Department of Neurobiology, Care Sciences and Society (NVS), Division of Nursing, Karolinska Institutet, Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, 4Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden

Objective: Accelerated atherosclerosis is believed to contribute to premature cardiovascular disease (CVD) in patients with Systemic Lupus Erythematosus (SLE). We investigated the prevalence of subclinical atherosclerosis in SLE patients and controls.

Patients and Methods: 223 SLE patients/ 223 population controls, individually matched for age, sex and region of living were included after overnight fasting. All were investigated clinically including CVD risk factors and inflammatory biomarkers. The same investigator performed B-mode ultrasonography of carotid arteries. Intima media thickness (IMT) and plaques.

Results: Mean age was 48.5 ± 14.3 years in patients and 48.7 ± 14.2 in controls. Manifest CVD (ischemic heart, cerebro- and peripheral vascular disease) was more common in SLE patients (13 % vs. 3 %, P < 0.0001). Patients were more likely to smoke, have antihypertensive and lipid lowering treatment, lower high density lipoprotein, higher triglycerides (TG). They had lower low density lipoprotein levels (P<0.05 for all).

Patients had thicker mean IMT than controls (P=0.02), but there was no difference in plaque occurrence, 21% and 17% respectively. After age adjustment:

Manifest CVD was associated with plaques in the SLE group, but not with IMT.

In SLE, IMT was positively associated with systolic blood pressure (sBP, <0.0001), TGs (p=0.008) and hemoglobin levels (p=0.04) and negatively with discoid skin lesions (p=0.03) and leukopenia (p=0.03). Plaques were associated positively with TGs (p=0.01) and systolic blood pressure (p=0.02) and negatively with discoid skin lesions (p=0.04).

In controls, IMT was associated with high CRP levels (p<0.02) and sBP (<0.0001). Smoking (p=0.03) and TG levels (p=0.03) were associated with plaques.

Multivariable adjusted models:

In patients age and sBP remained associated with IMT (p<0.001 for both) and plaques (p<0.001 and p=0.01 respectively). In controls age (p<0.001) and sBP (p=0.001) remained associated with IMT and age (p<0.001) and smoking (p=0.03) with plaques.

Conclusions: This is to our knowledge the largest study of subclinical atherosclerosis in SLE patients. Patients had thicker IMT, but we could not confirm the increased prevalence of carotid plaques previously reported. Selection of controls, definition of plaques and possibly ethnicity are possible underlying explanations. Plaques and IMT were mainly associated with
traditional CVD risk factors in both patients and controls. The relative contribution of subclinical atherosclerosis for hard outcomes i.e. events in SLE needs to be investigated and should be in focus of future studies.

Disclosure: J. T. Gustafsson: None; K. Ustad Jensen: None; M. Herlitz-Lindberg: None; S. Möller: None; S. Petterson: None; I. Gunnarsson: None; E. Svenungsson: None.

1847

Autoantibodies Predate the Onset of Systemic Lupus Erythematosus. Solfbritt Rantapää-Dahlqvist1, Catharina Eriksson1, Heidi Kokkonen1, Martin Johansson1, Göran Hallmans1 and Göran Wadell1, Umeå, Sweden, 2Rheumatology, Umeå, Sweden

Objective: To identify the presence of autoantibodies in a Northern European population antedating disease onset of SLE using blood samples donated to the Medical Biobank of Northern Sweden before onset of symptoms and relate the predicting antibodies with first symptoms of disease.

Methods: The register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of patients fulfilling the ACR criteria for SLE.

Results: In BLISS-76, mean improvements (MIs) in SF-36 and FACIT-Fatigue scores were significantly greater with belimumab 1 mg/kg vs placebo at wk 52 (Table 1). In BLISS-52, MIs from baseline in SF-36 PCS and FACIT-Fatigue scores were significantly greater with belimumab 1 and 10 mg/kg vs placebo at wk 52 (Table 1).

Table 1. PCS, MCS, and FACIT-Fatigue Data: BLISS-76 and -52

<table>
<thead>
<tr>
<th>Assessment</th>
<th>SOC+ Placebo</th>
<th>SOC+ Belimumab</th>
<th>SOC+ Placebo</th>
<th>SOC+ Belimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36</td>
<td>n=271</td>
<td>560</td>
<td>553</td>
<td>553</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean±SE</td>
<td>39.0±0.4</td>
<td>39.1±0.4</td>
<td>39.1±0.4</td>
</tr>
<tr>
<td>MI at wk 52</td>
<td>Mean±SE</td>
<td>2.9±0.3</td>
<td>4.3±0.4**</td>
<td>3.8±0.3*</td>
</tr>
<tr>
<td>Baseline</td>
<td>n=276</td>
<td>560</td>
<td>553</td>
<td>553</td>
</tr>
<tr>
<td>MI at wk 52</td>
<td>Mean±SE</td>
<td>2.1±0.5</td>
<td>3.4±0.4**</td>
<td>3.3±0.5</td>
</tr>
<tr>
<td>FACIT-Fatigue</td>
<td>Mean±SE</td>
<td>30.5±0.5</td>
<td>30.1±0.5</td>
<td>29.6±0.5</td>
</tr>
</tbody>
</table>

Results: In BLISS-76, mean improvements (MIs) in SF-36 and FACIT-Fatigue scores were significantly greater with belimumab 1 mg/kg vs placebo at wk 52 (Table 1). In BLISS-52, MIs from baseline in SF-36 PCS and FACIT-Fatigue scores were significantly greater with belimumab 1 and 10 mg/kg vs placebo at wk 52 (Table 1). Based on pooled data, MIs from baseline were significantly greater with belimumab 1 and 10 mg/kg for SF-36 PCS, and with 1 mg/kg for MCS vs placebo at wk 52 (Table 2). Both belimumab treatment groups demonstrated greater MIs in FACIT-Fatigue score vs placebo at wk 8, 12, and 52 (Figure 1).

Table 2. BLISS-76-52 Pooled Data

<table>
<thead>
<tr>
<th>Assessment</th>
<th>SOC+ Placebo</th>
<th>SOC+ Belimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36</td>
<td>n=275</td>
<td>560</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean±SE</td>
<td>39.0±0.4</td>
</tr>
<tr>
<td>MI at wk 52</td>
<td>Mean±SE</td>
<td>2.9±0.3</td>
</tr>
<tr>
<td>Baseline</td>
<td>n=270</td>
<td>560</td>
</tr>
<tr>
<td>MI at wk 52</td>
<td>Mean±SE</td>
<td>2.1±0.5</td>
</tr>
<tr>
<td>FACIT-Fatigue</td>
<td>Mean±SE</td>
<td>30.5±0.5</td>
</tr>
</tbody>
</table>

# p < 0.001; * p < 0.01; ** p < 0.05; *p < 0.05

Figure 1. Mean improvement in FACIT-Fatigue scores: BLISS-76-52 pooled data.

Disclosure: V. Strand: GlaxoSmithKline, 5, Human Genome Sciences, Inc., 5, 8, 9; R. A. Levy: GlaxoSmithKline, 8, Human Genome Sciences, Inc., 5, 8, 9; R. Cervera: GlaxoSmithKline, 5, Human Genome Sciences, Inc., 5, 9; M. A. Petri: GlaxoSmithKline, 5, Human Genome Sciences, Inc., 5; L. Pineda: Human Genome Sciences, Inc., 1, 3; W. Freimuth: Human Genome Sciences, Inc., 1, 3; Z. J. Zhong: Human Genome Sciences, Inc., 1, 3; A. E. Clarke: GlaxoSmithKline, 5, Human Genome Sciences, Inc., 9; for the BLISS-76 and -52 Study Group: None.

1848

Belimumab, a BlyS-Specific Inhibitor, Improved Fatigue and SF-36 Physical and Mental Component Summary Scores in Patients with SLE: BLISS-76 and -52 Studies. V. Strand1, R. A. Levy1, R. Cervera1, M. A. Petri1, H. Rudge2, L. Pineda2, W. Freimuth2, Z. J. Zhong2, A. E. Clarke and for the BLISS-76 and -52 Study Group. 1GlaxoSmithKline, Uxbridge, Uxbridge, UK, 2Hospital Clinic, Barcelona, Spain, 3Hospital Universitario Pedro Ernesto, Rio de Janeiro, Brazil, 4Human Genome Sciences, Inc, Rockville, MD, 5Human Genome Sciences, Inc, Rockville, Rockville, MD, 6Johns Hopkins University School of Medicine, Timonium, MD, 7McGill University Health Centre, Montreal, QC, Canada, 8Stanford University, Palo Alto, Portola Valley, CA

Purpose: To evaluate the effects of belimumab on fatigue and other health-related quality-of-life (HRQLQ) measures in patients with seropositive (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL) SLE.

Methods: BLISS-76 (NCT00410384) and BLISS-52 (NCT00424476) were phase 3, multicenter, randomized, double-blind, placebo-controlled studies of 819 and 865 seropositive SLE patients, respectively. Patients with screening...
2849

Cigarette Smoking and Cutaneous Damage in Patients with Systemic Lupus.
Rosa W. Telles2, Cristina C. D. Lanna2, Rodrigo C. P. Reis2, Fabiana L. Sousa2, Luciana A. Rodrigues2 and Antonio L. Ribeiro3. 1Hospital das Clínicas, School of Medicine, 2School of Medicine-Universidade Federal de Minas Gerais-Brazil, 3Statistics Department

Objective: To determine the causes and predictors of death in SLE patients.

Patients and Methods: 181 outpatients were enrolled from May 2005 to February 2006 (T0) in a prospective study. These patients were followed up to either the last visit at outpatient clinic, death or end of study visit (from October 2008 to July 2009). Causes of death were defined on the basis of death certificates, medical records and information collected from doctors and relatives. Variables predicting mortality were assessed by Kaplan-Meier and Cox regression methods. The final multivariate model was selected according to clinical and biological plausibility and was corrected for optimism.

Results: Two patients were lost to follow up. Median (IR) age at diagnosis and age at the T0 of the 179 patients was 26.7(21.8–34.6) and 38(29–46) years, respectively. Median (IR) disease duration was 8.2(4.3–12.4) years. After a median (IR) follow up of 3.3(3.1–3.5) years, 13(73%) patients died due to end-organ failure (5), infection (5), disease activity (1) and atherosclerosis (1). The cause of the mesenteric ischemia of one patient could not be determined. These 13 patients died a median (IR) of 9(6.76–19.3) years after being diagnosed as having SLE. Predictors of mortality observed at T0 were: nephritis, chronic renal disease (creatinin clearance<60ml/min/1.73m2), antiphospholipid syndrome, higher modified SLEDAI-2k and higher damage index score, cyclophosphamide intravenous use, higher daily dose of prednisone and higher systolic blood pressure.

Conclusion: This study presents a high frequency of late mortality in lupus patients due to SLE itself and infection. This result is not in agreement with the proposed bimodal pattern of lupus mortality and with the high frequency of atherosclerosis as a cause of death in developed countries. The most important predictors of death were related to lupus itself.

Disclosure: R. W. Telles: None; C. C. D. Lanna: None; R. C. P. Reis: None; F. L. Sousa: None; L. A. Rodrigues: None; A. L. Ribeiro: None.

2850

Cigarette Smoking and Cutaneous Damage in Patients with Systemic Lupus Erythematosus.
Josiane Bourné-Tessier1, Christine A. Peschken1, Lawrence Joseph2, Patrick Belisle3, Ann E. Clarke4, Sasha R. Bernatsky5, Marie Hudson6, Carol A. Hitchon7, Hector Arbillaga2, Dafna D. Gladman2, Marie Hudson6, Carol A. Hitchon7, Dafna D. Gladman2, Marie Hudson6, Carol A. Hitchon7, Paul R. Fortin1, C. Douglas Smith9, Hector Arbillaga2, Dafna D. Gladman2, Murray B. Urowitz9, C. D. Clarke5, Michel Zummer1, CANIOS 1000 Canadian Faces of Lupus Investi None; C. A. Peschken.

Purpose: To describe the clinical and serologic characteristics of multiplex systemic lupus erythematosus (SLE) in a Filipino Lupus Database, and compare these with patients with simplex or sporadic SLE from the same database.

Methods: An active search for multiplex SLE patients i.e. belonging to families with at least 2 first degree relatives diagnosed with SLE, was done among patients included in the Lupus Database of the University of Santo Tomas (UST) in Manila, Philippines. Simplex SLE patients i.e. ascertained by review of medical records and verified by phone interview to have no first to third degree family history of SLE or other autoimmune disease, were chosen from the same database to match disease duration. The demographic and cumulative clinical characteristics based on American College of Rheumatology (ACR) criteria and other SLE-related manifestations were compared between the 2 groups, with statistical significance at a p value <0.05.

Results: There were 166 patients (138 females) with an average age at diagnosis of 28.61±13.07 SD years (range 1–73), belonging to 75 multiplex families. The relationships included 21 parent-child and 54 siblings including three sets of twins. The average age at diagnosis of the simplex SLE patients (N=309, 257 females) was 36.53±15.04 SD years (range 4–85). The mean disease duration was 98.28±65.21 months SD (range 1–300) and 96.46±47 months SD among the multiplex and simplex patients respectively, p=0.77. Among the clinical manifestations, serositis (multiplex=36, 22.08% vs. simplex= 36, 11.65%, p=0.0027), neurologic manifestations (multiplex=25, 15.33% vs. simplex= 26, 8.41%, p=0.0283) and cutaneous vasculitis (multiplex=27, 17.0% vs. simplex= 23, 8.04%, p=0.0042) were more common in multiplex patients. The other clinical manifestations and serology including antinuclear antibody (ANA) and anti-dsDNA were comparable between both groups.

Conclusions: SLE patients from multiplex families were younger with relatively higher number of males than in those with sporadic SLE. Serositis, neurologic manifestations and cutaneous vasculitis were more frequently recorded in multiplex patients. These findings suggest a role for genetics in the clinical expression of SLE, with potentially more serious organ involvement among patients from multiplex families.

Disclosure: None

1851


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Disclosure: None

Disclosure: H. F. Soldevilla: None; S. V. Navarra: None.
CNS Lupus: The Prevalence and Antibodies Depend on the Definition. Results from the 1000 Faces of Lupus Cohort. Alan Borowoy1, Christine A. Peschken2 and Janet E. Pope1. 1St Joseph Health Care London, London, ON, Canada, 2Univ of Manitoba, Winnipeg, MB, Canada, 3University of Western Ontario, London, ON, Canada

Background: Neuropsychiatric involvement in SLE (NPSLE) is common and encompasses a broad spectrum of neurologic and psychiatric syndromes with significant impact on morbidity and mortality and prevalence varies depending on the definition used (from 12–80%). We determined the prevalence of NPSLE and associated factors in 1000 Faces of Lupus, a large multi-centre Canadian cohort.

Methods: Adults were enrolled who satisfied the ACR classification for SLE and had completed SLEDAI, SLAM and SLICC damage indices. NPSLE was defined as: (i) NPSLE by ACR classification criteria (seizure or psychosis), (ii) ACR, SLEDAI (seizure, psychosis, organic brain syndrome, cranial nerve disorder, headache and CVA), SLAM (CVA, seizure, cortical dysfunction and headache) and SLICC (cognitive impairment, psychosis, seizures, CVA, cranial or peripheral neuropathy or transverse myelitis) with and without (iii) NPSLE syndromes considered minor and nonspecific, and (iv) ACR criteria and SLEDAI NP indices. Factors associated with NPSLE were explored using univariate and multivariate regression including antibodies, # of ACR criteria, disease duration, disease activity, ethnicity, education and income.

Results: Cohort size was 1417, mean disease 12±10 years, mean age 41±16 years, 86% females. Subgroup size was dependent on the specific definition of NPSLE. The prevalence of NPSLE was: (i) 6.4%, (ii) 38.6%, (iii) 28.7% and (iv) 10.2%. In univariate analysis, Aboriginals had increased NPSLE (>twice as common) versus Caucasians, Asians and Blacks (p=0.04 in Group (i)). Anti-SSA/Ro was increased in groups (i) and (iv) and antiphospholipid (aPL) was increased in (i), (ii) and (iii). In Group (iv) absence of anti-Sm was significant. NPSLE was not increased in those with positive anti-DNA, anti-SSB/La, anti-RNP, LAC (lupus anticoagulant) or aCL (anti-cardiolipin antibody). Total number of ACR criteria, SLAM, age at diagnosis, disease duration and gender were not associated with NPSLE. If thromboembolic events were excluded, aPL was no longer associated. Education level was not associated with NPSLE (p=0.32) and income was only significant in group (i) (p=0.03). The results are shown below for Group (i).

Characteristics Group (i) NPSLE (n=80) Non-NPSLE (n=1173) p-value

Age at diagnosis 29.9 +/- 12.3 32.0 +/- 14.0 0.19

Disease duration 13.2 +/- 10.4 12.7 +/- 10.2 0.67

Gender n 69/10 1021/110 0.88

(%) F:M 90.8: 92.2% 90.3: 97.7% 0.04

Ethnicity (%)

Aboriginal 9 (12.5) 56 (5.3) 0.04

Asian 14 (19.4) 162 (15.3)

Black 5 (6.9) 106 (10.0)

White 44 (61.1) 732 (69.3)

Total ACR criteria 5.9 +/- 1.5 6.1 +/- 1.7 0.31

SLAM-2 Score 5.8 +/- 4.1 5.8 +/- 4.0 1.0

Antibody positive (%)

anti-dsDNA 26 (31.9) 448 (48.8) 0.12

Anti-Smith 18 (24.0) 305 (28.6) 0.43

Anti-RNP 18 (25.4) 291 (26.7) 0.89

Anti-Ro 36 (51.4) 369 (34.1) 0.004

Anti-La 14 (20.0) 136 (12.6) 0.19

LAC 3 (4.0) 26 (2.4) 0.43

aCL 10 (13.3) 76 (7.1) 0.66

aPL 27 (36.0) 191 (18.0) <0.001

Conclusions: The prevalence and factors associated with NPSLE varied depending on the definition used and was highest in the Aboriginal group, and may be higher if positive anti-Ro or aPL. SLAM, SLICC and SLEDAI include mild subjective disease manifestations, which contributed to a 10% higher prevalence of NPSLE compared to a strict definition. NPSLE may be less frequent in this database than other publications as it may be decreasing, or due to selection bias of those who enter an observational cohort.

Disclosure: A. Borowoy: None; C. A. Peschken: None; J. E. Pope: None.

Cognitive Dysfunction in Patients with SLE: A Prospective Study. Andres Piatti1, Tara Adhikari2 and Michael Luggen2. 1University of Cincinnati College of Medicine, Cincinnati, OH, 2University of Cincinnati College of Medicine

Background: Cognitive dysfunction (CD) has been reported to occur frequently in SLE. It is unclear, however, if this CD is transient, persistent, or progressive. Published reports have estimated persistence or progression in anywhere from 17% to 93% of patients. These widely divergent results may be due in part to the definition of CD and the control population employed. Chronic rheumatic diseases cause pain, fatigue, and depression which may affect cognitive function. All studies of progression to date have employed normal healthy individuals as controls. Definitions of CD relative to this population will identify some pts whose major problems are depression, pain, or fatigue, which may improve, and some who have structural CNS disease,
which may not. Previous work from our group utilizing an age, sex, and race matched RA control population and a community based cohort of SLE pts suggested that the frequency of CD was low (17.2%), but that most patients had persistent deficits. This work extends those observations.

**Methods:** Patients with SLE by ACR Criteria from several sources were examined at baseline and again after 6 months. Cognitive function was assessed by the ANAM (Automated Neuropsychologic Assessment Metrics), a validated, computerized, cognitive testing battery, utilizing as the primary outcome measure the total throughput score (TTS=total number of correct responses/time). Other differences were found but none were statistically significant, perhaps due to small numbers with CD. TTS improved significantly in those without CD (increase of 9.4% (95% CI: 0.1%, 19.0%) but decreased in those with CD by 4.0% (95% CI: −13.9%, 5.8%).

**Conclusions:** Using RA controls, 10.6% of SLE pts had CD and all remained unchanged over a 6 month interval. Age was a significant correlate of CD. Pts without CD improved scores over 6 mos perhaps demonstrating a learning effect. Those with CD had no such improvement. This may represent another measure of CD.

**Disclosure:** A. Piatti: None; T. Adhikari: None; M. Luggen: None.

1855

**Cognitive Dysfunction in Systemic Lupus Erythematosus: Development of a Screening Tool.** Tara Adhikari1, Andres Piatti2 and Michael Luggen1.

1University of Cincinnati College of Medicine, Cincinnati, OH; 2University of Cincinnati College of Medicine

**Background:** Cognitive Dysfunction (CD) is said to occur frequently is SLE and to be associated with increased unemployment rates and decreased quality of life. Yet, it is oftentimes undiagnosed because of difficulties in doing so. There are only two validated tools for detecting the CD in SLE patients. Traditional neuropsychologic testing (NPT), which consist of a variable battery of tests, administered and interpreted by a clinical psychologist, requiring 4 to 6 hours to complete, and costing oftentimes over $1000. And, the Automated Neuropsychologic Assessment Metrics (ANAM), a computerized battery of tests which assess some of the same cognitive domains as NPT, requires approximately 45 minutes, and costs approximately $400 for a software license. While more efficient and less costly, the ANAM is neither readily available nor practical for clinic administration or for screening larger populations. What is needed for both situations is a brief, sensitive, and reliable screening questionnaire.

**Methods:** The Montreal Cognitive Assessment Questionnaire (MoCA) has been developed and tested to identify mild cognitive impairment in the elderly. It is a brief (<10 mins), performance-based questionnaire that has been utilized in a number of other diseases with fair sensitivity (85–90%) and variable specificity (53–87%). The MoCA has never been utilized to screen for CD in patients with lupus.

Patients with SLE fulfilling American College of Rheumatology criteria were recruited and evaluated. Demographic, clinical, and treatment information was obtained. In addition, depression was assessed using the Beck Depression Inventory (BDI) and fatigue, pain, and overall well being scored on a 10 cm visual analogue scale. All subjects were administered the ANAM as the gold standard and the MoCA.

The total throughput score (TTS) is a standard measure of cognitive performance of the ANAM. It is the average of the total number of correct responses/time required for those responses. Abnormal was defined as any score 2 SD or more below the mean established for a comparable rheumatoid arthritis population. The scores of the MoCA were compared to the TTS and the classification of normal or abnormal by the ANAM compared to that of the MoCA using various cutoffs.

Descriptive statistics of the study population were computed. Using various cutpoints for the MoCA, the sensitivity, specificity, accuracy, predictive values, and likelihood ratios were also computed.

**Results:** Forty-four (44) patients have been recruited to date. Eleven (25%) were identified by the ANAM as being impaired in comparison to 13 (29.5%) by the MoCA. The scores of the two tests were significantly correlated ($r = 0.57, p < .001$). Using the standard cut-off of 26, the sensitivity of MoCA was 83%, specificity 73%, accuracy 75%, with a positive predictive value of 50% and negative predictive value of 92% compared to ANAM. Other cut points were less efficient.

**Conclusion:** The MoCA appears to be a useful screening tool for the detection of CD in SLE using the standard cutoff of 26. However, improved performance might be obtained by weighting individual questions differently or by developing additional items with enhanced discrimination.

**Disclosure:** T. Adhikari: None; A. Piatti: None; M. Luggen: None.

1856

**Determinants of Treatment Adherence in Patients with Systemic Lupus Erythematosus (SLE).** Shazia A. Beg1, Sofia de Achaval2, Michael A. Kallen3, Vanessa L. Cox2, Marsha N. Richardson2, John D. Reveille3 and Maria E. Suarez-Almazor4.

1Baylor College of Medicine, Houston, TX; 2The University of Texas M. D. Anderson Cancer Center, Houston, TX; 3Univ Texas Health Sci Ctr, Houston, TX; 4University of Texas, MD Anderson Cancer Center, Houston, TX

**Objective:** Patients’ health-related beliefs may ultimately influence their health-related behaviors, including their adherence to medications. The Health Belief Model (HBM) has been widely used to explain individual health behaviors under different chronic disease conditions. This study examines the relationships between HBM domains and medication adherence in SLE patients.

**Methods:** We examined a cohort of 110 ethnically diverse SLE patients from publicly funded hospitals in Houston, Texas. At baseline, 12 and 24 months patients completed a HBM questionnaire and two adherence questionnaires—the Compliance Questionnaire Rheumatology (CQ), with scores ranging from 0 to 100 and higher scores indicating better adherence; and the Adult AIDS Clinical Trials Group-Adherence (AACTG-Adh) with scores ranging from 0 to 3 and higher scores indicating worse adherence. HBM domains of study interest included perceived severity of disease, perceived benefits and risks of treatment, self efficacy and barriers to treatment. Statistical analyses included Pearson correlational analysis and multi-variable stepwise linear regression modeling.

**Results:** Of 110 SLE patients, 90% were female; mean age was 37 years; 55% were African-Americans and 38% Hispanic. Mean CQR score was 69.6 (sd=11.6), while mean AACTG-Adh score was 0.7 (sd=0.5). Both adherence measures showed similar correlational results; however, AACTG-Adh results are presented here, as these were consistently of higher magnitude. At baseline, HBM domains that were statistically significantly associated with better adherence included: (i) elements of self-efficacy i.e. function ($r = 0.20$), optimism ($r = 0.22$), pain ($r = 0.34$), and symptoms ($r = 0.41$); and (ii) perceived effectiveness ($r = 0.50$). Domains significantly associated with worse adherence included: (i) perceived disease severity ($r = 0.39$) and perceived threat ($r = 0.36$); (ii) barriers i.e. access ($r = 0.21$), transportation ($r = 0.39$), financial ($r = 0.36$), and clinic logistics ($r = 0.37$); (iii) forgetting ($r = 0.58$); (iv) perceived toxicity ($r = 0.44$); and (v) lack of benefit ($r = 0.45$). In the multi-variable regression analysis using AACTG-Adh as the dependent variable, the following beliefs were independent predictors in the final stepwise model: self-efficacy about symptom control which was associated with increased adherence, financial barriers, forgetting, perceived toxicity and perceived disease severity which were all associated with decreased adherence. Throughout the study’s time period, most HBM constructs and treatment adherence itself remained at generally constant levels, highlighting the stability of beliefs and behaviors in the absence of targeted interventions.

**Conclusions:** Several HBM dimensions are closely associated with adherence in SLE patients. While some barriers may be difficult to modify, educational interventions outlining medication benefits and risks, introducing strategies to remember taking medications and enhancing self efficacy could potentially increase treatment adherence in this patient population.

**Disclosure:** S. A. Beg: None; S. de Achaval: None; M. A. Kallen: None; V. L. Cox: None; M. N. Richardson: None; J. D. Reveille: None; M. E. Suarez-Almazor: None.
Discordance between Self-Report and Physician-Assessed Disease Activity in Patients with Systemic Lupus Erythematosus (SLE): Implications for Clinical Trial Design and Clinical Care. Anca D. Askanase1, Isabel Castrejon2, Jill P. Buyon1, Yusuf Yazici1 and Theodore Pincus1. 1Hospital for Joint Diseases, Hastings-on-Hudson, NY, 2New York University Hospital for Joint Disease, Hastings-on-Hudson, NY, 3NYU Hospital for Joint Diseases, New York, NY, 4NYU Hospital for Joint Diseases, 5NYU School of Medicine, New York, NY

Purpose: To analyze agreement levels between patient (PT) and physician (MD) assessments in 50 patients with SLE seen in usual care, including a) global PT and MD estimates of status; b) patient self-report scores on the SLAQ (Systemic Lupus Activity Questionnaire) and MDHAQ (Multidimensional Health Assessment Questionnaire) for physical function (FN), pain (PN), patient global estimate (PTGL), fatigue (FT), RAPID3 (FN, PN, and professional Health Assessment Questionnaire) for physical function (FN), pain of various measures were analyzed using Spearman rank order correlations.

Methods: A cross-sectional study was performed in 50 consecutive SLE patients of one rheumatologist. Patients completed the SLAQ and MDHAQ, including PTGL. The rheumatologist scored a physician global estimate (MDGL) (scored 0–3 in 0.1 increments) without knowledge of PTGL, and completed the SLEDAI-2K, BILAG, SLAM, and ECLAM. Agreement levels of various measures were analyzed using Spearman rank order correlations.

Results: The study included 45 women and 5 men, mean age 38.7 years, mean disease duration 7.3 years, 36% Caucasian, 26% Hispanic, 18% Asian. The mean MDGL (1.10±0.62), PTGL (3.11±2.81) and SLE indices (SLEDAI 5.02±3.75; BILAG 4.60±4.31; SLAM 3.86±2.92; ECLAM 1.97±1.37) indicated mild/moderate lupus activity. The correlation between MDGL and PTGL of rho=0.14 was not statistically significant. Correlations between MDGL and SLE indices were significant, rho=0.60–0.72 (p<0.001). Correlations between PTGL and patient measures also were significant, rho=0.58–0.87 (p<0.001). However, PTGL was correlated at lower levels with SLE indices – significantly with BILAG and SLAM (0.35–0.40; p<0.01), and not significantly with SLEDAI or ECLAM. MDGL was not correlated significantly with any patient measure or index.

Conclusion: MDGL and PTGL were not correlated significantly, an observation made previously. MDGL was correlated significantly with all physician-derived indices, and PTGL was correlated significantly with all patient-derived measures and indices. By contrast, MDGL was correlated at much lower, non-significant levels with patient-derived measures and indices, and PTGL was correlated at lower levels with physician-derived indices. Further analysis of these discordances may clarify the clinical relevance of various measures in clinical trials, and may lead to improved care and compliance in patients with SLE.

Disclosure: A. D. Askanase: None; I. Castrejon: None; J. P. Buyon: None; Y. Yazici: None; T. Pincus: None.

1858

Ethnicity Affects the Frequency of CNS Manifestations of SLE. Maryna Shayuk1, Hong Fang2 and Michelle A. Petri1. 1Timonium, MD, 2Johns Hopkins University

Purpose: The new SLICC classification criteria have added mononeuritis multiplex, myelitis, peripheral or cranial neuropathy and acute confusional state to the previous CNS manifestations (psychosis and seizure) of the neurologic criterion for SLE. We investigated the frequency of these neurologic manifestations, as well as depression, lupus headache and stroke in a prospective SLE cohort.

Method: 1889 SLE patients (88.5% female, 56.5% Caucasians, 36.9% African-Americans) were included. Neurologic manifestations were recorded at cohort entry and updated at every visit.

Result:

Table 1. Neurologic manifestations, by ethnicity

<table>
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<tr>
<th>Manifestation</th>
<th>Caucasian</th>
<th>Af-Am</th>
<th>P-value</th>
<th>Odds Ratio**</th>
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<td>Seizure</td>
<td>105/1135</td>
<td>95/1135</td>
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<td>0.8461</td>
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<td>Psychosis</td>
<td>34/1135</td>
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<td>0.0389</td>
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<tr>
<td>Headache from SLE</td>
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<td>67/1135</td>
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<tr>
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<td>0.3655</td>
<td>0.9584</td>
</tr>
</tbody>
</table>

*based on chi-square test for the binary outcomes.

Conclusion: Caucasians have significantly more depression, but African-Americans have significantly more psychosis, stroke, and mononeuritis multiplex. Depression is the most common neurologic manifestations in both ethnicities. The addition of acute confusional state, mononeuritis multiplex, optic neuritis, other cranial neuropathies, peripheral neuropathy and myelitis allow an additional 21% of SLE patients to meet the neurologic classification criterion who did NOT have seizures or psychosis.

Disclosure: M. Shayuk: None; H. Fang: None; M. A. Petri: None.

1859

Five Year Follow-Up Study of Bone Mineral Density in Patients with Systemic Lupus Erythematosus: The Influence of Corticosteroid Treatment. Anna M. Schilder, Jonathan Jacobs, Lindy-Anne Korswagen, Ben A. C. Dijkmans, Willem F. Lems, Alexandre E. Voskuyl and Irene E. M. Bultink. VU University Medical Center, Amsterdam, The Netherlands

Introduction and Objective: The influence of corticosteroids on bone mineral density (BMD) in systemic lupus erythematosus (SLE) is still under debate. Various studies have reported an association between corticosteroid use and low BMD in SLE but other studies did not demonstrate a significant relation. This discrepancy might be explained partially by the cross-sectional design of the far majority of studies. Only a few longitudinal studies on BMD change and the associated factors in patients with SLE have been performed. However, in these studies, the numbers of patients were small and the duration of follow-up was relatively short (three years).

The aim of this study was to assess change in BMD during long-term follow-up in patients with SLE and to identify factors associated with BMD loss. In particular the effect of corticosteroid treatment on BMD change was studied.

Methods: We prospectively studied 82 patients with SLE. Demographic and clinical data were collected and BMD measurements of the lumbar spine and total hip were performed by dual energy x-ray absorptiometry at baseline and at follow-up. Osteoporosis was defined as a T score less than -2.5 SD and osteopenia as a T score less than -1.0 SD in at least 1 region of measurement. Statistical analysis was performed using independent sample t-test for comparison of means, univariate and multiple regression analysis.

Results: At baseline, osteopenia was present in 49% of the patients and osteoporosis in 9% (93% female, mean age 38.8 years, mean disease duration 6.3 years). During the observation period, 67.1% of the patients were treated with corticosteroids. The mean cumulative dose of prednisone used between baseline and follow-up was 13.4 ± 8.5 grams. The mean daily dose of prednisone was 6.6 ± 3.9 mg in the corticosteroid users.

After a mean follow-up of 5.7 years, no significant change in BMD of the total hip or the lumbar spine was observed at group level. However, higher cumulative corticosteroid dose during the observation period was significantly

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Neurologic manifestations, by ethnicity

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<td>Transverse Myelitis</td>
<td>9/1113</td>
<td>7/1113</td>
<td>0.3655</td>
<td>0.9584</td>
</tr>
</tbody>
</table>

*based on chi-square test for the binary outcomes.

Conclusion: Caucasians have significantly more depression, but African-Americans have significantly more psychosis, stroke, and mononeuritis multiplex. Depression is the most common neurologic manifestations in both ethnicities. The addition of acute confusional state, mononeuritis multiplex, optic neuritis, other cranial neuropathies, peripheral neuropathy and myelitis allow an additional 21% of SLE patients to meet the neurologic classification criterion who did NOT have seizures or psychosis.

Disclosure: M. Shayuk: None; H. Fang: None; M. A. Petri: None.
associated with BMD loss in the lumbar spine, but not at the hip (p = 0.851). A mean daily dose of more than 7.5 mg prednisone was associated with significant BMD loss at the lumbar spine as compared to patients receiving less than 7.5 mg per day (P = 0.003).

**Conclusion:** In this long-term follow-up study, no significant change in BMD of the lumbar spine or the total hip is observed in patients with SLE. However, higher mean daily and cumulative corticosteroid dose is associated with BMD loss in the lumbar spine. The high prevalence of reduced BMD and the negative influence of corticosteroid use on bone density in the lumbar spine underline the importance of permanent attention for monitoring and treatment of low BMD in SLE, especially in patients using higher doses of corticosteroids.

**Disclosure:** A. M. Schilder: None; J. Jacobs: None; L.-A. Korwagen: None; B. A. C. Dijkmans: None; W. F. Lems: None; A. E. Voskuyl: None; I. E. M. Bultink: None.

**1860**

High Prevalence of Fetal Loss and Pregnancy Complications in African-American Lupus Patients: A Retrospective Case-Control Study. Kirk C. Edelman2 and Vikas Majithia1. 1University of Mississippi Medical Center, Jackson, MS, 2University of Mississippi Medical Center

**Introduction:** Pregnancy in Systemic Lupus Erythematosus (SLE) patients is associated with a high rate of fetal loss and pregnancy complications which is about 2–4 times higher than non-SLE patients. The rates are felt to be even higher in African-American (AA) patients, but an exact prevalence and risk is not yet characterized. We undertook this study to assess the risk of fetal loss and complications in SLE patients at University of Mississippi Medical Center, caring for predominantly (gt;90%) AA patients.

**Methods:** A retrospective chart review of pregnancies in 83 women with SLE and 99 age-matched controls was performed for time-period between 2004 and 2006. Patients were identified by cross referencing billing codes 710.0 (Lupus) and 648.1 or 648.3 (Pregnancy). Data included: demographics, SLE related information, medications, compliance with follow-up visits (>60%), fetal outcomes and complications. Odds ratio were calculated and statistical significance was determined using Fischer’s Exact test.

**Results:** Mean age of two groups were 22 years and both groups had 95 % AA patients. Results are summarized below.

**Table 1.** Fetal loss in SLE versus non-SLE patients

<table>
<thead>
<tr>
<th>SLE group</th>
<th>Control group</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Fetal Loss</td>
<td>16.9% (n=83)</td>
<td>3% (n=99)</td>
<td>6.49</td>
</tr>
<tr>
<td>Overall Fetal loss in hydroxychloroquine users</td>
<td>6% (n=30)</td>
<td>3% (n=99)</td>
<td>2.28</td>
</tr>
<tr>
<td>Overall Fetal loss in compliant patients*</td>
<td>3% (n=67)</td>
<td>1% (n=54)</td>
<td>1.6</td>
</tr>
</tbody>
</table>

(*compliance => 60% follow-up visits).

**Table 2.** Maternal Complications in pregnancy for SLE versus non-SLE patients

<table>
<thead>
<tr>
<th>SLE group</th>
<th>Control group</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-term Labor</td>
<td>50.7%</td>
<td>31.2%</td>
<td>2.26</td>
</tr>
<tr>
<td>Baseline Hypertension</td>
<td>33.7%</td>
<td>9%</td>
<td>5.09</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>31.3%</td>
<td>18.2%</td>
<td>2.05</td>
</tr>
<tr>
<td>HELLP Syndrome*</td>
<td>6%</td>
<td>2%</td>
<td>3.10</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2%</td>
<td>3%</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Discussion:** We found SLE significantly increased the risk of fetal loss in 2nd and 3rd trimesters (OR 6.49). The risk was similarly increased in this study for miscarriage (fetal loss<20 weeks) and stillbirth (fetal loss>20 weeks). In contrast, patients who were being treated with hydroxychloroquine (OR 2.28) or were compliant (OR 1.6) only had a minor increase in the risk as compared to control group. SLE patients had increased likelihood of having baseline hypertension, pre-eclampsia and pre-term labor. There was no increase in likelihood of association with hyperglycemia, C-sections, HELLP syndrome, anti-phospholipid antibodies or lupus activity markers in our comparison.

Our data suggest the likelihood of the fetal loss (6 vs 4 times), any complication (80% vs 50%), pre-eclampsia(33% vs 20%) or pre-term labor (50% vs 33%) may be higher than previously reported. The AA ethnicity may be a contributing factor here but a small sample size limits further characterization of the specific factors contributing to the increased risk.

**Conclusion:** There is a marked increase in risk of fetal loss and adverse pregnancy complications in African-American SLE patients many of which are higher than previously reported. Plaquenil and compliance with physician care seem to help decrease the likelihood of these adverse outcomes.

**Disclosure:** K. C. Edelman: None; V. Majithia: None.

**1861**

**Hyperuricemia Is a Predictor of Subclinical CVD in SLE Patients but Not Controls.** Joseph L. Enama1, Robert Gilkeson2 and Lisabeth Scalzi2.

1Case Western Reserve University, 2Penn State Univ Hershey, Hershey, PA

**Purpose:** Both systemic lupus erythematosus (SLE) and hyperuricemia are non-traditional risk factors for atherosclerotic cardiovascular disease (CVD). We compared the associations of serum uric acid levels (UA) and subclinical CVD, while adjusting for traditional CVD risk factors, between patients with SLE and controls.

**Methods:** 222 patients (140 with SLE, 82 controls), all without clinical CVD, were recruited from rheumatology clinics at two academic medical centers. Demographic information and fasting blood samples were collected from each patient. Coronary artery calcium scores (CAC) were calculated in each patient. Subclinical CVD (ICAC) was defined by [log (CAC +1)]. Associations of uric acid with traditional predictors of CVD were examined in univariate analyses. Traditional and non-traditional CVD risk factors— including dyslipidemia, body mass index (BMI), hypertension (HTN), high sensitivity C-reactive protein, smoking history, diabetes (DM), race, age, and UA—were examined as independent predictors of subclinical CVD. Variables were analyzed using either Chi-square or Student’s t-test, dependent on whether they were ordinal versus continuous measures respectively. Final linear regression models were calculated for SLE and controls, including all significant covariates (p < 0.1) for the analyses.

**Results:** Mean serum UA levels did not significantly differ between SLE and control patients. (6.0 mg/dL versus 6.4 mg/dL, p = 0.9). UA was significantly associated with advanced age (p = 0.01), hypertension (p < 0.01), and BMI (p < 0.01) in SLE patients. Significant covariates for ICAC in the control group included dyslipidemia (p = 0.05), HTN (p = 0.01), DM (p = 0.037), age (p < 0.01), and UA (p < 0.01). Significant covariates for ICAC in SLE patients included smoking history (p = 0.01), age (p < 0.01), and UA (p < 0.01). The linear regression model in controls demonstrated that only age was a significant predictor for ICAC (p = 0.01). UA was found to be a significant predictor for ICAC in SLE patients, when controlling for age and smoking (p = 0.03). SLE patients with UA in the upper tertile (uric acid ≥ 4.7 mg/dL) had a significantly higher ICAC (p = 0.04).

**Conclusions:** In patients with SLE, the presence of hyperuricemia in patients may predict CVD, independent of other traditional CVD risk factors. Larger studies are needed to determine if uric acid-lowering interventions may lower the risk of CVD in SLE.

**Disclosure:** J. L. Enama: None; R. Gilkeson: None; L. Scalzi: None.

**1862**


1Duke Univ Med, Durham, NC, 2Duke University, Durham, NC

**Background:** Depression is common (40%) in individuals with systemic lupus erythematosus (SLE), and may be exacerbated by disease activity and chronic pain. We aimed to measure the rate of depression in our SLE cohort, and to identify modifiable factors associated with depression.

**Methods:** Upon enrollment in our university-based SLE registry, each patient completed a questionnaire that included the Beck Depression Inventory II (BDI-II), pain scores, and demographic information. Disease activity was measured by the treating rheumatologist using the physician’s global assessment (PGA) and SLE disease activity index (SLEDAI). Current medications were recorded. For statistical analysis, patients were divided into two groups: depressed (BDI-II≥18) and not depressed (BDI-II<18). Student’s t-test was used to compare the means of continuous variables and z-test was used for dichotomous variables.

**Results:** The BDI-II was completed by 105 patients, 40 (38.1%) of whom were depressed (BDI≥18). Depression was associated with several measures of disease activity, prednisone and antidepressant use. It was not associated with demographic characteristics, including race, income, type of insurance, or age. (Table) Half of the patients with depression had clinically evident
arthritis as indicated on the SLEDAI (2 or more joints with current inflammation), but only 17% of those without depression had arthritis (p=0.0003). On the other hand, SLE rash, which can be disfiguring and lead to social isolation, was not associated with depression. The other individual measures of SLE activity in the SLEDAI, including hypocomplementemia and anti-dsDNA antibody, were not associated with depression. Prednisone dose and antidepressant use were associated with depression. Only 40% of patients with depression, however, were currently taking a selective serotonin-reuptake inhibitor (SSRI). In a multivariate analysis that included the measures that were independently associated with depression (including PGA, SLEDAI arthritis, current pain, prednisone dose, and antidepressant use), only the current level of pain remained significantly correlated with moderate to severe depression.

Conclusions: We found that depression was statistically significantly associated with pain, arthritis, lupus activity, prednisone dose and antidepressant use. In multivariate analysis, pain appeared to be the most important predictor of depression. It is unclear whether pain promotes depression or vice versa. However, pain may be a modifiable risk factor for depression in SLE patients, and treatment will likely be most successful when addressing both components.

Table. Demographics and independent variables in SLE patients with and without depression.

<table>
<thead>
<tr>
<th>Not Depressed (N=65)</th>
<th>Depressed (N=40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female no. (%)</td>
<td>60 (92%)</td>
<td>37 (93%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>31 (48%)</td>
<td>25 (63%)</td>
</tr>
<tr>
<td>African-American</td>
<td>29 (45%)</td>
<td>13 (33%)</td>
</tr>
<tr>
<td>Age</td>
<td>38 ± 12</td>
<td>40 ± 12</td>
</tr>
<tr>
<td><strong>Means of Lupus Activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGA†</td>
<td>0.6 ± 0.7</td>
<td>0.9 ± 0.7</td>
</tr>
<tr>
<td>SLEDAI‖</td>
<td>3.4 ± 3.7</td>
<td>4.9 ± 4.6</td>
</tr>
<tr>
<td>SLEDAI arthritis</td>
<td>11 (17%)</td>
<td>20 (50%)</td>
</tr>
<tr>
<td>SLEDAI rash</td>
<td>14 (22%)</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Current pain (0–10)</td>
<td>3.0 ± 3.0</td>
<td>6.0 ± 2.5</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone dose (mg)</td>
<td>5.6 ± 9.3</td>
<td>11.2 ± 16.7</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>13 (20%)</td>
<td>16 (40%)</td>
</tr>
</tbody>
</table>

†PGA: Physician’s Global Assessment, scale 0 (no activity) to 3 (severe activity)
‖SLEDAI: Systemic Lupus Erythematosus Disease Activity Index


1863

In Systemic Lupus Erythematosus (SLE) Patients, Patient Reported Outcomes and Physician Assessment of Disease Activity Are Poorly Correlated: Implications for Outcome Measures in SLE. Magaly Vil- lafradez Diaz1, Ashwini Shadakshari, Andy McCracken, Christopher Swearingen, Daniel Ricciardi and Yusuf Yazici2.1 Long Island College Hospital, 2NYU Hospital for Joint Diseases

Purpose: To evaluate the correlation of patient vs physician reported outcome measures in a routine care SLE cohort.

Methods: The first recorded physician global observations in patients with the primary diagnosis of systemic lupus were identified; corresponding demographic, patient reported functional outcomes and current usage of prednisone, hydroxychloroquine and non-steroidal anti-inflammatory medications and immunosuppressive medication use were abstracted. Current medication usage was operational defined as medications taken prior to and including the visit date; patient discontinuations prior to the selected visit and medication initiations at the selected visit were defined as non-current usage. Summary statistics for demographic, outcome measures and median visit of physician global observation were estimated by current medication usage. Lin’s concordance correlation was estimated for each patient reported functional outcome compared to the physician global. Spearman’s correlation coefficient were calculated for patient and physician measures.

Result: 180 patients were included in this analysis (mean age 42, disease duration 0.7 years, 93% female, education 14 years). On average patients had active disease, with (mean SD) pain 5.0 (3.0), function 2.5 (1.9), fatigue 6.1 (3.0) patient global assessment of disease activity 4.9 (2.6) and physician global assessment of disease activity 2.4 (1.7), (all measures range 0–10). Mean RAPID3 score (range 0–30) was 12.8 (6.1). Spearman and concordance correlations are given in Table 1. There was only moderate correlation seen with physician assessment of disease activity with all patient reported outcomes and the RAPID3 composite index.

<table>
<thead>
<tr>
<th>Table 1. Spearman and Concordance Correlations (95% Confidence Intervals) between Physician Global and Patient Reported Outcomes in SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Global Association</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Function</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Global</td>
</tr>
<tr>
<td>RAPID3</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
</tbody>
</table>

Conclusions: In this cohort of SLE patients seen in routine care, there was moderate correlation between what the patients reported about their disease activity and physicians perceptions of their disease activity. Measures that primarily depend on physician assessment of disease activity may be poor correlates of SLE activity and may not be ideal measures to be used in clinical trials of SLE.

Disclosure: M. V. Diaz: None; A. Shadakshari: None; A. McCracken: None; C. Swearingen: None; D. Ricciardi: None; Y. Yazici: None.

1864

Incidence and Predictors of Hospitalization in Systemic Lupus Erythematosus (SLE): Results from a Large Contemporary Multi-Ethnic Cohort. June Lee1, Janet E. Pope1, Christine A. Peschken2 and The 1000 Faces of Lupus. 1St Joseph Health Care London, London, ON, Canada, 2Univ of Manitoba, Winnipeg, MB, Canada, 3University of Western Ontario, London, ON, Canada

Background: Annual rates of hospitalization for lupus are as high as 30 to 40%. The aim of this study was to determine the rate of, causes for, and determinants of hospitalization in a large contemporary SLE cohort.

Methods: Data from the 1000 Canadian Faces of Lupus (a prospective multi-centre cohort study) were used. Data on hospitalization, lupus flares, demographics, medication history, disease activity and damage, and co-morbidities are collected annually. Univariate and regression analyses were performed.

Result: Data on hospitalization (yes or no) were available on 724 participants; 68 reported hospitalizations related to SLE (hospitalization rate of 9.4% overall and an annual hospital rate of 7.2%). The most common causes of SLE-related hospitalization were hematologic (18.1%), serositis (16.9%), musculoskeletal (13.3%), and renal (12.0%). Some were hospitalized for more than one reason. The occurrence of hospitalization was significantly associated with: Aboriginal compared to Caucasian, Asian and Blacks (p=0.003), having a lower household income (p=0.01), being work disabled (p=0.001), having greater disease activity as indicated by the SLAM-2 (p=0.004), having a greater number of ACR criteria (p=0.006), positive anti-Smith (anti-Smith)antibody (p=0.018) and use of azathioprine (p=0.039). There was no significant relationship between hospitalization and gender, age, number of co-morbidities (as indicated by the Charlson Co-morbidity Score), or number of medications used.

Table. Demographic Characteristics of the 2 Groups

<table>
<thead>
<tr>
<th>No. (%) of Patients</th>
<th>Non-Hospitalized</th>
<th>Hospitalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>656 (90.6)</td>
<td>68 (9.4)</td>
</tr>
<tr>
<td>Gender, Ratio F:M</td>
<td>8.8:1</td>
<td>8.5:1</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>40.5 (17.4)</td>
<td>39.8 (16.9)</td>
</tr>
<tr>
<td>Ethnicity†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>417 (92.7)</td>
<td>33 (7.3)</td>
</tr>
<tr>
<td>Black</td>
<td>56 (93.9)</td>
<td>4 (6.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>118 (95.9)</td>
<td>5 (4.1)</td>
</tr>
<tr>
<td>Aboriginal*</td>
<td>44 (81.5)</td>
<td>10 (18.5)</td>
</tr>
<tr>
<td>Work Disabled**</td>
<td>102 (15.5)</td>
<td>25 (36.6)</td>
</tr>
<tr>
<td>High School Education</td>
<td>55 (81.0)</td>
<td>24 (37.3)</td>
</tr>
<tr>
<td>Income Level††</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$15,000</td>
<td>63 (85.1)</td>
<td>11 (14.8)</td>
</tr>
<tr>
<td>$15,000–$29,999</td>
<td>72 (94.7)</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td>$30,000–$49,999</td>
<td>123 (95.3)</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>≥$50,000</td>
<td>247 (96.1)</td>
<td>10 (3.9)</td>
</tr>
</tbody>
</table>

†Excluded 37 participants whose ethnicity not available or belonged to ethnic group other than the 4 of interest.
†Significant relationship between being of Aboriginal race and hospitalization (p=0.004).
††$30,000–$49,999.
Conclusions: The rate of hospitalization of patients with SLE was lower than expected; however, this may indicate that the care of lupus is improving, that the cohort is biased towards healthy patients, or that flares are more likely to be handled as an outpatient. Also some renal lupus may be followed solely by a nephrologist. Some hospitalizations may have been under ascertainment and we did not record hospitalizations for non-lupus reasons such as pregnancy. The causes of hospitalization were varied and different than what other studies have shown. Several predictors of hospitalization are related to ethnicity, socioeconomic factors and disease activity, which is consistent with results of other studies.

Disclosure: J. Lee: None; J. E. Pope: None; C. A. Peschken: None; The 1000 Faces of Lupus: None.

1866

Mycophenolate Mofetil (MMF): Physician Prescribing Practices. Seema Malani and Ellen M. Ginzler. SUNY Downstate Medical Center, Brooklyn, NY, SUNY-Downstate Medical Center, Brooklyn, NY.

Purpose: MMF is commercially available and used off-label for the treatment of SLE but consensus guidelines for its use in lupus and other autoimmune diseases are lacking. We were interested in learning the prescribing practices for MMF among rheumatologists and nephrologists, and their experience with efficacy and toxicity.

Method: Approximately 700 adult and pediatric rheumatologists and nephrologists interested in SLE from the U.S. and Canada were invited via e-mail to complete an electronic survey, including 20 questions regarding their prescribing practices for MMF, MMF dose and duration of use, ethnic differences in response to MMF, and MMF use for extra-renal lupus manifestations.

Results: 141 physicians responded to the survey. The majority were rheumatologists (95.5%) with 3.5% nephrologists; 55% practice in an academic institution. The majority (60%) treat 10–50 SLE patients/month.

Conclusions: Adherence to drug therapy measured by electronic monitoring appears to be low in patients with SLE, and related to depression and overall mental health. Only 1 out of 5 patients was at least 80% adherent. Low adherence appeared to have a detrimental effect on health outcomes.

Acknowledgments: This work was supported in part by the Department of Veterans Affairs.

Disclosure: M. F. Marengo: None; C. A. Waimann: None; S. de Achaval: None; V. L. Cox: None; A. García Gonzalez: None; M. N. Richardson: None; M. E. Suarez-Almazor: AHRR, 2, NIH, 2.
Most respondents change from MMF to other maintenance drugs only for side effects or insurance coverage issues. GI side effects were the most common adverse events reported (84%), followed by infection (30%), and hematologic effects (27%).

Conclusion: Despite a lack of guidelines for MMF use, it is the first choice therapy both in remission induction and maintenance of lupus nephritis. Most physicians continue MMF for a long duration. There also appears to be considerable use of MMF for treatment of extra-renal manifestations of SLE.

Disclosure: S. Malani: None; E. M. Ginzler: None.

1867

Novel Cardiovascular Risk Prediction Models in Patients with Systemic Lupus Erythematosus. Vivian K. Kawai1, Annette M. Oesor3, Joseph Solus1, Dominique Iban‡e2, Dafna D. Gladman2 and Murray B. Urowitz3.

Background: With systemic lupus erythematosus (SLE) have accelerated atherosclerosis and increased coronary heart disease (CHD), but the Framingham risk score (FRS) underestimates risk. Several new approaches have improved prediction of CHD risk in the general population. These include the Reynolds risk score (RRS), that substitute “coronary age” in place of chronological age. We examined the hypothesis that these new CHD risk prediction models would better identify increased risk of CHD in women with SLE, particularly in those with subclinical coronary atherosclerosis.

Methods: We studied 121 women with SLE and 65 age-matched female-controls without a previous cardiovascular event. Demographic and clinical data were recorded and FRS and RRS calculated. Coronary artery calcium (CAC) was measured by computed tomography using the Agatston score, and coronary age was derived as described by McClelland. Coronary age-modified risk scores (camFRS, camRRS) were calculated in which chronological age in the existing FRS and RRS calculations was replaced with coronary age. Risk scores were compared in patients with SLE and controls, and in SLE patients with and without CAC, using Wilcoxon rank sum tests. We examined the association between risk scores and CAC using proportional odds logistic regression models. Paired analyses were performed using Wilcoxon signed-rank test or McNemar's test, as appropriate. All analyses used a 5% two-sided significance level.

Results: Coronary artery calcium was present in 21 patients with SLE (17%) and 4 controls (6%) (P=0.033). However, despite more frequent and severe atherosclerosis in SLE, the FRS, camFRS, RRS and camRRS did not differ significantly among women with SLE and controls (p=0.05). In women with SLE with CAC the FRS (OR=1.42, 95%CI (1.06,1.90), P=0.017) and RRS (OR=1.29, 95% CI (1.11-1.51), P=0.001) were higher than in those without CAC, however few patients (≤5%) with CAC had 10-year risk scores ≥10% - the threshold used to determine moderate CHD risk. Coronary age-modified risk scores were significantly lower than their respective conventional risk scores in lupus patients without CAC, and higher in those with CAC (both P values ≤0.001). Coronary age-modified risk scores assigned more patients with CAC to a risk category of ≥10% (camFRS 48%, cam RRS 29%) than conventional scores (FRS 0%, RRS 5%) (P =0.004 and P=0.073, respectively).

Conclusions: The RRS, a novel 10-year risk prediction model that includes C-reactive protein in the risk calculation, was of limited use in women with SLE. Incorporation of coronary age, calculated from CAC scores, into risk prediction models increases the number of patients with CAC with a predicted CHD risk above the 10% 10-year threshold. The ability of models that include coronary age to predict risk of cardiovascular events will be of interest.

Disclosure: V. K. Kawai: None; A. M. Oesor: None; J. Solus: None; Y. H. Rho: None; P. Raggi: None; A. Bian: None; T. Gebretsadik: None; A. Shintani: None; C. M. Stein: None.

1868

Optimal Frequency of Visits To Capture Disease Activity over Time. Dominique Ibanez1, Dafna D. Gladman2 and Murray B. Urowitz3.

Objective: Disease activity in SLE patients, measured by SLEDAI-2K, is evaluated at each clinic visit and covers a period of 30 days prior to the assessment. Having consecutive monthly clinic visits would capture the entire disease activity for that period of time. Adjusted Mean SLEDAI (AMS) calculates the areas under the curve of SLEDAI-2K over time. AMS evaluated using monthly visits would be the gold standard for disease activity over time. Usual clinical practice is to see patients every 3–6 months. The aim of this study is to compare the AMS obtained over a one year period when visits are done monthly and compare it to AMS obtained using quarterly, semi-annual or annual visits.

Methods: Patients followed monthly for 12 consecutive visits are included. AMS is evaluated using all of the SLEDAI-2K (AMSgold, using all 12 visits), only quarterly visits (AMSq, using visits 3 months apart), semi-annual visits (AMS, using 1st, middle and last visits only) and annual visits (AMS, using only the 1st and last visits). Comparisons between AMSq, ASMs, and AMSannual with AMSgold are made using descriptive statistics.

Results: 78 patients were seen monthly for a year. 72 (92%) were women with mean (std) age at SLE diagnosis of 30.1 (11.4) years and mean age and disease duration at study start of 46.2 (12.0) years and 15.5 (9.7) years respectively. The SLEDAI-2K values seen have a mean (std) of 2.05 (2.07) and range in values from 0 to 15, with 7% of all visits having a SLEDAI-2K ≥ 5. The mean (std) AMSgold for the entire year is 2.05 (1.66), for AMSq = 1.99 (1.65), for AMS = 2.12 (1.87) and for AMSannual = 2.08 (1.83).

Conclusion: Usual clinical visits occurring quarterly offer a good estimation of disease activity over a one year period and are preferred over semi-annual and annual visits.

Disclosure: D. Ibanez: None; D. D. Gladman: None; M. B. Urowitz: None.

Wednesday, November 10

S781
Percent of Errors Based on Visit Frequency and Level of Disease Activity

<table>
<thead>
<tr>
<th>Level of Disease Activity</th>
<th>Using Semi-annual Visits</th>
<th>Using Annual visits</th>
<th>Using Visits 18 months apart</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minor (n=82)</td>
<td>Mild (n=80)</td>
<td>Moderate (n=40)</td>
</tr>
<tr>
<td>Minor</td>
<td>56%</td>
<td>51%</td>
<td>45%</td>
</tr>
<tr>
<td>Acceptable</td>
<td>35%</td>
<td>31%</td>
<td>17%</td>
</tr>
<tr>
<td>Important</td>
<td>9%</td>
<td>18%</td>
<td>38%</td>
</tr>
<tr>
<td>Serious</td>
<td>0%</td>
<td>1%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Conclusion:** Quarterly visits are preferred over visits further apart. In patients with lower disease activity, semi-annual visits are a good estimation of disease activity over time while in patients with more active disease, shorter times between visits are necessary.

**Disclosure:** D. Ibanez: None; M. B. Urowitz: None; D. D. Gladman: None.

**1870**

**Performance of Anti-Nucleosome, Anti-C1q and Anti-dsDNA Antibodies for the Diagnosis of Concurrent Disease Activity of Systemic Lupus Erythematosus.** Chi Chiu Mok, Ling Yin Ho, Hoi Wah Leung and Lap Gate Wong, Tuen Mun Hospital

**Objectives:** To evaluate the specificity and sensitivity of anti-nucleosome, anti-C1q and anti-dsDNA antibodies in the diagnosis of disease activity in systemic lupus erythematosus (SLE)

**Methods:** Consecutive patients with SLE were recruited for serological testing of anti-dsDNA (Euro-diagnostica, Amherst, Netherlands), IgG-anti-nucleosome and IgG-anti-C1q (Euroimmun, Lubeck, Germany) antibodies by ELISA and complement levels by immunonephelometry (Siemens, Germany). Concurrent renal and extra-renal disease activity was assessed by SLEDAI-2K and physician global assessment (PGA). Correlation among levels of these antibodies, complements and disease activity scores was made by spearman’s rank correlation test. The specificity and sensitivity of these antibodies in diagnosing concurrent renal and extra-renal activity was calculated.

**Results:** 245 SLE patients were studied (95% women). The mean age was 40.6±12.2 years at the time of blood tests; and the duration of SLE was 8.7±7.1 years. The prevalence of positive anti-dsDNA (≥50IU/ml), anti-nucleosome (≥20RU/ml) and anti-C1q antibodies (≥20RU/ml) was 55%, 44% and 21%, respectively. All the 3 antibodies correlated significantly with complement levels (C3 and C4), SLEDAI (with deduction of scores due to elevation of anti-dsDNA and depression of complements) and PGA scores (P<0.001 in all). Positive anti-dsDNA and anti-C1q, but not anti-nucleosome antibodies correlated significantly with the presence of active renal disease as scored by the SLEDAI. The sensitivity of anti-dsDNA, anti-nucleosome and anti-C1q antibodies for the presence of active renal disease was 75%, 47% and 53%, respectively. The specificity was highest for anti-C1q for active lupus renal disease (84%), followed by anti-nucleosome (57%) and anti-dsDNA antibodies (49%). The specificity of combined anti-dsDNA and anti-C1q for active renal disease was 88%. The negative predictive value of a negative anti-dsDNA and anti-C1q for active renal disease was 91%. For the prediction of concurrent extra-renal SLE activity, the specificity was also highest with anti-C1q (83%), followed by anti-nucleosome (60%) and anti-dsDNA (48%) antibodies.

**Conclusions:** Anti-nucleosome does not perform better than anti-dsDNA for the presence of concurrent SLE activity. Anti-C1q antibodies, however, is more specific than anti-dsDNA for both renal and extra-renal lupus activity. The absence of both anti-dsDNA and anti-C1q has a high negative predictive value for concurrent active renal disease.

**Disclosure:** C. C. Mok: None; I. Y. Ho: None; H. W. Leung: None; L. G. Wong: None.

**1871**

**Predictive Value of High Levels of Antinuclear Antibodies in People without Other Feature of Autoimmunity. A Prospective Study.** Ignacio Villa-Blanco1, Marcos Lopez-Hoyos2, Ana Ruibal3 and Jaime Calvo-Alen4.

**Hospital Marques de Valdecilla**, 2Hospital Txagorrutz, 3Hospital Serrallana, Torrelavega, Spain, 4Hospital Serrallana, Spain

**Background:** Low levels of antinuclear antibodies (ANA) are not an uncommon finding in otherwise healthy people but the presence of high levels of ANA is a far less common situation. On the other hand, different studies have shown that diseases as systemic lupus erythematosus (LES) may be heralded by the presence of these autoantibodies several years before. Therefore, it is possible to hypothesize that people with high ANA titters may portend and special risk for the development of autoimmune diseases but prospective data to this regard are lacking.

**Objective:** To analyze the outcome of healthy people with high levels of ANA.

**Methods:** All patient of our centre with a positive ANA test with a titter ≥1/1280 obtained between January of 1996 and December of 2006 were identify regardless the reason to order such test. A medical record review was performed in all cases and only those cases where any type of inflammatory or autoimmune disease had been excluded at the moment when the ANA test was performed and with a minimum time of follow up (from the date when the positive ANA test was obtained up the time of study onset) of 36 months were selected. In all cases, the development of any autoimmune disease during the follow up was established by chart review and then the rest of patient were contacted for further clinical and laboratory evaluation at the outpatient clinic.

**Results:** Overall, 133 patient were identified with a positive ANA test with a titter ≥1/1280. Out of them, 68 had been diagnosed of having different types of inflammatory or autoimmune disease (11 Rheumatoid arthritis, 11 Sjögren syndrome (SS), 8 autoimmune hepatitis, 5 LES, 4 undifferentiated connective tissue disease, 4 CREST syndrome, 3 primary biliary cirrhosis (PBC), 3 Dermatomyositis, 3 Inflammatory Bowel disease, 2 Morfea, 2 pemigusus anaemia, 1 polymyalgia rheumatica, 1 Scleroderma, 1 antiphospholipid syndrome, 1 VIH, 1 VHC, 2 Hashimoto thyroiditis, 1 myelodysplastic syndrome, 1 mixed connective tissue disease, 1 sarcoidosis, 1 BONO, 1 ankylosing spondylitis. In 65 patients [78% women; mean age (range) 60.7 years (20-92)] this type of diseases were excluded. During the follow up [mean time (range) 86 months (36–120)], 8 patients (12%) developed systemic diseases; 2 LES with renal involvement after 96 and 48 months from the initial ANA test, 2 SS (45 and 59 months after the initial ANA test), 2 PBC (36 and 38 months after the initial ANA test), 1 autoimmune hepatitis (95 months after the initial ANA test) and 1 incomplete CREST syndrome (46 months after the initial ANA test). No other findings suggestive of autoimmune diseases were identify in the rest of 57 patients but in 39 % of them, ANA titers remained high (≥1/1280).

**Conclusions:** According to our data, during the follow up, a significant percentage (22%) of asymptomatic patients with ANA titters ≥1/1280 may develop an autoimmune disease. Patients with persistent positive ANA test have a special risk for the development of autoimmune disease and may need longer periods of follow up.

**Disclosure:** I. Villa-Blanco: None; M. Lopez-Hoyos: None; A. Ruibal: None; J. Calvo-Alen: None.

**1872**

**Preliminary Comparison of Health-Related Quality of Life in Children with Lupus across Different Continents.** Lakshmi Nandini Moorothy1, Claudia Saad-Magalhães2, Juliana Oliveira Sato3, Claudio A. Len4, Maria O. Hilario5, Flavio Sztajnbok6, Rozana Gasparello de Almeida7, Feng Qi Wu8, Xiaolan L. Huang9, Fernanda Falcini1, Donato Rigante1, Rolando Cimaz1, Jordi Antón Lopez10, Consuelo MODESTO11, Rubén J. Cuttica12, Lisette W. A. van Suljekom-Smit13, Mañeca H. Otten14, Maria J. Baratelli15, Margaret G. E. Peterson16, Affon L. Hassett15, Thomas J. A. Lehman4.

1Botucatu Medical School-São Paulo State University, Brazil, 2Capital Institute of Pediatrics, China, 3Erasmus MC, Sophia Childrens Hospital, The Netherlands, 4Hosp for Special Surgery, New York, NY, 5Hospital de Pediatría Pedro de Elizalde, Argentina, 6Hospital for Special Surgery, 7Hospital Infantil Valle de Hebron, Spain, 8Hospital Sant Joan de Deu, Spain, 9Universidade do Estado do Rio de Janeiro, Brazil, 10Universidade Federal de São Paulo, Brazil, 11Università Cattolica Sacro Cuore, Italy, 12University of Firenze, Firenze, Italy, 13University of Florence, Florence, Italy, 14University of Medicine and Dentistry of NJ-Robert Wood Johnson Medical School, New Brunswick, NJ, 15University of Michigan Medical School, Ann Arbor, MI
Background: Simple Measure of Impact of Lupus Erythematosus in Youngsters® (SMILEY®) is a brief 24-item health-related quality of life (HRQOL) assessment tool for pediatric systemic lupus erythematosus (SLE). Responses are in the form of a 5-faces scale for easy comprehension. Higher percentage scores indicate better HRQOL. SMILEY is valid in US-English and has been translated and adapted to 21 languages. Currently, we are conducting cross-cultural validation of SMILEY. We are also preliminarily exploring differences in HRQOL using SMILEY across different countries and examining factors influencing these differences.

Objective: We conducted preliminary analysis of SMILEY scores from various countries in South America, Europe and Asia.

Methods: Children ≤18 years with SLE and parents completed the appropriate SMILEY translation, and gold standard quality of life and physical function scales. Physicians completed the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Across the countries, we compared age, SMILEY and PedsQL generic total scores, Child Health Assessment Questionnaire (CHAQ) disability index, and SDI. Contingent upon the data distribution of the above variables, we used one-way ANOVA or the Kruskal-Wallis (KW) test. Because of the limited sample size for each country, we have combined data by similar geographic regions (continents).

Results: 125 children (106 girls) and parents participated from South America (Brazil = 45, Argentina = 11), Europe (Italy = 16, Spain = 15, Netherlands = 10), and Asia (China = 28). Table 1 shows the means/medians of child and parent reports of SMILEY and PedsQL generic total scores; parent CHAQ disability index; age; and SDI. Children from Asia had the highest SMILEY and PedsQL scores (indicating higher HRQOL), and lowest age. Significant differences between continents were found for age, parent PedsQL and child SMILEY scores. Parents’ PedsQL and SMILEY scores were lower compared to child scores and this difference was most pronounced for children from South America.

Table 1. HRQOL, SDI, SLE-duration and age across the continents

<table>
<thead>
<tr>
<th></th>
<th>South America</th>
<th>Europe</th>
<th>Asia</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMILEY total*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (range, n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child</td>
<td>68 ± 15 (33-97, 52)</td>
<td>70 ± 16 (26-93, 41)</td>
<td>77 ± 13 (56-96, 28)</td>
<td>3.03 (ANOVA)</td>
</tr>
<tr>
<td>Parent</td>
<td>64 ± 16 (36-100, 54)</td>
<td>69 ± 16 (15-94, 38)</td>
<td>72 ± 16 (39-100, 28)</td>
<td>0.01 (ANOVA)</td>
</tr>
<tr>
<td>PedsQL total*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (range, n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child</td>
<td>74 ± 15 (38-98, 42)</td>
<td>74 ± 21 (24-100, 38)</td>
<td>81 ± 11 (57-99, 27)</td>
<td>0.14 (ANOVA)</td>
</tr>
<tr>
<td>Parent</td>
<td>66 ± 22 (15-100, 40)</td>
<td>73 ± 19 (32-96, 28)</td>
<td>79 ± 19 (35-100, 28)</td>
<td>0.03 (ANOVA)</td>
</tr>
<tr>
<td>CHAQ score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range, n)</td>
<td>0 (0-2.375, 42)</td>
<td>0 (0-1.25, 25)</td>
<td>Not completed</td>
<td>0.3 (KW)</td>
</tr>
<tr>
<td>SDI</td>
<td>0 (0-4.45)</td>
<td>0 (0-4.40)</td>
<td>0 (0-3.1, 11)</td>
<td>0.7 (KW)</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>27 (1-116, 54)</td>
<td>31 (1-150, 49)</td>
<td>23 (1-188, 25)</td>
<td>0.2 (ANOVA)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>14 ± 3 (16-18, 52)</td>
<td>15 ± 2 (7-18, 40)</td>
<td>12 ± 3 (5-16, 27)</td>
<td>0.005 (ANOVA)</td>
</tr>
<tr>
<td>Mean ± SD (range, n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| *Higher percentage scores indicate better HRQOL.

Conclusion: On preliminary analysis, differences in HRQOL and age were found across continents. Children from Asia (China) were the youngest and had the highest HRQOL. Age and cultural differences can influence HRQOL. Parents seemed to perceive a lower HRQOL for children with SLE; either reflecting a greater perception of their child’s vulnerability, their own anxiety, or HRQOL.

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1874

Prolonged Serologically Active Clinically Quiescent (SACQ) Systemic Lupus Erythematosus (SLE): Novel Predictors of Flare? Amanda Steinberg1, Murray B Urowitz1, Don, I. Wither2, Dominique Iban˜ez1, Timothy Li3 and Dafna D. Gladman1. 1Toronto Western Hospital, Toronto, ON, Canada, 2Toronto Western Hospital, Toronto, ON, Canada, 3Toronto Western Hospital, University Health Network, Toronto, ON, Canada

Purpose: Anti-double stranded DNA antibodies (anti-dsDNA) and complement levels are routinely used to predict flare in SLE patients. Some SLE patients, however, are clinically quiescent despite persistent serologic activity, as evidenced by elevated anti-dsDNA and/or hypocomplementemia. Past studies reveal that nearly 60% of such SACQ patients flare, but do so only after average 182 weeks. In these patients changes in total serum anti-dsDNA and/or C3/C4 levels measured at routine clinic visits were not predictive of flare. Some studies suggest that anti-chromatin (-nucleosome) antibodies are more sensitive than anti-dsDNA to detect active SLE, and that the time to first flare after a SACQ period was significantly correlated with their presence. This study investigates whether levels of anti-dsDNA and anti-chromatin isotypes, measured during a prolonged SACQ period, differed in SACQ patients who remained SACQ versus those who flared. Archival serum: Archived serum samples of patients with a prolonged SACQ period, stored at ~80 °C, were retrieved and divided by disease activity (during a SACQ period vs during flare). Serum levels of IgM, IgA, IgG, IgG3, and IgG4 anti-dsDNA antibodies were measured by ELISA. H1-stripped chromatin was prepared from the human cell line, MOLT4. ELISA plates were coated overnight with dsDNA (40 µg/ml) and chromatin (8 µg/ml) diluted in PBS at 4°C. Serum was diluted 1/100 for measurement of IgM, IgG, and IgG3, or 1/50 for IgG4–1. SACQ was defined as at least a two year sustained period with SLEDAI of 2 or 4 from serologic activity only, during which patients could be taking antimalarials, but not steroids or immunosuppressives. Flare was defined as any increase in clinical disease activity. P-values were reported using Wilcoxon rank sum tests.

Results: Thirty-eight serum samples which corresponded to a prolonged SACQ period (from 23 patients) were analyzed. Fifteen of the 38 (39%) samples corresponded to patients whose SACQ period ended in flare. Anti-chromatin total IgG levels were significantly lower in SACQ patients who flared than in those who remained SACQ (0.361 ± 0.277 vs 0.835 ± 0.700, p = 0.007; normal < 0.147), however there was no significant difference between these groups when IgG was broken down by subtype. Anti-chromatin IgM and IgA values were comparable between groups. Anti-dsDNA IgG but not IgM or IgG3 was significantly lower in SACQ patients who flared compared to those who remained SACQ (0.028 ± 0.025 vs 0.081 ± 0.095, p = 0.018). When only the most recent sample from each SACQ patient was analyzed (9/23 (39%) of whom flared), there was no difference between anti-chromatin or anti-dsDNA isotype levels between patients who flared and those who remained SACQ.
Conclusions: In this small pilot study neither anti-chromatin nor anti-dsDNA antibody levels were predictive of flare in SACQ patients. Alternate serum biomarkers must be sought.

Disclosure: A. Steiman: None; M. B. Urowitz: None; J. E. Wither: None; D. Ibañez: None; T. Li: None; D. B. Gladman: None.

1875

Racial Disparities in Treatment Preferences among Lupus Patients. Ernest R. Vina, Christopher M. Mas, Stephanie L. Green and Tammy O. Uset. University of Chicago Medical Center, Chicago, IL.

Background: Worse health outcomes among African-American compared to white SLE patients are well documented. While racial differences in patient treatment decisions have been identified in other diseases, this phenomenon has not been explored in SLE. The objectives of this study are: (1) to determine whether there are differences between African American and white SLE patients’ willingness to a) receive an immunosuppressive medication (cyclophosphamide, CTX) when clinically indicated and b) participate in clinical trials involving novel, experimental medications; and (2) to determine whether demographic, psychosocial and clinical characteristics explain racial differences in either measure of medical management.

Methods: Data from 25 African-American and 25 white lupus patients were evaluated. Structured telephone interviews were conducted to determine treatment preferences, as well as characteristics and beliefs that may affect these preferences. Chart reviews were conducted to evaluate clinical characteristics (disease duration: SLEDAI, SLICC Damage Index, Charlson Comorbidity). Serial hierarchical multivariate logistic regression analyses using forward selection of variables with p<0.20 were conducted.

Results: Compared to white SLE patients, African American SLE patients were less willing to receive CTX (96% vs 56%, p=0.001). They also had lower incomes (p<0.005), were less likely to have private insurance (p=0.001), and were more likely to believe that prayer can affect health outcomes (p=0.047). While participating in clinical trials involving novel, experimental medications was more likely among white patients (62% vs 10%, p=0.001). Having a physician with a participatory decision-making (PDM) style (p=0.056), to be married (p<0.003), having private insurance (p=0.034), to be more educated (p=0.047) and to perceive CTX to be effective (p=0.001). Multivariate logistic regression analysis showed that age (OR=1.13, p=0.042), educational level (OR=8.90, p=0.025) and perception of effectiveness of treatment (OR=1.67, p=0.025) were significant predictors of willingness to receive CTX. After adjustment for these variables, willingness to receive CTX was higher among whites compared to African Americans (OR=11.74) but this effect did not reach significance (p=0.056).

In contrast, no significant racial differences were observed in willingness to participate in a clinical trial (84% among whites vs 68% among African-Americans, p=0.185). Willingness to participate in a clinical trial was positively associated with being married (p=0.015), having private insurance (p=0.05) and having a physician with a participatory decision-making (PDM) style (p=0.001). A logistic regression model showed that the CES-D score (OR=0.91, p=0.017) and physician PDM style (OR=1.08, p=0.003) were significant predictors of willingness to participate in a clinical trial.

Conclusions: We found a trend toward decreased likelihood of accepting CTX among African American compared to white lupus patients after adjusting for multiple covariates. In contrast, African American and white SLE patients did not differ in willingness to participate in a clinical trial. We continue to collect data and will determine whether these results persist with larger cohorts of African-American and white SLE patients.

Disclosure: E. R. Vina: None; C. M. Mas: None; S. L. Green: None; T. O. Uset: None.

1877


S784

West Hollywood, CA, 2Timonium, MD, 3Emory University, Atlanta, GA, 4Feinstein Institute, Manhasset, NY, 5Haaimyes Hospital, East Kilbride, United Kingdom, 6Hanyang University Medical Center, Seoul, Korea, Republic of, 7Hospital Clinico I Provincial, 8Hospital de Cruces, Universidad del Pais Vasco, 9Instituto Nacional Nutricion, Mexico City, DF, Mexico, 10Kan-tansapp Schaffhausen, Schaffhausen, Switzerland, 11Karolinska University Hospital, 12Landskapislinn University Hospital, 13Manchester Royal Infirmary, Manchester, United Kingdom, 14Medical University of South Carolina, Charleston, SC, 15Montreal General Hospital, Montreal, QC, Canada, 16North West Wales NHS Trust, Colwyn Bay, United Kingdom, 17Northwestern University, Chicago, IL, 18Oklahoma Medical Research Foundation, Oklahoma City, OK, 19Queen Elizabeth II Health Services Center, Halifax, NS, Canada, 20SUNY-Downstate Medical Center, Brooklyn, NY, 21The Rayne Institute, London, United Kingdom, 22Toronto Western Hospital, Toronto, ON, Canada, 23UBA Rheumatology, Birmingham, AL, 24UCI Div of Medicine, Medicine, United Kingdom, 25UCL Div of Medicine, 26UCSD School of Medicine, La Jolla, CA, 27University Hospital Lund, Lund, Sweden, 28University of Alabama, Oakland, CA, 29University of Birmingham, Birmingham, United Kingdom, 30University of Manitoba, Winnipeg, MB, Canada, 31University of North Carolina at Chapel Hill, Chapel Hill, NC, 32University of Toronto Lupus Clinic, Toronto Western Hospital, Toronto, ON, Canada, 33West Penn Allegheny Health System, Pittsburgh, PA
A large multicentre multinational inception cohort was established to study risk factors for atherosclerosis (AS) in SLE. We have previously shown that a significant number of atherosclerotic disease risk factors are present within the first year of SLE. This study examines the presence of SLE and atherosclerotic risk factors at inception in a multicenter, international cohort of SLE patients according to ethnic groups and by geographic distribution.

Methods: 30 centres from 11 countries assembled an inception cohort of SLE patients according to a standardized protocol between 2000 and 2010 to study risk factors for atherosclerosis. Simple statistics are provided. Comparisons between ethnic groups and geographic distributions were made using chi square tests and analysis of variance.

Results: Of the inception cohort of 1593 SLE patients 89% were female and age at diagnosis was 35±13 yrs. Patient characteristics are as follows:

Table 1. Distribution by Geographical Area of Residence

<table>
<thead>
<tr>
<th>Race</th>
<th>N</th>
<th>Canada</th>
<th>Europe</th>
<th>Mexico</th>
<th>USA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex F</td>
<td>257 (10.6)</td>
<td>247 (15.2)</td>
<td>772 (48.5)</td>
<td>250 (15.7)</td>
<td>65 (4.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>30 ± 11</td>
<td>34 ± 11</td>
<td>38 ± 15</td>
<td>35 ± 10</td>
<td>35 ± 14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SLEDAI-JK</td>
<td>7.1 ± 6.1</td>
<td>4.5 ± 5.0</td>
<td>4.5 ± 5.0</td>
<td>6.8 ± 5.9</td>
<td>5.7 ± 4.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SRI-50</td>
<td>2.79 ± 1.07</td>
<td>2.79 ± 1.07</td>
<td>2.79 ± 1.07</td>
<td>2.79 ± 1.07</td>
<td>2.79 ± 1.07</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Table 2. Distribution by Ethnic Group

<table>
<thead>
<tr>
<th>Race</th>
<th>N</th>
<th>Asian</th>
<th>Black</th>
<th>Caucasian</th>
<th>Hispanic</th>
<th>Other</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex F</td>
<td>257 (10.6)</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>30 ± 11</td>
<td>34 ± 11</td>
<td>38 ± 15</td>
<td>35 ± 10</td>
<td>35 ± 14</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>SLEDAI-JK</td>
<td>7.1 ± 6.1</td>
<td>4.5 ± 5.0</td>
<td>4.5 ± 5.0</td>
<td>6.8 ± 5.9</td>
<td>5.7 ± 4.8</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>SRI-50</td>
<td>2.79 ± 1.07</td>
<td>2.79 ± 1.07</td>
<td>2.79 ± 1.07</td>
<td>2.79 ± 1.07</td>
<td>2.79 ± 1.07</td>
<td>0.18</td>
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</tr>
</tbody>
</table>

SLEDAI-JK was higher in Asians and Hispanics and also in the geographical areas in which they are a majority. SDI on the other hand is not associated with ethnicity but is higher in the United States. Metabolic syndrome is higher in Mexicans and in Hispanics in general. Hypertension does not show a geographic distribution but is associated with Black ethnicity.

Conclusion: There are differences in the features of SLE and atherosclerotic risk factors at inception when studied by geographic and ethnicity origins. Whether there will be differences in the development of CAD events among these ethnic groups remains to be elucidated.

Disclosure: M. B. Urowitz: None; D. D. Gladman: None; D. Ibanez: None; C. P. Gordon: None; S.-C. Ba: None; A. E. Clarke: None; S. R. Bernatsky: None; F. J. Sanchez-Guerrero: None; J. G. Hanly: None; D. A. Isenberg: None; A. Rahman: None; P. R. Fortin: None; D. J. Wallace: None; E. M. Ginzler: None; J. T. Merrill: None; G. S. Alarcón: None; B. J. Fessler: None; I. N. Bruce: None; G. K. Sturla: None; O. Nived: None; K. Steinsson: None; M. A. Khamashta: None; M. A. Pietri: None; R. Ramsey-Goldman: None; S. Manzi: None; M. A. Dooley: None; R. V. Vollenhoven: None; C. B. Aranow: None; T. Stoll: None; M. Ramos: None; K. C. Kalunian: None; A. A. Zoma: None; G. Ruiz-Iturizar: None; P. J. Maddison: None; D. L. Kamen: None; S. S. Lim: None; C. A. Pescheken: None.

1878

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) Responder Index (SRI-50): A Valid Index for Measuring Improvement in Disease Activity. Zahi Touma1, Dafna D. Gladman1, Dominique Ibanez2, and Murray B. Urowitz2, 1Toronto Western Hospital, Toronto, ON, Canada; 2University of Toronto Lupus Clinic, Toronto Western Hospital, Toronto, ON, Canada

Background: We have previously described the development of SRI-50, an index that can describe partial improvement in disease activity between visits in lupus patients.

Objective: To determine whether SRI-50 would capture patients who have improved by ≥50% as determined by physician global assessment (PGA), construct validity of SRI-50 for assessing improvement in disease activity in SLE.

Methods: All patients attending the Lupus Clinic from September 2009 to December 2009 were enrolled in a prospective longitudinal study. Of the 298 patients enrolled 141 had a follow-up visit and were studied further. SLEDAI-2K and SRI-50 scores were determined initially and on a follow-up visit at 1–3 months. During the first visit a PGA was determined on a visual analog scale (VAS) line of 100 mm, with anchors of 0 “no disease activity” and 10 for very active disease”. During the follow-up visit a PGA was determined on a 7-point Likert VAS; 7 much, 6 moderately, and 5 slightly improved, 4 unchanged, 3 slightly, 2 moderately, and 1 much worse. We defined a 50% improvement as PGA≥6. An external clinician evaluated patients’ records and grouped them on follow-up visit into: improved, same and worse using standardized predefined definitions. The external construct was the Likert VAS. We hypothesized that patients who had ≥50% improvement (PGA≥6) would be captured by SRI-50 and the change in their SRI-50 scores would meet the definition of improvement by SLEDAI (decrease ≥4).

Results: The Characteristic of 141 patients are represented in Table 1.

Table 2. Statistical results in patients who changed their disease activity

<table>
<thead>
<tr>
<th>Race</th>
<th>Worse (n=14)</th>
<th>Same (n=65)</th>
<th>Improved (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLEDAI</td>
<td>4.47±3.4</td>
<td>3.57±4.19</td>
<td>6.57±4.8</td>
</tr>
<tr>
<td>SRI-50</td>
<td>7.22±4.6</td>
<td>2.79±3.7</td>
<td>6.28±4.0</td>
</tr>
</tbody>
</table>

Patients were assessed as: worse 14, same 65 and improved 62. SRI-50 scores did not decrease below their presenting SLEDAI-2K score in patients who remained stable or worsened. In patients who improved, the SRI-50 score decreased by a mean of −2.40±3.11 while SLEDAI scores did not decrease (Table 2).

Table 3. Change in SLEDAI and SRI-50 scores in patients who improved in association with the external construct

<table>
<thead>
<tr>
<th>PGA</th>
<th>SLEDAI</th>
<th>SRI-50</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50%</td>
<td>0.33±0.99</td>
<td>0.47±0.27</td>
</tr>
<tr>
<td>50%&lt;PGA&lt;60%</td>
<td>0.95±0.68</td>
<td>1.50±2.72</td>
</tr>
<tr>
<td>PGA&lt;50%</td>
<td>2.39±1.65</td>
<td>3.80±2.95</td>
</tr>
</tbody>
</table>

PGA 4–5: r=0.42, p=0.009; PGA 5–6: r=0.42, p=0.009; PGA 6–7: r=0.42, p=0.009. Improvement (n=62)

Improvement (n=62)
Conclusions: These results show that the SRI-50 has construct validity. SRI-50 is able to demonstrate incomplete improvement which would not have been discerned using SLEDAI-2K.

Disclosure: Z. Touma: None; D. D. Gladman: None; D. Ibañez: None; M. B. Urowitz: None.

1879

The Relative Importance of Current Versus Past Use of Medication in Excess Rates of Adverse Cardiovascular Events among Patients with SLE. Michelle A. Petri1 and Laurence S. Magder2. 1Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD

Background: Previous studies have suggested that some of the excess risk of adverse cardiovascular events (CVE) in patients with SLE may be due to treatments such as prednisone. Other studies have suggested that treatment with hydroxychloroquine results in reduced risk. In this study, we investigated whether past or current drug exposures have greater association with CVE.

Methods: We examined CVE rates in a large clinical cohort, in subgroups defined by medication history. CVE was defined as myocardial infarction (MI), stroke, coronary procedure, incident anemia, or claudication. The analysis was based a data set which had one record per patient-month of participation in the cohort. Each record contained data regarding the clinical history up until that time, the most recently measured levels of disease activity, medications taken at that time, and whether a CVE occurred during that month. This file was analyzed using pooled logistic regression.

Results: 134 CVE events were observed from among 1874 patients who were followed for 9485 person-years during periods between 1987 to 2010. Events included 65 strokes, 27 MI, 29 cases of angina or coronary procedures, and 13 cases of claudication. The table shows rates of CVE in subgroups defined by current and past medication use.

Table. Rates of CVE in Subgroups defined by Current and Past Medication Use

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of CVE</th>
<th>Rate of CVE per 1000 person-years</th>
<th>Rate Ratios based on a model that adjusts for age (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone exposure</td>
<td>None</td>
<td>22</td>
<td>13.3</td>
<td>1.0 (Ref. Group)</td>
</tr>
<tr>
<td></td>
<td>Past (not current)</td>
<td>23</td>
<td>7.9</td>
<td>0.6 (0.4, 1.2)</td>
</tr>
<tr>
<td></td>
<td>Currently taking (any dose)</td>
<td>88</td>
<td>18.2</td>
<td>1.6 (1.0, 2.5)</td>
</tr>
<tr>
<td></td>
<td>Currently using &gt;=20 mg/ day</td>
<td>25</td>
<td>35.4</td>
<td>4.0 (2.2, 7.1)</td>
</tr>
<tr>
<td>Plaquenil Use</td>
<td>None</td>
<td>46</td>
<td>17.9</td>
<td>1.0 (Ref. Group)</td>
</tr>
<tr>
<td></td>
<td>Past (not current)</td>
<td>20</td>
<td>20.3</td>
<td>1.1 (0.7, 1.9)</td>
</tr>
<tr>
<td></td>
<td>Currently used but for &lt;6 consec. mo</td>
<td>54</td>
<td>0.6</td>
<td>0.5 (0.4, 0.8)</td>
</tr>
<tr>
<td>NSAID Use</td>
<td>None</td>
<td>51</td>
<td>12.6</td>
<td>1.0 (Ref. Group)</td>
</tr>
<tr>
<td></td>
<td>Past (not current)</td>
<td>42</td>
<td>15.0</td>
<td>1.0 (0.7, 1.6)</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>41</td>
<td>15.6</td>
<td>1.1 (0.7, 1.6)</td>
</tr>
<tr>
<td>Immunosuppressant Use</td>
<td>None</td>
<td>56</td>
<td>12.1</td>
<td>1.0 (Ref. Group)</td>
</tr>
<tr>
<td></td>
<td>Past (not current)</td>
<td>5</td>
<td>10.1</td>
<td>0.8 (0.2, 2.5)</td>
</tr>
</tbody>
</table>

In multivariable models, cumulative (past) corticosteroid exposure was not associated with CVE after controlling for current use. Similarly, cumulative exposure to hydroxychloroquine was not protective after controlling for current use. Also, in multivariable models, the association between current corticosteroid use and CVE persisted after controlling for the most recent measure of disease activity.

Conclusion: Current (but not past) use of high-dose corticosteroids was associated with high rates of CVE. Current (but not past) use of hydroxychloroquine for 6 or more months was associated with lower rates of CVE. This study strongly supports long-term use of hydroxychloroquine in SLE.

Disclosure: M. A. Petri: None; L. S. Magder: None.

1880

Validation of CLASI Scale with Lupus Disease Activity, Damage, Body Image and Quality of Life. Mee Nakshi Jolly1, Rachel A. Mikolaitis2, Thomas F. Cash3 and Joel A. Block2. 3Rush University Medical Center, Chicago, IL, 2Rush University Medical Center, Chicago, IL, 1Rush University Medical Center

Purpose: Cutaneous Lupus Erythematosus Disease Area &Severity Index (CLASI) has been developed to assess cutaneous activity & damage in Systemic Lupus Erythematosus (SLE). Its validation against SLE disease activity & damage is not known. Also, its association with body image (BI) and quality of life (QOL) is not known. Herein, we present the results of correlation between CLASI items, CLASI total activity & CLASI total damage with (a) Physician global assessment (PGA), total SLE disease activity & itemized disease activity, (b) Total SLE disease damage (SDI), itemized SLE damage, (c) BI, and (d) QOL.

Methods: CLASI, BILS (body Image in Lupus Screen), BIQOL (body Image Quality of Life Index) and LupusPRO were administered to 14 consenting SLE patients. SLE disease activity & damage were evaluated using SELENA-SLEDAI and SLICC-SDI. Descriptive statistics & correlation analysis were obtained. A p value of ≤ 0.05 on two tailed test was considered significant.

Results: Mean ± SD age was 45.1 ± 12.7 yrs. Ninety three percent of participants were women; 71.4% African American, 14.3% Caucasian and 14.3% Hispanic. Mean ± SD (Median) PGA & SLEDAI score were 1.1 ± 0.7 (1.0) & 3.7 ± 4.6 (2.6). Mean ± SD (Median) SDI was 1.8 ± 1.5 (2.0). Mean ± SD (Median) CLASI activity and damage scores were 8.3 ± 4.2 (7.2) & 8.5 ± 5.8 (8.5).

Total CLASI activity score correlated with PGA (r 0.62, p = 0.03), SLEDAI- proteinuria (r 0.59, p = 0.03), CLASI activity item “Ear Scale” correlated with total SLEDAI (r 0.62, p = 0.02). CLASI activity items correlated with SLEDAI “rash” included “chest erythema” (r 0.63, p = 0.02), & “arms erythema” (r 0.56, p = 0.04). Mucous membrane lesions on CLASI correlated with SLEDAI-mucocutaneous membrane lesions (r 0.53, p = 0.05). Recent hair loss on CLASI correlated with SLEDAI recent hair loss (r 0.60, p = 0.02). Total CLASI damage score correlated with SDI-extensive skin scarring/panniculium (r 0.60, p = 0.05). CLASI “nose dys-pigmentation” correlated with SDI “skin ulceration” (p 0.77,p = 0.01). “Arms dys-pigmentation” (r 0.61, p = 0.05), “arms scarring” (r 0.63, p = 0.04), “hands dys-pigmentation” (r 0.69, p = 0.02), “hands scarring” (r 0.73, p = 0.01) & “feet dys-pigmentation” (r 0.62, p = 0.04) were associated with SDI “skin extensive scarring/panniculium”. CLASI ‘scalp scarring” correlated with SDI skin scarring/alopecia (r 0.99, p = 0.001).

CLASI “face scale” (r 0.56, p = 0.04) and “hand scale” (r 0.46, p = 0.09) were associated with BILS, CLASI “nose scale” (r 0.56, p = 0.04) & “V area neck erythema” (r 0.52, p = 0.06) correlated with BIQOL. Overall QOL was inversely associated with “ear Scale” (r 0.50, p = 0.07) & “chest erythema” (r 0.51, p = 0.06). Poor coping was associated with “nose scale” (r 0.60, p = 0.02), “V area of neck erythema” (r 0.58, p = 0.03), “posterior neck-shoulders erythema” (r 0.52, p = 0.06). Satisfaction with treatment & “hands scale” (r 0.59, p = 0.03) were related.

Conclusions: This is the first study on performance of CLASI against SLE disease activity & damage. CLASI activity and damage scores do correlate with muco-cutaneous manifestations of SLE activity & damage. Data suggest poor QOL (coping and body image) among SLE Patients with cutaneous manifestations of the disease.

Disclosure: M. Jolly: None; R. A. Mikolaitis: None; T. F. Cash: None; J. A. Block: None.

1881


Objective: To validate the 2007 ACR and the SLICC proposed criteria for the diagnosis and classification of SLE.

Methods: We included 55 patients (Group A) who were hospitalized in our Institute for the diagnosis of systemic manifestations of recent-onset
The validity of the ACR and SLICC criteria for SLE diagnosis was evaluated among patients in Group A and the validity for classification among all the patients in the 3 groups.

Results: Patients in group A had a mean (SD) age of 37.3 (17.7) years, and 40 (73%) were females. The main reasons for hospitalization were: chronic fever 16, nephritic/nephrotic syndrome 9, severe weight loss 8, polyarthritis 4, cytopenias 3, lymphadenopathy 2, others 13. Patients in group B had a mean age of 29.9 (8.8) years, and 43 (84%) were females. Patients in group C had a mean age of 40.4 (14.6) years, and 30 (86%) were females.

In group A, 21 (38%) patients were newly diagnosed as SLE, and the observed agreement between both sets of criteria was 87.3, kappa 74.5. Also, among all the patients in the three groups, the observed agreement for SLE classification was 92.2, kappa 84.3.

No significant differences were observed between both sets of criteria in terms of sensitivity (SN), specificity (SP), positive (PPV) and negative predictive value (NPV) for the diagnosis and the classification of SLE (table). Overall, the efficacy of both sets of criteria was inferior for diagnosis than classification.

Conclusion: The efficacy of the current ACR and the proposed SLICC criteria for the diagnosis and classification of SLE patients is similar; however, their utility for diagnosis is inferior to classification.

Disclosure: F. Rodriguez-Garcia: None; K. Santana-de Anda: None; A. Duarte-Garcia: None; V. Pascual-Ramos: None; G. Hernández-Medina: None; T. Rodriguez-Reyna: None; J. Sanchez-Guerrero: None.

Work Disability, Lost Productivity and Associated Risk Factors in Patients Diagnosed with Systemic Lupus Erythematosus (SLE). Tammy O. Utset1, Barbara M. Segal2, Laura Trupin2, Sarika Ogale1, Ellen Herberich3 and Kenneth C. Kalunian3. 1Genentech, 2Harris Interactive, 3UCSD School of Medicine, La Jolla, CA, 4University of California, San Francisco, 5University of Chicago, Chicago, IL, 6University of Minnesota, Minneapolis, MN

Purpose: To compare self-reported workplace and household productivity, physical function, and symptoms in SLE patients and healthy controls.

Methods: US-based adult ambulatory SLE patients without co-morbid rheumatoid arthritis (RA) completed a questionnaire. Patients gave a similar survey to two age and gender matched friends. Patient and control surveys included The Health and Work Performance Questionnaire (HPQ), Short Form 12 (SF-12), FACT-Fatigue, Thinking Scale and the Center for Epidemiologic Studies Depression Scale. Rheumatologists completed a survey which included the Mexican SLEDAl and a global rating of disease severity over the previous 12 months. Logistic regression was used to study the association between these measures and being unemployed due to health among SLE patients.

Results: 200 patients, and 221 controls have submitted surveys to date. In SLE patients, disease activity as measured by the Mex-SLEDAI had a mean score of 3.5 (median 1.0). Approximately 40% of lupus patients had no activity by the Mex-SLEDAI.

Mean scores for controls were close to the US population on all SF-12 domains (50 points) and on the FACT-Fatigue (40 points), indicating that the controls in our study had symptom levels representative of the US population. Patients reported higher levels of pain, fatigue and depression, and lower levels of physical, cognitive and social function, compared with controls (See table).

SLE patients were more likely to not be employed nor looking for work, compared to controls (31% vs 4%) and/or on extended sick leave or disability (34% vs. 5%). Among those not employed, 86% of patients report that they were not employed at least in part due to health, in comparison to 16% of controls. Average absenteeism (time missed from paid work), suggests that patients worked 8 hours less and controls worked 4 hours more than expected by their employer over a 7 day period. Presenteeism (the level of performance while working) was 75% for SLE patients and 85% for controls, where 100% indicates ideal performance. On average, patients were unable to do housework for 8 days and controls 1.9 days of the last 28 days due to problems with physical or mental health.

In multivariate logistic regression, pain severity (OR 1.07; p=0.009) and depression (OR = 1.07; p=0.024) were significantly associated with the odds of being unemployed due to health among SLE patients, but fatigue, SLE duration, global severity score and MEX-SLEDAI were not associated with this outcome.

Conclusions: SLE patients report significantly higher burden from symptoms such as pain, fatigue and depression relative to healthy controls. Despite
low disease activity on the Mex-SLEDAI work and household productivity is lower in SLE patients compared with healthy controls. Higher levels of pain severity and depression increase the likelihood of health-related unemployment in SLE patients.

Disclosure: T. O. Uset: None; B. M. Segal: None; L. Trupin: None; S. Ogale: Genentech, 3, Roche, 1; E. Herberich: None; K. C. Kalunian: Cephalon, 1, Cypress Biosciences, Inc., 1, Genentech and Biogen IDEC Inc., 1, Immune Tolerance Network, 1, Lupus Clinical Trials Consortium, 1, Medimmune, 1, UCB, Inc., 5.

1883

Activation of Innate Immunity and Sjögren’s Syndrome Development.
Seshagiri Rao Nandula1, Yogesh M. Scindia2, Harini Bagavant3 and Umesh S. Deshmukh4. 1University of Virginia, Charlottesville, VA; 2University of Virginia

Objectives: Previously our laboratory has demonstrated that activation of innate immunity through toll-like receptor 3 (TLR3) agonist poly IC causes an acute loss of salivary gland function. This study was undertaken to investigate the effects of innate immunity activation through TLR dependent and TLR independent pathways on development of Sjögren’s Syndrome (SS) in experimental mouse model systems.

Methods: To determine the role of TLR mediated innate immunity activation in SS, female NZB/W F1 mice were injected with TLR3 agonist, poly IC. To investigate TLR independent pathways, female NZM2758 mice were injected with alum, which activates innate immunity through the inflammasome pathway. Submandibular glands (SMG) were analyzed for sialadenitis and lymphocytic infiltrates were characterized by flow cytometry and immunohistochemistry. Gene expression levels of inflammatory cytokines and chemokines were determined by real time PCR. Mice were monitored for salivary gland hypofunction by checking pilocarpine induced saliva flow.

Results: Within 2 weeks of poly IC treatment, the SMG showed evidence for lymphocytic infiltration. The dominant cell types infiltrating the SMG with TLR3 agonist poly IC were identified as CD4+ T cells with the infiltrates showed presence of ICOS+CXC5R5+ cells indicative of the T follicular helper cell phenotype. SMG from poly IC treated mice showed increased levels of cytokines and chemokines were determined by real time PCR. Mice were monitored for salivary gland hypofunction by checking pilocarpine induced saliva flow.

Conclusions: Our data clearly demonstrates that activation of innate immunity accelerates the development of SS. Although the characteristics of disease development vary depending upon the innate stimulus, the models reinforce a lack of correlation between extent of sialadenitis and severity of glandular dysfunction, as observed in SS patients. The ability of alum to induce SS in genetically susceptible mouse strains suggests that exposure to aluminum compounds can be a novel risk factor for SS.

This work is supported by grants from Sjögren’s Syndrome Foundation USA and NIDCR.

Disclosure: S. R. Nandula: None; Y. M. Scindia: None; H. Bagavant: None; U. S. Deshmukh: None.

1884

Anticentromere Antibodies (ACA)-Positive Systemic Sclerosis (SSc) Patients with Sjögren’s Syndrome: A Distinctive Subset at High Risk of Lymphoma.
Chiara Baldini, Sara Grossi, Alessandra Della Rossa, Nicoletta Luciano, Marica Doveri, Antonio Gaetano Tavoni and Stefano Bombardieri. Rheumatology Unit, Department of Internal Medicine, University of Pisa, Italy

Background: Sjögren’s syndrome (SS) has been considerably associated with anticientromere positive (ACA)-limited cutaneous subtype Systemic Sclerosis (SSc). Nonetheless, only a few studies have analysed the pattern of clinical expression and disease evolution in ACA-SSc-SS patients.

Objectives: to compare the disease phenotype and clinical evolution of ACA-SSc-SS patients with (a) patients with ACA-SSc and no SS (ACA-SSc) and (b) patients with primary SS (pSS), in order to verify whether the concomitant association between SS and SSc influences the patients’ clinical presentation and outcome.

Patients and Methods: Seventy-eight ACA-SSc-SS patients (78 F: 0 M; mean age = 62 ± 12 yrs; mean follow-up = 5.4 ± 6.6 yrs), 127 ACA-SSc patients without SS (119 F: 8 M; mean age = 60 ± 13 yrs; mean follow-up = 4.9 ± 6 yrs), and 374 patients with primary SS (pSS) (363F: 11M; mean age 58 ± 14 yrs; mean follow-up = 7.3 ± 6.6 yrs) who had attended our Unit between 1989 and 2009 were included in the study. Diagnosis of SSc was based on the ARA criteria, while diagnosis of pSS and sSS on AECG criteria. Categorical data were compared using the chi-square test and continuous variables by the Student t-test.

Results: (a) When compared to ACA-SSc, ACA-SSc-SS patients presented a higher frequency of arthralgias (p<0.0001), peripheral nervous involvement (p=0.006), and altered laboratory findings (p<0.0001) (i.e. leukopenia, hypocomplementemia, hypergammaglobulinemia, anti-Ro/SSA, anti-La/SSB, Rheumatoid Factor). In addition, a longer mean disease duration of 19 ± 11 yrs, and was not correlated to skin sclerosis. (b) When compared to pSS patients, ACA-SSc-SS patients presented a higher frequency of signs and symptoms belonging to the spectrum of SSc (p<0.0001), i.e. Raynaud’s phenomenon, dysphagia, telangiectasias, heart involvement and pulmonary hypertension, but also an increased prevalence of salivary glands enlargement (p<0.0001). Altered laboratory findings were also more frequent in pSS patients while no differences were observed for lymphoproliferative disorders (p=0.09).

Conclusions: Patients with ACA-SSc-SS presented features from both diseases: we observed that the presence of SS in ACA-SSc dramatically increased the risk of lymphoma. A careful work up is thus mandatory in the follow-up of ACA-SSc-SS patients.

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1885

Association between Lymphotixin Alpha Genetic Variants and Primary Sjögren’s Syndrome in Scandinavian Samples.
Anne Isine Bolstad1, Stephanie Le Hellard2, Gudlaug Thora Kristjansdottir3, Gunnell Nordmark4, Lilian Vassaitis5, Marika Kvarnström6, Christopher Sjowall7, Svein Joar Augland Johnsen1, Per Eriksson1, Roald Omdal1, Johan G. Brun, Marie Wahl-Henriksen5, Elke Theander7, Anne-Christine Syvänen3, Lars Rönnblom8 and Roland Jonsson9. 1Department of Clinical Dentistry-Periodontics, University of Bergen, Bergen, Norway; 2Department of Clinical Medicine, University of Bergen, Center of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway; 3Department of Medical Sciences, Molecular Medicine, Uppsala University, Uppsala, Sweden; 4Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden; 5Department of Medicine, Section of Rheumatology, University of Bergen, Bergen, Norway; 6Karolinska Institutet, Stockholm, Sweden; 7Malmö University Hospital, Malmö, Sweden; 8Section of Rheumatology, Uppsala University, Uppsala, Sweden; 9Stavanger University Hospital, Stavanger, Norway; 10Stavanger University Hospital, Stavanger, Norway; 11The Gade Institute, University of Bergen, Bergen, Norway; 12University Hospital Linköping, Sweden, Linköping, Sweden; 13University Hospital Linköping, Linköping, Sweden

Primary Sjögren’s syndrome (pSS) is an autoimmune chronic inflammatory disease characterized by lymphoid infiltrations of exocrine glands and increased levels of autoantibodies against the ribonucleoproteins Ro/SSA and La/SSB. Microarray studies have demonstrated increased gene expression of lymphotixin alpha (LTA). LTA and tumor necrosis factor (TNF) gene clusters are associated with pSS.

A total of 527 pSS patients and 532 controls participated in the study. All
of them were of Caucasian origin from Sweden and Norway. Eleven SNP markers were genotyped and analysed for their association with pSS using single marker logistic regression and for genotypic association with a chi square test. Eight markers showed significant association with pSS. The SNP rs909253 in intron 1 of LTA showed the strongest association with pSS in both the Norwegian cohort (P = 1.3E-03) and the Swedish cohort (P = 2.6E-05). Importantly, the strength of the association increased (P = 1.3E-07) when the two cohorts were analysed together, showing a odds ratio (OR) of 1.59 [95% CI: 1.34 – 1.89]. When only pSS patients positive for anti-Ro/SSA -La/SSB (n = 381) were compared with the controls, the association with SNP rs909253 was even stronger (P = 4.2E-10, OR 1.82 95% CI: 1.51–2.20). Some SNPs within this locus were also associated with extraglandular manifestations such as high plasma levels of IgG, hypothyroidism, arthritis and leucopenia in pSS patients. In conclusion, a strong association was found between several SNPs in the LTA gene locus and pSS, some of which lead to amino acid changes. Our data together with previously published reports suggest a direct role for lymphotxin alpha in the development of pSS.

Importance of this finding for the inflammatory processes in pSS needs further investigation.

Disclosure: A. I. Bolstad: None; S. L. Hellard: None; G. T. Kristjansdottir: None; G. Nordmark: None; L. Vasaits: None; M. Kvarnström: None; C. Sjöwall: None; S. A. J. Johnson: None; P. Eriksson: None; R. Omdal: Roche, 9, sanofi-aventis, 9, Serono, 9; E. Theander: None; A.-C. Syvänen: None; L. Rönnblom: None; R. Jonsson: None.

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B-Cell Profiling Using Multi-Color Flow Cytometry as Biomarker of Disease Progression in Primary Sjögren’s Syndrome (pSS). Mustimbo Roberts1, Craig Maguire 3, Alex Rosenberg 3, Andreea Coca 2, Jennifer H. Anolik1 and Inaki Sanz2. 1University of Rochester, Rochester, NY, 2University of Rochester Medical Center, Rochester, NY, 3University of Rochester, Baltimore, MD, 4Johns Hopkins University School of Medicine.

Purpose: Current classification criteria for pSS are limited in their ability to conclusively diagnose patients with sub-clinical manifestations of disease. To remedy these limitations, we have initiated exploratory studies to identify candidate biomarkers for pSS. Multi-color flow cytometry was used cross-sectionally to identify a B-cell phenotypic signature of pSS and to determine if altered B-cell homeostasis in pSS is a predictive indicator of disease onset and/or progression. These signatures are currently being evaluated for their predictive value in an ongoing longitudinal analysis of patients with sicca symptoms, of no obvious clinical reason, that do not meet American European Consensus Group (AECG) criteria.

Methods: B cells from pSS (n=20), sicca (n=14) and healthy (HC) patients (n=20) were analyzed by multicolor flow cytometry to identify differential memory and transitional B-cell subsets. Clinical parameters were used to examine the relationship of phenotypic abnormalities to disease status using Spearman Correlation. Complex, multidimensional immunological data were analyzed using reduction techniques including Principal Component Analysis (PCA).

Results: We report decreased frequencies of switched (SM) (p<0.0001) and unswitched (UM) (p<0.0001) memory cells, and increased frequencies of IgD-CD27- switched B cells (p=0.03) and naïve B cells (p<0.0001) in pSS compared to HC. Additionally, pSS patients exhibit increased frequencies of T1 and T2 transitional B cells compared to HC (p<0.005). The increased frequency of T1 and T2 cells correlated significantly with serum levels of BAFF, the main survival factor for transitional cells, which were significantly increased in pSS (p<0.05). Similar to pSS, sicca patients also feature decreased frequencies of SM (p=0.02) and UM (p=0.01) and increased frequencies of naïve B cells (p=0.02). Longitudinally, sicca patients with normal UM frequencies at baseline experience a dramatic permanent decline in frequency at 1 year and 2 years of follow-up that precedes a relative expansion in the CD27-memory and naïve populations. Of note the decrease of UM cells correlated significantly with increased Ro/La, IgG, ESR and years in sicca patients. Of great interest, UM decline preceded in some patients the presence of anti-Ro/La antibodies and decreased salivary function.

Discussion: We have defined a B cell signature of pSS that allows for clustering/differentiation of Sicca patients that share a similar signature that clearly separates them from healthy controls and sicca patients that do not progress to pSS. Clinical parameters—elevated IgG, ESR and reduced C4 also cluster based on pSS B-cell signatures. The reduction of UM frequencies seem to be the first immunologic and permanent sign that Sicca patients may develop pSS. PCA of the complex multidimensional flow cytometric data identify the decrease in UM and increase in CD27-memory cells as the driving parameters of the B-cell signature in pSS. Further longitudinal examination of the pSS B-cell signature in Sicca patients will confirm the predictive value of peripheral blood multicolor flow cytometry as a diagnostic tool in pSS.

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Best Scintigraphic Measures of Parotid Gland Dysfunction in Sjögren’s Syndrome. Anthony Keyes4, Julius Birnbaum2, John Petronis3 and Alan N. Baer3. 1Johns Holins University School of Medicine, 2Johns Hopkins University, Baltimore, MD, 3Johns Hopkins University, Baltimore, MD, 4Johns Hopkins University School of Medicine.

Purpose: Parotid gland scintigraphy is utilized to document the oral component of Sjögren’s syndrome (SS); however the best parameters of dysfunction have not been defined. We sought to determine which parameters of parotid gland scintigraphy best differentiate patients with SS from those with suspected, but unconfirmed, SS.

Methods: In a 12-month period, 61 patients with suspected or confirmed SS underwent parotid gland scintigraphy in order to document or quantify parotid gland dysfunction. Following evaluation in our clinic, 23 had a confirmed diagnosis of SS according to the American-European Consensus Classification Criteria (AECG), independent of scintigraphy, and 32 had symptoms and/or signs of dry eyes and dry mouth but did not meet classification criteria (“sicca controls”). Five patients could not be classified further and were not included in subsequent analyses. Following an intravenous injection of pertechnetate, dynamic imaging was performed over 60 minutes. Hard lemon candy was provided after an elapsed of 45 minutes to stimulate parotid gland excretion. Quantitative parameters of parotid gland parenchymal function included the net uptake ratio (NUR, ratio of maximum count and the count at 60 seconds) and the maximum count time (MCT, time at which the maximum count was reached). The parameter of parotid gland excretion function was the discharge fraction (DF, (pre-stimulus maximum count-post-stimulus minimum count/pre-stimulus maximum count)).

Results: The 56 patients, 50 women and 6 men, had a mean age of 53 ± 14 yrs (SD). Measurements of NUR, MCT, and DF in the right and left parotid (P) glands showed strong correlations in all patients. NUR in the parotid gland had a negative correlation with the duration of dry mouth symptoms in the SS patients (left gland: r=-.27, p=0.02; right gland: r=-.15, p=0.19) but not in the sicca control patients. There was no correlation between these symptoms and MCT or DF in either group. The mean NUR and DF values for the right and left glands were each significantly lower in the SS patients compared with those of the sicca controls (p<0.05, Mann-Whitney test). The SS patient group could be differentiated from the sicca control group, using specific parotid gland scintigraphic parameters, as shown in the Table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cutoff value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>+LR</th>
<th>−LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net uptake ratio (%)</td>
<td>≤2</td>
<td>57</td>
<td>88</td>
<td>4.75</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>≤2.5</td>
<td>83</td>
<td>50</td>
<td>1.66</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>≤3</td>
<td>96</td>
<td>31</td>
<td>1.39</td>
<td>0.13</td>
</tr>
<tr>
<td>Maximum count time (min)</td>
<td>≤40</td>
<td>43</td>
<td>62</td>
<td>1.13</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>≤42</td>
<td>57</td>
<td>50</td>
<td>1.14</td>
<td>0.86</td>
</tr>
<tr>
<td>Discharge fraction (%)</td>
<td>≤40</td>
<td>36</td>
<td>97</td>
<td>12</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>≤50</td>
<td>50</td>
<td>87</td>
<td>3.85</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>≤55</td>
<td>59</td>
<td>77</td>
<td>2.57</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>≤60</td>
<td>73</td>
<td>71</td>
<td>2.52</td>
<td>0.38</td>
</tr>
<tr>
<td>Combination NUR ≤2.5, DF ≥60</td>
<td>68</td>
<td>84</td>
<td>4.25</td>
<td>0.38</td>
<td></td>
</tr>
</tbody>
</table>

+LR = positive likelihood ratio; −LR = negative likelihood ratio

The best individual parameter was a DF of ≤60%, which identified SS patients with 73% sensitivity and 71% specificity. A DF of >60% when combined with a NUR of ≤ 2.5 % identified SS patients with 68% sensitivity and 84% specificity.

Conclusions: Measures of radiotracer uptake and discharge, indicative of parenchymal and excretion function, are each lower in SS patients. A combination of these two parameters achieves the best balance of
sensitivity and specificity in differentiating SS patients from suspected SS patients with sicca symptoms and/or signs who do not meet AECC diagnostic criteria.

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Clinical and Immunological Profile of Patients with Primary Sjögren Syndrome Who Developed B-Cell Lymphoma. Analysis of 1010 Spanish Patients (The GEMESS Cohort). Manuel Ramos-Casals1, Roser Solans1, Jose Rosas1, Maria Teresa Camps2, Antonio Gill3, Javier Del-Pino4, Carmen Hidalgo3, Josep Calvo3, Maria Luisa Mico5, Roberto Perez-Alvarez6, Rafael Belenguer1 and Lucio Pallarés4.

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PATIENTS. The GEMESS Study Group was formed in 2005 with the aim of collecting a large series of Spanish patients with primary SS, and included twelve Spanish reference centers with substantial experience in the management of SS patients. By March 2007, the database included 1010 consecutive patients, recruited since 1994.

Results: The cohort consisted of 1010 patients, including 937 (93%) women and 73 (7%) men (female:male ratio, 13:1), with a mean age at diagnosis of 53.0 ± 48.4 years (range, 14–88) and of 58.7 ± 46.4 years (range, 16–94) at inclusion in the Registry. Twenty-six (2.57%) patients developed B-cell lymphoma. There were 22 (85%) women and 4 (15%) men with a mean age of 59 years at diagnosis of lymphoma and a length of SS evolution of 6 years from SS diagnosis to lymphoma diagnosis. Patients with B-cell lymphoma had a higher prevalence of vasculitis (23% vs 9%, p = 0.024), lung involvement (31% vs 11%, p = 0.005), anemia (38% vs 17%, p = 0.015), leukopenia (38% vs 15%, p = 0.004), thrombocytopenia (42% vs 12%, p < 0.001) and low C3/C4 levels (42% vs 13%, p = 0.001) in comparison with patients without lymphoma. Multivariate analysis adjusted by age, gender and length of SS evolution identified lung involvement (p = 0.022), thrombocytopenia (p < 0.001) and low C3/C4 levels (p = 0.004) as significant independent variables related to B-cell lymphoma.

Conclusion: We identified a specific clinical and immunological profile (vasculitic and pulmonary involvement, cytophenias and hypocomplementemia) in patients with primary SS who developed B-cell lymphoma. The adjusted odds associated with the clinical and laboratory markers and with low C3/C4 levels reported in previous series and identified as new factors associated with B-cell lymphoma lung involvement and thrombocytopenia in patients with primary SS.

Disclosure: M. Ramos-Casals: None; R. Solans: None; J. Rosas: None; M. T. Camps: None; A. Gill: None; J. Del-Pino: None; C. Hidalgo: None; J. Calvo: None; M. L. Mico: None; R. Perez-Alvarez: None; R. Belenguer: None; L. Pallarés: None.

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Background: B cell depletion by anti-CD20 treatment with Rituximab (RTX) has been shown to be clinically effective in patients with primary Sjögren’s syndrome (pSS) suggesting a role for B cells in the pathogenesis.

Methods: Parotid salivary gland biopsies were taken from 7 immune-suppressed naïve pSS patients before treatment and at 12 weeks after treatment (5 RTX and 2 placebo [PL]) and at 36 weeks after treatment (for 5 RTX patients only). All RTX patients improved clinically after treatment. Variable immunoglobulin heavy-chain gene (IGHV) cloning and sequence analysis were carried out on RNA extracted from each parotid biopsy, using a primer specific for IGHV-3 genes in combination with constant region primers for IgA and IgG isotypes.

Results: In total 747 unique Ig sequences were analyzed. Clonally related sequences were identified in biopsies of 4/5 RTX patients before and 12 weeks after RTX when there is complete depletion of B cells in the peripheral blood. Even at 36 weeks after RTX when B cells reappeared in the blood, sequences clonally related to the sequences before RTX were found. In one RTX patient a single clone set was found at all time points. Clonally related sets of sequences expressing IgA and/or IgG isotypes at different timepoints were observed. The same pattern was also seen in different biopsies of each patient in the PL-treated patient group.

Strikingly, in 3/5 RTX patients, significantly more non-unique (redundant) sequences were seen at 36 weeks after RTX compared to baseline (Fisher’s exact test, p ≤ 0.01).

The occurrence of Vh3–23 and Vh3–30 genes were found to be quite high at all timepoints in both PL and RTX patients.

Conclusions: In this study we show the presence of clonally related Ig sequences from parotid gland biopsies of pSS patients before and after RTX. These data indicate the persistence of some B cell clones despite RTX treatment. Furthermore, the diversity of the IgA and IgG repertoire becomes progressively more restricted with time after RTX, suggesting selective advantage for certain B cell clones. The high frequency of Vh3–23 and Vh3–30 genes seen in all pSS patients studied here, has also been previously noted in other autoimmune disorders. This study indicates that the selective persistence of particular B cell clones may contribute to the disease relapse and manifestations of the disease after RTX.

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Correlation of Serum BAFF and MIP-1β Levels with B-Cell Activation in Systemic Lupus Erythematosus. Christiane L. de Waard1,2, Libert D.A. Wijffels2, Gerard J.M. van der Meer2,3, Guido Akin2 and Rutger A. van Venrooij2.

Objective: To analyse the epidemiological, clinical and analytical features related to the development of B-cell lymphoma in a large cohort of Spanish patients with primary Sjögren syndrome (SS).

Methods: The GEMESS Study Group was formed in 2005 with the aim of collecting a large series of Spanish patients with primary SS, and included twelve Spanish reference centers with substantial experience in the management of SS patients. By March 2007, the database included 1010 consecutive patients, recruited since 1994.

Results: The cohort consisted of 1010 patients, including 937 (93%) women and 73 (7%) men (female:male ratio, 13:1), with a mean age at diagnosis of 53.0 ± 48.4 years (range, 14–88) and of 58.7 ± 46.4 years (range, 16–94) at inclusion in the Registry. Twenty-six (2.57%) patients developed B-cell lymphoma. There were 22 (85%) women and 4 (15%) men with a mean age of 59 years at diagnosis of lymphoma and a length of SS evolution of 6 years from SS diagnosis to lymphoma diagnosis. Patients with B-cell lymphoma had a higher prevalence of vasculitis (23% vs 9%, p = 0.024), lung involvement (31% vs 11%, p = 0.005), anemia (38% vs 17%, p = 0.015), leukopenia (38% vs 15%, p = 0.004), thrombocytopenia (42% vs 12%, p < 0.001) and low C3/C4 levels (42% vs 13%, p = 0.001) in comparison with patients without lymphoma. Multivariate analysis adjusted by age, gender and length of SS evolution identified lung involvement (p = 0.022), thrombocytopenia (p < 0.001) and low C3/C4 levels (p = 0.004) as significant independent variables related to B-cell lymphoma.

Conclusion: We identified a specific clinical and immunological profile (vasculitic and pulmonary involvement, cytophenias and hypocomplementemia) in patients with primary SS who developed B-cell lymphoma. The adjusted odds associated with the clinical and laboratory markers and with low C3/C4 levels reported in previous series and identified as new factors associated with B-cell lymphoma lung involvement and thrombocytopenia in patients with primary SS.

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Correlation of Serum BAFF and MIP-1β Levels with B-Cell Activation in Systemic Lupus Erythematosus. Christiane L. de Waard1,2, Libert D.A. Wijffels2, Gerard J.M. van der Meer2,3, Guido Akin2 and Rutger A. van Venrooij2.

Objective: In primary Sjögren’s syndrome (pSS), systemic disease activity might result from the stimulation of autoreactive B lymphocytes. Thus, markers of B-cell activation could be useful in the clinical assessment of the disease. However, due to the lack of consensus disease activity score and of prospective cohorts, the only available studies are retrospective and evaluated disease activity only by the presence/absence of extraglandular involvement. A multinational consensus disease activity score was recently established, the EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI). We therefore investigated the correlation between markers of B-cell activation and the ESSDAI at enrollment in a multicenter prospective cohort of patients with pSS.

Methods: 15 centers of Rheumatology and Internal Medicine have included patients with pSS according to AECG criteria in the “Assessment of Systemic Signs and Evolution of Sjögren’s Syndrome” (ASSESS) 5-year prospective cohort since May 2006. At enrollment, clinical data, ESSDAI disease activity and serum are collected and centralized. Serum IgG, A, M,
beta2-microglobulin and kappa and lambda free light chains (FLCs) of immunoglobulins were assessed at enrollment using nephelometry and B-cell activating factor of the TNF family (BAFF) was assessed using ELISA.

Results: In the 349 analyzed patients (women: 93.7%), mean age and disease duration were 60.5 ± 12.6 years and 9 ± 5.9 years (1st quartile: 5 years), respectively. Anti-SSA antibody was detected in 60.2% of patients, anti-SSB in 35.2% of patients. 189 patients (54.9%) had records of systemic involvement at enrollment, including 19 patients (5.4%) with previous lymphoma. Median BAFF and beta2-microglobulin at enrollment were higher in patients with a history of lymphoma (1187.7 vs 893.3 pg/ml, P < 0.0001) and 2.6 vs 2.1 mg/l, P < 0.01, respectively).

At inclusion, 31.8% of patients had features of systemic involvement. Median ESSDAI at enrollment, analyzed in 324 patients, was 4 (25th – 75th: 1–9).

At inclusion, patients with anti-SSA/SSB had a significantly higher ESSDAI (4(2–9] vs [2–6.6] in patients without anti-SSA/SSB, P = 0.04). The ESSDAI score at enrollment was significantly correlated with total IgG (r = 0.11, P = 0.05), kappa FLCs (r = 0.22, P < 0.0001), beta2-microglobulin (r = 0.2, P = 0.0003) and BAFF (r = 0.14, P = 0.015). Patients with an ESSDAI score greater than 4 had significantly more frequently increased levels of BAFF (> 908.8 pg/ml, 75th% value in the cohort, 31.5% of increased levels vs 18.3% in patients with an ESSDAI = 4, P = 0.009), kappa FLC (> 19.4 mg/l, 32.7% vs 15.7%), beta2-microglobulin (> 2.34 mg/l, 46.8% vs 25.5%, P = 0.0001).

Conclusion: In pSS, disease activity assessed by the ESSDAI is correlated with serum levels of BAFF, a pivotal B-cell activating cytokine, and markers of B-cell activation (anti-SSA/SSB, kappa FLCs, and beta2-microglobulin). Prospective follow-up in the ASSESS cohort will allow to determine whether these markers predict new systemic complications of the disease, including lymphomas.

Disclosure: J.-E. Gottenberg: None; R. Seror: None; J. Benussiano: None; K. Inamo: None; P. Dieude: None; J.-J. Dubost: None; A.-L. Fauchais: None; E. Hachulla: None; C. Larroche: None; V. Le Guern: None; J. Morel: None; A. Perdriger: None; X. Puatch: None; S. Rist: None; A. Saura: None; D. Sene: None; J. Sibilia: None; O. Vittecoq: None; C. Zarnitsky: None; P. Ravaud: None; X. Mariette: None.

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Detection of HTLV-1 p19 Protein in Labial Salivary Glands from Patients with Sjögren’s Syndrome: A Distinct Clinical Subgroup? Sung-Ji Lee1, Seong-Rye Seo1, Tae-Jong Kim1, Yong-Wook Park1 and Shin-Seok Sung-San2, Hospital/Paris Univ, Le Kremlin Bicetre, France, 4Caen Hospital, 5Hopital and Xavier Mariette3. 1Courbevoie, France, 2Avicenne Hospital, 3Bicetre Hospital/Paris Univ, 4Le Kremlin Bicetre, France, 5Caen Hospital, 6Hopital Purpan, Toulouse, France, 7Jean Verdier Hospital, 8La Rochelle Hospital, 9Nantes Hospital, 10National Scleroderma Centre, Lille Cedex, France, 11Orleans Hospital, 12Reims Hospital, 13Strasbourg Hospitals, Strasbourg, France

Purpose: Etiologically, human T-cell lymphotrophic virus type 1 (HTLV-1) is associated with two major diseases: adult T-cell leukemia and HTLV-1-associated myelopathy-tropical spastic paraparalysis. Of interest, recent studies have suggested that HTLV-1 is involved in the pathogenesis of Sjögren’s syndrome (SS). However, the clinical and serological differences in SS patients with and without this infection are not well characterized. Therefore, we examined whether SS patients could be distinguished based on the expression of HTLV-1 p19 protein and, if so, whether the subgroups differ in their clinical features and serological parameters.

Methods: The polymerase chain reaction was used to amplify viral DNA from peripheral blood mononuclear cells (PBMCs) in 54 patients with SS, using primers from the HTLV-1 p19 region and minor salivary gland (MSG) biopsy specimens from 33 SS patients who were examined for the presence of HTLV-1 p19 genes immunohistochemically. The sociodemographic, glandular, and extraglandular manifestations, and laboratory findings including autoantibodies, complements, and immunoglobulin levels, were analyzed.

Results: The HTLV-1 p19 gene was not detected in PBMC samples from 54 patients, while HTLV-1 p19 protein was expressed immunohistochemically in MSG specimens in 10 out of 33 SS patients (30%). On separating the SS patients into two groups based on HTLV-1 p19-positive immunohistochemistry, the p19-positive patients had lower anti-Ro/SS-A titers, rheumatoid factor, and C3 levels, and higher lymphocyte counts than the p19-negative patients (p = 0.049, p = 0.014, p = 0.018, and p < 0.001, respectively). The prevalence of glandular and extraglandular manifestations, including dryness of the eyes and mouth, enlargement of the parotid gland, photosensitivity, swollen hands, Raynaud’s phenomenon, arthralgia, lymphadenopathy, renal disease, psychosis, interstitial lung disease, peripheral neuropathy, and autoimmune thyroid disease, did not differ between the p19-positive and p19-negative patients.

Conclusions: Our findings suggest that the presence of HTLV-1 p19 in the salivary gland is involved in the pathogenesis of a subpopulation of SS, and HTLV-1-associated SS could have different immunological patterns compared to idiopathic SS, raising the possibility that HTLV-1 p19 is a marker of a pathogenetically distinct form of SS.

Disclosure: S.-J. Lee: None; S.-R. Seo: None; T.-J. Kim: None; Y.-W. Park: None; S.-S. Lee: None.

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Effect of Rituximab Treatment on BAFF Levels in Patients with Primary Sjögren’s Syndrome: A Placebo-Controlled Clinical Trial. Rodney Pollard,1, Wayel Abdullah,2, Isja Meijer,3 Frans Kroese,4 Fred Spijkervet,4 Cees Kallenberg,5 Arjan Vissink6 and Hendrika Bootsm.7 Univer Med Center Groningen, Groningen, The Netherlands, 8Univer Med Center Groningen.

Objective: To assess the effect of rituximab (anti-CD20) treatment on B-cell activating factor (BAFF) levels in patients with primary Sjögren’s syndrome (pSS).

Background: pSS is a systemic autoimmune disease characterized by mononuclear infiltrates of B-and T-cells in exocrine glands eventually leading to destruction of these glands. B-cell activating factor (BAFF), a member of the tumor necrosis factor (TNF)-ligand family, is essential for the control of B-cell maturation and survival.

Methods: In a randomised double-blind placebo-controlled trial patients were treated on days 1 and 15 with either rituximab (n = 20) or placebo (n = 10). To minimise side effects (infusion reactions, serum sickness), all patients were pre-medicated with methylprednisolone and oral prednisone. Fresh blood samples were collected at various time points (before, 5, 12, 36 and 48 weeks following treatment). In addition, age- and sex-matched blood samples were collected from healthy controls (n = 10). BAFF levels were assessed by Enzyme-Linked Immunosorbent Assay (R&D Systems). In addition, percentages and numbers of B-cell subsets were examined by four-color cytometry.

Results: Depletion of B-cells was observed in the rituximab treated group after infusion, while B-cell levels remained unchanged after placebo treatment. B-cells reappeared in the rituximab treated group within 24 to 48 weeks after treatment. Repopulation of the B-cell compartment started with reappearance of transitional B-cells, followed by naïve B-cells, and a relative late recovery of memory B-cells. At baseline, BAFF levels were significantly increased in all pSS-patients in comparison to healthy controls.

Placebo-treated patients showed a slight (0.5 fold, p < 0.05), but significant, increase in BAFF levels only at week 5, likely due to methylprednisolone administration.

Strikingly, long-term elevated levels of BAFF (3.0–4.0 fold, p < 0.05) were observed during 36 weeks following rituximab-treatment. By week 48, BAFF levels had reached baseline values in rituximab treated group.

Conclusion: These preliminary data show a sharp increase in BAFF levels after rituximab therapy. These levels appear to correlate negatively with the presence of B-cells in the peripheral blood. BAFF could be involved in the pathogenesis of SS, possibly by triggering the activation of self-antigen-driven autoimmune B-cells. Since BAFF levels are much higher after rituximab treatment, this may also have implications for manifestations of the disease, related to therapy. This observation might be important for treatment strategies with biologicals like anti-BAFF and/or B-cell depletion. Extended data are in progress and can be presented at the ACR meeting.

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Efficacy of Rituximab in Primary Sjögren’s Syndrome with Peripheral Nervous System Involvement: Results from the French AIR Registry. Arsenie Mekianian1, Eric Hachulla2, Claude Larroche3, Jean Leone3, Bruno Gomberg4, Mohamed Hamidou5, Alain G. Cantagrel6, Christian Marcelli7, Stephanie Rist8, Maxime A. Breban1, Olivier Fair9, Jacques E. Gottenberg10 and Xavier Mariette1. 1Courbevoie, France, 2Avicenne Hospital, 3Bicetre Hospital/Paris Univ, 4Le Kremlin Bicetre, France, 5Caen Hospital, 6Hopital Purpan, Toulouse, France, 7Jean Verdier Hospital, 8La Rochelle Hospital, 9Nantes Hospital, 10National Scleroderma Centre, Lille Cedex, France, 11Orleans Hospital, 12Reims Hospital, 13Strasbourg Hospitals, Strasbourg, France.
Purpose: To evaluate the efficacy of Rituximab in primary Sjogren’s syndrome with peripheral nervous system involvement.

Methods: Prospective data from patients with primary Sjogren’s syndrome and peripheral nervous involvement included in the French Autoimmunity and Rituximab (AIR) registry, were analyzed. Peripheral nervous involvement was defined by clinical signs of peripheral neuropathy confirmed by nerve conduction study. Vasculitis was defined by the presence positive neuromuscular biopsy and/or of purpura. Neurological response to Rituximab was defined by the clinician in charge of the patient.

Results: Seventeen patients (median age 63 years [31–82], 14 female sexes) with Sjogren’s syndrome and peripheral nervous involvement received treatment by Rituximab. The median duration of Sjogren’s syndrome was 10 years [2–26]. Median baseline ESSDAI index was 18 [10–44], joint and cutaneous involvement were present in 7 cases each. Neurological features were sensory neuropathy (n=3), axonal sensory-motor neuropathy (n=12) and multiple mononeuropathy (n=2). Twelve patients have been treated by another immunosuppressor before Rituximab and 10 patients were on corticoids. Other immunosuppressive treatment was associated to Rituximab in 5 cases (methotrexate in 2 cases, mycophenolate mofetil, azathioprine and plasma exchange in 1 case each).

Cryoglobulinemia was present in 9/17 cases (53%) and in these 9 patients neuropathy was considered to be related to the cryoglobulinemia (axonal sensory-motor neuropathy in 7 cases and multiple mononeuropathy in 2 case). Patients with cryoglobulinemia were significantly younger (56 vs 76 years; p=0.02), had more important ESSDAI (24 vs 14; p=0.003), and more profound hypocomplementa (p=0.0001). Vasculitis (defined by biopsy (n=2) or purpura (n=5)) was present in 7/17 patients (41%), and 6/7 (86%) had cryoglobulinemic vasculitis.

Neurological improvement was noted in 11 patients (65%) at 3 months and persisted in 9 cases (53%) at 6 months. Median ESSDAI index was 11 [7–21] at 3 month with joint and skin improvement in 9/12 cases each. Rituximab was effective at 3 month in 9/10 cases (90%) with vasculitis and/or cryoglobulinemia, and in 2/7 cases (29%) in the absence of cryoglobulinemia and vasculitis (p=0.03). Among responders to Rituximab, 4 (36%) experienced a relapse, and 3 of them responded after retreatment with Rituximab.

Conclusion: Rituximab could be effective in peripheral nervous system involvement of patients with primary Sjogren’s syndrome, in particular when related to cryoglobulinemia or vasculitis.

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Efficacy of Rituximab in Primary Sjogren’s Syndrome with Central Nervous System Involvement: Results from the French AIR Registry. Arsen Mekinian1, Claire Larroche1, Eric Hachulla1, Bruno Gomberg1, Claire Blanchard-Delaunay2, Alain G. Cantagrel3, Olivier Finn4, Jean Sibilia5, Jacques E. Gottenberg5 and Xavier Mariette6. 1Avicenne Hospital, 2Bicetre Hospital, 3Hospital Paris Univ, 4Le Kremlin Bicetre, France, 5Hospital Purpan, Toulouse, France, 6Jean Verdier Hospital, Jean Verdier Hospital, La Rochelle Hospital, National Schleroderma Centre, Lille Cedex, France, Niort Hospital, Strasbourg Hospital, Strasbourg Hospitals, Strasbourg, France

Purpose: To evaluate the efficacy of Rituximab in primary Sjogren’s syndrome with central nervous system (CNS) involvement.

Methods: Prospective data from patients with primary Sjogren’s syndrome and CNS involvement included in the French AutoImmunity and Rituximab (AIR) registry were analyzed. CNS involvement was defined by the presence of central nervous impairment associated with diffuse white matter T2-weighted hypersignal in the exclusion of other aetiologies. Neurological response was defined as complete disappearance of neurological signs and persisted in 9 cases (53%) at 6 months. Median ESSDAI index was 15 [5–19] at 3 month with articular and cutaneous improvement in all cases.

Conclusion: Rituximab is not effective in CNS progressive multiple sclerosis-like manifestations of patients with primary Sjogren’s syndrome.

Disclosure: A. Mekinian: None; C. Larroche: None; E. Hachulla: None; B. Gomberg: None; C. Blanchard-Delaunay: None; A. G. Cantagrel: None; O. Fain: None; J. Sibilia: None; J. E. Gottenberg: None; X. Mariette: None.

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Epitope Mapping of the Autoantigen Aquaporin-4 Reveals Linear Epitopes Located in the Intracellular Region of the Molecule. Eleni I. Kabyla1, John G. Routsias2, Haralampos Alexopoulos2 and Athanasios G. Tzioufas2. 1Department of Pathophysiology, Medical School of Athens, Athens, Greece, 2Medical School-Univ of Athens, Athens, Greece

Background: Autoantibodies to aquaporin-4 (AQP4), a water channel localized in astrocytic foot processes at the blood-brain barrier, have been shown to correlate with Neuromyelitis Optica (Devic’s syndrome), a rare syndrome. The main symptoms of the syndrome are optic neuritis and myelitis. The latter can be found in the context of a systemic autoimmune disease, such as Systemic Lupus Erythematosus (SLE), and primary Sjögren’s syndrome (pSS). Despite the fact that anti-AQP4 antibodies have an established role in the pathogenesis of Neuromyelitis Optica, their fine specificity and regulation of their production has not been clarified. The aim of the present study was to identify the B cell linear epitopes of the AQP4 protein, investigate putative similarities with other molecules and evaluate the sensitivity and specificity in detecting anti-AQP4 autoantibodies.

Methods: Sera from 21 patients with Devic’s syndrome, all positive for anti-AQP4 antibodies using indirect immunofluorescence on mouse brain tissue, were used. Sera from 23 SLE and 23 pSS patients, without neurologic involvement were utilized as disease controls. 26 healthy individuals were also used. 11 overlapping peptides, spanning the entire intracellular and extracellular domains of the AQP4 molecule, were synthesized (Bio-synthesis Inc, U.S.A.), and all sera were screened by ELISA for the presence of antibodies against the peptides. The cut-off values for each peptide assay were determined using the mean OD plus 2 SD of sera from 26 healthy controls. Specificity was evaluated by homologous inhibition assays.

Results: Reactivity against 3 different peptides spanning the sequences aa1–22, aa88–113 and aa252–275 was demonstrated in 33%, 24% and 24% of sera from Devic’s patients, respectively, while 38% of patients’ sera were reactive against at least one of the 3 peptides. All epitopes were localized in the intracellular domains of AQP4. A 73% sequence similarity was observed between the [aa252–275] peptide (amino acids 257–271), and the aa219–233 domain of the [aa252–275] peptide (amino acids 257–271), and the aa219–233 domain of AQP4.

Conclusion: This is the first epitope mapping of the autoantigen AQP4. Most of antibodies to AQP4 are directed against conformational epitopes but a significant proportion targets certain linear epitopes, located in the intracellular domains of the molecule. Future studies in our laboratory are aiming to determine the pathogenic relevance of these epitopes.

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EULAR Sjögren’s Syndrome Patient Reported Index (ESSPRI): Development of a Consensus Patient Index for Primary Sjögren’s Syndrome. Raphaële Seror, Philippe Ravaud, Xavier Mariette, Hendrika Bootsma, Elke Theander, Arne Hansen, Manel Ramos-Casals, Thomas Dörner, Stefan Börjesson,9 Erica Hachulla,11 Johan G. Brun,2 Anna A. Kruize,12 Sonja Praprotnik,14 Matija Tomsić,14 Jacques E. Gottenberg,2 Valerie Devauchelle,15 Salvatore Devita,3 Cristina Vollenweider,6 Thomas Mandl,16 Athanasios G. Tzioufas,16 Steven E. Carson,2 Alian Saraux,2 Nurhan Sutcliffe,2 Claudio Vitali,2 Simon J. Bowman15 and The EULAR Sjögren’s Task Force. “Josep Font”, Hospital Barcelona, 2 Barts & The Royal London Hospital, 3 Berlin Charité, University Hospital, 4 Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France, 5 Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France, 6 CHU de la Cavale Blanche, 7 CHU de la Cavale Blanche, Brest Cedex, France, 8 Germain Hospital, Buenos Aires, 9 Malmö University Hospital, 10 Medical School-Univ of Athens, Athens, Greece, 11 National Scleroderma Centre, Lille Cedex, France, 12 Strasbourg Hospitals, Strasbourg, France, 13 Université Paris Descartes, 14 University Clinical Centre of Ljubljana, 15 University Hospital Birmingham NHS Foundation, 16 University Hospital of Udine, 17 University Hospital, Bergen, 18 University Medical Center Groningen, 19 University Medical Center Utrecht, 20 University of Pisa, 21 Villamarna Hospital, 22 Winthrop Univ Hospital, Mineola, NY.

Background: We previously developed a score to assess disease activity in patients with systemic complications of primary Sjögren’s syndrome (SS): the ESSDAI. Objectives: We now aim to develop a second score: disease-specific patient-reported outcomes, complementary to ESSDAI, to assess patients’ symptoms: the EULAR Sjögren’s Syndrome Patient Reported Index (ESSPRI).

Methods: Based on studies developing the Sicca Symptoms Inventory (SSI) and the Profile of Fatigue and Discomfort (PROFAD), dryness, limb pain, mental and physical fatigue were selected as the main relevant symptoms for primary SS patients. It was suspected that, compared to these long questionnaires, a single 0–10 numerical scale for each of these 4 domains would be sufficient to assess these symptoms. These 4 scales were gathered to form the ESSPRI. Patients were included in 12 different countries by 21 SS experts participating in this international collaborative project promoted by EULAR. All patients completed the ESSPRI, SSI and PROFAD questionnaires and a 0–10 patient global assessment (PGA). Correlations between domains, dryness features and PGA were obtained. Multiple regression modelling, using PGA as the dependent variable, was used to select domains and estimate their weights, and construct the ESSPRI.

Results: 230 primary SS patients (mean age = 55.9 ± 13.9 yrs, 219 [95.6%] females, mean disease duration = 8.3 ± 5.6 yrs, 184 [80.0%] anti-SSA and/or SS/B positive) were included. In univariate analysis, PGA had good correlation with dryness, pain, mental and physical fatigue (rho: 0.50 to 0.58, all p<0.0001), but was less correlated with each separate dryness feature (rho: 0.38 to 0.48) except ocular dryness (rho: 0.54). In multivariate analysis, dryness, pain and physical fatigue, but not mental fatigue, were significantly associated with PGA; weights derived from the regression coefficients were identical for these 3 domains (R² = 0.49). Thus, we redefined ESSPRI as the mean of the 3 scales (dryness, limb pain and physical fatigue). Correlation with PGA (rho) was 0.70, 0.66 and 0.56 for ESSPRI, PROFAD and SSI, respectively. Last ESSPRI correlated with PROFAD (rho=0.73) and with SSI (rho=0.66).

Conclusion: ESSPRI is a patient index designed to measure patients’ symptoms in primary SS. This very simple index has good construct validity when PGA is considered as the gold standard and good correlations with more complicated validated indexes: SSI and PROFAD. ESSPRI and ESSDAI are currently being evaluated for sensitivity to change and validated in order to be used as an outcome measure in clinical trials.

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Evolution of Autoimmune Minor Salivary Gland (MSG) Lesions in Sjögren’s Syndrome (SS). Efstathia K. Kapsokeorgou, Maria I. Christodoulou,2 Demosthenes B. Panagiotakos, Spyros Paikos and Haralampos M. Moutsopoulos.1 Dental Department, “Laikon” General Hospital of Athens, Athens, Greece, University of Athens, 3Pathophysiology Dept, School of Medicine, National University of Athens, Athens, Attica, Greece, 4Pathophysiology Dept, School of Medicine, National University of Athens, Athens, Greece.

Purpose: The MSG lesions of SS patients extend from mild to severe. The prevalence of certain types of infiltrating mononuclear cells (MNC), including CD4+ T cells and their subpopulations, B cells, macrophages (MΦ), and interdigitating dendritic cells (iDC) varies according to lesion severity. MSG lesions are generally thought to develop stepwise, starting from mild infiltrates that progress through time. However, studies of sequential biopsies evaluating this progress are missing. The aim of this study was to evaluate repetitive MSG samples of SS patients and define the evolution of the grade and composition of lesions through time.

Methods: 28 SS patients, which agreed to perform second MSG biopsy, were studied. In 24 patients, the first biopsy had been performed at diagnosis. The median interval (range) between the two sequential biopsies was 55 (30–110) months. The evolution of the grade of MSG lesions was evaluated by the number of lymphohistiocytic/fibrosis/mm² of tissue (biopsy focus score), Tarpley score and the number of total infiltrating MNC/mm²-tissue. The percentage of total T, CD4+ T, CD8+ T, Treg and B cells, MΦ, iDC, follicular DC (iDC) and natural killer (NK) cells to total infiltrating MNC was analyzed immunohistochemically in the entire tissue. General linear model for repeated measures adjusted for biopsy time interval and non-parametric Wilcoxon test for paired observations were used.

Results: The biopsy focus score was found to change in 4 patients [1st to 2nd biopsy focus score (%-change): 8.2–11.4 (39), 1.8–3.1 (71), 4.0–11.6 (190) and 6.9–2.0 (−71)]; in two of them was followed by a change in Tarpley score (from 3+ to 4+ and 3+ to 2+, respectively). The number of infiltrating MNC/mm²-tissue was found to increase in 7 patients (% increase: 37, 38, 48, 70, 89, 185 and 204) and reduce in 2 patients (% decrease: 62 and 68). This progression was not found to associate with biopsy time interval, incidence of the various histological cell types, other histological, demographic and clinical features or therapy. Statistical analysis of all SS samples revealed that the biopsy focus score and MNC number/mm²-tissue did not change significantly between the two sequential biopsies. From the cell populations studied, only the CD4+ T cell incidence changed through time. The percentage of CD4+ T/MNC cells was found significantly decreased in the second biopsy (mean±SD in the 1st vs 2nd biopsy: 30.8±7.9 vs 26.9±10.2, p=0.038); however, without affecting the CD4+ /CD8+ T cell ratio (2.2±1.03 vs 1.4±0.9, p=0.29). Other histological parameters, such as fibrosis, fat infiltration or germinal center formation did not differ between the two sequential biopsies. The biopsy time interval was not found to affect the evolution of the lesion grade or composition. Finally, the histological parameters tested were not found to correlate with any demographic, clinical and therapeutic features of patients.

Conclusions: In the majority of SS patients, the grade and composition of MSG lesions at diagnosis remained mainly unchanged through follow-up. These findings suggest that the MSG autoimmune infiltrates do not significantly progress and accordingly, the progression of SS lesions is a rather slow process.

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Extra-Glandular Manifestations of Primary Sjögren’s Syndrome in the SICCA International Sjögren’s Syndrome Registry. Arundathi S. Maladi,12 Kenneth E. Sack,6 Stephen Shiboski,10 Caroline Shiboski,10 Alan N. Baer,2 Pekka Helin,1 Bruce Kirkham,5 Hisanori Umehara,5 Frederick B. Vivino,5 Cristina F. Vollenweider,5 Yan Zhao,5 John Greenspan,10 Troy Daniels6 and Lindsey A. Crisswell.13 German Hospital, Buenos Aires, Argentina, Johns Hopkins University, Baltimore, MD, Kanazawa Medical University, Ishikawa, Japan, “King’s College London, UK, 3Peking Union Medical College Hospital, Beijing, China, 4Penn Presbyterian Med Ctr, Philadelphia, PA, 5Righospitalet, Copenhagen, Denmark, 6UCSF, Tiberon, CA, 7UCSF, San Francisco, CA, 8UCSF, 9UCSF-Box 0500, San Francisco, CA, 10UCSF, 11UCSF-Box 0500, San Francisco, CA, 12University of California at San Francisco (UCSF), San Francisco, CA.
Purpose: To study the prevalence of extra-glandular manifestations (EGM) in patients with primary Sjögren’s Syndrome (pSS) among participants enrolled in the Sjögren’s International Collaborative Clinical Alliance (SICCA) cohort.

Methods: We studied 1618 participants (ppts) enrolled in the SICCA cohort. Inclusion required one of the following: symptoms of dry eyes or dry mouth; prior suspicion/diagnosis of SS; positive serum SSA, SSB, RF or ANA; increase in dental caries; parotid gland enlargement; or a possible diagnosis of secondary SS. We excluded ppts with RA, SLE or sclerodermia (n=87) from this analysis. Ppts underwent thorough rheumatologic, ocular, and oral examinations. Medical questionnaires were completed and ppts were asked about the presence of thyroid, liver, kidney disease or lymphoma. We then confirmed details of these diagnoses from treating physicians, specifically inquiring about the 8 diseases listed below. The frequency of EGM between the cases and each control group were compared using the chi square statistic.

Results: For the 1529 ppts in this analysis, average age at enrollment was 54 years; 92% were female; 47% were Caucasian, 34% Asian/Pacific Islander and 11% Hispanic; 84% had complaints of dry eye symptoms and 90% had complaints of dry mouth symptoms. 635 ppts met the 2002 American-European (AmEu) Consensus Group criteria for pSS. Two “control” groups were defined. Group 1 (N=744) consisted of all ppts who did not meet AmEu criteria. Group 2 (N=264), a subset of Group 1, included ppts who had negative labial salivary gland biopsy (FOCUS score <1), negative anti-SSA/SSB and negative ocular staining score (OSS) =3. Results are summarized in the table.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>pSS Number (%)</th>
<th>Control Group 1 Number (%)</th>
<th>Control Group 2 Number (%)</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>635 (293)</td>
<td>744 (326)</td>
<td>264 (171)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF positive</td>
<td>399 (63)</td>
<td>106 (14)</td>
<td>31 (12)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ANA ≥ 320</td>
<td>426 (67)</td>
<td>130 (18)</td>
<td>29 (11)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IgG &gt; 2013</td>
<td>200 (32)</td>
<td>19 (3)</td>
<td>1 (0.4)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IgA &gt; 463</td>
<td>63 (10)</td>
<td>18 (2)</td>
<td>4 (2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IgM≥368</td>
<td>22 (4)</td>
<td>19 (3)</td>
<td>6 (2)</td>
<td>0.32</td>
<td>0.35</td>
</tr>
<tr>
<td>C3 &lt; 90</td>
<td>74 (12)</td>
<td>85 (12)</td>
<td>34 (8)</td>
<td>0.89</td>
<td>0.61</td>
</tr>
<tr>
<td>C4 &lt; 16</td>
<td>103 (16)</td>
<td>56 (8)</td>
<td>14 (5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wbc &lt; 3.8</td>
<td>194 (30)</td>
<td>30 (4)</td>
<td>6 (2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hct &lt; 38.5</td>
<td>306 (48)</td>
<td>218 (29)</td>
<td>65 (25)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet &lt; 140</td>
<td>42 (7)</td>
<td>22 (3)</td>
<td>8 (3)</td>
<td>&lt;0.001</td>
<td>0.032</td>
</tr>
<tr>
<td>Graves Disease</td>
<td>12 8</td>
<td>24 (3)</td>
<td>8 (3)</td>
<td>&lt;0.001</td>
<td>0.032</td>
</tr>
<tr>
<td>Hashimoto’s</td>
<td>32 38</td>
<td>8 8</td>
<td>9.5 0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinial</td>
<td>2 1</td>
<td>0 47</td>
<td>0.36 0.36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P1 compares pSS with Group 1 controls
P2 compares pSS with Group 2 controls
Wbc: white blood cell; Hct: hematocrit; PBC: primary biliary cirrhosis; RTA: renal tubular acidosis. Sx: Symptoms

The frequency of positive RF, ANA titer ≥320, hypergammaglobulinemia (IgG and IgA) and low C4 are significantly higher in the patient group vs. control groups. Hematologic abnormalities (leukopenia, anemia and thrombocytopenia) are also more prevalent in the pSS cases. There was no significant difference in the frequency of the 8 diseases studied, with the exception of PBC. Joint and neurological symptoms were common in all three groups but significantly higher in the control groups.

Conclusions: Our results confirm that primary SS is associated with serum auto-antibodies, hypergammaglobulinemia, low C4 levels, and hematologic abnormalities. Furthermore, the prevalence of EGM such as thyroid, liver and kidney disease may be lower than reported in previous, smaller studies. While neurological symptoms may be common in pSS patients, our results suggest that the prevalence of these symptoms may be similarly high in control populations, thereby stressing the importance of controls when evaluating these symptoms in pSS. A limitation of our study is the difficulty in fully characterizing EGM due to the large size and international nature of the SICCA cohort.

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Germinal Center (GC) Formation in Salivary Gland Biopsies at Diagnosis of Primary Sjögren’s Syndrome (pSS) Is a New and Strong Predictor of Non-Hodgkin’s Lymphoma (NHL) during Follow-Up. Elke Theander1, Lilian Vasatis2, Eva Baecklund3, Gunnel Nordmark4, Gunnar Warffinge5, Rolf Liedholm6, Karl Brokstad7, Roland Jonsson7 and Malin V. Jonsson8. 1University of Bergen, Bergen, Norway, 2University of Bergen, Bergen, Norway, 3University of Lund, Uppsala, Sweden, 4University of Lund, Malmö, Sweden, 5University of Uppsala, Uppsala, Sweden

Background: Due to increased risk of NHL in pSS the identification of better markers for lymphoma development is crucial.

Objective: Does GC formation in salivary gland biopsies from the time point of pSS diagnosis predict NHL? Does GC formation correlate with other markers of NHL?

Methods: 174 pSS minor salivary gland biopsies from the Swedish SS centers in Malmo and Uppsala underwent blind and independent reevaluation by light-microscopy at the Broegelmann Research Laboratory, Bergen, Norway for the presence of GC-like structures. These were determined by a densely packed dark zone and a light zone in biopsies with classical focal infiltration within otherwise normal salivary glands. The presence of NHL was determined by linkage of the local SS registries to the Swedish cancer registry. Observation time was defined as time from the salivary gland biopsy until lymphoma diagnosis, death or end of follow-up. The median (IQ range) time between diagnosing pSS and biopsy was 1 week (0–16). The total observation time was 1859 patient years at risk (range: 1 month – 26 yrs). Time between salivary gland biopsy and NHL diagnosis was in median 8 years (range: 2 yrs and 4 months – 12 yrs and 7 months).

Statistics: Risk of developing NHL in patients with or without GC formation was compared by Cox regression analysis and Kaplan Meier statistics/log rank test. Associations between GC formation and other risk variables were determined by χ²-statistics.

Results: In total 136 biopsies showed focal sialadenitis (focus score ≥1) at reevaluation. In 43 (32%) of the biopsies with focal sialadenitis GC like structures were detected. Seven patients had developed NHL. Six of the 7 NHL patients (86%) had GC like structures at the time of diagnosing pSS. Patients with GC-like structures had 15 times increased risk of developing NHL patients (86%) had GC like structures at the time of diagnosing pSS. The total observation time was 1859 patient years at risk (range: 1 month – 26 yrs). Time between salivary gland biopsy and NHL diagnosis was in median 8 years (range: 2 yrs and 4 months – 12 yrs and 7 months).

Statistics: Risk of developing NHL in patients with or without GC formation was compared by Cox regression analysis and Kaplan Meier statistics/log rank test. Associations between GC formation and other risk variables were determined by χ²-statistics.

Results: In total 136 biopsies showed focal sialadenitis (focus score ≥1) at reevaluation. In 43 (32%) of the biopsies with focal sialadenitis GC like structures were detected. Seven patients had developed NHL. Six of the 7 NHL patients (86%) had GC like structures at the time of diagnosing pSS. Patients with GC-like structures had 15 times increased risk of developing NHL compared to those without. Hazard Ratio (HR) 15.4, 95%CI: 1.85–128, p=0.01. Log-rank test: p=0.001. Positive predictive value 16%, negative predictive value 99%.

Development of NHL in primary Sjögren’s syndrome patients with or without GC like structures in lower lip salivary gland biopsy

For the 1529 ppts in this analysis, average age at enrollment was 54 years; 92% were female; 47% were Caucasian, 34% Asian/Pacific Islander and 11% Hispanic; 84% had complaints of dry eye symptoms and 90% had complaints of dry mouth symptoms. 635 ppts met the 2002 American-European (AmEu) Consensus Group criteria for pSS. Two “control” groups were defined. Group 1 (N=744) consisted of all ppts who did not meet AmEu criteria. Group 2 (N=264), a subset of Group 1, included ppts who had negative labial salivary gland biopsy (FOCUS score <1), negative anti-SSA/SSB and negative ocular staining score (OSS) =3. Results are summarized in the table.
GC positivity correlated with autoantibodies to SSA/SSB, lymphadenopathy, systemic disease activity (ESSDAI domains), high-risk type of SS (all p<0.05).

**Conclusion:** The presence of GC-like structures in the diagnostic salivary gland biopsies in pSS is highly predictive of lymphoma development with a HR of >15. This marker is an important new prognostic factor in the care of pSS patients. It may be included in guidelines for selection of pSS patients for biological B-cell directed treatment.

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**1900**

**IL-7 Receptor Effector T Cells Are Increased in the Inflamed Salivary Glands of pSS Patients and Correlate with Inflammatory Markers.** A. Bikker, A. A. Kruize, M. J. G. Wenting, F. P. J. G. Lafeber and J. A. G. van Roon. Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

**Background:** In patients with primary Sjögren’s syndrome (pSS) local T cell-driven inflammation can contribute to destruction of exocrine glands associated with clinical symptoms of dryness. Recently we documented increased IL-7 in labial salivary glands (LSG) of pSS patients that was capable to induce Th1 and Th17 activity and proinflammatory cytokine secretion. IL-7 mediates its effects by signaling through the high affinity IL7R (IL-7Rα subunit in conjunction with the γc chain). We and others have shown that IL-7R+ CD4 T cells that strongly proliferate upon TCR activation, while IL-7R- CD4 T cells remain anergic and can be regulatory of naïve CD4 T cells. Therefore, the presence of increased local IL-7 expression might be a novel therapeutic strategy for pSS.

**Objective:** To identify IL-7R expression in the labial salivary gland of and to examine the phenotypical characteristics of IL-7R+ CD4 T cells between pSS and non-Sjögren’s syndrome sicca (nSS) patients. Additionally, to study the capacity of soluble human IL-7R in preventing immune activation.

**Methods:** The presence of infiltrating immune cells and IL-7R+ cells in inflamed salivary glands of pSS patients (n=14) and non-inflamed LSG of nSS patients (n=7) was studied by immunohistochemistry and FACS analysis upon tissue digestion.

**Results:** In the LSG of pSS patients significantly increased numbers of IL-7R+ cells were found as compared to nSS (pSS vs nSS: 244.3 ±40.7 vs 12.3 ±4.6 cells/mm²). IL-7R+ T cells were found throughout the tissue but mainly in the CD3-rich lymphocytic areas. In the salivary glands of nSS patients only a few resident CD3+ T cells were detected. IL-7R+ T cells strongly correlated with local disease parameters (lymphocytic focus score [LFS]; p=0.001, r=0.744 and % IgA+ cells p=0.005, r=0.658) as well as with immune cells present in the LSG (CD3 p=0.001, r=0.89; CD20 p=0.005, r=0.717; CD1a p=0.005, r=0.660; CD208 p=0.001, r=0.763).

FACS analysis of isolated cells from patients’ LSG confirmed a strongly increased percentage of both CD3 and IL-7R+ CD3 T cells in pSS as compared to nSS (both p<0.01). Furthermore, abundant IL-7R expression was detected on high proportions of CD4 and CD8 (on average 66% ± 5% and 56% ± 4% respectively). Other CD45+ leucocytes and CD45-tissue cells did not or hardly express the IL-7R. IL-7R+ CD3, CD4, and CD8 T cells as percentage of the total LSG cells showed a significant correlation with the LFS (p=0.05, r=0.533; p=0.01, r=0.593; p=0.01, r=0.631 respectively).

Blockade of IL-7R-mediated signaling by soluble human IL-7R furthermore inhibited lymphocyte proliferation that was induced by ligands for Toll-like receptors 7, 8 and 9 (all p<0.05).

**Conclusions:** The abundant presence of IL-7R+ T cells in the inflamed salivary glands of pSS patients, which correlates to inflammation, suggests that increased IL-7 expression could significantly contribute to glandular inflammation by activation of IL-7R+ effector T cells. Blockade of the IL-7R might be a novel therapeutic strategy for pSS.

This study was financially supported by the Dutch Arthritis Association (‘het Nationaal Reumaфонd’)

**Disclosure:** A. Bikker: None; A. A. Kruize: None; M. J. G. Wenting: None; J. W. J. Bijlsma: None; F. P. J. G. Lafeber: None; J. A. G. van Roon: None.

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**Immunization with Ro60 Peptide Leads to Sjögren’s Like Syndrome in Mice with Appropriate Genetic Background.** Biji T. Kurien1, Sima Asfa2, Anil D’souza3, Yaser Dorri4, Skyler P. Dillon5, Sherry Hubbel1, Ali W. Khalili1, Olga Yelisoy6, Yun Jong Lee, Shannon Maier7 and R. Hal Scalford2. 1Oklahoma Medical Research Foundation, 2University of Oklahoma, 3University of Oklahoma Health Science Center

**Purpose:** Our previous studies showed that BALB/c mice are amenable as an animal model for Sjögren’s syndrome (SS) with (a) diminished salivary flow (b) intramolecular epitope spreading to Ro 60 autoantigen and (c) salivary gland lymphocytic infiltration upon immunization with Ro 274 peptide derived from Ro 60 autoantigen. We hypothesized that there would be a strain dependent susceptibility for SS induction.

**Methods:** Fourteen mice each from BALB/c, DBA-2, SJL/J, C57Bl/6 and PL/J strains were used. Seven mice from each strain were immunized (day one) with 50 μg of a linear peptide (273–289 amino acid sequence from Ro 60) or saline emulsified in Freund’s Complete Adjuvant (FCA). Subsequent boosts were in Freund’s Incomplete Adjuvant. The first, second and third boosts were given on day 7, 27 and 60 respectively. Ro 60 multiple antigenic peptide ELISA, Ro 60 ELISA and immunoblots were performed. Epitope spreading, salivary flow (upon induction with pilocarpine and isopropenol) and histochemical lymphocytic infiltration were determined.

In the sacrifice, salivary glands were excised and a portion was saved for histopathological studies.

**Results:** Immunization with Ro-274 linear peptide resulted in anti-Ro-274 antibodies as early as the first bleed in BALB/c, DBA-2 and PL/J strain of mice. A milder anti-Ro 274 response was elicited in the B6 strain of mice by the sixth bleed while the SJL/J mice displayed a very poor response throughout the study. In the Ro-274 peptide immunized group 5/5 BALB/c, 1/5 DBA, 3/4 PL/J mouse bound Ro 60 antigen by immunoblot. SJL/J and C57Bl/6 mice did not bind. Except for one DBA control mouse that bound Ro 60 antigen on immunoblot the remaining control mice did not make antibodies to this antigen. Ro-peptide immunized BALB/c and DBA mice had lymphocytic infiltration of the salivary glands greater than controls. However, salivary flow was significantly decreased only in the BALB/c mice compared to controls.

**Conclusions:** Only BALB/c mice displayed the complete SS-like condition, with diminished salivary flow, anti-Ro 60 antibodies and salivary gland lymphocytic infiltration upon immunization with Ro 274 peptide. DBA mice had significant salivary infiltrates and anti-Ro 60 antibodies but no salivary dysfunction. PL/J mice made antibodies and had epitope spreading but did not have salivary pathology or dysfunction. C57Bl6 bound the peptide but had no further progression in the model while SJL/J never produced antibodies to the immunogen. These data suggest a stepwise, or quantum, genetic control of the response that leads to a Sjögren’s-like illness after Ro-peptide immunization.

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Methods: Gastric emptying was evaluated by the octanooate breath test, from which half time (t½) and lag time (tlag) were determined. The results were corrected according to age and gender and expressed as z-scores. AD was evaluated by 5 objective autonomic reflex tests (ART), i.e. the deep-breathing test (expiration/inspiration (E/I)-ratio), the orthostatic heart rate test (acceleration index (AI)), the finger-skin blood flow test (vasoconstrictory (VAC)-index), and the orthostatic blood pressure test (systolic and diastolic blood pressure (SBP & DBP)-ratios). The results were age-corrected and expressed as z-scores by comparison with three previously examined control groups. Patients also filled out the ASP and these results were corrected according to age, gender, height and weight and were mainly expressed as z-scores. Patients were also assessed regarding symptoms of functional bowel syndrome as well as by inflammatory and serological tests. For comparison between groups the Mann-Whitney-U test and Fisher’s exact test were used and for correlations the Spearman rank correlation test. Results: The t½ and the tlag were significantly prolonged in patients compared to controls (1.18 (−0.71, 2.06) vs. −0.06 (−0.72, 0.74); p=0.03 and 1.40 (−0.14, 3.11) vs. −0.03 (−0.57, 0.66); p=0.00 respectively). Thus 43% of pSS patients presented signs of IGE whilst 29% fulfilled criteria for gastroparesis. Significant correlations between t½ and increased levels of IgG (p=0.03) and erythrocyte sedimentation rate (ESR) (p=0.02) were found. In addition, rheumatoid factor (RF) seropositive showed objective signs of IGE to a greater extent than RF seronegatives. No associations between IGE, ART variables, ASP variables or functional bowel syndrome were found.

Conclusions: Impaired gastric emptying was common in pSS. Associations with inflammatory and serological features of pSS could imply immunological mechanisms behind the IGE. Objective signs of IGE were not associated with objective or subjective signs of AD nor functional bowel syndrome.

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1903

Increased Numbers of IL-7Rα-CD25+FoxP3+ T Cells in pSS Patients

Methods: Expression of CD25, and FoxP3 on IL-7Rα (CD127) positive and negative CD4 T cells from 15 pSS patients and 15 HC was assessed using FACS analysis. The functional properties of IL-7Rα+ and IL-7Rα- CD4 T cells were tested in vitro. Co-stimulation of CD4 T cells with anti-CD3 antibody led to CD25+FoxP3+ T cells, which were compared to CD25−T cells. The results showed that CD25+FoxP3+ T cells were more differentiated and had a higher proportion of memory T cells.

Results: The number of CD25+FoxP3+ T cells was significantly higher in pSS patients compared to healthy controls.

Conclusion: The increased numbers of CD25+FoxP3+ T cells in pSS patients suggest that this population of T cells may play a role in the pathogenesis of the disease.
Safety of rituximab (re)treatment was assessed in all patients. Efficacy was assessed up to 24 weeks after each course. Stimulated whole saliva (SWS) was chosen as primary end-point. Secondary end-points were IgM-Rf and level of general fatigue (Multidimensional Fatigue Inventory; MFI).

Results: Safety

The first 8 patients were treated with 4 infusions of rituximab per course (375 mg/m² per infusion; premedication 25mg prednisolone i.v.); 5 of these patients were retreated. Because of a high occurrence of serum sickness-like disorder in this initial cohort of pSS patients (in 3 out of 13 courses), the treatment schedule was changed; patients were treated with 2 infusions of rituximab per course (1000 mg per infusion; premedication 100 mg prednisolone i.v.; 1000 mg oral paracetamol and 2 mg clemastine i.v.). Both courses were accompanied by a tapering dosage of oral prednisone 60-15 mg/day in 5 days afterwards. Serum sickness-like disorder occurred in 2 patients after the schedule had changed (in 2 out of 52 courses).

Efficacy

After initial treatment, a rapid decrease in peripheral B cells occurred in all patients. In rituximab treated pSS patients, SWS stayed at the same or a higher level during follow-up, whereas SWS declined in untreated patients. At 24 weeks after the first course of rituximab, there was still a decrease in IgM-Rf levels and a decrease in general fatigue compared to baseline. Next a gradual return of the various complaints to baseline was observed. Most, but not all, complaints had returned to baseline by the 9th month. Additional treatments with a second, third and fourth course led to results comparable to initial treatment.

Conclusion: Rituximab was shown to be effective for 6–9 months in pSS patients after the first course of rituximab. Additional courses of rituximab resulted in a comparable beneficial effects in pSS patients on functional parameters, serological parameters and fatigue. Higher doses of corticosteroids led to a reduction of the occurrence of serum sickness-like disorder. Based on these interim results, additional courses with rituximab seem to be a safe and effective treatment for pSS.

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1906

Molecular and Cellular Evolution of Functional Tertiary Lymphoid Structures in Salivary Glands of NOD Mice, Elisa Astorri1, Michele Bombardieri2, Elisa Corsiero3, Francesca Barone1, Gordon Proctor2 and Costantino Pitzalis3.1Birmingham University, Birmingham, United Kingdom, 2King’s College, London, London, United Kingdom, 3Queen Mary University London, London, United Kingdom

Background: Tertiary Lymphoid Structures (TLSs) formation is a common feature of chronic inflammatory diseases including Sjögren’s syndrome (SS). We recently showed that these ectopic structures acquire functional properties typical of secondary lymphoid organs and are capable of supporting autoreactive B cell activation and autoantibody production as demonstrated by expression of activation-induced cytidine deaminase (AID) and class switching. Dissecting TLSs dynamics in humans is technically and ethically challenging. Thus, we used the NOD mouse model, a spontaneous model of autoimmune sialoadenitis, to characterize the cellular and molecular basis of autoreactive B cell activation and evolution of functional Ectopic Lymphoid Structures (ELS) in the chronically inflamed NOD salivary glands.

Methods: Submandibular (SUBM) glands from 110 female NOD mice from 4 to 35 weeks of age were collected. Paired snap-frozen, OCT-embedded samples were analysed by immunohistochemistry (IHC) for T and B lymphocytes (CD3/CD20) in order to evaluate immune cell infiltration and the degree of B/T cell segregation. ELS were detected by staining for FDC-M1 (follicular dendritic cell networks), GL7 (germinal centre B cells) and AID (marker for ELS functionality). Characterization of B cell subsets within the infiltrates was carried out by immunostaining and by FACS analysis with CD19, CD21, CD23, B220, IgD, IgM, CD1d and CXCR5 antibodies. Quantitative TaqMan real-time PCR was performed to investigate the mRNA expression of ELS related genes. The same analysis was performed in sex/age matched Balb/c mice as controls.

Results: NOD infiltrates in SUBM glands displayed progressive features of ELS from week 8, with 75% of mice developing B/T cell segregation, FDC networks and GL7+ ectopic germinal centers (GCs) from week 20. Formation of ectopic GCs was always associated with B/T segregation. Evolution of TLSs was closely associated with mRNA upregulation of genes regulating ectopic lymphoid tissue organization and function such as lymphoid chemokines CXCL13/CCL19 and their specific receptors CXCR5/CCR7, lymphotoxins and B cell survival factors BAFF and APRIL. In agreement with CXCL13/CXCR5 mRNA expression, B cells infiltrating NOD SUBM glands display strong CXCR5 expression and were mostly characterised by a follicular phenotype (B220+/IgD+/IgMlow/CD23+/CD21low) as demonstrated by both IHC and FACS analysis on isolated cells. Finally, functionality of ELS was demonstrated by expression of AID mRNA and protein within FDC networks, which paralleled the detection of circulating SS-related autoantibodies.

Conclusion: This work provided the first in depth characterization of the cellular and molecular mechanisms underlying the evolution of functional TLSs within SUBM infiltrates of NOD mice. These data strongly support the hypothesis that B cells can be activated within TLSs in the target organ and promote an in situ autoantibody response. Overall, these data support the critical importance of ELS formation in chronic autoimmune inflammation and identified NOD mice as a suitable model to test therapeutic strategies aimed at modulating B cell functionality.

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1907

New Classification Criteria for Childhood Sjögren’s Syndrome. Naoto Yokogawa1, Scott M. Lieberman1, Sharon M. Boul-Tabak2, Faizan Alawi1, Juan P. Palazzo3, Martha Guttenberg2, David D. Sherry2 and Frederick B. Vivino4.1Children’s Hosp of Philadelphia, Philadelphia, PA, 2Children’s Hosp of Philadelphia, 3Nationwide Children’s Hospital, Columbus, OH, 4Penn Presby Med Ctr, Philadelphia, PA, 5The Children’s Hospital of Philadelphia, Philadelphia, PA, 6Thomas Jefferson Univ., 7Univ. of Pennsylvania, 8Univ. of Pennsylvania/Tokyo Metropolitan Tama Medical Center

Purpose: To develop new classification criteria for childhood Sjögren’s syndrome (SS).

Background: Adult classification criteria for SS have not been validated in children and currently proposed pediatric criteria lack diagnostic sensitivity.

Methods: Retrospective review of medical records of 41 patients (pts) was performed at Children’s Hospital of Philadelphia and the Penn Sjögren Center to identify cases of suspected pediatric SS. Diagnosis by physician global assessment required 1) symptom onset at age <20 yrs, 2) consensus agreement on diagnosis by pediatric and adult rheumatologists, 3) abnormal serologies and/or lip biopsy. Pts with overlapping autoimmune disease were not excluded. Clinical presentation, serologies, objective tests for sicca and histopathology were reviewed. All available salivary gland biopsies were blindly reviewed by oral pathologists to calculate a focus score (FS) and compared to biopsy findings from non-SS pts. Pts were also classified as childhood SS (score:3 or more) or non SS (score 2 or less) using a novel scoring system (max = 8) based on a modification of American-European Consensus Group (AECG) criteria (Vitali et al, 2002).

<table>
<thead>
<tr>
<th>Point</th>
<th>Sicca symptoms</th>
<th>Objective findings</th>
<th>Laboratory findings</th>
<th>Biopsy findings</th>
</tr>
</thead>
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<tr>
<td>11</td>
<td>Dry eye (I) AND dry mouth (parotid swelling (II)†‡</td>
<td>Abnormal eye exams (III) AND abnormal salivary flow (V)</td>
<td>Positive SSA and/or SSB (VI)</td>
<td>Focus score &lt; 1 OR characteristic findings of SS*</td>
</tr>
<tr>
<td>10</td>
<td>Dry eye (I) OR dry mouth (parotid swelling (II)</td>
<td>Abnormal eye exams (III) OR abnormal salivary flow (V)</td>
<td>Positive ANA AND Negative SSA/SSB</td>
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</tr>
<tr>
<td>9</td>
<td>No sicca symptoms</td>
<td>Normal eye exams and normal salivary flow</td>
<td>Negative ANA/SSA/SSB</td>
<td></td>
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<tr>
<td>8</td>
<td></td>
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<td>Presence of focus AND Focus Score &lt; 1</td>
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<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>Absence of focus</td>
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*2Parotid biopsy may be sufficient to diagnose SS.
†Include parotid enlargement by radiological study.
‡Parotid biopsy may be sufficient to diagnose SS.

Results: Following global assessment and long term follow-up of the pediatric cohort (41 pts), 35 pts had confirmed childhood SS, 3 pts had suspected but unconfirmed SS, and 3 pts were diagnosed as HIV, sarcoidosis, or IPEX syndrome. Using the novel scoring system, all 35 pts with definite childhood SS were classified as SS and all 3 pts with other final diagnosis were classified as non SS.
Patients and Methods: 24 consecutive pSS-patients (according to American-European group criteria consensus revised on 2002) presenting a definite SFN were included. The SFN was defined by the presence of sensory painful symptoms with a DN4 score ≥4 and the evidence of abnormal nerve small fiber neurophysiological tests, including laser evoked potentials (LEP), quantitative sensory test (QST) and sensory skin reflex (SSR). The 24 included patients were compared to 89 SS-patients without peripheral neuropathy.

Results: the 24 patients included 20 female (83%) and 4 men (17%) with a mean age of 64±10 years. For 21 patients (87.5%), SFN led to pSS diagnosis. SFN involved both upper and lower limbs for 19 patients (79%) and lower limbs alone for 5 patients (21%). The neurophysiological tests abnormalities included altered LEP in 21 patients (87.5%), abnormal QST in 21 patients (87.5%) and abnormal SSR in 13 patients (54.2%). Compared to the 89 pSS-patients who did not present with a peripheral neuropathy, patients with a pSS-associated SFN were older at the time of pSS diagnosis (63±10 vs 48.5±14 years; P<10⁻⁴), and had more frequently a central nervous system involvement (25% vs 2%; P<10⁻⁴). They were featured by a lower frequency of serum B cell activation markers, i.e, less often positive ANA (58% vs 90%; P<10⁻²), anti-SSA (37.5% vs 73%; P<0.001), anti-SSB (12.5% vs 42%; P<0.008) and rheumatoid factor (37.5% vs 68%; P<0.008), and lower serum gammaglobulins levels (12.5±5 vs 16.7±5 mg/L; P<0.0045).

Conclusion: Our study reported for the first time the main features of SFN in pSS patients. Our results showed that patients with a pSS-associated SFN are characterized by an older age at SS diagnosis and a more frequent CNS involvement, and a distinctive immunological profile hallmark by a lower frequency of serum B cell activation markers (ANA, anti-SSA, anti-SSB, rheumatoid factor, and gammaglobulins).

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1909

Novel Lupus Susceptible Gene Polymorphisms in Patients with Sjögren’s Syndrome in Japanese Population. Tetsuya Horita1, Hisako Nakagawa1, Takashi Kurita1, Toshiho Odam1, Yuchiro Fujieda1, Kotaro Otori2, Masaru Kato1, Shinsuke Yasuda1, Tatsuya Atsumi1 and Takao Koike1. Medicine II, Hokkaido University, Sapporo, Hokkaido, Japan, 2Medicine II, Hokkaido University.

Background: Genetic background of Sjögren’s syndrome (SS) is still unknown. SS can occur alone (primary SS) or in conjunction with other autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (secondary SS). Several novel lupus susceptible genes were reported in the recent candidate gene approaches and genome wide association studies in Caucasian population. In this study, we analyzed these lupus susceptible gene polymorphisms in patients with SS in Japanese population.

Patients and Methods: This study comprised 190 SS patients and ethnically matched 428 healthy controls. Patients with SLE were excluded. B lymphocyte specific tyrosine kinase (BLK) rs13277113, B-cell scaffold protein with ankyrin repeats 1 (BANK1) rs10516487 and rs37331917, signal transducer and activator of transcription 4 (STAT4) rs7574865, interferon regulatory factor 5 (IRF5) rs2004640, tumor necrosis factor ligand superfamily member 13 (TNFSF13) rs1192845, tumor necrosis factor alpha induced protein 3 (TNFAIP3) rs13192841, interferon regulatory factor ligand superfamily member 4 (TNFSF4) rs844644, rs10798269 in 1q25.1 region were evaluated using TaqMan Genotyping Assay. Allele frequencies in each polymorphism were compared using chi-square test and the related risk was approximated by the odds ratios. In addition, stratification analysis by anti-SS-A and anti-SS-B was performed. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated.

Results: The allele frequencies of lupus risk in SS were significantly higher in BLK (odds ratio (OR) = 1.61, 95% confidence interval (CI) 1.21–2.15), STAT4 (OR = 1.83, 95%CI:1.43–2.36), IRF5 (OR = 1.40, 95%CI:1.07–1.82) and rs10798269 in 1q25.1 region (OR = 1.62, 95%CI:1.20–2.18), compared with those in healthy controls. No significant associations were found in BANK1, TNFSF13, TNFAIP3 and TNFSF4. In stratification analysis, STAT4 was associated with the presence of both anti-SS-A and anti-SS-B, whereas BLK and SNP (rs10798269) in 1q25.1 region were associated with anti-SS-A and IRF5 was associated with anti-SS-B. In genetic risk scoring system for SS, the presence of five or more risk alleles in 4 common susceptible genes (BLK, STAT4, IRF5 and 1q25.1) was strongly associated with SS (OR = 2.79, 95%CI:1.89–4.14).

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1908

New Insights in Sjögren Syndrome Associated Peripheral Neuropathies: The Small Fibre Neuropathy and Its Clinical, Immunological and Neurophysiological Features from a Moncentre Cohort of 24 Patients. Damien Sène1, Jean-Pascal Lefaucheur1, Julien Haroche1, David Saadoun2, Baptiste Hervier1, Jean-Charles Piette1, Zahir Amoura1 and Patrice Cacoub1. 1Hôpital Henri-Mondor, 2Hôpital Pitie-Salpêtrière Hospital.

Objective: Primary Sjögren syndrome (pSS) may account for 9 to 30% of causes of sensory small fibre neuropathies (SFN), clinically characterized by sensory painful symptoms mostly associated with normal clinical and electromyographic examinations. Nevertheless, the main features of SFN have never been evaluated in a large cohort of pSS-patients. The aim of this study was to analyze the clinical, immunological and neurophysiological features of pSS-associated SFN.

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1907

Genetic Background of Sjögren’s Syndrome (SS) is still unknown. SS is an autoimmune disease characterized by keratoconjunctivitis sicca, oral and genital dryness, Raynaud’s phenomenon, chronic fatigue, and, in some patients, arthritis and interstitial lung disease. The genetic background of SS is complex, involving both genetic and environmental factors. Previous studies have identified several genetic loci associated with SS, including the major histocompatibility complex (MHC), the tumour necrosis factor (TNF) and the interleukin (IL) families, and the interferon regulatory factor 5 (IRF5) gene. These genetic loci are involved in the immune response and inflammation, and may contribute to the pathogenesis of SS. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated.
Conclusions: BLK, STAT4, IRF5 and IQ2.51 region were not only lupus susceptible genes but SS susceptible genes in Japanese population. SS share, in part, common genetic background with SLE.

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1910

Patients’ Complaints Depend on Systemic Status in Patient with Primary Sjögren’s Syndrome: Concordant Results from 2 Independent Cohorts.


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Objectives: To determine whether common symptoms of dryness, fatigue and pain differed between patients with or without systemic complications in primary Sjögren’s syndrome (SS).

Methods: Data concerning primary SS patients were analyzed from 2 different prospective studies: 1-230 patients included by 21 SS experts participating in an EULAR study for the development of the EULAR Sjögren’s Syndrome Patient reported Index (ESSPRI), and 2-354 patients from the French prospective SS cohort (ASSESS). All patients completed the ESSPRI (0–10 numerical scales for pain, fatigue, and dryness features), Sicca Symptoms Inventory (SSI), Profile of Fatigue and Discomfort (PROFAD) questionnaires and a 0–10 patient global assessment (PGA). Severity of each symptom was compared between patients with and without systemic involvement.

Results: 140 (60.9%) of the 230 patients from the EULAR study (mean age = 55.2 ± 13.9 yrs, 219 [95.6%] females, mean disease duration = 8.3 ± 5.6 yrs, 80.0% anti-SSA and/or SSB positive), and 253 (71.5%) 354 patient age 13.9 yrs, 219 [95.6%] females, mean disease duration = 21.6 ± 9.3 yrs, 90.0% anti-SSA and/or SSB positive) had past or present systemic involvement. Systemic involvements included fatigue (60.9% of patients), pain (57.4% of patients), and dryness (50.0% of patients). Systemic features, but SSI scores were not.

Conclusion: In 2 independent cohorts of primary SS patients, we showed that patients with systemic complications have higher levels of fatigue, pain, but similar levels of dryness, compared to those without. Thus, alterations of common patient reported outcomes, present in most of the patients with pSS, are more intense in patients with systemic complications. This supports the interest of using ESSPRI in both groups of patients with and without systemic complications.

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1911

Primary Sjögren’s Syndrome-Associated Non Ataxic Sensory Neuropathies and Sensorimotor Neuropathies Are Characterized by Distinctive Immunological Profiles. Damien Sene2, Moez Jallouli2, Jean-Pascal Lefaucheux1, David Saadoun1, Thierry Maisonneuve2, Julien Haroche3, Marie-Claude Diemert4, Lucile Musset5, Jean-Charles Piette6, Zahir Amoura7 and Patrice Cacoub8.

1Hemimondor Hospital, 2Pitié-Salpêtrière Hospital.

Objective: To characterize the relationship between primary Sjögren’s Syndrome (pSS)-associated peripheral neuropathies (PN) and markers of B cell mononuclear proliferation and chronic activation.

Patients and Methods: 120 consecutive patients presenting with a definite pSS were included. Serum markers of chronic B-cell activation included auto-antibodies and hypergammaglobulinemia. Monoclonal B-cell proliferation markers included mixed cryoglobulin, monoclonal gammopathy, abnormal κ/λ free light chain (FLC) ratio or B-cell non Hodgkin lymphoma (B-NHL).

Results: A definite PN was present in 30 patients (25%) including 7 patients with a sensorimotor neuropathy (23%), 3 patients with an ataxic sensory neuropathy (10%) and 20 patients with a non-ataxic sensory neuropathy (67%). Patients with a sensorimotor neuropathy differed from those without PN by higher ratios of monoclonal B-cell proliferation markers, i.e. mixed cryoglobulin (57% vs. 11%; P = 0.008), monoclonal gammopathy (71% vs. 17%; P = 0.004), higher FLC ratio (2.7 ± 1.5 vs. 1.7 ± 1.8; P = 0.024) and B-NHL (57% vs. 3%; P < 0.001). Patients with non-ataxic sensory neuropathy were featured by a higher age (57.5 ± 10.7 vs. 48.7 ± 14.3 years; P = 0.007), a more frequent CNS involvement (15% vs. 2%; P = 0.04) and a lower prevalence of chronic B-cell activation serum markers, i.e., ANA (60% vs. 90%; P = 0.003), anti-SSA (Ro) (40% vs. 72%; P = 0.009), anti-SSB (La) (15% vs. 41%; P = 0.039), RF (37% vs. 67%; P = 0.02), and hypergammaglobulinemia (35% vs. 64%; P = 0.023). In multivariate analysis, a sensori-motor neuropathy was associated with the presence of B-NHL (OR = 3.90; P < 0.001), whereas a non-ataxic sensory neuropathy was associated with the presence of a CNS involvement (OR = 17.0; P = 0.025) and ANA (OR = 0.07; P < 0.001).

Conclusion: Up to 25% of pSS-patients presented with peripheral neuropathy, which was predominantly a sensory neuropathy. Distinctive immunological profiles were found according to the type of SS-associated neuropathy, as non-ataxic sensory neuropathy was hallmarkized by a low prevalence of B-cell activation markers and sensorimotor neuropathy by a high prevalence of B-cell monoclonal proliferation markers.

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1912


Background: Sjögren’s syndrome (SS) has been associated with the development of Non-Hodgkin’s lymphomas (NHL).

Methods: Fifty-three consecutive lymphoma cases (51 female/2 male), with a median age of 54 years (range 28 to 90 years) were retrospectively analyzed. Overall survival (OS), event-free survival (EFS) and standardized mortality ratio (SMR) were calculated. An event was defined as relapse, treatment failure, progression, transformation, or death, whichever occurred first following lymphoma diagnosis.

Results: Mucosa-associated lymphoid tissue (MALT) lymphomas constituted the majority (59%) of lymphoma subtypes, followed by nodal marginal zone lymphomas (NMZLs) (15%), diffuse large B-cell lymphomas (DLBCLs) (15%) and other histologies (11%). After a long median follow-up of 40.8 months for the entire lymphoma cohort, 6 patients died. Median survival was not reached, and 3-year OS was 0.96 (95% CI 0.83 to 0.98). Median EFS was 85.3 months. The corresponding
age-sex adjusted SMR of lymphoma compared to the general population was 3.25, suggesting a shorter life expectancy.

In nine localized MALT lymphomas with low International prognostic index(IP1), treatment was withheld. Among these cases, only one transformed to DCLBL. Eight patients with limited stage MALT and extrapolaginal manifestations were treated with rituximab monotherapy. The remaining MALT cases were treated with combined modality protocols. Treatment resulted in complete response rates (94%), upon completion of therapy. Overall, 3-year OS and EFS were 0.97 and 0.78 respectively for MALT cases.

Combined immunochemotherapy was the standard therapeutic intervention for DCLBLs, resulting in 100% OS and EFS at 3 years. NMZLs had a disappointing outcome (3-year OS 0.80 and EFS 0.53), warranting the urgent need for a new standard of treatment.

Conclusion: Our results explicitly describe the course and prognosis of SS-associated lymphomas and highlight the need for a risk-stratified treatment approach.

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1913
Risk of Non-Hodgkin’s Lymphoma in Primary Sjögren’s Syndrome.
Svein J. A. Johnsen1, Johan G. Brun1, Tom B. Johannesen2, Lasse Goransson1, Karstein Haldorsen1, Roland Jonsson4 and Roald Omdal3. 1Haukeland University Hospital, 2Norwegian Cancer Registry, 3Stavanger University Hospital, 4University of Bergen

Background: It is well known that patients with primary Sjögren’s syndrome (PSS) have an increased risk for developing non-Hodgkin lymphoma (NHL), although the exact risk reported has varied in different studies. Such discrepancies could be due to the use of different criteria applied for PSS diagnosis over time, and the inclusion of more or less biased patient samples. The aim of this study was to assess the risk of NHL and other hematological malignancies in a well-defined population in Western Norway applying the widely accepted American-European Consensus Group criteria for PSS (1).

Methods: All patients with PSS were identified in the two counties Hordaland and Rogaland (896 840 subjects—18.59% of the total population of Norway). A linked registry study between the PSS registry and the Cancer Registry of Norway was performed, and in addition all medical files were screened for ascertainment of diagnoses. The risk of NHL in PSS patients was compared with the risk in the general population based on the Cancer Registry data. Descriptive statistics with mean, SD and ranges were used to present patient demographic data.

Results: As of June 1st 2009, 432 Caucasian PSS-patients were alive, of which 406 (94%) were women and 26 men (6%). Mean age was 62 years, SD 13.2 [range 16–95]. Mean age at diagnosis was 53.8 years, SD 13.5 [range 15–89]. Mean duration of disease was 8.65 years, SD 5.2 [range 1–35]. Total follow-up was 3,722 patient years. Five cases of NHL (1.16%) were identified, all marginal zone lymphomas. Three of these were MALT-lymphomas of the salivary glands, one MALT-lymphoma from the lingual tonsil and one extranodal marginal zone lymphoma located in the bone marrow. In addition, the latter patient presented a monoclonal B-cell population consistent with a κ-positive B-cell chronic lymphocytic, also classified as NHL. No high-grade lymphomas were detected.

Conclusion: PSS patients have an increased risk of developing NHL compared with the risk in the general population (p<0.001). The risk, however, seems lower than previously reported.


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The FMS-Like Tyrosine Kinase3-Ligand (FL) Is a Marker for Lymphoma in Primary Sjögren’s Syndrome (SS). Jacques-Olivier Pers1, Gabrielle Morel2, Ste´phanie Rist6, Alain Saraux3 and Pierre Youinou1.

1Brest University, Brest, France, 2Brest University, 3CHU de la Cavale Blanche, Brest Cedex, France, 4Le Kremlin Bicetge Hospital, 5Montpellier University, 6Hautepign Hospital, Strasbourg, France

Background: The exocrine glands of patients with primary SS become sites of intense immunological activity and thereby present with tissue damage. Salivary glands exhibit a lymphoproliferative sialadenitis, associates with lymphocyte infiltration and epithelial cell apoptosis. Compared with healthy individuals, patients with SS are at greater risk of developing non-Hodgkin’s lymphoma. We recently published that FL, a cytokine implicated in B-cell ontogenesis and malignant proliferation, might unveil primary SS at risk of developing lymphoma (Tobón et al., Arthritis Rheum. 2010).

Methods: In order to confirm this observation, serum levels of FL were measured in 334 patients enrolled in the French cohort of primary SS patients. All fulfilled the European American criteria for SS. Association between FL positivity and: 1- criteria linked to a high risk of lymphoma such as purpura, low C4 levels, enlargement of the parotid glands, monoclonal Ig, cryoglobulinemia; 2- lymphoma development; 3- disease activity according to visual analogic score (VAS) for subjective signs and the EULAR SS Disease Activity Index (ESSDAI).

120 pg/mL of FL was considered as positive (FL+) i.e. 2 SD above the mean of 50 controls. Nevertheless, sensitivity and specificity were calculated at different cut-off values. To compare data FL+ and FL-, we used the chi-square or Fisher exact test for qualitative variables and the Mann-Whitney test for quantitative variables (Statistical Package for the Social Sciences).

Results: Main results are listed in the Table. FL+ patients were younger. The sex ratio, subjective symptoms of dryness and parotidomegaly were not statistically associated to FL. In contrast, purpura and lymphoma, as well as ESSDAI were significantly associated with elevated levels of FL. ROC analysis showed that 175 pg/mL was ideal cut-off to detect the association with lymphoma: sensitivity 44%, specificity 97.5%.

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1915
The Role of Immunostaining Against the Panaxonal Protein PGP 9.5 in the Evaluation of Sjogren’s Sensory Neuropathies, and the Increased Frequency of Male Sex and Seronegativity to Anti-La/SS-B Autoantibody with Peripheral Neuropathies. Julius Birbaum, Alan N. Baer and Michael Polydefkis. Johns Hopkins University, Baltimore, MD

Purpose: The frequency of different subtypes of peripheral neuropathies (PNS) in larger number of Sjogren’s patients has not been studied using diagnostic techniques which have been validated for other PNS syndromes. Specifically, the quantification of nerves immunostained against the PGP 9.5 panaxonal protein allows for the diagnosis of a “small-fiber” neuropathy affecting unmyelinated nerves. Therefore, we sought to understand the frequency of different subtypes of neuropathies in Sjogren’s patients, and to characterize whether Sjogren’s patients with neuropathies may have distinguishing demographic, clinical, and immunologic features.

Methods: We characterized the neuropathy occurring in 186 consecutively evaluated Sjogren’s patients, by examination, electrodiagnostic studies, and by skin biopsy when there was suspicion for a small-fiber neuropathy. The diagnosis of small-fiber neuropathy was based on decreased intra-epidermal innervation (IENF) of unmyelinated nerves immunostained against the PGP 9.5 panaxonal protein. Logistic regression analysis was performed to determine whether the presence of neuropathies (as the dependent variable), was independently associated with demographic, clinical, and autoantibody covariates.
Results: Forty-seven patients had peripheral neuropathies; of 41 patients with sensory neuropathies, 32 patients had neuropathies affecting the unmyelinated nerves, versus 9 patients with axonal sensory neuropathies and ganglionopathies assessed by electrodagnostic studies. The association of demographic, clinical, and immunologic covariates with peripheral neuropathies was assessed by logistic regression. Male sex ($p = 0.04$) and seronegativity to the anti-La/SS-B autoantibody ($p = 0.04$) were respectively and independently associated with neuropathies.

Conclusions: The most common subtype of neuropathy in Sjögren’s patients is a neuropathy targeting the unmyelinated nerves. The integrity of the smaller-fiber, unmyelinated nerves can be assessed by immunostaining against the PGP 9.5 protein 9.5, cannot be assessed by routine electrodagnostic studies, and may account for the lower frequency of neuropathies reported in larger cohort studies of Sjögren’s patients. The increased frequency of male sex and seronegativity of anti-La/SS-B autoantibodies seen in Sjögren’s patients with PNS manifestations suggests discriminating hormonal and immunologic mechanisms.

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1916

The Temporal Appearance of Symptoms and Signs in Primary Sjögren’s Syndrome. Chiara Baldini, Nicoletta Luciano, Pasquale Pepe, Rosaria Talarico, Sara Grossi, Antonio Gaetano Tanovi and Stefano Bombardieri. Rheumatology Unit, Department of Internal Medicine, University of Pisa, Italy.

Aims of the Study: (1) to characterise the clinical presentation of primary Sjögren’s syndrome (pSS) in a large cohort of patients and to determine whether epidemiological, clinical and analytical features modulate disease expression; (2) to determine possible changes in clinical and immunological patients’ profiles over time.

Methods: We reviewed the case records of 515 pSS patients (17 M: 498 F, mean age 57.4 years, median follow-up 6.5 ± 6.4 years) who had attended our Unit in the decades between 1989 and 2009. The diagnosis was made according to either the AECG criteria (390/515) or the European Preliminary Criteria for pSS (125/515). Patients’ cumulative clinical and immunological features were collected. The lag time between the onset of the disease and the onset of each pSS clinical and serological manifestation was recorded in order to group the disease features according to their mean periods of appearance. Logistic regression analysis was applied to explore clinical and serological associations.

Results: Demographic, clinical and immunologic features of the patients are summarised in Table 1.

<table>
<thead>
<tr>
<th>Disease manifestations</th>
<th>Prevalence (%)</th>
<th>Lag time from the disease onset (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth/Dry eyes</td>
<td>94% - 96%</td>
<td>0.3 ± 0.6/0.2 ± 0.6 At the onset</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>63%</td>
<td>0.8 ± 2.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45%</td>
<td>0.3 ± 0.7</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>26%</td>
<td>0.7 ± 2.7</td>
</tr>
<tr>
<td>Dry vagina</td>
<td>19%</td>
<td>0.5 ± 1.8</td>
</tr>
<tr>
<td>Skin involvement</td>
<td>16%</td>
<td>0.7 ± 1.4</td>
</tr>
<tr>
<td>Difficulty in swallowing</td>
<td>14%</td>
<td>0.3 ± 0.7</td>
</tr>
<tr>
<td>Hypocomplementemia</td>
<td>18%</td>
<td>0.3 ± 0.6</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>48%</td>
<td>0.2 ± 0.7</td>
</tr>
<tr>
<td>Antimuclear antibodies</td>
<td>83%</td>
<td>0.2 ± 0.2</td>
</tr>
<tr>
<td>Anti Ro/SSA/anti La/SSB</td>
<td>62% - 28%</td>
<td>0.2 ± 0.4</td>
</tr>
<tr>
<td>Salivary gland enlargement</td>
<td>32%</td>
<td>2.2 ± 4.7</td>
</tr>
<tr>
<td>Hematological manifestations</td>
<td>25%</td>
<td>2.3 ± 5.4</td>
</tr>
<tr>
<td>Kidney involvement</td>
<td>1%</td>
<td>1 ± 2</td>
</tr>
<tr>
<td>Arthritis</td>
<td>11%</td>
<td>3 ± 4.2</td>
</tr>
<tr>
<td>Lung</td>
<td>7%</td>
<td>5.8 ± 7.0</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>6%</td>
<td>5.1 ± 6.7</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>0.3%</td>
<td>11 ± 1.4</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3%</td>
<td>17.4 ± 10.8</td>
</tr>
</tbody>
</table>

Glandular manifestations were generally present at the onset of the disease. Among pSS extraglandular manifestations, arthralgias, Raynaud’s phenomenon (RP), skin involvement, fatigue and difficulty in swallowing were also mainly observed at the onset of the disease, and significantly correlated with the positivity for anti-Ro/SSA and hypocomplementemia. Parotid enlargement, cytopenias, kidney involvement, peripheral nervous system and lung involvement were more frequent within the first five years of the disease, especially in seropositive patients and in patients with a lower age at diagnosis. Finally, lymphoma was generally a late disease manifestation with the lymphoproliferative risk increasing over time with an exponential function ($p = 0.002$). The multivariate analysis identified a disease duration longer than 9 years ($p = 0.006$), salivary glands enlargement ($p = 0.003$) and hypocomplementemia ($p = 0.03$) as independent variables for lymphoma.

Conclusion: This study confirmed that pSS can be considered as a mild, benign chronic disorder, the most severe lymphoproliferative manifestations being usually late complications of the disease. Epidemiological, clinical and serological features have a significant impact on the clinical presentation of pSS influencing the prevalence of extraglandular involvement and the disease outcome.

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Vaccination of Patients with Primary Sjögren’s Syndrome Induces IL-7 and Skewed B Cell Maturation with Increased Levels of Plasmablasts Resulting in Higher Titers of Vaccine-Specific IgG Antibodies. Susanna R. Brauner1, Marika Kvarnström2, Sabrina Goergen3, Karl A. Brokstad4, Christina Trolmö5, Lars Klareskog6, Roland Jonsson7, Vivianne Malmström7 and Marie Wahren-Herlenius7. 1Karolinska University Hospital, Stockholm, Sweden, 2Reumatology Unit, Karolinska Institutet, Stockholm, Sweden, 3University of Bergen, Bergen, Norway.

Background: Multiple immune disturbances underlying disease development and progression have been implicated in Sjögren’s syndrome, including defects in the B cell compartment. In this study we used vaccination as a tool for in vivo intervention to understand defects in immune regulation by studying the primary immune response of individuals with primary Sjögren’s syndrome, and specifically to characterize B cell development and responses.

Methods: Fourteen SSA/Ro positive women with primary Sjögren’s syndrome and 18 gender and age matched healthy controls were vaccinated with A H1N1 influenza vaccine and boosted three weeks later. Blood samples were taken at vaccine administrations, as well as one and three weeks after, with a total of five sample points for each subject. At each sampling total Ig and vaccine specific immunity was analyzed by ELISPOT, ELISA and hemagglutination tests, lymphocyte phenotype was characterized by flow cytometry and routine laboratory tests were performed. Cytokine levels were analyzed in serum using a Luminex assay. Clinical parameters and potential adverse reactions of vaccination were monitored with a clinical questionnaire at each of the five visits.

Results: No significant differences in immunoglobulin levels or lymphocyte compartments were observed between patients and controls at the start of the study. After vaccination, all subjects developed protective immunity as determined by hemagglutination assay. However, already one week after the first vaccination the patients had developed significantly fewer class switched CD19+ B cells ($p < 0.05$), and more immature B cells (CD19+IgD+IgM+) persisted in circulation ($p < 0.05$). This skewed pattern of B cell maturation remained throughout the whole study. Surprisingly, plasmablasts (CD19lowCD138+) still increased, and were detected at a significantly higher level in patients after the second vaccination ($p < 0.01$). In accordance, significantly higher levels of several innate proinflammatory cytokines (IL-6, IL-10, IL-12p40 and TNF-alpha) as well as IL-7 ($p < 0.05$), a B cell promoting cytokine, were induced in the patients. Further, the Sjögren’s syndrome patients developed significantly higher titers of IgG vaccine specific antibodies ($p < 0.02$). Despite this humoral immune activation in the patients, SSA/Ro52 titers remained unaffected throughout the study.

Several commonly reported adverse reactions to the vaccine were observed. Surprisingly controls reported significantly more fever and myalgia as side effects after vaccinations.
Conclusions: Patients with Sjögren’s syndrome respond to vaccination and develop protective immunity. However, the induced titers of vaccine specific antibodies are significantly higher than in controls. Analysis of the immune reactions leading to antibody production revealed a skewed B cell maturation and proinflammatory cytokine response, which may retrace the mechanisms allowing high titers of autoantibodies to develop in autoimmune patients.

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Validation of microRNAs as Biomarkers of Salivary Gland Inflammation in Sjögren’s Syndrome. Seyed M. Emamian1, Ilias Alevizos1 and Gabor G. Illei2. 1NIDCR, 2NIDCR, NIH #10 1N114, Bethesda, MD

The diagnosis of Sjögren’s syndrome (SS) is based on a number of diagnostic criteria, including the assessment of inflammation (quantified by the focus score) in a minor salivary gland (MSG) biopsy. MicroRNAs (miRNAs) are a group of RNAs, 18–24 nucleotides in length, involved in the regulation of cellular processes. miRNAs are promising as biomarkers as they are resistant to degradation and can be isolated from various sources including formalin-fixed, paraffin-embedded (FFPE) biopsies. In a preliminary study done on frozen isolated from various sources including formalin-fixed, paraffin-embedded (FFPE) biopsies, we have demonstrated that the relative expression of two miRNAs showed good association with various degrees of inflammation in a small cohort.

Purpose: To validate hsa-mir-574-3p and hsa-mir-768-3p as biomarkers of inflammation in a larger cohort of subjects.

Methods: The training cohort consisted of 49 subjects 33 with primary Sjögren’s patients and 16 non-Sjögren’s controls. In the validation cohort 49 subjects had pSS, 26 had sicca symptoms but no SS and 12 were healthy controls. miRNA was isolated from FFPE biopsies. The relative expression of hsa-mir-574-3p and hsa-mir-768-3p was determined by calculating the difference of their Ct of hsa-mir-574-3p and hsa-mir-768-3p derived from FFPE samples from Sjögren’s and non-Sjögren’s MSGs.

Results: Using a teaching cohort of 49 subjects, we first showed the ΔCt of hsa-mir-574-3p and hsa-mir-768-3p derived from FFPE samples can distinguish samples from Sjögren’s from non-Sjögren’s MSGs regardless of focus score (r = 0.001, one-way analysis of variance) as well as groups with various degree of inflammation. To validate the applicability of these miRNAs as biomarkers we determined the correlation between individual focus scores and the ΔCt in an independent set of 87 subjects.

Conclusion: The relative expression of hsa-mir-574-3p and hsa-mir-768-3p shows a strong correlation with focus scores in MSGs of Sjögren’s patients validating these miRNAs are biomarkers of MSG inflammation and suggesting that they may be used to reduce the subjectivity involved in the diagnosis of SS.

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Validation of microRNAs as Biomarkers of Salivary Gland Inflammation in Sjögren’s Syndrome. Seyed M. Emamian1, Ilias Alevizos1 and Gabor G. Illei2. 1NIDCR, 2NIDCR, NIH #10 1N114, Bethesda, MD

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Abatacept (ABA) in the Treatment of Psoriatic Arthritis (PsA): 12-Month Results of a Phase II Study. Philip J. Mease3, Mark C. Genovese4, Geoffrey S. Gladstein5, Alan J. Kivitz2, Christopher T. Ritchlin6, Paul P. Tak7, Jurgen Wollenhaupt8, Jean-Claude P. Becker4, Sheila M. Kelly9, Yun Peng7 and Dafna D. Gladman10. 1Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, 2Altoona Arthritis & Osteo Ctr, Duncansville, PA, 3Arthritis Int Med Assoc LLC, Trumbull, CT, 4Bristol-Myers Squibb, Pennington, NJ, 5Bristol-Myers Squibb, Doylestown, PA, 6Bristol-Myers Squibb, Doylestown, PA, 7Schoen Klinik, Hamburg, Germany, 8Seattle Rheumatology Associate, Seattle, WA, 9Stanford University, Sunnyvale, CA, 10Toronto Western Hospital, Toronto, ON, Canada, 11University of Rochester Medical Center, Rochester, NY

Purpose: A phase II study evaluating ABA in PsA patients (pts) previously exposed to disease-modifying antirheumatic drugs (DMARDs) including anti-TNF agents demonstrated the efficacy of ABA against both arthritis and psoriasis after 6 months (mos) of double-blind (DB) treatment (Mease P, et al. Ann Rheum Dis 2010;69(Suppl3):98. Abstract SAT0288). Here, we assess the efficacy and safety of ABA after pts completed at least 6 mos of an open-label (OL) extension phase.

Methods: In the 6-mo DB study, 170 PsA pts previously exposed to DMARDs, including anti-TNF agents, were randomized (1:1:1:1) to receive placebo (PBO) or ABA 30/10 (2 initial doses of 30 mg/kg, followed by 10 mg/kg), 10 or 3 mg/kg on Days 1, 15, 29, and once every 28 days thereafter. Pts who completed this phase were eligible to continue in an OL study, and received ABA 10 mg/kg every 28 days for at least 6 mos. Endpoints included measures of joint disease (ACR20, DAS28), joint inflammation by magnetic resonance imaging (MRI), skin disease (target lesion [TL] score, Psoriasis Area and Severity Index [PASI]), physical function (Health Assessment Questionnaire-Disability Index [HAQ-DI]), and safety. Data were as-observed and analyzed on a modified intent-to-treat basis.

Results: A total of 147 pts from all 4 DB treatment groups entered the OL phase; baseline characteristics were similar among groups except for more pts being previously exposed to anti-TNF agents in the 30/10 mg/kg group (49%) than other groups (24–37%). Eighty-eight pts were still on treatment with 47 pts discontinuing due to lack of efficacy. Efficacy data are presented by original randomization group [Table 1]. At Day 169 of DB treatment, ABA improved ACR20 and DAS28, HAQ-DI, TL and PASI scores, and also resulted in less joint damage by MRI evaluation, as compared to PBO. Improvements in ACR and DAS28, reduction in joint damage by MRI and improvement in HAQ-DI continued through Day 365 in pts treated with ABA in the OL phase. Improvements in TL and PASI scores also continued through Day 365. Pts on PBO during the DB period achieved comparable improvements in joint and skin disease, joint inflammation and physical function after ABA treatment in the OL phase. Pts treated with ABA 10 mg/kg during the DB period appeared to have achieved the greatest overall improvements. The safety profile during the OL treatment was consistent with that during the DB period. Serious adverse events were numerically higher in the 10 mg/kg group (18%) vs other groups (8–12%); these were single events with no obvious pattern. One serious infection was reported in each group except for 2 cases in the 10 mg/kg group. There was 1 malignancy, a lentigo maligna, in the 3 mg/kg group. There were no autoimmune events or deaths.

Conclusions: The efficacy of ABA in pts with PsA, demonstrated during short-term DB treatment, was sustained throughout 6 mos of OL treatment. No new safety issue was detected.
Using DAS28 joint count, at T0 51.9% (T1 60.5%, T2 65.5%) of the patients met minimal disease activity criteria. Of these, 7.5% (T1 12.0%, T2 5.1%) would not meet the criteria when using the total joint count (Kappa index = 0.923).

Conclusions: At three different time-points, there are differences between total tender and swollen joint count and DAS 28 joint count, however the agreement between total joint count and DAS28 is high. On the other hand the agreement to classify patients with minimal disease activity is fairly good. These data suggest that DAS 28 joint count may be reliable for evaluating peripheral involvement in PsA.

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An Initial Diagnosis of Lumbar Disc Herniation Is Associated with a Late Referral to the Rheumatologist and a Delay in the Diagnosis of Ankylosing Spondylitis. Servet Akar1, Vedat Gerdan1, Dilek Solmaz2, Mehmet Sayarioglu3, Mehmet Akif Ozturk4, Ahmet Mesut Onat1, B¨unyamin Kısakı0,5, Mehmet Emin Tezcan6, Merih Birlik7, Fatos Onen8 and Nurullah Akkoc1,1. Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, 2Rheumatology, Gazi University, Ankara, Turkey, 3Rheumatology, Gaziantep University Faculty of Medicine, Gaziantep, Turkey, 4Rheumatology, KahrmanMaras Sutcu Imam University Faculty of Medicine, KahrmanMaras, Turkey

Background: Among all the rheumatologic diseases, AS still remains to be the one with, the longest diagnostic delay mostly due to the slow development of radiographic sacroiliitis. In clinical practice, many patients with AS are diagnosed to have lumbar disk herniation (LDH), which in our opinion might be one of the the possible determinants of diagnostic delay in these patients. In this study we assessed the diagnostic delay in AS patients with an initial diagnosis of LDH compared with those without such diagnosis.

Patients and Methods: 393 patients (258 male [65.6%], mean age 39.3 ± 10.8 years) with AS according to the modified New York criteria from five rheumatology clinics in different cities were included in this analysis. A face to face interview was performed by using a structured questionnaire addressing all the possible factors that may lead to diagnostic delay, including the specialty of the first consulted physician, the initial diagnosis and history for LDH. Total diagnostic delay was calculated as the time elapsed from the initial visit to the physician due to back pain until the diagnosis of AS. Factors associated with the diagnostic delay were evaluated by Spearman’s correlation and linear regression methods.

Results: An initial diagnosis of LDH was reported by 33% of the 300 patients who could answer this question. The diagnostic delay in patients with an initial diagnosis of LDH vs those without such diagnosis was 9.1 ± 8.5 years and 6.2 ± 7.4 years, respectively (p = 0.002). Twenty six patients had undergone operation for LDH and the diagnostic delay in those patients was markedly higher than the patients without LDH surgery (13.3 ± 11.3 vs 6.2 ± years, P = 0.023). Referral time to the rheumatologist was also significantly greater in patients with an initial diagnosis of LDH and in patients with a history of LDH surgery compared to the others.

Rheumatologists were seen as the initial physicians by only 4% of the patients whereas, 30% consulted physician, 25% consulted orthopedists and 16% consulted orthopedists at their 1st medical visit due to back pain. The shortest delay in diagnosis was observed when rheumatologists were the first consulted physicians (2.9 ± 5.3 years). The delay period for the physiatrists was shorter (6.3 ± 7.6 years) than the orthopedists (9.6 ± 9.1 years) and neurosurgeons (8.8 ± 6.6 years). However, diagnostic delay was not found to be correlated with sex, family history, HLA-B 27 status and acute phase reaction in the linear regression model. The symptoms with symptom onset (p = 0.013), age at back pain onset (p = 0.01), and education level (p = 0.003) were also found to be significant predictors of the diagnostic delay.

Conclusion: Our results suggest that prior diagnosis of LDH may lead to late referral of AS patients to rheumatologists resulting in a delay in diagnosis. A relatively high percentage of patients with LDH surgery is of concern, pointing out the necessity of continuous medical education of the specialists who are likely to see patients with AS, on the concept of spondyloarthritis.

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Ankylosing Spondylitis Disease Activity Score (ASDAS): Defining Cut-Off Values for Disease Activity States and Improvement Scores. Pedro Machado1, Robert Landewe2, Elisabeth Lie2, Tore K. Kvien3, Juergen Braun4, Daniel G. Baker5 and Desiree M. Van Der Heijde6. 1Coimbra University Hospital, Coimbra, Portugal; Leiden University Medical Center, Leiden, The Netherlands; 2Diakoniehospital, Oslo, Oslo, Norway; 3Leiden University Medical Center, Meerssen, The Netherlands; 4Research and Development, Centocor Inc, Malvern, PA, 5Rheumazentrum Ruhrgebiet, Herne, Germany; 6Univ Hosp Maastricht, Maastricht, The Netherlands

Purpose: ASDAS is a new composite index to assess disease activity in ankylosing spondylitis (AS). It has high construct and discriminatory validity. Criteria for disease activity states and improvement scores using the ASDAS have been developed. They proved to have external validity and a very good performance compared to existing criteria.

Methods: The ASDAS is calculated using BASDAI questions 2, 3 and 6, patient global assessment (all 0–10cm VAS) and CRP (mg/L). We performed receiver operating characteristic (ROC)-curve analysis against several external criteria (ExCr) and used several approaches to determine the optimal cut-off (fixed 90% specificity, Youden index and closest point to (0,1)). The final choice was made on clinical and statistical grounds, after debate and voting by Assessment in SpondyloArthritis Society (ASAS) members. For the identification of proposed cut-offs we used baseline (BL) and 3-month (M) data of NOR-DMARD (N=295–477), a registry that includes AS patients starting a conventional DMARD or a TNF-blocker. Cross-validation was performed in ASSERT, a database of AS patients participating in a randomized placebo-controlled trial with infliximab.

Results: Four disease activity states were chosen by consensus: inactive disease, moderate-, high- and very high disease activity. The 3 cut-offs for separating them were: 1.3 (ExCr: ASAS partial remission, patient and physician global <1cm), 2.1 (ExCr: patient and physician global <3cm) and 3.5 (ExCr: patient and physician global >6cm). Selected cut-offs for improvement scores were: change ≥1.1 units for clinically important improvement (ExCr: patient reporting as being "better" or "much better" since start of treatment) and change ≥2.0 units for major improvement (ExCr: patient reporting as being "much better" since start of treatment). Results of the cross-validation in ASSERT strongly supported the cut-offs (tables 1 and 2).

Table 1. Disease activity states (%) in ASSERT: Infliximab vs Placebo (Chi^2, p-value)

<table>
<thead>
<tr>
<th>Time-point</th>
<th>n</th>
<th>ASAS Partial Remission</th>
<th>ASAS &lt;1.3</th>
<th>1.3 ≤ ASAS ≤ 2.1</th>
<th>2.1 ≤ ASAS ≤ 3.5</th>
<th>ASAS &gt; 3.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>166 vs 57</td>
<td>0 vs 0</td>
<td>0 vs 0</td>
<td>1.2 vs 1.8</td>
<td>30.1 vs 26.3</td>
<td>68.7 vs 71.9</td>
</tr>
<tr>
<td>(NA)</td>
<td></td>
<td>(NA)</td>
<td>(0.1, 0.756)</td>
<td>(0.3, 0.586)</td>
<td>(0.2, 0.645)</td>
<td></td>
</tr>
<tr>
<td>3M</td>
<td>163 vs 56</td>
<td>0.8 vs 1.8</td>
<td>26.4 vs 3.6</td>
<td>38.7 vs 39.3</td>
<td>9.2 vs 9.9</td>
<td>(11.8, 0.001)</td>
</tr>
<tr>
<td>(15.2, &lt;0.001)</td>
<td>(13.3, &lt;0.001)</td>
<td>(1.0, 0.933)</td>
<td>(5.3, &lt;0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6M</td>
<td>163 vs 56</td>
<td>23.3 vs 1.8</td>
<td>31.9 vs 0</td>
<td>23.5 vs 12.5</td>
<td>32.5 vs 33.9</td>
<td>12.3 vs 33.6</td>
</tr>
<tr>
<td>(13.2, &lt;0.001)</td>
<td>(23.4, &lt;0.001)</td>
<td>(3.9, 0.004)</td>
<td>(0.04, 0.846)</td>
<td>(0.46, &lt;0.001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Improvement criteria (%) in ASSERT: Infliximab vs Placebo

<table>
<thead>
<tr>
<th>Improvement criteria</th>
<th>3 months (n=164 vs 56)</th>
<th>6 months (n=163 vs 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ ASDAS&lt;1.1</td>
<td>71.3 vs 19.6</td>
<td>69.3 vs 23.2</td>
</tr>
<tr>
<td>∆ ASDAS&gt;2.0</td>
<td>40.9 vs 3.6</td>
<td>50.9 vs 5.4</td>
</tr>
<tr>
<td>∆ BASDAI&lt;2.0</td>
<td>60.4 vs 23.2</td>
<td>62.6 vs 19.6</td>
</tr>
<tr>
<td>BASDAI&gt;100A</td>
<td>50.6 vs 10.7</td>
<td>51.5 vs 22.6</td>
</tr>
<tr>
<td>ASAS20</td>
<td>64.0 vs 25.0</td>
<td>63.2 vs 21.4</td>
</tr>
<tr>
<td>ASAS40</td>
<td>50.6 vs 16.1</td>
<td>47.2 vs 14.3</td>
</tr>
</tbody>
</table>

Conclusions: Cut-off values for disease activity states and improvement scores using the ASDAS have been developed. Theyproved to have external validity and a very good performance compared to existing criteria.


Ankylosing Spondylitis Patient Organisations—Are There Benefits of Membership? In-Ho Song1, Cornelie Brennies1, Ludwig Hammel2, Ernst Feldkeller3, Joachim Listing4, Joachim Sieper5 and Martin Rudwaleit6. 1Charite Campus Benjamin-Franklin, Medical Clinic I, Rheumatology, Berlin, Germany; 2German Ankylosing Spondylitis Society (DVMB), Schwenfurt, Germany; 3German Rheumatism Research Center, Berlin, Germany

Background: Patient organisations for ankylosing spondylitis (AS) exist in many countries. The aims of these patient organisations are to inform and to educate patients in order to help them better deal and cope with the disease, to organize supervised physiotherapy groups, to support the exchange of experiences, and to represent the interests of patients in society and law (see www.spondylitis-international.org).

Objective: To evaluate differences between AS patients who are members of a patient organisation and AS patients who are not such members.

Methods: The German Ankylosing Spondylitis Society (DVMB) is a large patient organisation with more than 14,000 members in Germany. A cross-sectional survey based on a questionnaire was performed between December 2008 and April 2009. The questionnaire consisted of 82 questions regarding demographics, diagnosis, smoking, acquisition of information about the disease, disease activity, mobility, functional status, patient satisfaction, quality of life, treatment and disability to work and educational level. The questionnaire was distributed to AS patients by rheumatologists in 51 hospitals and/ or private practices. In addition, the questionnaire was sent to 3400 randomly selected members of the German AS society. Data collection and analysis was done anonymously.

Results: In total, 1273 DVMB members responded (1068 members of the patient organisation and 205 non-members). As DVMB members and non-members were not comparable regarding age (mean 54.9 vs. 46.6 years) and disease duration (mean 30.2 vs. 20.1 years) we performed a 2:1-matching of members to non-members regarding age, disease duration and also sex. In the matched population (n=549), members (n=366, mean age 47.0 years, mean disease duration 21.1 years, 63.9% male, HLA-B27 positive 89.0%) and non-members (n=183, mean age 46.3 years, mean disease duration 20.1 years, 63.9% male, HLA-B27 positive 94.6%) differed in the following aspects: members more often felt that they were well informed (62.2% vs. 35.4%, p=0.001), more often used the information provided by the patient organisation (58.5% vs. 11.3%, p=0.001), and more often had a positive family history for AS (34.4% vs. 23.3%, p=0.004). There were no differences regarding disease activity (BASDAI 4.0 vs. 4.2, p=0.172) or in the percentage of patients taking NSAIDs, DMARDs or anti-TNF-blocking agents.

Members as opposed to non-members had a better functional status (BASFI 3.4 vs. 3.9, p=0.021), had less work days missed during the last year (15.1 days vs. 31.2 days, p=0.003), were more often non-smokers (55.9% vs. 71.0%, p=0.001). However, significantly more members had a higher educational status (e.g. percentage with university diploma 26.0% vs. 12.4%, p=0.001).

Conclusion: There are numerous benefits associated with the membership in an ankylosing spondylitis patient organisation. AS patients who are members feel better informed about AS, have a better functional status and a healthier life style, and, overall, seem to cope better with the disease than non-members. Whether the educational status and the degree of physically challenging jobs influence the findings needs further examination.

Disclosure: I.-H. Song: None; C. Brennies: None; L. Hammel: German Ankylosing Spondylitis Society (DVMB), 3; E. Feldkeller: German Ankylosing Spondylitis Society (DVMB), 3; J. Listing: None; J. Sieper: None; M. Rudwaleit: None.

Anterior Chest Wall Pain in Spondyloarthritis Is a Frequent Manifestation, Appearing Early in the Disease Course, Which May Respond to NSAIDs. Muriel Elhai1, Simon Paternotte1, Fanny Roure1, Eugene Koumakis1, Judith Payet1, Vincent Burki1, Isabelle Fabreguet1, Magali Meyer1, Maxime Dougados2 and Laure Gossec1. 1Cochin Hospital and Paris Descartes University, Paris, France; 2Hospital Cochin, Paris, France

Background: Chest pain is a common but little studied feature of spondyloarthritis (SpA). Several studies have already reported the correlation between anterior chest wall pain (ACWP) and specific SpA clinical characteristics such as axial AA. However, the prevalence, clinical manifestation, and treatment of ACWP remain poorly known.

Objective: To determine the prevalence and characteristics of anterior chest wall pain in a cohort of patients with SpA, in a tertiary care center and to describe clinical characteristics of ACWP.

Method: Study design: retrospective single center observational study in
2010 (COSPA). Patients: definite SpA (Amor’s criteria). Each patient underwent direct interview by a physician. Data collection: prevalence of ACWP, according to SpA subtype (axial versus peripheral, enthesitic or extra-articular) and if present, the date of appearance, the localization and nature of the pain, and effectiveness of the different treatments. Analysis: descriptive analysis.

Results: To date, 151 consecutive SpA patients were assessed: median age 43 (inter-quartile range 35–55) years, median disease duration 15 (8–25) years, 97 (64%) were men. In all, 56 patients (37%) suffered from SpA-associated ACWP. ACWP appeared before the diagnosis of SpA in 38% (17/45) cases; it was the first symptom of SpA in 5% (3/56) cases, and it appeared during the first 5 years of disease duration in 69% (31/45) cases. ACWP was localized in the sternoclavicular joint (26%), the manubrio-sternal joint (48%), the upper sternocostal joints (67%) and/or the lower sternocostal joints (55%). ACWP was usually acute, with painful flares (76%), with (N = 16) or without (N = 24) chronic pain. Coronary tests were performed for this pain in 2 cases. Respiratory movements and movements of the arm increased the pain in respectively 78% (40/51) and 55% (26/47) of cases; pain during the night was less frequent (40%, 21/53). Nonsteroidal anti-inflammatory drugs prescribed for this indication were effective in 53 % of cases (17/32), whereas anti-tumor necrosis factor agents were reported as effective in 73 % of cases (19/26).

Conclusion: This is the largest clinical description of ACWP in SpA. ACWP is a frequent manifestation in SpA (37%); it occurs early in the disease which may be a challenge for diagnosis. ACWP in SpA is usually acute; it does not frequently lead to night pain. NSAIDs may be a useful first line treatment.

Disclosure: M. Elahi: None; S. Paternotte: None; F. Roure: None; E. Koumakis: None; J. Payet: None; V. Burki: None; I. Fabreguet: None; M. Meyer: None; M. Dougados: None; L. Gossec: None.

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Background: Undifferentiated spondyloarthropathy (uSpA) represents an incomplete form or early phase of Ankylosing spondylitis (AS) or another distinct type of spondyloarthropathy, whereas nonsteroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs) are still mainstay of treatment, tumour necrosis factor antagonists have shown good results in patients (pts) with severe symptoms or axial involvement but are very expensive and suppresses immunity. Pamidronate, an aminobisphosphonate, has shown anti-tumour necrosis factor properties. We evaluated efficacy and safety of Pamidronate in Indian uSpA pts refractory to NSAIDs therapy.

Methods: Fifty four pts fulfilling the modified Amor criteria for diagnosis of uSpA, having active disease even after 3 month’s continuous therapy with two NSAIDs in maximal dose were selected. Active disease was defined as parameters: pts’ global assessment, pain, Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI-morning stiffness). Patients receiving Sulfasalazine, 2–3g orally per day for peripheral arthritis were allowed to continue.

Patients were divided into Pamidronate group (N = 14), received 60 mg monthly i.v. infusion in 500 ml Normal saline and Placebo group (N = 14), received Normal saline monthly i.v. infusion. Pts allowed continuing the analgesics. Efficacy assessment at the baseline and at 6-month was done using BASMI, BASFI, BASDAI, Bath Ankylosing Spondylitis Global Score (BAS-G), CRP and ESR. Proportion of pts achieving ASAS-20 and BASDAI-50 were also recorded at 6 months. Pts were observed for any AE. This study has clearance from Institutional Ethics Committee.

Results: Pts with uSpA (n = 54, M: F: 8:1), mean (SD) age was 46.54 (8.57) years, mean (SD) disease duration was 3.94 (1.14) years. Baseline characteristics and the disease activity in both treatment groups were similar. Changes in the parameters from baseline to 6 months in both groups are as described in Table 1. In Pamidronate group, there was significant reduction in all parameters compared to baseline while 32 pts (80 %) achieved ASAS-20 and 27 pts (67.5 %) achieved BASDAI-50 response. Pts in the placebo group showed increase in all the parameters. Very early feel good response was found in 23 pts (57.5 %) within 36 hours of first Pamidronate infusion. Mild fever, arthralgia, myalgia noted in 7 (17.5%) pts after first dose and in 3 cases (7.5 %) after second dose of Pamidronate.

Conclusion: Different clinical phenotype cannot be relied upon to identify early psoriatic arthritis. Enthesitis and DIP joint involvement are...
Clinical Improvement with Etanercept Versus Sulfasalazine Treatment in Patients with Ankylosing Spondylitis: Comparative Performance of Various Efficacy Measurements (ASCEND). Desirée M. Van Der Heijde1, Juergen Braun1, Maxime Dougados2, Annette Szumski3, Ronald Pedersen3, Bonnie Vlahos3, Bruce Freundlich4 and Andrew S. Koenig5. 1Hospital Cochin, Paris, France, 2Leiden University Medical Center, Meerssen, The Netherlands, 3Pfizer, Inc., Pottstown, PA, 4Pfizer, Inc., Collegeville, PA, 5Pfizer, Inc., Collegeville, PA, 6Rheumazentrum Ruhrgebiet, Herne, Germany.

Background: Ankylosing spondylitis (AS) is a form of spondyloarthritis characterized by inflammatory back pain, peripheral arthritis, enthesitis, and extra-articular features such as uveitis. The disease frequently has an early onset and can seriously impair patients’ quality of life and ability to work. Sulfasalazine (SSZ) is commonly used for the treatment of predominantly peripheral as well as axial symptoms of AS. Etanercept (ETN), a fully human TNF soluble receptor, has demonstrated short- and long-term efficacy in patients with AS. Outcome measures used in clinical trials need to be highly responsive to help detect improvement and discriminate between treatment effects. The ASCEND trial, a randomized, double-blind study that compared the efficacy of ETN and SSZ in subjects with axial and peripheral manifestations of AS, did not include a placebo arm, which hampered assessment of the net benefits of treatment. To gain more insight, we compared the discriminatory capacity of several AS assessments used in the trial.

Methods: In the ASCEND trial, subjects with AS received ETN 50 mg once weekly (n=379) or SSZ titrated to a maximum of 3 g daily (n=187) for 16 weeks. Week-16 adjusted treatment differences and effect sizes of improvement from baseline of several outcomes were used to assess their ability to detect improvement and discriminate between the effects of ETN and SSZ. All randomized subjects who received ≥1 dose of study drug and provided data at baseline and Week 16 were included in this analysis.

Results: The adjusted treatment differences and effect sizes of improvement from baseline between treatment groups for several efficacy outcomes are shown in descending order based on their treatment effect size (Table). All measures detected a greater treatment effect with ETN than with SSZ after 16 weeks of treatment.

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Adjusted Week-16 Treatment Difference (SD)</th>
<th>Adjusted Effect Size (95% CI)</th>
<th>Outcome Measure</th>
<th>Adjusted Week-16 Treatment Difference (SD)</th>
<th>Adjusted Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASDAS</td>
<td>0.80 (0.80)</td>
<td>0.72 (0.19)</td>
<td>CRP</td>
<td>8.81 (11.59)</td>
<td>0.74 (0.56, 0.93)</td>
</tr>
<tr>
<td>CRP</td>
<td>16.41 (24.83)</td>
<td>0.60 (0.48, 0.85)</td>
<td>Baseline pain</td>
<td>14.73 (24.48)</td>
<td>0.60 (0.42, 0.79)</td>
</tr>
<tr>
<td>Baseline pain</td>
<td>11.44 (19.35)</td>
<td>0.59 (0.41, 0.78)</td>
<td>Physician Global Assessment of disease activity (0-100 mm VAS)</td>
<td>12.08 (20.93)</td>
<td>0.58 (0.39, 0.76)</td>
</tr>
<tr>
<td>Physician Global Assessment of disease activity (0-100 mm VAS)</td>
<td>9.92 (20.89)</td>
<td>0.49 (0.28, 0.66)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted Week-16 treatment differences and effect sizes of improvement from baseline for ETN vs SSZ.

Conclusions: In this blinded head-to-head trial conducted in subjects with active AS, the ASDAS showed the best discriminatory capacity followed by the objective measure CRP. Overall, subjective outcome measures, such as nocturnal back pain, back pain, Physical Global Assessment of disease activity, and BASDAI, showed a somewhat lower discriminatory capacity than CRP. Including objective measures either as part of the ASDAS or alone as CRP improved the discriminatory capacity of the outcome assessments.


Comparison of Comorbid Disease Burden in Psoriasis and Psoriatic Arthritis (PsA). Janice Husted1, Arane Thavaneswaran, Vinod Chandran, Lih Eder3, Sutha Shanmugarajah3, Cheryl F. Rosen1 and Dafna D. Gladman1. 1Department of Health Studies & Gerontology, University of Water-loo, 2Division of Dermatology, Toronto Western Hospital, 3Toronto Western Hospital, Toronto, ON, Canada, 4University of Toronto Psoriatic Arthritis Clinic.

Background: The purpose of this study was to determine whether the presence of psoriatic arthritis (PsA) is associated with a higher comorbid disease burden compared to psoriasis without arthritis.

Methods: In 2006, lifetime prevalence of comorbid physical and mental conditions was collected for 449 psoriasis patients (without PsA) and 611 PsA patients who attended clinics affiliated with teaching hospitals. All patients were confirmed to have psoriasis by a dermatologist. Patients classified as psoriasis had PsA excluded after evaluation by a rheumatologist. The information on comorbidities was ascertained by clinic physicians using a standard protocol. Descriptive statistics were used to compare frequency of: sociodemographic and illness characteristics; specific comorbid conditions; and health-related quality of life (HRQOL) between groups. We also calculated the Functional Comorbidity Index (FCI), a summary count of all comorbidities, modified for this study to exclude arthritis. Linear regression models were used to compare FCI scores between psoriasis and PsA, adjusting for age, sex, and psoriasis duration.

Results: PsA patients were significantly older than psoriasis patients (mean age (SD) = 50.0 yrs (13.4) versus 46.6 yrs (13.1), p < 0.0001) and experienced a longer psoriasis duration (mean duration (SD) = 22.3 yrs (13.4) versus 16.2 yrs (14.1), p < 0.0001). Males comprised 58% of both patient groups. There was no significant difference in psoriasis severity as measured by the body surface area affected by psoriasis and PASI score. PsA patients reported lower HRQOL as measured by both SF-36 and HAQ, but higher HRQOL on the Dermatology Life Quality Index (DLQI). PsA patients, on average, reported a higher number of comorbidities than psoriasis patients (mean FCI score = 1.44 (1.4), range = 0, 7 versus 0.75 (0.9), range = 0, 6, p < 0.0001). This difference remained significant after adjusting for covariates (age, sex and psoriasis duration). In PsA 39% of patients reported a history of cardiovascular disease, including hypertension compared to 19.6 % of patients with psoriasis (p < 0.0001, adjusted for covariates). Respiratory illnesses, depression, diabetes and cancer, these differences were statistically significant (p < 0.05). PsA patients had a significantly higher mean BMI than psoriasis patients (31.0 (16.5) versus 27.8 (5.5), p=0.0005, adjusted for covariates). However, the frequency of autoimmune disease was significantly higher in psoriasis than in PsA (6.3% versus 3.0%, p = 0.0027, adjusted for covariates). Finally, the observed group differences in HRQOL remained after adjusting for FCI score and covariates.

Conclusion: Patients with PsA have a higher comorbid disease burden (excluding arthritis) than patients with psoriasis without arthritis. This is associated with a reduced quality of life.

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Continued Efficacy of Infliximab in the Treatment of HLA B27 Positive Very Early Ankylosing Spondylitis Following Its Discontinuation: Clinical and Imaging Results of the 40 Week Follow-Up Study of a Three Month, Randomised, Placebo-Controlled Trial. Nick Barkham3, Helen Keen1, Laura Coates3, Phil O’connor2, Elizabeth Hensor4, Dennis McGonagle4, Helena Marzo-Ortega5 and Paul Emery1. 1Chapel Allerton Hospital, Leeds, United Kingdom, 2Leeds University, 3Leeds University, Leeds, Yorkshire, United Kingdom, 4Leeds University.
Objective: Treatment of early inflammatory back pain (AS in evolution) with infliximab, was shown to be efficacious during a 3 month treatment period. The current report describes the clinical and imaging outcomes following discontinuation of infliximab treatment.

Methods: Following an initial randomised, placebo controlled trial, all patients who had received either infliximab or placebo for 3 months discontinued treatment and were followed up to week 40 or time of clinical flare (BASDAI>=4).

MRI scans of the spine and sacroiliac joints were performed at baseline, week 16, and week 40 or time of clinical flare. MRIs were scored by 2 observers blinded to treatment group and order using the Leeds 0–3 MRI grading system.

Results: In the placebo group, 17/19 patients (89.5%) had a high BASDAI at some point between the end of treatment (12 weeks) and the end of observation (40 weeks), compared to 12/19 (60.0%) in the infliximab group (Chi-square = 4.44, df = 1, P = 0.035). Time to BASDAI>=4 was shorter in patients who had received placebo [median (IQR) 5.0 weeks (4.0 to 16.0)] than those who had received infliximab [20.0 weeks (7.9 to 28.0), Log-rank Chi-square = 5.77, P = 0.016]. Between baseline and endpoint (at first BASDAI>=4 or week 40), infliximab patients showed significantly greater improvements in ASQoL (p = 0.05), BASFI (p = 0.033) and BASDAI (p = 0.045).

Considering MRI lesions >= grade 2 (lesions not seen in normal spine MRI scans), in the 10 patients who reached week 40 without clinical flare (8 infliximab treated, 2 placebo), there was only one lesion >= grade 2 present at week 16 and no new lesions developed on the follow-up scan. In the 11 patients who flared between wk 16 and week 40 (6 infliximab 5 placebo) there were 8 grade>1 lesions present at week 16 and 12 new lesions developed.

Conclusions: A short course of infliximab treatment results in prompt suppression of disease activity and improvement in quality of life in early AS, which is sustained on withdrawal of therapy. Fewer patients who had received active therapy flared by week 40, and those who did not flare demonstrated no progression of grade>1 lesions on MRI. This raises the possibility that the “remission induction” approach could work in a subset of patients with early AS. As previously reported for the SIJ, the prognostic value of persistent >=grade 2 lesions is demonstrated, and MRI could allow early identification of patients with subclinical disease prior to the onset of clinical flare.

Disclosure: N. Barkham: None; H. Keen: None; L. Coates: None; P. O’connor: None; E. Hensor: None; D. McGonagle: None; H. Marzo-Ortega: None; P. Emery: None.

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Correlation of Disease Activity, but Not Radiographic Progression, with Functional Outcomes in Adalimumab-Treated Patients with Active Psoriatic Arthritis. Arthur Kavanaugh1, Philip Mease2, Michele Olds3 and Frederic Lavie1

Background: In patients with rheumatoid arthritis, physical function is correlated with both disease activity and radiographic progression1; these relationships are unexplored in patients with Psoriatic Arthritis (PsA).

Objective: To explore the association of disease activity and radiographic progression with physical function in PsA patients treated with adalimumab (ADA).

Methods: ADEPT was a 24-week, randomized, placebo-controlled trial of ADA for the treatment of active PsA2. Treatment groups were randomized following stratification of subjects with methotrexate usage (≥3 months duration, 51% of patients) and extent of psoriasis (≥3% BSA, 45% of patients). In this post hoc analysis, DAS28 was used to assess disease activity, physical function was assessed using the Health Assessment Questionnaire (HAQ), and radiographic changes were determined using the modified Total Sharp Score (mTSS). Longitudinal 2 generalized linear modeling was used to characterize the dependence of the HAQ on concurrent DAS28 and mTSS, following adjustment for baseline age and gender, and for concurrent CRP.

Results: Physical function following 48 weeks of treatment with adalimumab was linearly related to DAS28 (P<0.001). Increasing disease activity scores were predictive of higher HAQ scores (figure 1).

Conclusion: In psoriatic arthritis patients recently treated with adalimumab, physical function is associated with resolution of disease activity, confirming the close relationship between HAQ and DAS28 early in the disease. HAQ scores appear to relate to radiographic progression in patients with severe radiographic progression, supporting the hypothesis that HAQ is associated with radiographic progression at more advanced stages of the disease.

References:

Disclosure: A. Kavanaugh: Abbott Laboratories, 2; P. Mease: Abbott Laboratories, 2, 5, 8, Amgen Inc., 2, 5, 8, Biogen Idec, 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Centocor, Inc., 2, 5, 8, Genentech and Biogen IDEC Inc., 2, 5, 8, Pfizer Inc, 2, 5, 8, Roche, 2, 5, UCB, Inc., 2, 5, 8; M. Olds: Abbott Laboratories, 1, 3; P. Lavie: Abbott Laboratories, 1, 3.

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CT Scan Facilitates the Diagnosis of Sacroiliitis in Patients with Suspected Spondyloarthropathy, and without Proven Sacroiliitis on Pelvic X-Ray—Results of the ECHOSPA Cohort. Valérie Devauchelle-Pensec1, Maria-Antonietta d’Agostino1, Julien Marion1, Sandrine Joussou-Joulin1, Marie Lapierre1, Daniele Colin1, Isabelle Chary-Valkenaere2, Christian Marcelli3, Damien Louville1, Philippe Aeberter1, Sandrine Guis5, Philippe Gaudin1, Maxime Bréban1 and Alain Saura1.

CHU Brest, 2CHU Brest, 3CHU Caen, France, 4CHU Grenoble, 5CHU Marseille, France, 6CHU Nancy, 7CHU Nancy, 8Hospital Ambroise Paré, France
Objective: To assess the performance of CT-scan for detecting sacroiliitis in patients with suspected spondylarthritides, and without obvious abnormalities of sacroiliac joints on X-ray.

Methods: 489 outpatients with suspected spondyloarthritides were recruited in a multicenter cohort study. At entry, they were submitted to clinical examination, pelvic X-ray, and HLA-B typing. Pelvic CT-scan was performed when rheumatologist was uncertain about the presence of sacroiliitis on X-ray. A set of 100 paired radiographs/CT-scan was read blindly by two radiologists, and the kappa coefficient was used to assess their reliability. One of them read the 173 pairs of X-ray/CT-scan available.

Results: After training, inter-reader reliability was moderate for sacroiliitis staging on X-ray (kappa = 0.52), excellent on CT-scan (kappa = 0.92), and perfect for diagnosing sacroiliitis on X-ray (New York criteria; kappa = 1). Quality was considered as good in 66, and 67 of 100 X-rays (kappa = 0.88), and in 93, and 92 of 100 CT-scans (kappa = 0.93), by readers one and two, respectively. Reliability between X-ray and CT-scan was low for sacroiliitis staging (kappa = 0.08), and diagnosing (kappa = 0.02). Sacroiliitis was retained in 6 (3.5%) patients on X-ray (4 confirmed by CT-scan), and in 32 (18.5%) patients on CT-scan. Uveitis was associated with sacroiliitis on both X-rays (P = 0.04) and CT-scan (P = 0.0001). Age, sex, HLA B27, arthralgia, enthesitis, rachialgia and buttock pain were not associated to sacroiliacit in our population.

Conclusions: Radiographic sacroiliitis was underestimated on X-ray, whereas CT-scan increased the detection of structural abnormalities leading to a proven diagnosis of sacroiliitis. CT-scan should facilitate the diagnosis of ankylosing spondylitis in patients with suspected spondyloarthritides.

Disclosure: V. Dechauxelle-Pense: None; M.-A. d’Agostino: None; J. Marion: None; S. Jousse-Joulin: None; M. Lapiere: None; D. Colin: None; I. Chassy-Valkenaere: None; C. Marcelli: None; D. Leouille: None; P. Aegerter: None; S. Guis: None; P. Gaudin: None; M. Bérian: None; A. Saraux: None.

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Dactylitis in Psoriatic Arthritis (PsA): Prevalence and Response to Therapy in the Biologics Era, Olga Ziouzina1, Arane Thavaneswaran2, Vinod Chandran2 and Dafna D. Gladman.1 Toronto Western Hospital, Toronto, ON, Canada, 2University of Toronto Psoriatic Arthritis Clinic

Background: Dactylitis is a common feature of PsA and one of the CASPAR criteria for the classification of PsA. It is associated with impaired function and is a marker of disease severity. Randomized clinical trials in PsA have shown remarkable response to treatment with biological agents with improvement in the active joint count, psoriasis, quality of life and function. However, the data on improvement of dactylitis has been sparse. Here we studied the prevalence and response of new dactylitis to treatment in a longitudinal PsA cohort.

Methods: Patients with PsA were followed at a PsA clinic January 2000 to January 2010 were included in this study. Patients were followed at 6 and 12 months according to a standard protocol. Acute dactylitis was defined as the presence of painful swelling of an entire digit. Response was defined as either complete resolution of dactylitis or > 50% improvement in the number of dactylitic digits. The prevalence of dactylitis in this cohort was determined. A multivariate generalized estimating equations analysis using a negative binomial model to account for repeated measures was conducted to determine predictors for response to treatment of dactylitis. The variables entered in the model were age, sex, duration of disease, treatment and intra-articular steroid use where treatment was categorized as no treatment, biologicals (≥DMARDs) and DMARDs.

Results: 294 patients of the 752 seen in clinic during this period had dactylitis at, at least one visit giving a prevalence of (39%). 252 patients (34% females, mean age 47 years, PsA duration 11 years, mean actively inflamed joint count 13.3, and mean damage joints 9.7, PASI score 5.6) with acute dactylitis and data available for response at 6 and 12 months were included in the study on predictors of response to treatment. Multivariate analysis showed only treatment type was a significant predictor of response to dactylitis at 12 months [relative risk 0.528, 95% CI (0.283, 0.985, p = 0.045]. There was a trend showing response at 6 months (p = 0.061). At 6 months, 77.3% of the patients responded to therapy when on biologics in comparison to 51.5% on DMARDs. Similarly, at 12 months, 87.2% of the patients responded to therapy when on biologics in comparison to 69.9% on DMARDs.

Conclusion: The prevalence of dactylitis on at least one visit during the period from January 2000 to January 2010 was 39%. Treatment was associated with improvement of dactylitis. Patients treated with biologics had better response to treatment compared to those treated with DMARDs alone.

Disclosure: O. Ziouzina: None; A. Thavaneswaran: None; V. Chandran: None; D. D. Gladman: None.

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Decreased Recurrence Rate of Anterior Uveitis in Ankylosing Spondylitis Treated with Adalimumab—An Interim Analysis. Irene E. van der Horst-Bruinsma1, J. Christiaan van Denderen1, Ingrid Visman, Maria S. A. Suttorp-Schulten, Ben A. C. Dijkmans and Michael T. Nurmohamed.1 Amsterdam, NH, The Netherlands. 2VU University Medical Centre, Amsterdam, NH, The Netherlands

Introduction: A high percentage (30–40%) of patients with Ankylosing Spondylitis (AS) suffers from acute anterior uveitis (AAU) attacks. Local treatment with corticosteroids is a beneficial treatment and in addition, there are suggestions that TNF blocking agents also decrease the recurrence rate of AAU attacks. However, proper prospective studies investigating the effect of TNF treatment on the recurrence rate of AAU attacks in AS are lacking.

Objective: To examine whether the use of adalimumab decreases the frequency of attacks of AAU in patients with AS, who receive this treatment due to their spinal disease activity.

Methods: Consecutive AS patients, who were treated with ≥40 mg of adalimumab every other week according to the international ASAS consensus statement, were enrolled. The number of attacks of AAU before and after treatment were assessed by patient history and ophthalmological controls at baseline and yearly thereafter.

Results: A total of 60 patients was enrolled. After 1 year of treatment 29 patients had their control visit, and follow up data were completed of 6 patients after 2 years. Fourteen out of these 29 (48 %) patients did not have any attacks of uveitis before and after treatment with adalimumab. Fifteen patients (52 %) suffered from recurrent attacks of uveitis with a mean number of 3.8/year (range 1–12). After one year, the recurrence rate per year in these 15 patients was reduced to none attacks in 11 cases (73%), from 5 attacks to only one attack/year in 2 cases (13%) and remained the same in the other 2 patients (13%, one attack). Interestingly, even the patient with a very high number of attacks of AAU (12 per year) was completely free of attacks after the start of adalimumab, during 2 years of follow up. The recurrence rate decreased significantly (p = 0.001) from 15/29 (52%) to 4/29 (14%), with a 73% reduction in the recurrence of uveitis.

Conclusions: Our interim analysis revealed a significant reduction of recurrence rate of attacks of acute anterior uveitis during adalimumab treatment, even in patients with a high recurrence rate of the attacks.

Disclosure: I. E. van der Horst-Bruinsma: None; J. C. van Denderen: None; I. Visman: None; M. S. A. Suttorp-Schulten: None; B. A. C. Dijkmans: None; M. T. Nurmohamed: None.

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Purpose: Post-hoc analysis of clinical trial data has demonstrated that AS patients who have extensive spinal ankylosis on radiographs experience clinical improvement with adalimumab that is similar to patients without extensive ankylosis. This benefit has been documented by patient self-report and not objectively using imaging data. We aimed to assess the impact of treatment in AS patients where both radiographs and MR scans were available to analyze the fate of vertebral corner inflammatory lesions (CIL) that demonstrated synovialphores and ankylosis on the baseline radiograph.

Methods: MRI scans were performed at baseline, 12, and 52 weeks while radiographs were done at baseline and 104 weeks in 76 AS patients randomized to receive either adalimumab (ADA) 40 mg every other week or placebo (PBO) for 24 weeks in a, double-blind, Phase III study of active AS with an inadequate response to at least one NSAID or DMARD. After the week 12 assessment, patients not achieving an ASAS20 response were eligible for early escape therapy with ADA and after 24 weeks all patients received ADA. The anterior vertebral corners (VC) of the cervical (C2 lower to T1 upper) and lumbar (T12 lower to S1 upper) spine were examined for...
syndesmophytes and ankylosis on lateral radiographs of the cervical and lumbar spine by 2 readers scoring independently. Anonymized MR scans were read independently by 2 readers who recorded the presence/absence of both typical CIL (Type A) and complex CIL (dimorphic) at the same anterior VC that were assessed by radiography. The primary analysis was based on concordant radiographic and MRI data. A CIL was defined as being persistent if it was recorded as being present on each MRI scan (baseline, 12, and 52 weeks) and as being completely resolved if either the baseline or 12 week MR scan showed a CIL that was no longer present at the 52 week final MRI examination.

Results: Ankylosis across the disc space was recorded on the baseline radiograph at 248 of 1736 (14.3%) VC that were assessed by both radiography and MRI. A syndesmophyte was recorded in 131 (7.9%) of VC at baseline. A CIL was observed significantly more frequently at VC without either ankylosis or syndesmophytes (212/1351 (15.7%)) as compared to those with ankylosis (13/248 (5.2%), p < 0.0001) on baseline radiographs. Over half of CIL at VC with ankylosis at baseline resolved completely (713 (53.8%)) as compared to 157/212 (74.1%) of CIL at those VC without syndesmophytes/ankylosis at baseline (P = NS). For VC with baseline ankylosis, complete resolution was observed for almost all Type A CIL (5/6) but in only 2/7 dimorphic CIL.

Conclusion: Our data provide objective evidence for ongoing inflammation at sites of complete spinal ankylosis that can resolve completely with adalimumab, and that complete resolution of inflammation is observed more often in those CIL with a typical configuration than in more complex, dimorphic inflammatory lesions.


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Disconnection between Radiographic Progression and Clinical Outcomes in Psoriatic Arthritis Patients Treated with Adalimumab, Philip Mease1, Christopher Ritchlin2, Michele Olds3 and Frederic Lavie1, 1Abbott Laboratories, Rungis, France, 2Abbott Laboratories, Abbott Park, IL, 3Swedish Medical Center and University of Washington, Seattle, WA, 3University of Rochester School of Medicine and Dentistry, Rochester, NY

Background: Treatment with adalimumab (ADA) diminishes disease activity and radiographic progression in subjects with active psoriatic arthritis (PsA).1 In subjects with rheumatoid arthritis (RA), inhibition of radiographic progression can occur independently of improvements in clinical symptoms following treatment with anti-TNF agents;2 it is not known if such a disconnection in treatment responses exists in PsA patients.

Objective: To explore the relationship between disease activity and radiographic progression in subjects with active PsA following treatment with ADA or placebo (PBO).

Methods: ADEPT was a 24-week, randomized, placebo-controlled trial of ADA for the treatment of active PsA.1 Treatment groups were randomized following stratification for methotrexate usage and extent of psoriasis and disease activity. In this post hoc analysis, disease activity was monitored by DAS28 and ACR response rates at week 12. The change in modified Total Sharp Score (mTSS) was calculated from X-rays obtained at baseline and week 24; radiographic progression was defined as TSS >0.25.

Results: Radiographic progression occurred at a lower frequency following treatment with ADA; 54% of ADA-treated subjects were nonprogressors, while 62% of subjects in the PBO group had mTSS >0.25 through week 24 (P <0.001). ADA-treated subjects were more likely to exhibit lower disease activity and improved ACR responses at week 12 (Table 1). Even in subjects with active clinical symptoms at week 12, treatment with ADA resulted in significantly better radiographic outcomes at week 24 than treatment with PBO; for example, ADA subjects with moderrate disease activity (DAS28 ≥3.2 <5.1) still had reduced bone damage.

Conversely, subjects exhibiting radiographic progression from baseline to week 24 had higher mean DAS28 scores at week 12 in both treatment groups. PBO-treated subjects with mTSS >0.25 had a mean±SD DAS28 of 5.0±1.3, while those showing no progression had a mean DAS28 of 4.3±1.3 at week 12 (P =0.001). Subjects treated with ADA with mTSS >0.25 had a mean DAS28 of 3.9±1.6 at week 12, while those without radiographic progression had a mean DAS28 of 3.0±1.2 (P =0.004). DAS28 at week 12 showed a mild correlation with mTSS at week 24 in the PBO group (correlation coefficient: 0.36) However, there was a weaker pattern of radiographic progression relative to DAS28 in the ADA group (correlation coefficient: 0.13).

Table. Pattern of radiographic progression (mTSS) relative to disease activity

<table>
<thead>
<tr>
<th>Week 12 DAS28</th>
<th>PBO</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.6</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>2.6–3.2</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>3.2–5.1</td>
<td>65</td>
<td>42</td>
</tr>
<tr>
<td>≥5.1</td>
<td>51</td>
<td>14</td>
</tr>
</tbody>
</table>

n/a = not available

Week 12 ACR

<table>
<thead>
<tr>
<th>ACR0</th>
<th>0</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR70, not ACR0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>ACR50, not ACR70</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>ACR20, not ACR50</td>
<td>12</td>
<td>54</td>
</tr>
</tbody>
</table>

Conclusions: Radiographic progression is lower in patients with active PsA who are treated with adalimumab compared with placebo, regardless of the treatment response in clinical symptoms. As in RA, it appears that a disconnection in the normal relationship between radiographic progression and disease activity can occur in subjects treated with adalimumab.

References:
2Landewe R et al. Arthritis Rheum 2006; 54:3119

1936
Environmental Risk Factors for Psoriatic Arthritis among Patients with Psoriasis—A Case-Control Study. Lihi Eder1, Tamryn Loo2, Vinod Chandran3, Gideon Kalman-Lamb4, Sutha Shannugarajah5, Richard Cook1 and Dafna D. Gladman2. 1Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada, 2Toronto Western Hospital, Toronto, ON, Canada, 3University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital, Toronto, ON, Canada

Aim: To investigate the association between potential environmental exposures and the development of psoriatic arthritis in patients with psoriasis.

Methods: In this case-control study, the cases were patients with recent onset psoriatic arthritis (PsA) of less than 7 years since the diagnosis. The control group was composed of psoriasis patients in whom arthritis was excluded after an evaluation by a rheumatologist. Patients and controls were matched by duration of psoriasis. The occurrence of the following environmental exposures was evaluated by a self administered questionnaire: infections, injuries and fractures, physically demanding occupational tasks, stressful life-events and vaccinations. The patients were asked to report any such event that occurred in the past 10 years and a positive exposure was defined as the occurrence of an event prior to the year of diagnosis. Participants in the control group were assigned a reference year corresponding to the year of PsA diagnosis in the matched case. The association between each exposure to environmental events and disease status were assessed through logistic regression after adjustment for age, sex and duration of psoriasis.

Results: There were 159 subjects in each group. There were no differences in age, sex, ethnicity, and severity of psoriasis as measured by PASI score between the 2 groups. The mean duration of PsA was 3.1 ± 2.2 years. The associations between each of the exposure variables and PsA are presented in Table 1 after adjustment for age, sex and duration of psoriasis.
Background: Psoriatic arthritis (PsA) affects an estimated 30% of patients with psoriasis and may cause irreversible joint damage, underscores the need for early PsA screening and prompt initiation of therapy. The Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire is a validated tool that can be used to screen for active PsA among individuals with psoriasis and is being evaluated as a measurement of treatment response. We tested the PASE questionnaire in exploratory analyses in a large multinational study of etanercept (ETN), a biological agent approved for the treatment of PsA and psoriasis, to assess whether it is a useful tool for PsA screening and for evaluation of treatment effect in a clinical trial setting.

Methods: The PRISTINE trial evaluated the efficacy and safety of 2 ETN doses for the treatment of psoriasis. The PASE questionnaire was administered during the PRISTINE trial at baseline to estimate the prevalence of PsA using the PASE cutoff scores (absent if $<47$ or present if $\geq 47$) and re-administered at 12 weeks to evaluate changes in PASE score with treatment. Participants were randomized to receive ETN 50 mg once weekly (OW) or 50 mg twice weekly (BIW) for 12 weeks double blind, followed by ETN 50 mg OW open label for 12 weeks in all subjects. Participants were $\pm 18$ years old and had stable plaque psoriasis, with BSA $\geq 10$% or PASI $\geq 10$. At baseline, the number of participants who self-reported a history of PsA was assessed by medical history. Within-group p-values for comparison of PASE score at baseline and week 12 were based on a paired sample T-test.

Results: A total of 273 subjects were enrolled (OW, n=137; BIW, n=136). Subjects were 70% male, and 64% Caucasian; mean age was 44 years, mean PASI was 21, and mean psoriasis duration was 17 years. At baseline, 31% had a self-reported history of physician-diagnosed PsA (mean duration, 8 years). Data from the PASE questionnaire at baseline and week 12 are shown (Table). Approximately 25% of subjects had a PASE total baseline score $\geq 47$, meeting criteria for possible active PsA. After 12 weeks of ETN treatment, 13% had a score suggesting the presence of active PsA.

### Table 1. Proportion of environmental exposures

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Frequency PsA (%)</th>
<th>Frequency Psoriasis (%)</th>
<th>Adjusted P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Car accidents that required medical consult</td>
<td>6 (4%)</td>
<td>5 (3%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Fractures</td>
<td>16 (10%)</td>
<td>14 (9%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Any other injury</td>
<td>34 (21%)</td>
<td>17 (11%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Infective disease</td>
<td>20 (13%)</td>
<td>11 (7%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Infections that required Ab</td>
<td>53 (34%)</td>
<td>37 (24%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Infections that required hospitalization</td>
<td>11 (7%)</td>
<td>6 (0%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Vaccination - Hepatitis A</td>
<td>3 (3%)</td>
<td>4 (5%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Vaccination - Hepatitis B</td>
<td>29 (23%)</td>
<td>19 (16%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Vaccination - Pneumovax</td>
<td>30 (24%)</td>
<td>20 (17%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Vaccination - Flu</td>
<td>59 (42%)</td>
<td>60 (45%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Vaccination - Rabella</td>
<td>4 (3%)</td>
<td>5 (4%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Vaccination - Tetanus</td>
<td>6 (5%)</td>
<td>4 (4%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Death in the family</td>
<td>41 (27%)</td>
<td>44 (29%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Divorce</td>
<td>17 (10.9%)</td>
<td>12 (8%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Movehouse</td>
<td>74 (50%)</td>
<td>64 (41%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Changed job</td>
<td>70 (47%)</td>
<td>56 (40%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Becoming unemployed</td>
<td>34 (23%)</td>
<td>35 (23%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Treated for anxiety/depression</td>
<td>21 (14%)</td>
<td>26 (17%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Occupational risk: Prolonged standing</td>
<td>95 (65%)</td>
<td>85 (58%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Squatting</td>
<td>45 (31%)</td>
<td>32 (22%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Lifting heavy weights</td>
<td>44 (30%)</td>
<td>19 (13%)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Pushing heavy weights</td>
<td>29 (20%)</td>
<td>12 (8%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Using vibrating tools</td>
<td>7 (5%)</td>
<td>8 (6%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Repetitive hand movement</td>
<td>88 (60%)</td>
<td>85 (58%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Forceful gripping</td>
<td>28 (19%)</td>
<td>21 (14%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Bending the wrist</td>
<td>65 (45%)</td>
<td>65 (45%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Smoking - Current</td>
<td>28 (23%)</td>
<td>38 (35%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Past</td>
<td>36 (27%)</td>
<td>51 (42%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, PsA duration.

The following exposures remained significantly associated with PsA following multivariate logistic regression: lifting cumulative loads of at least 20 pounds/hr (OR 2.9, p<0.001), infections that required antibiotics (OR 1.8, p=0.04), current smoking (OR 0.5, p=0.03) and past smoking (OR 0.5, p=0.02). Injury was significantly associated with PsA after adjustment for age, sex and duration of psoriasis, however it was no longer significant after inclusion in the full logistic regression model (OR 1.8, p=0.07). No association was found between PsA and vaccination, stressful life events and fractures.

Conclusion: Lifting heavy loads and infections that required antibiotics were associated with the occurrence of arthritis among patients with psoriasis. Smoking and past smoking were negatively associated with PsA. Further studies are necessary to determine whether these and other environmental factors are moderated by predisposing genetic factors.

Disclosure: L. Eder: None; T. Loo: None; V. Chandran: None; G. Kalman-Lamb: None; S. Shannumrajah: None; R. Cook: None; D. D. Gladman: None.

### 1937

Estimate of the Prevalence of Psoriatic Arthritis and Improvement with Etanercept Treatment in Moderate-to-Severe Plaque Psoriasis: PASE Results from the PRISTINE Trial. M. Elaine Husni, Pfizer Inc, 1, 3; A. A. Qureshi: Pfizer Inc, 9; D. Robertson: Pfizer Inc, 3; R. Pedersen: Pfizer Inc, 1, 3; B. Freundlich: Pfizer Inc, 1, 3; C. T. Molta: Pfizer Inc, 1, 3.;

### 1938

Evaluation of the New Akylosing Spondylitis Disease Activity Score (ASDAS) To Assess Disease Activity in Patient with Active Non-Radiographic Axial Spondyloarthritis Treated with Adalimumab and Retreated after Interruption of Therapy and Flare. Hildrun Hajeb, Frank Heldmann, Joachim Listing, Hartmut Kupper, Jürgen Braun and Joachim Sieper; Abbott GmbH & Co. KG, Ludwigshafen, Germany; 1Centre of Rheumatology, Charité CBF, Berlin, Germany, 2German Rheumatism Research Centre, Berlin, Germany.

Background: The Spondyloarthritis International Society (ASAS) has recently developed a new disease activity score, the ASDAS, which includes...
clinical measures and CRP and has a high discriminatory capacity for assessing disease activity in AS. Adalimumab has demonstrated good efficacy for 46 patients with active, non-radiographic, axial SpA during a 12-week, placebo-controlled trial and its 40-week, open-label extension \([1]\).

**Objective:** To evaluate long-term efficacy after re-treatment with adalimumab for patients whose disease flared after treatment was discontinued at Week 52 using the ASDAS instrument.

**Methods:** All 46 enrolled patients discontinued therapy at Week 52 and 19 patients with a good response at week 52 had to be retreated because of a flare (defined as not longer reaching ASAS40 response compared to baseline). Patients were treated for up to two additional years (108 weeks of retreatment). An ASDAS < 1.3 was considered as ‘inactive’, 1.3–2.1 as ‘moderate’, 2.1–3.5 as ‘high’ and > 3.5 as very high disease activity. An ASDAS change ≥2 was defined as ‘major improvement’, as recently proposed.

**Results:** Of the 19 patients who had to be retreated, 52.6% were male; mean age was 32.5 years [range 24–45]; mean disease duration before treatment was 4 years [range 1–10]; and 74% were HLA-B27+. In these 19 patients, the mean ASDAS decreased from 3.4 at baseline to 1.2 (p<0.001) at week 52. At baseline of the retreatment period the mean ASDAS was 2.8 and after 1 and 2 years of retreatment 1.5 (p=0.001). For the percentage of patients reaching different disease activity categories see table 1.

Table 1. Percentage of patients (%) reaching different disease activity categories and mean ASDAS and BASDAI during treatment with adalimumab 40 mg eow.

<table>
<thead>
<tr>
<th>ASDAS Baseline</th>
<th>Week 52</th>
<th>R-Baseline</th>
<th>R-48</th>
<th>R-108</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘inactive’ (%)</td>
<td>0</td>
<td>63.2</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>‘moderate’ (%)</td>
<td>10.5</td>
<td>26.3</td>
<td>21.1</td>
<td>22.2</td>
</tr>
<tr>
<td>‘high’ (%)</td>
<td>47.4</td>
<td>10.5</td>
<td>52.6</td>
<td>22.2</td>
</tr>
<tr>
<td>‘very high’ (%)</td>
<td>42.1</td>
<td>0</td>
<td>26.3</td>
<td>5</td>
</tr>
<tr>
<td>ASAS 40 (%)</td>
<td>NA</td>
<td>100.0</td>
<td>NA</td>
<td>52.6</td>
</tr>
<tr>
<td>ASAS p.R. (%)</td>
<td>NA</td>
<td>57.9</td>
<td>NA</td>
<td>47.4</td>
</tr>
<tr>
<td>ASDAS (Mean)</td>
<td>3.4</td>
<td>1.2</td>
<td>2.8</td>
<td>1.5</td>
</tr>
<tr>
<td>BASDAI (Mean)</td>
<td>6.1</td>
<td>1.4</td>
<td>5.1</td>
<td>2.8</td>
</tr>
<tr>
<td>ASDAS improvement &gt; 1.1 (%)</td>
<td>NA</td>
<td>94.7</td>
<td>NA</td>
<td>50</td>
</tr>
<tr>
<td>ASDAS improvement ≥ 2.0 (%)</td>
<td>NA</td>
<td>36.8</td>
<td>NA</td>
<td>27.8</td>
</tr>
</tbody>
</table>

**R** = Retreatment, ASAS40=40% improvement according to the Assessments in SpondyloArthritis Society Criteria, p.R. = partial Remission.

**Conclusions:** All patients retreated reached a similar level of response as before interruption of adalimumab therapy, as judged by the percentage of patients reaching inactive or moderate ASDAS or ASAS p.R. This was not well reflected in the ASAS 40 or ASDAS major improvement rates, probably because the baseline level of activity at retreatment was lower than before. Thus, the ASDAS and its definition of different levels of disease activity performed well in this analysis.

**References:**


**Disclosure:** H. Haibel: Abbott Laboratories. 2; F. Feldmann: Abbott Laboratories. 2; J. Listing: None; H. Kupper: Abbott Laboratories, 1, 3; J. Braun: Abbott Laboratories, 2, 5; J. Sieper: Abbott Laboratories, 2, 5, 8.

**1939**

**High Prevalence of Psoriatic Arthritis in a Psoriasis Patients Cohort.** Majed M. Khraishi\(^1\), Trevor Newhook\(^2\), Ian Landells\(^3\), Jonathan Mong\(^2\) and Kassem Aboushede\(^2\).

**Nexus Clinical Research, St. Johns, NL, Canada, 1Nexus Clinical Research, St. Johns, NL, Canada, 2Nexus Clinical Research, St. Johns, NL, Canada, 3Nexus Clinical Research**

**Objective(s):** The prevalence of PsA is reported to range from 5 to 40% in individuals with psoriasis. We set out to detect the prevalence of PsA in psoriasis patients seen in a dermatology practice and define their characteristics utilizing a validated self-administered screening questionnaire, PASQ (the Psoriatic Arthritis Screening Questionnaire)

**Method(s):** Patients with definite Plaque psoriasis (as determined by the dermatologist) completed the PASQ, a validated screening tool which has an optimal cut-off of 9 in established PsA. To ascertain that all patients with PsA are captured, we chose a lower cutoff point of 7 on the questionnaire. All patients scored 7 and higher on the PASQ were assessed by a rheumatologist to ascertain the diagnosis of PsA according to the CASPAR criteria. Epidemiological, clinical and laboratory parameters were measured in addition to the score of the PASQ. Statistical analyses were performed utilizing SPSS 17.0.

**Results:** Sixty six patients consecutive patients with confirmed diagnosis of psoriasis who were seen by the dermatologist were enrolled. The mean age (SD) was 45.6 (13.5) years, 30 (45.5%) were females. Average duration of psoriasis was 12.4 (10.1) years. 28 (42.4%) of the patients had baseline PASQ scores of 7 or higher and 17 of those patients were assessed by a rheumatologist where 12 were determined to have definite PsA, three had osteoarthritis, one had undifferentiated synovitis and one had anklyosing spondylitis. Of those 38 patients with a PASQ ≥ 7, five had definite diagnosis of PsA which was reconfirmed by the rheumatologist resulting in 17 patients with PsA in this cohort. Assuming none of the remaining patients were later diagnosed with PsA, the prevalence of psoriatic arthritis in our psoriasis cohort is 25.8%. This would be an underestimate of the true prevalence since 11 of the patients with a PASQ ≥ 7 had not yet been assessed by a rheumatologist yet.

Khraishi et al. determined that when using the PASQ as a screening tool on patients with early PsA (mean symptom duration of 12 months) a cut-off point of greater or equal to 7 yielded a sensitivity and specificity of 82% and 75%, respectively. If the sensitivity is applied to those 11 patients with a PASQ ≥ 7 that were not seen by a rheumatologist, approximately 9 (11*0.82) of these patients should eventually be diagnosed with PsA (assuming they have early PsA). This will result in a total of 26 PsA patients indicating that the estimated prevalence (95% CI) of PsA in patients with psoriasis is 39.4% (27.6%, 51.2%) in a dermatology setting.

**Conclusion:** Our estimated prevalence of PsA in psoriasis patients from a population of patients drawn from a dermatology practice is larger than most prior estimates. This fact illustrates the importance of screening for PsA in psoriasis patients as this comorbidity may affect the course of treatment and if left untreated may have a profound effect on the disability and quality of life of a large number of psoriasis patients.

**Disclosure:** M. M. Khraishi: Amgen Inc., 2, Wyeth Pharmaceuticals, 2; T. Newhook: None; I. Landells: None; J. Mong: None; K. Aboushede: None.

1940

**Improved Health-Related Quality of Life (HRQOL) with Apremilast (APR) Treatment in Psoriatic Arthritis (PsA): Results from a Phase 2 Randomized Controlled Study, Vibeke Strand\(^3\), Adele Vessey\(^4\), Angela Hu\(^\) and Victor S. Sloan\(^2\). 1Celgene Corporation, Richlandtown, PA, 2Celgene Corporation, Basking Ridge, NJ, 3Stanford University, Portola Valley, CA**

**Purpose:** PsA is a form of inflammatory arthritis with well-established deleterious effects on HRQOL. We evaluated the effect of APR on patient-reported outcomes (PROs) in subjects with PsA.

**Methods:** A phase 2, multicenter, randomized, double-blind, placebo (PBO)-controlled, efficacy/safety study was conducted in subjects with active PsA (duration >6 mo; ≥3 swollen joints; ≥3 tender joints). Subjects were randomized 1:1:1 to oral APR (40 mg QD or 20 mg BID) or PBO for 12 wk. PROs included Functional Assessment of Chronic Illness Therapy-Fatigue (FACT-F), Health Assessment Questionnaire–Disability Index (HAQ-DI), global and pain visual analog scales (VAS), physical (PCS) and mental (MCS) component summaries and individual domain scores of Short-Form 36-item (SF-36) and Short-Form 6-Dimension (SF-6D) health utilities.

Minimum clinically important differences (MCID) are 4.0 points for FACT-F, 0.22 for HAQ-DI, 10.0 for VAS, 2.5 – 5.0 for PCS and MCS, and 5.0 – 10.0 for SF-36 domain scores. Minimally important differences (MID) for SF-6D are ≥0.041.

**Results:** 204 subjects were randomized (52.5% M; mean age 50.6 y). At 12 wk, statistically significant (P<0.05) treatment-associated improvements in mean PCS (2.4) and MCS (3.4) scores that met or exceeded MCID in 20-mg BID group were observed vs PBO (0.8 and –0.8, respectively). Statistically significant (P<0.05) mean changes in SF-36 domain scores were observed in 7 of 8 domains in the 20-mg BID group: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), social functioning (SF), role emotional (RE), and mental health (MH). These changes were ≥MCID in the PF, BP, SF, RE, and MH domains. Endpoint domain scores in the 20-mg BID group differed from age/gender–matched US normative values by ≥20 points in physical domains, and <10 points in mental domains (except RE), indicating large and clinically meaningful improvements. Mean treatment-associated changes in PCS and MCS in the 40-mg QD group did not meet or exceed MCID and were not statistically significant vs PBO, with the exception of the BP domain (P=0.037). Treatment-associated improvements in the 20-mg BID and 40-mg QD groups resulted in mean increases of 0.076 and 0.047 in SF-6D scores, respectively, both exceeding MID. More subjects in the 40-mg QD and 20-mg BID groups reported improvements in
Incidence of Tuberculosis in Korean Patients with Ankylosing Spondylitis

Objectives: To assess the incidence rate and relative risk of tuberculosis (TB) in patients with ankylosing spondylitis (AS) and in patients with AS treated with tumor necrosis factor (TNF) blockers in Korea.

Methods: Using data from the Korean National Tuberculosis Association(KNTA) as a control and data from a single-center cohort of AS patients, we examined the incidence rate of TB in AS patients in Korea. All biologically-naive patients with active AS commencing TNF inhibitor (TNFi) therapy in a single center were followed to March 31, 2010. The effectiveness of treatment was examined by drug survival using life table analysis and multivariate Cox proportional hazards analysis.

Results: We examined 209 consecutive patients who received a total of 326 TNFi courses for active AS over 581.0 patient-years; the median treatment duration was 32.9 months (range: 0.4–68.3). The first TNFi was infliximab in 87 (41.6%), adalimumab in 66 (31.6%) and etanercept in 56 (26.8%). Men constituted 153 (73.2%) of the study sample and the mean age at inclusion was 42.4 (SD 11.9) years with disease duration of 19.1 (SD 11.3) years. At the end of follow-up, 128 (61.2%) remained on their first TNFi while 52 (24.9%) had switched to their second, and 24 (11.5%) to a third TNFi. The reasons for TNFi discontinuation were secondary inefficacy (34.6%), adverse event (24.1%), primary inefficacy (21.1%), convenience (12.0%) and other (8.3%). Treatment discontinuation due to adverse events occurred more commonly for infliximab 19 (17.0%) compared with adalimumab 6 (5.0%) (odds ratio (OR) 3.9, 95CI, 1.4–12.4) and etanercept 7 (7.5%) (OR 2.5, 95CI, 0.9–7.4). Only 13 patients (6.2%) had ceased TNFI therapy entirely (primary inefficacy), adverse event (5), planning to conceive (1), other (4). Drug survival for the first TNFi was 0.82, 0.72, 0.60, 0.53 and 0.43 at 6, 12, 24, 36 and 60 months, respectively. At similar time points, drug survival for the second TNFi was lower only for the first 12 months: 0.74, 0.64, 0.58, 0.52 and 0.44, respectively (p=0.32). For the second course of TNFI, primary inefficacy to the first TNFI was associated with drug survival at 6 months of only 0.50 compared with 0.84 for prior secondary inefficacy and 0.82 for adverse events (p=0.11). Survivor function was equivalent for all TNFIs, by log rank test. Predictors for treatment discontinuation in multivariate analysis were absence of HLA-B27 (hazards ratio (HR) 2.0, 95CI, 1.1–3.8) and female sex (HR 2.0, 95CI, 1.3–3.0).

Conclusions: Switching to an alternative TNFI is common in AS but few patients entirely cease treatment. Primary inefficacy to initial TNFI is associated with low continuation rates of a second TNFI.

Disclosure: Q. Li: None; M. Y. Seah: None; J. A. Burgess: None; S. Dharmage: None; B. J. Martin: None; R. Buchanan: None; L. Schachna: None.

1943

Long-Term Radiographic Outcome in Psoriatic Arthritis Patients Treated with Golimumab: 104 Week Results from the GO-REVEAL Study.

Objectives: Golimumab (GLM), a human monoclonal anti-TNFα antibody administered as every 4 weeks subcutaneous injections demonstrated long-term clinical efficacy and acceptable safety through wk104. The effect of GLM on inhibition of progression of structural damage PsA pts has been shown through wk52. Week 104 radiographic results are being reported now.

Methods: Adult PsA pts with ≥3 swollen & ≥3 tender joints (SJC/TJC) were randomized to receive SC placebo (PBO) or GLM 50 mg or 100 mg q4 wks. At wk16, pts with <10% improvement in SJC/TJC’s entered early escape (EE) in a double-blinded manner to GLM 50 mg...

1944

Low Doses of Etanercept Can Be Effective in Ankylosing Spondylitis Patients Who Achieve Remission of the Disease. Victoria Navarro Compañ, Rafael Ariza Ariza, Carmen Vargas Lebrón, Blanca Hernández Cruz, Virginia Moreira Navarrete and Federico Navarro Sarabia. Hospital Universitario Virgen Macarena

Background: There is no evidence other than symptoms control to maintain the antiTNF therapy in patients with ankylosing spondylitis (AS). In this regard, low dose regimens could be considered in patients whose disease is clinically controlled. Moreover, the economic implications of this strategy can be important. However, although dose reduction can be common in clinical practice, the available data about it are scarce.

Objective: to explore the effectiveness of low dose of etanercept (ETN) in patients with ankylosing spondylitis (AS) who achieves a good control of their disease in daily clinical practice.

Methods: case series of AS patients treated with ETN. According to the judgment of the treating rheumatologist and patient’s preferences, a dose reduction was done in those patients who achieved a good control of their disease defined by BASDAI < 5 and C-reactive protein normal values. Descriptive statistics were calculated with mean, mode, median, ranges percent and lower and upper quartiles.

Results: 51 AS patients treated with ETN were identified and 16 of them (32%) were on dose reduction regimen.

Several regimens of dose reduction were used. Mean time receiving ETN before adjusting the dose was 17 ± 12 months. Mean follow-up after dose change was 21 ± 21 months. At this point all the patients in whom dose reduction was done remained in the low dose regimen. Median BASDAI (range) at starting the low dose regimen and 6 months later was 1.6 (0.9–2.4), and 1.4 (0.3–3.2), respectively. Median CRP values (range) at starting the low dose regimen and 6 months later were 1mg/L (0.1–2.8), and 1.3mg/L (0.3–4.1), respectively. Other disease-related variables also remained unchanged. Patients with follow up at 12 and 24 months and longer remained in clinical remission with BASDAI values <2 and normal CRP values.

Conclusions: our data suggest that AS patients in clinical remission can use low doses of ETN without increasing disease activity. So, it can be a promising strategy but additional studies are needed to prove it.

Disclosure: V. Navarro Compañ: None; R. Ariza Ariza: None; C. Vargas Lebrón: None; B. Hernández Cruz: None; V. Moreira Navarrete: None; F. Navarro Sarabia: Abbott Immuno, 2, Bristol-Myers Squibb, 2, 5, Roche, 2, 5, Schering-Plough, 2, 5, UCB, Inc., 5, Wyeth Pharmaceuticals, 2, 5.

1945

Methotrexate Does Not Influence Infliximab Pharmacokinetics and Concentration-Effect Relationship in Ankylosing Spondylitis. Emilie Ducourau2, David Temant2, Francine Lafuèron2, Denis Mullemann2, Daniel Wendling1, Gilles Paintaud2 and Philippe Goupille2. 1Université de Franche-Comté, Besançon, France, 2Université François Rabelais de Tours, Tours, France

Introduction: Methotrexate (MTX) was shown to modify IFX pharmacokinetics in rheumatoid arthritis (1). However, its combination with infliximab in the treatment of ankylosing spondylitis (AS) is not recommended. The objective of this study was to investigate the influence of MTX on IFX pharmacokinetics and pharmacokinetic-pharmacodynamics (PK-PD) in axial AS patients.

Methods: Patients with axial AS were randomized to receive infliximab alone (infusions of 5mg/kg at week 0, 2, 6, 12 and 18) or infliximab combined with MTX (10mg/week). A clinical and laboratory evaluation was performed at each visit. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was the primary endpoint of clinical response. The pharmacokinetics of IFX was described using a two-compartment model with
first order distribution and elimination constants. The relationship between IFX concentration and BASDAI score was described using an indirect response model with inhibition of BASDAI input. A population approach was used and models were run simultaneously. The influence of MTX was tested as a covariate on each pharmacokinetic and PK-PD parameter.

**Results:** Twenty six patients were included (14 with MTX, 12 without MTX). A total of 507 blood samples were available for measurement of serum infliximab (2). The PK analysis showed an influence of body size and history of a previous anti-TNF failure on the distribution volume of the central compartment but did not identify any influence of MTX on the estimated parameters (3). The evolution of BASDAI, clinical measurements and biomarkers of inflammation were no different in both groups. Main pharmacodynamic parameters were the maximum inhibition of BASDAI input (Em) = 46% (39%) and the concentration leading to 50% of Em (SC0) = 6.3 mg/L. MTX did not influence any of pharmacokinetic or PK-PD parameters.

**Conclusion:** MTX influenced neither pharmacokinetics nor PK-PD of IFX. Our study does not support the combination of methotrexate with infliximab in axial AS.

clinicaltrials.gov as NCT00507403

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Disclosure: E. Ducourau:
None; D. Ternant: None; F. Laufèron: None; D. Mulleram: Abbott Laboratories, 2; D. Wendling: None; G. Painaud: Roche, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5; P. Goupille: Abbott Laboratories, 5, Bristol-Myers Squibb, 5, Roche, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5.

1946

Nonsteroidal Anti-Inflammatory (NSAIDs) Drug-Sparing Effect and Sustained Clinical Improvement of Etanercept in Advanced Ankylosing Spondylitis. Results of an Open Label Extension Following a Randomized Double Blind Placebo-Controlled Study (SPINE). Maxime Dougados 1, Jürgen Braun 1, Sandor Szanto 2, Bernard Combe 3, Pal Geher 3, Veronique Leblanc 2 and Isabelle Logeat 3, 1Lapeyronie Hospital, Montpellier, France, 2Pépinière des Descartes Univ, Cochin Hospital, Paris, France, 3Pfizer France, Paris La Défense, France, 4Polyclinic of the Hospitalier Brothers of St. John of God, Budapest, Hungary, 5Ruhrgesund Univ, Herne, Germany, 6Univ of Debrecen, Debrecen, Hungary

**Background:** Etanercept (ETN) was showed to significantly improve rheumatic signs, symptoms and pulmonary function in patients with advanced ankylosing spondylitis during the randomized placebo-controlled trial (RCT) phase of SPINE study (1). A pre-planned open label extension (OLE) was aimed at assessing the sustained rheumatic effects of ETN for 3 additional months. In contrast to the RCT phase, the NSAID intake was at the discretion of the patients during this OLE phase. The purpose was to evaluate whether ETN therapy could be maintained with a concomitant NSAID treatment reduction.

**Methods:** Patients: Definite AS patients (modified New York criteria) with active (BASDAI ≥40), refractory (at least 2 NSAIDs), severe (at least 2, 3 or 2 inter-vertebral radiological consecutive bridges at the lumbar, thoracic or cervical level respectively), anti-TNF naive. Study design: Multicenter, double blind, RCT vs placebo of 12-week duration followed by a 12-week OLE. Patients who completed RCT phase entered the OLE and received etanercept (ETN). Study drugs: ETN 50 mg OW and identical placebo (PBO) during RCT phase and ETN 50 mg OW during the OLE phase. Outcome measures: BASDAI, BASFI, BAI, and intake of NSAIDs using the ASAS-NSAIDs scoring system (2).

**Results:** Of the 82 randomized patients, 77 (males: 92%; age: 47.5±10.5 y, disease duration (since AS diagnosis): 16±10.7 y, B27 positive: 83.1%) entered the OLE phase (original ETN group: n=38; original PBO group, n=39). At baseline, patients had an active (BASDAI: 61.5±13.2, CRP: 20.5±26.1 mg/l) and severe (BASMI: 5.7±1.4, mSASSS: 37±20.2) disease and 83.1% of patients were receiving concomitant NSAID at least at baseline. During the 12 weeks of the OLE trial, 3 patients discontinued the treatment (1 in the original PBO arm [due to withdrawal of consent] and 2 in the original ETN arm [due to withdrawal of consent: 1 due to lost to follow-up:1]). The mean change in BASDAI from baseline showed a sustained improvement reaching −15.2±20 and −27.4±23.8 at Week 12 and −28.6±24.3 and −37.6±22.4 at Week 24 in the original PBO group and ETN group, respectively.

Whatever the original group, the concomitant intake of NSAIDs significantly decreased during OLE phase in comparison to RCT phase: mean absolute change in ASAS-NSAID equivalent score between OLE and RCT was −39.5 (−36%), p=0.005 and −20.9 (−17%), p=0.0005 in the original ETN and placebo group, respectively.

**Conclusion:** This prospective study conducted in advanced AS patients confirms the sustained symptomatic efficacy of ETN. Despite a relevant decrease in NSAIDs intake, such findings might be beneficial for the patients, not only in terms of long term symptomatic status but also in terms of prevention of long term NSAIDs toxicity.

This study was sponsored by Wyeth Pharmaceuticals France (Wyeth has been acquired by Pfizer in October 2009).


Disclosure: M. Dougados: Pfizer Inc, 5; J. Braun: Pfizer Inc, 5; S. Szanto: Pfizer Inc, 5; B. Combe: Pfizer Inc, 2; 5, 8, Schering, 2; 5, 8, UCB, Inc., 2; 5; P. Geher: Abbott Laboratories, 5, Pfizer Inc, 5, Schering-Plough, 5; V. Leblanc: Pfizer Inc, 3; I. Logeat: Pfizer Inc, 3.

1947

Periarticular Bone Changes in Psoriatic and Rheumatoid Arthritis Patients Following Anti-TNF-alpha Therapy. Agnes Szentpetery 1, Phil Gallagher 2, Susan Van der Kamp 3, Malachi J. McKenna 4, Douglas J. Veale 5 and Oliver Fitzgerald 6, 1St. Vincent’s University Hospital, Department of Endocrinology, Dublin, Ireland, 2St. Vincent’s University Hospital, Department of Rheumatology, Dublin, Ireland

**Purpose:** to examine the effect of anti-TNF-alpha therapy on periarticular bone mineral density (BMD) in patients with psoriatic arthritis (PsA) and rheumatoid arthritis (RA) prior to and 3 months, 1 and 3 years after receiving biologic treatment. Further, to explore associations between hand BMD and clinical responses in PsA and RA.

**Methods:** PsA and RA patients with active disease were selected following a decision to commence anti-TNF-alpha therapy. Global hand dual-energy x ray absorptiometry (DXA) including all hand bones distal to the wrist joint and 7 sub-regions of interests (ROI) were analysed at baseline, 3 months, 1 and 3 years. These included the carpus (R1) and the periarticular regions of 2nd (R2), 3rd (R3) and 4th (R4) MCPs and the 2nd (R5), 3rd (R6) and 4th (R7) PIPs. Clinical assessments including ESR, CRP, DAS28-CRP and HAQ were recorded at all time points.

**Results:** Of the 82 randomized patients, 77 (males: 92%; age: 47.5±10.5 y, disease duration: 7 years (0.16–40)). At baseline, global hand BMD (g/cm2) was significantly greater in PsA than RA (0.349 v. 0.327 p=0.025) and remained higher at all time points. BMD was higher in PsA than in RA in each ROI at all time points except in R2 at 3 years. BMD was significantly higher in PsA than in RA at baseline and at 3 months in R5 (0.316 v. 0.292 p=0.035 and 0.316 v. 0.279 p=0.028) and R6 (0.331 v. 0.302 p=0.042 and 0.329 v. 0.293 p=0.04). ESR remained significantly lower in PsA than in RA at all time points (p<0.05). In PsA CRP was lower at baseline and at 3 month whilst DAS28-CRP at 3 months and 12 months compared with RA (p<0.05). SJC, DAS28-CRP and HAQ remained lower in PsA during the study period.

In PsA, there were significant negative correlations between ESR and global hand BMD at 1 year (r = −0.6; p=0.028) and at 3 years (r = −0.6; p=0.008) and in RA between DAS28-CRP and global BMD at 3 years (r = −0.4; p = 0.025).

**Conclusions:** Periarticular bone density was higher in PsA at all time points but increased with anti-TNF-alpha treatment in both diseases. Higher periarticular bone density was associated with lower inflammatory activity in both diseases but earlier in PsA. Anti-TNF-alpha therapy reduces periarticular bone loss in patients with inflammatory arthritis.

Disclosure: A. Szentpetery: None; P. Gallagher: None; S. Van der Kamp: None; M. J. McKenna: None; D. J. Veale: Abbott Immunology Pharmaceuticals, 2, 5, 8, Centocor, Inc., 5, 8, GlaxoSmithKline, 2, 5, 8, Mundipharma Medical GmbH, 2, 8, Opsona Therapeutics, 2, 8, Pfizer Inc, 5, 8, Schering-Plough, 5, 8, Wyeth Pharmaceuticals, 2, 5, 8, Bristol-Myers Squibb, 2, Pfizer Inc, 5, 8.
**Prediction of Early Response to Anti-TNF Therapy and Disease Activity State Using the Ankylosing Spondylitis Disease Activity Score (ASDAS).**

Nathan Vastesaeger1, Yanxin Wang2, Robert D. Inman3, Atul A. Deodhar4, Benjamin L. Hsu5, Mahboob U. Rahman6, B. A. C. Dijkmans7,1, Juergen Braun8, Piet P. Geusens9, Joachim Sieper10 and Desiree M. Van Der Heijde8,9. 1Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Wynnewood, PA, 2Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, 3Charite Campus Benjamin Franklin, Berlin, Germany, 4Leiden University Medical Center, Meerssen, The Netherlands, 5Mercer and Co., Inc., Whitehouse Station, NJ, 6Mercer and Co., Inc., 7Oregon Health Sciences University, Portland, OR, 8Rheumazentrum Ruhrgebiet, Herne, Germany, 9Toronto Western Hospital, Toronto, ON, Canada, 10University Hasselt, Genk, Belgium, 11VU Medical Centre, Amsterdam, The Netherlands

**Objectives:** We previously reported that in the ASSERT and GO-RAISE studies, BASDAI50 response can be accurately predicted with a combination of baseline characteristics. This analysis compares the accuracy of predicted response rates and disease activity as measured by different assessments, including the ASDAS.

**Methods:** The ASSERT and GO-RAISE trial data were combined and baseline characteristics were used to predict the probability for achieving week 12 ASDAS20, BASDAI50 and ASDAS scores and ASDAS and BASDAI scores at week 12. Univariate analyses identified baseline predictors for response. Variable associations were explored using Spearman correlation analysis. A stepwise selection procedure using logistic regression, ROC and correlation analyses was used to select a final set of predictors. Logistic regression was used to calculate the predicted week 12 ASDAS and BASDAI scores and the probability of week 12 response to anti-TNF or placebo respective to combined selected predictors at baseline. The accuracy of prediction between the different assessments was compared using ROC analyses and R-square.

**Results:** 479 AS patients (NY modified criteria) treated with anti-TNF and 156 patients treated with placebo with continued conventional therapy, with BASDAI and spinal pain assessment ≥4 were included. Age (mean 39.5; SD 11.3 yrs), BASFI (mean 5.4; SD 2.2 cm), Berlin enthesitis-score (mean 2.4; SD 2.9), therapy (anti-TNF or placebo), CRP (mean 2.1; SD 2.4 mg/dL) and HLA-B27 genotype (+ or −) were retained as final predictors of response. The area under the ROC curve of the model which included the six selected predictors (log transfer of CRP values) and interactions between predictors was 0.85, 0.79 and 0.75 and the R-square was 0.43, 0.33 and 0.24 for week 12 ASDAS major response, BASDAI50 response and ASAS20 response, respectively. This indicates good accuracy for prediction of BASDAI50 and ASDAS major response and fair accuracy for ASAS20 response. The R-squares of 0.49 and 0.27 for ASDAS and BASDAI scores respectively, indicate that the week 12 disease activity measured by ASDAS could be more reliably predicted. The figure shows the predicted change in ASDAS from baseline to week 12 versus actual changes.

**Conclusion:** Elevated CRP, lower age, lower enthesitis score, lower BASFI, and presence of HLA-B27 genotype are associated with a better treatment response at week 12 in ASSERT and GO-RAISE. The values of these characteristics at baseline allow calculating the predicted response rates and future disease activity of an individual patient. The accuracy of predicting ASDAS and ASDAS response is good and higher than that of other assessments.


**1948**

**Predictors of Radiographic Progression in Adalimumab-Treated Patients with Ankylosing Spondylitis.** Walter Maksymowych1, Desiree van der Heijde2, Robert Landewe3, Aileen Pangan2, Steve Brown2 and Frederic Lavie4. 1Abbott Laboratories, Rungis, France, 2Abbott Laboratories, Abbott Park, IL, 3Leiden University Medical Center, Leiden, The Netherlands, 4Maastricht University Medical Center, Maastricht, The Netherlands, 5University of Alberta, Alberta, BC, Canada

**Objective:** To identify factors contributing to radiographic progression over 2 years in patients with Ankylosing Spondylitis (AS) who are treated with adalimumab (ADA).

**Methods:** The ATLAS trial randomized AS patients to treatment with ADA or placebo for a 24-wk double-blind period, followed by an open-label extension with ADA. Two independent blinded readers scored X-rays obtained at baseline and year 2 using the mSASSS method. Dependent variables were: 1) change in mSASSS ≥2 and ≥4 (severe progression) from baseline through 2 years, and 2) development of new syndesmophytes at year 2. Independent variables were age, disease duration, spinal mobility (cervical rotation and lateral lumbar flexion), area under the curve (AUC) from baseline to 2 years for CRP and ASDAS, and baseline ASDAS and mSASSS. Categorical variables were also included: HLA-B27, sex, peripheral synovitis at baseline (SJC=0), peripheral enthesitis at baseline (MASES=0), presence of baseline syndesmophytes, and history of uveitis. Associations were tested univariately; significantly associated variables were entered as explanatory variables in a multivariate analysis.

**Results:** This analysis includes 275 subjects with 2 years of exposure to ADA; at baseline, subjects had mean disease duration of 10.8 years, mean ASDAS of 3.7, and mean mSASSS of 20.3; syndesmophytes were present in 85% of patients at baseline. Radiographic progression (mSASSS ≥2) was found in 61 subjects (22%), and severe radiographic progression (mSASSS ≥4) was observed in 22 subjects (8%). New syndesmophytes were found by either reader in 106 subjects (39%).

Univariate analysis identified significant associations for age, mobility, and baseline bone damage with radiographic progression (Table). Linear regression revealed similar findings. Sex, HLA-B27, uveitis, peripheral synovitis or enthesitis, disease duration, baseline ASDAS, and CRP levels were not predictive in any analysis.

**Table.** Logistic regression for factors associated with radiographic progression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>ΔmSASSS ≥2</th>
<th>ΔmSASSS ≥4</th>
<th>new syndesmophytes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04 (1.009, 1.062)</td>
<td>1.04 (1.003, 1.084)</td>
<td>1.02 (0.996, 1.049)</td>
<td>0.01; P = 0.04</td>
</tr>
<tr>
<td>Syndesmophytes (BL)</td>
<td>3.87 (1.126, 13.391)</td>
<td>n/a</td>
<td>6.45 (2.165, 19.200)</td>
<td>0.01; †</td>
</tr>
<tr>
<td>mSASSS (BL)</td>
<td>1.03 (1.011, 1.039)</td>
<td>1.03 (1.009, 1.049)</td>
<td>1.01 (1.002, 1.026)</td>
<td>0.05</td>
</tr>
<tr>
<td>Cervical rotation (BL)</td>
<td>0.98 (0.968, 0.995)</td>
<td>0.99 (0.966, 1.006)</td>
<td>0.99 (0.974, 0.996)</td>
<td>0.01; †</td>
</tr>
<tr>
<td>Lateral lumbar flexion (BL)</td>
<td>0.98 (0.980, 1.007)</td>
<td>0.64 (0.476, 0.859)</td>
<td>0.91 (0.842, 0.993)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Identified by either Reader 1 or Reader 2; BL: baseline; n/a: not a valid logistic regression model; † P ≤ 0.01; † P < 0.05

Multivariate analysis was conducted using significant factors from univariate analysis, with the exception of mobility scores, which are intermediate variables. Only baseline mSASSS was consistently identified as a significant contributor to radiographic progression (ΔmSASSS ≥2 and ≥4, OR [95% CI]: 1.02 [1.005, 1.036], P<0.01 and 1.02 [1.001, 1.046], P = 0.04) and only baseline syndesmophytes were predictive of the development of new syndesmophytes (OR [95%CI]: 7.63 [2.381, 24.476], P<0.01).
Conclusion: Clinical measures of disease activity were not related to radiographic progression. Only the presence of radiographic damage at initiation of therapy was consistently associated with the formation of new syndesmophytes through 2 years in AS patients treated with adalimumab. These results support previous studies suggesting a disconnect between disease activity and bone formation in patients with long-standing AS.


1950

Prevalence of Psoriatic Arthritis in Thai Psoriasis at Ramathibodi Hospital. Bodin Butthum1, Stephanewon Javoisilada2, Pintip Ngamjanyaporn3, Surachai Nithiketkul4, and Suchela Janwityanujit6. 1Department of Radiology Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand, 2Department of Allergy Immunology and Rheumatology, Department of Medicine Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, 3Department of Allergy Immunology and Rheumatology, Department of Medicine Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 4Naersaan University, Department of Medicine, Phitsanulok, Thailand.

Objective: To determine the prevalence as well as the clinical features of psoriatic arthritis (PsA) in Thai patients with psoriasis. Factors highly associated with the diagnosis of PsA will also be identified.

Methods: Psoriatic patients who visited the dermatology clinic at Ramathibodi hospital during July 1 to December 31, 2009 were prospectively studied. A standard clinical protocol for PsA was used to assess patients for arthritis, psoriasis, dactylitis, enthesitis, nail change, range of body movement and the presence of back disease. X-ray films of the hands, feet, whole spine and the sacroiliac (SI) joints were taken. Based on the clinical and radiological information, the diagnosis of psoriatic arthritis was classified by CASPAR Classification Criteria for Psoriatic Arthritis (1) and the five clinical subsets defined by Moll and W Right (2) were assigned to each patient. Clinical variables indicative of PsA were also collected.

Results: Three hundred and two psoriatic patients (149 males and 153 females) who had complete X-ray studies as defined in the protocol were analyzed. The prevalence of PsA in psoriatic patients was 43.05% (130/302; 73 males and 57 females). Mean age, mean duration of disease and male to female ratio in patients with PsA were 51.3 years old, 12.2 years and 1:1.1 respectively, not differed from those with psoriasis alone. Spondylitis was the most common pattern of PsA (83.1%) followed by polyarthritides, oligoarthritides, DIP involvement and arthritis mutilans in our group of PsA patients. Interestingly, more than half of our psoriatic patients (150/179) had radiographic abnormalities without clinical criteria for PsA.

Conclusion: Radiological assessment gives additional arthritic findings not gained by clinical examination alone. Nail change, morning stiffness more than 1 hour, buttock pain and history of joint inflammation are suggestive of PsA in psoriatic patient.

References:

Disclosure: B. Butthum: None; S. Javoisilada: None; P. Ngamjanyaporn: None; S. Nithiketkul: None; S. Janwityanujit: None.

1952

Psoriatic Arthritis: Oligoarticular or Polyarticular Presentation? Car lotta Nannini, Laura Niccoli, Emanuele Cassarà, Olga Kaloudi and Fabrizio Cantini. Rheumatology Unit, Hospital of Prato, Prato, Italy, Rheumatology Unit, Hospital of Prato, Italy.

Background: Psoriasis has been reported as the most frequent pattern in patients (p.) with Psoriatic Arthritis (PsA), with an estimated frequency of 60%.

Objective: To determine the occurrence of the different PsA subgroups in a cohort of p. with early PsA selected using the CASPAR criteria.

Methods: We evaluated a cohort of 242 new consecutive outpatient with PsA observed between January 2000 and December 2009 at a secondary referral center. As controls 184 new consecutive early rheumatoid arthritis (RA) outpatients were used. Demographic, clinical, laboratory and radiological data were collected and stored in a computed database. In PsA p. the following clinical patterns were considered: peripheral (oligoarthritides ≤4 and polyarthritides ≤5 involved joints), axial (calin’s criteria for inflammatory spine pain, radiologic or MRI evidence of sacroiliitis), mixed (concomitant axial and peripheral features). Involved joints were counted separately without grouping hand and foot small joints.

Results: Female gender (137/242; 57%) was significantly lower in PsA compared to RA (140/184; 78.2%) (p<0.0001). Mean age was 50.33 ± 11.7 years in PsA and 57.2 ± 13.55 years in RA (p<0.001). Mean disease duration of symptoms was 9.38 ± 2.0 mo. in PsA cohort and 10.1 ± 1.75 mo. in PsA cohort. At diagnosis, the total number of involved joints was significantly lower in PsA compared to RA (p<0.001). Table 1 summarizes the comparison between the demographic and clinical features of early PsA and early RA.
Table 1.
Total N of patients
Age at PsA or RA Dx (yrs)
Female N(%)
Duration of sympthoms (mo)
Total N of involved joints at Dx
ESR at Dx (mm1h)
CRP at Dx (mg/dl)
Low back pain N(%)
Dactylitis N(%)
Enthesitis N(%)
Tenosinovitis N(%)
Peripheral involvement N(%)
Back involvement N(%)
Mix involvement N(%)
Sacroileitis N(%)
Monolateral sacroileitis N(%)
Bilateral sacroileitis N(%)
HLA B27 N(%)
HLA CW6 N(%)
HLA B39 N(%)

PsA total
242
50.3 ⫾ 11.7
137 (57%)
9.38 ⫾ 2.0
3 ⫾ 3.5
31 ⫾ 18
1.83 ⫾ 2.28
117 (48%)
62 (26%)
79 (33%)
55 (23%)
132 (51%)
41 (17%)
69 (28%)
105 (43%)
41 (17%)
60 (25%)
30 (12.4%)
58 (24%)
9 (4%)

RA
184
57.2 ⫾ 13.55
140 (78.2%)
10.1 ⫾ 1.75
16.2 ⫾ 7.98
56.2 ⫾ 25.03
3.3 ⫾ 3.37
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA

P value
⬍0.001
⬍0.001
NS 0.8
⬍0.001
⬍0.001
⬍0.001

As shown in table 2, polyarthritis was present in 54 (22%) PsA p. and 164
(89.3%) RA p. (p⬍0.001), oligoarticular and monoarticular involvement in
PsA was present in 188 patients (78%).
Table 2.
PsA
Non Polyart
188 (78%)
49.3 ⫾ 11.07
88 (55.3%)
10.0 ⫾ 1.62
1.6 ⫾ 1.54
29.2 ⫾ 18.62
1.7 ⫾ 2.31
93 (58.5%)
47 (29.6%)
7 (6.4%)
44 (27.7%)

RA polyart
164 (89.3%)
57.2 ⫾ 13.76
86 (78.9%)
9.9 ⫾ 1.74
17.6 ⫾ 7.12
39.3 ⫾ 33.77
2.0 ⫾ 2.35
NA
NA
NA
NA

P value
⬍0.001
⬍0.001
⬍0.001
NS 0.74
⬍0.001
0.005
NA 0.48
⬍0.001
NS 0.08
NS 0.25
NS 0.42

Conclusion: Differently from other reports we found oligoarthritis as the
most frequent pattern of early PsA with a significant lower number of
involved joints compared to RA. This may reflect possible selection biases
due to the lack of validated criteria before CASPAR set availability and the
referral of p. with more severe disease to tertiary centres.

Table 1. Changes in inflammatory parameters (CRP, IL-6 and MRI) versus
radiographic progression

Disclosure: C. Nannini: None; L. Niccoli: None; E. Cassarà: None; O. Kaloudi:
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Changes from baseline to
week 0–22

1953
Radiographic Progression Is Associated with Resolution of Systemic Inflammation in Patients with Axial Spondyloarthritis Treated with TNF␣ Inhibitors. Susanne Juhl Pedersen8, Inge Juul Sørensen13, Kay-Geert Hermann4,
Patrick Garnero17, Julia S. Johansen1, Ole Rintek Madsen9, Annette Hansen15,
Michael Sejer Hansen10, Gorm Thamsborg9, Lis Smedegaard Andersen18, Ole
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Bioassays Bagnols/Cèze, France, 18Rheumatism Hospital, University of Southern
Denmark, Graasten, Denmark

Radiographic progression week 0–46
New syndesmophyte
mSASSS progression
(>1)
(>1)
No
Yes
No
Yes
Nⴝ25 Nⴝ11 p-value Nⴝ18 Nⴝ18 p-value

CRP decreased to ⱕ8 mg/l 11 (52) 10 (48)
CRP remained ⬎8 mg/l
7 (100) 0 (0)
CRP remained ⱕ8 mg/l
7 (87)
1 (13)
IL-6 decreased to ⱕ3.3 ng/l 10 (50) 10 (50)
IL-6 remained ⬎3.3 ng/l
7 (100) 0 (0)
IL-6 remained ⱕ3.3 ng/l
8 (89)
1 (11)
Change in MRI SIJ IS ⬍0
7 (47)
8 (53)
Change in MRI SIJ IS ⱖ1
10 (91)
1 (9)
MRI SIJ IS⫽0 at week 0
6 (86)
1 (14)

0.03†
NS§
0.03†
NS§
0.04†
NS§

7 (33)
6 (86)
5 (63)
7 (65)
7 (100)
5 (55)
6 (40)
6 (55)
5 (71)

14 (67)
1 (14)
3 (38)
13 (35)
0 (0)
4 (45)
9 (60)
5 (45)
2 (29)

0.03†
NS§
0.006†
NS§
NS
NS

Number (%). Chi2 test and Fisher’s Exact test. †Normalization vs. persistently
increased biomarker levels. §Normalization vs. normal levels at baseline.

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Østergaard: None.

1954
Reliability of Radiographic Scoring Methods in Axial Psoriatic Arthritis.
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Wakhlu3, Michael Li3, Hua Shen1 and Dafna D. Gladman2. 1Department of
Statistics and Actuarial Science, University of Waterloo, 2Toronto Western
Hospital, Toronto, ON, Canada, 3University of Toronto Psoriatic Arthritis
Clinic, Toronto Western Hospital

S817

Wednesday, November 10

PsA polyart
Total N of patients
54 (22%)
Age at PsA or RA Dx (yrs)
54.1 ⫾ 13.49
Female N (%)
25 (54.3%)
Duration of sympthoms (mo)
6 ⫾ 5.12
Total N of involved joints at Dx
6 ⫾ 4.84
ESR at Dx (mm1h)
33 ⫾ 19.36
CRP at Dx (mg/dl)
1.7 ⫾ 2.26
Low back pain N (%)
12 (26.1%)
Dactylitis N(%)
7 (15.2%)
Enthesitis N(%)
4 (12.5%)
Tenosinovitis N(%)
10 (21.7%)

Objectives: To explore the relation between radiographic progression and
biomarkers of inflammation (C-reactive protein (CRP), interleukin-6 (IL-6),
YKL-40), angiogenesis (vascular endothelial growth factor (VEGF)), cartilage turnover (CTX-II, matrix metalloproteinase 3 (MMP3), total aggrecan,
cartilage oligomeric matrix protein (COMP)) and bone turnover (CTX-I, total
osteocalcin) and MRI inflammation in patients with axial spondyloarthritis
(SpA) treated with TNF␣ inhibitor.
Methods: Thirty-six patients (27 men, 9 women; median age 40 yrs
(range 21–62); disease duration 15 yrs (1–45)) initiated treatment with TNF␣
inhibitors (infliximab (n⫽28), etanercept (n⫽7) and adalimumab (n⫽1)) and
were followed for 46 weeks. Radiographs were evaluated according to the
modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) at baseline
and week 46. Patients developing new syndesmophytes (0 vs. ⱖ1) or
increased in mSASSS (0 vs. ⱖ1 unit) were compared with those who did not,
regarding biomarker levels and MRI inflammation scores of the sacroiliac
joints and lumbar spine (Berlin scores) and with biomarker levels of healthy
subjects.
Results: The patients increased in mSASSS from median 13 (IQR: 6–24)
at baseline to 15 (6–24) (p⫽0.005) at week 46 (p⫽0.005). Eighteen (50%)
patients increased in mSASSS (i.e. progressed) and 11 (30%) developed new
syndesmophytes. mSASSS and biomarkers did not correlate. Compared to
mSASSS non-progressors, mSASSS progressors had higher pretreatment
total aggrecan (666 ng/ml (537–820) vs. 507 (401–646), p⫽0.007) and higher
time-integrated mean concentrations of total aggrecan from baseline to week
22 (743 ng/ml (612–849) vs. 602 (446–707), p⫽0.02) and 46 (746 ng/ml
(636–895) vs. 638 (450–735), p⫽0.02). Patients developing new syndesmophytes also had higher time-integrated mean concentration of total aggrecan
from baseline to week 22 and 46 as compared to patients without new
syndesmophytes (results like above). Development of new syndesmophytes
was associated with larger percentage decreases in CRP (⫺90% (⫺96;⫺78)
vs. ⫺58 (⫺88;⫺25), p⫽0.007) and IL-6 (⫺81% (⫺93;⫺75) vs. ⫺67
(⫺89;⫺16), p⫽0.02) and increases in osteocalcin (20% (9;36) vs. 9%
(⫺10;25), p⫽0.049). Radiographic progression was associated with normalization of CRP and IL-6 at week 22 (i.e. CRP ⱕ8 mg/l and IL-6ⱕ3.3 ng/l)
and decrease in MRI inflammation. Radiographic non-progression was
associated with persistent systemic inflammation and unchanged/increased
MRI inflammation scores (Table 1).
Conclusion: Radiographic progression in patients with axial SpA during
treatment with TNF␣ inhibitors was associated with resolution of systemic
inflammation and reduction in MRI inflammation but not with baseline
inflammation.


Background: More than a third of patients with psoriatic arthritis (PsA) have axial arthritis. Although there are similarities, important differences exist between axial PsA (AxPsA) and Ankylosing Spondylitis (AS). The Bath AS Radiology Index (BASRI), modified Stokes AS Spinal Score (mSASSS) and Radiographic AS Spinal Score (RASSS) were developed to score AS, and Psoriatic Arthritis Spondylitis Radiology Index (PASRI) to score AxPsA. Our aim was to determine the reliability of these scoring systems in AxPsA.

Methods: A computerized scoring module that facilitated scoring radiographic features of axial arthritis on vertebrae, sacroiliac and cervical facet joints, and calculated total scores for all the available scoring methods for AS and AxPsA was developed. Four assessors all rheumatologists blinded to patient information were provided with an e-handbook and one hour training session. Radiographic images of 18 patients with AS (satisfying modified NY criteria) and 40 patients with AxPsA (defined as at least unilateral grade 2 sacroiliitis and/or inflammatory back pain and/or restricted spinal mobility) were duplicated, patient identifiers removed, and order randomized. Radiographs were read by the four assessors individually, data entered into the module and scores obtained. Intra-class correlation coefficient (ICC) estimates of the inter- and intra-assessor reliability of scores for each method were obtained. A consensus score for AxPsA patients was also obtained.

Results: The intra-and inter-assessor reliability for the radiographic scoring methods in AS are given in table 1.

Table 1. Inter-class and intra-class correlation coefficients and 95% confidence intervals of radiographic scores in AS (N=18).

<table>
<thead>
<tr>
<th>Scoring System</th>
<th>Reliability</th>
<th>ICC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacroiliitis grade (NY criteria)</td>
<td>Between Assessor</td>
<td>0.795</td>
<td>0.646, 0.905</td>
</tr>
<tr>
<td>Within Assessor</td>
<td>0.908</td>
<td>0.837, 0.957</td>
<td></td>
</tr>
<tr>
<td>BASRI-spin</td>
<td>Between Assessor</td>
<td>0.861</td>
<td>0.746, 0.938</td>
</tr>
<tr>
<td>Within Assessor</td>
<td>0.955</td>
<td>0.917, 0.998</td>
<td></td>
</tr>
<tr>
<td>mSASSS</td>
<td>Between Assessor</td>
<td>0.857</td>
<td>0.735, 0.938</td>
</tr>
<tr>
<td>Within Assessor</td>
<td>0.952</td>
<td>0.967, 0.992</td>
<td></td>
</tr>
<tr>
<td>RASSS</td>
<td>Between Assessor</td>
<td>0.748</td>
<td>0.562, 0.888</td>
</tr>
<tr>
<td>Within Assessor</td>
<td>0.961</td>
<td>0.929, 0.983</td>
<td></td>
</tr>
<tr>
<td>PASRI</td>
<td>Between Assessor</td>
<td>0.926</td>
<td>0.858, 0.968</td>
</tr>
<tr>
<td>Within Assessor</td>
<td>0.985</td>
<td>0.971, 0.993</td>
<td></td>
</tr>
</tbody>
</table>

All methods had excellent inter- and intra-assessor reliability in AS. Scoring was completed by the assessors within an average duration of 7 minutes. The 40 patients with AxPsA (24 males, age 54 years, disease duration 18 years, mean cervical rotation of 61 degrees, Occiput to wall distance of 2.3 cm, Schober’s test of 4.7 cm, Domjan lumbar lateral flexion of 15.5 cm, actively inflamed joint count of 5 and damaged joint count of 16 at the time of radiographic assessment) by consensus read had mean (± standard deviation) BASRI-spin score of 3.98 (2.38), mSASSS of 8 (13.4), RASSS 6.54 (14.1) and PASRI score of 12 (12.3) units. The intra- and inter-assessor reliability for the radiographic scoring methods in AxPsA are given in table 2.

Table 2. Inter-class and intra-class correlation coefficients and 95% confidence intervals of radiographic scores in AxPsA (N=40).

<table>
<thead>
<tr>
<th>Scoring System</th>
<th>Reliability</th>
<th>ICC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacroiliitis grade (NY criteria)</td>
<td>Between Assessor</td>
<td>0.67</td>
<td>0.544, 0.785</td>
</tr>
<tr>
<td>Within Assessor</td>
<td>0.807</td>
<td>0.726, 0.875</td>
<td></td>
</tr>
<tr>
<td>BASRI-spin</td>
<td>Between Assessor</td>
<td>0.521</td>
<td>0.375, 0.669</td>
</tr>
<tr>
<td>Within Assessor</td>
<td>0.771</td>
<td>0.688, 0.845</td>
<td></td>
</tr>
<tr>
<td>mSASSS</td>
<td>Between Assessor</td>
<td>0.652</td>
<td>0.488, 0.798</td>
</tr>
<tr>
<td>Within Assessor</td>
<td>0.911</td>
<td>0.862, 0.949</td>
<td></td>
</tr>
<tr>
<td>RASSS</td>
<td>Between Assessor</td>
<td>0.68</td>
<td>0.513, 0.823</td>
</tr>
<tr>
<td>Within Assessor</td>
<td>0.902</td>
<td>0.845, 0.946</td>
<td></td>
</tr>
<tr>
<td>PASRI</td>
<td>Between Assessor</td>
<td>0.88</td>
<td>0.817, 0.927</td>
</tr>
<tr>
<td>Within Assessor</td>
<td>0.917</td>
<td>0.874, 0.95</td>
<td></td>
</tr>
</tbody>
</table>

Only PASRI had excellent intra- and inter-rater reliability in AxPsA.

Conclusions: Available radiographic scoring systems have at least moderate inter- and intra-rater reliability when applied to AxPsA. The PASRI has the highest reliability in AxPsA and performs well in AS.

Disclosure: V. Chandran: None; B. Biagioni: None; R. Cook: None; L. Eder: None; A. Wakhlu: None; M. Li: None; H. Shen: None; D. D. Gladman: None.
The Dimorphic Vertebral Corner Inflammatory Lesion (CIL): A Magnetic Resonance Imaging Biomarker Associated with New Bone Formation in Patients with Ankylosing Spondylitis.

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Purpose: One hypothesis proposed to explain the lack of impact of TNF blockers on radiographic progression in established AS is the activation of bone forming pathways in spinal lesions that have advanced from acute inflammation to more complex lesions. The latter may be visible on spinal MRI as a dimorphic corner inflammatory lesion (CIL) where the inflammatory signal at the vertebral corner (VC) on the STIR sequence does not itself extend all the way to the VC as in a typical CIL (Type A) but surrounds an area of decreased signal intensity at the VC which, on the T1 weighted images, may appear to be due to fat infiltration or erosion/bone sclerosis. It is proposed that the overall development of new bone during TNF blocker therapy may depend on the balance between the number of early and more mature inflammatory lesions. We tested the relative association between dimorphic or Type A CIL (lower and upper anterior VC in figure, respectively) and the subsequent development of new bone at the VC.

Methods: Data collected from two prospective cohorts, PsA and psoriasis uncomplicated with arthritis, was analyzed. In the psoriasis cohort, the presence of clinical inflammatory arthritis was ruled out by rheumatologic exam. Smoking status was determined at the time of the diagnosis for PsA patients and at the first visit to the clinic for the psoriasis patients. A logistic regression model was constructed to determine the association between smoking status and PsA after adjusting for age, sex and duration of psoriasis. The prevalence of current smokers in each group was compared with that of smokers in the general population from Statistics Canada through standardized prevalence ratios (SPRs). Smoking status was defined as current or past smoker and lifetime non-smoker. Results: 791 PsA and 404 psoriasis patients were included in the study. The mean age and duration of psoriasis were 46.3±13.1 and 16.1±14.1 years, respectively, for the PsA group and 36.7±13 and 8.5±10.2 years, respectively, for the psoriasis group. The proportions of females in the PsA and psoriasis groups were similar (41.6% vs. 43.8%, respectively). The proportion of lifetime non-smokers was higher compared to current smokers in the PsA group (54.7% vs. 43%, p<0.001), while the proportion of past smokers was higher in the psoriasis group (30.2% vs. 23.4%, p=0.001). The number of pack years was similar in the psoriasis and the PsA patients (11.7±14 and 11.3±12.1 pack years respectively). On multivariate analysis after adjusting for age, sex and duration of psoriasis, current smoker status vs. lifetime non-smoker remained negatively associated with PsA (Odds Ratio (OR) 0.6, 95% Confidence Intervals (CI) 0.5–0.8, p=0.003), while past smoker vs. lifetime non-smoker status was no longer significantly associated with PsA (OR 0.8, 95% CI 0.6–1.1, p=0.2). The SPRs for current smoking for males with psoriasis and PsA were 1.12 (95% CI 1.00–1.26) and 1.0 (95% CI 0.91–1.11), respectively, while the SPRs for females with psoriasis and PsA were 1.29 (95% CI 1.12–1.47) and 1.18 (95% CI 1.13–1.23), respectively. Conclusion: Active smoking is negatively associated with PsA among psoriasis patients. The prevalence of active smoking is higher in females with psoriasis and PsA compared to the general population.

Disclosure: L. Eder: None; S. Shanmugarajah: None; A. Thavaneswaran: None; V. Chandran: None; R. Cook: None; D. D. Gladman: None.

1957

The Impact of Anti-TNF Therapy on Erosive Structural Changes in the Spine of Patients with Ankylosing Spondylitis. Xenofon Baraliakos1, Joachim Listing2, Martin Rudwaleit1, Joachim Sieper1 and Juergen Braun2.1Charite Campus Benjamin Frankl, Berlin, Germany, 2German Rheumatism Research Center, 3Rheumazentrum Ruhrgebiet, Herne, Germany, 4Rheumazentrum Ruhrgebiet Herne

Background: Axial inflammation, potentially leading to osteodestructive and/or osteoproliferative bony changes is visualized by magnetic resonance imaging (MRI). The role of erosions, known to be important in RA, has not been extensively studied in AS to date, especially not in patients receiving anti-TNF therapy. We have analyzed these changes in AS patients treated with anti-TNF therapy.

Objective: To study the course of osteodestructive changes and their relationship to spinal inflammation in AS by MRI.

Methods: T1 and STIR MR images of patients with active AS patients at baseline (BL, n=42), after 3 months (n=38) of therapy with TNF blockers or placebo and after 2 years (n=21) of continuous treatment with TNF blockers were analyzed by the ASspiMRI-a (scores inflammation and erosion) and its modification, the Berlin score (‘S2’, scores only inflammation), both scoring vertebral units (VU). Only patients with complete sets of images of BL and 3 months or 2 years of anti-TNF treatment were included in the study.

Results: At BL, 7.8% and 3.5% of the VUs showed active and inactive erosions, respectively, while 29% had signs of inflammation without erosions. In comparison, osteoproliferative changes were seen in 20% of all available VUs. On the patient level at BL, spinal inflammation was seen in 95% and active erosions in 73%, while active erosions were found in 38% of patients at BL. At 3 months, the percentage of inflated VUs decreased in the anti-TNF treated patients from 27.4% to 14.6%: inflammatory lesions without erosions decreased from 21.5% to 10% and with erosions from 5.9% to 4.6% of all VUs. In the placebo group, inflamed VUs decreased from 30% to 23.5%: without erosions from 22% to 15.5% while inflammatory lesions with erosions (8%) did not show any change. There was similar improvement after anti-TNF with both scoring systems (56.7% for S1 and 54.7% for S2, both p<0.001 as compared to BL) after 3 months, while inflammation changed by 13% with either system in the placebo group.

After 2 years of anti-TNF treatment, inflammatory lesions decreased from to 33.7% to 11.2% of all VUs: in VUs with inflammation only from 24.8% to 9.5% and in VUs with active erosions from 8.9% to 1.7%. On a patient basis, spinal inflammation was seen in all patients at baseline and in 76% after 2 years, while active erosions were found in 81% at BL and in 31% after 2 years. In contrast, the percentage of inactive erosions in all available VUs increased from 3.5% at BL to 4.1% after 2 years. Overall 38% patients at BL and 52% at after 2 years had at

1958

The Impact of Anti-TNF Therapy on Erosive Structural Changes in the Spine of Patients with Ankylosing Spondylitis.
least 1 inactive erosion. There were no differences in the occurrence of erosions between the 3 spinal segments.

**Conclusions:** Erosions occur in the majority of AS patients but in less than 10% of the spinal structures analysed. The percentage of inflammatory lesions and active erosions was clearly reduced after 2 years of anti-TNF therapy. However, many patients still had spinal inflammation (76%) and about 30% still had active erosions. This suggests that the anti-inflammatory efficacy of anti-TNF treatment is not sufficient to completely eliminate inflammation. The Berlin MRI scoring system is sufficient for differentiation between different treatment strategies in the assessment of inflammatory activity in AS patients.

**Disclosure:** X. Baraliakos: None; J. Listing: None; M. Rudwaleit: None; J. Sieper: None; J. Braun: None.

### 1959

**TNF Blocking Agents Promote Resolution of Vertebral Erosions in Patients with Spondyloarthritis.** Walter P. Maksymowycz, Praveena Chiowchanwisawakit and Robert Lambert. 1Mahidol University, Bangkok, Thailand, 2University of Alberta, Edmonton, AB, Canada

**Purpose:** While the impact of anti-TNF agents on new bone formation remains unclear their impact on other structural lesions such as erosions has not yet been studied in SpA because these lesions are not commonly observed in the spine on radiography. Bone erosion is readily discerned on T1-weighted (T1W) MRI at vertebral corners (VC) and affecting the vertebral endplate. MRI can reliably detect these lesions and systemic study has demonstrated erosions in the majority of patients. It is possible that such lesions could be a secondary cause of symptoms in SpA. We aimed to assess the impact of both TNF blocking agents and standard treatment on the evolution of bone erosions using MRI.

**Method:** MRI scans were independently performed at baseline and 2 years in 61 AS patients of whom 28 received TNF blocking agents in open label follow up of clinical trials while 33 received either standard therapy (n = 16) or standard therapy (n = 17) in an observational cohort. A bone erosion on MRI was defined as full-thickness loss of the dark appearance of cortical bone at its anticipated location and loss of the normal bright appearance of adjacent bone marrow on T1W MRI. Via televideoconference, reference images were developed in which erosions were assigned by consensus amongst an international MRI working group. Lesions were independently recorded dichotomously (present/absent) from lower C2 to the upper sacrum of the spine at both anterior and posterior vertebral corners and at each vertebral endplate. Anonymized MRI scans were assessed independently by 2 readers who were blinded to treatment and time point. The primary analysis compared the resolution of lesions according to treatment and was based on concordant data indicating agreement on resolution of erosions. Improvement or complete resolution was defined on the basis of ≥50% and complete resolution respectively, towards a normal vertebral contour. Proportions were compared by Fisher’s exact test.

**Results:** Analysis was based on concordant reads for 2801 VC and vertebral endplate sites. Complete resolution of VC erosions was recorded significantly more frequently in the TNF blocker treatment group (11 of 13 erosions (84.6%)) whereas this was not observed in a single erosion in patients on standard therapy (p = 0.0002). Similar differences between treatments were noted for individual readers. Vertebral endplate erosions were more frequent than corner erosions but showed minimal resolution after 2 years regardless of treatment.

**Table 1.** Number (percentage) of vertebral erosions resolving.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>VC Erosion</th>
<th>Vertebral Endplate Erosion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF</td>
<td>Resolved</td>
<td>Improved</td>
</tr>
<tr>
<td>Concordant</td>
<td>11 (84.6)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Reader 1</td>
<td>26 (74.3)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Reader 2</td>
<td>19 (59)</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Standard</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Conclusion:** Our preliminary data supports a beneficial effect of TNF blocker treatment on the resolution of vertebral erosions. The lack of impact on vertebral endplate erosions may reflect greater time dependence due to larger size and/or differences in etiology.

**Disclosure:** W. P. Maksymowycz: Abbott Laboratories, 2, 5, Merck Pharmaceuticals, 2, 5, Pfizer Inc, 2, 5; P. Chiowchanwisawakit: None; R. Lambert: None.

### 1960

**TNF Switching in PsA Patients.** Eliza F. Chakravarty, 1George Reed, 2Dennis Decker, 3Susan Bolge, 2Rebecca Bolce, 2Michael Ingham, 1Raphael J. DeHoratius, 1Ying Shan5 and Mark C. Genovese. 1Mountain View, CA, 2Centocor Ortho-Biotech, Horsham, PA, 3Centocor Ortho-Biotech, 5Stanford University, Sunnyvale, CA, 5University of Massachusetts Medical School

**Purpose:** To examine patterns of Anti-TNF switching in psoriatic arthritis (PsA) patients and patient factors associated with switching.

**Methods:** We identified biologic naïve PsA patients cared for by US rheumatologists participating in the CORRONA registry that initiated their first anti-TNF (Etanercept, Infliximab, Adalimumab) and followed for 2 years. Maintainers were defined as patients with no change of anti-TNF over two years. Switchers were defined as patients who discontinued and started another biologic within 6 months of discontinuation. Discontinuers were defined as patients who discontinued and did not initiate another biologic within 6 months. We defined early switchers as patients who switched within the first year and late switchers as patients who switched between 12 and 24 months. Maintainers were compared to switchers at time of switch using a comparable follow-up time point. Multivariable logistic regression estimated associations of characteristics with switching in early and late switchers.

**Results:** There were 139 biologic naïve PsA patients who initiated an anti-TNF and had ≥2 years of follow up. Of these, 91 (65%) were maintainers, 18 (13%) were discontinuers, and 30 (22%) were switchers. Distribution of maintainers and switchers were significantly different between IV anti-TNF and subcutaneous (SC) anti-TNF with 85% maintainers, 9% discontinuers, 6% switchers in IV vs. 59% maintainers, 14% discontinuers and 27% switchers in SC anti-TNF (p = 0.012). Among those patients who switched from any of the anti-TNFs the proportion achieving a Modified ACR 20 at 6 and 12 months was 23%, and 29%.

**Table 1.** Patient Characteristics (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Maintainers</th>
<th>Discontinuers</th>
<th>Switchers</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=91</td>
<td>n=18</td>
<td>n=30</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>52 ± 10.6</td>
<td>52 ± 9.1</td>
<td>47 ± 14.2</td>
<td>0.095</td>
</tr>
<tr>
<td>BMI</td>
<td>31.0 ± 5.5</td>
<td>33.2 ± 5.7</td>
<td>34.3 ± 8.2</td>
<td>0.029</td>
</tr>
<tr>
<td>Duration PsA</td>
<td>10.5 ± 10.4</td>
<td>7.8 ± 7.7</td>
<td>6.3 ± 7.8</td>
<td>0.092</td>
</tr>
<tr>
<td>At Initiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt pain (0–100)</td>
<td>34.4 ± 22</td>
<td>51.4 ± 22.0</td>
<td>47.7 ± 19.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MD global (0–100)</td>
<td>25.3 ± 20</td>
<td>29.2 ± 22.3</td>
<td>34.1 ± 19.3</td>
<td>0.112</td>
</tr>
<tr>
<td>Pt global (0–100)</td>
<td>35.1 ± 25</td>
<td>46.3 ± 23.1</td>
<td>44.2 ± 17.8</td>
<td>0.068</td>
</tr>
<tr>
<td>At time of Switch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt pain (0–100)</td>
<td>27.8 ± 23</td>
<td>45.0 ± 29.0</td>
<td>40.1 ± 24.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MD global (0–100)</td>
<td>13.5 ± 14.7</td>
<td>21.7 ± 19.6</td>
<td>22.9 ± 16.9</td>
<td>0.008</td>
</tr>
<tr>
<td>Pt global (0–100)</td>
<td>24.4 ± 22</td>
<td>33.8 ± 27.7</td>
<td>44.4 ± 19.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* use comparable time after initiation in Maintainers.

## Treatment of Active Ankylosing Spondylitis with Abatacept—An Open Label 24-Week Study

In-Ho Song,1 Frank Heldmann,1 Martin Rudwaleit,1 Hildrun Habelt,1 Anja Weiss,2 Jurgen Braun3 and Joachim Sieper.1
1Centre of Rheumatology, Herne, Germany; 2Charlie Campus Benjamin-Franklin, Medical Clinic I, Rheumatology, Berlin, Germany; 3Charlie Campus Benjamin-Franklin, Medical Clinic I, Rheumatology, Berlin, Germany

### Background:
An immunotherapy targeting T cells in ankylosing spondylitis (AS) might be of interest, given histological studies have shown T-cell clusters in facet jointes and antigen-specific T cell response has been described in AS [1]. There is still an unmet medical need as some patients with AS may even not respond to anti-TNF agents.

### Objective:
To explore prospectively the short term efficacy and safety of abatacept in patients either naïve or with an inadequate response (IR) to anti-TNF agents.

### Methods:
In this open label (OL) pilot study, abatacept (10mg/kg) was administered intravenously on days 1, 15, 29 and every 28 days thereafter up to week 24 in 15 anti-TNF-naive patients (group 1) and 15 patients with IR to anti-TNF (group 2) with active AS. The primary end point was the proportion of patients with assessment of SpondyloArthritis International Society criteria (ASAS 40) in both groups at week 24 for which the likelihood of targeted minimum true response rates of 30% was investigated by estimating the 95% confidence interval [95% CI] of the observed response rates. Disease activity was assessed using ASAS and BASDAI responses, pain and CRP levels in the intent to treat population using LOCF. Safety was assessed in patients who received at least 1 dose of OL abatacept.

### Results:
Of 15 patients enrolled in group 1 and group 2 respectively, each 12 completed 24 weeks (withdrawals for inefficacy each 2 in group 1 and 2) and SAE (each 1 in group1 and 2). In group 1 and 2, baseline characteristics were: 60% and 73% of males, mean disease duration of 14.5 (SD 10.3) and 20.5 (SD 10.8) years; 100% and 93% HLA-B27 positive and mean age of 38.0 (SD 7.2) and 45.3 years (SD 9.8), respectively.

At week 24, 13.3% [2.4%; 38.4%] of patients in group 1 and 0% [0%; 21.3%] of group 2 achieved ASAS 40 (Table). The upper limit of the 95% CI in group 1 but not in group 2 exceeded the pre-specified minimum true response rates of 30%. We found no change of T cell function in regards of interferon-gamma (IFN-gamma) (% of IFN-gamma positive cells out of CD4+ T cells) and interleukin-6 secretion (% of IL-6 positive cells out of CD4+ T cells under stimulation with PMA and ionomycin) 14.8% at screening and 13.1% at week 24) or interleukin-17 secretion (% of IL-17 positive cells out of CD4+ T cells under stimulation with PMA and ionomycin) 1.5% at screening and 0.9% at week 24) supporting that T cell function is not suppressed but only modulated. Overall, abatacept was well-tolerated with 5 serious events (SAEs), including 1 gastroenteritis. Three mild to moderate acute infusion reactions were reported. There was no death, opportunistic infection, malignancy or TB reported.

### Conclusions:
In this pilot AS study, Abatacept was well tolerated. A major response was not observed in our study, but an efficacy cannot be excluded based on the limited sample size. Its short term therapeutic potential needs to be further evaluated.

### Table:

<table>
<thead>
<tr>
<th>TNF-blocker-naive patients (n=15)</th>
<th>TNF-blocker failure patients (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAS20</td>
<td>26.7%</td>
</tr>
<tr>
<td>ASAS40</td>
<td>13.3%</td>
</tr>
<tr>
<td>ASAS PR</td>
<td>6.7%</td>
</tr>
<tr>
<td>BASDAI20</td>
<td>33.3%</td>
</tr>
<tr>
<td>BASDAI50</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

### References:

### Disclosure:
- **L-H. Song**: Abbott Immunology Pharmaceuticals, 5, Schering-Plough, 5
- **F. Heldmann**: Schering-Plough, 5, M. Rudwaleit: Abbott Immunology Pharmaceuticals, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5
- **H. Habelt**: Abbott Immunology Pharmaceuticals, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5
- **J. Sieper**: Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5

## 1961

### Ultrasound (US) and X Rays (XR) Entheal, Synovial and Sacroilartic Abnormalities in Early Psoriatic Arthritis (ePsA)
Francesca Bandinelli, Diletta Bonciani, Francesca Prignano, Leonardo Giovannini, Giuliana Salvadorini, L. Collaku, Antonio Candelieri, Francesca Bartoli, Torino Lotti and Marco Matucci Cerinic

### Objective:
To investigate enthesal/synovial and sacroilartic abnormalities in ePsA respectively with ultrasound (US) and traditional X rays (XR) and the correlation with ePsA features (familiarity, psoriasis, inflammatory markers, HLA) useful for diagnosis.

### Methods:
92 ePsA patients (51±15 years old, 51 female and 41 male), with duration of symptoms < 1 year, diagnosed according to CASPAR criteria (1) were consecutively studied with US (My Lab 70 XVG US Esaote 7–18 MHz linear array transducer) of entheses (Achilles, quadriceps, patellar and plantar fascia) and joints (radiocarpal, intercarpal, hands MCP, IPF and IFD, tibio-tarsal, feet MTP and IP) joints and with radiography (XR) of sacroiliac joints. Patients were scored respectively for entheses with Glasgow Ultrasound Enthesitis Scoring System (GUESS) (2) and Power Doppler signal (PD) (semiquantitative system, score 0–3), for peripheral joints with Power Doppler absence of PD for active synovitis was assessed in patients who received at least 1 dose of OL abatacept.

### Results:
Abnormalities are present in high percentage: in entheses (GUESS>1:100%, PD 40,2%), in peripheral joints (40,2% PD active synovitis), in sacroiliac joints (NYS>1: 25%). GUESS and PD of entheses correlated with the presence of lower limb psoriasis (respectively p<0.02, p<0.05, Mann Whitney test) but not with PASI and entheses PD with ESR (p<0.005) (linear correlation Pearson). GUESS was higher (p<0.05 Mann Whitney test) in CW6 positive patients (29,6%) but not other significant difference were found in other autopolyses. Synovitis and sacroilartics didn’t correlate with familiarity, psoriasis, ESR, CRP, HLA.

### Conclusions:
In ePsA patients, enthesal and synovial US and sacroiliac XR modifications are present in high percentage. Our data clearly indicate that a thorough US and XR investigations must be always perform in early phase.


### Disclosure:
- **F. Bandinelli**: None; **D. Bonciani**: None; **F. Prignano**: None; **L. Giovannini**: None; **G. Salvadorini**: None; **L. Collaku**: None; **A. Candelieri**: None; **F. Bartoli**: None; **T. Lotti**: None; **M. Matteucci Cerinic**: None.

## 1962

### Validation of the ASAS Definition of a Positive MRI in a Cohort of Patients with Early SpA Followed for Eight Years
Helena Marzo-Ortega, Alexander N. Bennett, Dennis McDonagle, Paul Emery and Walter P. Maksymowych

### Background:
The Assessment of SpondyloArthritis International Society (ASAS) recently proposed a definition of a positive MRI for sacroiliitis based on the finding of bone marrow edema (BME) on STIR in subchondral or periarticular bone marrow of the sacroiliac joint (SIJ). MRI is considered positive for SpA if there are two BME lesions on the same coronal slice through the SIJ or a single BME lesion present on two consecutive slices. This
proposal requires validation, preferably in prospective cohorts to evaluate development of radiographic changes of sacroiliitis.

**Objective:** To compare the diagnostic utility of global assessment of MR scans versus the ASAS definition using a standardized approach to evaluation of the SIJ in an early SpA cohort followed over 8 years.

**Method:** Four rheumatologists blinded to patient and diagnosis independently assessed MRI scans (T1W and STIR) from 37 patients with SpA according to ESSG criteria (median symptom duration 24 weeks); 13 developed radiographic sacroiliitis after 8 years, 11 controls mechanical low back pain (mLBP). Semi-coronal slices through the SIJ were read systematically according to a standardized online training module: BME, fat infiltration, erosions, and ankylosis was recorded using an online data entry system. Schematics of the SIJ divided into quadrants allowed recording of these lesions (yes/no) in each quadrant of each coronal slice. The ASAS definition was defined as met when BME was recorded in 2 SIJ quadrants on the same slice or when a single lesion in one SIJ quadrant was present in 2 consecutive slices. Readers also answered (yes/no) whether this SIJ scan confirmed the presence of SpA. Sensitivity, specificity, and LRs for individual and concordant data (at least 2 readers) were calculated according to clinical diagnosis at baseline and according to the development of radiographic sacroiliitis.

**Results:** MRI had high diagnostic utility for SpA according to global assessment by individual readers (mean for 4 readers (range) sensitivity/ specificity: 66.9% (61.8–70.6)/94.4% (88.9–100), LR+ 11.9, LR- 0.2) as well as concordant data (sensitivity/specificity: 67.6%/94.4%, LR+ 12.1, LR- 0.3). By comparison, sensitivity for SpA of the ASAS definition was higher but there was reduction in specificity with 11.1% of control scans (3 mLBP) meeting the ASAS definition so that diagnostic utility was lower than for SpA. Diagnostic utility of baseline MRI for radiographic sacroiliitis after 8 years follow up was even higher: global assessment (sensitivity/specificity: 100%/94.4%, LR+17, LR- not calculable (nc), ASAS definition (sensitivity/specificity: 100%/88.9%, LR+ 9, LR- nc).

**Conclusion:** The diagnostic utility of the ASAS definition resembles global evaluation by expert readers, the principle limitation being the finding of BME in patients with mLBP.

### Global Assessment ASAS Definition

<table>
<thead>
<tr>
<th>Sensitivity Specificity</th>
<th>LR+</th>
<th>LR-</th>
<th>Sensitivity Specificity</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>70.6</td>
<td>54.4</td>
<td>12.6</td>
<td>0.3</td>
<td>75.5</td>
</tr>
<tr>
<td>R2</td>
<td>70.6</td>
<td>94.4</td>
<td>12.6</td>
<td>0.3</td>
<td>70.4</td>
</tr>
<tr>
<td>R3</td>
<td>64.7</td>
<td>88.9</td>
<td>5.8</td>
<td>0.3</td>
<td>67.4</td>
</tr>
<tr>
<td>R4</td>
<td>61.8</td>
<td>100</td>
<td>na</td>
<td>0.3</td>
<td>58.8</td>
</tr>
<tr>
<td>Concordant*</td>
<td>67.6</td>
<td>94.4</td>
<td>12.1</td>
<td>0.3</td>
<td>79.4</td>
</tr>
</tbody>
</table>


### 1965

**Ankylosing Spondylitis Macrophages Produce Greater IL-23 in Response to Lipopolysaccharide without Significant Unfolded Protein Response Induction.** Ling Zeng, Mary Lindstrom and Judith Smith. University of Wisconsin

**Purpose:** Inflamed tissue from Ankylosing Spondylitis (AS) patients display a preponderance of macrophages. Previous work from an HLA-B27 transgenic rat model suggests that macrophages from arthritic animals develop an intracellular stress response called the Unfolded Protein Response (UPR) and as a result, secrete increased cytokines in response to Toll-like receptor agonists such as lipopolysaccharide (LPS). Our objective was to determine if macrophages from AS patients undergo a UPR and secrete increased cytokines/chemokines in response to LPS.

**Methods:** Peripheral blood monocytes were isolated from 10 AS patients (median age 46.5y, 90% male, 70%HHLA-B27+ and 2ND) and 10 controls (HC, median age 45y, 90% male, all HLA-B27-), and differentiated in vitro with M-CSF for 5 days. Select samples were then treated with 1000U/mL IFN-γ for 24h to up-regulate MHC class I prior to stimulation with LPS for 3h (for RNA collection), or 8–24h (supernatants). UPR induction was assessed by up-regulation of ERdj4, BiP and CHOP mRNA detected by quantitative PCR. Supernatants were analyzed for cytokine/chemokine production by ELISA or Luminex. Statistical analysis involved 2-sample Wilcoxon tests for cytokine data, and a linear mixed effect model following log transformation of gene expression data.

**Results:** In response to LPS alone, AS macrophages secreted more CXCL9, IL-10, IL-12p70, IL-23, and TNFα than HC macrophages (p < 0.01). We did not detect significant differences between AS and HC for IL-6, IL-8, CXCL10, IL-1β, IFN-β or MCP-1. IFN pre-treatment tended to minimize differences between AS and HC for all cytokines/chemokines except IL-12p70. The most striking difference between AS and HC macrophages was for IL-23 production (median HC 9pg/mL vs. AS 265 pg/mL at 24h, p = 0.0007). 3h LPS treatment had no effect on UPR gene expression. Although IFN treatment up-regulated HLA-B expression by 2–3 fold, it did not enhance BiP or CHOP expression. ERdj4 expression weakly increased (2-fold, p = 0.03–0.06) in IFN+LPS AS samples only.

**ACR Poster Session C**

Poster Spondylarthritides and Psoriatic Arthritis - Pathogenesis, Etiology, and Animal Models

Wednesday, November 10, 2010, 9:00 AM–6:00 PM
Conclusions: Gene association studies and animal models have implicated the IL-23/Th17 pathway in pathogenesis. These results showing greater IL-23 production by AS patient macrophages in response to LPS further support the development of IL-23-directed therapy. Since we were unable to detect significant UPR induction in AS macrophages, the relationship between UPR and inflammatory cytokine production remains unclear.

Disclosure: L. Zeng: None; M. Lindstrom: None; J. Smith: None.

1966

Association between Killer-Cell Immunoglobulin-Like Receptor (KIR) Gene Polymorphisms and Psoriatic Arthritis (PsA), Vinod Chandran1, Fawnda Pellett2, Renise Ayearst3, Reny Pollock2 and Dafina D. Gladman1. 1Toronto Western Hospital, Toronto, ON, Canada; 2University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital

Background: KIR genes within the leucocyte receptor complex on chromosome 19q are associated with PsA. We sought to further characterize this association and determine whether the associations are independent of HLA allele associations.

Methods: 685 cases of European ethnicity (295 females, mean age 43 years, PsA duration 7 years, psoriasis duration 15 years, actively inflamed joint count 11, PASI score 5.2) with PsA and 706 ethnically matched controls determined using Fisher’s exact test using a dominant model. Multivariate logistic regressions were performed, including all KIR genes present in >5% of cases and controls, and HLA alleles present in >5% of cases and controls and significant in univariate analyses. Association of KIR2DS1 and KIR2DS2 with PsA was performed on genomic DNA obtained from peripheral blood using PCR-SSO reverse line blot. Phenotype frequencies (frequencies of individual genotypes) were calculated and differences between cases and controls determined using Fisher’s exact test using a dominant model. Multivariate logistic regressions were performed, including all KIR genes present in >5% of cases and controls, and HLA alleles present in >5% of cases and controls and significant in univariate analyses. Association of KIR2DS1 and KIR2DS2 with PsA in the presence/absence of HLA-Cgrp1 alleles. The risk for PsA increases with the presence of KIR2DS2 in the absence of HLA-Cgrp1 alleles.

Results: Of multivariate logistic regression analyses using HLA alleles as covariates, HLA-B*27 3.52, 2.46, 5.03, p = 0.016, B*07 0.71, 0.54, 0.94, p = 0.019; KIR2DS2 1.31, 1.04, 1.64, p = 0.025 were significantly associated with PsA. The results of the multivariate analysis using logistic regression with backward selection are given in Table 1.

Table 1. Results of multivariate logistic regression analyses using HLA alleles found significant in the univariate analyses as well as KIR genes present in >5% of the population as explanatory variables.

<table>
<thead>
<tr>
<th>Allele/Genotype</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B*07</td>
<td>0.71</td>
<td>0.54, 0.94</td>
<td>0.0169</td>
</tr>
<tr>
<td>HLA-B*13</td>
<td>2.14</td>
<td>1.35, 3.4</td>
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</tr>
<tr>
<td>HLA-B*27</td>
<td>3.52</td>
<td>2.46, 5.03</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HLA-B*38</td>
<td>8.22</td>
<td>4.66, 14.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HLA-B*39</td>
<td>2.54</td>
<td>1.49, 4.34</td>
<td>0.0006</td>
</tr>
<tr>
<td>HLA-B*51</td>
<td>0.53</td>
<td>0.34, 0.81</td>
<td>0.0038</td>
</tr>
<tr>
<td>HLA-B*57</td>
<td>2.30</td>
<td>1.61, 3.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HLA-C*03</td>
<td>0.74</td>
<td>0.56, 0.99</td>
<td>0.0457</td>
</tr>
<tr>
<td>KIR2DS2</td>
<td>1.31</td>
<td>1.04, 1.64</td>
<td>0.0205</td>
</tr>
</tbody>
</table>

Conclusions: KIR2DS2 is associated with PsA independent of HLA alleles. The risk for PsA increases with the presence of KIR2DS2 in the absence of ligands for KIR2DL2/2DL3 with risk being highest when KIR2DS2 is present in the absence of HLA-Cgrp1 alleles.

Disclosure: V. Chandran: None; F. Pellett: None; R. Ayearst: None; R. Pollock: None; D. D. Gladman: None.

1967

Decreased Th17 Cells in the Peripheral Blood of Patients with Early Spondyloarthritis (EsPA), Maria Belen Bautista-Caro1, Irene Arroyo-Villa2, Concepcion Castillo-Gallego2, Eugenio de Miguel-Mendietaa, Emilio Martin-Mola1 and Maria Eugenia Miranda-Caruss. 1Hospital La Paz, Madrid, Spain; 2Hospital La Paz

Background: Th17 cells may be implicated in the pathogenesis of Spondyloarthritides (SpA). Previous data regarding the percentage of Th17 cells in the peripheral blood of Early SpA (EsPA) patients are limited and contradictory.

Objective: To determine the frequency and phenotype of Th17 cells in the peripheral blood of patients with EsPA.

Patients: We studied 22 healthy controls and 22 patients with EsPA (who met ESSG or other accepted SpA Classification Criteria) from the “Esperanza” programme of the Spanish Rheumatology Foundation. The inclusion criteria were inflammatory back pain or asymmetric peripheral arthritis, duration of disease of three to 24 months and age of 18 to 45 years. At the time of visit, medical history, physical examination, ESR, CRP, HLAB27 and pelvis conventional x-Ray were recorded.

Methods: CD4 T cells were magnetically sorted from freshly isolated peripheral blood and cultured overnight in the presence of PMA and ionomycin. IL-17 was determined by ELISA of culture supernatants and by flow cytometry of monensin-treated cells. In addition the expression of CCR6, IL-23R and RORαT were examined by flow cytometry.

Results: EsPA patients were 7 females, 15 males. Age was (mean ± SD) 36 ± 7 years, duration of disease 17 ± 10 months. BASDAI index was 3.7 ± 2.2 (median 3.55, range 1.2–8.3) and BASFI was 1.82 ± 1.69 (median 1.65, range 0.3–6.1). CD4 T cells of EsPA patients secreted significantly lower amounts of IL-17 into the culture medium (1134.9 ± 488.6, median 687.97, range 99.02–3156.33) when compared with controls (2059.3 ± 664.9 pg/ml median 1719.67, range 448.11–6243.9), p < 0.05. Likewise, the percentage of IL-17 producing CD4 T cells (Th17 cells) was significantly lower in EsPA patients: 0.93 ± 0.26, median 0.84, range 0.22–2.15 in patients vs 1.50 ± 0.56,median 1.13, range 0.66–3.92 in controls, p < 0.05. Th17 cells expressed CCR6, RORYT and IL-23R. Disease activity as assessed by BASDAI index was negatively correlated with IL-17 concentration and with the percentage of Th17 cells. Likewise, BASFI function index showed a negative correlation with soluble IL-17 and with the percentage of Th17 cells.

Conclusion: Peripheral blood CD4 T cells from EsPA patients demonstrate a decreased secretion capacity of IL-17 together with decreased percentage of Th17 cells, that are related with disease activity as assessed by BASDAI index and with the functional index BASFI.

Disclosure: M. B. Bautista-Caro: None; I. Arroyo-Villa: None; C. Castillo-Gallego: None; E. de Miguel-Mendietaa: None; E. Martin-Mola1: None; M. E. Miranda-Caruss: None.

1968

Distinctive Patterns of Gene Expression Post-Infliximab Therapy in Psoriasis, Rheumatoid and Psoriatic Arthritis, Christopher T. Ritchlin1, Yahui Grace Chu1, Alexander Rosenberg1, Darren Tabechian1, Sharon Moorehead2, Rick Barrett2, Hangtao Fan3, Fred Baribaud3, H. Liu4, Nancy Peller2, David Shealy1 and Edward S. Schwarz2. 1Centocor R&D, 2Univer-

Background: Despite divergent phenotypes, psoriasis (Ps), rheumatoid (RA) and psoriatic arthritis (PsA) often improve after anti-Tumor Necrosis Factor (TNF) therapy but the comparative effect of TNF inhibition on gene expression in circulating CD14+ monocytes, synovium and skin in these disorders is not well understood.

Objectives: To compare gene expression profiles in RA and PsA monocytes and synovium and Ps monocytes and skin plaques following infliximab (IFX) therapy.

Methods: Microarray analyses with Affymetrix hgu133 plus 2.0 PM
Only a single gene, GTP binding protein (GBP4), changed significantly in monocytes from all 3 groups. Based on gene-expression analysis, the most significant changes in Ps monocytes were noted in immunoglobulin (Ig), antigen binding and immune response genes similar to RA monocytes in which both immune response and Ig genes showed the greatest change. In PsA monocytes, genes related to phosphoproteins, cell motion and migration and 5'-nucleotidase showed the greatest change. In Ps monocytes, genes associated with the cell cycle, cell division, the immune response and leucocyte activation showed the greatest change compared to RA synovium where genes that control cell adhesion, Wnt and G-protein signaling were most highly affected. Lastly, PsA synovium showed significant changes in gene expression associated with protein kinase A (PKA) and the following signaling pathways: IL-6, IL-17, IL-27 and JAK-STAT following treatment with IFX.

Conclusions: IFX was highly effective for skin and joint inflammation in this cohort yet the impact of TNF inhibition on gene expression was surprisingly distinctive in the 3 disorders. These data suggest the presence of unique pathophysiologic mechanisms in immune mediated disorders downstream of TNF. If so, disease biomarkers in Ps, RA, and PsA are likely to be disease-specific.


1969


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Objective: Recent genetic studies have demonstrated that polymorphisms in ERAP are strongly associated with spondylarthritides. But the mechanism of this interaction has not been resolved. In the present study we examine the host immune response to Yersinia enterocolitica (Ye) using mice with genetic deficiency for HLA class I MHC (DKO) or ERAP.

Methods: The following mice (all on a B6 background) were compared: (i) deficient in endogenous class I MHC (DKO) (ii) transgenic for HLA B*2705 (B27) (iii) transgenic for B*2705/human β2M (B27/β2M) (iv) transgenic for HLA B*2705 and deficient in ERAP (B27/ERAP−/−). Mice were challenged intragastrically with 10^7 Yersinia enterocolitica 0:8. Survival curves were generated and cytokine responses were assessed by quantitative PCR on mesenteric lymph nodes and liver.

Results: Survival curve (figure 1) indicated the following ranking: B27/β2M−/− > B27/ERAP−/− > B27> DKO. Only DKO showed significant effects (<3 days) on early survival, confirming that ERAP effects on host immune responses implicate adaptive immunity not innate immunity. With respect to cytokine profiles, the clearest differential was an elevated expression of IL-17 in B27/ERAP−/− mice, which coincided with the temporal course of mortality. There was no consistent impact of ERAP deficiency on IL-4, IL-23, IFN-γ, TGF-β, or TNF-α after Yersinia infection.

Conclusions: ERAP deficiency was associated with enhanced IL-17 production after gastrointestinal infection with Yersinia (figure 2). These findings suggest that polymorphisms which affect ERAP function might play a deleterious role in IL-17-mediated immune responses to arthritogenic pathogens.

Disclosure: R. D. Inman: None; F. Zhu: None.

1970

Evaluation of T Helper 17 Axis in Ankylosing Spondylitis. Ali Taylan, Ismail Sari, Didem Koçaci, Arif Yüksel, Saffak Bilge, Yasar Yıldız, Gultan Sop, ISIL Coker, Necati Gunay and Nurullah AKKOC. İzmir Tepedik Training and Research Hospital, Department of Internal Medicine, İzmir, Turkey

Background: Ankylosing spondylitis (AS) is a chronic inflammatory disorder which primarily affects the axial skeleton. Although the etiology of AS is unknown, available data strongly suggests the importance of genetic factors in the susceptibility to the disease. Recent studies suggest that interleukin-23 receptor (IL-23R) is one of the major genetic factors involved in susceptibility to AS. In accordance with this observation, recent studies focused on the T helper 17 (Th17) axis in patients who have AS or spondylarthropathy (SpA).

Objectives: To evaluate T helper 17 (Th17) axis and its relation with tumor necrosis factor (TNF) alpha blockage and disease activity in ankylosing spondylitis (AS).

Methods: 127 AS patients (100M/27F) and 38 (27M/11F) controls were studied. Spinal mobility was assessed by the Bath Ankylosing Spondylitis Metrology Index (BASMI). Patients were also evaluated with the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Serum sample measurement of cytokines including IL-6, IL-12, IL-17A and IL-23 were performed by using commercially available ELISA kits.

Results: Age, and sex distributions were similar between patients and controls (p>0.05). Cytokines including IL-6, IL-12, IL-17, and IL-23 were significantly higher in the AS patients than the controls (p<0.05; 3.06 [0.73–339.4] vs. 1.42 [0.74–4] pg/mL, 4.65 [3.4–41] vs. 4.27 [3.47–57.8] pg/mL, 0.72 [0–31.6] vs. 0.15 [0–3.85] pg/mL, 98 [38–206] vs. 57 (36–160) pg/mL respectively).
Comparison of the patients who were on anti-TNF and conventional therapy revealed Th-17 related Cytokines were not different between the groups (p>0.05). Cytokines also were similar between the active vs. inactive patients’ groups (p>0.05).

On correlation analysis, IL-17 was correlated with IL-23 and IL-12 (p<0.05). IL-23 showed correlations with IL-17, IL-12 and BASMI (p<0.05). Other correlations (p<0.05) were as follows:IL-6 with CRP, IL-12 with IL-17 and IL-23.

Table 1. Clinical and laboratory characteristics of the patients and controls

<table>
<thead>
<tr>
<th></th>
<th>AS Patients (n=127)</th>
<th>Controls (n=38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38 (16–64)</td>
<td>38 (23–56)</td>
<td>0.94</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>100/27</td>
<td>27/11</td>
<td>0.38</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 (16.3–30.7)</td>
<td>25.3 (18.2–34.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>10 (1–35)</td>
<td>3.5 (0.0–5.0)</td>
<td></td>
</tr>
<tr>
<td>BASFI</td>
<td>3 (0.9–5.9)</td>
<td>2 (1–9)</td>
<td></td>
</tr>
<tr>
<td>BASDAI</td>
<td>4 (0.0–9.2)</td>
<td>2 (1–9)</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>7.5 (0.27–119.1)</td>
<td>1.15 (0.19–6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>3.06 (0.73–339.4)</td>
<td>1.42 (0.74–4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-12 (pg/mL)</td>
<td>4.65 (3.4–41.1)</td>
<td>4.27 (3.47–57.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>IL-17 (pg/mL)</td>
<td>0.72 (0.31–1.6)</td>
<td>0.15 (0.3–8.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-23 (pg/mL)</td>
<td>98.0 (38–206)</td>
<td>57 (36–160)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TGF-beta (pg/mL)</td>
<td>26.4 (5.2–87)</td>
<td>22.1 (0.4–39)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Conclusions: In this study we found serum levels of Th-17 axis related cytokines to be significantly increased in the sera of AS patients. Disease activity, treatment type and history of peripheral arthritis (not shown) seem no effect on these cytokines. Targeting the cytokines related with the Th-17 axis may be a reasonable approach in AS patients who don’t respond anti-TNF therapies.

Disclosure: A. Taylan: None; I. Sari: None; D. Koazei: None; A. Yuksel: None; S. Bilge: None; Y. Yildiz: None; G. Sob: None; I. Coker: None; N. Gunay: None; N. AKKOC: None.

1971

Functional Significance of mTOR in FLS Proliferation and Its Role in the Pathogenesis of Psoriatic Arthritis. Siba P. Raychaudhuri, Ankit Saxena and Smriti K. Raychaudhuri.

Purpose: Hyperproliferation and impaired apoptosis of resident synoviocytes (FLS) are critical pathogenic events in the pathogenesis of autoimmune inflammatory arthritis like in rheumatoid arthritis (RA) and psoriatic arthritis (PsA). Synovial hyperplasia leads to cartilage and bone damage in the inflamed joints. Increasing evidence places mammalian target of rapamycin (mTOR) as a central regulator of both cell growth (size) and proliferation, this is achieved in part by regulation of translation initiation. We hypothesize that mTOR signaling cascade proteins are upregulated in the FLS obtained from PsA patients and thus maintains proliferation and survival of these cells causing disease pathology. The aim of this study was to investigate the association of mTOR signaling proteins in regulating the proliferation and survival of these synoviocytes of psoriatic arthritis.

Methods: FLS were isolated and prepared from the synovial tissue collected from PsA patients (n=5). FLS obtained from OA (n=5) were used as control. Cell lysates were prepared from these FLS. By western blot assay denovo expression of mTOR and its phosphorylated downstream signaling protein p-mTOR was determined. Also effect of mTOR inhibitors were observed on the proliferation and survival of these FLS. FLS were cultured with rapamycin (10nM) and NVP-BEZ235 (50nM) for 3–5 days at 37°C in 5% CO2. FACS based CFSE dilution and MTT assays were used for proliferation studies.

Results: We found enhanced expression of mTOR (relative intensity (R.I.) = 1.9±0.1) and its downstream activated signaling protein p-mTOR (R.I. = 0.73±0.02) in FLS obtained from PsA in comparison to the non inflammatory OA FLS (R.I. = 0.9 ± 0.05; p-mTOR R.I. = 0.26±0.05). The difference of mTOR and p-mTOR was found to be significant at p<0.01. Also the FLS proliferation was found to be significantly reduced when cultured in presence of rapamycin (proliferation index (PI)=3.5±0.04) and NVP-BEZ 235 (PI=0.28± 0.02), in comparison to untreated controls (1.2±0.035), data were found to be significantly different between treated and untreated groups at p<0.01.

Conclusions: We observed high expression of mTOR signaling cascade proteins in the FLS obtained from PsA in comparison to noninflammatory OA cells. We used FLS from RA patients as positive controls and observations were similar to that of FLS of PsA. Further inhibition of proliferation of these cells in presence of mTOR inhibitors rapamycin and NVP-BEZ235 substantiates the role of mTOR signaling pathway in regulating the proliferation of FLS cell. Proliferating FLS is the major component of the invading pannus in inflammatory arthritis. The novel observations described herein provide new insights for the molecular mechanism of FLS proliferation as well as provides new avenues for treatment of psoriatic disease and RA.

Disclosure: S. P. Raychaudhuri: None; A. Saxena: None; S. K. Raychaudhuri: None.

1972


Objective: Ankylosing spondylitis (AS) is a chronic disabling disorder and pathogenesis is not understood. Multiple genetic factors are thought to be important contributors to disease susceptibility and MHC, IL23R, ERAP1, 2p15 and 21q22 are known to be associated with AS. TASC investigators have recently reported additional genes associated with AS susceptibility including IL1R2, ANTXR2, and gene deserts at 2p15 and 21q22. We evaluated these new candidate genes in a large cohort of Korean AS cases.

Methods: A total of 1164 AS cases and 752 ethnically matched, healthy controls who are native Koreans were enrolled for this study. 8 SNPs were analyzed to define genetic association with Korean AS. The MassARRAY® system (Sequenom, San Diego, CA) was used to genotype each study participant in a two-well reaction designed using Assay Designer 3.1.

Results: Significant positive associations of AS with ERAP1 SNPs, rs27037 (p=4.63×10^-10) and its downstream activated signaling protein p-mTOR (R.I. = 0.73±0.02) in FLS obtained from PsA in comparison to untreated cells (p=4.58×10^-2). We observed the SNP rs10865331 of gene desert at 2p15 also showed a significant association with AS (p = 4.63×10^-8).

Conclusions: This is the first confirmation in a non-Caucasian population that genetic polymorphisms of rs27037, rs27434 and rs10865331 are associated with AS, implicating common pathogenetic mechanisms in Korean and Caucasian AS.

Disclosure: S.-Y. Bang: None; T.-H. Kim: None; B. Lee: None; E. Kwon: None; S. H. Choi: None; K. S. Lee: None; S. Shim: None; A. Pope: None; P. Rahman: None; J. D. Reveille: None; R. D. Inman: None.
Methods: In this population based association study, we performed HLA typing in 3 groups: PsA, psoriasis without arthritis and healthy controls. The PsA group included adult patients satisfying the CASPAR criteria that were part of a large prospective PsA cohort. The psoriasis patients were recruited from a recently established psoriasis cohort that was confirmed by a dermatologist. These patients were examined annually by a rheumatologist to rule out the presence of inflammatory arthritis. Control DNA was from healthy Caucasian volunteers, cadaveric organ donors from laboratories of the University Health Network and from a commercial biobank. Extracted genomic DNA was amplified by PCR using locus specific primers for each of the HLA-A, -B, -C, -DR and DQ loci. PCR amplicons were identified by Sequence Specific Oligonucleotide probes using a reverse line blot technique. Caucasian subjects from the PsA and psoriasis cohorts were combined into a “Psoriatic disease” group that was compared to the healthy controls. The differences in allelic distributions for each of the HLA loci were compared using chi square test and Fisher exact test. Bonferroni corrected p values were calculated to adjust for multiple testing. A logistic regression analysis was performed to account for the strong linkage disequilibrium between the HLA alleles.

Results: 804 PsA patients, 412 psoriasis patients without arthritis and 719 healthy controls were included in the study. The median ages for the psoriasis, PsA and control subjects were: 45.7±13.1, 42.3±12.6 and 43.6±17.2 years respectively. The proportions of females were: 41.9%, 43.5% and 49.3% respectively. The following HLA alleles were found to be significantly different between the psoriatic disease group and healthy controls: A*03 (20% vs. 27.3%, Odds Ratio (OR) 0.6, p=0.05), B*07 (15.4% vs. 25.8%, OR 0.6, p=0.05), B*13 (13.7% vs. 2.2%, OR 0.01), B*27 (14.1% vs. 7.2%, OR 2.1, 95% CI 1.3–3.0), B*38 (11.9% vs. 2.5%, OR 5.3, p=10^-6), B*51 (5.7% vs. 10.7%, OR 0.5, p=3*10^-5), Cw*03 (15.9% vs. 22.5%, OR 0.7, p=0.05), Cw*06 (32.8% vs. 18.1%, OR 2.2, p=8*10^-10), Cw*07 (44.2% vs. 56.6%, OR 0.6, p=4*10^-5), Cw*12 (19.4% vs. 10.2%, OR 2.1, p=2*10^-4), DRB1*15 (19.2% vs. 25.6%, OR 0.7, p=0.03), DRB1*0602 (17% vs. 24.7%, OR 0.6, p=0.099). When the PsA group was compared to the psoriasis alone group the only HLA alleles that were found to be significantly different were: B*27 (17.7% vs. 4.1%, OR 5, p=4*10^-10), Cw*02 (11.6% vs. 4.8%, OR 2.7, p=0.01) and Cw*06 (26.9% vs. 42.1%, OR 0.5, p=8*10^-6). On logistic regression analysis only HLA B*27 (OR 4.6, 95% confidence interval (CI) 2.5–8.3) and Cw*06 (OR 0.5, 95% CI 0.4–0.7) remained significantly associated with PsA compared to psoriasis.

Conclusions: HLA*B*27 is a risk allele for PsA among psoriasis patients, while HLA-Cw*06 is a protective allele.

Disclosure: L. Eder: None; F. Pellett: None; V. Chandran: None; S. Shanmugarajah: None; D. D. Gladman: None.

1975

HLA-Bw4 Alleles and HLA-C Alleles That Have High Cell-Surface Expression Are Associated with Susceptibility to Psoriatic Arthritis (PsA). Vinod Chandran1, Fawnda Pellett2, Renise Ayearst2, Remy Pollock3 and Dafna D. Gladman1, 4, 1Toronto Western Hospital, Toronto, ON, Canada, 2University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital, Toronto, ON, Canada, 3University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital

Background: Natural-Killer (NK) cells and NK-T cells are important in the pathogenesis of PsA. The killer-cell immunoglobulin-like receptors (KIRs) on NK cells regulate the inhibition and activation of NK-cell responses through recognition of HLA class I molecules on target cells. It was previously shown that individuals with KIR3DS1 and HLA-B alleles with the serological Bw4 epitope and amino acid isoleucine at position 80 (HLA Bw4 80ile*B*1513, 1516, 1517, 1524, 2702, 3801, 4901, 51, 5201, 5301, 5302, 57, 58) as well as those with expressing HLA-C alleles that have high cell-surface expression (HLA-C Hi- C*02, 05, 06, 08, 12, 15, 16) progress more slowly to AIDS. Given the important epidemiological relationship between PsA and AIDS we sought to determine whether these genotypes are associated with susceptibility to PsA.

Methods: 685 cases of European ethnicity (295 females, mean age 43 years, PsA duration 7 years, psoriasis duration 15 years, actively inflamed joint count 11, PASI score 5.2) with PsA and 706 ethnically matched controls (273 females, mean age 53 years) were recruited for the study. Genotyping for HLA-B, and -C alleles was performed using PCR-SSO reverse line blot and that for KIR genes was performed
using PCR-SSP on genomic DNA obtained from peripheral blood. Association between genotypes and PsA was investigated using chi square, Mantel-Haenszel trend test and logistic regression.

Results: HLA-Bw4 80Ile was associated with PsA with risk being higher in subjects with two Bw4 80Ile alleles compared to those with one or no alleles [Bw4 80Ile 2 copies vs. none OR = 1.91, p = 0.03; 1 copy vs. none OR = 1.61, p < 0.0001] independent of HLA-C*07. KIR3DS1 was not associated with PsA in univariate analysis (p = 0.82), although in a multivariate logistic regression analysis including all KIR genes, KIR3DS1 was protective (OR = 0.54, p = 0.038). Analysis for association of Bw4 80Ile and/or KIR3DS1 with PsA where the hierarchy of putative biological effects, namely, Bw4 80Ile absence and KIR3DS1 presence < absence of both Bw4 80Ile and KIR3DS1 < Bw4 80Ile presence and KIR3DS1 absence < presence of Bw4 80Ile and KIR3DS1 (highest risk group) was taken into account showed that the combined genotype was associated with PsA (p trend < 0.0005). HLA-C*07 Hi alleles also were associated with PsA with risk being higher in subjects with two HLA-C*07 Hi alleles compared to those with one or no alleles (C*07 Hi two copies vs. none OR = 2.56, p < 0.0001; 1 copy vs. none OR = 1.49, p = 0.0012, trend p < 0.0001) independent of HLA-C*07, KIR2DS1 and KIR2DS2. Multivariate regression analysis including both Bw4 80Ile and C*07 Hi alleles in a logistic model revealed that both KIR2DS1 and KIR2DS2. Multivariate regression analysis including both Bw4 80Ile and C*07 Hi alleles in a logistic model revealed that both KIR2DS1 and KIR2DS2.

Conclusions: HLA and KIR genes that are associated with better control of HIV/AIDS are independently associated with increased susceptibility to PsA.

Disclosure: V. Chandra: None; F. Pellett: None; R. Ayestar: None; R. Pollock: None; D. D. Gladman: None.

1976

IL-17 Receptor and Its Functional Significance in Psoriatic Arthritis.
Siba P. Raychaudhuri1, Ankkit Saxena1 and Smriti K. Raychaudhuri1. UC Davis, 2UC Davis/VAMC Sacramento, Davis, CA

Purpose: The infiltration of T lymphocytes into the synovium involves a dynamic interaction between the subintimal endothelial cells and the fibroblast-like-synovial cells (FLS) in autoimmune arthritis. Overproduction of the pro-inflammatory cytokine, IL-17 has been reported in the rheumatoid arthritis (RA), psoriatic arthritis (PsA) synovium compared to osteoarthritis (OA) patients. Increased levels of IL-17 induce a multitude of factors contributing to the degradation of the articular cartilage and erosion of the underlying bone. In contrast to the restricted site of synthesis of IL-17, the IL-17 receptor (IL-17R) is expressed ubiquitously. Moreover, the CD5

Method: FLS were isolated from the synovium of RA (n = 5), PsA (n = 5) and OA (n = 5) patients. IL-17R expression in FLS was identified by western blotting (WB) and flowcytometry. We also measured IL-17 levels in the synovial fluid (SF) of PsA, RA and OA by ELISA. T lymphocytes derived from synovial fluid (SF) of these patients were studied to identify and phenotype the Th17 cells. Further we determined the functional significance IL-17R in respect to the production of proinflammatory cytokines and endopeptidase.

Results: Western blotting that IL-17R expressing cells in FLS obtained from the synovium of RA, PsA and OA were 16.5%±5.37, 12.5%±3.04, 0.3%±0.9 respectively. WB analyses showed that relative intensity (RI) of IL-17R protein were higher in RA and PsA compared to OA. RI of IL-17R for RA, PsA and OA were 0.74±0.034, 0.68±0.02, 0.044±0.01 respectively. The difference between the groups was found to be significant at p < 0.01. The IL-17 level in SF was highest in the PsA group (289.5 pg/ml ± 85.2, n = 12). In RA (n = 12) and OA (n = 12) the level of IL-17 were 225 pg/ml ± 55 and 52 pg/ml±16 respectively. A significant enrichment of IL-17-producing CD4+ T cells (10%±3.2) was noticed in the SF of the PsA patients compared to the OA (p < 0.01). Compared to OA, recombinant IL-17 induced higher levels of IL-6, IL-8, and MMP-3 in PsA derived FLS. Further blockade of the IL-17R inhibits production of IL-6, IL-8, and MMP-3.

Conclusion: IL-17R in PsA correlates with the inflammatory outcome of the disease. Our results support the hypothesis that IL-17/IL-17R interaction may contribute to an unbalanced production of cytokines and likely to play a significant role in the pathogenesis of PsA.

Disclosure: S. P. Raychaudhuri: None; A. Saxena: None; S. K. Raychaudhuri: None.

1977

Increase of CD5+ ‘Innate’ B Lymphocytes with Regulatory Capacities in Spondyloarthropathies. Tineke Cantaert, Gabriela FrancoSalinas, Jackie Paramarta, Yvonne Tiersma, Christine Teitsma, Paul P. Tak and Dominique Baeten. Academic Medical Center/University of Amsterdam

Background: B lymphocytes play a pivotal role in many autoimmune diseases by terminal differentiation to autobody-producing plasma cells, by antigen presentation to T cells, and by cytokine production. However, innate-like CD5+ B cells have recently been shown to down-regulate inflammation by IL-10 production in several colitis models. Considering the relationship between gut and joint inflammation as well as the unknown role of B cells in spondyloarthropathy (SpA), we aimed to characterize the presence and function of CD5+ B cells in this seronegative disease.

Materials and Methods: Peripheral blood B cells were analyzed and sorted by flow cytometry in patients with SpA as well as in healthy controls (HC) and patients with rheumatoid arthritis (RA). Sorted cells were stimulated in vitro with either anti-IgM and CD40L or with CpG. Production of cytokines was measured by real-time PCR and ELISA. Synovial biopsies were obtained from actively inflamed joints by needle arthroscopy and were analyzed by double immunohistochemistry.

Results: B cell phenotyping revealed no alterations in naïve, memory, and extra-follicular B cells as well as plasmablasts in SpA. However, there was a significant increase of CD5+ B cells in SpA compared to HC in all B cell subsets (p < 0.05). This was not due to increased B cell activation in SpA as the early activation marker CD69 was not increased and both HLA-DR (p < 0.01) and CD40 (p = 0.013) expression were even decreased on SpA versus HC B cells. Moreover, activation in vitro did not result in an upregulation of CD5. The increase of CD5+ B cells was also specific for SpA and not due to preferential migration of CD5- B cells to the inflamed target tissues as there was no increase in CD5+ B cells in RA peripheral blood and as CD5+ CD19+ B cells were detected in the inflamed synovial tissue. As to the function of the CD5+ B cells in SpA, they displayed not only lower levels of HLA-DR and CD40 but also lower expression of CD80 and CD86 when analyzed directly ex vivo as well as after in vivo activation, suggesting a decreased ability to fully activate T cells. Moreover, the CD5+ B cells produced increased levels of IL-10 but lower levels of IL-6 after BCR stimulation in vitro. This was not the case after innate immune activation by CpG.

Conclusion: CD5+ innate-like B cells are specifically increased in SpA. Their reduced expression of molecules involved in antigen-specific cross-talk with T lymphocytes as well as their ability to produce IL-10 indicate that this B cells subset has regulatory capacities. These data warrant further investigation of their potential contribution to the pathophysiology of SpA in vivo.

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1978

Increased Expression of Carbonic Anhydrase I in the Synovium of Patients with Ankylosing Spondylitis. Xiaotian Chang1, Yani Zhao, Xinfeng Yan and Yunzhong Zhang1. 1China, 2Shandong Academy of Medical Sciences, China

Background: The most distinctive features of ankylosing spondylitis (AS) is new bone formation and bone resorption at sites of chronic inflammation. Previous studies have indicated that the hyperplasia and inflammation of synovial tissues are significantly related to the pathogenic
process of AS. The present study applied a proteomics approach to identify novel AS-specific proteins by simultaneously comparing the expression profiles of synovial membranes from patients with AS, rheumatoid arthritis (RA) and osteoarthritis (OA).

**Methods:** Proteins extracted from synovial tissues (n=10 for each disease) were separated by 2-D electrophoresis, and the proteins with significantly increased expression in the AS samples were subjected to MALDI-TOF/TOF-MS analysis. The results were verified using western blotting and immunohistochemistry. The levels of candidate proteins in synovial fluids (n=40 for each disease) were measured using ELISA.

**Results:** Compared with RA and OA tissue samples, the proteomics approach revealed significantly increased expression of carbonic anhydrase I (CA1) in the synovial membrane of patients with AS. Immunohistochemistry and western blotting analysis confirmed the above finding. ELISA detected a higher level of CA1 in synovial fluids from patients with AS than in RA and OA samples. The study also detected increased expression of alpha-1-antitrypsin in the synovial tissues from AS patients, which corresponds to other reports.

**Conclusion:** *In vitro* experiments by other groups indicated that CA1 catalyzes the generation of HCO$_3^-$ through hydration of CO$_2$, which then combines with Ca$^{2+}$ to form a precipitation of CaCO$_3$. Many evidences indicated that carbonic anhydrase also stimulates bone resorption. Hence, over-expression of CA1 in synovium of AS may promote improper calcification and bone resorption in AS.

**Disclosure:** X. Chang: None; Y. Zhao: None; X. Yan: None; Y. Zhang: None.

**1979**


**Background:** The Major Histocompatibility Complex Class 1 Chain-Related Gene A (MICA) is a multiallelic locus in the MHC region that encodes a 43 kDa cell-surface protein that functions to activate pathways in innate and adaptive immunity. Previous studies have shown associations between psoriatic arthritis (PsA) and MICA-A9 corresponding to MICA*00201 and MICA*017, and MICA-A4, corresponding to MICA*001, MICA*00701, and MICA*018, when compared to healthy controls. However, it is not clear whether the associations are with psoriasis or with PsA, and if the associations are independent of HLA alleles. Our purpose was to delineate the contributions of MICA alleles to susceptibility to skin and joint manifestations of psoriatic disease.

**Methods:** 249 unrelated Caucasian subjects with PsA (96 females, mean age 41 years, PsA duration 7 years, psoriasis duration 14 years, actively inflamed joint count 10, PASI score 5.3), 243 with psoriasis (100 females,
mean age 47 years, psoriasis duration 17 years, PASI score 5) and 248 healthy controls (141 females, mean age 49 years) were recruited for this study. Genotyping for 55 MICA alleles was done by PCR-SSP and for HLA-B, and -C alleles by PCR-SSO reverse line blot. Allele frequencies were calculated and univariate and multivariate logistic regressions performed, adjusting for HLA-B and C alleles previously shown to be associated with psoriasis and/or PsA.

Results: In univariate analyses MICA*00201/020, MICA*016 frequencies were significantly increased in psoriatic disease (PsA and psoriasis combined) compared to controls, while MICA*00801, MICA*018 and MICA*049 frequencies were decreased. MICA*00201/020 and MICA*00701/026 were increased in PsA compared to controls and MICA*004, MICA*00801 and MICA*018 were decreased. MICA*00201/020, MICA*016 and MICA*017 frequencies were significantly increased in psoriasis compared to controls, while MICA*00801 was decreased. Finally, MICA*00701/026 was increased in PsA compared to psoriasis, and MICA*016 was decreased. There was a significant effect of homozygosity for the allele MICA*00801. Results of the multivariate analyses are provided in the table.

Table. Results of multivariate logistic regression analyses using MICA alleles found significant in the univariate analyses as explanatory variables, as well as the results after the inclusion of HLA alleles that were found to be at least marginally significant in univariate analyses.

<table>
<thead>
<tr>
<th>Allele</th>
<th>After Adjustment for HLA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>MICA*00201/020</td>
<td>1.694</td>
</tr>
<tr>
<td>MICA*00801</td>
<td>0.686</td>
</tr>
<tr>
<td>MICA*016</td>
<td>3.022</td>
</tr>
<tr>
<td>MICA*018</td>
<td>0.451</td>
</tr>
<tr>
<td>MICA*049</td>
<td>0.125</td>
</tr>
<tr>
<td>PsA vs. Controls</td>
<td></td>
</tr>
<tr>
<td>MICA*00201/020</td>
<td>1.824</td>
</tr>
<tr>
<td>MICA*004</td>
<td>0.528</td>
</tr>
<tr>
<td>MICA*00701/026</td>
<td>2.602</td>
</tr>
<tr>
<td>MICA*00801</td>
<td>0.764</td>
</tr>
<tr>
<td>MICA*018</td>
<td>0.437</td>
</tr>
</tbody>
</table>

After adjusting for HLA-B*13, −27, −38, −57 and HLA-Cw*01, −02, −06, −12 alleles, no MICA alleles were associated with PsA, but MICA*016 remained significantly associated with psoriasis (Odds Ratio (OR) = 4.4, p = 0.011) and MICA*00801 remained protective [OR = 0.69, p = 0.036]. MICA*00801 homozygosity significantly increased susceptibility to PsA for patients with psoriasis.

Conclusions: MICA allele associations with psoriasis and PsA are dependent on linkage disequilibrium with HLA-B and HLA-C risk alleles. Independent of HLA, only MICA*016 and MICA*00801 influence the risk of developing psoriasis without arthritis, and homozygosity for MICA*00801 increases the risk of developing PsA.

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1980

Peripheral Joint Ankylosis in the Spontaneous Model of Arthritis in DBA/1 Mice Is Associated with a Locus on Chromosome 3 That Contains the BMP Receptor Type 1b. Rik Lories1, Inge Derese1, Shea Carter1, Kirsten Braem1, Ana Valdes1 and Frank P. Luyten1. 1King’s College, 1KU Leuven, Leuven, Belgium, 1KU Leuven

Background: Progression of ankylosis in patients with ankylosing spondylitis is highly variable. Disease such as diffuse idiopathic skeletal hyperostosis (DISH) and fibrodysplasia ossificans progressiva (FOP), show new bone formation with striking similarities to AS both at the histomorphological and molecular level. This suggests that ankylosis is at least partially due to genetic factors. We used the ankylosing enthesitis model in DBA/1 mice to search for associated regions and genes.

Methods: Male DBA/1 were crossed with female BALB/c mice. Male F2 mice from different litters were studied by histomorphology at 26 weeks. 159 markers with sequence-length polymorphisms on the autosomes were selected. Median spacing between the markers was 6.9 cM. 162 F2 male mice were studied. Genes in regions of interests were linked to skeletal development, bone morphogenetic protein (BMP) and Wnt signaling pathways with the Genome Ontology database. The association was evaluated by Chi-square tests with a False Discovery Rate (FDR) algorithm.

Results: Incidence of ankylosing enthesitis was lower in the F2 generation as compared to wild-type DBA/1 males (42% vs. 72%; p<0.0001). When applying the FDR algorithm for 159 markers, associations with D3MIT199 and D3MIT160 were significant (p<0.016). Additional markers were additionally genotyped. In the associated region between markers D3MIT42 and D3MIT199, 162 genes were found among which BMP11, Cxcl4, Left1, Paps1, Pitx2, and Ube2d3. Only BMP receptor type 1b (BMPR1b) was specifically upregulated in mice with spontaneous arthritis as demonstrated by quantitative RT-PCR.

Conclusion: By using F2 mouse genetics in the analysis of a specific phenotype of joint ankylosis, we identified a locus on chromosome 3 that shows association. Within this locus, several genes could play a role in ankylosis but the expression profile suggests that BMP receptor 1b is involved, further supporting a critical role for BMPs in this process.

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1981

Phenotypic, Functional, and Transcriptomic Analysis of Monocyte-Derived Dendritic Cells from SpA Patients Revealed Their Hypo-Stimulatory and Specific Molecular Response to LPS Compared to Healthy Controls. Maxime Brebant1, Nelly Bonilla2, Badredine Mohand Oumoussa3, Alice Talpins4, Henri-Jean Garchon5 and Gilles Chiocchia2. 2AP-HP, 2Inserm

Purpose: DCs from B27 transgenic rats have a diminished ability to interact with CD4+ T cells and to stimulate a proliferative response, as compared to control DCs. Such results raised the hypothesis that an altered interaction between antigen-presenting cells and CD4+ T lymphocytes might be critical in AS pathogenesis. Nevertheless, we need data in the human disease. Thus, it is of first importance to analyse the expression of HLA molecules and to evaluate the function and genes expression profiling of DCs in AS patients.

Objectives: To study HLA and accessory molecules expression in monocyte-derived DCs (MD-DC), to examine the functional capacity of MD-DC from patients compared to normal controls and the genes expression profiling in monocytes and their derived dendritic cells before and after stimulation.

Method: AS patients (11 HLA-B27+: mean age 44+12 years; BASDAI = 38+22; B2SF = 19+21) and 10 healthy controls were studied. Multi-colours FACS analysis of in vitro MD-DCs was used to compare the expression level of HLA-DR and a full set of cell markers; CD4, CD8, CD11c, CD14, CD40, CD80, CD83, CD86. In vitro derived DCs were obtained from purified CD14+ population cultured for 7 days in the presence of IL-4 and GM-CSF. HuGene 3.0 microarrays were used for genes expression profiling of both monocytes and their derived dendritic cells.

Results: The expression of HLA-DR was higher in AS patients than in controls (p=0.009) on monocyte-derived DCs obtained after 7 days of culture and activated with LPS.We observed that like it was reported in rat, the monocytes-derived DCs from AS patients exhibited a weaker stimulatory efficiency of CD4+ T cells than DCs from controls both on autologous and heterologous stimulation conditions. The analysis of genes differentiallyexpressed between CD14+ monocytes from AS patients and controls showed that inflammatory mediators genes transcripts such as CCL2 chemokine, IL-1b and IL-6 cytokines were significantly overexpressed on AS patients CD14+ cells. We also observed a specific molecular signature response to LPS by MD-DC from AS patients compared to controls.
Conclusions: Our findings revealed consistent differences in HLA expression on DCs from AS patients, as compared to healthy controls. We bring evidence that DC from SpA patients have a lower ability to stimulate CD4+ T cell proliferation, as compared to control DC. Transcriptomic analysis of monocytes CD14+ from patients compared with healthy controls showed an inflammatory signature in which genes of inflammatory mediators are significantly overexpressed in SpA. Furthermore, transcriptomic analysis of MD-DCs stimulated with LPS revealed a difference in molecular signature between patients and healthy controls.

Disclosure: M. Brehan: None; N. Bonilla: None; B. Mohand Oumoussa: None; A. Talpin: None; H.-J. Garchon: None; G. Chioceha: None.

1982

Plasma Cytokine Profiles in Ankylosing Spondylitis. Brock E. Harper1, Michael H. Weisman2, Pravitt Gourh3, Shervin Assassi1, Laura A. Diekman4, Michael M. Ward5, John D. Revelle6 and Sandeep K. Agarwal1, 1 Cedars-Sinai Medical Center, Los Angeles, CA, 2NIH, NIAMS, IRP, Bethesda, MD, 3Univ Texas Health Sci Ctr, Houston, TX, 4Univ. of Texas Health Science Center Houston, 5Univ. of Texas Health Science Center Houston

Background: Ankylosing spondylitis (AS) is commonly treated with TNF inhibitors (TNFi) with success; however, our understanding of the immunology of AS is limited. Identification of the genetic association of IL23R with AS susceptibility implicates involvement of the Th17 pathway in the pathogenesis of AS. This study aims to investigate the possible effects of TNFi use and patterns of lymphocyte activation in AS.

Methods: Plasma from 128 AS patients and 144 nonautoimmune controls were obtained from patients seen at the University of Texas Health Science Center at Houston Rheumatology Division within the PSOAS cohort. Levels of 13 cytokines were evaluated by electrochemiluminescent multiplex assays.

Results: AS patients had higher levels of IL-23 (p<0.004), IL-4 (p=0.0007), IL-6 (p<0.0001) and lower levels of IL-1β (p=0.002) and IL-8 (p=0.0001) compared to controls after adjustment for age and gender. Results of analysis of TNFi subsets are shown in Table 1. No differences were seen between either subset of AS patients and controls for IFNγ, IL-5, IL-12, IL-13 or IL-10.

Table 1. Comparison of Cytokine Levels in Patients On and Off TNFi inhibitors. Cytokine values are listed as mean±SD in pg/mL. P-values are of data after log-transformation and adjustment for age and gender.

<table>
<thead>
<tr>
<th>Control On TNFi (N=114)</th>
<th>AS Off TNFi (N=92)</th>
<th>AS On TNFi (N=36)</th>
<th>Adjusted P-value</th>
<th>Adjusted P-value</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL 17</td>
<td>1.85 ± 2.27</td>
<td>2.28 ± 2.66</td>
<td>0.61 ± 0</td>
<td>NS</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL 23</td>
<td>4.67 ± 12.38</td>
<td>7.65 ± 20.4</td>
<td>10.86 ± 36.97</td>
<td>0.003</td>
<td>NS</td>
</tr>
<tr>
<td>IL 2</td>
<td>1.80 ± 6.98</td>
<td>1.40 ± 2.88</td>
<td>0.74 ± 0.56</td>
<td>NS</td>
<td>0.008</td>
</tr>
<tr>
<td>IL 4</td>
<td>1.69 ± 3.08</td>
<td>3.30 ± 4.21</td>
<td>2.40 ± 3.47</td>
<td>&lt;&lt;0.0001</td>
<td>0.08</td>
</tr>
<tr>
<td>IL 1β</td>
<td>4.91 ± 11.97</td>
<td>11.05 ± 1.90</td>
<td>1.05 ± 1.59</td>
<td>0.015</td>
<td>NS</td>
</tr>
<tr>
<td>IL 6</td>
<td>6.19 ± 11.79</td>
<td>15.06 ± 22.77</td>
<td>4.27 ± 7.38</td>
<td>&lt;0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>IL 8</td>
<td>7.69 ± 343.32</td>
<td>2.82 ± 8.10</td>
<td>4.19 ± 12.00</td>
<td>&lt;&lt;0.0001</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Significant correlations with clinical parameters were found with IL-6 and higher BASDAI, ESR, CRP and limited spinal movement. IL-2 and IL-4 were also associated with higher BASDAI. IL-17, IL-23, IL-2, IL-4, IL-1β, IL-8 were associated with ESR and CRP.

Conclusions: Plasma cytokines differences between controls and patients with AS particularly with respect to TNFi use support the potential role of dysregulation of the Th17 pathway in AS.

Disclosure: B. E. Harper: None; M. H. Weisman: None; P. Gourh: None; S. Assassi: None; L. A. Diekman: None; M. M. Ward: None; J. D. Revelle: None; S. K. Agarwal: None.

1983

Stromal Cell Derived Mediators of Bone Remodeling in Psoriatic Arthritis: Implications for Disordered Osteoclastogenesis and Bone Erosion.

Nicola Dalbeth1, Bregina Pool, Timothy Smith, Karen Callon, Maria Lobo, William J. Taylor, Peter B. Jones, Jillian Cornish and Fiona M. McQueen2. 1Univ Auckland, Auckland, New Zealand, 2Univ of Auckland Sch of Med, Auckland, New Zealand

**Background:** Diverse bone pathologies are observed in patients with psoriatic arthritis (PsA). Uncoupling of bone remodeling with disordered osteoclastogenesis has been implicated in the pathogenesis of bone resorption in PsA. The aim of this study was to examine the role of stromal cell derived mediators of bone remodeling in PsA.

**Methods:** Patients with PsA (n=38), with psoriasis (n=10) and healthy controls (n=12) were studied. Serum was obtained for testing of Dikkopf-1 (Dkk-1), macrophage-colony stimulating factor (M-CSF), osteoprotegerin (OPG) and receptor activator of nuclear factor-κB ligand (RANKL) by ELISA. These stromal cell derived mediators were selected as all have been definitively implicated in bone remodelling in models of inflammatory arthritis. Patients with PsA also had bone densitometry, plain radiographs of the hands and feet, and assessment of peripheral blood osteoclast precursors. Radiographs were scored for erosion and joint space narrowing using the Sharp-van der Heijde (SvdH) method modified for PsA, and for the number of joints with new bone formation.

**Results:** Compared with psoriasis and healthy controls, patients with PsA had higher circulating concentrations of Dkk-1 and M-CSF (Figure). In patients with PsA, the SvdH radiographic scores correlated with M-CSF concentrations (r=0.52, p<0.01) and RANKL concentrations (r=0.36, p<0.05), but not Dkk-1 concentrations (r=0.15, p>0.05). Circulating mediators of bone remodeling did not correlate with the number of joints with new bone formation or with total hip bone mineral density. The radiographic SvdH scores correlated with the percentage of peripheral blood osteoclast precursors (r=0.38, p<0.05), the number of osteoclast-like cells (r=0.37, p<0.05) and resorptive pits (r=0.47, p<0.01) following culture with RANKL and M-CSF. Circulating M-CSF concentrations correlated with the percentage of peripheral blood osteoclast precursors (r=0.40, p<0.05).

**Conclusions:** Systemic expression of stromal cell derived factors that promote osteoclastogenesis and bone loss is disordered in patients with PsA. The data do not support a role for these factors in other bone pathologies of PsA, such as new bone formation.

Disclosure: N. Dalbeth: None; B. Pool: None; T. Smith: None; K. Callon: None; M. Lobo: None; W. J. Taylor: None; P. B. Jones: None; J. Cornish: None; F. M. McQueen: Novartis Pharmaceuticals Corporation, 2.

1984

The Association of IL-13 Polymorphism with Psoriatic Arthritis among Psoriasis Patients. Liti Eder2, Vinod Chandran3, Fawnda Pellett4, Remy Pollock5, Sutha Shanmugarajah6 and Dafina D. Gladman7. 1Toronto Western Hospital, Toronto, ON, Canada, 2Toronto Western Hospital, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto, ON, Canada

**Aim:** The IL-13 cytokine is involved in T helper type 2 signaling pathway. IL-13 polymorphisms confer a risk for Asthma. Recently, these were found to be associated with a reduced risk for Psoriatic Arthritis (PsA) but not with psoriasis. Smoking was found to abrogate this effect. We aimed to study the association of IL-13 polymorphisms with PsA and psoriasis and their combined effect with smoking.

**Methods:** We genotyped three groups of Caucasian individuals: patients with PsA, patients with psoriasis (Ps) and patients with PsA. **p<0.01, ***p<0.001, one-way analysis of variance with Dunns’s multiple comparison test.

Disclosure: N. Dalbeth: None; B. Pool: None; T. Smith: None; K. Callon: None; M. Lobo: None; W. J. Taylor: None; P. B. Jones: None; J. Cornish: None; F. M. McQueen: Novartis Pharmaceuticals Corporation, 2.

**Figure.** Stromal cell derived mediators of bone remodeling. Box and whisker plots showing concentrations of A. Dkk-1, and B. M-CSF in healthy controls (HC), patients with psoriasis (Ps) and patients with PsA. **p<0.01, ***p<0.001, one-way analysis of variance with Dunns’s multiple comparison test.
ing was performed using TaqMan allelic discrimination assays and SDS 2.2.2 software was used for data collection and allele calling.

The differences in allelic distributions were compared by chi square test using PLINK software. The combined effect of genotype and smoking was tested by comparing the proportions of PsA and psoriasis patients and the different combination groups of rs1800925*CT/TT status and smoking status.

**Results:** 555 PsA patients, 342 psoriasis patients without arthritids and 216 healthy controls were included in the study. Smoking was negatively associated with PsA (258/492 (47.6%) in the PsA group and 139/342 (59.4%) in the psoriasis alone, p<0.0008). The minor alleles of rs20541*A and rs485*A were protective for PsA compared to controls (Odds Ratio (OR) 0.61, p<0.0005, OR 0.62, p=0.0007, respectively). The same alleles were not found to be associated with psoriasis alone (OR 0.75, p=0.06, OR 0.79, p=0.11, respectively). When PsA patients were compared to those with psoriasis alone, the minor alleles of rs1800925*T (OR 0.78, p=0.04) and rs485*A (OR 0.77, p=0.05) were found to be protective. A stronger protection was found with the rs1800925*T/rs20541*A haplotype (OR 0.64, p=0.007). The combined effect of rs1800925*CT/TT status and smoking status is presented in Table 1. The combination of smoking and the protective genotype rs1800925*CT/TT was the most protective for PsA. Among non-smokers rs1800925*CT/TT was no longer associated with PsA.

**Table 1.** The combined effect of smoking status and rs1800925*CT/TT genotype status on the prevalence of PsA

<table>
<thead>
<tr>
<th>rs1800925 genotype</th>
<th>Smoking</th>
<th>PsA</th>
<th>Psoriasis</th>
<th>OR*</th>
<th>95% CI**</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/CT</td>
<td>Yes</td>
<td>82  (48.5%)</td>
<td>87  (51.5%)</td>
<td>0.49</td>
<td>0.33–0.73</td>
<td>0.0003</td>
</tr>
<tr>
<td>CC</td>
<td>Yes</td>
<td>146 (55.7%)</td>
<td>116 (44.3%)</td>
<td>0.66</td>
<td>0.46–0.93</td>
<td>0.02</td>
</tr>
<tr>
<td>CT/TT</td>
<td>No</td>
<td>69  (61.1%)</td>
<td>44  (38.9%)</td>
<td>0.82</td>
<td>0.52–1.29</td>
<td>0.39</td>
</tr>
<tr>
<td>CC</td>
<td>No</td>
<td>196 (60.7%)</td>
<td>127 (39.3%)</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
</tbody>
</table>

**Conclusions:** An IL-13 polymorphism is protective for PsA among psoriasis patients. This effect was not significant among non-smokers.

**Disclosure:** L. Eder: None; V. Chandran: None; F. Pellett: None; R. Pollock: None; S. Shanmugarajah: None; D. B. Gladman: None.

1985

The Relationship of Biomarkers and Radiographic Progression in Patients with Ankylosing Spondylitis. X. Baraliakos1, R. Landewe2, D. Van Der Heijde3, J. Listing2, D. Baker1, H. Benjamin1 and J. Braun6. 1Centocor Inc, R&D; 2German Rheumatism Research Center, Leiden;3Maastricht University Medical Center, Meerssen, The Netherlands; 4Maastricht University Medical Center, Maastricht, The Netherlands; 5Rheumazentrum Ruhrgebet, Herne; 6Rheumazentrum Ruhrgebet, Herne, Germany

**Background:** Structural damage in patients with ankylosing spondylitis (AS) is characterized by the development of syndesmophytes. How this is influenced by inflammation and bone metabolism is not entirely clear, and the role of biomarkers associated with new bone formation in this scenario remains to be clarified.

**Objective:** To determine the level of different biomarkers, analyse their relevance in correlation to clinical, MRI and radiographic measurements and define their role in the prediction of syndesmophyte formation in AS patients under anti-TNF treatment.

**Methods:** Data of AS patients who participated in ASSERT were retrospectively analyzed. Complete data from radiographs and of the follow-up biomarkers (measured by ELISA) were available at baseline and after 2 years: interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), transforming growth factor-β (TGFβ) for inflammation and osteocalcin (OC), bone alkaline phosphate (BAP), C Telopeptide 1 (CTX), N Telopeptide (NTX), osteoprotegerin (OPG) and cartilage oligomeric matrix protein (COMP) for bone turnover.

Assessment of disease activity (BASDAI), function (BASFI), metrology (BASMI), laboratory parameters (CRP, ESR), radiographs and MRIs were available at baseline and after 2 yrs. Analyses were performed based on a pairwise radiographic progression (SRP), increase of ≥3 mSASSS units/year and/or the development of new syndesmophytes by the 2-year follow-up.

Summary statistics were used for the baseline data, and linear and logistic regression to test for the association of serum markers with MRI activity, mSASSS scores, clinical indices and the development of new syndesmophytes. ROC analysis was used for cut-point determination.

**Results:** Data of 148 patients could be analyzed, 15% of those showed SRP and 19% syndesmophyte formation. Baseline characteristics and the mean serum levels of biomarkers were not significantly different in patients with and without syndesmophytes/radiographic baseline damage. By logistic regression analysis, only OPG serum levels correlated significantly with SRP. The best cut-off for OPG in discriminating between patients with and without SRP was 3.1 units (OR (95%CI): 8.0 (2.6–24), p=0.001), sensitivity 67%, specificity 71% (AUC 0.66, LR+: 1.7, LR−: 0.54). Furthermore, baseline radiographic damage (OR (95%CI): 31 (3.2–298), p=0.003) and female gender (OR (0.17 (0.03–0.77), p=0.032) were also predictive of SRP. HLA-B27 could not be investigated due to low prevalence of HLA-B27 negativity. No correlations with the development of syndesmophytes were found. Among the markers for inflammation, only IL-6 showed a trend towards higher levels for patients with (mean (SD): 14.7 (18.2)) vs. without (13.3 (23.6)) SRP.

**Conclusion:** Increased levels of OPG, an osteoclastogenesis inhibitory factor, were predictive of severe radiographic progression over 2 years on the group level only. In contrast to previous studies with AS patients and patients with active RA or OA, none of the biomarkers indicative of bone degradation or hyperpolarization were predictive of radiographic progression.

**Disclosure:** X. Baraliakos: None; R. Landewe: None; D. Van Der Heijde: None; J. Listing: None; D. Baker: Centocor, Inc., J. Benjamin: Centocor, Inc., J. Braun: None.

1986

Whole Blood Transcriptional Profiling in Ankylosing Spondylitis Identifies Novel Putative Candidate Genes for Both the Inflammatory and Tissue-Destructive Aspects of the Disease. Fernando Manuel Pimentel-Santos1, Dario Ligeiro2, Malafaia Matos3, Ana F. Mourão4, José Costa5, Helena Santos2, Elisa Sousa1, Ana Bela Barcelos, Fátima Godinho1, João E. Fonseca1, Henrique Gueds-Pinto2, Jaime C. Branco1, Matthew A. Brown1 and Gethin Thomas3. 1(IMM), Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal, 2CDECOC, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisboa, Portugal, 3Centro de Histocompatibilidade do Sul, Lisboa, Portugal, 4Centro Hospitalar do Alto Minho (CHAM), Hospital de Ponte de Lima, Ponte de Lima, 5Diamantina Institute for Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Brisbane, Australia, 6Hospital Garcia de Orta, Almada, Portugal, 7Hospital Infante D. Pedro, Aveiro, Portugal, 8Instituto de Biotelemcia e Bioengenharia, Centro de Genetica e Biotecnologia, da Universidade de Trás-os-Montes e Alto Douro (IBB/CGB–UTAD), Vila Real, Portugal, 9Instituto Português de Reumatologia (IPR), Lisboa, Portugal, 10UTAD, Universidade de Tás-os-Montes e Alto Douro, Vila Real, Portugal

**Background:** The aetopathology of ankylosing spondylitis (AS) is poorly understood. A number of genetic-association studies have identified genes contributing to AS susceptibility but such approaches provide little information on the true gene activity changes occurring during the disease process. Transcriptional profiling generates a “snapshot” of the sampled cells activity and thus can provide insights into the molecular processes driving the disease process. Several recent studies have defined transcriptional profiles generated from peripheral blood mononuclear cells (PBMCs) however PBMC isolation is not viable in multicentre studies and limits the viability of such an approach. An alternate approach is to use whole blood samples collected using PAXgene technology which preserves integrity of the RNA.

**Objective:** We undertook a whole-genome microarray approach to identify candidate genes associated with AS and validated these gene-expression changes in a larger sample cohort.

**Methods:** 18 active AS patients, classified according to the New York criteria, and 18 gender-and age-matched controls were profiled using Illumina HT-12 Whole-Genome Expression BeadChips which carry cDNAs for 48000 genes and transcripts. Class comparison analysis identified a number of differentially expressed candidate genes. These candidate genes were then validated in a larger cohort using qPCR-based TaqMan Low Density Arrays (TLDA). A total of 239 probes corresponding to 221 genes were identified as being significantly different between patients and controls with a p-value <0.0005 (80% confidence level of false discovery rate). Forty eight genes were then selected for validation studies, using the TLDA. Thirteen of these genes were validated in the second patient cohort with 12 down-regulated (1.3–2-fold) and only 1 upregulated (1.6-fold).
A number of these genes, with well-documented inflammatory roles with specific interest to AS progression are the established genes SPOCK2 (osteocentin) and EP300 in cartilage. DNMT1 and EP300 both mediate STAT3 functionality which has also been in genetic studies with AS.

Conclusion: We have validated a gene expression signature for AS from whole blood and identified strong candidate genes that may play roles in both the inflammatory and joint destruction aspects of the disease.

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ACR Poster Session C
Systemic Sclerosis, Fibrosing Syndromes and Raynaud’s-Pathogenesis and Genetics II
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1987

Methods: The non-synonymous polymorphism rs763361 of the CD226 gene, which encodes the DNAX accessory molecule 1, involved in T cell co-stimulation pathways, has recently been identified as a genetic risk factor for autoimmunity.

Objectives: To test for association the CD226 rs763361 polymorphism with systemic sclerosis (SSc) in European Caucasian populations.

Methods: CD226 rs763361 was genotyped in 3645 individuals comprising a discovery set (991 SSc patients and 1008 controls) and a replication set (999 SSc patients and 634 controls), all individuals being of European Caucasian origin.

Results: The CD226 rs763361 T allele was found to be associated with SSc in both discovery and replication samples providing the following results in the combined populations: OR 1.22 95%CI [1.01–1.43], P=5.09×10^{-2}. The CD226 T allele was also associated with various SSc subsets highlighting a potential contribution in disease severity. The most remarkable associations of the CD226 TT risk genotype were observed with diffuse cutaneous subtype, anti-topoisomerase I antibodies positive and SSc-related fibrosing alveolitis subsets: OR 1.86 95%CI [1.42–2.43], P=5.15×10^{-6}; OR 1.82 95%CI [1.38–2.40], P=2.16×10^{-5} and OR 1.61 95%CI [1.25–2.08], P=2.73×10^{-5}, respectively.

Discussion: Our results establish CD226 as a new SSc genetic susceptibility factor.
in SSc (n = 3) as compared to healthy controls under basal conditions. It has been reported that some microRNAs regulate Hox genes. Therefore, we hypothesize that microRNAs prevent the transcription of HDAC1 mRNA and regulate thereby the expression of HoxA9.

Conclusions: We conclude that vasculopathy in SSc might be related to the different expression of HDACs in endothelial cells. Altered expression of HDACs could possibly regulate the expression of important genes involved in vascular formation via transcription factors like HoxA9 and contribute to altered angiogenesis in SSc.

Disclosure: H. Hemmatzadaz: None; B. Maurer: None; B. A. Michel: None; R. E. Gay: None; G. Steffen: None; J. Avouac: None; O. Distler: None; Y. Allanore: None; A. Jungel: None.

1989

Circulating T Cell Polarization Is Associated with Respiratory Decline in Scleroderma Patients with Active Interstitial Lung Disease. 
Francesco Boni1, Frederick Wigley2, Robert Wise3 and Antony Rosen4. 1 Johns Hopkins University, University, Baltimore, MD, 2 Johns Hopkins University

Purpose: Immune activation plays a role in the pathogenesis of systemic sclerosis (SSc) and may be relevant for the initiation and propagation of target tissue injury. In particular, development of interstitial lung disease (ILD) is associated with lung inflammation. The presence of neutrophilia and/or eosinophilia (alveolitis) in the bronchoalveolar lavage (BAL) fluid of SSc patients has been considered indicative of active ILD. However, this measure has not consistently provided reliable prediction of lung disease outcomes. A pro-fibrotic type 2 (Th2/Tc2) T cell response has been detected in the periphery of SSc patients with ILD. In this study we investigated whether an abnormal distribution of polarized T cell subsets in the periphery or the bronchoalveolar lavage (BAL) fluid of SSc patients is associated with the presence of active ILD.

Methods: Peripheral blood and BAL were simultaneously obtained from 22 SSc patients undergoing bronchoscopy for suspected active ILD based on increasing respiratory symptoms, worsening lung volumes or abnormal imaging studies. Decline of the forced vital capacity (FVC) >10% of predicted within 6–10 months prior to the procedure was considered as significant for active ILD. The presence of active BAL alveolitis was defined as neutrophils >3% and/or eosinophils >2.2% on differential cell count. T cell subsets were characterized by flow cytometry using CD3, CD4, CD8, chemokine receptor CCR5 (Th1/Th2 specific) and CRTH2 (Th2/Th2 specific) surface markers. CCR5/CRTH2 ratio was used to determine polarization of the immune response towards a type 1 (high ratio) or type 2 (low ratio) phenotype.

Results: Active ILD (FVC decline >10%) was identified in 12 patients and was significantly associated with a relative Th2/Tc2 polarization in the peripheral blood based on a lower CD3+CCR5/CRTH2 ratio (3.9 vs. 11, p<0.001). This finding was mostly determined by a lower number of circulating CCR5+ T cells in active vs. non-active ILD patients (CD3 8.6% vs. 24.8%, p<0.001; CD4 7.7% vs. 19.4%, p=0.005; CD8 14.9% vs. 40%, p<0.001). Conversely, the presence of BAL alveolitis was not significantly associated with declining FVC volumes, nor it was correlated with any absolute or relative difference among polarized T cell subsets in the peripheral blood or BAL fluid.

Conclusions: Distinct polarized T cell subsets in the peripheral blood of SSc patients are associated with declining respiratory function and should be prospectively explored as a novel biomarkers to measure disease activity and predict outcomes in ILD and other clinical manifestations of scleroderma.

Disclosure: F. Boin: None; F. Wigley: None; R. Wise: None; A. Rosen: None.

1990

Does Treatment with Imatinib Modify Gene Expression in the Skin and Peripheral Blood Mononuclear Cells of Patients with Systemic Sclerosis? 
Jessica K. Gordon1, Robert Spiera2, Jamie N. Mersten3, Horatio F. Wildman4, Ziad Taimel3, Neil Hackett3, Sasa Vukelic5, Kyriakos A. Kirou6 and Mary K. Crow5. 1 Johns Hopkins University, Baltimore, MD, 2 Johns Hopkins University

Objectives: Given the potential for imatinib to inhibit tyrosine kinases in vascular endothelial cells, express them on vascular cells, and cause their release from platelets, we investigated the hypothesis that treatment with imatinib may lead to modulation of gene expression in skin and blood. 

Methods: Gene expression in blood mononuclear cells (PBMC) of treated patients with diffuse cutaneous (dc)SSc was measured using the Affymetrix Human U133 Plus 2.0 GeneChip. 

Results: Paired t-tests were performed using Genespring GX11 and Ingenuity Pathways was used to evaluate pathways of interest.

Conclusions: Treatment with imatinib may lead to modulation of gene expression in skin and PBMC. Hierarchical clustering in PBMC is supportive of a treatment effect. One common pathway affected in skin and blood is P38 MAPK signaling which was not expected but which may be pathogenically relevant in the transdifferentiation of myofibroblasts. It is important to note that the changes seen are modest and do not stand up to statistical correction for multiple testing in this small number of patients. We plan to analyze this data in the context of several controls – treated patients without clinical improvement, longitudinal disease controls, and healthy controls. Validation of this microarray data by qPCR is planned.

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1991

Enhanced Expression of Ephrins and Thrombospondins in the Dermis of Patients with Early Diffuse Systemic Sclerosis: Potential Contribution to Perturbed Angiogenesis and Fibrosis. 
Jorge Avouac1,2, Maud Clemmesty1, Jorg H. W. Distler3, Jean Marie Gasc4, Barbara Ruiz4, Marie Cecile Vacher-Lavenu5, Julien Wipff6, Andre Kahane2, Catherine Boileau2, Pierre Corvol7 and Yannick Allanoere8. 1 INSERM U781, Necker Hospital, Paris, France, 2 INSERM U783 and College de France, Paris, France, 3 Paris Descartes University, Pathophysiology Department, Cochin Hospital, Paris, France, 4 Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP, Paris, France, 5 Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP, Paris, France, 6 INSERM U781, Necker Hospital, Paris, France, 7 Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP, Paris and INSERM U781, Necker Hospital, Paris, France, 8 University of Erlangen, Erlangen, Germany

Objectives: Ephrins have emerged as essential regulators of angiogenesis and thrombospondins are inhibitors of angiogenesis and strong promoters of fibrosis that are both involved in systemic sclerosis (SSc). Our aim was to investigate whether ephrins and thrombospondins contribute to the dysregulation of angiogenic homeostasis related to systemic sclerosis (SSc) and to the pathologic activation of SSc dermal fibroblasts.

Methods: Skin biopsies were obtained from 8 patients with early diffuse cutaneous subset and from 4 healthy volunteers, matched for age and sex with SSc patients. Skin biopsy samples were taken from both clinically involved and
non-involved skin. Dermal fibroblasts were cultured from control and clinically involved and non-involved SSc skin. Ephrin (EphB4 and EphB2) and thrombospondin (TSP-1 and 2) mRNA and protein levels were analyzed in skin tissue respectively by in situ hybridization and immunohistochemistry. EphB4/EphB2 and TSP-1/2 mRNA and protein levels were assessed in SSc and control dermal fibroblasts in basal conditions and after stimulation by TGFβ or 6 hours of hypoxic exposure. Ephrin and thrombospondin expression was also determined in SSc and control dermal fibroblasts cultured with a pan-TGFβ blocking antibody.

**Results:** Increased mRNA and protein levels of EphB2 and EphB4 were detected in clinically involved skin of SSc patients. EphB2, but not EphB4, was also upregulated in clinically non-involved skin. The expression of Ephrins was restricted to the vessels. Low levels of EphrinB2 and EphB4 were detected in control and SSc cultured dermal fibroblasts, in basal conditions or after stimulation by TGFβ or hypoxia, suggesting that fibroblasts do not produce ephrins. TSP-1 and 2 were upregulated in SSc skin biopsies taken from both involved and non-involved skin. Their expression was mainly detected in the extracellular matrix located at the periphery of vessels. The overactivation of TSP-1 and TSP-2 persisted in cultured SSc dermal fibroblasts issued from involved and non-involved skin, and might contribute to the activated phenotype of SSc fibroblasts. Culture with TGFβ blocking antibody markedly reduced the upregulated expression of TSP-1 and TSP-2 in SSc dermal fibroblasts.

**Conclusion:** We investigated for the first time the expression of EphB4/EphB2 and TSP-1/TSP-2 expression in the skin and in dermal fibroblasts of patients affected by SSc. EphB4 and EphB2 are upregulated in clinically involved and non-involved SSc patients, suggesting their participation in SSc perturbed angiogenesis. TSP-1 and 2 are upregulated in both clinically involved and non-involved SSc skin and are constitutively activated in a TGFβ dependent/hypoxia independent manner in SSc dermal fibroblasts. Further studies are now warranted to assess the role of TSP-1 and TSP-2 respectively in the early activation of TGFβ and in the assembly of extracellular matrix proteins accumulated under the overproduction of TGFβ.

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**1992**

**Enhanced IL-17A and IL-22 Production by Peripheral Blood Mononuclear Cells Distinguish Systemic Sclerosis from Healthy Individuals.** Niccolò C. Brembilla1, Marie-Elise Truchetet1, Elisa Montanari1, Yannick Allanore3 and Carlo Chizzolini1. 1Immunology & Allergy, Geneva University Hospital, Geneva, Switzerland, 2Rheumatology, Cochin Hospital, Paris, France

In systemic sclerosis (SSc) inappropriate T cell responses are thought to participate in initiating events ultimately leading to excessive extracellular matrix deposition and fibrosis. The pattern of cytokine production distinguished T cell subsets with distinct functional capabilities and the pattern of chemokine receptor expressed at the surface of T cells participate to the code used for homing in peripheral tissues, including the skin. Aim of the present work was to assess whether T cells present in the peripheral blood (PB) of SSc patients could be distinguished from those of healthy controls in terms of cytokine production and whether the chemokine receptor expression on T cells could further predict their functional subset and homing capacity.

PB mononuclear cells and clinical characteristics were obtained from 19 immunosuppressant agents naive SSc and 18 healthy controls (Ctrl) upon informed consent and approval by the ethical committee. Multiparameter cytofluorimetric analysis was performed to assess the surface expression of CD4, CD45RA,CCR4,CCR6,CCR10, CXCR3, and CD161 as well the intracellular accumulation of IL-17A, IL-22, IFN-gamma, and IL-4 upon activation by CD3/CD28 croslinking in PB mononuclear cells at time 0 and after 7 days of culture. The results were stratified according to the presence of SSc, limited (lSSc) or diffuse disease (dSSc). The results of the various patient populations were compared using the Mann Whitney U test and correlations between variables computed using the Spearman r test.

SSc individuals had higher frequencies of CD4+ T cells and higher frequencies of IL-17A and IL-22 producing CD4+ T cells both at time 0 and upon 7 days of culture when compared to Ctrl. A significant increase in IL-4 production was observed only in the dSSc subset. The intracellular levels of IL-17A and IL-22 with the exclusion of IFN-gamma were tightly correlated indicating co-production by the same CD4+ T cell in SSc and not in Ctrl.

When the expression level of various chemokine receptors on CD4+ T cells was taken into account, the production level of IL-17A was positively correlated with the lack of CXCR3 expression (p = 0.0009) and particularly so in the CXCR3-CXCR6+ subset (p = 0.0006). Furthermore, the frequency of CD161+ CD4+ T cells was higher in SSc than in Ctrl.

Our results for the first time show that increased IL-17A is accompanied by IL-22 but not IFN-gamma production in SSc CD4+ T cells, thus stressing a preferential Th17 cell expansion in SSc. Furthermore, the production of these cytokines correlated with the expression levels of chemokine receptors important for skin homing, strongly indicating that they may participate to dysregulated matrix deposition at least in this target organ. These results provide a rationale for targeting IL-17 and the Th17 differentiation pathways as novel approaches to harness the clinical course of SSc.

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**1993**

**Gd Compounds Signaling through Toll-Like Receptors 4 and 7 in Normal Human Macrophages: Establishment of a Proinflammatory Phenotype and Implications for the Pathogenesis of Nephrogenic Systemic Fibrosis.** Peter J. Wermuth1 and Sergio A. Jimenez2. 1Jefferson Institute of Molecular Medicine and Division of Connective Tissue Diseases, Thomas Jefferson University, Philadelphia, PA, 2Thomas Jefferson Univ, Philadelphia, PA

**Purpose:** Nephrogenic Systemic Fibrosis (NSF) is a progressive and generalized disorder occurring in some patients with renal insufficiency following exposure to Gd based contrast agents (GdBCA). Previous studies showed that GdBCA induced, normal human macrophages to secrete increased levels of profibrotic and proinflammatory cytokines but the mechanisms involved are not known. Increased production of proinflammatory cytokines by macrophages is often triggered via signaling through Toll-like receptors (TLRs) or Nod-like receptors (NLRs), which recognize bacterial and viral components based on common molecular shapes. Here, we examined the hypothesis that GdBCAs can signal through one or more TLRs or NLRs.

**Methods:** Normal human differentiated macrophages were exposed to 50 mM Omniscan® or saline. RNA was isolated and examined employing Affymetrix human U133 2.0 Plus Microarrays and the data was analyzed by Volcano Plot and pathway analysis (DAVID; NIH). Human embryonic kidney 293 (HEK293) cells engineered to express one of seven different human TLRs (TLR2, 3, 4, 5, 7, 8 and 9) or two human NODs (NOD1 and 2) were exposed for 24 h to varying concentrations of Gd compounds Gd-DTPA, Dotarem®, Multihance®, ProHance®, OptiMark®, Omniscan®, gadodiamide, Gd-EDTA or Gd-Citrato or to caldiamide, the chelate molecule present in Omniscan®. The signaling activity of each compound was evaluated on its ability to activate expression of a reporter gene under control of an NFκB promoter. Macrophages were pretreated with inhibitory and control peptides targeting the TLR downstream effectors NPκB followed by exposure to Omniscan®. RNA was isolated and proinflammatory cytokine expression measured by real-time PCR.

**Results:** Pathway analysis of differential gene expression of normal differentiated human macrophages exposed to Omniscan® suggested the involvement of TLR signaling. Studies using engineered HEK293 cells each expressing one of a panel of human TLRs or NODs identified TLRs 4 and 7 mediating activation of the NFκB dependent reporter gene following exposure to 5 mM Omniscan® or gadodiamide. Subsequent testing in HEK293 cells expressing either TLR4 or TLR7 showed that Omniscan® and gadodiamide strongly activated TLR4 and TLR7-mediated reporter gene expression in a concentration dependent manner. No or minimal activity was observed for Gd-DTPA, Dotarem®, MultiHance®, ProHance®, OptiMark®, Gd-EDTA and Gd-Citrato. Inhibition of activation of the TLR downstream effector molecule NFκB with specific inhibitory peptides in normal differentiated human macrophages strongly blocked Omniscan®-induced expression of proinflammatory cytokines.

**Conclusions:** We demonstrate that Omniscan® and gadodiamide induce expression of an NFκB dependent reporter via TLRs 4 and 7. Further, we demonstrate that blocking the TLR effector molecule NFκB greatly reduces the Omniscan® dependent expression of proinflammatory molecules in normal human macrophages. The ability of GdBCA to signal via TLRs results in increased production of proinflammatory/ profibrotic cytokine and growth factor expression by normal human macrophages may be an important component in the pathogenesis of NSF.

**Disclosure:** P. J. Wermuth: GE Healthcare, 2; S. A. Jimenez: GE Healthcare, 2.
**1994**

**Genome-Wide Association Study in Systemic Sclerosis**, Yannick Allane*, Mohammad Saad†, Philippe Dieude†, Catherine Boileau†, Maria Martinez‡ and GENESYS Consortium.† Biochimie A. Pâris Hospital, Université V5Q, Boulogne, France, †INSERM U563 Université Paul Sabatier, Toulouse, France, ‡INSERM U563 Université Paul Sabatier, Toulouse, France, ¶Rhumatologie, Inserm u699, Bichat, Paris Diderot Universite, France, ‡Université Paris Descartes, Rhumatologie A, INSERM U781, Paris, Paris, France

Systemic sclerosis (SSc) is an orphan multi-organ disease affecting the immune system, the microvascular network and the connective tissue. SSc leads to major disability and premature death. Epidemiological data suggest a complex genetic etiology.

To dissect genetic susceptibility to SSc we have performed a genome-wide association study in 654 SSc patients of French Caucasian origin from the GENESYS study, and 2,543 French controls (subjects without SSc from GENESYS project and neurologically healthy subjects from the Three-City cohort- Lambert et al, Nat Genet. 2009;41:1094–9). Subjects were genotyped using the Illumina Human 610 QUD bead chip. The final post-QC discovery (stage-1) sample comprised 564 SSc cases and 2,466 controls, and a total of 489,814 SNPs passed quality control criteria. Association was tested using logistic regression assuming additive genetic effects and adjusted for the two principal components to account for population substructure. The genome-wide association results revealed a number of SNPs with strong evidence (P<10−5) of association. Interestingly, in our discovery sample, stronger signals were detected for 6 non-HLA SNPs that spanned 5 distinct genomic loci. Two SNPs belong to a candidate gene previously reported associated with other autoimmune disease of high relevance with regards to SSc pathogenesis. Furthermore, the remaining 4 SNPs are located on 3 previously unreported putative SSc loci. 2 SNPs are close to genes coding for neuro-mediators and 1 SNP is close to a metabolic gene recently showed to deeply contribute to extra-cellular matrix remodeling.

**1996**

**IL-6 Overexpression in Early dcSSc Associates with Poor Clinical Outcome and May Drive Fibrotic Response**, Korsa Khan1, Shiwen Xu1, Christopher P. Denton2 and Voon Ong1. 1Center for Rheumatology and Connective Tissue Diseases, UCL Medical School, Royal Free Hospital, London, United Kingdom, 2Royal Free Hospital, London, United Kingdom

**Introduction:** We previously reported that thrombocytosis may identify a subgroup of diffuse SSc with elevated IL-6 and a high modified Rodnan skin score (mRSS). In this study, we explore the predictive value of IL-6 overexpression in dcSSc and its potential role in driving fibrosis.

**Method:** Expression levels of IL-6 were examined with immunohistochemistry and Western blot analysis. Skin biopsies from patients with early dcSSc and thrombocytosis (n=10, mean platelet count: 472 × 10³/µL, mean disease duration: 12 years) were used in this study. IL-6 ligand and receptor levels were measured in the supernatant from cultured SSc fibroblasts and their effect on collagen production was studied in normal fibroblasts stimulated with recombinant IL-6.

**Results:** To explore the potential link between IL-6 levels and clinical outcome in dcSSc, serum IL-6 from 39 patients (74% female) was quantified by ELISA. The cases were categorised into high IL-6 (≥10pg/ml) and low (<10pg/ml) cohorts. Association between IL-6 levels at presentation and mRSS at 36 month from disease onset was determined by Pearson’s correlation. Mean difference of mRSS between the cohorts of IL-6 expression over the 36 month period was compared by Student t-test. Difference in survival between cohorts was examined using Kaplan-Meier methods.

**Conclusion:** There was significantly greater dermal IL-6 expression in patients with early dcSSc and thrombocytosis than patients with established dcSSc. Prominent staining for IL-6 was associated with dermal vascular structures and mononuclear inflammatory infiltrate in 8/10 (80%) patients with early dcSSc and with fibroblastic staining. Moderate vascular expression for IL-6 was observed in 4/12 (33%) controls. Similar expression pattern was observed in 2/8 (25%) patients with established dcSSc with faint staining for IL-6 in some dermal fibroblasts and inflammatory infiltrates.

**Results:** IL-6 ligand and receptor levels were elevated in supernatant from SSc fibroblasts (n=3) by 17-fold and 13-fold (Densitometric Image Unit, DIU p<0.05), respectively. Collagen was upregulated by at least 5-fold in SSc fibroblasts and similar induction by recombinant IL-6 (20 ng/ml) was observed in normal fibroblasts (17.94 ± 3.41 vs 2.18 ± 1.85 DIU control, p<0.05). This was partially abrogated with neutralising antibody against IL-6 receptor (4.26 ± 2.07 DIU, p<0.05). Interestingly, serum IL-6 level at presentation positively correlated with mRSS at 36 months follow-up in dcSSc cases with available data (r=0.81, p<0.01, n=16). There was a significant difference in mean mRSS between the two groups based upon IL-6 expression (10.9, 95% Confidence interval, 3.8, 18.2, p<0.01). Kaplan-Meier analysis showed that the 5-year survival was 93% and 81% in the group with low and high IL-6 levels respectively (p=0.02, log rank test).

**Conclusions:** These results confirm overexpression of IL-6 in selected
cases of dSSc and support the utility of IL-6 as a surrogate marker for our outcome. Also, provides strong support for the potential benefit of targeting the IL-6 axis in some cases of early dSSc.

Disclosure: K. Khan: None; S. Xu: None; C. P. Denton: None; V. Ong: None.

1997


Purpose: Tissue fibrosis, most prominent in the skin, lungs, and microvasculature, is the pathological hallmark of systemic sclerosis (SSc). The origin of the mesenchymal cells responsible for the tissue and vascular fibrosis in SSc has not been fully identified. Recent studies have shown that transdifferentiation of endothelial cells into myofibroblasts via endothelial-to-mesenchymal transition (EndoMT) may participate in the development of tissue fibrosis in various fibrotic diseases. Here we used small molecule kinase inhibitors to investigate the signaling pathways involved in TGF-β-induced EndoMT in murine pulmonary endothelial cells (EC) to identify potential therapeutic targets for the fibroproliferative vasculopathy characteristic of SSc.

Methods: Primary mouse pulmonary EC were isolated by immunomagnetic methods employing sequential anti-CD34 and anti-CD102 antibody selection. The induction of EndoMT was assessed by immunofluorescence and Western blot for α-smooth muscle actin (α-SMA) expression. Expression of the transcriptional repressor Snail-1 was examined by RT-PCR. Western blot of cell lyases and immunofluorescence staining of cultured cells. The signaling pathways involved were examined employing small molecule kinase inhibitors.

Results: 1) TGF-β1 induced α-SMA and type I collagen expression in primary pulmonary EC. The induction of α-SMA in pulmonary EC by TGF-β was mediated by a marked increase in Snail-1 expression, evidenced both at mRNA and protein levels. 2) The TGF-β-induced α-SMA and Snail-1 expression was abolished by treatment with either the c-Abl kinase inhibitor, imatinib mesylate, or the PKC-δ inhibitor, rottlerin. Imatinib mesylate also inhibited Snail-1 mRNA expression (Figure) and α-SMA stress fiber organization. 3) The effects of imatinib mesylate and rottlerin were not mediated by PI-3 kinase or Smad-2 phosphorylation but were mediated by inhibition of GSK-3β. The results suggest that mice harboring a fibroblast-specific deletion of GSK-3β displayed accelerated wound closure, increased fibrogenesis, and excessive scarring. Fibroblasts isolated from those mice showed increased expression of α-smooth muscle actin and contraction of extracellular matrix. Thus, these results suggested that the presence of the active GSK-3β played a crucial role in maintaining physiological levels of extracellular matrix proteins and normal wound healing. The specific way in which GSK-3β participates in regulation of fibrosis is currently not well understood. Here, we studied the effects of GSK-3β activity modulation on the expression of COL1A1 in human dorsal fibroblasts derived from patients with systemic sclerosis (SSc). Thus, the fundamental purpose of this study was to determine whether GSK-3β should be considered a target to treat SSc and other fibrotic disorders.

Methods: Normal and SSc dermal fibroblasts were treated with various concentrations of two different GSK-3β inhibitors: (i) Inhibitor XV (EMD4 Biosciences) and (ii) inhibitor IX (BIO, Cayman Chemical). In addition, normal dermal fibroblasts treated with TGF-β were also analyzed. Following treatment with the GSK-3 inhibitors the expression of collagen I at protein and mRNA levels was analyzed by Western blot assays and RT-PCR, respectively.

Results: Quantitative Western blot assays demonstrated that, in comparison to non-treated cells, both normal and SSc dermal fibroblasts cultured in the presence of either GSK-3β inhibitor produced significantly less collagen I. Furthermore, GSK-3 inhibitors also abrogated the stimulation of COL1A1 expression induced by TGF-β. A similar decrease was also observed at the level of expression of COL1A1.

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1999

Inhibition of Glycogen Synthase Kinase (GSK)-3β Downregulates Collagen I Gene Expression in Normal and Scleroderma Fibroblasts and Abrogates the Profibrotic Effects of Transforming Growth Factor β (TGF-β). Jolanta Fertala and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, PA

Background and Purpose: GSK-3β is a ubiquitously expressed, highly conserved serine/threonine protein kinase which phosphorylates numerous substrates including enzymes and transcription factors and it is a core component of many important cell signaling pathways. Recently, GSK-3 has emerged as an important participant in wound healing and fibrosis. In particular, it has been shown that mice harboring a fibroblast-specific deletion of GSK-3β displayed accelerated wound closure, increased fibrogenesis, and excessive scarring. Fibroblasts isolated from those mice showed increased expression of α-smooth muscle actin and contraction of extracellular matrix. Thus, these results suggested that the presence of the active GSK-3β played a crucial role in maintaining physiological levels of extracellular matrix proteins and normal wound healing. The specific way in which GSK-3β participates in regulation of fibrosis is currently not well understood. Here, we studied the effects of GSK-3β activity modulation on the expression of COL1A1 in human dorsal fibroblasts derived from patients with systemic sclerosis (SSc). Thus, the fundamental purpose of this study was to determine whether GSK-3β should be considered a target to treat SSc and other fibrotic disorders.

Methods: Normal and SSc dermal fibroblasts were treated with various concentrations of two different GSK-3β inhibitors: (i) Inhibitor XV (EMD4 Biosciences) and (ii) inhibitor IX (BIO, Cayman Chemical). In addition, normal dermal fibroblasts treated with TGF-β were also analyzed. Following treatment with the GSK-3 inhibitors the expression of collagen I at protein and mRNA levels was analyzed by Western blot assays and RT-PCR, respectively.

Results: Quantitative Western blot assays demonstrated that, in comparison to non-treated cells, both normal and SSc dermal fibroblasts cultured in the presence of either GSK-3β inhibitor produced significantly less collagen I. Furthermore, GSK-3 inhibitors also abrogated the stimulation of COL1A1 expression induced by TGF-β. A similar decrease was also observed at the level of expression of COL1A1.

Disclosure: A. Francois: None; D. Wachsmann: None; J. Sibilia: None; J. E. Gottenberg: None.

1998

In Systemic Sclerosis, Cooperation between B-Cells and Skin Fibroblasts Promotes Fibrogenic Cytokines and Collagen Production. Antoine Francois1, Dominique Wachsmann1, Jean Sibilia2 and Jacques E. Gottenberg2. 1Strasbourg Hospitals, Illkirch Graffenstaden, France; 2Strasbourg Hospitals, Strasbourg, France; 1Université de Strasbourg, Illkirch Graffenstaden, France

Background: B-cells might play a role in the induction of skin and pulmonary fibrosis in systemic sclerosis. BAFF and APRIL, key cytokines for B-cell activation, are increased in serum and skin from patients with systemic sclerosis. The role of B-cells in fibrosis has been demonstrated in several studies (Novobrantseva, 2005, Komura, 2008) but the mechanisms implicated in B-cells and fibroblasts collaboration as well as the role of BAFF remains unclear. We therefore cocultivate B-cells and fibroblasts and assessed the release of soluble collagen and fibrogenic cytokines.

Methods: We performed cocultures of blood B cells and SSc skin fibroblasts stimulated with BAFF. IL-6, IL-1β, TGF-β1, and CCL2 mRNA expression was determined by quantitative RT-PCR. Cytokine release was evaluated by ELISA. We also analysed the release of soluble collagen in cell culture supernatants using the Sircol Collagen Dye.

Results: Coculture of skin fibroblasts isolated from SSc patients with blood B-cells induced IL-6 (35ng/mL), TGF-β1 (200pg/mL) and CCL2 (6300pg/mL) release in culture supernatants. IL-1β, which is a strong inducer of collagen, was not detected. Interestingly, BAFF stimulation increased IL-6 (315ng/mL) and CCL2 (17ng/mL) release in cell culture supernatants but TGF-β1 was not modified. We also showed that coculture of SSc fibroblasts with B-cells increased the production of soluble collagen by fibroblasts (from 25mg/mL for fibroblasts alone to 113mg/mL with B-cells) but this effect was not enhanced in presence of BAFF.

Conclusion: Taken together, these data suggest that interaction of B-cells with SSc fibroblasts promotes the production of fibrogenic cytokines and soluble collagen. We found that BAFF enhanced the release of cytokines but had no direct effect on collagen synthesis.

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Figure: Analysis of expression of collagen I in normal and scleroderma fibroblasts treated with a GSK-3 inhibitor.
Conclusion: These data demonstrate that inhibition of GSK-3β activity results in a significant decrease in the expression and production of collagen I. These data are in contrast with the previously published study demonstrating that conditional GSK-3 knock-out in mice was associated with accelerated fibrosis. Our observation that inhibiting GSK-3 activity in SSC fibroblasts is associated with a substantial decrease of production of collagen I suggests that this enzyme may be a potential target for treatment of SSC and other fibrotic disorders.

Disclosure: J. Fertala: None; S. A. Jimenez: None.

2000

Insights into the Pathogenesis of Systemic Sclerosis Vasculopathy Based on Gene Expression Profile of Endothelial Cells Issued from Progenitors.

Objective: To determine the pattern of gene expression in endothelial cells (ECs) derived from late outgrowth endothelial progenitor cells (EPCs), in basal conditions and after hypoxic exposure, in patients with systemic sclerosis (SSc).

Methods: Late outgrowth EPCs were isolated from the peripheral blood of 10 SSc patients (5 limited and 5 diffuse cutaneous subset) and 5 healthy controls matched for age and sex. Total RNA was extracted and amplified from these cells in basal conditions and after 6 hours of hypoxic exposure. Affymetrix Human Genome HGU133 plus 2.0 Array microarrays were used. The data was analyzed in the GeneSpring program, and potential pathways were identified with the Ingenuity software. Validation of genes of interest was performed by quantitative RT-PCR. Protein expression of identified mediators was then assessed in SSC and control skin sections by immunohistochemistry.

Results: Signals from 92 probe sets (33 known genes) were different from controls in basal conditions. The largest group of transcripts included 9 genes related to cell-to-cell interaction. Within this group, was identified in SSc-EPC-derived cells a downregulation of tumor necrosis factor ligand superfamily member 10 (TNFSF10, odds ratio, OR: 0.5, p=0.04), which prevents the interaction between PBMCs and ECs. Signals from 188 probe sets (53 known genes) were different from controls after hypoxic exposure. The largest group of transcripts included 5 genes involved in the regulation of vascular remodeling. Within this group, was identified in SSc-EPC-derived cells a downregulation of homeobox gene HOXA9 (OR: 0.5, p=0.02), which play a role in the activation of ECs. A respective 2 and 1.5-fold downregulation of TNFSF10 mRNA levels in basal conditions and HOXA9 mRNA levels after hypoxic exposure in SSC-EPC-derived cells further validated these observations. In SSC and control skin sections, no differential expression of TNFSF10 and HOXA9 was found. Signals from 221 and 307 probe sets (92 and 307 known genes) were different from controls in basal conditions and after hypoxic exposure respectively. Included among these transcripts was a group related to inflammatory response. In particular, was identified after hypoxic exposure, in EPC-derived cells from patients with diffuse SSC, an upregulation of tumor necrosis factor alpha-induced protein-3 (TNFAIP3, OR: 1.5, p=0.04) and prostaglandin-endoperoxide synthase-2 (PTGS2, OR: 1.75, p=0.02). Quantitative RT-PCR analysis confirmed the upregulation of these two genes (respectively 1.5 and 2-fold), TNFAIP3 and PTGS2 were also overexpressed in the skin of patients with the diffuse cutaneous subset.

Conclusion: Our data reveal important gene expression changes in EPC-derived cells from SSc patients, characterized by a proadhesive and activated profile. Our results also support a proinflammatory profile of these cells in the diffuse cutaneous subset. These results emphasize the presence of an endothelial signature in SSC and point to novel mediators in this disease that warrant more in-depth exploration to increase the understanding of the pathogenesis of this incurable disease.

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2001

PDGF Receptor as Therapeutic and Diagnostic Target in Systemic Sclerosis.

Background: Systemic sclerosis or scleroderma (SSc) is a disease characterized by fibrosis of skin and visceral organs. We have provided evidence that the serum of SSc patients contains stimulatory auto-antibodies (auto-abs) directed to the PDGF receptor (PDGFR) that elicit Ha Ras-ERK 1/2 signaling and collagen production in normal human fibroblasts in vitro (Baroni SS et al. NEJM 2006). A recent study (Olson LE, Soriano P, Dev Cell 2009) has confirmed the central role of increased PDGFR activation and signaling in driving systemic fibrosis in vivo in transgenic mice.

Objectives: To identify the epitopes of PDGFR extracellular domains bound by stimulatory auto-abs. This information will be used to generate i) PDGFR selective inhibitors and ii) binding assays for detection of functional auto-abs in serum.

Methods and Results: IgG-positive memory B cells obtained from peripheral blood of SSc patients were immortalized by EBV infection. Supernatants of individual lymphocyte clones were screened by immunofluorescence and flow cytometry for the ability to react selectively with F alpha cells (mouse fibroblasts expressing the human PDGFR alpha), but not with F→-/ cells (mock-transfected mouse fibroblasts). Positive clones were further screened for the production of antibodies stimulating reactive oxygen species (ROS) generation in normal human fibroblasts in vitro. Positive clones were expanded in serum-free medium, IgG were purified from supernatants and tested to confirm both binding and biological activity on fibroblasts. mRNA was obtained from such positive B cell clones for sequencing and cloning of antibody variable regions into a human IgG expression vector. Human IgG constructs were expressed in CHO cells, recombinant (rec.) monoclonal antibodies (mAbs) were purified from medium and tested by immunoprecipitation and stimulation experiments. These rec. monoclonal human IgG showed different extents of PDGFR binding and stimulation. Few mAbs displayed the properties identified in total IgG pools purified from serum of SSc patients, since they bound to PDGFR and induced ROS, p-ERK and type I collagen gene expression in normal human fibroblasts. Molecular docking simulation indicated that the PDGFR epitopes bound by stimulatory mAbs differ from those of non-biologically active mAbs.Envelope mapping was confirmed by binding competition experiments using a rec. PDGFR immobilized onto a biosensor. A peptide library is under construction to further define the map of PDGFR epitopes targeted by the different mAbs.

Conclusions: We identified the specific epitopes bound by functional PDGFR auto-abs that trigger PDGFR signaling. This information is shedding light on the structure of active PDGFR domains, on SSc pathogenesis, and can be used to devise new therapeutic strategies to block PDGFR signaling and, specifically, the progression of SSc. Moreover, synthetic polypeptides corresponding to these functional PDGFR domains will be employed to selectively detect stimulatory auto-abs in serum, possibly implicated in the early phases of SSc pathogenesis.

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2002

Proteomic Analysis of Systemic Sclerosis Serum Identifies the Toll-Like Receptor Agonists S100A4/A8 as a Novel Possible Pathogenic Marker.

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**Background:** Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of the skin and the internal organs. The etiology is still unknown but prominent features are vascular injury and chronic inflammation resulting in fibrosis. Except for anticientromere and antitopoisoensare I antibodies there are no markers available that predict SSC susceptibility and/or prognosis. This study is the first study that exploits a proteome-wide profiling to identify new targets in the pathogenesis of SSC.

**Method:** 40 SSc patients were included for initial proteomic identification. Patients were stratified as having diffuse SSC (dSSC) (n= 19) or limited SSC (lSSC) (n= 21) according to the extent of skin involvement. As controls 20 healthy donors were included. Blood was drawn and serum was stored before analyzing with the SELDI-TOF-MS. In the first run 10 dSSC patients, 10 lSSC patients and 10 healthy controls were measured as a training set. The rest of the samples were then use as a validation of the training results. SELDI-TOF-MS technology consists of three major components: the ProteinChip array, a mass spectrometer and the data analysis software. For replication a cohort compromising 30 dSSC patients and 60 lSSC was available.

**Results:** Analysis revealed a list of 29 masspeaks of interest of which 21 could be predicted using Tagident. Six peaks were increased in dSSC and three peaks in lSSC, 18 peaks were increased in both disease subtypes. One of the main significant peaks was S100A8. Since accumulating evidence points to a crucial role of toll like receptors in SSC, and S100A8 is reported to be an endogenous TLR ligand, we next aimed to replicate the increased expression of S100A8. Further stratification for SSC disease phenotype reveals it to be increased solely in lSSC patients with lungfibrosis. This finding is replicated with an ELISA in 60 lSSC patients S100A8/A9 being 415 pg/ml in lSSC without lungfibrosis and 659 pg/ml in lSSC with lungfibrosis (p<0.05) (fig 1). Furthermore we show an increased presence of S100A8 in SSC skin sections.

**Conclusion:** This is the first study identifying new targets in SSC using proteome wide profiling in serum. S100A8 revealed to be increased specifically in lSSC patients with lungfibrosis. This finding is replicated with an ELISA in 60 lSSC patients and 60 lSSC was available.

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2004


**Objectives:** To investigate the role of X chromosome inactivation (XCI) in systemic sclerosis and its effects on Foxp3 expression in T regulatory cells.

**Methods:** A total of 217 female SSc patients and 107 female healthy controls were included. From these subjects DNA was isolated from total PBMCs, plasmacytoid dendritic cells, T cells, B cells, myeloid dendritic cells and monocytes after magnetic bead separation. All samples were assessed for skewed XCI patterns with the HUMARA assay. Outcome was assessed with linear regression. Next, CD4+CD25+ cells were isolated and intracellular Foxp3 expression was assessed by flowcytometry.

**Results:** Skewing was not associated with increased age in SSC, in contrast to the controlpopulation (r=0.45, P<0.001). Taking this into account, we found a significantly higher frequency of skewed XCI in SSc patients (P=0.001) compared to controls. No difference in skewing was observed between the immune cell subsets. In addition, we found a higher concentration of Foxp3+ cells, exhibiting a lower Foxp3 MFI in the SSc patients with profound XCI skewing (both P<0.001), associated with less efficient suppressive activity (P=0.012).

**Conclusions:** Skewed XCI plays a role in susceptibility to SSC, is not restricted and influences Foxp3 expression and suppressive capacity of Tregs.

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Structural and Vasomotor Dysfunction in the Thoracic and Pulmonary Vessels of the Tight-Skin 1 (Tsk-1/+) Mouse: Role of Endogenous Nitric Oxide

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Center for Rheumatology and Connective Tissue Diseases, UCL Medical School, London, United Kingdom; Centre for Pharmacology, UCL Medical School, Rayne Institute, London, United Kingdom; Institute of Structural and Molecular Biology, UCL Medical School, London, United Kingdom; Royal Free Hospital, London, United Kingdom; University College London, London, United Kingdom

Background: Systemic sclerosis (SSc) is a disease that features excessive collagen overproduction, fibrosis, as well as large and small vessel dysfunction. Previously we have shown that nitric oxide (NO), an important physiological signalling molecule and vasodilator, has abnormal metabolism in the skin of SSc patients and in the scleroderma-like syndrome of the tight-skin 1 (Tsk-1/+) mouse, an experimental model predisposed to the development of a connective tissue disease (CTD). The present study investigates contractile dysfunction and also the role of NO, in the thoracic aorta and pulmonary artery of the Tsk-1/+/ mouse.

Methods: Thoracic aortae and pulmonary arteries from heterozygous TSK-1+/− mice (age: 4, 8, 12 months) were compared with piallittered mice as control. Histology was used to stain sections for collagen or elastin expression. Vessel wall structure was further assessed by EM microscopy, and soluble collagen quantified by Sirius assay. Vascular isometric tension measurements of contractile function were studied using an organ bath or small vessel myographs. Tsk-1+/− mice were compared with controls. L-NAME was used to inhibit endogenous NO production in aortic control vessels, by either pre-incubation with L-NAME (100 μM), or as control. Histology was used to stain sections for collagen or elastin expression. Vascular rings were also pre-incubated with L-NAME (100 μM), a specific NO synthase (NOS) inhibitor, or 1400W (5 μM), a specific inducible NOS inhibitor. The NO donor sodium nitroprusside (SNP; 1 mM–50 μM) was used to assess endothelial-dependent relaxation.

Results: In Tsk-1+/− thoracic aorta, using histological staining and EM microscopy we observed thickened of the aortic arch wall, disruption of the elastin fiber architecture, and elevated levels of collagen in the aortic adventitia. Aortic soluble collagen content was greater in the Tsk-1+/− group compared to controls. Isometric tension measurement revealed that both KCl and PE-induced contractions were reduced in aortic Tsk-1+/− vessels at all ages studied. PE-induced maximal responses (Emax) at 4 months were (Tsk-1/+) 217.2 ± 6.3 mg; control 411.0 ± 10.1 mg), at 8 months (Tsk-1/+) 322.5 ± 32.4 mg; control 618.1 ± 17.9 mg), and at 12 months (Tsk-1/+) 319.4 ± 44.7 mg; control 576.2 ± 31.0 mg). Similarly, at 4 months in pulmonary Tsk-1+/− vessels, PE-induced maximal responses were reduced. Inhibition of endogenous NO production in aortic control vessels, by either pre-treatment with L-NAME or removal of the endothelium, increased PE-induced contractions by 61% but had no significant effect in the aortic Tsk-1+/− group, indicating reduced basal NO bioavailability. Pre-treatment with 1400W had no significant effect on either group. SNP-induced endothelium-independent relaxations, completely dilated PE-induced contraction of both control and Tsk-1+/− aortas, indicating no difference in smooth muscle sensitivity to NO.

Conclusion: The pathogenesis of the Tsk-1/+(+) mouse model of CTD exhibits vasomotor dysfunction of the thoracic aorta that could be associated with increased collagen deposition and reduced NO bioavailability.

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2006

Th1 and Th17 Cytokine Signatures in Early Pediatric Localized Scleroderma

Kathryn S. Torok, Thaschawee Arkachaisri, Thomas A. Medsger, and Carol A. Feghali-Bostwick.

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Purpose: Skin fibrosis is a main characteristic of systemic sclerosis (SSc). Platelet-derived growth factor (PDGF) and its receptor (PDGFR) have been shown to play key roles in promoting fibrosis in SSc. Upon PDGF stimulation, the PDGFR is phosphorylated, and its downstream signaling pathways, including ERK1/2, are activated. The PDGFR is diphosphorylated by phosphatases, including protein tyrosine phosphatase 1B (PTP1B), and the signaling cascade is hence terminated. In addition, increased superoxide production is observed in SSc dermal fibroblasts compared to normal fibroblasts (NL). In this study we sought to determine whether the thiol-sensitive PTP1B is affected by oxidative stress in these cells, enhancing the ERK1/2 signaling pathway of PDGFR. The effect of the thiol antioxidant n-acetylcysteine (NAC) on PTP1B activity was also investigated.

Methods: SSc and NL fibroblasts were isolated from skin biopsies. Cells were stimulated with 30 ng/ml PDGF and phosphorylation of ERK1/2 as well as PTP1B levels were measured by Western blotting. A phosphate release assay was used to determine PTP1B activity. Superoxide was measured by dihydroethidium.

Results: Activation of PDGFR by PDGF resulted in phosphorylation of ERK1/2. In NL fibroblasts, ERK1/2 phosphorylation was maximal at 45 min (3 fold increase vs. unstimulated [US], p = 0.05, n = 5) and returned to baseline at 4 hr. In contrast, in SSc cells, ERK1/2 was significantly phosphorylated at 10 min and remained phosphorylated at 4 hr (2 fold increase vs. US, p = 0.05). PDGF increased PTP1B protein expression significantly at 45 min and 2 hr in NL. In contrast, PTP1B expression in SSc fibroblasts remained the same, and at 45 min the level of PTP1B in NLs was significantly higher than that in SSc.
peri-nuclear free radicals (ROS) and breaks in the genomic DNA. Systemic sclerosis (SSc) patients contain high levels of cytoplasmatic and nuclear SSc fibroblasts. The inability to dephosphorylate ERK1/2 in SSc fibroblasts suggests that the phosphatases that are responsible for ERK1/2 dephosphorylation are deficient in SSc. The ability to produce PTPIβ after PDGF stimulation, and hence terminate PDGF signaling, was hampered in SSc dermal fibroblasts. PTPIβ activity was significantly inactivated in SSc fibroblasts, which may have resulted from higher levels of superoxide than in NL. NAC treatment both restored the low PTPIβ activity and decreased superoxide levels in SSc dermal fibroblasts. This led us to introduce a new class of proteins dysregulated in SSc. Our study also provides a novel molecular mechanism by which NAC therapy may act on these proteins to benefit SSc patients.

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2008

The Wnt Signalling Inhibitor Gene, WIF1, Expression Is Downregulated in Fibroblasts Derived from Systemic Sclerosis Patients by a Persistent Oxidative Stress. Silvia Svegliati1, Giusi Marrone2, Antonella Greco2, Tatiana Spadoni2, Lucia De Gemmaro2, Gianluca Moroncini2, Enrico Avvedimento1 and Armando Gabrielli2. 1Dipartimento di Biologia e Patologia Cellulare e Molecolare, Università Federico II, Napoli, Italy, 2Dipartimento di Scienze Mediche e Chirurgiche, Università Politecnica delle Marche, Ancona, Italy, 3Oncogenomic Center, NOGEC, CEINGE, Italy.

Background: Systemic sclerosis is an autoimmune disease characterized by extensive fibrosis and vascular lesions. Primary fibroblasts derived from systemic sclerosis patients, which stimulate fibrosis, induced by unrestrained Wnt signaling. Negative regulators that interfere either with receptor-ligand binding or with transcription and quantitative real-time PCR. Total RNA isolation was performed with total RNA mini kit (BioRad) and reverse transcription PCR was performed using iScript cDNA synthesis kit from BioRad. Quantitative PCR was performed in triplicate with SYBR Green (Biorad).

Results: WIF gene expression was significantly down-regulated in cells derived from systemic sclerosis patients. Moreover, the gene was not methylated, as in breast cancer cells, and its expression was reactivated by inhibiting histone de-acyetylase enzymes, trichostatin (TSA). PDGF in 24 hours robustly stimulated WIF-1 expression and this effect was prevented by inhibiting NADPH oxidase. Prolonged oxidative stress induced by IgG SSc silenced WIF1 by triggering DNA damage. Inhibition of ATM kinase by the pan-ATM inhibitor KU-55933 rescued WIF expression in fibroblasts exposed to long term oxidative stress.

Conclusions: These data indicate that in SSc fibroblasts a persistent oxidative stress, triggered by PDGF or anti PDGF receptor autoantibodies, induce WIF-1 downregulation and possibly altered WNT signaling. Our data indicate that the ultimate cause of silencing WIF-1 is DNA damage.

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ACR Poster Session C
Vasculitis II
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

2009

Alveolar Hemorrhage (AH) in ANCA-Associated Vasculitis: Characteristics and Prognostic Factors in 65 Patients. Alex M. Kostianovsky2, Thomas Hauser3, Christian Pagnoux2, Pascal Cohen2, Eric Daugas2, Luc Mouthon2, Jean-François Cordier2 and Loïc P. Guillevin1. 1Hopital Cochin-Paris Univ, Paris, France, 2Internal Medicine, Hospital Cochin, APHP, Universite Paris Descartes, Paris, France, 3Nephrology, Assistance Publique de Paris, Paris, France, 3Pulmonology, Hopispe Civils de Lyon, Lyon, France

AH can be a mild or a life-threatening sign of ANCA-associated vasculitis, but its prognostic impact and specific characteristics have not been determined. To do so, we retrospectively analyzed AH episodes that occurred, between 1991 and 2010, in patients with ANCA-associated vasculitis entered in the EVSG database.

Patients and Methods: We selected confirmed AH cases, as assessed by the presence of hemoptysis and ground-glass images on X-rays or CT scans and/or bloody bronchoalveolar lavage fluid. Renal insufficiency was defined as creatinine >150 mmol/l. Severity criteria were: hypoxia, Hb decline >1 g/dl over 48 h after AH occurred and requiring mechanical ventilation.

Results: For the 65 cases (35 men and 30 women) analyzed, their mean age at the 1st AH episode was 53 years. ANCA-associated vasculitis diagnoses were: 55% Wegener’s granulomatosis (WG), 34% microscopic polyangiitis (MPA) and 9% Churg–Strauss syndrome (CSS). Pre-AH hemoptysis occurred in 41 (63%) patients: 39% the week preceding, 23.2% 2-4 weeks before and 19.5% >1 month prior to AH diagnosis, which led to ANCA-associated vasculitis diagnosis for 45 (69.2%) patients. Among 10 (15.4%) patients (4 WG, 4 MPA, 2 CSS) requiring mechanical ventilation, 4 had hemoptysis previously. Twenty-three (35%) patients were hypoxic and 23 (35%) had major Hb decreases; 36 (55%) had concomitant renal insufficiency (pusulo-renal syndrome): 18 WG (51% of all WG) and 18 MPA (81% of all MPA). Paucimmune glomerulonephritis was seen in 31/33 kidney biopsies. Intriguingly, no CSS patient had renal impairment when AH occurred.

Treatments included a combination of corticosteroids and intravenous cyclophosphamide (CYC) for 55 (85%) patients; oral CYC was used in 5, methotrexate in 4 and plasma exchange in 7. Rituximab and remicade were prescribed to 1 patient each. Mean time between AH and treatment onset was 5.87 (range 0–60) days. Mean follow-up was 8.3 years (range 1 month–19 years). Follow-up information was not available for 8 patients. A total of 38 (58%) patients relapsed: 7 with AH and other organ involvement, 21 with non-AH manifestation(s) and 10 with AH alone. Three patients underwent kidney transplantation.

The 13 (20%) deaths (6 WG and 7 MPA) were attributed to: septic shock for 4, lung cancer for 2, and 1 each of the following: bladder cancer, AH, sudden death, hemorrhagic stroke, ARDS due to misplaced nasogastric tube and probably drug-related (methotrexate). Although 9/13 patients with pulmo-renal syndrome died, no death resulted directly from the initial AH.

Conclusion: These findings highlight the importance of recognizing premonitory hemoptysis as an early sign of AH in ANCA-associated vasculitides, since 63% of the cohort patients had bloody sputum before AH was diagnosed. Also, patients with AH and renal insufficiency have poorer survival prognoses. As demonstrated by the five-factor score, AH alone is not predictive poor prognosis; conversely, kidney involvement dictates a poor outcome.

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Background: Hepatitis C virus infection is the main cause of mixed cryoglobulinemia vasculitis (CryoVas). Data are lacking regarding demographic, clinical and biological features of patients with non-infectious mixed CryoVas.

Objectives: To analyze the baseline clinical and biological features of type I monoclonal cryoglobulinemia vasculitis (CryoVas) diagnosed between January, 1995 and June, 2010. Demographical, clinical and biological data, as well as first line therapy, were assessed.

Results: Hundred and forty-five women and 60 men (sex ratio F/M 2.4), mean age 63.2 ± 14.6 years were included. Main causes of CryoVas included autoimmune disorders in 66 patients (31%) [mainly primary Sjögren syndrome in 56 and systemic lupus erythematosus in 4], and B-cell lymphoma in 44 (21%). Mixed CryoVas was essential in 101 patients (49%). At inclusion, clinical manifestations included purpura (74%), peripheral neuropathy (52%), glomerulonephritis (36%), Raynaud's phenomenon (27%), articulargia/arthritis (41%), skin ulcers (17%), skin necrosis (14%), gastrointestinal (6%), central nervous system (2%) and pulmonary involvement (2%). Immunohemological characterization and quantification of cryoglobulinaemia were available in 200 (95%) and 140 (66%), respectively. Cryoglobulinaemia was type II in 175 patients (88%) and type III in 25 (12%). Median cryoglobulin level was 0.36 g/L (0.05–10.0), and median C3 and C4 complement levels were 0.82 (0.14–1.94) and 0.04 g/L (0.01–0.44). Histological confirmation of vasculitis was available in 74%.

Most patients (n=194) were treated and received as first-line therapy corticosteroids in 85% [median dose of 57.5 mg/day (5–180)], cyclophosphamide in 24%, rituximab in 19%, plasma exchange in 14% [median number of 9 (2–46)], and colchicine in 4%. Seventeen patients (8%) were not treated because of mild symptoms attributable to CryoVas and followed-up before starting therapy (n=5) or refused treatment (n=1).

Conclusion: Our study is the largest clinical and epidemiological survey describing the features of type I monoclonal cryoglobulinemia vasculitis to date. Type I CryoVas was always associated with B-cell lymphoproliferative disorders, including malignant B-cell lymphoma in almost 50% of cases.

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Circulating Markers of Vascular Injury in ANCA-Associated Vasculitis.

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Background: There is a need for biomarkers associated with ANCA-associated vasculitis that are associated with disease activity, are useful in guiding clinical care, and reflect underlying pathophysiology. We investigated multiple markers of vascular injury and angiogenesis before and after induction of remission, in a large trial.

Methods: Subjects (n=127) enrolled in the Rituximab in ANCA-Associated Vasculitis (RAVE) trial were selected if they were in remission (BVAS/WG = 0) at 6 months after starting treatment with glucocorticoids and either rituximab or cyclophosphamide. Serum levels of E-selectin, ICAM-3, MMP1, MMP3, MMP9, P-selectin, thrombomodulin, and VEGF were measured by immunoassays (Meso Scale Diagnostics). ESR and CRP levels were used for comparison. Change in marker level from baseline to 6 months was analyzed by paired T-test. Marker levels in subjects with AAV were compared to marker levels in a group of 20 healthy controls (T-test). Correlations were calculated using Pearson coefficients.

Results: All subjects had highly active vasculitis (mean BVAS/WG score 8.6 ± 3.2 (SD) at baseline; 49% (n = 62) had active renal disease, and 27% (n = 34) had pulmonary hemorrhage. All subjects were clinically in remission (BVAS/WG = 0) at month 6; only 7 subjects were still receiving prednisone for minor flares that occurred before month 6. All markers levels except E-selectin and MMP9 were significantly elevated at baseline compared to controls, and all except E-selectin declined significantly by 6 months.
Cocaine Abuse. Clinical and Autoimmune Manifestations of Levamisole-Adulterated Cocaine.

2013


Background: Levamisole (LVS) has been detected as an adulterant in cocaine, but its clinical utility remains unclear. We report on 5 patients with a history of crack cocaine use presented with arthralgias and purpuric skin lesions affecting the ears and extremities. There was no evidence of desquamative interstitial pneumonia or hypersensitivity pneumonitis on biopsy.

Conclusions: Many markers of vascular injury and angiogenesis are elevated in highly-active ANCA-associated vasculitides and decline with treatment. Further study of MMP3 and VEGF is warranted to determine their clinical utility in combination with conventional markers of inflammation.

Discussion: We have described a novel syndrome of a cocaine-associated cutaneous vasculopathy likely secondary to LVS. Cardinal features include purpura for purpura to involve the ears, and a lack of evidence of systemic vasculitis. Interestingly, HNE reactivity was detected in both of the patients tested.

It is important for clinicians to recognize LVS exposure through adulterated cocaine as a cause of a cutaneous vasculopathy that can be mistaken for a systemic ANCA-associated vasculitis.

2014


Background: Wegener’s granulomatosis (WG) and microscopic polyangiitis (MPA) have widely overlapping clinical, serological, and histological features and are increasingly considered phenotypic variants of a single entity termed “ANCA-associated vasculitis (AAV”). Applying current definitions to distinguish between WG and MPA is sometimes problematic, and physicians’ and researchers’ disease classifications are heterogeneous. In addition, clinical practice and observational study findings suggest that WG and MPA clinical forms may not reflect the full range of AAV expressions. This study applied cluster analysis of a large combined cohort to explore the clinical phenotyping spectrum of AAV.

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Male/Female</th>
<th>Race</th>
<th>Smoking Status</th>
<th>Last Drug Use</th>
<th>History of ANCA-Associated Vasculitis</th>
<th>Other Conditions</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>White</td>
<td>None</td>
<td>Cocaine</td>
<td>Yes</td>
<td>none</td>
<td>Cyclophosphamide/Corticosteroids</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>Black</td>
<td>Yes</td>
<td>Cocaine</td>
<td>Yes</td>
<td>Rheumatoid Arthritis</td>
<td>Methotrexate/Cyclophosphamide</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>White</td>
<td>Yes</td>
<td>Cocaine</td>
<td>Yes</td>
<td>none</td>
<td>Prednisone/Immunosuppressive Therapy</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>White</td>
<td>Yes</td>
<td>Cocaine</td>
<td>Yes</td>
<td>none</td>
<td>Cyclophosphamide/Corticosteroids</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>White</td>
<td>No</td>
<td>Cocaine</td>
<td>Yes</td>
<td>Rheumatoid Arthritis</td>
<td>Methotrexate/Cyclophosphamide</td>
</tr>
</tbody>
</table>

Discussion: We have described a novel syndrome of a cocaine-associated cutaneous vasculopathy likely secondary to LVS. Cardiovascular features include antiphospholipid (aPL) positivity, polyclonal ANCA, the tendency for purpura to involve the ears, and a lack of evidence of systemic vasculitis. Interestingly, HNE reactivity was detected in both of the patients tested.

It is important for clinicians to recognize LVS exposure through adulterated cocaine as a cause of a cutaneous vasculopathy that can be mistaken for a systemic ANCA-associated vasculitis. Owing to its short half-life of approximately 5 hours LVS may be undetectable in the urine in as little as 48 hours after ingestion, so negative test results do not exclude the diagnosis. As demonstrated by our patients’ diverse courses, the natural history of this disorder and the relationship to lung disease are unclear at this time. The role of immunosuppression also remains uncertain, but may be warranted in severe cases. Cessation of cocaine is necessary, and relapses of the syndrome do occur with ongoing use.

Disclosure: K. R. Ullrich: None; S. G. West: None; W. High: None; R. J. Koval: None; E. Koval: None; S. Bapoje: None; J. M. Hirsh: None.

2014
Methods: A large dataset of patients with newly diagnosed WG and MPA originally enrolled in 5 clinical trials on AAV was analyzed. Eleven baseline variables, including 9 clinical variables (age at diagnosis, sex, ear/nose/throat, ocular, lung, renal, neurological, skin and cardiovascular manifestations), PR3-ANCA, and MPO-ANCA, served as primary variables for the cluster analysis. The clinical relevance of the generated clusters was analyzed by describing their summary characteristics and their patient outcomes.

Results: The dataset comprised 673 subjects, diagnosed as follows: 396 (59%) WG and 281 (41%) MPA. Over a mean follow-up of 4.4 years, 136 (20%) patients died. The analyses yielded 4 distinct phenotypic classes: 87 (13%) non-renal AAV, 291 (43%) renal AAV with PR3-ANCA, 231 (34%) renal AAV without PR3-ANCA, and 64 (10%) AAV with cardiovascular involvement. The distribution of WG-diagnosed patients into those 4 respective classes was 95%, 79%, 18% and 64%. Those 4 classes represented highly distinct mortality rates ($P < 0.0001$, log-rank test) (Figure) and frequencies of patients relapsing or the absence of renal involvement, cardiovascular involvement, and PR3-ANCA, 651 of the 673 subjects (97%) were accurately allocated to 1 of the 4 classes.

Conclusion: Our cluster analysis results suggest that AAV encompasses 4 phenotypic classes: non-renal AAV, renal AAV with PR3-ANCA, renal AAV without PR3-ANCA and AAV with cardiovascular involvement, associated with different outcomes. Compared to the traditional WG–MPA separation, this new classification might better reflect the phenotypic groupings within the AAV spectrum and more accurately stratify patients into homogeneous disease groups for clinical, epidemiological and basic research.

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2015

CpG Stimulation of Neutrophils: A Possible Role for Bacterial DNA in Neutrophil-Mediated Pathogenesis of ANCA-Associated Vasculitis?

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Background: Several chemokines associate with the initiation and progression of vasculitis. A recombinant congenic strain, MeH5/lpr, was established by rearrangement of the genetic background of MRL/lpr mice by hybridization with C3H/lpr mice. MeH5/lpr mice developed severe granulomatous polyarteritis but not glomerulonephritis, referred to as a monoclonal of periarteritis nodosa. CXCL16 expression is induced on activated macrophages and vascular endothelial cells, but it undergoes marked up-regulation after stimulation of TNF-alpha and IFN-gamma. We investigated the expression of CXCL16 during the process of granulomatous polyarteritis in MeH5/lpr mice and the therapeutic effect of CXCL16 antagonist (CXCL16-AT) on vasculitis.

Methods: The NH₂-terminally truncated CXCL16 analogs were converted to secreting forms by addition of signal sequence of IFN-beta, inserted into the pCXN2 expression vector and transfected into a non-metastatic fibroblastoid cell line, MRL/N-1. These transfecteds were injected subcutaneously into MeH5/lpr mice.

Summary of the Results: CXCL16 analogs (secreting form) truncated by 4 or more amino acid residues from N-terminus failed to induce chemotaxis by CXCR6-expression cells. Significantly increased expression of CXCL16 was induced mainly endothelial cells, epithelial cells, and infiltrating macrophages in the perivascular region at 8–10 weeks of age. CXCL16-AT-transfected MRL/N-1 cells were injected subcutaneously into MeH5/lpr mice aged 8 wk (at the early stage of polyarteritis). CXCL16 antagonist was present in the serum of mice 2 wk after injection. After 8 weeks, inoculation of CXCL16-AT into MeH5/lpr mice significantly reduced infiltrating mononuclear cells and destruction of the vessel wall associated with the formation of granulomatous lesions

2016

CXCL16 Antagonist Ameliorates the Progression of Vasculitis in MeH5/lpr Mice.

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compared with control mice. This seemed to be due to a marked reduction in macrophage and activated T-cell accumulation. However, there were no significant differences in serum anti-DNA antibodies and circulating immune complex at low levels among control, and CXCL16-ATT-bearing McH5/lpr mice.

**Conclusion:** CXCL16 antagonist may provide a new therapeutic approach to vasculitis.

**Disclosure:** H. Hasegawa: None; J. Lei: None; T. Matsumoto: None; M. Yasukawa: None; T. Miyazaki: None; M. Nose: None.

2017

**Describing the Performance of the Birmingham Vasculitis Activity Score (BVAS) at Diagnosis for Children with ANCA-Associated Vasculitis (AAV) in A Registry for Children with Vasculitis (ARCHiVe).** Kimberly A. Morishita1, America Uribe2, Jaime Guzman2, Leslie S. Abramson3, Matthew D. Adams4, Susanne M. Benseler5, Elizabeth B. Brooks6, Sarah S. C. Campillo7, Peter Chira8, B. Anne Eberhard9, Kaleo C. Ede10, Aimee O. Hersi11, Gloria C. Higgins12, Adam Huber13, Lisa F. Imano14, Rita S. Jerath15, Susan Kim16, Daniel J. Kingsbury17, Marisa S. Klein-Gitelman18, Lorien A. Nassi19, Kathleen M. O’Neil20, Egla C. Rabinovich21, Andreas O. Jerath22, Susan Kim11, Daniel J. Kingsbury19, Marisa S. Klein-Gitelman1, Suzanne C. Li2, Daniel J. Lovell23, Thomas G. Mason24, Deborah K. McCurdy25, Renee F. Modica26, Lakshmi N. Moorthy27, Eyal Muscal28, Mary B. Toth29, Linda Wagner-Weiner30, Dawn M. Wahezi31, Andrew J. Woods, MI,32Children’s Hospital of Pittsburg, Pittsburgh, PA,33Children’s Hosp LA MS60, Los Angeles, CA,34Children’s Hospital Boston, Boston, MA,35Children’s Hospital Medical Center, Cincinnati, OH,36Children’s Hospital of NY, New York, NY,37Children’s Hospital Med Ctr Med Schl GA, University of Louisville SOM, Louisville, KY,38Children, Houston, TX,39BC Children’s Hospital, BC Children’s Hospital, Vancouver, BC, Canada,40Case Western Beachwood OH, Children’s Hospital at Montefiore, Bronx, NY,41Children’s Hospital Med Ctr, Akron, OH,42Children’s Hospital of Boston, Short Hills, NJ,43Children’s Hospital of Michigan, Huntington Woods, MI,44Children’s Hospital of Pittsburgh, Pittsburgh, PA,45Children’s Hosp, New Hyde Park, NY,46Children’s Hosp, Portland, OR,47Mattel Children’s UCLA, Los Angeles, CA,48Mayo Clinic Rochester, Rochester, MN,49Montreal Children’s Hospital, Montreal, QC, Canada,50Nationwide Childrens Hosp, Columbus, OH,51OU Health Science Center, Oklahoma City, OK,52Pediatrics, U. of Washington, Seattle, WA,53Phoenix Children’s Hospital, Phoenix, AZ,54Robert Wood Johnson Medical School, Metuchen, NJ,55Schneider Children’s Hospital, New Hyde Park, NY,56St Louis Childrens Hosp, St Louis, MO,57Stanford Univ Schol of Med, Stanford, CA,58The Hospital for Sick Children, Toronto, ON, Canada,59TX Scottish Rite Hosp, Dallas, TX,60UCSF, San Francisco, CA,61University of Florida, Orlando, FL,62University of Michigan, Ann Arbor, MI,63University of Vermont, Morrisville, VT,64Vanderbilt Univ, School of Medicine, Nashville, TN.

**Background:** There are no validated paediatric assessment tools for measuring disease activity in chronic vasculitis. The BVAS, a valid and reliable assessment tool for measuring disease activity in adults with vasculitis, may not necessarily capture the clinical features or components of disease activity assessment that might be unique to, or more characteristic of, the growing and developing child. In adult vasculitis, BVAS correlates highly with physician’s global assessment of disease activity (PGA).

**Objectives:** To describe the performance of BVAS applied at the time of diagnosis in children with AAV in relationship to PGA.

**Methods:** Eligible patients were those diagnosed since 2004 with an AAV, according to expert site rheumatologist (MD-diagnosis) at 37 ARChiVe centers. Data collection items in the registry included all elements of BVAS and a PGA for patients at the time of diagnosis. After BVAS items were extracted and individual patient scores calculated, the association between BVAS (version 3) and PGA scores was assessed using the Spearman rank correlation coefficient. The statistical analysis was performed using SPSS statistical software.

**Results:** 155 patients with an AAV were recruited into the ARChiVe cohort between January 2004 and March 2010. Five patients were excluded from analysis because data was insufficient to score BVAS. The MD-diagnosis of the remaining 150 patients were Wegener’s granulomatosis (n = 98), microscopic polyangiitis (n = 25), Churg-Strauss syndrome (n = 3), ANCA-positive pauci-immune glomerulonephritis (n = 5), and unclassified vasculitis (n = 19). The correlation between BVAS and PGA scores was weak in children (rho = 0.379, 95% CI 0.233 to 0.509, p < 0.0001) (Figure).

**Conclusion:** The poor correlation of BVAS with PGA suggests either that BVAS requires significant paediatric specific modification, or, that there is no uniformity or standards of disease activity assessment among paediatric rheumatologists. The tool may also perform better measuring change of activity between visits rather than quantifying disease activity at diagnosis. Development of a standardized tool to enable clinical trials in children to improve outcomes is essential.

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2018

**Differences between PR3 and MPO-ANCA Associated Vasculitis—Population Based Study from Southern Sweden.** Aladdin Mohammad1 and Märten Segelmark2.1Helsingborg Hospital, Helsingborg, Sweden,2Skåne University Hospital

**Background:** Antineutrophil cytoplasmic antibodies (ANCA) are useful serologic markers for diagnosis of small vessel vasculitis. Two main specificities are recognized by ELISA: proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA). Even though PR3-ANCA is usually found in patients with Wegener’s granulomatosis (WG) and MPO-ANCA in microscopic polyangiitis (MPA), there are many exceptions to this rule. The lack of diagnostic criteria for WG and MPA make distinction between these disease phenotypes difficult, especially early during the disease course. A separation based on serology is, however, simple and reproducible.

**Objectives:** To study differences at disease presentation and outcome based on ANCA type among patients diagnosed with ANCA associated systemic vasculitis (AASV) from a defined population in southern Sweden.

**Method:** Demographic, clinical and laboratory data at presentation in patients with AASV diagnosed during 13 years period (1997–2009) retrieved from a defined population in southern Sweden were compared by ANCA type (PR3- vs. MPO-ANCA). Organ involvement was recorded using the definitions of the Birmingham Vasculitis Activity Score. Differences in renal and patients survival were studied by Kaplan-Meier analysis.

**Results:** A total of 163 patients for whom positive test for either PR3- (n=92) or MPO-ANCA (n=71) was available were included in the study. The demographics, clinical and laboratory characteristics are listed in Table 1. Among patients with PR3-ANCA 56 (61%) were men compared with 31 (43%) for MPO-ANCA, p = 0.029. Patients with PR3-ANCA have had significantly higher inflammatory activity and larger number of organ involvement at diagnosis. Ear-Nose-Throat involvement was more common in patients with PR3-ANCA while renal disease was more prevalent in...
MPO-ANCA disease (Table 1). Among patients with MPO-ANCA and renal involvement at diagnosis, nineteen (32%) went in End Stage Renal Disease compared to 10 (16%) of PR3-ANCA (p = 0.032). There were no differences in the mortality rates between the 2 groups.

**Conclusions:** In this population based cohort of patients with AASV, statistically significant differences in clinical and laboratory characteristics at presentation were clearly evident. In term of outcome, renal survival was worse for patients with MPO-ANCA. These findings should be taken in consideration when stratifying patients with AASV in different therapeutic strategies.

<table>
<thead>
<tr>
<th></th>
<th>PR3-ANCA</th>
<th>MPO-ANCA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Male (%) N.</td>
<td>56 (61%)</td>
<td>31 (43%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Age at diagnosis, median (range), years</td>
<td>65 (20–88)</td>
<td>70.5 (32–92)</td>
<td>0.203</td>
</tr>
<tr>
<td>Diagnosis delay, median (range), months</td>
<td>2 (0–12)</td>
<td>2 (0–62)</td>
<td>0.037</td>
</tr>
<tr>
<td>Laboratory results, median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-Reactive Protein g/l</td>
<td>119 (13–294)</td>
<td>50 (1–328)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate mm/hr</td>
<td>80 (4–126)</td>
<td>55 (8–150)</td>
<td>0.029</td>
</tr>
<tr>
<td>Hemoglobin g/l</td>
<td>111 (75–155)</td>
<td>107 (72–142)</td>
<td>0.12</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>410 (150–838)</td>
<td>324 (90–652)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>White Blood Cells</td>
<td>12 (7–26)</td>
<td>9.5 (2–20)</td>
<td>0.002</td>
</tr>
<tr>
<td>Creatinine μmol/l</td>
<td>134 (41–1214)</td>
<td>205 (43–1369)</td>
<td>0.024</td>
</tr>
<tr>
<td>N. of patients with &gt; = 3 organ systems involved</td>
<td>70 (76%)</td>
<td>40 (56%)</td>
<td>0.008</td>
</tr>
<tr>
<td>N. (%) of patients went in ESRD</td>
<td>10 (16%)</td>
<td>19 (32%)</td>
<td>0.032</td>
</tr>
<tr>
<td>N. of patients died during follow-up</td>
<td>26 (28%)</td>
<td>25 (35%)</td>
<td>0.423</td>
</tr>
<tr>
<td>Organ systems involved at diagnosis N. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>86 (93%)</td>
<td>60 (84%)</td>
<td>0.063</td>
</tr>
<tr>
<td>ENT</td>
<td>56 (61%)</td>
<td>12 (17%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chest</td>
<td>48 (52%)</td>
<td>27 (38%)</td>
<td>0.072</td>
</tr>
<tr>
<td>Nervous</td>
<td>42 (13%)</td>
<td>7 (10%)</td>
<td>0.530</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>4 (4%)</td>
<td>6 (6%)</td>
<td>0.706</td>
</tr>
<tr>
<td>Musculoskeletal and eyes</td>
<td>10 (11%)</td>
<td>2 (3%)</td>
<td>0.051</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4 (4%)</td>
<td>6 (6%)</td>
<td>0.706</td>
</tr>
<tr>
<td>Abdominal</td>
<td>5 (5%)</td>
<td>7 (10%)</td>
<td>0.284</td>
</tr>
<tr>
<td>Renal</td>
<td>62 (67%)</td>
<td>59 (83%)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

1 patient with renal involvement at diagnosis (PR3: 61; MPO: 59); 2 between January 1997 and June 2010.

**Disclosure:** A. Mohammad: None; M. Segelman: None.

**2019**

Early Predictors of Neurological Long-Term Deficits in Children with Primary CNS Vasculitis, Gordon S. Soon, Ivanna Yau, Gabrielle Deveher, Derek Armstrong, Pascal Tyrrell, Jeffrey Templeton, Suzanne Laughlin and Susanne M. Benseler. The Hospital for Sick Children

**Purpose:** Childhood non-progressive primary CNS vasculitis (NPcPACNS) accounts for the majority of strokes in children. The aims of the study were 1) to report the neurological long-term outcome of NPcPACNS and 2) to determine early risk factors of long-term deficits in childhood vasculitis and stroke.

**Methods:** A single-centre cohort study of consecutive children diagnosed with cPACNS based on Calabrese criteria between January 1990 and December 2009 was performed. Patients were included if they 1) had non-progressive cPACNS (unilateral proximal stenoses and no evidence of progression > 3 months) and 2) had serial clinical assessments and neuroimaging. The study excluded progressive cPACNS and angiography negative cPACNS. Data collection: 1) Demographics, preceding chickenpox; 2) Clinical characteristics, diffuse and focal neurological deficits recorded by two independent investigators, recurrence of ischemic events, 3) laboratory tests including inflammatory and prothrombotic markers and CSF analysis; 3) neuroimaging: serial Magnetic Resonance Imaging (MRI), MR angiography (MRA) and conventional angiography were blindly reviewed by two independent neuroradiologists following a previous developed protocol; 5) treatment with initial anticoagulation, antiplatelet and adjunctive immunosuppressive therapy. Outcome: Neurological deficit impacting on function as determined by Pediatric Stroke Outcome Measure (PSOM) at last follow-up. Analysis: putative early predictors of long-term deficits were tested in univariate and multivariable regression analyses.

**Results:** A total of 44 children with NP-cPACNS were included; were 32 were boys and 12 were girls; median age at diagnosis was 5.5 years (range 0.5–16.4 years) and median follow-up was 6.4 years; 25 (57%) had preceding chickenpox <12 months. All children presented with arterial ischemic stroke, 28 (64%) had right-sided symptoms. Headache was seen in 17 (39%), 16 (36%) had diffuse deficits and only 6 (14%) seizures. Recurrent ischemic events were observed in 13 (30%). Inflammatory markers were elevated 23 (52%). All patient had unilateral ischemic MRI lesions, including 21 (48%) with isolated basal ganglia lesions. The majority (58%) had vessel stenoses of ≥50%. Initial therapy: Anticoagulation in 61%, antiplatelet in 31%, both in 5% and adjunctive corticosteroids in 13 (30%). Outcome: Neurological long-term deficits were seen in 20 (45%). Children presenting with seizures (p = 0.006), evidence of MRI beyond the basal ganglia (p = 0.001) and/or high degree of vascular stenosis (p = 0.04) were at highest risk for long-term deficits.

**Conclusions:** The long-term outcome of childhood vascular stroke is devastating: Neurological deficits impacting on function can be found in 45% of children with non-progressive primary CNS vasculitis, the most common cause of childhood stroke. Early predictors including seizures at diagnosis, evidence of extensive MRI lesions and high degree of vascular stenosis can identify children at highest risk for long-term deficits. Innovative, tailored treatment strategies have to target high risk patients to prevent long-term neurological damage.

**Disclosure:** G. S. Soon: None; I. Yau: None; G. Deveher: None; D. Armstrong: None; P. Tyrrell: None; J. Templeton: None; S. Laughlin: None; S. M. Benseler: None.

**2020**

Effects of Imatinib Mesylate on Pulmonary Vascular Remodeling of Allergic Vasculitis in Murine Mode. Nobuhiro Sasaki1, Koheri Yamashi1 and Takashi Sawai1. 1Department of Pathology, Iwate Medical University School of Medicine, Morioka, Iwate, Japan, 2Division of Pulmonary Medicine, Allergy and Rheumatology, Department of Internal Medicine, Iwate Medical University School of Medicine, Morioka, Iwate, Japan

**Objectives:** We investigated the effects of imatinib mesylate (IM) on remodeling the murine model of allergic vasculitis with eosinophil infiltration (Exp. Lung Res. 2009. in press).

**Methods:** C57BL/6 mice (6–8 weeks) were sensitized with ovalbumin (OVA) and alum. The positive controls (n = 12) were exposed to aerosolized OVA daily for 7 days. The other group of mice (IM treated mice) were administered with IM (4.5mg/kg, p.o.) in parallel with daily exposure to aerosolized OVA for 7 days. On 7th day, bronchoalveolar lavage (BAL) was performed and the lungs were excised for pathological analysis. Cell differentials were determined and concentrations of IL-2, IL-4, IL-5, IFN gamma and TNF-alpha in BAL fluid were measured.

**Results:** While there was no significant difference of total cell number in BAL fluids in between the control and the IM treated group, the ratio of eosinophils reduced significantly in the IM treated group. (control vs IM treated; 64.8±2.1 vs 37.6±4.3 %, p = 0.004). There was no significant difference of concentrations of IL-2, IL-4, IL-5, IFN gamma or TNF-alpha in BAL fluids or serum in between the control and the IM treated group. The pathological scores reduced significantly in the IM treated group compared to the control group (control vs IM treated; 3.67±0.2 vs 2.29±0.2, p = 0.0043). Intra luminal infiltration and proliferation of myofibroblasts in pulmonary arteries were reduced dramatically in the IM treated group compared to the control group. Intra luminal infiltration and proliferation of MIB1 positive myofibroblasts in pulmonary arteries were reduced dramatically in the IM treated group compared to the control group.

**Conclusion:** IM suppressed pulmonary vascular remodeling in the murine model of allergic vasculitis with eosinophil infiltration.
A total of 21 healthy donors (12 female, 9 male [40.3 ± 9.2 years]) and 31 WG patients (13 female, 18 male [59.2 ± 15.3 years]) were included into the study. The total percentages of EPCs were not different between the two groups. WG patients displayed lower proliferative activity of EPCs (22.3 ± 4.1 vs. 45.9 ± 6.8, CFU-ECs, p = 0.0027). In addition PR3 expression was significantly higher in the total as well as in the Flk-1+ (sub)population of myelomonocytic cells in WG (10.4 ± 14.4% vs. 0.3 ± 0.4%, p = 0.02 bzw. 0.3 ± 0.3% vs. 0.1 ± 0.1%, p = 0.04). Finally, WG patients showed lower mean serum levels of Angiopoietin 1 and higher mean serum levels of TNF-α as compared to controls (689 ± 224 pg/ml vs. 1542 ± 315 pg/ml, p = 0.034 and 13 ± 1 vs. 8.9 ± 0.5 pg/ml, p = 0.04), the serum levels of both cytokines did not linearly correlate with either clinical activity or the total number of circulating EPCs or the numbers of colonies formed (EPC regeneration).

In addition to reduced EPC regeneration and decreased serum levels of Angiopoietin 1, both indicating impairment of the endothelial system, patients with WG show significantly increased expression of PR3 in the total and in the Flk-1+ myelomonocytic cell population. These data imply, that PR3 could be involved in the pathogenesis of microvascular endothelial damage in patients with WG.

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2022

Epidemiology of Lupus Nephritis (LN) and ANCA Associated Nephritis (AAN) — Comparison Study from a Defined Population. Aladinn Mohammadi, Christina Stahl-Hallengren, Ola Nived, Gunnar K. Sturfelt, Anders Bengtsson, and Mårten Segelmark. Helsingborg Hospital, Helsingborg, Sweden, Skåne University Hospital, Lund, Sweden, Skåne University Hospital, Lund, Lund, Sweden

Purpose: The aims of this study were to compare incidence rates, renal and patients’ survival between Lupus Nephritis (LN) and ANCA Associated Nephritis (AAN) during a 12-year-period in a well defined population in southern Sweden.

Method: The study was carried out over a 12 year period (1997–2009) in a health care district in southern Sweden with a total population (> 95% Caucasian) of 238 069. Patients were retrieved from two existing cohorts of patients with systemic lupus erythematosus (SLE) and ANCA Associated Vasculitis (AAV). To be included in the study, patients had to (i) reside within the study area at the time of diagnosis, (ii) have a clinical diagnosis of either SLE or AAV and (iii) experience a first flare of biopsy proven nephritis during the study period. The indications for kidney biopsy were the same in both cohorts; and includes rising s-creatinine, excessive proteinuria and / or urinary sediment consistent with active nephritis. The clinical diagnosis of all patients was verified by review of case records. All patients with SLE fulfilled the American College of Rheumatology (ACR) classification criteria 1987. For AAV patients, classification was made according to an algorithm based on the ACR criteria 1990 and the Chapel Hill Consensus Conference definitions 1994.

Results: We identified a total of 43 patients with AAN (33 microscopic polyangitis, 10 Wegener’s granulomatosis) and 13 patients with LN, with new onset of biopsy proven nephritis (Table 1). The annual incidence per million of the population (95% confidence interval) was estimated to be 15.1 (10.6–19.6) for AAN and 4.6 (2.1–7.0) for LN. 42 patients with AAN tested positive for ANCA (20 with pos. c-PR3-ANCA and 22 with p-MPO-ANCA). One patient with MPA was ANCA-negative. Eight patients (62%) with LN tested positive for anti-ds-DNA and 11 had complement consumption. Patients were followed until June, 2010 (median 48 months; range 1–144). During follow up 19 patients died [AAN 18; LN 1 (p = 0.049)], and 13 patients went into ESRD (all with AAN). Among patients who were alive and not on renal replacement therapy at the end of follow up, 41% of the AAN patients had an estimated GFR <50 mL/min/1.73 m² compared to 8.3% for the LN patients (p = 0.046). The 1-, 5-, and 10-year survival for patients with AAN was 84%, 59% and 53% respectively.

Table 1.

<table>
<thead>
<tr>
<th>Disease</th>
<th>n. of patients</th>
<th>Age at diagnosis (median yrs (range))</th>
<th>s-creatinine at diagnosis (µmol/l, median (range))</th>
<th>Incidence106 (95% CI)</th>
<th>Mortality (%)</th>
<th>ESRD (n.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAN</td>
<td>43</td>
<td>17/26</td>
<td>70 (20–88)</td>
<td>267 (66–1369)</td>
<td>15.1 (10.6–19.6)</td>
<td>18</td>
</tr>
<tr>
<td>MPA</td>
<td>33</td>
<td>16/17</td>
<td>71 (29–88)</td>
<td>339 (79–1369)</td>
<td>11.6 (7.6–15.5)</td>
<td>16</td>
</tr>
<tr>
<td>LN</td>
<td>13</td>
<td>10/3</td>
<td>43 (25–72)</td>
<td>78 (51–173)</td>
<td>4.6 (2.1–7.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

AAN: ANCA associated nephritis; LN: lupus nephritis; MPA: microscopic polyangiitis; WG: Wegener’s granulomatosis; CI: confidence interval; ESRD: end stage renal disease.

2021

Endothelial Lineage Impairment and Increased PR3 Expression on Peripheral Cells of Endothelial Phenotype in Wegener’s Granulomatosis. Susann Patschan, Daniel Patschan, Elvira Henze, Johannes Wessels, Sabine Blaschke and Gerhard Anton Müller. Department of Nephrology and Rheumatology, University Hospital Göttingen

Wegener’s Granulomatosis (WG) is characterized by microvascular endothelial damage and by alterations of the endothelial progenitor cell (EPC) system. Interactions between anti-Proteinase 3 antibodies and their respective antigens (PR3) on neutrophils are pathogenetically relevant in WG. Aim of this study was to analyze total circulating EPCs and regenerative activity of blood-derived EPCs, and (II) to evaluate PR3 expression patterns on circulating myelomonocytic and endothelial cells in WG.

Blood samples from WG patients were analyzed for total and for Flk-1+ myelomonocytic cells (cytometric analysis). Healthy donors served as controls. For evaluating the proliferative activity of EPCs, a colony forming unit assay (CFU) was performed. PR3 expression by the cells was quantified by cytometric analysis. Serum Angiopoietin 1 and serum TNF-α were measured by ELISA technique.
G. K. Sturfelt: University Medical Center Groningen, Dept of Rheumatology and Wayel H. Abdulahad, Coen A. Stegeman, Cees G. M. Kalleenberg and Peter Heerings. University Medical Center Groningen, Dept of Neuroradiology, Groningen, The Netherlands, University Medical Center Groningen, Dept of Pathology and Medical Biology, Groningen, The Netherlands, University Medical Center Groningen, Dept of Rheumatology and Clinical Immunology, Groningen, The Netherlands.

Background: Bacterial infections have been linked to the pathogenesis of ANCA-associated vasculitis (AAV), and nasal carriage of Staphylococcus aureus is associated with an increased risk for relapses. Toll-like receptors (TLRs) are important sensors of pathogen-associated molecular patterns, and these receptors may be important during the development of relapses in AAV. Here, we characterized the expression of TLRs 2, 4, and 9 by peripheral blood mononuclear cells from AAV patients who were nasal carriers of S. aureus and non-carriers. Furthermore, we studied the effect of in vitro ANCA-priming on TLR expression by monocytes.

Methods: Expression of TLRs was determined using 9-color flow cytometry. Whole blood from 29 AAV patients (17 PR3-ANCA and 12 MPO-ANCA) and 19 matched healthy controls was stained for membrane markers CD3, CD14, CD16, CD19, CD27, and CD56 to distinguish between cell populations, and expression of membrane toll-like receptors (mTLR) 2, 4, and 9, and intracellular levels of TLR9 were determined. We compared TLR expression in AAV patients who were nasal carriers of S. aureus (n=9) and non-carriers (n=20). Peripheral blood mononuclear cells were stimulated in vitro with mononclonal anti-PR3 or PR3-ANCA IgG, and mTLR2 and mTLR4 expression by monocytes was determined.

Results: Membrane expression of TLRs 2, 4, and 9 by B lymphocytes and T lymphocytes was comparable in AAV patients and controls. In AAV patients, we observed increased percentages of mTLR2 (median = 0.46% in AAV vs 0.18% in HC, p = 0.01), and mTLR4 (median = 0.37% in AAV vs 0.22% in HC, p = 0.02) NK cells. Monocytes from AAV patients expressed increased levels of mTLR2, compared to HC (median ΔMFI = 31.7 in AAV vs ΔMFI = 19.8 in HC, p = 0.01). mTLR-expression by granulocytes was comparable in patients and controls. Intracellular levels of TLR9 (iTLR9) were decreased in B lymphocytes, T lymphocytes and NK cells from AAV patients, whereas monocytes and granulocytes expressed increased iTLR9 levels. Within AAV patients, we observed increased mTLR4 expression by monocytes from nasal carriers of S. aureus, compared to non-carriers (mean ΔMFI = 12.6 in Aureus vs mean ΔMFI = 5.8 in Aureus, p = 0.02). Priming with PR3-ANCA in vitro did not influence mTLR2 and mTLR4 expression by monocytes.

Conclusions: We observed increased TLR expression by a proportion of NK cells and monocytes in AAV patients in remission, compared to healthy controls. It has been suggested that ANCA trigger monocytes to increase TLR expression, but we did not observe increased TLR expression after priming with PR3-ANCA in vitro. Interestingly, monocytes from nasal carriers of S. aureus expressed increased mTLR4 levels compared to non-carriers, indicating proinflammatory conditions. Increased TLR levels on NK cells and monocytes may reflect increased activation of these cells in AAV patients, but whether relapses can be triggered via TLRs will need further investigation.

Disclosure: H. Tadema: None; W. H. Abdulahad: None; C. A. Stegeman: None; C. G. M. Kalleenberg: None; P. Heerings: None.


Objective: To analyse the main characteristics and outcome of polyarteritis nodosa (PAN)-type vasculitis associated with hepatitis C virus (HCV).

Methods: We reported characteristics and outcome of 31 patients chronically infected with HCV who satisfied American College of Rheumatology and Chapel Hill criteria of PAN, seen between 1990 and 2009, in a university center.

Results: Among a cohort of 161 patients with HCV-related vasculitis, 31 (19.2%) were diagnosed as having PAN. The median (Q1,Q3) age was 64.5 (49.5, 70.5) years with 54.8% of female. Compared with HCV-mixed cryoglobulinemia (MC) vasculitis, HCV-PAN displayed a more severe and acute clinical presentation with more frequent fever and weight loss (p<0.001), severe hypertension (p=0.0006), gastrointestinal tract involvement (p<0.001), severe acute sensory-motor multifocal mononeuropathy (p<0.001), kidney and liver microaneurisms (p=0.0002) and increased C-reactive protein (p<0.001). Complete clinical remission of vasculitis was achieved in 79.3% of HCV-PAN compared to 57.5% HCV-MC (p=0.050). In multivariate analysis, skin involvement (OR, 2.81; 95% CI 1.27 to 6.33), and PAN type vasculitis (OR, 3.01; 95% CI 1.16 to 8.96) were independently associated with a complete clinical response of HCV-vasculitis. A glomerular filtration rate lower than 70 ml/min (OR 0.54; 95% CI 0.24 to 1.21) was negatively associated with a complete clinical response of HCV-vasculitis. Clinical relapse rate was higher in HCV-PAN compared to HCV-MC (75% vs 12%, p=0.002, respectively under rituximab). Five-years survival rate was 86% in the whole cohort, regardless of the vasculitis type.

Conclusion: HCV-PAN account for 19.2% of our cohort of HCV vasculitis. HCV-PAN display a more severe and acute clinical presentation and higher rate of clinical remission.

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2025 IL-25: A Cytokine Linking Eosinophils and Adaptive Immunity in Churg-Strauss Syndrome. Benjamin Terrier1, Ivan Bieche2, Thierry Maisonneuve1, Ingrid Laurendeau1, Michele Rosenzwajg3, Marie-Claude Diemert1, Lucille Musset1, Michel Vidaud2, Damien Sene1, Nathalie Costedoat-Chalumeau1, Du Le Thi Huong1, Zahir Amoura1, David Klatzmann1, Patrice Cacoub1 and David Saadoun1. 1Pitié-Salpêtrière, 2UMR745 INSERM.

Background: Churg-Strauss Syndrome (CSS) is characterized by systemic vasculitis, and blood and tissue eosinophilia. Blood eosinophils correlate with disease activity. Activated T cells from CSS patients are predominantly Th2. IL-25 has been shown to be a potent target for novel therapy.

Methods: We performed quantitative measurement of serum human IL-25 by ELISA, analysis of cell surface markers and cytokine production by flow cytometry. Blood eosinophils were assessed by flow cytometry and bone marrow eosinophils (BME) were assessed by immunohistochemistry.

Results: We found increased level of IL-25 in the serum of active patient with CSS (952±697 vs. 75±49 pg/ml in inactive patients and 47±4 pg/ml in healthy donors). IL-25 correlated with disease activity and eosinophil blood level. Eosinophils were the main source of IL-25, whereas activated CD4 memory T cells were the main IL-17RB (IL-17R) in the pathogenesis of CSS.

Conclusion: Our study is the first to demonstrate the implication of IL-25 in the pathogenesis of CSS and its correlation with disease activity. Eosinophils, through the production of IL-25, may exert a critical role in promoting Th2 responses in peripheral blood and target tissues in CSS, and represent a potential target for novel therapy.

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Incidence and Predictors of Urotoxic Adverse Events in Cyclophosphamide-Treated Patients with Systemic Necrotizing Vasculitides. Guillaume Le Guenno1, Alfred Mahr2, Christian Pagnoux2, Robin Dhole1 and Loïc Guillevin1, 2Internal Medicine, Hospital Avicenne, Bobigny, France, 3Internal Medicine, Hospital Cochin, Paris, France, 4Internal Medicine, Hospital Cochin, Paris, France

Background: Cyclophosphamide (CYC) is widely used to treat systemic necrotizing vasculitides (SNV) but its uroside effects, i.e., hemorrhagic cystitis (HC) and urinary tract cancer (UTC), have raised important concerns. However, reported UTC incidence rates in CYC-treated SNV patients varied according to the study. In addition, while the cumulative CYC dose was identified as a major determinant of urotoxicity, it is not clear whether a cutoff exists below which cumulative CYC has no urotoxic effect and whether oral or intravenous CYC administration affects the urotoxic risk. Moreover, no information is available on CYC-related urotoxicity for SNV other than Wegener’s granulomatosis (WG). To address these questions, we undertook a study that aimed at assessing the frequencies and predictors of HC and/or UTC in CYC-treated SNV patients.

Patients and Methods: The French Vasculitis Study Group database, which contains longitudinal data on SNV patients, was searched for UTC and/or HC occurrences in SNV patients diagnosed with WG, microscopic polyangiitis, Churg-Strauss syndrome or polyarteritis nodosa. The observed UTC incidence was compared to that expected in the French general population by calculating age- and sex-standardized incidence ratios (SIR). UTC and/or HC relationships with 10 variables, including CYC dose and administration route, were investigated by uni- and multivariate Cox proportional hazards models for a nested subgroup of patients with detailed information on CYC exposure; the variables “prior HC episode” and “cumulative CYC dose” were analyzed as time-varying covariates.

Results: Among the 805 patients analyzed (mean follow-up: 5.3 years), 22 HC and 7 UTC (6 bladder cancers, 1 ureter cancer) were identified in 27 patients. SIR for UTC was 5.00 (P = 0.001) and 5.96 for WG-diagnosed patients (P = 0.03). Based on 467 patients with detailed CYC information (mean cumulative CYC dose: 25.1 ± 38.0 g), cumulative CYC dose [hazard ratio [HR] for 10-g increments: 1.08; P = 0.03], ever-oral CYC administration (HR: 5.69; P = 0.001) and WG (HR: 2.98; P = 0.01) independently predicted UTC and/or HC development. Results of analyses using the effect of cumulative CYC doses as a categorical variable suggested that UTC and/or HC risk increased steadily with increasing cumulative CYC doses. Ever-to-bins (HR: 7.64; P = 0.02) and a prior HC episode (HR: 10.91; P = 0.006) significantly predicted UTC.

Conclusion: CYC treatment of SNV is associated with a 5-fold higher risk of developing UTC. The urotoxicity risk for SNV patients is determined by the cumulative CYC dose and its oral intake, and might be higher for WG patients. This study’s findings also support that HC should be recognized as a precursor of UTC and plead for sustained heightened awareness when prescribing this drug to tobacco smokers.

Objective: to describe the diagnostic performance of UTC for inflammatory aortitis.

Method: This was a retrospective study from January 2005 to March 2010 including only patients who 1) had received a diagnosis of aortitis (expert diagnosis); 2) had performed a CT-scan and a PET-scan. For each case, one control was selected among patients who had performed a CT-scan and a PET-scan for the diagnosis of lymphoma in our institution. Cases and controls were matched for gender and age. Maximal AWT was measured by the same physician (JG) using a standardized procedure at the ascending aorta, descending thoracic aorta and abdominal aorta. AWT increase was validated only when it was circumferential and extended in the absence of obvious calcified atheroma plaque. The diagnostic performances of three different aortitis definitions were tested. Definition 1: at least one AWT value above the 99 percentile observed in the control group at one of the following sites: ascending aorta, thoracic descending aorta and abdominal aorta; definition 2: increase of AWT above the 99 percentile of the maximal value observed in the control group whatever the aorta portion; definition 3: increase of AWT at one site or more above the more discriminating threshold determined using ROC curves.

Results: Thirty-one aortitis patients (24 women and 7 men) were recorded. Mean age was 58.1 years (range: 20 – 82). They suffered from giant cell arteritis (GCA; n=16), Takayasu arteritis (TA; n=8), ANCA-vasculitis (n=2), spondyloarthritids (n=1) or unclassified aortitis (n=4). Among controls, the 99 percentile of AWT was 3 mm at the ascending aorta, 2.6 mm at the descending aorta and 2.7 mm at the abdominal aorta; the 99 percentile of maximal AWT was 3.2 mm. The best discriminating threshold determined by the ROC curves analysis was 2.6 mm, 2.2 mm and 2.4 mm respectively for the ascending, the descending and the abdominal aorta. The diagnostic performances of each definition are reported below.

Table 1. Diagnostic performance of three inflammatory aortitis definitions based on the measure of the aorta wall thickness using computed-tomography.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition 1</td>
<td>71</td>
<td>100</td>
<td>100</td>
<td>77.5</td>
</tr>
<tr>
<td>Definition 2</td>
<td>61</td>
<td>100</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>Definition 3</td>
<td>91.2</td>
<td>71</td>
<td>75.7</td>
<td>91.7</td>
</tr>
</tbody>
</table>

Se: sensibility; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value

The diagnosis of aortitis had not been mentioned on the routine CT-scan report in 11 patients despite an increased AWT, an arterial wall contrast enhancement and/or peri-aortic edema. All these patients had a clearly abnormal PET-scan vessels imaging. All patients with a maximal AWT below 2 mm had a normal vessel’s PET-scan.

Conclusion: The diagnosis of aortitis is frequently missed on routine CT-scan despite clear abnormalities. PET-scan seemed especially useful when the AWT was thicker than 2 mm and thinner than 3 mm at the descending aorta, 2.6 mm at the descending aorta and 2.7 mm at the abdominal aorta.

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Inflammatory Aortitis: Diagnostic Performance of Aorta Wall Thickness CT-scan Measuring. Maia Forgues1, Jacques Giron2, Anne Hitzel1, Anne Julian1, Pierre Payoux1, Daniel Adone1, Frédéric Degraeve1, Serge Madauile1, Laurent Prudhomme2, Yann Leveneur2, Francis Gaches2, Xavier Delbrel2, Leonardo Astudillo3, Bruno Marchou2, Philippe Arlet2 and Laurent Sailer1.

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Interleukin-32 and Its Autoantibody Are Elevated in Patients with Wegener’s Granulomatosis and Correlated with Treatment Response. Suyoung Bae1, Yong-Gil Kim2, Sijoung Lee3, MinWook So2, Chang-Keun Lee4, Bin Yoo5, Yong-Beom Park6 and Soohyun Kim7. 1ASAN Medical Ctr, Seoul, Korea, Republic of; 2ASAN Medical Ctr, Konkuk University, Seoul, Korea, Republic of; 3Konkuk University; 4Yonsei University

Background: Wegener’s granulomatosis (WG) is a primary small systemic vessel vasculitis, involved prominently the respiratory tract and the kidneys. However, the etiology and pathogenesis are currently not characterized precisely. Human proteinase 3 (PR3), the major autoantigen, and anti-neutrophil cytoplasmic antibody to PR3 (PR3-ANCA) are associated with the pathogenesis of vascular damages in WG and cytotoxins including IFN-γ and TNFα have been thought to be pivotal signal transmitters in granulomatous lesions due to recruiting lymphoid cells and activating macrophages in WG. PR3 has the ability to bind and activate IL-32, which has been recently described as a novel cytokine that induces proinflammatory cytokines (IL-1β, IL-6 and TNFα) and chemokines (IL-8 and MIP-2).
Objective: To evaluate the role of IL-32 in WG patients and the relationship between IL-32 and disease activity.

Methods and Results: The blood samples were collected from nine WG patients and the disease activity was assessed using Birmingham Vasculitis Activity Score (BVAS). We investigated the plasma levels of PR3, IL-32, TNFα, and IL-6 in WG patients using ELISA. Among them, we observed that IL-32 and PR-3 level of WG patients were increased significantly compared with healthy volunteers and each was tightly associated (p < 0.01). Northern blot analysis revealed that the mRNA level of IL-32 was significantly elevated in leukocytes of WG patients. The intracellular colocalization of IL-32 and PR3 in leukocyte from WG patients versus healthy volunteers was verified by immunofluorescence staining. Furthermore, the specificity in plasma concentration of IL-32 and IL-32 autoantibodies between healthy controls and WG patients was more noticeable than that in plasma levels of PR3 and PR3-ANCA. Although the significant relationship between IL-32 level and BVAS was not found, the change of IL-32 levels between pre- and post-treatment sample of three WG patients was well correlated with the change of BVAS.

Conclusion: In WG patients, the plasma level of IL-32 was increased and the decrease of this might imply the good response of treatment. Our results suggest that IL-32 could be a helpful index in WG patients and may have an important role in the disease pathogenesis.

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2029

Investigation of the Effect of Histone Deacetylase 2 Function on Wegener’s Granulomatosis. Dai Takagi1, Yui Nakamura2, Shigera Akazawa2 and Satoshi Fukuda2. 1Department of Otolaryngology and Head & Neck Surgery Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan, 2Department of Otolaryngology and Head & Neck Surgery Hokkaido University Graduate School of Medicine

Background: Wegener’s Granulomatosis (WG) is a systemic vasculitic disease characterized by necrotizing granulomas and vasculitides of arterioles and venules. It has been reported that anti-neutrophil cytoplasmic antibodies (ANCA) activate neutrophils result in induction of glomerulonephritis in WG by released hydrogen peroxide.

Histone deacetylase (HDAC) deacetylates histone and deacetylation of histone associates with gene repression or gene silencing. Even more importantly, HDAC2 is also key molecule of steroid action, and this reduction causes steroid insensitive inflammation, which is seen in COPD, severe asthma, rheumatoid arthritis. In this study, we investigated whether HDAC2 function decreased in WG patients, and effect of oxidative stress on function of HDAC2.

Patients and Methods: A549 cells (lung epithelial cells) were stimulated by H2O2 (200 μM) to induce oxidative stress and expression of HDAC 2 were measured. We also measured HDAC2 2 activity.

Six patients of WG (mean ± S.D. age 62 ± 5 ± 17 ± 5) diagnosed according to American College of Rheumatology criteria were examined.

Fresh PBMCs were isolated from heparinized blood by Ficoll-Conray separation and then whole cell protein was prepared. Target proteins were detected by Western blot analysis. We also measured HDAC 2 activity of PBMCs on patients.

Results: Treatment of A549 cells with H2O2 did not suppress expression of HDAC2. However, treatment of H2O2 significantly decreased total HDAC2 activity (p < 0.05).

We found that HDAC 2 activity was significantly decreased in WG patients compared to those from healthy subjects (HS), 75.5 ± 7.4 Arbitrary Units at HS, 35.2 ± 12.3 Arbitrary Units at WG (p < 0.05). Furthermore, we found negative correlation between HDAC 2 activity and titer of c-reactive protein and titer of PR3-ANCA. However, expression of HDAC2 did not increased in WG patients.

Discussion: These results suggest that function of HDAC 2 is reduced in WG and that this reduction affects inflammation and vasculitides of WG. We have also confirmed that oxidative stress suppressed HDAC activity in lung epithelial cell line. Oxidative stress may worsen the disease via reduction of HDAC2 function without reduction of HDAC2 expression.

Thus, HDAC2 may serve therapeutic targets by modulating the function, which eventually regulates the development of WG.

Disclosure: D. Takagi: None; Y. Nakamura: None; S. Akazawa: None; S. Fukuda: None.

2030

Low 25-OH Vitamin D Serum Levels Correlate with Extra-Hepatic Manifestations in Chronic Hepatitis C Virus Infection. Benjamin Terrier1, Jean-Claude Souberbielle2, David Saadoun1, Guillaume Geri1, Yolanda Schoindre3, Damien Sène2, Lucile Musset4 and Patrice Cacoub5. 1Necker, 2Pitié-Salpêtrière, Paris, France, 3Pitié-Salpêtrière, 4Pitié-Salpêtrière

Background: Recent studies have suggested the critical role of vitamin D in the regulation of the immune system, in promoting the development of regulatory T cells and decreasing pro-inflammatory cytokines and B cell differentiation. Correlation between low levels of 25-OH vitamin D and disease activity have been reported in various autoimmune disorders. The beneficial role of vitamin D administration was also suggested in chronic HCV infection.

Objective: To evaluate the association between serum 25-OH vitamin D levels and the presence of extra-hepatic manifestations and immunological abnormalities during chronic HCV infection.

Patients and Methods: Ninety-four HCV+ RNA+ untreated patients (36 without mixed cryoglobulinemia (MC), 10 with asymptomatic MC and 48 with MC-vasculitis) were included. Clinical and biological characteristics were recorded and compared according to vitamin D status. Vitamin D status was classified as: deficiency if serum 25-OH vitamin D level < 12, insufficiency between 12 and 30, and sufficiency > 30 ng/ml. Kruskal-Wallis test was used to compare groups. Correlations between serum 25-OH vitamin D levels and biological and immunological features were analyzed using nonparametric Spearman correlation.

Results: Overall, 84 (89%) patients had hypovitaminosis D (< 30 ng/ml). Patients were distinguished according to vitamin D status: sufficiency (n=10), insufficiency (n=52), and deficiency (n=32). Demographical and HCV infection characteristics were similar between groups. Patients with vitamin D deficiency vs. insufficiency vs. sufficiency had more frequently: vasculitis (75 vs. 42 vs. 20%; P=0.002), arthralgia (50 vs. 31 vs. 20%; P<0.01), neuropathy (59 vs. 38 vs. 20%; P=0.048), purpura (63 vs. 35 vs. 10%; P=0.004), and renal involvement (28 vs. 12 vs. 10%; P<0.01). Biologically, patients with vitamin D deficiency vs. insufficiency vs. sufficiency had more frequently type II MC (77 vs. 46 vs. 10%; P=0.002) and low C4 serum levels (86 vs. 47 vs. 0%; P<0.0001). A negative correlation was found between 25-OH vitamin D and C4 serum levels (r2=0.20; P=0.001) and the level of marginal zone B cells (r2=0.24; P=0.001), and a positive correlation with regulatory T cells (r2=0.23; P=0.005).

Conclusion: In chronic HCV infection, low 25-OH vitamin D serum levels correlate with clinical and biological immune system abnormalities. These findings suggest the potential benefit of vitamin D supplementation in HCV infected patients with extra-hepatic manifestations.

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2031

Patulous Eustachian Tube: A Novel Form of Damage in Wegener’s Granulomatosis. Philip Seo1 and Howard W. Francis2. Johns Hopkins Bayview Medical Center, Baltimore, MD, Johns Hopkins University

Background: The patulous eustachian tube (PET) is an uncommon syndrome caused by intermittent inappropriate patency of the eustachian tube that results in autophony. We explored whether this disorder might be more common among patients with Wegener’s granulomatosis.

Methods: Symptoms associated with the patulous eustachian tube were elicited from patients with a known diagnosis of systemic vasculitis using a standardized survey form. Demographics, vasculitis type, and treatment history were also recorded. Descriptive statistical analyses were performed based on patients who reported symptoms commonly associated with this disorder. Pearson chi-square analysis was used for group comparisons.

Results: One hundred fifty-two surveys were sent to patients evaluated at the Johns Hopkins Vasculitis Center; 123 subjects (80.9%) completed the survey and returned for tabulation. The respondents were comprised of 43 men and 80 women (1.2 ratio), who had a median age of 30 years (range: 17-85). One hundred twenty (97.6%) of subjects had autoimmune disease. One hundred thirteen subjects (91.2%) had a diagnosis of vasculitis that had been confirmed by a rheumatologist; these patients carried a diagnosis of vasculitis for a median of 7 years. 64.2% of subjects had ANCA-associated vasculitis (i.e., Wegener’s granulomatosis, microscopic polyangiitis, or the Churg-Strauss syndrome).

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Of the patients who had been diagnosed with vasculitis, 2/113 had been diagnosed previously with patulous eustachian tube; neither subject had received treatment for this diagnosis. Fifty-four subjects (47.8%) reported having at least one symptom associated with PET, most commonly ear fullness (44.2%). Forty subjects (35.4%) complained of an increased awareness of his or her own voice. Based on their reported symptoms, 16 subjects were considered “highly probable” for having PET. These patients had symptoms for a median of 5 years, and 11/16 (68.6%) are still symptomatic. On a Likert scale of 0–5, where 5 represents “intolerable” symptoms, these subjects rated their current symptoms with a median score of 2. Nine patients report having developed symptoms prior to or at the time they were diagnosed with vasculitis; 3 patients report developing symptoms only after they had been in remission.

Of the 60 patients surveyed who had Wegener’s granulomatosis, 36 (60%) had at least one symptom attributable to PET. Eleven patients with Wegener’s granulomatosis (18.3%) were “highly probable” for having PET.

Conclusions: Symptoms attributable to PET are common among patients with Wegener’s granulomatosis, possibly due to direct involvement of the eustachian tube. The majority of these patients are both symptomatic and undiagnosed. In many cases, these symptoms predate the diagnosis of vasculitis, implying that this may be a presenting symptom of Wegener’s granulomatosis in some patients.

Disclosure: P. Seo: None; H. W. Francis: None.

2032

Phase 1 Clinical Safety, Pharmacokinetic and Pharmacodynamic Evaluation of the Novel C5aR Antagonist CCX168, a Potential Therapeutic for ANCA-Vasculitis.

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Purpose: A single and multiple-ascending dose Phase 1 study has been conducted in healthy volunteers (HV) to establish the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profile of the orally administered C5aR antagonist CCX168. This compound has been shown to completely block anti-MPO induced glomerulonephritis (GN) in mice. This work has paved the way for clinical evaluation of CCX168 in patients with ANCA-associated vasculitis/glomerulonephritis.

Methods: In the Phase 1 program, 40 male or female HVs received either placebo or 1–100 mg CCX168 orally, in a single-dose or a multiple-dose (7 days) regimen. Blood was collected at pre-specified time points for PK and PD analyses. Ex vivo analysis of C5aR receptor coverage on blood neutrophils was performed based on C5a-induced chemotaxis and CD11b expression. A similar PD assay was performed on blood samples from mice dosed orally with CCX168. PK/PD requirements were defined for complete inhibition of C5aRmediated neutrophil activation and anti-MPO induced GN by CCX168 in transgenic C5aR knock-out mice expressing human C5aR.

Results: CCX168 potently blocks C5a-mediated chemotaxis of human neutrophils in human blood (IC50 2 nM) and CD11b upregulation (IC50 4 nM). CCX168 was well tolerated, with excellent oral bioavailability and dose-proportional increases in exposure in both periods of the Phase-1 clinical study. No serious adverse events or withdrawals due to adverse events were observed. Plasma levels of CCX168 of 197 ng/mL (~400 nM) were reached after a 100-mg dose. These levels of CCX168 far exceed those required in the anti-MPO mouse model for near-maximal GN prevention. Twelve hours following a 100-mg single dose of CCX168 in HVs, there was a 94% reduction in C5a-induced CD11b upregulation on blood neutrophils (ex vivo PD assay). At this dose, plasma distribution half-life was 7.8 hours and terminal half-life was about 29 hours.

Conclusions: CCX168 showed an excellent safety and tolerability profile in HVs. PK and PD data indicate that 30–50 mg CCX168 bid in humans should result in greater than 90% C5aR coverage in blood at all times, considered optimal for CCX168 evaluation in Phase 2 trials in vasculitis.

Disclosure: D. J. Dairagh: ChemoCentryx, 3; J. C. Jaen: ChemoCentryx, 3; K. Deshayes: ChemoCentryx, 3; D. A. Johnson: ChemoCentryx, 3; M. R. Lele: ChemoCentryx, 3; S. Miao: ChemoCentryx, 3; J. P. Powers: ChemoCentryx, 3; L. C. Seitz: ChemoCentryx, 3; Y. Wang: ChemoCentryx, 3; T. J. Schall: ChemoCentryx, 3; P. J. Bekker: ChemoCentryx, 3.

2033

Predictors of Outcome in Juvenile Polyarteritis Nodosa: A Multicenter Study.

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Background: Polyarteritis nodosa (PAN) is a necrotizing vasculitis, seldom reported in childhood and adolescence. The disease is more frequent in Asian populations but it has been reported in all ethnic groups.

Aims: 1. To describe the clinical features, at onset and during the disease course; 2. To look for possible predictive factors related with outcome or persistent damage in a cohort of Italian pts with paediatric onset PAN.

Method: A retrospective data collection of demographic, clinical and therapeutic characteristics from 50 Caucasian pts (21M, 29F) fulfilling EULAR/PRES criteria for the diagnosis of PAN, from 8 Paediatric Rheumatology Units and 1 Transition Unit, were collected. Mean age at onset was 7.9 yrs (range 2–16 yrs) and the mean follow up 6.2 yrs (range 0.3–16.4 yrs). Correlation among symptoms and internal organs involvement at onset, during the disease course and final outcome or persistent damage was made.

Results: At onset, skin involvement and systemic symptoms were the most common findings in 36/50 pts (72%); nodules the main cutaneous manifestation (40%), fever the most frequent systemic symptom (60%). Other early clinical manifestations were musculo-skeletal symptoms (54%), renal (12%), CNS involvement (10%), peripheral nervous system (6%), cardiac involvement (6%), and gastrointestinal manifestations (4%). All pts received corticosteroids either oral or IV, 16 pts (32%) azathioprine, 20 pts cyclophosphamide (20%, 15 oral and 5 iv), 9 (18%) thalidomide, 7 (14%) IVIG, 5 (10%) mexitheotide, 4 (8%) mycophenolate mofetil, and 2 (4%) biological agents (etanercept and infiximab). At the last follow up visit, 25 pts (50%) were in remission off therapy, 17 (34%) were under control on immunosuppressive drugs and 6 (12%) had persistent relapsing course. Two pts deceased because of ischemic cerebral infarction. At onset, the presence of renal involvement and fatigue significantly correlated with a bad outcome. CNS involvement, as seizures and paralysis, and nephrogenic hypertension, during the disease course, significantly correlated with the development of persistent damage.

Conclusion: The present study shows that in Caucasian children, PAN is quite severe despite the use of immunosuppressive drugs. Renal and CNS involvement seem to be the main factors affecting the final outcome.

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2034


Objective: To describe pregnancies of women with systemic necrotizing vasculitides (SNV), i.e., polyarteritis nodosa (PAN), Wegener’s granulomatosis (WG), Churg-Strauss syndrome (CSS) or microscopic polyangiitis (MPA), followed over the past 15 years at 4 French centers.

Methods: Retrospective analysis of women whose SNV appeared during pregnancy or who became pregnant after SNV diagnosis.

Results: Among the 12 women identified, 1 had rupture of pancreatic artery microaneurysms at 27 weeks of gestation revealing PAN, leading to surgical hemostasis and cesarean delivery. Other 11 had pregnancies after SNV diagnosis (8 in 4 WG, 6 in 3 CSS, 1 each in 3 PAN, and 2 in 1 MPA); 14 conceived during vasculitis remission. Two ended in first-trimester
abotions, 4 miscarried: the remaining 13 yielded 14 live newborns (1 twin pregnancy), with 7 preterm births. Life-threatening complications occurred during 3 of these latter 13 pregnancies and required cesarean deliveries. The twin pregnancy (in a CSS patient with initial vasculitis-related cardiac involvement, but in remission at conception) was complicated by transient maternal cardiac failure at 32 weeks. One WG patient with vasculitis-related renal damage developed thrombotic microangiopathy-associated renal impairment at 32 weeks, and another WG patient had severe pneumonia at 37 weeks. Other pregnancies were uneventful or with minor vasculitis manifestations.

**Conclusion:** Pregnant SNV patients should be closely monitored, since miscarriages and preterm births are not uncommon. Pregnancy does not seem to have a major impact on vasculitis activity. However, life-threatening manifestations can occur, especially in patients with vasculitis-related cardiac or renal damage.

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**2035**

**Pregnancy Related Morbidity and Mortality in Patients with Systemic Vasculitis—A Single Centre Controlled Study.** Shirish R. Sangle1, Periklis Vououriypidis1, Ashlelh Chahb2, Veronica Salas-Manzanedo1, Annette I. Briley1, Simon Angel1, Andrew Shennan1, Munther A. Khamashta1 and David P. D’Cruz1, 1St Thomas’ Hospital, London, United Kingdom, 2St Thomas’ Hospital

**Objective:** To study the outcome of pregnancy and effect of pregnancy on disease activity in patients with systemic vasculitis (SV) compared to age and ethnicity matched controls

**Patients and Methods:** We retrospectively studied 20 SV patients and 25 pregnancies attending the clinic since 1998. There were 4 with Wegener’s WG, 3 Churg-Strauss syndrome (CSS), 3 Takayasu arteritis (TA), and 2 ANCA positive vasculitis with renal involvement and 1 Henoch Schonlein purpura (HSP). All fulfilled the Chapel Hill Consensus Criteria and/or ACR Criteria for SV. Two others had Behçet’s disease, 3 urticarial vasculitis (UV), 1 adult onset Still’s disease (AOSD) and 1 primary cerebral vasculitis (PCV). Two patients with WG had 2 pregnancies each and each patient with CSS, TA and UV had 2 pregnancies. Details regarding the duration of SV, antibody and hepatitis profile, disease activity—Birmingham vasculitis disease activity score (BVAS) and vasculitis damage index (VDI) were retrospectively evaluated from the notes during the pregnancy. Pregnancy outcome along with maternal and foetal complications were documented. Data regarding 19 healthy women who were matched for age, ethnicity and year of delivery formed the control group which was collected from the Obstetrics database of St Thomas’ Hospital.

**Results:** The median age of the patients at the conception was 36 (24–46) and in the control group 35 (25–43) years. There were 16 Caucasian, 3 Asian and 1 Afro Caribbean in the SV group and 16 Caucasian, 2 Asian and 1 Afro Caribbean in the control subjects. The mean duration of SV was 3 (0–14) years. Six patients were receiving prednisolone, 10 azathioprine, 3 hydroxychloroquine and 2 no treatment during the pregnancy.

In the SV group, there were 19 successful pregnancies. There were 16 miscarriages in 7 patients. Median age of the gestation in SV was 38 (34–42) and in the controls 40 (37–42) weeks. Median birth weights in the SV group was 3.0 (2.0–5.2) and in the control subjects was 3.5 (2.28–4.32) kgs (p = NS). Six patients had pregnancy morbidity: 2 had pre-eclamptic toxemia (PET), 2 each had still births and premature deliveries and 1 patient had a post partum haemorrhage (she received heparin during pregnancy). In the control group 2 had miscarriages and 1 had PET. One patient with WG and HSP flared during the pregnancy and one other with WG required surgery in the 3rd trimester for sublentic stenosis. Eight patients with SV (2 WG, 1 each of HSP, CSS, TA, UV, AOSD and ANCA positive) flared after delivery. Four women were positive for antiphospholipid antibodies (aPL) and 2 had previous miscarriages. Three patients in the SV and 4 in the control groups were smokers. The median BVAS during pregnancy was 2 (range 1–5) and VDI was 2 (range 1–3).

**Conclusions:** Patients with systemic vasculitis are likely to flare during pregnancy and the post-partum period and may have significant pregnancy morbidity.

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**2036**

**Preliminary Classification Criteria for the Cryoglobulinemic Syndrome.** Salvatore De Vita1, Franca Soldano1, Miriam Isola2, Giuseppe Monti2, Armando Gabrielli3, Athanasios Tzioufas2, Clodoveo Ferri2, Gianfranco Ferraccioli1, Luca Quartuccio1, Laura Corazza1, Vineva De Marchi1, Manuel Ramos-Casals3, Michael Voulgarelis3, Marco Lenzi3, Francesco Saccardo3, Paolo Fratielli2, Maria Teresa Mascia4, Domenico Sanso0no5, Patrice Cabouc6, Matja Tomisc7, Antonio Taverni7, Maurizio Pietrogrande8, Anna Linda Zignego1, Salvatore Scarpato2, Cesare Mazza9, Silvia Piozzi10, Serge Stahl11, Vincent de Laforce12, Stefano Modena13, Bernardi14 and Massimo Galici15. 1Center for Systemic Manifestations of Hepatitis Viruses (MaSVE), Department of Internal Medicine, University of Florence, Florence, Italy, 2Centre de Références Maladies Auto-Immunes, Service de Médecine Interne II, Hôpital Pitié-Salpêtrière, Paris, France, 3Chair of Statistics, University of Udine, 4Department of Clinical Medicine, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy, 5Department of Hematology, Medical School, University of Athens, Greece, 6Department of Internal Medicine, Pordenone General Hospital, Pordenone, Italy, 7Department of Pathophysiology, Medical School of Athens, Athens, Greece, 8Department of Rheumatology, University Medical Centre, Ljubljana, Slovenia, 9Erasmus University Hospital, Department of Rheumatology, Brussels, Belgium, 10Institute of Immunology, University of Kiel, Kiel, Germany, 11Internal Medicine Unit, Policlinico San Marco, Bergamo, Italy, 12Internal Medicine Unit, Sarorno Hospital, Azienda Ospedaliera di Busto Arsizio, Sarono, VA, Italy, 13Internal Medicine, Donizetti Hospital, Monza, Italy, 14Internal Medicine, Università Politecnica delle Marche, Ancona, Italy, 15Istituto di Malattie Infettive e Tropicali, Università di Milano e/o Ospedale L. Sacco, Milan, Italy, 16Laboratorio de Enfermedades Autoinmunes Josep Font, IDIBAPS, Hospital Clinic, Barcelona, Spain, 17Rheumatology Clinic, AOU SMM, University of Udine, 18Rheumatology Clinic, AOU SMM, University of Udine, Udine, Italy, 19Rheumatology Division, Catholic University of Sacred Heart, Rome, Italy, 20Rheumatology Unit, Department of Internal Medicine, University of Modena, Italy, 21Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy, 22Rheumatology Unit, M. Scarlato Hospital, Scafati, Salerno, Italy, 23Section of Internal Medicine and Clinical Oncology, Department of Biomedical Sciences and Human Oncology, University of Bari, Medical School, Bari, Italy

**Objectives:** To develop international classification criteria for the CS.

**Methods:** The study was proposed by the GISC (Italian Study Group on Cryoglobulinemia), discussed between European EULAR experts, and divided in Part I, developing a questionnaire to be included in the formal, second part of the study (Part II). Positivity of serum cryoglobulins was defined as a "condition sine qua non" for CS classification. In Part I experts agreed on 17 questions putatively more sensitive and specific for CS. The questionnaire was administered to CS patients and controls (with diseases to be differentiated from CS). Study Part II involved 16 Centres from Italy and Europe. A dedicated chart included 1) a questionnaire for CS (with the discriminant questions identified by study Part I); 2) the pattern of organ involvement; 3) laboratory tests; 4) instrumental tests, as agreed. New patients with the CS (Group A) and controls, i.e., subjects with serum cryoglobulins but lacking a CS based on the golden standard judgment (Group B) and subjects without serum cryoglobulins but with clinico-laboratory features which can be observed in the course of CS (Group C), were studied. Monovariate and multivariate analyses, additive or multiplicative combinations of items in terms of sensitivity and specificity, and the best combination

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* PET: Pre-eclamptic toxemia
* Median gestational age
* Median birth weight
Results: In Part I, among 472 questionnaires (188 cases, 284 controls), a positive response to at least 2 of 3 selected resulted the best combination, showing a sensitivity of 81.9% and a specificity of 83.5% for CS. Study Part II included 272 patients in Group A, 228 controls in Group B, and 425 controls in Group C (173 C1 and 252 C2). The questionnaire developed in study Part I was validated, showing 83.8% CI 95% [79.4–88.2] specificity and 93.8% CI 95% [90.7–97.0] specificity for CS. The final Classification Criteria for CS, by pooling Group A and Group B data, are shown: at least 2 out of the following three anamnestic, clinical and laboratory items (questionnaire + clinical; questionnaire + laboratory; or clinical + laboratory) provided a sensitivity of 88.5% CI 95% [84.3–92.8] and a specificity of 93.6% CI 95% [89.5–97.7] for CS. The same criteria proved also useful for the comparison of group A vs. C, to suspect a CS in patients erythrocylogin-negative by initial testing, since sensitivity for CS was 88.5% CI 95% [84.3–92.8] and specificity 97.0% CI 95% [94.6–99.4] (a sensitivity of 88.5% [84.3-92.8] and a specificity of 95.4% [90.9-98.8] respectively, when comparing A only with the C1/ systemic vasculitis subgroup).

1. Preliminary Classification Criteria for the CS

   I. Anamnestic criteria (at least 1 of the following is present)

   a. Depressed awareness over several episodes of an acute confusional state, particularly involving the lower limb
   b. Had you ever had a spout in your eye that disappeared without taking anything by mouth or after some days?
   c. Data from the ventriculostomy on lavage and repeated punction

   II. Clinical criteria (at least 2 of the following 3 present)

   a. Constitutional symptoms
   b. Vascular involvement
   c. Neurological involvement

   a. Constitutional symptoms
   i. Low-grade fever (fever lasting for 7 days to several weeks)
   a. Vascular involvement
   i. Arterial involvement
   a. Arterial involvement
   b. Vascular involvement
   i. Vascular involvement
   b. Vascular involvement
   c. Neurological involvement
   i. Neurological involvement

   b. Laboratory criteria (at least 2 of the following 3 present)

   a. Reduced serum complement 4
   b. Positive serum rheumatoid factor
   c. Positive serum complement component C3

Conclusion: International classification criteria for the CS were developed, including items easily accessible, and showing a very high specificity and a good sensitivity. A validated questionnaire is available for epidemiologic studies.

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2038

Primary Central Nervous System Vasculitis: Analysis of 131 Patients

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Purpose: To analyze the clinical findings, response to therapy, outcome, and clinical subsets of primary central nervous system vasculitis (PCNSV) in a large cohort from a single center.

Methods: In the present study we used our updated cohort of 131 consecutive patients with PCNSV seen over the 25 year period of 1983 to 2007 at Mayo Clinic, Rochester, MN. The diagnosis of PCNSV was based on brain/spinal cord biopsy or cerebral angiography. The modified Rankin scale was used to evaluate the functional status. CNS tissue specimens from 63 cases were examined histologically. Clinical findings and outcomes were compared among patients categorized by method of diagnosis, response to therapy, survival, and degree of disability.

Results: Ninety patients were diagnosed by angiography and 41 by CNS biopsy. A granulomatous inflammatory histologic pattern was found in 23 patients (accompanied by vascular deposits of amyloid beta peptide in 11), a granulomatous and necrotizing pattern in 1, an acute necrotizing pattern in 9, and a lymphocytic pattern in 6. Headache (61.8%), altered cognition (52.7%), hemiparesis (40.5%), and persistent neurologic deficit or stroke (38.9%) were the most common initial symptoms. Intracranial hemorrhage occurred 16 cases (12.2%) within 3 months of the date of PCNSV diagnosis. Erythrocyte sedimentation rates at diagnosis were normal in most of the patients (median: 8 mm/hr, range: 0–110 mm/hr). Cerebrospinal fluid specimens showed 1 or more abnormal findings for 81/101 (80.2%) patients. Of the 97 patients with angiograms showing vasculitic changes, multiple-vein abnormalities were bilateral in 94.8%. Magnetic resonance imaging (MRI) was performed initially in 118 patients and showed abnormal findings in 113 (95.8%). Infarctions were seen in 65 (55.1%). Bilateral multiple infarctions were found in 48 of the 65 (73.8%) patients. Gadolinium-enhanced intracranial lesions were observed in 39% of the patients. Glucocorticoid therapy was prescribed for 128 of the 131 patients. In 55 patients, glucocorticoids were the only therapeutic agents used, while 73 patients received medication in addition to glucocorticoids (cyclophosphamide in 60 patients). A favourable response to glucocorticoid alone was observed in 78% and to glucocorticoid plus cyclophosphamide in 76%. 26% had relapses that led to a change in therapy. Survival of patients with PCNSV was significantly reduced. The reduced survival rate was due to 10 patients who died for stroke-related fatalities within 6 months after the diagnosis. These patients more frequently had paraparesis/quadriparesis at presentation, angiographic presence of bilateral, larger-vessel vasculitis, and MRI evidence of multiple and bilateral cerebral infarctions.
Conclusions: PCNSV is a rare disease that may result in serious neurological outcomes or death. Angiography and brain biopsy may complement each other when determining the diagnosis. Early recognition and treatment may reduce poor outcomes.

Disclosure: C. Salvarani: None; R. D. Brown, Jr: None; K. T. Calamia: None; T. T. H. Christianson: None; J. Huston III: None; J. F. Moschia: None; C. Giannini: None; G. G. Hunder: None.

2039 Prognostic Factors in Hepatitis C Virus Patients with Systemic Vasculitis. Benjamin Terrier¹, Oren Semoun², David Saadoun¹, Damien Séné³, Matthieu Resche-Rignon⁴ and Patrice Cacoub⁵. ¹Pitié-Salpêtrière, ²Saint-Louis, ³Saint-Louis University Hospital and RECIF, Amiens, France, ⁴Department of Clinical Epidemiology, Aarhus University Hospital, Aalborg, Denmark

Objective: Hepatitis C virus (HCV)-related systemic vasculitis can cause significant morbidity and mortality. Most of the prognostic studies reported in the literature are derived from old heterogeneous studies performed before the antiviral therapy era.

Methods: 151 consecutive HCV RNA+ patients with systemic vasculitis prospectively followed-up between 1993 and 2009 were analyzed for clinical, biological and therapeutic factors associated with survival.

Results: After a median follow-up of 54 months, 32 patients (21%) died, mainly of infection (n=10) and end-stage liver disease (n=10). One-year, 3-year, 5-year and 10-year survival rates were 96, 86, 75 and 63%, respectively. Two main factors associated with a poor prognosis were the presence of severe liver fibrosis (Metavir score ≥ 3) [hazard ratio (HR) 5.31], central nervous system (HR 2.74), kidney (HR 1.91), and heart involvement (HR 4.2). The Five Factor Score (FFS), a vasculitis scoring system, was significantly associated with outcome in HCV-related systemic vasculitis patients. In multivariate analysis, the Metavir liver fibrosis score (HR 10.8) and the FFS (HR 2.49) were significantly associated with a poor prognosis. During the follow-up, the use of the Peg-interferon plus ribavirin combination was associated with a good prognosis (HR 0.34). On the contrary, the use of immunosuppressant agents was associated with a poor outcome after adjustment for vasculitis severity (HR 4.05). In patients without severe liver fibrosis, the FFS was a good predictor of outcome, while in those with severe fibrosis, the vasculitis severity no longer had prognostic value.

Conclusion: In HCV-related systemic vasculitis patients, at the time of vasculitis diagnosis, severe liver fibrosis and vasculitis severity are the main prognostic factors. Use of antivirals is associated with a good prognosis, whereas immunosuppressants have a negative impact.

Disclosure: B. Terrier: None; O. Semoun: None; D. Saadoun: None; D. Séné: None; M. Resche-Rignon: None; P. Cacoub: Roche, 5.

2040 Risk Factors for Aortitis among Patients with Pathological Examination after Resection of the Thoracic Aorta in Denmark 1997–2009: A 12-Year Nationwide Population-Based Cross-Sectional Study. Jean Schmidt¹, Kaare Sunesen², Jette Kornum², Pierre Duhaut¹ and Reimar Thomsen². ¹Amiens University Hospital and RECIF, Amiens, France, ²Department of Clinical Epidemiology, Aarhus University Hospital, Aalborg, Denmark

Background: Population-based data on prevalence and risk factors for aortitis are scarce. The aim of our study was to assess them in a nationwide population-based cross-sectional study in Denmark.

Patients and Methods: We identified all adults hospitalized for first surgery of the thoracic ascending aorta between January 1, 1997 and March 1, 2009. Aortic inflammation was ascertained by linkage with nationwide pathological and biopsy databases. Logistic regression to examine whether sex, age at surgery, cardiovascular risk factors, cancer, and infectious diseases were associated with aortitis.

Results: During the study period, 1,210 adults underwent a resection of the ascending part of the aorta, and 610 (50.4%) had a pathological examination. Aortitis was found in 37 (6.1%). Ten of the 37 patients were diagnosed with conditions associated with aortitis or aortic aneurysm: five with temporal arteritis, one with Crohn’s disease, one with rheumatoid arthritis, one with systemic lupus erythematos, one with infectious aortitis, and one with Marfan’s disease. Twenty-seven patients had idiopathic aortitis. Predictors of aortitis included a history of connective tissue disease (adjusted OR 4.7, 95% CI 1.6 to 13.6), diabetes (OR 5.2, 96% CI 0.9–29.7), age > 67 years (OR 2.5, 95% CI 0.8–7.6), and aortic valve pathology (OR 2.3, 95% CI 1.1–4.9).

Conclusions: Aortitis was present in 6.1 % of adults with ascending aorta resection. This highlights the relevance of systematic pathological examination of aorta. Predictors of inflammation included connective tissue disease, with a tendency for diabetes and advanced age.

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2041 Rituximab Maintenance Therapy for Relapsed Wegener’s Granulomatosis and Microscopic Polyangiitis. Claire Roubaud-Baudron¹, Christian Pagnoux², Julien Le Guen³, Mathilde de Menthon³, Sandra Camps², Jessie Aouizerate³, Véronique Le Guern³, Pascal Cohen³, Luc Mouton³ and Loic Guillemin⁴. ¹Department of Pharmacy, Hôpital Cochin, APHP, Université Paris Descartes, ²Hôpital Cochin-Paris Univ, Paris, France, ³Internal Medicine, Hôpital Cochin, APHP, Université Paris Descartes, France

Background: After induction therapy, 50% of Wegener’s granulomatosis (WG) and 33% of microscopic polyangiitis (MPA) patients relapse. Rituximab (RTX) effectively induced remission of 1st relapses and refractory disease, but its place in remission maintenance is unknown. In this study, we retrospectively analyzed RTX efficacy as maintenance therapy.

Methods: Patients entered in our department database who had received ≥2 RTX maintenance infusions, regardless of induction regimen, between 2003 and 2010, were selected. Their main characteristics (diagnosis, clinical and biological data (ANCA, CD19 and Ig levels) and treatment histories), RTX maintenance details (number, dose and periodicity), tolerance and outcomes were analyzed.

Results: Four MPA and 24 WG patients (median age 55.5 (range 18–78) yr; 18 (58%) men) were included. The cumulative median cyclophosphamide (CYC) dose was 48 (range 10–250) g. At last relapse, patients had several organ involvements: 19 ENT, 17 lung, 11 arthralgias, 11 fever, 9 nephropathy, 3 neuropathy and/or 4 eyes.

Induction treatment had been RTX for 21, conventional corticosteroid (CS)+CYC for 5, and IVlg for 2 (1 also with methotrexate). RTX maintenance (375 mg/m² biannually for 15 patients, 1 g yearly for 3 and different regimens for 6) was chosen because RTX had obtained remission for 21, cytotoxic agent side effects for 2, persistent manifestations after >4 yr of azathioprine (AZA) or mycophenolate mofetil (MMF) for 1 each, previous relapse(s) under cytotoxic maintenance therapy for 2, or renal failure for 1. Patients had received 4 (range 2–10) RTX infusions at 38 (range: 21–97) months of follow-up since their last relapses. Cotreatments included CS for 23 (82%) patients and other cytotoxic agents (AZA for 5, MMF for 5, leflunomide for 1 and/or MTX for 4) for 14 (50%). At the last assessment, 5 (17%) patients were still taking cytotoxic agent(s); median CS dose was 5 (range: 2–20) mg/day. RTX infusions were well-tolerated; 3 patients developed infections (1 cutaneous abscess, 1 otitis and 1 H1N1-flu death).

Two major pulmonary relapses (at follow-up months 48 & 6) and 2 minor ENT relapses (at follow-up months 108 & 34) occurred. Fifteen patients had hypogammaglobulinemia (predominantly IgM). Notably, the 3 patients not CD19-depleted did not relapse. Nine (including 3/4 who relapsed) patients’ CD19 levels rose before their biannual RTX infusion. Five patients ANCA-negative at vasculitis onset, remained so. ANCA levels increased before reinfusion in 7 (including 3/4 who relapsed) patients. Overall, at their last assessment, mean ANCA titers for all 28 patients had declined significantly since the last relapse and the last RTX infusion (ANOVA, p=<0.001).

Conclusions: RTX effectively maintained remission and was well-tolerated. It can be indicated, especially for noncompliant patients or when cytotoxic drugs are contraindicated. Only 2 major relapsed occurred. It is too early to conclude as to the place of CD19 and ANCA levels as indicators to determine infusion periodicity. The ongoing randomized controlled “MAINRITSAN” trial was designed to compare RTX to AZA maintenance therapy for ANCA-associated vasculitides.

Disclosure: C. Roubaud-Baudron: None; C. Pagnoux: None; J. Le Guen: None; M. de Menthon: None; S. Camps: None; J. Aouizerate: None; V. Le Guern: None; P. Cohen: None; L. Mouton: None; L. P. Guillemin: Roche, 2, 5.
Safety and Efficacy of Rituximab in Non-Viral Cryoglobulinemia Vasculitis: Prospective Data from the French AIR Registry. Benjamin Terrier1, David Launay2, Gilles Kaplan1, Arnaud Hot3, Claire Larroche2, Pascal Chabert5, Bernard Combe4, Jean-Pierre Jaureguiberry5, Olivier Meyer6, Thierry Schaeverbeke7, Alexandre Somogyi5, Leila Tricot13, Thierry Zenone8, Philippe Ravaud9, Jacques-Eric Gottenberg10, Xavier Mariette11 and Patrice Cacoub12.

Background: Therapeutic management of non-hepatitis C virus cryoglobulinemia vasculitides (CryoVas) has still to be defined, although it is traditionally based on a combination of corticosteroids and immunosuppressants or plasmapheresis. Rituximab (RTX) has emerged as a novel and promising therapeutic alternative, but data are scarce since only few case reports have been reported in the literature.

Objectives: To evaluate safety and efficacy of RTX in non-viral CryoVas in off-trial real life patients.

Methods: Prospective data from the French Autoimmunity and Rituximab (AIR) registry, which includes patients with autoimmune disorders treated with RTX, were analyzed. The epidemiologic, clinical, and biologic data from every patient were collected at baseline, 3 and 6 month follow-up and then every 6 months. Toxicity and side effects were recorded on the standardized e-CRF.

Results: Twenty-three patients received treatment with RTX for non-viral CryoVas. Tolerance was marked by the occurrence of side effects in almost half of patients, including severe infections in 6/23 (26%), with a rate of 14/100 patient-years. These infections occurred in a particular subset of patients with age >70 years, essential type II mixed cryoglobulinemia, renal failure with GFR <60 mL/min and using high dose corticosteroids. Three of these patients died. In contrast, clinical and immunological improvement was noted in all evaluable patients. Clinical relapses occurred in half of patients after a median time of 13.5 months following RTX administration and were more frequent in patients refractory to previous immunosuppressive therapy than in previously untreated patients.

Conclusion: Data from the AIR registry show a dramatic efficacy and a steroid-sparing effect of RTX, but the occurrence of severe infections in aged patients with renal failure and high dose steroids. The role of RTX in non-viral CryoVas remains to be defined in well designed randomized controlled trials.

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Purpose: Small-vessel vasculitis (SVV) surrounding an uninflamed temporal artery (TA) is an often neglected pathological form of giant cell arteritis (GCA). A recent study showed a strong association between SVV and polymyalgia rheumatica (PMR). The aim of this study was to evaluate the prevalence and clinical significance of SVV surrounding an uninflamed temporal artery (TA) in an Italian population-based cohort of patients who received TA biopsy for a suspected diagnosis of GCA.

Methods: All TA biopsies performed in our Hospital between January 1986 and December 2005 were reviewed by a pathologist (AC) who was blinded to the clinical diagnosis. SVV was defined as aggregates of mononuclear inflammatory cells surrounding a capillary, distant from an uninflamed temporal artery. 180 patients residing in Reggio Emilia area with biopsy-proven GCA and 44 with SVV were identified. The identified patients with SVV were randomly matched to an equal number of biopsy-proven GCA patients. All inpatient and outpatient medical records were reviewed. Demographic, clinical, and laboratory data of patients in SVV group (n=44) were compared with data of control group with biopsy proven GCA (n=47).

Results: The table shows the comparisons between the patients with SVV and those with biopsy proven GCA.

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Seasonal- (SFV) and H1N1-Flu Virus (HFV) Vaccination for Patients with Autoimmune Diseases (AID): The Prospective MAIVAX Trial on 174 Patients. Alex Kostianovsky1, Michele Goulet2, Jean Francois Alves3, Veronique Le Guern2, Christian Pagnoux2, Pascal Cathebras1, Bernard Combe4, J.-E. Gottenberg5, Olivier Meyer5, Jean Francois Alves2, Pierre Cohen2, Alice Berezne2, Germain3, CHRU Lille, 7CHRU Strasbourg, 8CHU Bordeaux, 9CHU Lyon, 10CHU Marseille, 12CHU Montpellier, 12CHU St Etienne, 13CMC Foch, 14HIA Toulon, 15Pitié-Salpêtrière.

Background: In the historical debate on the role of vaccination in the context of AID patients exposed to the new H1N1 flu pandemic in June 2009, along with others.

Objective: To evaluate safety and efficacy of RTX in non-viral CryoVas in off-trial real life patients.

Methods: Prospective data from the French Autoimmunity and Rituximab (AIR) registry, which includes patients with autoimmune disorders treated with RTX, were analyzed. The epidemiologic, clinical, and biologic data from every patient were collected at baseline, 3 and 6 month follow-up and then every 6 months. Toxicity and side effects were recorded on the standardized e-CRF.

Results: Twenty-three patients received treatment with RTX for non-viral CryoVas. Tolerance was marked by the occurrence of side effects in almost half of patients, including severe infections in 6/23 (26%), with a rate of 14/100 patient-years. These infections occurred in a particular subset of patients with age >70 years, essential type II mixed cryoglobulinemia, renal failure with GFR <60 mL/min and using high dose corticosteroids. Three of these patients died. In contrast, clinical and immunological improvement was noted in all evaluable patients. Clinical relapses occurred in half of patients after a median time of 13.5 months following RTX administration and were more frequent in patients refractory to previous immunosuppressive therapy than in previously untreated patients.

Conclusion: Data from the AIR registry show a dramatic efficacy and a steroid-sparing effect of RTX, but the occurrence of severe infections in aged patients with renal failure and high dose steroids. The role of RTX in non-viral CryoVas remains to be defined in well designed randomized controlled trials.

Disclosure: B. Terrier: None; D. Launay: None; G. Kaplan: None; A. Hot: None; C. Larroche: None; P. Chabert: None; B. Combe: None; J.-P. Jaureguiberry: None; O. Meyer: None; T. Schaeverbeke: None; A. Somogyi: None; L. Tricot: None; T. Zenone: None; P. Ravaud: None; J.-E. Gottenberg: None; X. Mariette: None; P. Cacoub: Roche, S.


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Methods: All TA biopsies performed in our Hospital between January 1986 and December 2005 were reviewed by a pathologist (AC) who was blinded to the clinical diagnosis. SVV was defined as aggregates of mononuclear inflammatory cells surrounding a capillary, distant from an uninflamed temporal artery. 180 patients residing in Reggio Emilia area were identified. All inpatient and outpatient medical records were reviewed. Demographic, clinical, and laboratory data of patients in SVV group (n=44) were compared with data of control group with biopsy proven GCA (n=47).

Results: The table shows the comparisons between the patients with SVV and those with biopsy proven GCA.
Conclusion: SVV appears to be a less severe form of GCA characterized by a reduced frequency of cranial manifestations, lower values of ESR at diagnosis, and lower cumulative prednisone dose. Differently from previous findings, SVV was not associated with PMR.

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2045

Systemic Necrotizing Vasculitides in the Elderly: Baseline Data on the 101 Patients ≥65 Years Old Enrolled in the CORTAGE Multicenter Trial

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Objective: To analyze baseline characteristics of patients with systemic necrotizing vasculitides (SNV; polyarthritides nodosa (PAN), Wegener’s granulomatosis (WG), microscopic polyangiitis (MPA), Churg–Strauss syndrome (CSS)) enrolled in the corticosteroid-based treatment for SNV patients aged ≥65 yr (CORTAGE) trial.

Methods: We analyzed their baseline clinical and biological manifestations, i.e., at diagnosis. At that time, patients were classified according to their prognostic five-factor score (FFS) and randomized to receive conventional treatment (corticosteroids alone for ~28 months for CSS or PAN patients with FFS = 0; or combined with 500-mg/m2 cyclophosphamide pulses every 2 wk for the first 3 pulses then every 3 wk until remission, for WG or MPA patients, and CSS or PAN patients with FFS > 1, then switched to azathioprine or methotrexate for maintenance) or the experimental regimen (for all patients, corticosteroids for ~9 months, combined with cyclophosphamide pulses at a fixed 500-mg dose every 2 Wk for the first 3 pulses then every 3 wk until remission, and switched after a maximum of 6 pulses to azathioprine or methotrexate for maintenance). The CORTAGE primary endpoint is morbidity at 3 years.

Results: Between July 2005 and February 2008, 108 patients were randomized; 7 were excluded (early consent withdrawn, protocol violation, wrong diagnosis). Mean age at diagnosis of the 101 analyzed patients (54 males, 47 females; 8 PAN, 12 CSS, 34 WG, 47 MPA) was 75.3 ± 6.3 yr, with a maximum of 92 years for 1 MPA patient. Sixteen PAN or CSS patients had FFS = 0 (7/8 PAN, 9/12 CSS). Complete data on clinical features at diagnosis were comparably distributed between arms: 50 (50%) with fever, 36 (36%) arthralgias, 58 (57%) lung (15 nodules, 16 alveolar hemorrhages, 4 ARDS), 37 (37%) ENT, 20 (20%) GI, 18 (18%) heart (4 severe cardiac insufficiencies), 16 (16%) skin purpura, 13 (13%) ophthalmological (5 epipicieraties), 24 (24%) PNS and 3 (3%) CNS manifestations. Mean creatinine was 236 ± 210 μmol/l (61 microscopic hematuria, 8 initially required dialysis). Mean hemoglobin level was 10.2 ± 2.0 g/dl, neutrophils 8538 ± 4098/mm3, lymphocytes 1452 ± 674/mm3, C-reactive protein 103 ± 89 mg/l, albumin 28.0 ± 6.3 g/l.

Seven (6.9%); 4 conventional-arm, 3 experimental-arm) patients died during induction. All had received cyclophosphamide: 4 (3 MPA, 1 WG) died of SNV progression, 2 (WG) of sepsis and 1 (MPA) of previously unknown cholangiocarcinoma.

Conclusion: Despite having severe disease, as reflected by their high mean creatinine level at diagnosis, mortality of SNV patients ≥65 years old included in the CORTAGE trial was relatively low during induction. Treatment-related morbidity and relapse rate remain to be determined (end of trial follow-up: April 2011).

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Systemic Vasculitis in Patients with Hepatitis C Virus Infection with and without Detectable Mixed Cryoglobulinemia: Towards a Unique Entity

Benjamin Terrier1, Damien Sene2, Agnès Dechartres2, David Saadoun3, Lucile Musset1, Matthieu Resche-Rigon3, Thierry Maisonobe3 and Patrice Cacoub4. 1Pitié-Salpêtrière, ‘Saint-Louis

Background: More than 80% of mixed cryoglobulinemia (MC) are associated with hepatitis C virus (HCV) infection. Some patients develop symptomatic MC, a systemic vasculitis that mainly affects the small and, less frequently, medium-sized vessels. MC vasculitis leads to clinical manifestations ranging from the so-called MC syndrome (purpura, arthralgia, and asthenia) to more serious lesions with neurologic and renal involvement. It has been described few patients with peripheral neuropathy occurring with HCV infection without detectable MC.

Objectives: To describe HCV-related systemic vasculitis without detectable MC and to compare them to typical HCV-MC vasculitis.

Methods: The study population consisted of 60 patients with HCV infection (HCV RNA+) and chronic active liver disease. The 12 cases (men/women 5/7, mean age 60±17 years) were defined as patients with histologically proven systemic vasculitis who had not shown evidence of MC on numerous occasions during a follow-up of 55±38 months. Each case was matched for age and sex with 4 controls. The 48 controls (men/women 20/28, mean age 60±14 years) were randomly selected from our data base of patients with typical HCV-MC, i.e., patients who had serum MC levels > 0.05 g/L on at least on two occasions associated with the triad of purpura/arthralgia/asthenia and sometimes renal or neurological involvement.

Results: The main epidemiological and virologic features were similar between cases and controls. No clinical difference was found, except for lower rates of arthralgia (33% vs. 71%, p = 0.02) and purpura (50% vs. 83%, p = 0.03) in cases. Cases compared to controls showed higher mean serum C3 (1.17 ± 0.21 vs. 0.93 ± 0.23 g/L, p = 0.01) and median C4 levels (0.25 vs. 0.04 g/L, p = 0.001), lower median serum IgM levels (0.6 vs. 1.9 g/L, p < 0.001), and lower rates of rheumatoid factor positivity (8% vs. 82%, p < 0.001). Main pathologic features were similar between cases and controls. After treatment, overall clinical response of vasculitis (75% vs. 83%) and sustained virologic response (40% vs. 64%, p = 0.3) were similar between cases and controls, except for higher complete clinical response (42% vs. 73%, p = 0.05) in controls.
Conclusions: Practitioners should be aware of the occurrence of systemic vasculitis during HCV infection in the absence of detectable serum MC. Systemic vasculitis without MC showed quite similar epidemiological, clinical, biological, virologic and pathological features as MC vasculitis. Therapeutic management and response to therapy were also comparable between patients with and without MC. Such similarities suggest that vasculitis induced by chronic HCV infection, whatever the presence or the absence of MC, should be considered as a unique entity.

Disclosure: B. Terrier: None; D. Senc: None; A. Dechartres: None; D. Saadoun: None; L. Musset: None; M. Resche-Rigon: None; T. Maisonnebe: None; P. Cacoub: Roche, 5.

2047

The Correlation between Circulating Microparticles and Platelet Aggregation and Disease Activity in Wegener Granulomatosis, Rula Hajj-Ali1, Roy Silverstein1, Gary Hoffman1, Li Zhang1, Peter Imrey1 and Carol A. Langford2. 1Cleveland Clinic, 2Cleveland Clinic Foundation, Cleveland, OH, 3Cleveland Clinic, Cleveland, OH

Background: The objective of this study is to determine whether there are correlations between platelet aggregation and/or circulating microparticles (MP) and disease activity in Wegener’s granulomatosis (WG).

Methods: Eligible consenting adult patients who met the ACR 1990 classification criteria for WG were enrolled from the Cleveland Clinic Center for Vasculitis Care and Research. Controls were subjects who did not have WG or other chronic inflammatory diseases. Exclusion criteria for patients and controls included acute or chronic infection within the past 3 months, NSAID or aspirin use within a week of platelet and MP collection for patients and controls included acute or chronic infection within the past 3 months, NSAID or aspirin use within a week of platelet and MP collection.

Results: 46 patients were included; 38 in remission and 8 during acute disease relapse. The two groups did not differ in age or gender. Subjects in relapse had

1. a significant increase in leukocyte derived MP compared to those in remission, and
2. platelets with increased sensitivity to activation by ADP (Table 1).

Table 1. Comparison of MP counts and platelet aggregation between flare and remission groups

<table>
<thead>
<tr>
<th>Factor</th>
<th>Flare (N=8)</th>
<th>Remission (N=38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 13</td>
<td>54 ± 13</td>
<td>0.20</td>
</tr>
<tr>
<td>Female</td>
<td>5 (63)</td>
<td>17 (45)</td>
<td>0.45</td>
</tr>
<tr>
<td>CD14 - MP counts</td>
<td>477 (386, 797)</td>
<td>249 (67, 409)</td>
<td>0.030*</td>
</tr>
<tr>
<td>CD16 - MP counts</td>
<td>182 (127, 219)</td>
<td>56 (26, 100)</td>
<td>0.006*</td>
</tr>
<tr>
<td>CD18 - MP counts</td>
<td>210 (314)</td>
<td>63 (36, 100)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Platelet aggregation (1µM ADP)</td>
<td>28 (18, 38)</td>
<td>5 (2, 10)</td>
<td>0.055*</td>
</tr>
<tr>
<td>Platelet aggregation (2 µM ADP)</td>
<td>49 (43, 71)</td>
<td>19 (7, 26)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Platelet aggregation (5 µM ADP)</td>
<td>82 (78, 98)</td>
<td>36 (26, 57)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Platelet aggregation (10 µM ADP)</td>
<td>87 (78, 92)</td>
<td>51 (38, 70)</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

Normally distributed data were expressed as mean ± SD and analyzed with the P from the T-test; Non-normally distributed data were expressed as median (25th, 75th) percentiles and analyzed with the P from the Wilcoxon rank sum test. N and percentage for categorical variables with Fisher exact test.

We also assessed the association of MP levels to platelet aggregation in WG vs. healthy controls (N=21). There were moderately positive linear relationships between levels of CD14, CD16 and CD18 expressing MP and platelet aggregation responses in WG patients. There were no statistically significant associations in the control group (Table 2).

Table 2. Correlation of Platelet aggregation and MP counts in WG and healthy controls

<table>
<thead>
<tr>
<th>Platelet aggregation</th>
<th>MP</th>
<th>N</th>
<th>rho</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WG Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADP 1µM CD14</td>
<td>41</td>
<td>0.43</td>
<td>(0.14, 0.65)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>CD16</td>
<td>41</td>
<td>0.47</td>
<td>(0.19, 0.68)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>CD18</td>
<td>41</td>
<td>0.64</td>
<td>(0.41, 0.79)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ADP 2µM CD14</td>
<td>44</td>
<td>0.38</td>
<td>(0.09, 0.61)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>CD16</td>
<td>44</td>
<td>0.40</td>
<td>(0.12, 0.63)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>CD18</td>
<td>44</td>
<td>0.54</td>
<td>(0.28, 0.72)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ADP 5µM CD14</td>
<td>44</td>
<td>0.35</td>
<td>(0.06, 0.58)</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>CD16</td>
<td>44</td>
<td>0.31</td>
<td>(0.01, 0.55)</td>
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<tr>
<td>CD18</td>
<td>44</td>
<td>0.45</td>
<td>(0.18, 0.66)</td>
<td>0.002</td>
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</tr>
<tr>
<td>ADP 10 µM CD14</td>
<td>41</td>
<td>0.32</td>
<td>(0.02, 0.57)</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>CD16</td>
<td>41</td>
<td>0.30</td>
<td>(0.01, 0.06)</td>
<td>0.058</td>
<td></td>
</tr>
<tr>
<td>CD18</td>
<td>41</td>
<td>0.43</td>
<td>(0.14, 0.65)</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

Controls

<table>
<thead>
<tr>
<th>MP</th>
<th>N</th>
<th>rho</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP 1µM CD14</td>
<td>19</td>
<td>0.31</td>
<td>(0.11, 0.84)</td>
<td>0.13</td>
</tr>
<tr>
<td>CD16</td>
<td>19</td>
<td>0.25</td>
<td>(0.18, 0.79)</td>
<td>0.13</td>
</tr>
<tr>
<td>CD18</td>
<td>19</td>
<td>0.28</td>
<td>(0.21, 0.77)</td>
<td>0.25</td>
</tr>
<tr>
<td>ADP 2µM CD14</td>
<td>21</td>
<td>0.25</td>
<td>(0.21, 0.72)</td>
<td>0.27</td>
</tr>
<tr>
<td>CD16</td>
<td>21</td>
<td>0.18</td>
<td>(0.29, 0.65)</td>
<td>0.43</td>
</tr>
<tr>
<td>CD18</td>
<td>21</td>
<td>0.28</td>
<td>(0.18, 0.74)</td>
<td>0.22</td>
</tr>
<tr>
<td>ADP 5µM CD14</td>
<td>21</td>
<td>0.41</td>
<td>(0.03, 0.85)</td>
<td>0.067</td>
</tr>
<tr>
<td>CD16</td>
<td>21</td>
<td>0.38</td>
<td>(0.43, 0.56)</td>
<td>0.78</td>
</tr>
<tr>
<td>CD18</td>
<td>21</td>
<td>0.44</td>
<td>(0.01, 0.87)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Conclusions: Levels of leukocyte derived MP and sensitivity of platelets to ADP-induced aggregation correlate with disease flares in WG. The correlation between MP counts and platelet reactivity seen in WG but not controls suggest that elevated levels of leukocyte-derived MP generated during chronic inflammation may sensitize platelets to activation and contribute to athero-thrombotic complications. Whether these events also contribute to injury in WG is worthy of further studies.

Disclosure: R. Hajj-Ali: American Heart Association, 2; R. Silverstein: NIH; 2; G. Hoffman: None; L. Zhang: American Heart Association, 2; P. Imrey: None; C. A. Langford: None.

2048

The Human C5a Receptor (hC5aR) Antagonist CCX168 Effectively Ameliorates a Model of ANCA Glomerulonephritis (GN) in hC5aR Knock-in Mice. Hong Xiao1, J. C. Jennette1, D. J. Danahill1, L. Ertl1, T. Baumgart2, S. Miao1, J. P. Powers1, L. C. Seitz1, Y. Wang1, P. Hu3, R. J. Falk4, T. J. Schall1 and J. C. Jaen1. 1ChemoCentryx, 2University of North Carolina, Chapel Hill, NC, 3University of North Carolina, chapel Hill, NC, 4University of North Carolina

Purpose: Intravenous injection of mouse anti-mylolperoxidase (anti-MPO) IgG causes GN and vasculitis in mice that mimics antineutrophil cytoplasmic autoantibody (ANCA) disease in patients. We have shown that alternative pathway complement activation and resultant C5a are involved in pathogenesis. Here we study the effects on this model of CCX168, an orally active antagonist of human C5a receptor (hC5aR) that has completed Phase 1 trials. We also evaluated CCX168 pharmacokinetic, pharmacodynamic and therapeutic endpoints in mice using the same assays of hC5aR blockade used in the human Phase 1 trial.

Methods: Humanized mice with knock-in of human C5aR and knock-out of mouse C5aR (hC5aR KI mice) were injected with anti-MPO IgG; and received CCX168 doses ranging from 0.1–30 mg/kg qd, or vehicle alone. The potency of CCX168 for C5ar in hC5aR KI mice was assessed by 125I-C5a binding and chemotaxis assays. C5a-induced neutrophil CD11b expression was used to assess CCX168 C5aR blockade in mice and compared to results using the same assay in humans.

Results: CCX168 had similar C5aR antagonist potency on human and hC5aR KI mouse neutrophils (inhibition of C5a-mediated chemotaxis in blood, IC50 2 nM; inhibition of C5a-induced CD11b upregulation in blood, IC50 4 nM). 30 mg/kg CCX168 markedly reduced the severity of anti-MPO induced GN. Glomerular crescent formation was reduced from 29.3% with vehicle alone to 8.2% with vehicle alone to 30% with CCX168 (p<0.001) and glomerular necrosis from 12% to 2% with CCX168 (p<0.001). Urine protein, leukocytes and RBCs, and serum BUN and creatinine also were reduced in mice receiving CCX168. 0.1 mg/kg/d CCX168 caused 30% reduction in crescents. The lowest dose that produced a near-maximal therapeutic benefit was 4 mg/kg CCX168 bid (with plasma levels from 35 to 200 ng/mL throughout the day, and C5aR blockade ranging from 95 to 99%). As reported in
a separate meting abstract, plasma CCX168 levels of 197 ng/mL (~400 nM) were reached with a 100-mg dose in a human Phase 1 trial.

**Conclusions:** Orally active human CSAR antagonist CCX168 markedly suppresses the induction of GN by anti-MPO IgG in mice with knock-in human CSAR. CCX168 doses that induce a near-maximal therapeutic benefit in mice produce CCX168 plasma levels and CSAR blockade that are attainable and well tolerated in Phase I human trials. These results support an important role for CSAR engagement by C5a in the pathogenesis of anti-MPO induced GN, which is a model for human ANCA GN, and thus support the possible therapeutic benefit of CSAR blockade in human ANCA disease.

**Disclosure:** H. Xiao: Chemocentryx, 9; J. C. Jennette: Chemocentryx, 9; D. J. Dairaghi: Chemocentryx, 3; L. Erti: Chemocentryx, 3; T. Baumgart: Chemocentryx, 3; S. Miao: Chemocentryx, 3; J. P. Powers: Chemocentryx, 3; L. C. Seitz: Chemocentryx, 3; Y. Wang: Chemocentryx, 3; P. Hu: Chemocentryx, 9; R. J. Falk: Chemocentryx, 9; T. J. Schall: Chemocentryx, 3; J. C. Jaen: Chemocentryx, 3.

**2049**

The Relationship between Disease Status in Wegener’s Granulomatosis with the Development of Subclinical Atherosclerosis. Rula Hajj-Ali1, Roy Silverstein2, Douglas Joseph1, Peter Imrey2, Gary S. Hoffman3, Li Zhang4 and Carol A. Langford3.1 Cleveland Clinic; 2 Cleveland Clinic Foundation, Pepper Pike, OH, 3 Cleveland Clinic, Cleveland Clinic Foundation, Cleveland, OH, 4 Cleveland Clinic Foundation, Pepper Pike, OH, 5 Cleveland Clinic, Cleveland, OH

**Background:** A role for inflammation in the development of accelerated atherosclerosis in patients with chronic inflammatory disease has been proposed. However, the pathophysiology of this process is not fully understood. The objective of this study was to assess the relationship between inflammatory disease in Wegener’s granulomatosis (WG) with the development of subclinical atherosclerosis.

**Methods:** Eligible consenting adult patients who met the 1990 ACR classification criteria for WG were enrolled from the Cleveland Clinic Center for Vasculitis Care and Research. Exclusion criteria included history of coronary heart disease, heart failure, stroke, peripheral vascular diseases, acute or chronic infection within the past 3 months, NSAID or aspirin use within a week of MP and platelet studies, or diagnosis of chronic inflammatory disease, an autoimmune disease, or thrombophilia. Disease status was measured by BVAS-WG, VDI, disease duration and numbers of relapses (from onset of disease diagnosis until enrollment in the current study). Classic atherosclerotic risk factors and other co-morbidities were recorded in addition to platelet aggregation responses and circulating microparticle (MP) levels. All patients underwent ultrasound of the carotid arteries to assess intima media thickness (IMT) as an outcome for subclinical atherosclerosis.

**Results:** 45 WG patients were included. In univariate analyses, systolic and diastolic blood pressure, creatinine, and age at onset of disease were significantly associated with a higher IMT with rho values of 0.37, 0.38, 0.35 and 0.54 respectively (p < 0.02 for all), determined by Spearman rank correlation (Table 1).

**Table 1.** Spearman rank correlation between IMT and patient characteristics

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Variable</th>
<th>N</th>
<th>r</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT BMI</td>
<td></td>
<td>44</td>
<td>0.19</td>
<td>(-0.12, 0.49)</td>
<td>0.23</td>
</tr>
<tr>
<td>IMT Systolic blood pressure</td>
<td>45</td>
<td>0.37</td>
<td>(0.09, 0.66)</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>IMT Diastolic blood pressure</td>
<td>45</td>
<td>0.38</td>
<td>(0.09, 0.66)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>IMT Creatinine</td>
<td>45</td>
<td>0.35</td>
<td>(0.06, 0.64)</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>IMT HDL</td>
<td>45</td>
<td>0.21</td>
<td>(-0.51, 0.10)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>IMT LDL</td>
<td>45</td>
<td>0.19</td>
<td>(-0.5, 0.23)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>IMT FBG</td>
<td>45</td>
<td>0.12</td>
<td>(-0.18, 0.43)</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>IMT Age at onset of disease</td>
<td>45</td>
<td>0.54</td>
<td>(0.28, 0.80)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>IMT Disease Duration</td>
<td>45</td>
<td>0.23</td>
<td>(-0.07, 0.53)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>IMT Azathioprine Duration</td>
<td>45</td>
<td>0.24</td>
<td>(-0.53, 0.06)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>IMT Methotrexate Duration</td>
<td>45</td>
<td>0.11</td>
<td>(-0.20, 0.41)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>IMT Cyclophosphamide Duration</td>
<td>45</td>
<td>0.13</td>
<td>(-0.43, 0.18)</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>IMT Cumulative Dose of cyclophosphamide</td>
<td>45</td>
<td>0.15</td>
<td>(-0.45, 0.16)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>IMT Total MP counts</td>
<td>45</td>
<td>0.18</td>
<td>(-0.48, 0.12)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>IMT Annexin counts</td>
<td>45</td>
<td>0.02</td>
<td>(-0.50, 0.10)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>IMT CD_14 MP counts</td>
<td>45</td>
<td>-0.04</td>
<td>(-0.34, 0.27)</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>IMT CD_16 MP counts</td>
<td>45</td>
<td>-0.12</td>
<td>(-0.42, 0.19)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>IMT CD_18 MP counts</td>
<td>45</td>
<td>0</td>
<td>(-0.31, 0.31)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>IMT CD_41 MP counts</td>
<td>45</td>
<td>-0.16</td>
<td>(-0.47, 0.14)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>IMT CD_105 MP counts</td>
<td>45</td>
<td>0.21</td>
<td>(-0.53, 0.09)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>IMT CD_144 MP counts</td>
<td>45</td>
<td>0</td>
<td>(-0.31, 0.31)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>IMT CD_235 MP counts</td>
<td>45</td>
<td>-0.03</td>
<td>(-0.37, 0.26)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>IMT Platelet aggregation</td>
<td>40</td>
<td>0.24</td>
<td>(-0.08, 0.56)</td>
<td>0.14</td>
<td></td>
</tr>
</tbody>
</table>

When all variables were considered in a multiple regression model that included the total number of disease relapses, and after adjusting for the other significant factors, higher relapse number, older age at onset of disease, and higher diastolic blood pressure were found to be associated with higher IMT as shown in Table 2.

**Table 2.** Multiple regression model for assessing the association between IMT and sum of Flares

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Parameter</th>
<th>Estimate (%95 CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT Flare sum</td>
<td>0.0119 (0.0001, 0.0236)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>IMT Age at onset of disease</td>
<td>0.005 (0.003, 0.008)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>IMT Diastolic blood pressure</td>
<td>0.0033 (0.0003, 0.0064)</td>
<td>0.031</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** This is the first study that addresses disease status as it relates to atherosclerosis in WG. Our data suggests that total number of disease relapses, but not disease duration, is a more important risk factor for atherosclerosis and implies that the cumulative inflammatory events contributes to the development of atherosclerosis.

**Disclosure:** R. Hajj-Ali: American Heart Association, 2; R. Silverstein: NIH, 2; D. Joseph: None; P. Imrey: None; G. S. Hoffman: None; L. Zhang: American Heart Association, 2; C. A. Langford: None.

**ACR Poster Session C**

ACR/ARHP Poster Session C: ARHP: Physical Exercise

Wednesday, November 10, 2010, 9:00 AM–6:00 PM

**2050**

'Specialized Generalists': How Do Rehabilitation Therapists Practice in Rural Areas? Robin K. Roots, Linda C. Li, Lesley Bainbridge and Helen Brown. University of British Columbia, Vancouver, BC, Canada

**Background:** The health disparity between rural and urban residents, including higher rates of arthritis and other chronic diseases, necessitates innovative practice models for rehabilitation professionals, who are already in short supply in rural areas. The purpose of this research is to better understand the barriers and facilitators to rehabilitation practice from the perspectives of occupational therapists (OTs) and physical therapists (PTs) working in rural regions.

**Methods:** OTs and PTs living and working in rural communities within a provincial health authority were recruited through a mail out to workplaces. Using purposive sampling, therapists were selected according to their range of experience in rural practice and the health care setting, source of funding and service delivery model in which they worked. Following a semi-structured interview guide, therapists were asked to describe how the rural context shapes their practice using an example of service provision for a patient with arthritis. Face-to-face interviews were recorded and transcribed. Guided by the methodological approach of interpretive description, data was analysed inductively to identify concepts of rural practice and extrapolate practice insights and exemplary strategies used by therapists. An analytic framework was used to map relationships between themes, concepts and cases. Rural rehabilitation practice paradigms will be interpreted to consider implications for practice change.

**Results:** Of the 43 eligible clinicians, 11 PTs, 6 OTs and 2 combined trained OT/PTs agreed to participate. Consistent with the literature, rural therapists described themselves as ‘specialized generalists’ referring to the broad scope of practice deemed essential to providing service to the diversity of their caseloads. While maintaining competency in a large number of practice areas presents significant challenges, therapists articulated strategies based on the unique context and features of rural practice. Skills and knowledge listed by therapists as essential to rural practice included: 1) waitlist priority setting; 2) drawing upon a large network of professional and community resources; 3) recognizing boundaries to competency through reflective practice; and 4) the importance of collaborating with other practitioners. Collaborative practice was seen as optimal in providing client centred care but not always achievable given limited resources, isolation and professional barriers. When asked what supports would be beneficial for practitioners new to rural practice, participants highlighted the importance of practice education placements in rural communities during training, formal mentoring programs, and a greater emphasis on interprofessional education.
Conclusion: Despite the growing interest in professional specialization, rural therapists appear to maintain general practice and interprofessional collaborative service delivery models in order to equitably meet the demands of the rural population and transcend the limited local health resources and services.

Disclosure: R. K. Roots: None; L. C. Li: None; L. Bainbridge: None; H. Brown: None.

2051


Background: In 2001 the Royal Dutch Society for Physical Therapy (KNGF) Guideline for hip and knee osteoarthritis (HKOA) was developed. Since then, many scientific papers on physical therapy interventions as well as national and international guidelines were published.

Objectives: To update the physical therapy guideline based on current evidence and best practice.

Methods: Topics concerning the three guideline chapters: initial assessment, treatment and evaluation were selected by a guideline development committee consisting of 10 expert physical therapists. With respect to treatment a systematic literature search (up to June 2009) within various databases was performed aiming to identify reviews and randomized controlled trials (RCTs) on the effectiveness of physical therapy interventions and the evidence was graded (1–4). For initial assessment and evaluation mainly review papers and textbooks were used. Based on evidence and expert opinion, recommendations were formulated (5 consensus meetings and 6 feedback rounds) and graded (A-D). A first draft of the guideline was reviewed by 17 experts from different professional backgrounds (2 feedback rounds). A second draft was field-tested by 45 physical therapists.

Results: For the initial assessment, a description of relevant health related topics in HKOA was made according to the International Classification of Functioning, disability and health (ICF) core set for osteoarthritis (OA). Concerning treatment, 22 systematic reviews and 74 RCTs were reviewed. Recommended were: exercise therapy, education and self management interventions, a combination of exercise and manual therapy, and postoperative exercise therapy in HKOA, and taping of the patella in knee OA. Neither recommended nor advised against were: balneotherapy, hydromassage, ultrasound, electrotherapy, electromagnetic field and Low Level Laser Therapy. For the evaluation of treatment goals the use of one or more of the following measurement instruments was recommended: daily activities and participation: Lequesne index questionnaire, Hip and Knee disability and Osteoarthritis Outcome Scores, 6 Minute Walk test, Timed Stand Up and Go test and Patient Specific Complaint list; body functions and structures: Visual Analogue Scale for pain, Intermittent and Constant Osteoarthritis Pain questionnaire, goniometry, Medical Research Council for strength, Handheld Dynamometer.

Conclusions: This update of the Dutch physical therapy guideline on HKOA included recommendations on the initial assessment, treatment and evaluation. The revised guideline will be published on www.kngf.nl (including an English translation).

Disclosure: W. F. H. Peter: None; M. J. Jansen: None; E. J. Hurkmans: None; H. Bloo: None; R. G. Dilling: None; W. K. H. A. Hilberdink: None; C. Kersten-Smit: None; M. de Rooij: None; C. Veenhof: None; E. M. Vermeulen: None; I. de Vos: None; J. W. Schoones: None; T. F. M. Vliet Vlieland: None.

2052


Background: Self-reported knee instability is a common symptom that can affect physical function in people with KOA. Very little has been reported concerning factors that may be associated with self-reported knee instability in KOA. Understanding factors associated with knee instability is the first step in understanding how to treat this symptom. The purpose of this study was to examine the association between clinical assessment variables and self-reported knee instability in subjects with KOA.

Method: 158 subjects (107 female) with KOA participated in the study. Person specific measures of independent clinical variables included age, gender, body mass index, fear of physical activity, anxiety, and depression. Knee specific variables were taken on the index knee (most symptomatic knee as reported by the subject) and included radiographic severity of the medial, lateral, and patellofemoral compartments, knee pain, quadriceps muscle strength, lower extremity muscle flexibility (hip flexors, quadriceps, hamstrings, gastrocnemius) knee range of motion, frontal plane and sagittal plane passive knee laxity, and knee alignment. The dependent measure was the Knee Outcome Survey Self-Reported Instability item (KOS-SRI) 5 = no instability, 4 = instability present but does not affect function, 3 = instability minimally affects function, 2 = instability moderately affects function, 1 = instability severely affects function) participated in the study. Subjects were dichotomized as stable if the KOS-SRI score was ≥ 4 and unstable if ≤ 3. A stepwise, forward (likelihood ratio), logistic multiple regression analysis was performed to identify which clinical variables were associated with the KOS-SRI score.

Results: Table 1 summarizes the results of the regression analysis. Medial compartment radiographic severity, knee pain, depression, and hamstring flexibility were associated with the KOS-SRI score.

Table 1. Results of Stepwise Linear Regression. Nagelkerke R²=0.45

<table>
<thead>
<tr>
<th>Variable</th>
<th>beta</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial Compartment Knee OA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity (KL grade)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KL=1</td>
<td>-2.62</td>
<td>0.07</td>
<td>0.01; 0.87</td>
<td>.04</td>
</tr>
<tr>
<td>KL=2</td>
<td>2.76</td>
<td>15.77</td>
<td>0.95; 290.99</td>
<td>.054</td>
</tr>
<tr>
<td>KL=3</td>
<td>-0.29</td>
<td>0.75</td>
<td>0.22; 2.49</td>
<td>.63</td>
</tr>
<tr>
<td>KL=4</td>
<td>-0.20</td>
<td>0.82</td>
<td>0.27; 2.51</td>
<td>.73</td>
</tr>
<tr>
<td>Knee Pain (VAS)</td>
<td>-0.39</td>
<td>0.68</td>
<td>0.56; 0.82</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Depression (CES-D)</td>
<td>-0.09</td>
<td>0.91</td>
<td>0.86; 0.97</td>
<td>.01</td>
</tr>
<tr>
<td>Hamstring Tightness</td>
<td>0.07</td>
<td>1.07</td>
<td>1.03; 1.11</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Conclusion: The results indicate that a medial compartment Kellgren and Lawrence (KL) grade < 2, lower numeric knee pain rating, less depression, and tighter hamstring muscles are protective against self-reported knee instability in our sample of subjects with KOA. Longitudinal study is needed to determine if changes in these variables mediate the progression of self-reported knee instability over time.

Disclosure: G. K. Fitzgerald: None; S. R. Piva: None; S. R. Wisniewski: None.
Describing the Pattern of Outpatient Physical Therapy Utilization Following Total Knee Replacement (TKR). Carol A. Oatis1, Jessica M. DiRusso1, Mindy J. Hoover1, Katherine K. Johnston1, Monika Kasinova1, Patricia D. Franklin1. Arcadia University, Glenside, PA, 1Univ of MA Med Schl, Worcester, MA

Purpose: Incidence of TKR is projected to rise 673% by 2030 to 3.48 million from 450,000 procedures in 2005. According to the 2003 NIH Consensus Statement, post-operative rehabilitation is the most understudied aspect of the management of TKR. The purpose of this study was to examine outpatient physical therapy (PT) utilization by patients who have undergone primary TKR surgery.

Methods: PT records from TKR patients participating in a NIAMS-funded clinical trial at the University of Massachusetts Medical Center were included in the study. Patients who attended outpatient PT, completed their course of care and the study’s 6-month assessment were eligible for review. Records from 65 patients who underwent primary TKR were eligible for review. Forty-four outpatient PT records were reviewed from 18 facilities. Twenty-one records were not reviewed because the facilities did not respond to requests for the records. Of these 21 records, 14 were from facilities that had sent at least 1 other record. Frequency and duration of physical therapy and total number of visits were recorded. “Usual care” was operationally defined as more than 85% agreement in delivery. Univariate regression analysis assessed the associations between PT utilization and patient baseline characteristics that could be associated with greater PT need (e.g., poorer pre-op function or self-care).

Results: No agreement or consensus existed regarding timing of initiation of outpatient PT (2–8 weeks postoperatively). There was no agreement on the total number of outpatient visits (7–34) or on when to discontinue outpatient PT (7–30 weeks postoperatively). The average number of visits was 15 (SD 6.3). Although there was a trend toward correlation between time to start of post-operative outpatient PT and age (r = 0.8; r2 = 0.67), no other relationship existed between PT utilization and baseline characteristics, including function (PCS scale of the SF36, WOMAC), emotional health (MCS scale of SF36), arthritis self-efficacy, depression (CESD) or BMI.

Conclusions: Considerable variability exists in outpatient PT utilization despite the prevalence of the procedure. Utilization appears unrelated to preoperative patient characteristics that could be associated with greater PT need. People who undergo a primary TKR still have varied functional gains one year after the surgical intervention. Research is needed to determine if the variability in post-operative outpatient PT utilization contributes to sub-optimal patient outcomes. Better understanding of outpatient PT utilization may lead to rehabilitation practices that yield optimal outcomes and are cost efficient.


Describing the Pattern of Physical Therapy Intervention Following Total Knee Replacement (TKR). Jessica M. DiRusso1, Mindy J. Hoover1, Katherine K. Johnston1, Monika Kasinova1, Patricia D. Franklin1 and Carol A. Oatis1. Arcadia University, Glenside, PA, 1Univ of MA Med Schl, Worcester, MA

Purpose: The incidence of TKR is projected to rise 673% by 2030 to 3.48 million from 450,000 procedures in 2005. According to the 2003 NIH Consensus Statement, post-operative rehabilitation is the most understudied aspect of the management of TKR. Quadriiceps strength remains diminished one year after surgery and aggressive quadriiceps strengthening has been shown to improve functional outcomes. The purpose of this study was to describe the outpatient physical therapy (PT) provided to patients who have undergone primary TKR surgery.

Methods: PT records from patients participating in the Joint Action clinical trial at the University of Massachusetts Medical Center were included in the study. Only records from patients who had attended outpatient PT, completed their course of care and their 6-month study assessment were eligible for review. Records from 65 patients who underwent primary TKR were eligible for review. 44 records were reviewed from 18 facilities. 21 records were not reviewed because the facilities did not respond to requests for the records. Of these 21 records, 14 were from facilities that had sent at least 1 other record. Outpatient PT records were reviewed to identify all interventions provided. Physical therapy exercise interventions were classified into open chain, functional mobility, closed chain, and advanced closed chain. Progression was operationally defined as one or more exercises that increased resistance or difficulty. “Usual care” was operationally defined as interventions used with more than 85% of patients. “Consensus” was operationally defined as interventions used with more than 85% of patients.

Results: No agreement was reached regarding strength progression. 9% of records reported no exercise progression. 30% of patients progressed in only 1 exercise (13 progressed straight leg raises, 9 resisted straight leg raises). The progression of strength reached usual care (60%). Step-up exercises were the only closed chain activity that reached consensus. Step-downs reached usual care. There was no agreement on bridging or wall slides. No agreement existed in the use of advanced closed chain activities (squats was the closest at 48%). Balance and coordination training reached usual care (59%). The only modalities that reached usual care were cold packs (68%) and patellar mobilizations (57%).

Conclusions: Little uniformity exists in the post-acute outpatient physical therapy treatment of patients following TKR. Patients who undergo a primary TKR have varied functional outcomes one year after the surgical intervention. Research is needed to determine if the variability in post-operative physical therapy interventions contributes to patient outcomes.


Factors Associated with the Use of Physical Therapy by People with Hip and Knee Osteoarthritis (OA). Physical therapists (PTs) are trained to prescribe exercise for managing arthritis; however, little is known about the factors associated with the use of physical therapy services by people with OA. This study aimed to assess factors associated with the use of physical therapy by people with hip and/or knee OA.

Methods: Eligible participants were those identified from a provincial administrative database between 1992 and 2006 as meeting the case definition for OA, and had two or more medical visits or one hospitalization for OA within a 365-day period. We collected information on the WOMAC, use of healthcare service such as physical therapy in the past 12 months, and sociodemographics. Logistic regression was used to assess the factors associated with PT visits. Guided by the Andersen Model of Health Services Use, the dependent variables were grouped into predisposing characteristics (age, sex, body mass index), enabling factors (education, employment status, health authority region), and need factors (duration of diagnosis, number of comorbid conditions, estimated baseline WOMAC score). Because the WOMAC was collected after the PT visits, we penalized the WOMAC scores of those who visited a PT by 15% (i.e., assuming that those who saw a PT improved by 15% after treatment). Sensitivity analyses were done by varying this assumption from 10 to 20%. Contribution of the enabling factors to PT visits was estimated by the difference of 10 minus the ratio of R2 of the reduced model (with predisposing and need factors only) versus the R2 of the full model.

Results: 1,349 participants completed the survey and reported having knee/hip OA (knee OA only = 70%; hip OA only = 261; knee and hip OA = 38%). The mean age was 67.1 (SD = 11.1), 816 (60.5%) were females, and 921 (68.3%) were diagnosed with OA 6 years ago or longer. They had an average of 1.8 (SD = 1.5) comorbid conditions. 325 participants (24.1%) visited a PT in the past 12 months. Mean estimated baseline WOMAC score was 34.3 (SD = 20.4). Higher education (OR = 3.17, 95% CI = 2.02, 4.97), living in the Fraser Health Authority (OR = 0.62, 95% CI = 0.40, 0.96) or Northern Health Authority (OR = 0.46, 95% CI = 0.29, 0.74), and having an estimated baseline WOMAC score ≥ 50 vs. ≤ 10 (OR = 3.57, 95% CI = 2.07, 6.16) were significant predictors for seeing a PT. Assuming physical therapy improved the WOMAC score by 15%, enabling factors accounted for 68.3% of the variance for seeing a PT that the full model accounted for. Sensitivity analyses indicated that this percentage ranged from 61.4% to 77.1%.
Conclusion: Enabling factors, rather than patients’ needs, appeared to be the largest driver of the use of physical therapy by people with hip/knee OA. The findings indicated potential inequity in the use of physical therapy for the management of hip/knee OA.

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Impaired Knee Frontal Plane Neuro-Muscular Stabilization in Persons with Knee Osteoarthritis (KOA): A Biomechanical Study. Alison H. Chang1, Song Joo Lee1, Yupeng Ren1, Heng Zhao2 and Li-Qun Zhang3.

Northwestern University,1 Northwestern University; Rehabilitation Institute of Chicago,2 Rehabilitation Institute of Chicago.

Purpose: Persons with KOA often report instability during activities. Lower passive capsulo-ligamentous stiffness or poor muscular stabilization in the frontal plane may compromise knee stability and lead to excessive varus-valgus (V-V) motions during walking. Understanding these frontal plane neuro-mechanical properties in KOA will help elucidate the factors contributing to knee instability and aid in the development of targeted intervention strategies. The objectives of this study were to quantify knee frontal plane passive and active stiffness and muscle strength in persons with medial KOA.

Method: 28 subjects: 14 with symptomatic radiographic medial KOA and 14 age- and gender-matched healthy controls (8 women/6 men in each group) were evaluated. A joint driving device (JDD) with a customized motor and a 6-axis force sensor measured knee frontal plane neuro-mechanical parameters. With the participant sitting on a custom built chair at knee extension, the JDD moved the knee into varus and valgus with controlled external torques, and recorded joint angle and torque outputs. For passive tissue V-V stiffness, the motor moved the knee into varus and valgus at 1 degree/sec with a maximum torque limit of 12 Nm in each direction and recorded the hysteresis curves of passive knee tissues for 12 cycles. Varus stiffness was analyzed by the ratio of the applied external torques to the resulting varus angular motion at the range of 0 to 1 degree (deg) varus. Valgus stiffness was computed similarly. For active muscle contribution to V-V stiffness, similar protocol described above was used; expect the participant was asked to contract his/her muscles to stiffen the knee and stabilize the knee against V-V motion imposed by the motor. Contribution of active muscle activity on V-V stiffness was computed by the difference in stiffness with vs. without voluntary muscle contraction. For V-V muscle strength, the participant performed knee adductor (varus) and abductor (valgus) maximal voluntary contractions, 3 trials in each direction. Visual feedback of torque output was displayed to facilitate muscle torque generation. Body weight normalized maximal V-V torque was used for analysis. We used ANCOVA with BMI as covariate to test for differences between OA and control groups with p < 0.05 as significant.

Results: The mean age was 60 ± 8 (OA) and 58 ± 9 years (control); BMI 30 ± 8 (OA) and 24 ± 3 kg/m2 (control). There were no-between-group differences in passive tissue V-V stiffness (varus: 3.57 ± 1.47 vs. 3.96 ± 1.25 Nm/deg, p > 0.05; valgus: 4.11 ± 1.83 vs. 4.07 ± 1.07 Nm/deg, p > 0.05). OA group had a significantly smaller change of V-V stiffness with voluntary muscle contraction (OA: 4.67 ± 2.86 vs. control: 8.26 ± 5.95 Nm/deg, p < 0.05), decreased varus muscle strength (0.013 ± 0.008 vs. 0.018 ± 0.008, p < 0.05), and a trend toward decreased valgus muscle strength (0.013 ± 0.007 vs. 0.019 ± 0.010, p = 0.054).

Conclusion: Persons with medial KOA had impaired active neuro-muscular control in the frontal plane, including diminished ability to actively stabilize the knee in the frontal plane and to generate varus and valgus muscle torques; but did not show comprised stiffness in the passive capsulo-ligamentous tissues.

Disclosure: A. H. Chang: None; S. J. Lee: None; Y. Ren: None; H. Zhao: None; L.-Q. Zhang: None.

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Physical Activity Level and Poor Disability Profile: A Population-Based Study of US Adults with Arthritis. Jennifer M. Hootman1 and Daniel White1, Yang Zhang2, Jingbo Niu3, Michael Nevitt4, C. Elizabeth Lewis5, James Torner6 and Tuhina Neogi7. 1Boston University, Boston, MA, 2Boston University, 3University California San Francisco, 4University of Alabama, 5University of Iowa

Background: Physical activity (PA) has been shown to improve pain and function among adults with arthritis but the relationship between PA and an overall disability profile based on the International Classification of Function (ICF) is unknown.

Methods: Data were from the 2009 Behavioral Risk Factor Surveillance System, an annual telephone health survey conducted in all 50 states and the District of Columbia (n = 424,592 adults). Arthritis (ARTH; n = 151,120) was defined as a ‘yes’ response to “Have you ever been told by a doctor or other health care professional that you have arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?”*. Three outcome measures, based on ICF domains, were created: 1) limitation in pain (PAIN), 2) limitation in activity limitation (AL) and 3) restriction = social participation restriction (SPR). PAIN was defined as 7 or higher on a 0–10 point scale. AL was defined as a limitation in usual activities due to arthritis. SPR was defined with a question asking about the extent that arthritis interfered with social activities such as shopping, going to movies or social gatherings. Respondents reporting “A lot” (versus “A little/Not at all”) were defined as having SPR.

Persons who reported PAIN, AL, and SPR were classified as having a POOR disability profile. Respondents were asked how often (frequency) and for how long (duration) they did moderate and vigorous intensity PA outside of their occupation for at least 10 minutes at a time (minimum value 10 minutes/week). Minutes per week of moderate and vigorous intensity self-reported PA were summed (1 vigorous minute = 2 moderate minutes) and categorized as: Inactive (0 min/wk = referent group), Insufficient (10–149 min/wk), and Recommended (150+ min/wk). Logistic regression was used to estimate the relationship (odds ratio = OR, 95% confidence interval = CI) between PA level and each ICF domain separately and overall POOR disability profile adjusting for age, sex, race/ethnicity, education, body mass index, and self-rated health status. All analyses used statistical weights to account for the complex sample design.

Results: Among adults with arthritis, 26.3% reported PAIN, 45.6% AL, 16.8% SPR, and 11.9% were classified as having a POOR disability profile. The prevalence of having a POOR disability profile by PA level was 26.2% (CI 25.2–27.2) inactive, 12.7% (CI 12.0–13.4) insufficient, and 6.7% (CI 6.4–7.1) recommended. Higher levels of PA were associated with significantly lower odds of PAIN, AL, and SPR and a 41–63% reduced likelihood of having a POOR disability profile even after adjusting for age, sex, race/ethnicity, education, body mass index and self-rated health status (table).

Conclusions: At least 1 in 10 adults with arthritis have a poor disability profile. Increasing PA in this population may improve one’s disability profile, although this needs to be tested in prospective randomized controlled trials.

Disclosure: J. M. Hootman: None; D. Brown: None.

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The Association of Arm and Back Pain with Incidence of Slow Walking in Persons with Knee Osteoarthritis: The MOST Study. Daniel White1, Yuqing Zhang2, Jingbo Niu3, Michael Nevitt4, C. Elizabeth Lewis5, James Torner6 and Tuhina Neogi7. 1Boston University, Boston, MA, 2Boston University, 3University California San Francisco, 4University of Alabama, 5University of Iowa

Slow walking is a marker for adverse outcomes such as persistent limitation and mortality. Due to factors such as knee pain, persons with knee osteoarthritis (OA) are already at increased risk for slow walking. However, it is not known if upper body pain, such as shoulder pain affecting arm swing during gait, or back pain that may limit activity, is associated with the development of slow walking speed. Thus, we examined the independent effects of pain in the arm and back with the incidence of slow walking speed among persons with or at risk for knee osteoarthritis (OA).

The Multicenter Osteoarthritis Study (MOST) is a NIH funded longitudinal study of persons who have or are at high risk for knee OA. Pain assessments were taken at baseline, and walking speed at baseline and 30 months. We defined incidence of slow walking as < 1.0 meter per second (m/s) at 30 months, a speed shown to be a risk factor for persistent functional limitation and death in older adults, among participants whose walking speed was ≥1.0m/s at baseline. We quantified pain as the number of areas subjects marked on a homunculus, counted as 0, 1, or > 2. For the arm, this included both hands, wrists, elbows and shoulders, and for the back, the lumbar, thoracic, and cervical areas. We examined the association of the number of
painful areas within arm and back areas with the incidence of slow walking using risk ratios adjusted for age, sex, BMI, race, radiographic knee OA (ROA), knee pain, and pain in the hip, ankle, or foot. We additionally adjusted for the presence of widespread pain in separate analyses.

Of the 2204 persons walking at least 1.0 m/s at baseline (mean age 62 ± 8 y, BMI 30 ± 6 kg/m², female 57%) 8% had incidence of slow walking at 30 months. Arm pain was present in 1, 1, and ≥2 areas in 39%, 15%, and 46% of persons, and back pain in 32%, 48%, and 20%, respectively. Adjusting for potential confounders, persons with arm pain in 1 and 2 or more areas were 1.6 and 1.5 times more likely to have incidence of slow walking, respectively, compared with persons without any arm pain. No association between back pain and incident slow walking was found. (see Table) We found similar results in analyses adjusted for the dependence of widespread pain.

The presence of arm but not back pain was associated with the incidence of slow walking. Providers should consider that pain not only in the lower body, but also in the arms is important for future walking function.

% (Number with incident slow walking/total number of subjects) Adjusted Risk Ratio* 95% CI
Number of arm areas with pain

0 4 (39/882) 1.0 Ref

1 1 10 (31/324) 1.6 [1.1, 2.5]

≥2 10 (102/983) 1.5 [1.0, 2.2]
Number of back areas with pain

0 7 (50/741) 1.0 Ref

1 7 (77/1031) 0.8 [0.6, 1.1]

≥2 11 (45/422) 0.9 [0.6, 1.4]

*Mutually adjusted for age, sex, BMI, depressive symptoms, ROA, knee pain, and pain in the lower body apart from the knee (the hip, ankle, or foot)

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The Effect of an Exercise Program in Gait Asymmetry in Patients after Total Knee Arthroplasty. Francisco J. Maia Neto1, Gustavo J. M. Almeida2, G. Kelley Fitzgerald3 and Sara R. Piva4, 5.1 Univ of Pittsburgh, Pittsburgh, PA, 2University of Pittsburgh, 3University of Pittsburgh, Pittsburgh, PA

Purpose: Total knee arthroplasty (TKA) relieves pain and improves quality of life in end-stage knee osteoarthritis (OA). Unfortunately, significant functional deficits, such as gait asymmetry, often persist for years after TKA. Gait asymmetry may expose subjects to greater risk of developing OA in other weight-bearing joints. To prevent possible consequences of gait asymmetry, exercise interventions should target such impairment. We have developed and implemented an intense exercise program after TKA. The program includes balance exercises and movement control activities. The aim of this study was to determine if an intense exercise program that included balance and movement control activities decreases gait asymmetry in subjects after TKA.

Methods: Pre-test/post-test design. Subjects underwent unilaterial TKA 2–6 months prior to the study. Patients completed 12 sessions of supervised exercise over 6 weeks, followed by 4 months of home exercise program (2x/week). Data were collected prior to intervention (pre) and at the end of the home exercise program (6 mo). Gait parameters were measured using the GAITRite walkway (CIR Systems Inc). Patients walked at a self-selected pace over the GAITRite. Step length was the spatial gait parameter; while the temporal parameters were loading, single support, and unloading times of the stance phase. To account for the effect of gait speed, the temporal parameters were analyzed as a percentage of the gait cycle. Spatial and temporal gait parameters between the surgical and non-surgical legs (at pre and 6mo) were analyzed as a percentage of the gait cycle. Spatial and temporal gait parameters decreased gait asymmetry in subjects after TKA.

Conclusion: Spatial and temporal gait asymmetries after TKA were mainly during the loading and single support phases of stance. The exercise program seemed beneficial to decrease temporal gait asymmetry. Our results are confirmed in larger studies, intense exercises programs that include balance and movement control activities should be considered for subjects after TKA with asymmetrical gait.

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The Effectiveness of Thoracic Spine Manipulation on Pain and Disability in Patients with Neck Pain: A Pilot Randomized Clinical Trial. Saman-naz Shamsuddin Khoja, Daniel Daliman and Piva Regina Sara. University of Pittsburgh, Pittsburgh, PA

Background: Mechanical neck pain is generally treated with a multimodal neck program (MNP) that includes electro/thermal modalities, active exercises and some form of manual therapy (commonly non thrust) directed at the cervical spine. Recent studies reported beneficial effects of using Thoracic Thrust Manipulation (TTM) to treat mechanical neck pain. The aim of this pilot study was to compare the effects of a MNP and the same MNP supplemented by TTM on neck pain and disability, and to gather preliminary data to calculate sample size for future larger studies.

Methods: Subjects were randomized to receive MNP only or MNP + TTM for a maximum of 12 sessions 2x/week. Primary outcomes were 11-point numeric pain rating scale (NPS), Neck Disability Index (NDI), and a 15-point Global Rating of Change (GRC) to measure perceived change in health status. Neck active range of motion (AROM) was a secondary outcome. Outcomes were collected at baseline, 2, 4, and 6 weeks (GRC was not collected at baseline). As the goal of the study was parameter estimate, hypotheses testing were not done. We determined clinically important changes by comparing the point estimates of within-patient changes for NPS and NDI to their established minimal clinical important differences (MCIDs). MCIDs for the NPS and NDI are 2 points and 10% change respectively. We calculated the percentage of subjects in each group who reported a moderate or higher improvement in the GRC at each follow-up. For neck AROM, changes greater than the published values of minimal detectable change (MDC) were considered a noticeable change. The between-groups differences at 6 weeks in primary outcomes were used to estimate sample size.

Results: Twenty two subjects were randomized (68% female, mean age 38.2 ± 10.7 yrs). Characteristics of both groups were similar at baseline. Both groups showed clinically important changes at 6 weeks on all primary outcome measures. Clinically important changes on the NDI were observed for the MNP + TTM group at 4 weeks as well. The only improvement in neck AROM was observed for right side rotation in the MNP + TTM group at 6 weeks. Compliance with intervention was similar in both groups. The difference between the two groups was very small for all outcomes (Figure). Results of sample size indicated that to have 80% power, α of .05, we would require over 150 subjects per group for pain and NDI, and over one thousand subjects per group for the GRC, which do not seem feasible.
Validity of Portable Devices To Assess Physical Activity in Patients with Total Knee Arthroplasty. Gustavo J. M. Almeida1, Kelly S. Brower2, Derya Celik2, Hua-Chen Chang2 and Sara R. Piva1, 1University of Pittsburgh, Pittsburgh, PA, 2University of Pittsburgh

Total knee arthroplasty (TKA) is one of the most successful surgeries to reduce pain, improve function, and health-related quality of life in end-stage knee osteoarthritis. Thus, patient expectations on having a more active lifestyle after surgery are increasing, and accurate/valid measures of physical activity (PA) are needed to monitor these changes. To date, there is limited information about the validity of portable PA monitors in patients after TKA. The aim of this study was to compare measures of energy expenditure (EE) given by the SenseWear armband (SWA) (Bodymedia, Pittsburgh, PA) and the Actigraph (ACT; Pensacola, FL), against measures of EE estimated by indirect calorimetry. In addition, we aimed at characterizing PA of patients with TKA measured by the SWA and ACT in a free-living condition.

EE (kcal/min) was estimated by indirect calorimetry (MedGraphics VO2000), and by the SWA and ACT simultaneously. Patients performed several standardized activities in a laboratory setting while concurrently wearing the SWA on the arm, the ACT on the waist, and the facemask of the indirect calorimeter. Each activity was performed during 7 minutes (see Table). To characterize PA in a free-living condition, patients wore the SWA and ACT over 8 consecutive days. Pearson correlation or Spearman coefficients were calculated according to data distribution.

Table. Correlation coefficients between energy expenditure measured by indirect calorimetry and the Sensewear Armband (SWA) and the Actigraph (ACT)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Lying</th>
<th>Seated Reading</th>
<th>Seated Typing</th>
<th>Standing Talking</th>
<th>Standing</th>
<th>Mowing</th>
<th>Usual Walk</th>
<th>Slow Walk</th>
<th>Fast Walk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SWA (kcal/min)</strong></td>
<td>0.80**</td>
<td>0.68**</td>
<td>0.71**</td>
<td>0.823**</td>
<td>0.45*</td>
<td>0.75**</td>
<td>0.31</td>
<td>0.40</td>
<td>0.52**</td>
</tr>
<tr>
<td><strong>ACT (kcal/min)</strong></td>
<td>0.63**</td>
<td>0.60**</td>
<td>0.46*</td>
<td>0.61**</td>
<td>0.33</td>
<td>0.17</td>
<td>0.76**</td>
<td>0.67**</td>
<td>0.68**</td>
</tr>
</tbody>
</table>

(Spearman’s rho; *p < 0.05; **p < 0.01)

21 patients, 14 females (67%), with unilateral TKA underwent one testing session. Mean age and BMI were 68±7 and 29±4 respectively; time after surgery was 3.3±0.3 years; and physical function measured by the Western Ontario and McMaster Universities Osteoarthritis Index 14.6±9.6, indicating only moderate functional limitations. During the standardized activities (Table) the correlations between EE measured by indirect calorimetry and SWA ranged from moderate to high (r=0.31 to 0.82), and between indirect calorimetry and ACT they ranged from weak to high (r=0.45 to 0.75). In a free-living condition, patients wore the SWA and ACT for 97% of the time each day (23:20hr/24hr). Daily values of physical activity EE (PAEE) measured by the SWA (145 [73–260]kcal/day) was lower than the one measured by the ACT (268 [222–281]kcal/day). The correlation between these two measures was weak (r=0.22, p=0.37).

Results of correlations between measures from the portable PA monitors and indirect calorimetry support the validity of the SWA and the ACT to measure EE in patients with TKA in a laboratory setting. The SWA was more accurate in measuring EE during non-walking activities, whereas the ACT was more accurate in measuring EE during waking activities. Measures of PA EE given by the SWA and ACT in a free-living condition did not agree. When assessing EE in patients with TKA, it is essential to consider type of PA monitor to use according to type of activity performed. Studies comparing SWA and ACT to a reference standard measure of PA in free-living condition are warranted.

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Conclusions: Based on RCT analysis, the small group English ASMP has robust psychological benefits (ANX, DEP, SE) that persist at 12 mo., along with short term benefits in FAT and COMM. In Overall analysis, benefits were also seen in health behaviors and HD; most persisted at 12 mo. Consistent with previous meta-analyses, the impact of ASMP on DIS at 4–6 mo. is significant but small, and not maintained at 12 mo. The impact of ASMP on Pain and MD-V is only found in LON long studies, and should be interpreted cautiously.

Disclosure: T. J. Brady: None; B. J. O’Colmain: None; B. S. Mohley: None; M. C. Greenberg: None; L. Murphy: None.

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Development of the UK-Evaluation of Daily Activity Questionnaire (UK-EDAQ): Phase 2. Alison Hammond1, Rachel E. Gill1, Sarah Tyson1, Ulla Nordenskiöld2 and Alan Tennant3. 1 Sahlgrenska Academy, Goteborg, Sweden, 2 University of Leeds, Leeds, Yorkshire, United Kingdom, 3 University of Salford, Salford, Greater Manchester, United Kingdom

Aims: The Swedish Evaluation of Daily Activity Questionnaire (S-EDAQ) is a comprehensive tool for reporting activity/activity limitations in Rheumatoid Arthritis (RA) [1]. It includes: (i) sub-scales of personal and instrumental activities of daily living (with 4–13 items in each; 102 in total). It is used in Occupational Therapy (OT) for clinical, audit and research purposes. We have already undertaken linguistic validation and generated potential new activity items for the UK from analysis of patient activity diaries and OT assessments (Phase 1). In Phase 2 we evaluated acceptability of wording and relevance of items for the UK.

Methods: Three stages were undertaken: (i) cognitive debriefing interviews with people with RA (n = 20) who completed the prototype UK-EDAQ and then rated importance of items for inclusion on a 1=not to 5=very important scale; (ii) postal questionnaires with Rheumatology OTs (n=11) similarly rating items and (iii) 4 focus groups with RA participants (n=18) and 1 with OTs (n=7) to obtain consensus on item retention and wording. Items were considered for exclusion if RA participants and/or OTs rated these ≤3. The Project Steering Group (PSC) reviewed results from all stages to finalise the UK-EDAQ.

Results: RA participants (16 women: 4 men) were aged 61.55 (range 26–85); RA duration (16.42y SD 14.14); HAQ score 0.87 (range 0.12–1.88); 4 employed; 4 with children at home. Participants took between 25–120 minutes to complete the EDAQ. Whilst OTs rated 73/152 items with a median score ≤3, RA participants only rated 18/152 items ≤3; with only 15 items agreed for exclusion between groups.

Focus groups thus discussed items for modification or exclusion. From the S-EDAQ the consensus was for: 4 items to be deleted (get to toilet; get to bathroom; move round kitchen; open balcony door – as included in “move round house”); 20 S-EDAQ items merged to 10 items (eg slicing bread & slicing cheese to “slicing”). 53 new UK items were included: 26 to S-EDAQ sub-scales (eg “use a computer and mouse” “use a kettle”) and 25 to 3 new scales (Hobbies; Caring; Household Maintenance). The PSC recommended 7 S-EDAQ items were slightly worded (eg “go for a long walk” specified as 1 mile).

Many RA and OT participants expressed initial concerns on assessment length. However, once its purpose and completion at home were understood, most considered it appropriately detailed. RA participants were confident it would help an OT get a clearer picture of their abilities and difficulties in order to better help them. Comments from OTs were: “it is more patient oriented... It takes out the time of having to actually go through it all with them.” “A lot of our patients say the time they spent with OT was very fleeting... filling this out would be very thorough.” “You identify the talking points straight away, which helps focus it [assessment] a lot more.” Both groups considered the length meant not all patients could complete it.

Conclusion: UK-EDAQ content was finalised reflecting what people with RA consider the most important daily activities to assess in the UK. We will next psychometrically test for reliability and validity.

References:


Disclosure: A. Hammond: None; R. E. Gill: None; S. Tyson: None; U. Nordenskiöld: None; A. Tennant: None.

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Factors Associated with Attrition in a Longitudinal Rheumatoid Arthritis (RA) Registry. Christine K. Iannaccone1, Anne Fossel2, Hsun Tsao2, Jing Cui1, Michael E. Weinblatt1 and Nancy A. Shadick1. 1 Brigham & Women’s Hospital, Boston, MA; 2 Brigham and Women’s Hospital, Boston, MA

Background: Loss of participants in longitudinal data collection can affect the validity of RA registries if the characteristics of patients who drop out are systematically different from those who remain. Several studies have previously assessed factors associated with attrition with different conclusions. Some reports suggest that psychosocial and socioeconomic factors play an important role while others indicate attrition is more likely associated with population demographics. This study looks at multiple factors of attrition in a hospital-based registry over five years to identify contributors to attrition in the BRASS cohort.

Methods: The attrition patterns of RA patients enrolled in a prospective observational registry were examined. Follow-up of patients occurred every six months. Attrition rates were calculated as the proportion of patients who dropped out of the study over five years of follow-up. Demographics, clinical factors, and psychological factors were evaluated in univariate analyses to determine differences between participants who dropped out of the study and participants who completed five years of follow-up. Univariate factors with a p<0.05 were used in a survival analysis to determine significant factors associated with attrition.

Results: Overall, 1095 RA patients were enrolled in the registry with 461 patients completing five years of follow-up, 327 still actively enrolled and 307 having dropped out. At baseline, the mean age was 56.2 (±14.1), the mean disease duration was 13.8 (±12.4) years, 93% of patients were Caucasian and 82% were female. The attrition rate for each 6 month follow-up cycle was 3.23%. Level of education, disease duration, DAS28-CRP3 score (disease severity), MHAQ depression score, total MHAQ score (functional status) and Self-Efficacy score were associated with attrition in univariate analyses. However, in survival analyses, shorter disease duration, higher MHAQ and higher DAS28-CRP3 scores were the only factors associated with attrition.

Table 1. Multivariate survival analysis of factors associated with attrition

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Duration, years</td>
<td>0.97</td>
<td>0.95–0.98*</td>
</tr>
<tr>
<td>DAS28-CRP3</td>
<td>1.29</td>
<td>1.19–1.40*</td>
</tr>
<tr>
<td>MHAQ Score</td>
<td>1.50</td>
<td>1.24–1.82*</td>
</tr>
</tbody>
</table>

* p < 0.001

Conclusions: The attrition rate for this registry is similar to rates reported by other registries. In contrast to previous studies, worse functional status and higher disease activity were associated with attrition in this population. This suggests that in some populations, disease specific measures are major contributors to attrition. Specific population differences in each registry may play a greater role in attrition than general demographic factors indicating that each longitudinal registry may need to conduct its own analyses.

Disclosure: C. K. Iannaccone: Biogen Idec, 2, Crescendo Bioscience, INC, 2; A. Fossel: Biogen Idec, 2, Crescendo Bioscience, INC, 2; H. Tsao: Biogen Idec, 2, Crescendo Bioscience, INC, 2; J. Cui: Biogen Idec, 2, Crescendo Bioscience, INC, 2; M. E. Weinblatt: Biogen Idec, 5, Crescendo Bioscience, 5; N. A. Shadick: Amgen Inc., 2, Biogen Idec, 2, Crescendo Bioscience, 2.

2065

Measuring Fatigue in Patients with Inflammatory Arthritis in Clinical Practice: Single Dimension and Multidimensional Scale Comparison. Patricia Mimmock1, Barry Bresnihan1, McKee Gabriele1, Oliver FitzGerald1 and Douglas Veale2. 1 RHEUMATOLOGY REHABILITATION, Our Lady’s Hospice and Care Services, Dublin, Ireland; 2 St Vincent’s University Hospital, Dublin, Ireland; 3 Trinity College Dublin, Dublin, Ireland

Background: The ease of use of a measurement instrument frequently determines instrument choice and is an important consideration for outcome assessment in routine clinical practice. The aim of this study was to compare the measurement properties of (i) one-dimensional and multidimensional fatigue scales in patients with inflammatory arthritis.

Methods: Patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) commencing anti-TNF therapy were clinically evaluated using the 6-core outcome measures, and fatigue at baseline, 3-months and 6-months. Fatigue was measured using 2 fatigue scales validated for use in RA 1) a one
dimensional 5 point ordinal scale (OS), and 2) a multidimensional assessment of fatigue scales (MAF). Fatigue levels were quantified and the properties of a one-dimensional scale versus a multidimensional fatigue scale were evaluated.

**Results:** One-hundred thirty patients were evaluated (RA, 90; PsA, 40). Mean age (SD) years, and disease duration at inclusion were 52 (13), 12 (11), respectively. Mean (SD) MAF levels (range 1–50) were 27.5 (11.1) at baseline, 18.07 (12.1) at 3-months, and 19.04 (11.8) at 6-months and demonstrated statistical difference (ANOVA p<0.001). Change in fatigue captured by the OS were statistically significant at both 3-months and 6-months χ² (2) = 31.5; p = 0.000 (Friedman test). MAF and OS scores demonstrated strong and significant correlations at the 3 time points, r=0.587; r=0.689, and r=0.686 (p<0.000), respectively, (Kendall’s tau_b). Fatigue scores corresponded as follows

<table>
<thead>
<tr>
<th>Fatigue Scores</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 5-point ordinal scale (%)</td>
<td>10 (8)</td>
<td>19 (15)</td>
<td>47 (38)</td>
<td>41 (33)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>MAF Mean (SD)</td>
<td>8.7 (8.4)</td>
<td>18. (8.2)</td>
<td>27 (8.1)</td>
<td>35 (7.1)</td>
<td>40 (5.1)</td>
</tr>
<tr>
<td>3-months 5-point ordinal scale (%)</td>
<td>17 (16)</td>
<td>40 (37)</td>
<td>41 (38)</td>
<td>11 (10)</td>
<td></td>
</tr>
<tr>
<td>MAF Mean (SD)</td>
<td>6 (11.9)</td>
<td>10 (10.2)</td>
<td>19 (10)</td>
<td>24 (11)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>6-months 5-point ordinal scale (%)</td>
<td>12 (14)</td>
<td>33 (39)</td>
<td>29 (34)</td>
<td>9 (11)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>MAF Mean (SD)</td>
<td>6.7 (6.1)</td>
<td>11 (11)</td>
<td>19 (10)</td>
<td>26 (11)</td>
<td>24 (7)</td>
</tr>
</tbody>
</table>

MAF scores moderately correlated with Pain 0.423 (0.578), (0.482); GH 0.425 (0.578), (0.500) and HAQ 0.470 (0.345), (0.344) (p<0.001) at baseline, at 3-months, and at 6-months, respectively. Similarly, OS scores correlated with Pain 0.405 (0.495), (0.456); GH 0.532 (0.536), (0.515) and HAQ 0.407; (0.346), (0.347) (p= 0.001) at baseline, at 3-months, and at 6-months, respectively. The correlations between fatigue and the core outcome measures were equivalent at all time points regardless of the scale employed. Using the standardised response mean (SRM), sensitivity to change of MAF was moderate (0.78) at 3-months and large (0.66) at 6-months. Fatigue ranked third at 3-months, next to TJC and SJC, and sixth at 6-months relative to the other measures. Noteworthy was the observation that fatigue was ranked higher than CRP at 6-months.

**Conclusion:** These finding support the use of a single-item ordinal fatigue scale, in the quantification of this multi-dimensional patient reported symptom, in busy routine clinical practice.

Disclosure: P. Minnock: None; B. Bresnihan: None; M. Gabrielle: None; O. FitzGerald: None; D. Veale: None.

**2066**

**One Monthly Patient Reported Disability, Disease Activity and Fatigue Shows More Fluctuation Then Expected Based on the 3-Monthly Clinical Evaluation by DAS-28.** Margot Walter, Siti Haslinda Binti Mohd Din, Mieke Hazes and Jolanda Luime. Erasmus MC

Background: In clinical practice disease activity is monitored using a physician based instrument such as DAS or SDAI. In between these clinical measurement disease activity could fluctuate which is currently missed by the clinicians. Patient Reported Outcomes (PRO) may pick these fluctuations enabling early identification of disease activity increase requiring treatment change.

Objective: i To describe the monthly change of functional status (HAQ), self-reported disease activity (RA), and VAS fatigue among patients diagnosed with RA ii To identify patients with DAS28 >3.2 by proposed cut off points for RADAI and HAQ.

Methods: RA patients and patients with poly arthritis using DMARD’s for at least 3 months from one outpatient clinic in Rotterdam were invited to participate in this study. They were asked to complete online the HAQ, RADAI, VAS fatigue monthly during 1 year and were clinically assessed by the DAS28 3-monthly. Descriptive statistics were used to analyze the data.

Results: 159 out of 174 invited patients (53 yrs (sd 13); 76% female, median 4.5 yrs disease, median DAS28 2.66; 37% erosions) consented to the study in September-December 2008. Stratified summary of the PRO’s by DAS28 categories showed the increased values when the DAS increased (table 1) which stayed stable over time (data not shown).

<table>
<thead>
<tr>
<th>Table 1.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28 (median; IQR)</td>
</tr>
<tr>
<td>&lt;2.6 (n=72)</td>
</tr>
<tr>
<td>2.6 &lt; C ≤ 3.2 (n=29)</td>
</tr>
<tr>
<td>&gt;3.2 &amp; &lt;5.1 (n=39)</td>
</tr>
<tr>
<td>&gt;5.1 (n=9)</td>
</tr>
<tr>
<td>Overall (n=159)</td>
</tr>
</tbody>
</table>

Between 8% and 18% of the patients had an increase of DAS28>3.2 at any of the time points. On individual level the DAS28 and the PRO’s fluctuated over time (figure 1).

![Figure 1.](image)

Using the baseline data, the sensitivity of HAQ>1.0 to identify patients with DAS28>3.2 was 0.51 with a specificity of 0.75. For the RADAI>2.2 the sensitivity was 0.61 with a specificity of 0.83.

Conclusion: Individual patients showed fluctuating patterns of disease activity, while on group level the DAS28 and the PRO were stable over time. To identify individual patients with DAS28>3.2 the proposed cut off points for the HAQ and RADAI showed moderate sensitivity and high specificity.

Disclosure: M. Walter: None; S. H. Binti Mohd Din: None; M. Hazes: None; J. Luime: None.

2067

**Secular Trend of Adhesive Capsulitis over 13 Years: A United Kingdom General Population Cohort.** Daniel K. White¹, Hyon K. Choi², Christine Pelouquin³, Yanyan Zhu⁴ and Yuqing Zhang⁵. ¹Boston Univ School of Med, Boston, MA, ²Boston Univ School of Medicine, Boston, MA, ³Boston Univ School of Medicine, ⁴Univ of British Columbia, Vancouver, BC, Canada

Purpose: Adhesive capsulitis (AC) is a shoulder disorder characterized by a loss in range of motion and pain, resulting in restrictions with activities of daily living. Though common, few population-based studies have investigated the epidemiology of AC. Given the recent epidemic of diabetes, a known risk factor for AC, one would expect that the incidence of AC may be rising. The purpose of this study was to estimate effect of age, sex, birth cohort (birth year) and period (year of diagnosis) on the incidence of AC in a United Kingdom (UK) general population cohort.

Methods: Incident cases of AC were identified from The Health Improvement Network (THIN), an electronic medical record database of 6.3 million patients from general practices across the UK from 1995 to 2008. General practitioners recorded diagnosis of AC. We included subjects aged 40 to 79 years and defined an incident case of AC as the first diagnosis of AC following at least one year of enrollment in the database and had no prior AC diagnosis prior to their enrollment within the practice. Crude incidence rates were calculated as number of incident AC cases divided by total person-years. We plotted age- and gender-specific incidence rates of AC, and the relative incidence rates of AC for birth cohorts and periods using an age-period-cohort spline curve based on a Poisson-type likelihood. We estimated the effects of age, sex, birth cohort (born 1920–29, 1930–39, 1940–49, 1950–59, 1960–69), and period (1995–98, 1999–2002, 2003–06, 2007–08) using a proportional hazard model.
Results: Of 2,209,672 subjects included (mean age 51.7 yrs, 50.0% women, mean follow-up 7 years), the incidence rates of AC were 2.20 and 3.15 per 1000 person-years for men and women, respectively. Incidence rate of AC increased with age in both men and women. For every 5-year age increment, AC incidence increased by 9.1% (Relative Risk [RR]=1.09, 95%CI: 1.08, 1.10). The incidence rate was higher in women than in men (RR=1.43, 95%CI: 1.40, 1.45), and was higher for more recent birth cohorts compared with later (older) cohorts (RR for each 10-year increment=1.10, 95% CI: 1.08, 1.12). We did not observe a period effect for the incidence of AC. (See figure 2).

Conclusion: We found that more recent birth cohorts had a higher risk of incident AC independent of age, sex, and calendar year at diagnosis within the UK general population compared with later cohorts. An increased presence of risk factors, such as diabetes, in those born more recently may account for this increase, though future research should formally identify and examine these factors.

Disclosure: D. K. White: None; H. K. Choi: None; C. Pelouquin: None; Y. Zhu: None; Y. Zhang: None.

2068

The American Myositis Activities Profile—A Valid Disease-Specific Activity/Participation Measure. Helene Alexander2,1Department of Medicine, Karolinska Institutet, Department of Physical Therapy, Karolinska University Hospital, Solna, Stockholm, Sweden, 2Rheumatology Division, Mayo Clinic, Rochester, MN

Background: The Myositis Activities Profile is an activity limitation measure developed and validated for patients with polymyositis and dermatomyositis in Sweden. It was recently translated into American English.

Objectives: To evaluate validity and reliability of the American version of the disease-specific 31-item Myositis Activities Profile (MAP) in patients with polymyositis (PM) and dermatomyositis (DM) in the USA.

Methods: Patients diagnosed with PM or DM seen during March-May 2007 and May-July 2008 were included. To assess content validity 30 strategically chosen patients as to gender, age, ethnicity, disease activity, disease duration and employment status were selected. They rated difficulty and importance of each activity of the American MAP on a 10-grade scale and were invited to suggest additional items. Based on the initial findings a second draft of the American MAP was developed. For construct validity purpose unselected patients with PM and DM (n=64) were included. The six-item core set for myositis disease activity, the Manual Muscle test (MMT) and measures of muscle endurance using the Functional Index 2 (FI-2) were performed. Patients filled out the second draft of the American MAP, the Health Assessment Questionnaire (HAQ) and rated disease impact on general well-being. All patients with stable disease activity and medication for three months (n=48) were given another copy of the American MAP to fill out one week later.

Results: The median value for pooled difficulty and importance of each item was 5.00 (2.10–5.95) for the 31 activities in the first draft of the American MAP. Although two activities were rated < 5.0: “Standing for a longer period” and “Using public transportation” they were still taken to the second draft of the MAP as they were considered relevant to patients living in larger cities. Five patients suggested the activity “Opening jars” which was added to the Movement subscale, giving a 32-item second draft of the American MAP. Correlations between median of subscales of the American MAP and disease activity on general well-being and the HAQ were r = 0.68 and r = 0.70 respectively. There were lower correlations between the American MAP and MMT 8 (r = −0.36), the FI-2 (ranging between r = -0.29 to 0.44) and physician’s global assessment of disease activity (r = 0.40). Thirty-three patients sent back questionnaires to assess test-retest reliability. Weighted Kappa (κw) ranged between 0.65 and 0.81 for the 4 subscales and between 0.52 and 0.73 for the four single items of the American MAP without systematic variations, p>0.05. The single item ‘avoid overexertion’ were excluded due to poor test-retest reliability (Kw<0.52) giving a 31-item final draft of the American MAP.

Conclusion: The American MAP seems to be a valid and reliable outcome measure assessing activity / participation in patients with adult PM and DM in the USA and could potentially improve clinical assessment of treatment of these patients although further studies are needed to establish sensitivity to change of the American MAP.

Disclosure: H. Alexanderson: None; A. M. Reed: None; S. R. Ytterberg: None.

ACR Poster Session C
ACR/ARHP Poster Session C: ARHP: Quality of Life

Wednesday, November 10, 2010, 9:00 AM–6:00 PM

2069

Arthritis Hurts . . . Your Resume: State-Specific Arthritis-Attributable Work Limitation and Employment among Working-Age (18–64) Adults. Kristina Theis1, Jennifer M. Hootman1 and Charles G. Helmick1,1Centers for Disease Control and Prevention

Background: State-specific estimates of arthritis-attributable work limitation (AAWL) help define and raise awareness of an important consequence of arthritis, and provide state programs and policy-makers with data for planning interventions. We estimate the state-specific prevalence of AAWL and employment status among people with and without arthritis.

Methods: The Behavioral Risk Factor Surveillance System (BRFSS) survey is a state-based, random-digit-dialed telephone health survey of noninstitutionalized US civilian adults ≥18 years conducted annually in all 50 states and the District of Columbia. Data were from the 2009 BRFSS survey (n = 424,592). Arthritis was defined as ‘yes’ to: “Have you ever been told by a doctor or other health care professional that you have arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?” AAWL was defined as ‘yes’ to: “In this next question, we are referring to work for pay. Do arthritis or joint symptoms now affect whether you work, the type of work you do, or the amount of work you do?” Employment rate, as defined by the Bureau of Labor Statistics, requires information on specific efforts to find employment, which is unavailable in BRFSS; so, we examined employment status by report of being: employed, out-of-work, or retired/unable to work. Students and homemakers were excluded from the analysis. Weighted point estimates and 95% confidence intervals (95% CI) were calculated for AAWL and employment, accounting for the complex survey design. Statistical significance was p < 0.05.

Results: Median state-specific prevalence of AAWL among all working-age adults was 6.4% (range 4.3% (NJ) to 13.2% (KY)) Among working-age adults with arthritis, median AAWL was 33.9% (range 26.2% (CT) to 44.9% (KY)) The median percent employed among people without arthritis was 81.9% (range 73.5% (NV) to 90.5% (SD)), was significantly lower in every state for those with arthritis (median 64.2%, range 50.0% (TN) to 77.3% (SD)), and lowest for adults with AAWL (median 44.5%, range 32.4% (TN) to 64.0% (IA)). There were few statistically significant differences in the prevalence of being out-of-work. With the exception of 6 states (same patterns but not significant), those with AAWL reported being retired/unable to work statistically significantly more often than those with arthritis but no AAWL (median 40.9% vs. 26.0%) In all states, those with arthritis (with or without reported AAWL) reported being retired/unable to work statistically significantly more often than those without arthritis (median 6.5%).

Conclusion: AAWL affects approximately 1-in-16 working-age adults. Working-age adults with arthritis (with and without AAWL) are more likely to report being retired/unable to work than out-of-work, suggesting that they may have given up on trying to be an active part of the labor force. These data identify higher risk states which can be targeted for expanding the reach of evidence-based programs addressing disability, as well as increasing the use of vocational rehabilitation and job retraining programs.

Disclosure: K. Theis: None; J. M. Hootman: None; C. G. Helmick: None.
2070
Assessment of Physical and Mental Health Related Quality of Life, Disease Activity and Damage, Mental Health Status, and Cognitive Impairment in Chilean Women with Systemic Lupus Erythematosus. Carla Henriquez1, Patricia Flores2, Babul Marcela3, Jorge Calderon1 and Loretta Massardo1. ¹Pontificia Universidad Catolica de Chile, Santiago, Chile, 2Pontificia Universidad Catolica de Chile, Santiago, 3Pontificia Universidad Catolica de Chile

Background: Psychosocial factors play an important role in the course of SLE. The aim of this study is to characterize the health-related quality of life (HRQoL) in Chilean women with SLE and their relationship with disease activity, and mental health status including cognitive function.

Methods: In this cross sectional study, 52 non selected Chilean women with SLE attending out patient clinic in Santiago were recruited in an 18 months period, they pay their medications from their own pocket. Completed the following measurements (i) HRQoL, using the SF-12 questionnaire (assessing general health status [GHS], physical component summary [PCS] and mental component summary [MCS], (ii) SLE disease activity (SLEDAI-2K), (iii) damage (SLICC-ACR), (iv) 26 common mental disorders (CMD), according to the DSM-IV, using the Mini-International Neuropsychiatric Interview (MINI-plus), and (v) cognitive impairment (CI) in five domains of the Cambridge neuropsychological automated test battery (CANTAB): memory, attention, executive function, work memory, and decision making. CI was considered one or more test with a -1SD performance compared to 26 Chilean healthy controls paired by sex, age, and educational level.

Results: Characteristics of participants: median age: 33 years (range=17–64); median disease duration from diagnosis: 2 years (0.1–26); stable couple: 37%; active working/students: 65%; median years of formal education: 14 (9–19); median SLEDAI-2K: 7 (0–25); median SLICC: 0 (0–4). At least one CMD was present in 27 (53%), 14 (28%) major depressive episode (MDE), 15 (30%) at suicidal risk (29%): four were at high level, 5 at moderate and 6 at low risk. Patients considered their GHS as poor (16%), regular (47%), good or very good (37%). PCS median was 39.1 (24.2–57.58) and MCS median was 35.8 (20.1–51.2). HRQoL components PCS and MCS inversely correlated with disease activity (Spearman Rho = -0.327; P = 0.023; R = -0.349; P= 0.015, respectively). Accrued damage disease inversely correlated with PCS (R = -0.347; P=0.015). Patients affected with MDE had lower PCS and MCS than those without MDE (P=0.045; P=0.00, respectively). Disease activity was similar in both groups. CI in two domains attention and executive function were found in 22 (42%) not associated with MDE (P=NS).

Conclusions: This survey found 53% of presence of CMD and 28% of MDE. These frequencies are considerably higher than those previously reported in the general population living in Santiago, Chile (18% and 8%, respectively), moreover the number of patients at suicidal risk is high (<0.1%). HRQoL components PCS and MCS were > 1 SD lower compared to Chilean general population (score 50 ± 10). Disease activity related to a worse HRQoL in both components while accrued damage associated only with lower PCS score. MDE affected both components of HRQoL. CI in attention and executive function is a relevant problem in this study. Overall 63% of patients considered their general health status as bad or regular implying a challenge for the rheumatology staff to provide a better health care involving transdisciplinary teamwork.

Supported by FONDECYT grant number 1085283

Disclosure: C. Henriquez: None; P. Flores: None; B. Marcela: None; J. Calderon: None; L. Massardo: GlaxoSmithKline, 8.

2072
Depression Rates Reported by Scleroderma (SSc) Patients Using Online Subject Recruitment and Questionnaire Completion. Feasibility of Data Collection Method and Comparison of Reported Depression Rates. Evelyn Rajan1, Meagan Crofoot2, Jibran Fateh3 and Ann J. Impens. 1Briarcliff High School, 2University of Michigan, Ann Arbor, MI, 3University of Michigan

Objective: To evaluate the effectiveness and quality of online survey data in the assessment of depressive symptoms in SSc patients.

Methods: Data was obtained from SSc patients through a link posted on The Scleroderma Foundation website informing patient members about a study conducted by a high school student as part of the Intel Science Competition. Local IRB approval was obtained. Patients completed demographic information and the Center for Epidemiologic Studies Depression Scale (CES-D) which has been validated in SSc. CES-D is a 20-item instrument scored from 0 to 3 for a total possible score of 0 (best) to 60 (worst). Scores 16 and above indicate significant depressive symptoms.

Results: 186 completed surveys were received over a period of 2 weeks. 171 (91.9%) were female. Mean age was 49.9 ± 11.5 years. 47.1 ± 10.6yrs for males and 50.2 ± 11yrs for females. Average disease duration was 8.2 ± 8.2 yrs; 7.1 ± 7.7 yrs for males and 8.3 ± 8.3yrs for females.

The mean CES-D was 18.9 ± 12.7 with 51.6% reporting a score of 16 and higher. Total CES-D score for males was 23.9 ± 14.1 and 18.6 ± 12.6 for females. This difference was not statistically significant. Mean scores on each item were compared and differences between males and females were small. Males scored significantly (p < 0.05) higher on 2 items: “I felt as good as other people” (1.71 vs 1.06) and “My sleep was restless” (2.29 vs 1.6). A significant, although low, negative correlation was found for females between CES-D scores and age (r = -0.160), implying that with age there was less reported depression. The correlation between CES-D and years of illness was not significant (r = -0.09).
Conclusion: A CES-D score of 16 or higher is commonly considered as a cut-off for significant depression. Rates of depression between 35 to 65% have been reported in studies of SSc patients. The rate of significant depression, 51.6%, found in this online sample falls within the range of depression rates previously reported in clinic samples. This is also similar to depression rates reported in other chronic diseases. A recent study (Thombs, Fuss et al. 2008) compared SSc patients with online gender and age/race matched controls (no SSc). They noted that online respondents scored differently on certain items (higher on items related to appetite, sleep, effort, and bothered) suggesting qualitative differences in depressive symptom presentation between data collection methods. The item differences found in this study between males and females need to be further investigated and compared to gender item differences found in clinical and/or other community samples. The ease of administration and scoring makes the use of online questionnaires a very attractive method of data collection. The effectiveness of this method was proven by a high rate of completed surveys within a short period of time. More research is needed in comparing the composition of respondent characteristics (demographic as well as clinical) and the impact of data collection methods on results in SSc patients.


Disclosure: E. Rajan: None; M. Crofoot: None; J. Fateh: None; A. J. Impens: None.

2073

Effects of Tadalafil on Sexual Activity and Quality of Sexual Functioning in Female Scleroderma (SSc) Patients. Ann J. Impens1, Elena Schiopu5, Kristine Phillips1 and James R. Seibold1. 1University of Connecticut Health Center, Farmington, CT, 2University of Michigan, Ann Arbor, MI

Objective: To evaluate the potential effects of Tadalafil on quality and frequency of female sexual function as assessed by Female Sexual Function Index (FSFI) and sexual activity log.

Methods: Prospective randomized, double-blinded, placebo controlled, cross-over study comparing oral Tadalafil at fixed 20 mg dose daily for 4 weeks compared to placebo in female SSc patients. FSFI assesses six domains of sexual functioning: desire, subjective arousal, lubrication, orgasm, satisfaction, and pain.

Results: 39 patients met inclusion criteria, agreed to attempt sexual activity at least once per week, and completed a series of 5 visits. Mean scores on the FSFI domains and frequency of sexual activity are as follows:

Baseline, Drug, Placebo Mean scores FSFI Domains

<table>
<thead>
<tr>
<th></th>
<th>Baseline (sd)</th>
<th>Drug (sd)</th>
<th>Placebo (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desire</td>
<td>2.77 (1.28)</td>
<td>3.23 (1.21)*</td>
<td>2.98 (1.37)</td>
</tr>
<tr>
<td>Arousal</td>
<td>3.38 (1.77)</td>
<td>3.92 (1.85)</td>
<td>3.64 (1.86)</td>
</tr>
<tr>
<td>Lubrication</td>
<td>3.60 (2.11)</td>
<td>3.89 (2.14)</td>
<td>3.77 (2.15)</td>
</tr>
<tr>
<td>Orgasm</td>
<td>3.54 (1.90)</td>
<td>4.02 (1.96)</td>
<td>3.73 (2.0)</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>4.06 (1.56)</td>
<td>4.43 (1.50)</td>
<td>4.23 (1.55)</td>
</tr>
<tr>
<td>Pain</td>
<td>4.30 (2.43)</td>
<td>4.51 (2.26)</td>
<td>4.37 (2.37)</td>
</tr>
</tbody>
</table>

*p < .007, 2-tailed

Frequency sexual activity

<table>
<thead>
<tr>
<th></th>
<th>Baseline (sd)</th>
<th>Drug (sd)</th>
<th>Placebo (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>5.75</td>
<td>7.24 (4.53)</td>
<td>6.12 (3.3)</td>
</tr>
</tbody>
</table>

*p < .021, 2-tailed

Conclusions: To our knowledge this is the first study to report on the use of PDE-5 inhibitor and its impact on sexual function in female SSc patients. Patients reported a significantly higher frequency of sexual activity on drug than placebo. Greater change from baseline was reported on all domains of FSFI on drug versus placebo but none of these were statistically significant. A statistically significant difference was found in change from baseline in the sexual desire domain for drug although this was not statistically different from the change in the placebo group.

While the majority of scleroderma patients are female most studies on sexual function have focused on male sexual dysfunction. Same holds true for the study of sexual function in the general population where many studies focus on the use of PDE-5 inhibitors in the treatment of erectile dysfunction. Few studies exist on the use of PDE-5 inhibitors in the treatment of female sexual arousal problems and their effectiveness is in question (Chivers and Rosen 2010). Chivers et al (Chivers and Rosen 2010) attribute this lack of efficacy of PDE-5 inhibitors in women to gender differences in the concordance between physiological and psychological components of sexual response. This study did not include physiological outcome measures which are likely to measure the pharmacological effects of PDE-5 inhibitors as direct vasodilators. Classification and measurement of FSD in women lacks meaningful endpoints due to the complexity of female sexual response. Research is needed for a better understanding of outcome measures (physiological and patient-reported) specifically for female sexual dysfunction.


Disclosure: A. J. Impens: None; E. Schiopu: None; K. Phillips: None; J. R. Seibold: None.

2074

Fibromyalgia Patients Often Visit Many Physicians before Receiving a Diagnosis. Robert S. Katz3, Jessica L. Polyak2 and Lauren Kwan. 1Rheumatology Associates, 2Rush University Medical Center, Chicago, IL

Introduction: Fibromyalgia patients see many types of medical professionals and often have difficulty obtaining a diagnosis. This study utilized on-line and written surveys to investigate the number and types of health professionals consulted before receiving a diagnosis of the fibromyalgia syndrome (FMS). To avoid confounding by gender, only female patients were included in the analyses.

Methods: 606 self-described female fibromyalgia patients responded to a survey through the community volunteer fibromyalgia organization, AFFTER (Advocates for Fibromyalgia Funding, Treatment, Education and Research). Respondents were asked about who had diagnosed their fibromyalgia and the number of physicians they had seen for fibromyalgia symptoms before reaching a diagnosis. Spearman correlations were obtained to assess linear relationships between non-categorical variables.

Results: Respondents were predominately middle-aged (58% aged 36–55) and Caucasian (91%). Fifty percent were diagnosed with fibromyalgia by rheumatologists, 13% by internists, 4% by neurologists, 26% by other physicians, and 2% by chiropractors. Only 30% of patients obtained a diagnosis after seeing 1 or 2 physicians, while 24% saw 7 or more physicians before being diagnosed, and 10% saw 11 or more physicians before being diagnosed. A statistically significant, negative correlation was found between the number of physicians seen before reaching a diagnosis and how well the respondent coped with fibromyalgia (rho = −0.14, p = 0.001). In addition, statistically significant, positive correlations were found between the number of physicians seen before reaching a diagnosis and the amount of pain (rho = 0.16, p < 0.001) and fatigue (rho = 0.16, p < 0.001) experienced during an average week and the total number of areas with pain or tenderness (rho = 0.17, p < 0.001).

Conclusions: Most fibromyalgia patients saw at least three physicians before receiving a diagnosis, and a quarter went to at least 7 doctors for fibromyalgia related symptoms before obtaining a diagnosis. Larger numbers of physicians seen before reaching the diagnosis of FMS was associated with worse symptoms and worse ability to cope with fibromyalgia. Those with more intense symptoms tended to ‘doctor shop’ looking for a diagnosis they could understand. Rheumatologists made the diagnosis much more often than other physicians. Better education of non-rheumatologists in the diagnosis of fibromyalgia and more acceptance of the diagnostic criteria in the general medical community would help patients with fibromyalgia receive an earlier diagnosis.

Disclosure: R. S. Katz: None; J. L. Polyak: None; L. Kwan: None.

2075

Impact of Fibromyalgia (FMS) on Work, Robert S. Katz3, Sharon M. Ferbert1, Susan Shott4 and Katrin F. Katz2. 1Advocates for Funding Fibromyalgia Treatment, Education and Research (AFFTER), Libertyville, IL, 2Rheumatology Associates, 3Rush University Medical Center, Chicago, IL, 4Rush University Medical Center

Purpose: The pain, fatigue, and cognitive difficulties associated with FMS can make it difficult for patients to perform well in most work environments. In order to investigate the extent to which FMS affects the capacity to work, we asked fibromyalgia patients about their work experiences.
2077

The Mary Kirkland Center for Lupus Care (MKCLC): A Multi-Disciplinary Specialized Disease Center. Prentima Persad1, Suzy Kim2, Monica Richey1, Jane E. Salmon1, Doruk Erkan1 and Kyriakos A. Kirou1. 1Hospital for Special Surgery, New York, NY, 2Hospital for Special Surgery, New York, NY, 1Hospital for Special Surgery

Background: The complexity of disease in Systemic Lupus Erythematosus (SLE) and Antiphospholipid Syndrome (APS) creates management challenges that require a multi-disciplinary approach for optimal patient outcomes. Additionally, the increased interest of research in the field has generated the need for better organization in rheumatology practices and clinics in order to more efficiently recruit for research. We responded to these challenges by founding the MKCLC with the primary goal of integrating patient care, patient/physician education, and research.

Purpose: To report on the organization and growth of the MKCLC over the last year and show that the MKCLC is a candidate model for other multi-disciplinary specialized disease centers at our hospital.

Methods and Structure: Creation: The Center was launched by its current Co-Directors and Steering Committee with the generous support from Rheuminations, Inc.

Patient Care and Multi-disciplinary Model: The Center was built around the Friday Lupus Clinic and its corresponding multi-disciplinary conference with participation of fellows, “lupus attendings” and social workers (SW). A Center Manager was given the key task to oversee the execution of the Center’s goals and its growth. Additional important support roles have been the Center’s Nurse Practitioner, who performs initial patient triage and the SW Manager who screens all new patients for their psychosocial needs.

Patient/Physician Education: Formal multi-disciplinary monthly conferences integrate SLE and related fields, embracing all aspects of care, with an emphasis on lupus nephritis. The Center has created a unique website within the hospital’s main site, which highlights the Center’s developments and provides resources for patients and staff.

Research: Patient access to research has been streamlined through the Center’s Manager in order to maximize recruitment for industry or investigator-initiated research.

Results: Since April 2007, 186 SLE and/or APS clinic patients (87% female, mean age: 40, range: 18–78) have been included in the MKCLC database. Of 186 patients: a) 161 (87%) have been assessed by the SW Manager and referred to one of the five culturally relevant support and education programs offered by the Department of SW Programs; b) 99 (53%) have participated in our pre-existing Autoimmune Disease Registry and Repository; c) 88 (47%) have been referred to the Cardiovascular Disease Prevention Counseling Program and d) 42 (23%) have participated in cross sectional, observational or interventional research studies.

Conclusion: A multi-disciplinary specialized disease center dedicated to SLE and APS has been created to facilitate comprehensive care of patients, physician education, and research. Our Center provides the opportunity to examine whether: (1) specific patient-related education and support initiatives improve clinical outcomes; (2) our coordinated multi-disciplinary approach improves physician education and patient quality of care; and (3) a structured research database and patient screening improves research participation at our center.

Disclosure: R. S. Katz: None; S. M. Ferbert: None; S. Shott: None; K. F. Katz: None.

2076

Improvement of Hand Function in African Americans with Scleroderma: Use of a Hand Continuous Passive Motion. Paula Fenter1, Samina Hayat1 and Carla Saulsbury1. 1Shreveport, LA, Louisiana State University Health Sciences Center, Shreveport, Shreveport, LA

Introduction: Movement in the hands is essential to daily functional activities however persons with Scleroderma are at high risk for losing this function which can lead to loss of independence. It is therefore essential that rehabilitation healthcare professionals work to maintain hand function in these individuals so that independent living can continue while living with this disease and that a good quality of life can be preserved.

Subjects: Three African American individuals who were diagnosed with Scleroderma and had hand involvement were assessed for hand function and given standard exercise program.

Methods: Active range of motion (ROM) was performed on bilateral wrists and hands and the Arthritis Hand Function Test (AHFT) was performed. Each individual was instructed to participate in a daily active motion exercise program for both hands. A continuous passive motion (CPM) machine was placed on the right hand of each individual and the left hand received no CPM intervention. The Arthritis Hand Function Test was also administered. Each individual wore the CPM at night from 2–4 hours on the right hand only. Measurements were taken after at least four weeks of CPM for comparison. The medical records of these individuals were reviewed for this study.

Results: Two of the subjects gained greater than 60 degrees of total active movement of the digits on the hand that received the CPM as compared to the hand that had only active exercise. The other subject gained more active movement in the hand that did not have CPM treatment but did did have daily active exercise. All of the subjects had improvement in the AHFT.

Significance: This pilot study shows that improvement in hand function can improve with intervention addressing motion of the hands. Whether active motion alone or active motion with the addition of continuous passive motion is optimal treatment intervention is not clear. This pilot should provide a basis for further research into which is the best treatment for individuals at risk of losing hand function and independence.

Disclosure: P. Fenter: None; S. Hayat: None; C. Saulsbury: None.
Purpose: Previous studies have shown that patients with spondyloarthritids (SpA) have a significant higher risk of periodontal disease (PD). SpA also can induce periosteal bone formation suggesting that the impact of inflammation on bone is specific to the site at which inflammation occurs. Therefore, we have evaluated the local effect of TNF-antagonist therapy in PD of SpA patients.

Methods: Nineteen SpA patients (ESSG criteria) were prospectively evaluated at baseline (BL) and after 6 months (6M) of anti-TNF therapy. A dentist performed systematic periodontal assessment that included: clinical measurements of periodontal disease severity [probing pocket depth (PPD), cementoenamel junction (CEJ), clinical attachment level (CAL)], gingival inflammation (gingival bleeding index), and oral hygiene (plaque index). All patients were examined by a rheumatologist, blinded to dentist assessment, in order to evaluate demographic data and outcome measures (BASDAI, BASMI, BASFI, A SiQoL, CRP, ESPR).

Results: Eleven patients (58%) were male, with median age 45 (20–61) years and median disease duration 8 (1–41) years. Infliximab was used by 12 (63%) patients, adalimumab by 6, and etanercept by 1. CRP (16 vs. 4.2 mg/L, p = 0.003), BASDAI (5.25 vs. 2.65, p = 0.001) and BASFI (5.25 vs. 1.95, p = 0.017) improved significantly at 6M. No differences were observed in the median of clinical measurements of periodontal disease severity, gingival inflammation and oral hygiene 6M after TNF antagonist use in the whole group. Eight patients (42%) had PD; in these patients, the periodontal gingival inflammation and oral hygiene 6M after TNF antagonist use in the whole group. Eight patients (42%) had PD; in these patients, the periodontal assessment of all teeth showed no differences in the median of plaque, gingival bleeding indices, PPD, CEJ, CAL at BL versus 6M period (p > 0.05). However, the specific longitudinal analysis of teeth with periodontal disease revealed that only PPD had a significant improvement comparing BL versus 6M visit [3.67 (3.8–4.27) vs. 2.77 (2.47–3.03), p = 0.003] whereas CEJ [0.53 (0.58–2.03) vs. 1.66 (0.74–2.04), p = 1.0] and CAL [3.98 (2.83–5.93) vs. 3.54 (2.09–4.7), p = 0.130] remained stable; this isolated PPD improvement without change in other PD measurements suggests a local bone formation. Despite the PPD improvement, there was no significant resolution of the local inflammation after 6M of anti-TNF therapy, as demonstrated by the persistence of plaque [75.3 vs. 79.8%, p = 0.049] and gingival bleeding index [32.4 vs. 39.6%, p = 0.041].

Conclusions: This study suggests that blockade of TNF activity in SpA patients with periodontal disease may induce a local bone growth. The most likely mechanism underlying this process is a persistent periodontal inflammation disrupting local bone remodeling.

Disclosure: G. M. C. Fabri: None; C. Savioli: None; C. G. S. Saad: None; A. L. G. Calich: None; J. C. B. Moraes: None; A. C. M. Ribeiro: None; J. F. Carvalho: None; P. Sampiao-Barros: Abbott Immunology Pharmaceuticals, 8, Merck Pharmaceuticals, 8, Pfizer Inc, 8, Schering-Plough, 8, Wyeth Pharmaceuticals, 8; C. A. Silva: None; R. M. Pereira: None; J. T. T. Siqueira: None; E. Bonfá: None.

2079


Background: Work disability results from many rheumatic conditions and is known to have substantial personal and societal consequences. Much of what we know about arthritis impact on employment comes from condition-specific cross-sectional studies. A comprehensive search strategy was conducted to identify prospective studies demonstrating how arthritis impacts work.

Methods: Publications were identified by an online electronic search of 6 databases (MEDLINE, JSTOR, PsychINFO, CINAL, EMBASE, and Social Science Abstracts) conducted in early 2010 together with a hand search of references in all obtained literature. Searches were performed with the following terms: “arthritis (in title or abstract) AND work (in title or abstract)”, in combination (independently) with: moderate, mediat*, interaction, buffer, buffering “path analysis”, longitudinal, causal, “risk factor”, mitigate, associat*, predictor, and explanatory. Inclusion criteria for review: prospective study design assessing work impact at 2 or more time points in adults (≥ 18 years) with an arthritis/rheumatic condition, published in English. Biomedical, scale/instrument development, drug trial, and intervention studies were out of scope. Compliance with the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) consensus statement was examined as a marker for study quality.

Results: Electronic searches returned 2,877 potential publications; after duplicate removal and title/abstract review 90 remained and were retrieved for complete review. An additional 110 records were identified through hand searching and assessed for eligibility. In total, 15 publications met inclusion criteria for abstraction, 10 of which concerned rheumatoid arthritis, 1 each on fibromyalgia and osteoarthritis, 2 on systemic lupus erythematosus, and 1 included multiple conditions. No study included all relevant STROBE items, with the most commonly omitted including discussion of potential biases and clear reporting of participants at each stage. Definitions of work impact varied but were most often related to work cessation; 3 studies examined more subtle impacts (i.e., productivity, sick leave, work transitions). Methodological approaches were diverse including path and survival analyses and logistic and Cox regression. Characteristics examined could be categorized into 4 general groups (demographics, arthritis-specific, general health/disability, and work-specific). Preliminary results indicated that disability/functional limitation and age were the strongest and most consistently identified predictors of work impacts with less consistent results for work-specific, arthritis-specific, and social characteristics.

Conclusion: With the exceptions of age and disability, there is little consistent evidence for predictors of arthritis impact on employment from prospective studies. Robust conclusions are limited by differences in potential predictors examined, work impact definitions, and methods. However, findings from this systematic review indicate reasonable starting places for policy and public health efforts to mitigate arthritis impact on work.

Disclosure: K. A. Theis: None; R. Wilkie: None; L. Busija: None; G. Elsworth: None; R. Osborne: None.

ARHP Concurrent Abstract Sessions

Be Creative with Rheumatic Education: Where and How to Get It


2080

Where Do Adults with Arthritis Get Information about Arthritis? Louise Murphy1, Kristina A. Theis2, Teresa J. Brady2, Julie Bolen3 and Patience White1. 1Arthritis Foundation, 2Center for Disease Control, Atlanta, GA, 3Centers for Disease Control and Prevention

Background: Knowing what sources people with arthritis rely upon for information is important for identifying channels for disseminating arthritis information. Our study objective was to identify what existing sources adults with arthritis rely on for information about arthritis and to assess their interest in specific potential resources.

Method: We analyzed data from a national U.S. phone survey of white and black adults (n = 1,002), ages 40–70 years old, who have doctor diagnosed arthritis (“Have you EVER been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?”), and “some” or “many” limitations due to arthritis. Participants rated how much (a lot, somewhat, a little, not at all) they relied on the following sources for information about arthritis: doctor, pharmacist, family/friends, magazine/newspaper, internet, TV/radio. They also reported how likely (very or somewhat likely or very or somewhat unlikely) they would be to use a 1–800 number, arthritis expo (with exhibits and booths), and periodic 1–4 page publication for general information on arthritis. For each information source, we studied the distribution of ratings overall and by socio-demographic (S-D) variables (age, sex, race, education, income, employment status).

Results: Two thirds (68%) reported relying “a lot” on doctors for information about arthritis, with considerably less reliance on other information sources: “a lot” ratings for other sources ranged from 20% for pharmacists to 8% for TV/radio. The high reliance on doctors and substantial gap in “a lot” of reliance on other sources persisted across S-D groups. There was variation in the S-D characteristics of those reporting a “lot” of reliance on the other information sources (e.g., 28% of blacks reported “a lot” of reliance on pharmacists compared with 18% of whites). Whereas almost half of respondents reported “not at all” for reliance on TV/radio (47%) and the internet (46%), only 6% indicated no reliance on doctors for arthritis information. When asked about potential resources, 20% were “very likely” to use a 1–800 number and 24% for both an arthritis expo and the periodical. For each proposed resource, approximately a quarter indicated they would be “very unlikely” to access. Likelihood of using resources varied across S-D characteristics (e.g., 38% of blacks reported being “very likely” to use a toll-free number compared with 16% of whites).
**Conclusion:** Doctors were the most relied upon information source, eclipsing all other existing information sources studied; this was consistent across all S-D groups. There was some variation in the S-D characteristics of those who reported “a lot” of reliance on information sources other than doctors. This indicates that the choice of these channels should vary according to the target group. The high percent indicating no reliance on the internet or TV/radio suggests that these are less desirable channels for disseminating arthritis information to the general population of adults with arthritis.

**Disclosure:** L. Murphy: None; K. A. Theis: None; T. J. Brady: None; J. Bolen: None; P. White: None.

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**2081**

Rheuma on the Road—The Rheuma Truck Mass Communication, Educational Advertising and Creative Community Care. Matthias K. Schneider and Martina Blumenroth. Cooperative Rheumatology Association Rheine-Ruhr MNR-Klinik, Duesseldorf, Germany, MNR-Klinik, Dusseldorf, Germany

**Aim:** In Germany, the public is uninformed about symptoms and treatment of RA.

People are entertaining an outmoded image, e.g. that RA is an old-age disease. This has undesired consequences for early diagnosis in young RA-patients.

As the disease needs public relation in Germany, an educational advertising campaign with “The Rheuma Truck” as a mass communication medium was initiated. The truck was sent to public places to generate awareness, especially with younger people. Early diagnosis of the disease was promoted by informing the public about early symptoms of RA and to check people for RA.

**Methods:** The German Coop. Rheumatology Assn. Rheine-Ruhr (RZ-RR) hired a 35-ton truck, furnished with a spectacular design, slide-out extended floors on both sides, and equipped with facilities suitable for educating and screening several thousand people for rheumatic diseases. The Rheuma Truck was scientifically guided and evaluated as a screening tool for early diagnosis and mass communication.

The truck visited 22 cities during 26 days in the Rhine-Ruhr area. Participation was at no charge, there were no restrictions for participation except established diagnoses of inflammatory rheumatic disease.

Twelve medical students from the whole range of medical education accomplished the tests. Rheumatologists from RZ-RR gave advice to visitors who were assigned a consultation depending on test results.

We used the German version of the CQ, called RheumaCheck, and also a questionnaire for ankylosing spondylitis (AS), a computer network, a rapid diagnostic bloodtest for RF and MCV-antibodies yielding qualitative results in 15 minutes, venous blood collection for quantitative results of RF and MCV-antibodies and HLA-B27, a capillary microscope and an ultrasonic device for arthroscopy.

The German patients' organization “Deutsche Rheuma-Liga” supported the crew with information leaflets and talks about early symptoms.

**Results:** 193 press releases with 42,728,291 contacts and 6,250 google hits were counted for the event. 3,196 visitors were tested, 2/3 female, with an average age of 54.9 years. The RheumaCheck questionnaire yielded 347 times a positive result, 65 visitors were positive for MCV-antibodies and 230 for RF, 34 were positive for RF+MCV. The AS-check was positive 711 times with 11% of those being positive for HLA-B27, too.

The costs were $ 97,000.00 ($30 for each tested person, $ 15 for each google hit and $ 0.002 for each contact).

**Conclusion:** The Rheuma Truck with its eye-catching design highly attracted attention. It achieved great awareness with 42,728,291 contacts for a low price of $ 0.002 each. Visitors became aware about their risk and know the symptoms of RA, in order not to lose time when they occur, and thus achieve specialized treatment within six months. It was therefore suitable for informing the public and identifying people at early stages of RA and those at risk even before symptoms occur.

**Disclosure:** M. K. Schneider: None; M. Blumenroth: None.

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**2082**

A Study of Pictorial Representation (Mind Map) To Convey Health Education on Osteomalacia to People with Low Language Literacy Skills. Adewale O. Adebajo, David Walker, Sandra Robinson, Yogenjagat Singh, Philip Hellwell and Anisur Rahman. Feinstein Institute for Medical Research, London, London, United Kingdom, University of Leeds, Leeds, United Kingdom, University of Newcastle, Newcastle, United Kingdom, University of Newcastle, Newcastle, United Kingdom, University of Sheffield Medical School Sheffield United Kingdom, Sheffield, United Kingdom

**Background:** It is well recognised that health education needs to be provided in different ways to match different learning styles and literacy skills in order to ensure effective patient education for everyone. In order to achieve this, we have through an iterative process and in partnership with Arthritis Research UK developed a Mind Map based on pictorial representation which provides health education on the topic of osteomalacia. We were particularly keen to ascertain whether this novel health education tool was acceptable to ethnic minorities who originate from the South Asian Sub Continent and particularly those with low language literacy skills. Against this background we have performed this ethnicity study using this Mind Map.

**Methods:** In depth studies were carried out amongst ten English speakers, six Bangali speakers, ten Gujerati speakers, ten Hindi speakers, ten Punjabi speakers and ten Urdu speakers (N = 56). Participants were given sample images from the Mind Map and asked to comment on meaning to ascertain suitability, effectiveness and potential to cause inadvertent offence.

**Results:** Overwhelmingly, the respondents felt that the Mind Map was an effective and appropriate way of communicating health education on osteomalacia, particularly for those people with low language literacy skills. The Mind Maps were also felt to be of particular benefit to those ethnic minorities, for whom English is not their first language.

Cultural specific comments were made in relation to the depiction of food with 4/20 Gujerati and Hindu speakers saying that the picture should represent what they eat, for example depicting a vegetarian diet. Appropriateness responses divided into those which are generic and would apply to anyone, and those that were culturally specific. The general comments were that the bone metabolism depiction could be confusing (31/56), the muscle weakness could be confused with knee pain (16/56), the mending and cracking bone was confusing (22/56) and the picture of a man with bone pain could be confused with toothache (21/56). Inadvertent offence was felt to be highly unlikely and only related to the picture of an old lady in a bed (1/56) and venepuncture (2/56).

**Conclusions:** Our study indicates that the use of pictorial representation (Mind Maps) are an effective way of achieving patient education. Specifically our study has shown this novel health education tool to be considered appropriate and effective by participants from several ethnic minority groups arising from the South Asian Sub Continent. We recommend Mind Maps as part of the range of tools available for Health Care Professionals to provide health education about musculoskeletal conditions, especially for people who have low language or literacy skills.

**Disclosure:** A. O. Adebajo: None; D. Walker: None; S. Robinson: None; Y. Singh: None; P. Hellwell: None; A. Rahman: None.

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**2083**

Using Social Media To Recruit for a Translational Lupus Research Study for the Millennial Generation—The SisSLE Experience. Marlene H. Kern, Sally Kaplan, Bonnie Gonzales, Betty Diamond and Peter K. Gregersen. Feinstein Institute for Medical Research, Manhasset, NY, Feinstein Institute for Medical Research, Manhasset, NY

We report on our experience with a pilot registry with the goal to enroll 400 sisters, one diagnosed with lupus, along with one or more sisters without lupus to determine early risk factors of lupus. The enrollment age group is 10–35 years of age. Initially, recruitment by traditional means (i.e. newspaper articles, posters, flyers, health fair recruitment) was not effective and we moved to the use of the Internet and social media. Incorporating the use of the internet enhanced the
response rate. Most people in this age group are “connected” to the internet and we recognized we needed to utilize new methods.

We developed an interactive website that would appeal to this age group: www.SisSLE.org. The nature of the photos, graphics and presentation were intended to attract young users to the site. Study forms are available for read only to prepare the potential study subject for their interview. A contact us page allows users to email us directly from the website.

We developed standard press releases; template email letters and responses for pre-approval by the IRB. We established liaisons with lupus support organizations throughout the United States asking them to add our website link to their website, Facebook page, Twitter feeds, and any other social networking accounts.

As we enrolled young women into our study, we asked them to add a link to our website on their Facebook pages, Twitter feeds and any other internet interaction with lupus groups. Some study subjects took it upon themselves to blog about their participation in the study or add a step-by-step accounting of the process of joining the study. While HIPAA is still respected and research confidentiality has been maintained, these women have taken it upon themselves to share their lives with the world creating a ripple effect and reaching other potential study subjects. The bloggers share their written experiences with others thus becoming ambassadors for the study. Our newest recruitment addition is the use of Craigslist. Every 48 hours our posting can appear in a new city. Inquiries are directed to our email address. We have begun to receive responses at this time.

Social networking in research recruitment is new and rapidly evolving. These are new enrollment methods for many healthcare professionals and IRB’s and present challenges to maintaining order and confidentiality while keeping current with trends.

Disclosure: M. H. Kern: None; S. Kaplan: None; B. Gonzales: None; B. Diamond: None; P. K. Gregersen: None.

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**ACR Plenary Sessions**

**ACR Plenary Session III: Discovery 2010**

Wednesday, November 10, 2010, 11:00 AM–12:30 PM

**2084**

**Rates of Malignancy Associated with Juvenile Idiopathic Arthritis and Its Treatment: An Observational Study of National U.S. Medicaid Administrative Claims Data.** Timothy Beukelman 1, Kevin Haynes 1, Jeffrey R. Curtis 2, Fenglong Xie 1, Lang Chen 1, Elizabeth Delzell 1, Hopy Kim 1, Kenneth G. Saag 1 and James D. Lewis 2. 1Univ of Alabama at Birmingham, 2Univ of Pennsylvania, 3University of Alabama-Birmingham, Birmingham, AL

**Background:** A possible increased risk of malignancy in children with juvenile idiopathic arthritis (JIA), particularly in those receiving treatment with tumor necrosis factor alpha inhibitors (anti-TNF) has been reported. We analyzed national Medicaid administrative claims data to determine standardized rates of malignancy among children with JIA.

**Methods:** Using Medicaid data from all 50 U.S. states from 2000 through 2005, we identified a cohort of children with JIA based on physician diagnosis codes and dispensed medication prescriptions. We identified non-JIA control cohorts of children diagnosed with asthma and attention deficit hyperactivity disorder (ADHD). Subjects were excluded if they had any physician diagnosis code for malignancy prior to study entry. All subjects had a minimum 9 month baseline assessment period prior to study entry in which to identify prevalent malignancies. For all subjects this baseline assessment period included at least 3 months subsequent to satisfying the disease cohort definitions in order to identify potential incident cancers that were initially misdiagnosed as JIA. Exposure to methotrexate (MTX) and anti-TNF was determined based on dispensed medication prescriptions. Exposed subjects were considered forever exposed and all follow-up time was categorized into 3 groups: (1) no MTX and no anti-TNF; (2) any MTX and no anti-TNF; (3) any anti-TNF. Subjects could contribute follow-up time to more than 1 exposure category sequentially. Malignancy outcomes were defined using physician diagnosis codes, medication codes, and procedure codes using an extension of a previously validated algorithm. Follow-up was censored at loss to follow-up, malignancy outcome, and study end. We calculated crude incidence rates for all malignancies and lymphoma/leukemia for all study groups. Crude rates were standardized to the age, sex, and race distribution of the overall JIA cohort.

**Results:** The JIA cohort included 7,321 subjects with a median follow-up study time of 1.1 years. Among the JIA subjects, 3,194 were exposed to MTX and 1,413 were exposed to anti-TNF. The asthma (N = 623,663) and ADHD (N = 308,454) cohorts had median follow-up study times of 0.7 and 0.9 years, respectively. Malignancies were identified in 183, 63, and less than 11 patients with asthma, ADHD, and JIA respectively. Crude and standardized rates for all malignancies and for lymphoma/leukemia are shown in the Table. The standardized malignancy rates for JIA were 2 to 3-fold higher than those for ADHD and asthma. No cases of malignancy were identified in JIA subjects who had been exposed to anti-TNF.

**Disclosure:** T. Beukelman: None; K. Haynes: None; J. R. Curtis: Amgen Inc., 2, Centocor, Inc., 2, 5, Corrona, 2, 5, Roche, 2, 5, 8, UCB, Inc., 5, 8; F. Xie: None; L. Chen: None; E. Delzell: Amgen Inc., 2, H. Kim: None; K. G. Saag: Amgen Inc., 2, 5, 8, AstraZeneca, 5, Eli Lilly and Company, 2, 5, Genentech and Biogen IDEC Inc, 5, GlaxoSmithKline, 5, 2, 5, Merck, 2, 5, Novartis Pharmaceuticals Corporation, 2, 5, 8, Pfizer Inc; J. D. Lewis: Amgen Inc., 5, AstraZeneca, 5, Centocor, Inc., 2, GlaxoSmithKline, 5, Millenium Pharmaceuticals, 5, Roche, 5, Shire, 2, Takeda Pharmaceuticals North America, 2.

**Background:** The 36-month, maintenance phase of the ALMS study (NCT00377637) compared the efficacy and safety of mycophenolate mofetil (MMF) with azathioprine (AZA) in patients with active lupus nephritis (LN) achieving partial or complete response during the 6-month induction phase.

**Methods:** Patients were re-randomized 1:1 to a double-blind comparison of oral MMF (n=330) or oral AZA (n=328) plus placebo. Patients were permitted to receive corticosteroids (CS); maximum dose: 10 mg/d prednisone or equivalent. The primary efficacy outcome measure was time to treatment failure (death, end-stage renal disease [ESRD], sustained doubling of serum creatinine, renal flare [proteinuric or nephritic, and/or requirement for rescue CS). Key secondary parameters included time to event for each individual component of treatment failure: complete renal remission; combined renal and extra-renal remission; major extra-renal flare (British Isles Lupus Assessment Group score category A in 1 extra-renal system or 3 systems with concurrent category B scores); and adverse events (AEs).

**Results:** Of 227 patients randomized (intent-to-treat population, 127 completed (MMF, 73/116 [62.9%]; AZA, 54/111 [48.6%]). Demographic and disease characteristics were similar across groups at baseline. MMF was superior (log-rank test) to AZA in time to treatment failure (primary endpoint, P=0.003). MMF was superior to AZA (log-rank test) with respect to the following components of treatment failure: time to renal flare (P=0.027) and time to rescue therapy for LN (P=0.017). All other elements of the primary efficacy parameter showed numerical benefit in favor of MMF: time to ESRD (P=0.069) and time to sustained doubling of serum creatinine (P=0.073). MMF was superior to AZA with respect to the key secondary endpoint: time to first confirmed or suspected renal flare (P=0.012). Times to combined renal and extra-renal remission, and major extra-renal flare did not differ between the 2 groups (P=0.416 and P=0.936, respectively). The superiority of MMF over AZA was consistent regardless of induction treatment (MMF or
cyclophosphamide [IVC], race, or geographic region. The incidence of AEs was similar between MME and AZA groups; the most common AEs in both groups were infections/infestations and gastrointestinal disorders. Numerically fewer patients treated with MME than AZA reported at least 1 serious AE (27/115 [23.5%] vs 37/111 [33.3%]). One death (AZA group, unrelated to treatment) occurred during the study.

**Conclusions:** MME was superior to AZA in maintaining renal response and preventing relapse in patients with active LN who responded to induction therapy with CS and either MME or IVC.


**2086**

**Efficacy of Tadalafil in Raynaud’s Phenomenon Secondary to Systemic Sclerosis: A Double Blind Randomized Placebo Controlled Parallel Group Multicentric Study.** Vikas Agarwal, Parampar Gosh, Aman Sharma, Darshan Singh Bhakuni, Sudeep Kumar, Upendra Narayan Singh, Rajesh Vijayvergiya, Mukesh Kumar Yadav, Geetaabali Devi Laishram, Alakendu Gohsh, Bhuban Majhi, Dipankar Mukherjee, S. S. Islam and Aditya Karwom, Lucknow, India, Chandigarh, India, Army Hospital Research & Referral, New Delhi, India, IPGIMER, Kolkata, PGIMER, Chandigarh, India, SGPGIMS, Lucknow, UP, India

**Objective:** To evaluate the efficacy of Tadalafil in Raynaud’s phenomenon (RP) secondary to systemic sclerosis (SSc).

**Methods:** Patients with scleroderma (as per ACR criteria) having ≥4 Raynaud’s attacks/week were randomized to receive either placebo or Tadalafil (20 mg) on alternate days as add-on-therapy to their current vasodilators for eight weeks. Primary end points were improvement in RP parameters (daily frequency, duration and severity of RP). Secondary outcome measures included number of RP attacks/week, duration of RP and mean daily RCS was significant in the Tadalafil group (p = 0.039) as compared with colchicine (rate ratio estimates 25 mg 0.60, 50 mg 0.34, 100 mg 0.28, 200 mg 0.37, 300 mg 0.29, q4wk 0.38; p ≤0.05). The percentage of patients with RP was lower for all canakinumab groups (25 mg 27.3%, 50 mg 16.7%, 100 mg 14.8%, 200 mg 15.8%, 300 mg 15.1%, q4wk 16.7%) as compared to colchicine (44.4%). All patients taking canakinumab were significantly less likely to experience at least one gout flare than patients taking colchicine (odds ratio range [0.22 – 0.47]; p ≤0.05 for all). The median baseline CRP levels were 2.86 mg/L for 25 mg, 3.42 mg/L for 50 mg, 1.76 mg/L for 100 mg, 3.66 mg/L for 200 mg, 3.21 mg/L for 300 mg, 3.23 mg/L for q4wk canakinumab groups and 2.69 mg/L for colchicine group.

**Results:** 432 patients were randomized and 391 (91%) completed the study. All canakinumab doses were better than colchicine in preventing flares and therefore, a canakinumab dose comparable to colchicine could not be determined. Based on a negative binomial model, all canakinumab groups, except 25 mg, reduced the flare rate per patient significantly compared to colchicine group (rate ratio 25 mg 0.60, 50 mg 0.34, 100 mg 0.28, 200 mg 0.37, 300 mg 0.29, q4wk 0.38; p ≤0.05). The percentage of patients with flares was lower for all canakinumab groups (25 mg 27.3%, 50 mg 16.7%, 100 mg 14.8%, 200 mg 15.8%, 300 mg 15.1%, q4wk 16.7%) as compared to colchicine (44.4%). All patients taking canakinumab were significantly less likely to experience at least one gout flare than patients taking colchicine (odds ratio range [0.22 – 0.47]; p ≤0.05 for all). The median baseline CRP levels were 2.86 mg/L for 25 mg, 3.42 mg/L for 50 mg, 1.76 mg/L for 100 mg, 3.66 mg/L for 200 mg, 3.21 mg/L for 300 mg, 3.23 mg/L for q4wk canakinumab groups and 2.69 mg/L for colchicine group.

**Conclusion:** In this large randomized, double-blind active controlled study of flare prevention in gout patients initiating allopurinol therapy, treatment with canakinumab led to a statistically significant reduction in flares compared with colchicine (standard of care), and was well tolerated.

**Disclosure:** N. Schlesinger: Novartis Pharmaceuticals Corporation, 2; H-Y. Lin: None; M. De Meulemeester: None; E. L. Nasonov: Roche, 5; J. Rovensky: None; E. F. Mysler: Novartis Pharmaceuticals Corporation, 2; L. Arulmani: Novartis Pharma AG, 1, 3; G. Krammer: Novartis Pharma AG, 1, 3; D. Balfour: Novartis Pharma AG, 1, 3; P. Sallstig: Novartis Pharma AG, 1, 3; A. K. Sae: Abbott Laboratories, 5; Bristol-Myers Squibb, 5; Essex, 5; MSD, 5; Novartis Pharma AG, 5; Pfizer Inc, 5; Roche, 5; UBC, 5; Wyeth Pharmaceuticals, 5.

**2088**

**Effects of Urate Lowering Therapy on Cardiovascular Mortality: A Taiwanese Cohort Study.** Jiunn-Horng Chen and Wen-Harn Pan. 1China Medical University, Taichung City, Taichung, Taiwan, 2Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, Province of China

**Objective:** Gout and elevated serum uric acid (sUA) level have been associated with cardiovascular disease (CVD); however, whether urate lowering therapy (ULT) is beneficial is still inconclusive. This study aimed
to clarify whether controlling sUA with ULT can improve outcomes of CVD.

Method: This prospective cohort study linked baseline clinical data of examinees from the MJ Health Clinical Center in Taiwan with drug dispensed database from the National Health Insurance, and outcome information from the National Mortality Registry for CVD death (ICD-9 code 390–459). Multivariate Cox proportional hazard model was applied to adjust for confounders including age, sex, hyperuricemia (>7.7 mg/dl for men or >6.6 mg/dl for women), overweight (BMI >24 kg/m²), hyperglycemia (>100 mg/dl), hypertension (SBP ≥130 mmHg, or DBP ≥80 mmHg), hypercholesterolemia (>200 mg/dl), hypertriglyceridemia (>150 mg/dl), renal insufficiency (GFR <90 ml/min per 1.73 m²), and heart disease, kidney disease, arthritis, prior use of antihypertensive, anti-diabetic, steroid or analgesics, cigarette smoking, alcohol consumption, exercise, education, occupation, and working load.

Results: Among 45,215 participants (20,677 men and 24,538 women), 519 subjects died of CVD (308 men and 211 women) after a mean follow-up of 11.3 years. A preventive effect of ULT on CVD and stroke mortality was defined with respective hazard ratio (HR) of 0.56 (95% confidence interval, 0.46–0.70) and 0.42 (0.29–0.59) after multivariate adjustment. These effects were prominent for mortalities of hemorrhagic stroke and hypertension with corresponding HR of 0.12 (0.05–0.28) and 0.29 (0.13–0.63). Comparing with participants who did not use ULT, the users who continued treatment until outcome event or censor had better outcome (HR, 0.32; 0.21–0.49) than subjects who discontinue ULT for more than one year (HR, 0.68; 0.53–0.84). In the renal failure status (glomerular filtration rate <30 ml/min per 1.73 m²), allopurinol usage was more beneficial (HR, 0.64; 0.01–0.25) than benzbromarone (HR, 0.60; 0.11–3.18) for CVD outcomes.

Conclusion: This study demonstrates a preventive effect of ULT for CVD mortality. Further replication studies are needed in the future.


2009

Increased Fracture Rates among Female Osteoporosis Patients Taking Oral Bisphosphonates and Proton Pump Inhibitors Concurrently, Neetu Agashivala1 and Wing Chan2, 1Novartis Pharmaceutical Corp, East Hanover, NJ, 2Novartis Pharmaceutical Corp

Background: Oral bisphosphonates can cause upset stomach and inflammation, and erosions of the esophagus. Oesophageal and stomach symptoms have been reported in patients taking oral bisphosphonates which may require proton pump inhibitor (PPI) therapy. However, PPIs may interfere with calcium absorption through induction of hypochlorhydria resulting in increased bone resorption. Recent epidemiologic studies have also found that people receiving high doses of PPIs or using them for one year or more are at an increased risk of fractures of the hip, wrist, and spine. The objective of this study was to determine the fracture rates among female osteoporosis patients taking oral bisphosphonates and PPI therapy.

Methods: A retrospective database analysis was conducted using the commercial and Medicare data from the MarketScan claims database for year 2005–06. All osteoporosis females age 50 years or above currently on oral bisphosphonates (alendronate or risedronate) for at least 90 days were included in this study. These patients were stratified into two groups based on PPI intake. The PPI group included lansoprazole, esomeprazole, omeprazole, pantoprazole, and rabeprazole. PPI usage was defined as concurrent use of bisphosphonates and PPIs for 90 days or more.

Combined fracture rates for hip, vertebral, and non-vertebral fractures were assessed among the two groups. Chi square analysis was performed by age categories using SAS software, version [8.2] of the SAS system for Windows.

Results: Of the 153,899 female osteoporosis patients age 50 and above taking oral bisphosphonates that were identified in the database, 28,304 were taking PPI concurrently. There were a total of 13,388 patients who had experienced a fracture, 3,780 in the PPI group and 9,608 in the non-PPI group. The chi square analysis showed that there was an increased fracture rate in the PPI group compared to the non-PPI group by all age groups (cmm=1.7044; p<0.0001). The odds ratio were 1.8216, 1.9074, 1.6091, and 1.5166 in the >=50 and <65, >=65 and <75, >=75 and <85 and >=85 respectively (p<0.0001).

Conclusion: PPIs appear to be associated with an increased fracture rate among female osteoporosis patients taking oral bisphosphonates. Further research in the area is required using case-control cohorts.

Disclosure: N. Agashivala: Novartis Pharmaceuticals Corporation, 3; W. Chan: Novartis Pharmaceuticals Corporation, 3.

ACR Concurrent Abstract Sessions
Epidemiology and Health Services Research: Osteoarthritis
Wednesday, November 10, 2010, 2:30 pm–4:00 pm

2009 Quality-Adjusted Life Expectancy Losses Due to Disparities in Total Knee Replacement (TKR) Offer and Acceptance Rates in African American (AA) Men and Women. Elena Losina1, Lisa G. Suter1, Alexander M. Weinstein2, Ilya Golovaty3, William M. Reichmann4, Sara A. Burbine5, Edward H. Yelin6 and Jeffrey N. Katz1. 1Brigham & Women's Hosp, Boston, MA, 2Brigham and Women's Hospital, 3Brigham and Women's Hospital, Boston University, Boston, MA, 4Brigham and Women's Hospital, Boston University, Harvard Medical School, 5University of California, San Francisco, CA, 6Yale University, New Haven, CT

Background: The pathway to TKR in persons with end-stage knee OA requires both a health care provider's offer of surgery and patient's acceptance of that offer. A growing body of evidence has documented lower offer and acceptance rates of TKR in racial minorities. However, quality-adjusted life year (QALY) losses due to underutilization of TKR in racial minorities have not been described.

Methods: We defined the need for TKR as reaching Kellgren-Lawrence (K-L) grade 4 radiographic OA in persons with consistent pain. Based on published data we estimated that only about 50% of racial minorities deemed suitable for TKR are offered surgery, with immediate acceptance rates varying from 21% for African-American (AA) men to 10% for AA women for the first year following by 7% during subsequent years. We defined index of participation (IoP) as a product of offer and acceptance rates. The base case IoP ranged from 11% for AA men to 5% for AA women. We used the Osteoarthritis Policy (OAPOL) model, a validated computer simulation model of knee OA natural history and treatment, combined with published population-based estimates of TKR outcomes and sex-race specific mortality, to determine the QALY losses. Using lower IoP in AA men and women compared to White men (IoP=0.5; offer = 100%, offer=50%). Future QALYs were discounted at 3% per year. We estimated QALYs across offer rates from 40 to 100% coupled with acceptance rates from 20% to 60% resulting in IoP varying from 8% to 60%.

Results: Estimated discounted QALYs in African American persons eligible for TKR at average age 73 years (SD 9) who did not receive TKR ranged from 6.0 QALYs for AA men to 7.1 QALYs for AA women. QALYs stratified by IoP for AA men and women are presented in the Figure. Base case IoP (11% and 5% for AA men and women respectively) resulted in estimated 6.2 QALYs for AA men and 7.2 QALYs for AA women. Compared to the IoP in White men the QALY losses were 0.62 and 0.92 QALYs for AA men and women respectively (Figure). For the same values of IoP, higher QALYs were evident in scenarios with greater acceptance (vs. offer) rates.
Conclusions: Documented underutilization of TKR in racial minorities leads to substantial losses in quality adjusted life expectancy. The same values of IOp for different offer and acceptance rates do not confer the same quality of life benefits. Interventions focused on better acceptance of TKR among those who have been offered TKR will lead to greater improvement in quality adjusted life expectancy in persons with end-stage knee OA.

Disclosure: E. Losina: None; L. G. Suter: None; A. M. Weinstein: None; I. Golovaty: None; W. M. Reichmann: None; S. A. Burbine: None; E. H. Yelin: None; J. N. Katz: None.

2091

Age of Symptomatic Knee OA Onset: Impact on Costs and Quality of Life.

Methods: We used a validated computer simulation model of the natural history and management of knee OA, combined with published population-based estimates of incidence, progression, and impact on quality of life, to determine the age of onset, and the lifetime risk and costs associated with symptomatic knee OA and total knee replacement (TKR). We followed a simulated cohort representative of the US general population from age 45 to death. Knee OA treatment costs were derived from the Medicare reimbursement schedule and the Red Book, ranging from $609/yr for PT, NSAIDs, assistive devices and capsaicin to $20,456/yr for TKR. Costs related to comorbidities ranged from $557/yr for 0–1 to $3,603/yr for >3 comorbidities. We defined TKR eligibility by Kellgren-Lawrence (K-L) grade 4 radiographic OA in persons with consistent pain. Costs (in 2008 US$) were reported as total direct medical costs and costs attributable to knee OA. Both costs and quality-adjusted life expectancy (QALE) were discounted at 3%/yr.

Results: The estimated lifetime risk of symptomatic knee OA was 15.3% with a mean age at onset of 68.7 (SD 13.6) years. Nineteen percent of those with symptomatic knee OA (2.9% of the overall population) developed it before the age of 55, 35.6% of those with symptomatic knee OA (5.4% of overall population) developed knee OA before age 65, and 62% (9.5% of overall population) developed symptomatic knee OA by 75 years of age. The discounted QALE in persons with early onset (before age 55) was 16.7 quality-adjusted life years (QALYs) compared to 17.8 for those with late onset (ages 75+). Early onset led to mean discounted lifetime costs attributable to knee OA of $14,156 per-person, compared to $1,658 for those with late onset. (Table) Among those who developed knee OA early, lifetime risk of TKR was 57.6% compared to 9.7% for those who developed knee OA late. Lifetime risk for revision TKR ranged from 12.1% for those with early onset to 0.4% for those with late onset of disease.

Conclusions: Early onset of symptomatic knee OA is prevalent in the general US population. It leads to substantial decrements in QALE and increases OA-associated costs. Early onset of symptomatic knee OA leads to 6- and 25-fold increases in the lifetime risk for primary and revision TKR. Injury prevention and weight management, implemented early in life, may delay the onset of symptomatic knee OA, improve quality of life and decrease the economic burden associated with knee OA.

Disclosure: E. Losina: None; W. M. Reichmann: None; I. Golovaty: None; E. H. Yelin: None; H. Gerlovin: None; E. A. Wright: None; D. J. Hunter: None; D. H. Solomon: Pfizer Inc, 6, J. N. Katz: None.

2092

Projecting Lifetime Risk of Symptomatic Knee OA and Total Knee Replacement (TKR) in Persons Sustaining a Complete Anterior Cruciate Ligament (ACL) Tear in Early Adulthood.

Background: Over 175,000 persons sustain anterior cruciate ligament (ACL) tears annually in the US. ACL tears are especially common in active, younger persons. ACL tears are often accompanied by meniscal tears. We sought to forecast the lifetime risk of radiographic and symptomatic knee OA, and total knee replacement (TKR) in persons who sustain a complete ACL tear in early adulthood.

Methods: We used the Osteoarthritis Policy (OAPol) Model, a state-transition computer simulation model for the natural progression and management of knee OA, to estimate the lifetime risk of radiographic symptomatic knee OA, and TKR in persons with and without a history of a complete ACL tear by early adulthood (before age 25). Rates of OA progression in the absence of an ACL tear were estimated from the Johnston County Osteoarthritis Project. Rates of knee OA incidence in the absence of an ACL tear were derived from published literature and coupled with published estimates on the increased risk of incidence and progression of knee OA following an ACL tear, with or without a concomitant meniscal tear. Persons with symptomatic end-stage OA, defined as Kellgren-Lawrence grade 4 radiographic OA with knee pain, were considered eligible for TKA.

Results: By age 50, 43% of those who sustained a complete ACL tear in early adulthood (by age 25) developed radiographic knee OA and 19% had symptomatic knee OA, as compared with 8% and 3% respectively for those without an ACL tear. For those with a history of an ACL tear accompanied by a meniscal tear, 53% developed radiographic knee OA and 21% developed symptomatic knee OA by age 50. Among persons without an ACL tear, 0.3% were eligible for TKA by age 50, while among those sustaining an ACL tear by age 25, 2% were eligible for TKA, and for those with ACL and meniscal tears by age 25, 11% reached eligibility for TKA (Figure). By age 60, 32% of those with ACL and meniscal tears were eligible for TKA, as compared to 7% of those with an ACL tear alone and 1% of patients with neither ACL nor meniscal tears.

Conclusions: Based upon established evidence, our model-based analysis showed that sustaining an ACL tear at a young age accelerates lifetime risk of symptomatic knee OA and TKR. Subjects with an ACL tear history are likely to develop knee OA earlier than those without an ACL tear. Concomitant meniscal tears lead to even faster progression of knee OA. These findings provide a compelling rationale for developing and implementing sustainable injury prevention strategies for young adults.
2093

Validation of an Internet-Based Questionnaire for Ascertaining Cases of Hip and Knee Osteoarthritis. Charles R. Ratzlaff, Jacek Kopec and Mieke Koehoorn.

Statement of Purpose: To evaluate the validity of an internet-based questionnaire to ascertain cases of osteoarthritis (OA) of the hip and knee, in a sub-sample of a population-based study, in comparison to the American College of Rheumatology (ACR) criteria.

Methods: The validation study was nested in the Physical Activity and Joint Health (PAJH) cohort study, a population-based, 3-cycle Internet study of Canadians, which included 4,269 subjects. A sub-cohort of 100 subjects from British Columbia were recruited for interviews and clinical examination. Interviews followed a standardized questionnaire format and reporting form. Clinical exams were conducted with the examiner blinded to subject history, interview and self-report status. ACR criteria for classification of hip and knee OA were used as the reference.

Questionnaire items on hip and knee joint health included current and historic pain, aching and stiffness, previous injury, surgery and joint replacement. Separate items inquired about knee and hip-related physical function. The questions regarding a diagnosis were as follows:

‘Have you ever been diagnosed by a health professional with OSTEO-ARTHRITIS of the knee/hip?’ (Please note that osteoarthritis, rheumatoid arthritis, and osteoporosis are different conditions.)

This question was asked separately for each joint, and confirmation of response required.

Results:

Table 1. Characteristics of Participants in the PAJH baseline cohort and validity study sub-cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All PAJH Subjects (N=4,244)</th>
<th>Sub-Cohort* (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td>61.5 (7.6)</td>
<td>63.3 (7.2)</td>
</tr>
<tr>
<td><strong>Height, in</strong></td>
<td>67.4 (5.0)</td>
<td>66.8 (3.6)</td>
</tr>
<tr>
<td><strong>Sex, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>37%</td>
<td>46%</td>
</tr>
<tr>
<td><strong>Body weight, lbs</strong></td>
<td>177.3 (39.5)</td>
<td>174.8 (40.4)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>27.3 (5.9)</td>
<td>27.4 (4.91)</td>
</tr>
<tr>
<td><strong>Prevalence SR knee OA</strong></td>
<td>19.9%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Prevalence hip OA</strong></td>
<td>9.5%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Prevalence KOA-ACR criteria</strong></td>
<td>17.5%</td>
<td>10.5%</td>
</tr>
<tr>
<td><strong>Prevalence HOA-ACR criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Marital Status, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Married/Common-law</strong></td>
<td>58.0%</td>
<td>64%</td>
</tr>
<tr>
<td><strong>Widowed/Seperated/Divorced</strong></td>
<td>33.0%</td>
<td>26%</td>
</tr>
<tr>
<td><strong>Single</strong></td>
<td>4.7%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Ethnic Origin, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>93.6%</td>
<td>91.0%</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>6.3%</td>
<td>9.0%</td>
</tr>
<tr>
<td><strong>Level of Education, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>College/Univ/Post Grad</strong></td>
<td>47.7%</td>
<td>54.1%</td>
</tr>
<tr>
<td><strong>Elementary/High school</strong></td>
<td>33.8%</td>
<td>30.1%</td>
</tr>
<tr>
<td><strong>Technical or Trade school</strong></td>
<td>17.4%</td>
<td>15.3%</td>
</tr>
</tbody>
</table>

*Sub-cohort subjects are part of Physical Activity and Joint Health (PAJH) cohort and participated in interviews and clinical exams

Validity subjects were older, had a more equal gender distribution, less self-reported knee OA and more hip OA, but did not differ significantly across physical characteristics and demographic variables including marital status, ethnic origin and highest level of education.

Self-reported health professional diagnosis had moderate sensitivity and very good specificity, and had better measurement properties than items on pain and symptoms. Cohen’s kappa was 0.76 and 0.65 for knee and hip respectively indicating substantial agreement. Consistent with previous postal questionnaires and telephone surveys, this internet-based study reports that the greatest accuracy is achieved by asking about self-report of a health-professional diagnosis.

Conclusion: An Internet-based questionnaire using self-report of a health professional diagnosis of hip or knee OA appears to be a valid measure in large epidemiological studies for assessment of OA, though some misclassification results. Self-reported diagnosis is substantially more specific than asking about pain and symptoms. Estimation of error can be used to interpret and possibly correct results derived from this case definition in analytic studies.

Disclosure: C. R. Ratzlaff; J. Kopec; M. Koehoorn.

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Methods: A two-phase survey was designed. Using a random digit dialing phone survey, subjects 40 to 75 years old were screened with a validated questionnaire. In case of a positive screening question (presence of at least one of the listed characteristic symptoms), subjects were invited to participate to the confirmation phase including physical examination and hip or knee X-rays. Cases were all the subjects with symptoms suggestive of symptomatic knee or hip OA according to the clinical examination and X-Rays (Kellgren-Lawrence ≥ 2). Prevalence was determined using multiple imputation to account for refusals at different phases in order to obtain more accurate estimates and to limit non-response bias. Estimates were also corrected to account for the sensitivity error of the screening questionnaire. Standardised prevalence estimates were calculated using European age and sex distribution 2006 (Eurostat).

Results: The prevalence survey, conducted in 6 regions started in April 2007. In two years, 63 232 homes answered a phone call and 27 632 had at least one subject aged between 40 and 75 years old. Among them, screening detected 9621 positive subjects, of which 3707 (39%) participated fully to the

Table 2. Sensitivity, Specificity, Predictive values and Kappa for self-report of knee or hip OA, in comparison to ACR clinical criteria

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knee OA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.74</td>
<td>(0.60, 0.89)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.98</td>
<td>(0.96, 1.00)</td>
</tr>
<tr>
<td>PPV</td>
<td>0.87</td>
<td>(0.81, 0.93)</td>
</tr>
<tr>
<td>NPV</td>
<td>0.95</td>
<td>(0.93, 0.97)</td>
</tr>
<tr>
<td>Kappa</td>
<td>0.76</td>
<td>(0.64, 0.89)</td>
</tr>
<tr>
<td><strong>Hip OA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.81</td>
<td>(0.64, 0.97)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.94</td>
<td>(0.91, 0.97)</td>
</tr>
<tr>
<td>PPV</td>
<td>0.61</td>
<td>(0.52, 0.70)</td>
</tr>
<tr>
<td>NPV</td>
<td>0.98</td>
<td>(0.97, 0.99)</td>
</tr>
<tr>
<td>Kappa</td>
<td>0.65</td>
<td>(0.49, 0.81)</td>
</tr>
</tbody>
</table>

Purpose: Although osteo-arthritis (OA) is a major public health problem, there is a lack of epidemiological data in Europe. The aim of our study was to estimate the prevalence of symptomatic knee and hip OA in a multiregional representative sample in France.
confirmation phase. Reasons for non participation in the latter phase included 514 subjects not reached for setting visit in the clinic, 3389 refusals and 933 subjects who did not show up at the visit. Among subjects having completed the whole ascertainment procedure, 1010 had a symptomatic OA: 317 hips, 756 knees.

Participation was different according to region, age, sex, socio-professional category and the different items of the screening questionnaire. Missing data were mostly not at random. Multiple imputation of all eligible subjects accounted for these characteristics: corrected estimates of the prevalence are given by joint, sex and age.

Table. Estimates of the prevalence according to joint, age and sex.

<table>
<thead>
<tr>
<th></th>
<th>Knee % [IC 95%]</th>
<th>Hip % [IC 95%]</th>
<th>Knee % [IC 95%]</th>
<th>Hip % [IC 95%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49 years</td>
<td>2.1 [0.9; 3.9]</td>
<td>1.0 [0.3; 1.9]</td>
<td>1.6 [0.7; 2.6]</td>
<td>0.8 [0.2; 1.5]</td>
</tr>
<tr>
<td>50–59 years</td>
<td>4.7 [3.0; 7.0]</td>
<td>1.6 [0.6; 2.8]</td>
<td>5.9 [4.3; 7.5]</td>
<td>2.2 [1.2; 3.2]</td>
</tr>
<tr>
<td>60–69 years</td>
<td>6.8 [4.5; 9.9]</td>
<td>3.2 [1.6; 4.9]</td>
<td>10.5 [8.2; 12.9]</td>
<td>4.2 [2.6; 5.8]</td>
</tr>
<tr>
<td>70–75 years</td>
<td>10.1 [6.3; 15.3]</td>
<td>3.9 [1.4; 6.9]</td>
<td>15.0 [11.4; 18.5]</td>
<td>5.1 [2.9; 7.5]</td>
</tr>
<tr>
<td>Women</td>
<td></td>
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</tbody>
</table>

Prevalence increases with age and after 50 years old is more frequent among women. Standardized prevalence was 1.9% in men and 2.5% in women, and 4.7% in men and 6.6% in women for hip and knee symptomatic OA, respectively.

Conclusion: This survey is the first estimation of the prevalence of symptomatic hip and knee OA in France, increasing knowledge about population-based estimates of this condition in Europe. The use of a screening questionnaire validated during pilot studies, the application of multiple imputation to account for missing data, and the correction method to account for the sensitivity error of the screening questionnaire warrant the accuracy of the results.

This study also confirms the feasibility of using a screening questionnaire in two-phase population based surveys in this disease.

Disclosure: F. Guillemin: None; A.-C. Rat: None; B. Mazières: None; J. Pouchot: None; L. Euler Ziegler: None; B. Fautrel: None; P. Fardellone: None; J. Morvan: None; C. H. Roux: None; E. Verrouil: None; A. Sarasu: None; J. Coste: None; The KHOALA Group: None.

2095

Modifiable Predictors of Racial Differences in Gait Velocity in an Elderly Urban Cohort. Irene Blanco1, Joe Verghese2, Richard B. Lipton2, Chaim Putterman1 and Carol A. Derby2. 1Albert Einstein College of Med, Bronx, NY, 2Albert Einstein College of Medicine, Bronx, NY

Background: Gait velocity (GV) is predictive of health status, hospitalizations and mortality and is used to assess functional status the elderly. In this urban cohort.

Methods: The Einstein Aging Study (EAS) is a longitudinal study of community residing elderly. Participants are recruited using Medicare beneficiary lists and voter registration records. Demographics and medical history are collected as well as the Geriatric Depression Scale, Blessed Information Memory Concentration Test, the SF-36, and the Total Pain Index (TPI) which is used to assess functional status the elderly. In the EAS, Gait velocity of less than 100cm/sec in the elderly has been associated with increased hospitalizations and mortality. Therefore using GV to screen and develop interventions may limit and reduce health disparities in functional decline in the elderly.

Disclosure: I. Blanco: None; J. Verghese: None; R. B. Lipton: None; C. Putterman: None; C. A. Derby: None.

ACR Concurrent Abstract Sessions

Osteoarthritis - Clinical Aspects: Pain and Biomechanics

Wednesday, November 10, 2010, 2:30 PM–4:00 PM

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Physical Activity Assessed by Accelerometry in Persons with Knee OA Compared to National Guidelines: The Osteoarthritis Initiative (OAI). Dorothy D. Dunlop1, Jing Song2, Pamela Semanik3, Leena Sharma4, Rowland W. Chang5, Joan M. Bathon6, Charles Eaton1, Marc C. Hochberg7, W. Jerry Mysiw8, Rebecca Jackson9, C. Kent Kwoh10, Michael C. Nevitt8 and Jennifer M. Hootman1. 1Brown University, 2Centers for Disease Control, Kennesaw, GA, 3Johns Hopkins Univ Ste, Baltimore, MD, 4Northwestern Univ, Chicago, IL, 5Northwestern University, Chicago, IL, 6Northwestern University Medical School, Chicago, IL, 7Ohio State University, 8Rehabilitation Institute of Chicago, Chicago, IL, 9UCSF, San Francisco, CA, 10Univ of Pittsburgh, Pittsburgh, PA, 11University of Maryland, Baltimore, MD

Purpose: Knee osteoarthritis (OA) is the most prevalent form of arthritis in the US. OA clinical practice guidelines identify a substantial therapeutic role for physical activity. However, we lack objective evidence on the physical activity experience of this population. Reports of physical activity in OA populations are largely based on self-report, which can overestimate activity time and intensity. This study uses accelerometers to objectively assess physical activity intensity and duration from a national knee OA cohort.

Methods: Physical activity was measured via accelerometers at the year 4 clinic visit on 1056 participants in the OAI with baseline radiographic knee OA (KL grade ≥2). Of these, 1021 (97%) had 4–7 valid days of accelerometer monitoring. Activity intensity was determined from accelerometer count cutpoints: light (≤2019), moderate (2020–5998), vigorous (≥5999). Time spent in bouts lasting ≥10 minutes of moderate-to-vigorous physical activity (MVPA) was determined. Gender differences in median intensity times were compared using quantile regression. Attainment of Centers for Disease Control and Prevention (CDC) guidelines for arthritis populations (≥150 bouted MVPA minutes/week) was assessed.

Results: Persons with knee OA primarily engaged in light intensity activity and no measurable activity during a large portion of the day (Table). Overall, a median of only 9.9 minutes/day was spent in moderate-to-vigorous physical activity (MVPA) activity; less than 20% (1.4 minutes) of this time was done in bouts lasting more than 10 minutes. Men with knee OA had more minutes of no activity than women. However, men also had more MVPA minutes than women. These differences persisted after controlling for age and BMI. Recommended CDC physical activity guidelines were attained by only 18% of men and 10% of women.
Table. Median daily minutes of physical activity intensity among n=1021 persons with radiographic knee OA

<table>
<thead>
<tr>
<th>Unadjusted Results</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Minutes Any Activity (0-99 counts)</td>
<td>Median</td>
<td>Minutes Light PA (1-209 counts)</td>
</tr>
<tr>
<td>Men</td>
<td>469</td>
<td>429.6</td>
<td>433.9</td>
<td>15.9</td>
</tr>
<tr>
<td>Women</td>
<td>552</td>
<td>395.0</td>
<td>478.0</td>
<td>7.3</td>
</tr>
<tr>
<td>Men vs Women</td>
<td>Difference</td>
<td>34.6</td>
<td>-44.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Adjusted for Age, BMI, Race</td>
<td>Difference</td>
<td>32.9</td>
<td>-42.7</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Conclusion: Despite substantial health benefits from physical activity, persons with knee OA were particularly inactive. Physical activity guideline attainment among persons with knee OA based on accelerometer was under half the proportion previously reported based on self-reported activity, underscoring the importance of objective measures for accurate assessments. Although men were more likely than women to meet recommended physical activity guidelines they were also more likely to be inactive. These findings point to the importance of public health efforts to increase physical activity among persons with knee OA.

Disclosure: D. D. Dunlop: NIH, 2; J. Song: NIH, 2; P. Semanik: NIH, 2; L. Sharma: NIH, 2; R. W. Chang: NIH, 2; J. M. Bathon: NIH, 2; C. Eaton: NIH, 2; M. C. Hochberg: NIH, 2; W. J. Mysiw: NIH, 2; R. Jackson: NIH, 2; C. K. Kwoh: NIH, 2; M. C. Nevitt: NIH, 2; J. M. Hootman: None.

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Brain Activity in Patients with Chronic Knee Pain Due to Osteoarthritis: Dissociating Evoked from Spontaneous Pain. Elle L. Parks,2 Marwan N. Balti,2 Paul Y. Gheaa,3 Thomas J. Schnitzer1 and Apkar V. Apkarian.1 Northwestern University, Chicago, IL, 2Northwestern University, 3Yale University

Background: Although chronic pain is a primary manifestation of osteoarthritis (OA), its properties and representation in the brain have not been fully explored. Prior work from our group indicated that brain activity for spontaneous pain and evoked pain in people suffering chronic pain activate brain areas distinct from that observed for acute pain in healthy subjects1,2 but this has not been studied in people with OA.

Objectives: To define: 1) Psychophysical differences in knee joint pressure-induced pain between OA and healthy subjects, and between OA patients’ reported better and worse knees; 2) brain activity differences for knee joint pressure-induced pain in these groups; 3) brain activity differences for evoked and spontaneous pain in OA; 4) the representation of clinical OA pain characteristics in the brain and their relationship with spontaneous and evoked pain-related activity.

Methods: Fourteen OA patients (10 males; age 56.1 ± 2.09 years) and nine healthy controls (6 males; age 46.55 ± 2.6 years) were recruited for this study. Subjects rated pain using a finger-span device in response to pressure applied by means of a custom-made apparatus to the most sensitive part of each knee for patients, and at the center of the knee joint in healthy controls. During each scan run subjects were presented with up to nine stimuli distributed in time in a pseudo-random design of variable intensities and durations. The pressure signal and finger-spanning device were synchronized in time locked with the fMRI acquisition sequence.

Durations. The pressure signal and finger-spanning device were synchronized distributed in time in a pseudo-random design of variable intensities and durations. The pressure signal and finger-spanning device were synchronized.

During each scan run subjects were presented with up to nine stimuli distributed in time in a pseudo-random design of variable intensities and durations. The pressure signal and finger-spanning device were synchronized in time locked with the fMRI acquisition sequence.

Results: Psychophysical properties and brain activation patterns of evoked pain were similar between OA patients and healthy controls, and between worse and better OA knees. In OA patients, stimulus-related brain activity could be distinguished from brain activity associated with ongoing pain. The former activated brain regions (bilateral insula, SII, ACC, SMA, inferior and posterior parietal cortices) commonly observed for acute painful stimuli in healthy subjects, while the spontaneous pain of OA engaged prefrontal-limbic regions closely corresponding to areas observed for spontaneous pain in other chronic pain conditions, such as chronic back pain and post-herpetic neuralgia. We also identified, for the first time, arthritis and chronic pain-related clinical characteristics in the brain, which mapped to distinctive but overlapping prefrontal-limbic regions similar to those involved in spontaneous OA pain.

Conclusion: This study demonstrates the existence of two distinct pain states in knee OA patients. Knee pressure-evoked pain activates brain regions commonly observed for acute pain in healthy subjects for the same stimulus while ongoing spontaneous OA pain activates mainly medial prefrontal-limbic cortical areas, corresponding closely to brain areas activated for spontaneous pain in chronic back pain patients.

References:


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1Aalborg University, Denmark, 2Boston Childrens Hospital, 3Boston Univ SchI of Med, Boston, MA, 4Boston Univ School of Medicine, Boston, MA, 5Boston University School of Medicine, Boston, MA, 6UCSF, San Francisco, CA, 7UCSF, University of Alabama at Birmingham, University of Iowa

Purpose: Mechanisms contributing to knee pain in osteoarthritis (OA) are not well understood. Sustained mechanical and inflammatory stimuli in the joint may lead both to changes in the peripheral threshold of nociceptors (peripheral sensitization) and a central amplification of signals in the CNS (central sensitization), resulting in heightened pain sensitivity. We hypothesized that findings of central sensitization may be associated with symptomatic knee OA (SxOA).

Methods: The Multicenter Osteoarthritis (MOST) Study is cohort study of persons with or at high risk of knee OA. At the 60-month clinic visit, participants underwent knee radiography, answered pain questionnaires, and had an assessment of temporal summation (TS). TS is an augmented pain response to repetitive mechanical stimuli associated with central sensitization. A 60-g monofilament was applied repeatedly over the skin of each patella at a frequency of 1 Hz for 30 seconds. TS was defined as being present when the subject reported an increase in pain following the mechanical stimulation at the site being tested. Knees were categorized according to presence of SxOA based on KL≥2 and presence of consistent frequent knee pain (answering yes to a question about frequent knee pain at a telephone screen and a subsequent clinical visit within 30 days). Pain severity was dichotomized as moderate or greater pain on any of the 5 knee-specific WOMAC pain questions versus none/mild. We used a within-person knee-matched approach to explore the relationships of interest while eliminating between-person confounding using matched conditional logistic regression. In the first matched analyses, we examined the relation of TS with presence of SxOA among persons with knees discordant for SxOA. In the second matched analyses, we examined the relation of TS with pain severity among persons with knees discordant for pain severity, adjusting for radiographic severity.

Results: To date, data on 920 participants’ 60-month clinic visit are available (mean age 68.0, mean BMI 30.8, 67.3% female). Among persons with no SxOA, unilateral SxOA, and bilateral SxOA, the age- and sex-adjusted prevalences of TS at the patella were: 59%, 60%, and 61%, respectively. In the within-person knee-matched analyses for SxOA (N=135 that met criteria), radiographic knee OA without regards to knee pain symptoms was associated with 2.3 times higher odds of TS than no OA (95% CI 1.1–4.8, p<0.03), but SxOA itself was not significantly associated with TS once radiographic severity was accounted for (crude OR 1.7, 95% CI 0.7–3.8, adjusted OR 1.1, 95% CI 0.3–3.4). For the knee-matched analyses regarding pain severity (N=152 that met criteria), TS was associated with WOMAC pain severity (OR 3.3, 95% CI 1.3–8.3), but this was attenuated when adjusting for radiographic severity (OR 2.6, 95% CI 0.7–9.5).

Conclusions: In these preliminary results from a large cohort, TS was associated with the presence of radiographic knee OA and knee pain severity in the same knee, but not significantly with SxOA. Such findings suggest that the pathology of OA may be the source of prolonged sensory input required for central sensitization, and in turn, central sensitization may be related to pain severity.

Gait Adaptation after 6 Months of Specialized Shoes in Knee Osteoarthritis, Naja Shakoor1, Roy H. Lidtke2, Markus A. Wimmer2, Kharna C. Foucher3, Rachel A. Mikolaitis3, Louis F. Fogg3, Alan J. Shoelson3 and Joel A. Block1. 1Rush University Medical Center, Chicago, IL, 2Rush University Medical Center, 3Rush-University Medical Center, Chicago, IL, 4University of Iowa

Purpose: Biomechanical interventions for knee osteoarthritis (OA) aim to improve pain and retard disease progression by decreasing knee loading. These interventions require chronic use to achieve maximum efficacy and may have a delayed response. Chronic load alterations may also result in neuromuscular gait adaptations that persist even after the intervention is removed. Here, we evaluate the effects of 6 months’ use of a “mobility shoe”, intended to replicate the advantages of barefoot gait, on knee loading in symptomatic knee OA.

Methods: Subjects with radiographic (KL grades ≥ 2) and symptomatic (at least 30mm pain of 100mm scale while walking) medial compartment knee OA were recruited. Baseline gait analyses were performed using an optoelectronic camera system and multi-component force plate in subjects’ “own shoes”, “mobility shoes”, and barefoot. Subjects were instructed to wear the mobility shoes at least 6 hours/day for 6 days/week. Gait analysis was then repeated at 6, 12, and 24 weeks. The peak knee adduction moment (PAddM), a validated marker of medial compartment loading, represented the primary endpoint. An intent to treat analysis (ITT) was performed using repeated measures analyses of variance and simple main effects were used to further evaluate differences between shoes at various time points.

Results: Complete data are available for 16 subjects. Three terminated early: two due to lack of efficacy (6 and 12 weeks), and one was unable to return for study visits after 8 weeks. All data were carried forward for the ITT analysis. Mean PAddM during all footwear conditions are represented over time in Figure 1. Overall, in comparison to conventional shoes, the “mobility” shoes were associated with significantly decreased loads during gait (p<0.001)(Figure 1). Whereas at baseline the reduction in load with the mobility shoe compared to conventional shoes was only 3.7% (p=0.081), this increased to 9.4% (p<0.001) after 6 weeks of use, and reached an overall reduction of 18% at 6 months compared to conventional shoes (p<0.001). Interestingly, by 24 weeks, a gait adaptation was evident yielding an 11% (p<0.001) reduction in PAddM from baseline even when tested in conventional shoes (Figure 1).

Discussion: This study suggests that 6 months’ use of mobility shoes results in significant reductions in knee loading in subjects with knee OA. This effect is delayed, taking 6 weeks to achieve significant reductions, and it is associated with a gait adaptation by 24 weeks that maintains load reduction even when the mobility shoes are removed. This gait adaptation, likely resulting from beneficial neuromuscular and behavioral changes, may be especially important in OA, which progresses slowly and for which subtle alterations may have profound long-term consequences. The durability of these adaptations will need to be evaluated in longer term studies.

Disclosure: N. Shakoor: None; R. H. Lidtke: None; M. A. Wimmer: None; K. C. Foucher: None; R. A. Mikolaitis: None; L. F. Fogg: None; A. J. Shoelson: None; J. A. Block: None.

The Role of Varus and Valgus Alignment in the Initial Development of Cartilage Damage at the Knee: The MOST Study. Leena Sharma2, Orit Almagor1, Joan S. Chmiel1, David T. Felson1, Ali Guermazi2, Frank Roemer3, James Torner4, Cora E. Lewis5, Neil Segal3, John A. Lynch6, Derek Cook7, Jean Hietpas3 and Michael C. Nevitt7. 1Boston University, Boston, MA, 2Boston University, 3Northwestern University, Chicago, IL, 4Northwestern University, 5Queens University, 6UCSF, San Francisco, CA, 7UCSF, 8University of Iowa

Purpose: Varus and valgus alignment are each associated with subsequent progression of knee OA but their role in incident disease is less certain. Radiographic measures of incident OA cannot capture cartilage tissue change directly or reveal the compartment of initial disease. We identified knees with normal cartilage morphology by MRI in all tibial and femoral subregions at baseline to test the hypothesis: varus alignment is associated with incident medial cartilage damage and valgus alignment is associated with incident lateral cartilage damage.

Methods: MOST includes persons at risk for or with knee OA. In all participants, full-lead x-rays were acquired at baseline, and MRI (1.0T extremity system) at baseline and 30 months later. Varus malalignment was defined as ≤ 178° (hip-knee-ankle angle) and valgus as ≥ 182°. Cartilage and menisci were assessed using WORMS. In knees with normal baseline cartilage morphology (WORMS score 0 in all subregions), we used logistic regression with GEE to examine the association between baseline alignment and incident cartilage damage (WORMS score ≥ 2 at 30 months in ≥ 1 subregion) adjusting for age, gender, BMI, laxity, and meniscal tear and extrusion.

Results: Of 1881 knees, 293 knees (110 varus, 55 valgus, 128 neutral) from 256 persons (mean age 60 years, BMI 28.6, 67% women) had normal cartilage morphology in all subregions at baseline. At 30 months, 34 had incident medial and 15 had incident lateral cartilage damage. As shown in Table 1, varus alignment was associated with a significantly increased risk of new medial cartilage damage vs. either reference group (non-varus or neutral) and when analyzed as a continuous variable. This relationship held even when knees with medial meniscal tear or extrusion were excluded (adjusted OR 1.37/° varus, 95% CI 1.11, 1.68). Significant relationships were not detected for valgus and incident lateral disease (Table 2), possibly due in part to the low frequency of this outcome. In addition, varus was protective against incident lateral damage [adjusted OR 0.75/°, 95% CI 0.59, 0.95] and valgus against incident medial damage [adjusted OR 0.72/°, 95% CI 0.63, 0.83].

Table. Median daily minutes of physical activity intensity among n=1021 persons with radiographic knee OA

<table>
<thead>
<tr>
<th>Unadjusted Results</th>
<th>n</th>
<th>Minutes No activity (0 counts)</th>
<th>Minutes Light PA (1–2019 counts)</th>
<th>Minutes MVPA (≥2020 counts)</th>
<th>Minutes Any activity (&gt;9 counts)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>Median</td>
<td>Median</td>
<td>Median</td>
</tr>
<tr>
<td>Men</td>
<td>469</td>
<td>429.6</td>
<td>433.9</td>
<td>7.3</td>
<td>490.3</td>
</tr>
<tr>
<td>Women</td>
<td>552</td>
<td>472.0</td>
<td>395.0</td>
<td>-3.3</td>
<td>490.3</td>
</tr>
<tr>
<td>Men vs Women</td>
<td></td>
<td>34.6</td>
<td>-44.1</td>
<td>8.6</td>
<td>-32.3</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td></td>
<td>22.0 (47.2)</td>
<td>-58.2 (~30.1)</td>
<td>6.1 (11.1)</td>
<td>-46.5 (~18.1)</td>
</tr>
<tr>
<td>Adjusted for Age,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>469</td>
<td>432.1</td>
<td>438.9</td>
<td>14.7</td>
<td>457.0</td>
</tr>
<tr>
<td>Women</td>
<td>552</td>
<td>402.4</td>
<td>409.7</td>
<td>6.9</td>
<td>494.4</td>
</tr>
<tr>
<td>Men vs Women</td>
<td></td>
<td>35.9</td>
<td>-2.5</td>
<td>5.4</td>
<td>-36.9</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td></td>
<td>17.3 (48.5)</td>
<td>-55.3 (~30.1)</td>
<td>3.3 (7.5)</td>
<td>-51.6 (~22.1)</td>
</tr>
</tbody>
</table>

Table 2. Valgus Alignment (Baseline) and Incident Lateral Cartilage Defect (Outcome Variable) between Baseline and 30 Month Follow-up (n=293 knees with normal cartilage morphology at baseline)

<table>
<thead>
<tr>
<th>Alignment</th>
<th>OR (95% CI) adjusted for age, gender, BMI, medial laxity</th>
<th>OR (95% CI) adjusted for age, gender, BMI, lateral meniscal tear, lateral meniscal extrusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-valgus (reference)</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td>Valgus</td>
<td>1.49 (0.40, 5.50)</td>
<td>0.97 (0.26, 3.70)</td>
</tr>
<tr>
<td>Neutral (reference)</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td>Valgus</td>
<td>0.97 (0.25, 3.85)</td>
<td>0.62 (0.14, 2.77)</td>
</tr>
<tr>
<td>Valgus (continuous), OR per 1*</td>
<td>1.31 (1.04, 1.66)</td>
<td>1.18 (0.94, 1.48)</td>
</tr>
</tbody>
</table>

Conclusion: In knees with normal cartilage morphology, varus alignment was associated with the initial development of cartilage damage in the more loaded compartment, and both varus and valgus were associated with a reduced risk of incident damage in the less loaded compartment. These results
suggest that varus alignment is a risk factor for incident cartilage damage in knees without OA, and provide further evidence that varus alignment increases the risk of incident knee OA.

Disclosure: L. Sharma: None; O. Almagor: None; J. S. Chmiel: None; D. T. Felson: None; A. Guernaz: None; F. Roemer: None; J. Torner: None; C. E. Lewis: None; N. Segal: None; J. A. Lynch: None; D. Cooke: None; J. Hirtpas: None; M. C. Nevitt: None.

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Varus Thrust Is Associated with Worse Physical Function. William F. Harvey1, Grace H. Lo1, Erica McAdams2, Melanie A. Ripley2, Melynn Nuite1 and Timothy E. McAlindon2. 1Tufts Medical Center, Houston, TX, 2Tufts Medical Center Box 406, Boston, MA, 3Tufts Medical Ctr, Boston, MA, 4Tufts Medical Ctr

Purpose: Varus Thrust (VT) is rapid lateral bowing of the knee during ambulation and represents a combination of malalignment and instability. VT has been associated with knee cartilage loss, medial joint space narrowing and knee pain. It is unknown how presence of VT affects function in knee osteoarthritis (KOA). We hypothesize that presence of VT would be associated with worse functional outcomes in persons with KOA.

Method: This is a cross-sectional study of a convenience sample selected from participants of a randomized controlled trial of vitamin D for symptom-atric radiographic KOA. All those in the RCT were eligible to participate in this study except participants who used ambulatory devices. Participants were video recorded in the frontal plane using a standard digital video camera (60 Hz) walking at a self-selected speed. These videos were viewed at separate reading sessions by two rheumatologists trained to evaluate VT. Participants were classified as VT present vs. absent. Disagreements were adjudicated by consensus of both (achieved in all cases). The functional outcomes were WOMAC function subscale and SF-36 function subscale. We also examined the standard functional performance measures chair stand (total time for 5 sequential sit-to-stands) and timed 20 meter walk. We used linear regression to model the association of these functional outcomes and presence of VT. As a ‘control’ we examined a variable we hypothesized should not be associated with VT, the SF-36 Mental Health Subscale.

Results: Participants (N=82) had a mean age 63.0 (±8.5), BMI 30.2 (±5.4), 60% female, 49% with varus alignment, 23% with valgus alignment, and 31% with definite VT. Those with VT and without VT were not different in mean age or height, but were more likely to be male (68% vs. 29% male, p<0.01). Although not reaching statistical significance, those with VT were somewhat heavier (Mean weight 87 ± 16 kg vs. 81 ± 15 kg p=0.35). Results did not change when adjusting for age, BMI or sex. Table 1 shows the results of the linear regression of functional outcomes. For WOMAC function, chair stand and walk time (for all higher number of the linear regression of functional outcomes. For WOMAC function, chair stand and walk time (for all higher number

Table 1. Linear Regression of Functional outcomes.

<table>
<thead>
<tr>
<th>Functional Outcome</th>
<th>VT Absent (n = 57)</th>
<th>VT Present (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC function (Mean (SD))**</td>
<td>12.4 (9.4)</td>
<td>21.4 (13.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SF-36 Physical Function Subscale (Mean (SD))**</td>
<td>44.6 (8.7)</td>
<td>38.2 (12.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SF 36 Mental Health Subscale (Mean (SD))**</td>
<td>51.5 (8.7)</td>
<td>49.9 (8.5)</td>
<td>0.43</td>
</tr>
<tr>
<td>Walk Time (Mean (SD)) seconds*</td>
<td>153.2 (3.7)</td>
<td>174.3 (3.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chair Stand Time (Mean (SD)) seconds*</td>
<td>14.8 (2.0)</td>
<td>17.0 (3.4)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Lower = better function
**Lower = worse function

Conclusion: VT is associated with worse physical function, as measured by WOMAC function and SF-36 and worse performance in the functional performance measures of chair stand and timed walk. The mental health component score was not associated with VT. The interpretation of the results is limited by the cross-sectional nature of the analysis and should be confirmed prospectively. The results also raise the question of whether a modification of VT (i.e. through bracing, shoe modification, gait modification, etc) may lead to improved physical function.

Disclosure: W. F. Harvey: None; G. H. Lo: None; E. McAdams: None; M. A. Ripley: None; M. Nuite: None; T. E. McAlindon: NIAMS-NIH, 2.

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Pediatric Rheumatic Disease in the Intensive Care Unit: Lessons Learned from 15 Years Experience in a Tertiary Care Pediatric Hospital. Sujhas M. Radhakrishna1, Bracha Shahn2, Katherine A. B. Marzan2, Diane E. Brown2 and Andreas O. Reiff1. 1Childrens Hosp LA MS60, Los Angeles, CA, 2Childrens Hospital of Los Angeles, Los Angeles, CA, 3Childrens Hospital of Los Angeles

Purpose: Pediatric rheumatic diseases and their treatment can cause significant morbidity requiring admission and treatment in the pediatric intensive care unit (PICU). No studies describe the reasons for PICU admission and outcomes of pediatric rheumatology patients. This study describes a large urban single center experience for critically ill patients with rheumatic disease requiring PICU admission. Understanding these data may aid in decreasing morbidity and improving survival.

Methods: The PICU internal database at this tertiary care pediatric hospital was searched for patients with rheumatic disease admitted between January 1, 1995 and July 30, 2009. Medical records were reviewed for demographics, diagnosis, comorbidities, and prior treatments, reason for admission, types of organ dysfunction, supportive care needs, infections, and outcomes. PRISM III (Pediatric Risk of Mortality III) was calculated from the PICU database. Area under receiver operative characteristic curve (AUR) for PRISMIII was calculated. Standard mortality ratio (SMR) was calculated based on PRISMIII estimated mortality with mid-P exact 95% CI. Fisher’s exact test was used to determine risk factors for patient mortality.

Results: 90 patients with 122 total admissions were identified. Female: male ratio was 7:3. Mean age at first PICU admission was 14.2 ± 4.3 years. 63% were Hispanic, 20% African American, 12% Caucasian, and 5% Asian. Rheumatic diagnoses included SLE (n=57), systemic vasculitides (n=13), JIA (n=12), 8 with systemic JIA), and dermatomyositis (n=8). Cause of admission was related to rheumatic disease in 61 (50%), infection in 26 (21%), both infection and rheumatic disease in 18 (15%), iatrogenic causes in 5 (4%), and other causes in 12 (10%). Multi-organ dysfunction was present in 39 (32%) and single organ dysfunction occurred as follows: pulmonary in 23 (19%), CNS in 13(10%), GI and renal each in 11 (9%), cardiac in 87%, and other in 17 (14%). In 30 admissions (24.6%) a new rheumatologic diagnosis was made. Median length of PICU stay was 3.1 (0–55) days. In 105 (86%) admissions, the patient was discharged from PICU. There were 18 deaths (20%). 9 from combined infection and active rheumatic disease, 4 from infection alone, 2 from rheumatic disease only, and 3 from other causes. There were a higher proportion of SLE patients (83% vs 58%, p=0.06) and patients on hemodialysis (33% vs 13%, p=0.07) in the non-survivor group compared to survivors. AUR for PRISMIII was 0.84 (SE 0.06). SMR based on PRISMIII was 0.72 (95% CI 0.38 – 1.25) for pediatric rheumatology patients and 0.87 (95% CI 0.79–0.96) for all PICU patients.

Conclusions: Rheumatic disease related illness accounted for the majority of PICU admissions, most often with multi-organ dysfunction. Deaths occurred most often from severe infections in patients receiving multiple immunosuppressive medications for active rheumatic disease. Non-statistically significant risk factors for mortality included a diagnosis of SLE and concurrent hemodialysis. Observed mortality in pediatric rheumatology patients correlated well with PRISMIII and SMR was similar to the general PICU population at this institution.

Disclosure: S. M. Radhakrishna: None; B. Shahn: None; K. A. B. Marzan: None; D. E. Brown: None; A. O. Reiff: None.

2103

Rates of Hospitalized Bacterial Infection in Juvenile Idiopathic Arthritis and Its Treatment: An Observational Study of National U.S. Medicaid Administrative Claims Data. Timothy Beukelman2, Fenglong Xie2, Lang Chen2, John W. Baddley2, Elizabeth Delzell2, Carlos G. Grijalva1, Nivedita M. Patkar2, Kenneth G. Saag2, Kevin L. Winthrop1 and Jeffrey R. Curtis2. 1Oregon Health and Science University, 2Univ of Alabama at Birmingham, Birmingham, AL, 1Vanderbilt University
Purpose: We analyzed national Medicaid administrative claims data to examine incidence rates of hospitalized bacterial infection among children with juvenile idiopathic arthritis (JIA) in clinical practice.

Methods: Using Medicaid administrative claims data from all 50 U.S. states from 2000 through 2005, we identified a cohort of children with JIA based on physician diagnosis codes and dispensed medication prescriptions. We defined a control cohort of children diagnosed with attention deficit hyperactivity disorder (ADHD). All subjects had a 6-month baseline period for assessment of covariates prior to study entry. Exposures to MTX and anti-TNF were based on dispensed prescriptions and were classified as current use (within 30 days of a missed prescription refill) or recent use (current use within past 6 months). New and prevalent medication exposures were included. All anti-TNF agents were grouped together. Hospitalized bacterial infection definitions were used defining inpatient discharge diagnosis codes in any position. Follow-up was censored at loss to follow-up, first hospitalized infection outcome, and study end. We calculated crude infection rates for children with JIA with various drug exposures and for children with ADHD. Using Cox proportional hazard models, we calculated hazard ratios (HR) for infection while adjusting for age, sex, race, baseline oral glucocorticoid (GC) use, time-varying current oral GC use, and hospitalized bacterial infection during the baseline period. A secondary analysis of JIA subjects restricted to new-users of MTX and anti-TNF was performed.

Results: The JIA cohort included 8,348 subjects with mean follow-up of 1.6 years. 3,482 JIA subjects were MTX users and 1,477 were anti-TNF users (89% etanercept). The ADHD cohort included 358,534 subjects with mean follow-up of 1.3 years. Crude rates of hospitalized bacterial infection are shown in Table. The crude rate for current oral GC users was 2 to 3-fold higher in all JIA drug exposure groups. The adjusted HR for JIA subjects without any MTX or anti-TNF use was 1.25 (1.07–1.47) compared to ADHD. The adjusted HR for current and recent anti-TNF use was 1.2 (0.9–1.6) compared to JIA subjects without any MTX or anti-TNF use and was 1.3 (1.0–1.8) compared to current and recent MTX users without any anti-TNF use. The analysis of new-users produced an adjusted HR of 1.6 (0.8–3.1) for new anti-TNF compared to new MTX without any anti-TNF.

Methods: We identified children ages 5–19 years with new onset ESRD due to lupus nephritis from 1995–2006, as defined by Medicare eligibility and entry into the U.S. Renal Data System, which includes data on approximately 94% of all U.S. ESRD patients. Lupus was identified as the cause of ESRD on medical evidence forms. We investigated baseline demographic and clinical characteristics of patients at ESRD onset, rates of kidney transplantation and overall survival, and causes of death. Predictors of these outcomes in the first five years of ESRD were identified using Cox proportional hazards models, adjusting for sociodemographic and clinical factors. Results: We identified 583 children in the U.S. who had incident ESRD due to lupus nephritis. Mean age at ESRD onset was 16.2 (SD 2.4) years. Sex, race, ethnicity, region of residence and medical insurance type at ESRD are shown in Table 1. Within 5 years after onset of ESRD, 193 (33% overall) received a kidney transplantation and 131 (22%) died. Mean age at kidney transplantation was 18.2 (SD 3.4) years and at death was 19.5 (SD 3.5) years. Causes of death were cardiorespiratory (39%), infectious (19%), hemorrhagic (10%), neurologic (9%) and other (19%). In multivariable models, residence in the U.S. Northeast, compared to the South, was associated with increased rates of kidney transplantation. Five year rates of both kidney transplantation and overall survival were less than half among Black compared to white children. Sex, ethnicity, medical insurance and clinical factors were not independent predictors of outcomes in these children.

Table 1. Multivariable-adjusted* Five Year Hazard Ratios (HRs) according to Sociodemographic Factors for Children ages 5–19 years with End-Stage Renal Disease (ESRD) due to Lupus Nephritis in the U.S., 1995–2006

<table>
<thead>
<tr>
<th>Sociodemographic factor (n)</th>
<th>Renal Transplantation**</th>
<th>Survival***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Male</td>
<td>0.99 (0.68, 1.43)</td>
<td>0.68 (0.45, 1.03)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Black</td>
<td>0.48 (0.32, 0.71)</td>
<td>0.44 (0.24, 0.80)</td>
</tr>
<tr>
<td>Asian</td>
<td>0.85 (0.49, 1.48)</td>
<td>1.01 (0.36, 2.86)</td>
</tr>
<tr>
<td>Other</td>
<td>0.66 (0.20, 2.17)</td>
<td>0.39 (0.13, 1.2)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic (441)</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Hispanic (142)</td>
<td>0.65 (0.41, 1.01)</td>
<td>1.1 (0.55, 2.22)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South (247)</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Northeast (82)</td>
<td>1.84 (1.21, 2.80)</td>
<td>1.56 (0.53, 2.94)</td>
</tr>
<tr>
<td>MidWest (97)</td>
<td>1.04 (0.66, 1.64)</td>
<td>1.56 (0.9, 2.78)</td>
</tr>
<tr>
<td>West (146)</td>
<td>1.12 (0.80, 1.81)</td>
<td>1.12 (0.66, 1.92)</td>
</tr>
<tr>
<td>Medical Insurance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private (224)</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Medicaid (285)</td>
<td>0.79 (0.57, 1.09)</td>
<td>1.06 (0.51, 1.52)</td>
</tr>
<tr>
<td>None (52)</td>
<td>0.71 (0.38, 1.32)</td>
<td>0.78 (0.41, 1.45)</td>
</tr>
<tr>
<td>Other (145)</td>
<td>0.78 (0.47, 1.35)</td>
<td>0.78 (0.18, 3.33)</td>
</tr>
</tbody>
</table>

*Multivariable model: Age, sex, race, ethnicity, medical insurance, region, diabetes mellitus, hypertension, erythropoietin use, body mass index (kg/m²), and initial ESRD therapy (hemodialysis, peritoneal dialysis or pre-emptive transplant) **Renal transplantation among all incident dialysis patients (n = 579) and survival among all incident ESRD patients (including pre-emptively transplanted, n = 583) ***95% Confidence Interval by Wald method

Conclusions: Among children with ESRD due to lupus nephritis in the U.S., geographic region and race were the most important predictors of five year kidney transplantation and survival rates. Although these analyses do not account for WHO class of nephritis or lupus disease activity, the results suggest that important disparities in access to care and outcomes exist by region and race in the U.S.

Disclosure: L. T. Hiraki: None; B. Lu: None; M. A. Brookhart: None; T. Shaykevich: None; G. S. Alarcon: None; D. H. Solomon: None; W. Winkelmayer: None.

2105

The Clinical Significance of a Single MVK Mutation in HIDS, Karyl S. Barron1, Amanda K. Ombrello2, Donald P. Goldsmith1, Ivona AkSENTIJEVICH1, Anne Jones3, Beverly K. Barham4, and Daniel L. Kastner1. 1Drexel Univ College Med, Philadelphia, PA, 2NIAID/NIH, Bethesda, MD, 3NIAMS, NIH, Bethesda, MD, 4NIAMS/NIH, 5NIH, 6NIAMS, Damascus, MD, 7Natl Inst of Arthritis & MSK SD, Bethesda, MD

Purpose: Little information is available on kidney transplantation and overall survival among children with end-stage renal disease (ESRD) due to lupus nephritis in the U.S. We examined rates and predictors of kidney transplantation and overall survival among children with ESRD due to lupus nephritis from 1995–2006.
Background: HyperIgD syndrome (HIDS) is an autoinflammatory disorder caused by mutations in the MIFK gene that encodes mevalonate kinase. Traditionally it is considered to be transmitted as an autosomal recessive disorder. As a large referral center for children with periodic fever syndromes, we have seen a cohort of symptomatic patients with only 1 mutation in the MIFK gene. Since there are no defined diagnostic criteria for HIDS, we compared these patients with our cohort of HIDS patients with 2 MIFK mutations.

Methods: Patients were evaluated in the Periodic Fever Clinic at the National Institutes of Health. Clinical and laboratory information were collected at each visit. CHI square and Mann-Whitney U tests were performed to compare patients with 2 MIFK mutations and those with only 1 MIFK mutation.

Summary: 22 patients with mutations in MIFK were evaluated in our clinic; 15 patients were found to have 2 mutations (V377I and 1 other MVK mutation). We have seen a cohort of symptomatic patients with only 1 mutation in the MVK gene. As a large referral center for children with periodic fever syndromes, Traditionally it is considered to be transmitted as an autosomal recessive disorder. As a large referral center for children with periodic fever syndromes, we have seen a cohort of symptomatic patients with only 1 mutation in the MIFK gene.

Clinical presentation at the time of a flare was compared between the 2 groups:

<table>
<thead>
<tr>
<th></th>
<th>2 mutations</th>
<th>1 mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (mo)</td>
<td>5.4</td>
<td>5.9</td>
</tr>
<tr>
<td>Duration (d)</td>
<td>5.1</td>
<td>5.3</td>
</tr>
<tr>
<td>Frequency (wks)</td>
<td>3.6</td>
<td>4.5</td>
</tr>
<tr>
<td>T max</td>
<td>104.8</td>
<td>105.1</td>
</tr>
<tr>
<td>Flare with immunizations</td>
<td>12/13 (92.3)</td>
<td>5/7 (71.4)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15/15 (100)</td>
<td>6/7 (85.7)</td>
</tr>
<tr>
<td>Diarhea</td>
<td>14/15 (93.3)</td>
<td>6/7 (85.7)</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>11/15 (73.3)</td>
<td>4/7 (57.1)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>13/15 (86.7)</td>
<td>5/7 (71.4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13/15 (86.7)</td>
<td>5/7 (71.4)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>4/5 (28.6)</td>
<td>2/7 (28.6)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8/15 (53.3)</td>
<td>5/7 (71.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>11/15 (73.3)</td>
<td>5/7 (71.4)</td>
</tr>
<tr>
<td>Cervical adenopathy</td>
<td>15/15 (100)</td>
<td>6/7 (85.7)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>7/15 (46.7)</td>
<td>1/7 (14.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>11/14 (78.6)</td>
<td>4/6 (66.7)</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>4/5 (26.7)</td>
<td>2/7 (28.6)</td>
</tr>
</tbody>
</table>

There was no significant difference in clinical presentation between the 2 groups of patients. The two groups were similar in percentage with documented elevations of acute phase reactants with flares and mild elevations of IgA. Mean serum IgD levels for those with 2 MIFK mutations was 103 mg/dl vs. 31 mg/dl for those with 1 mutation (p = 0.03).

Conclusions: Aside from the higher IgD levels in those children with 2 MIFK mutations, there does not appear to be any significant clinical differences between these 2 groups. Prior studies in children with 2 mutations have not correlated IgD levels with disease severity. The relatively small number of children with 1 mutation in our cohort may influence the analyses, but thus far there are no clear trends to offer the clinician in the identification or predictability of the disease course in children with either 1 or 2 mutations. Given the higher frequency of V377I heterozygotes in our patient cohort as opposed to the general population, our data suggests that under some circumstances this could be associated with clinical HIDS, although clearly other factors must play a role given the 0.3% frequency in the general population.

Disclosure: K. S. Barron: None; A. K. Ombrello: None; D. P. Goldsmith: None; I. Aksentijevich: None; A. Jones: None; B. K. Barham: None; D. L. Kastner: None.

Biomarkers for Global and Renal Disease Activity in Juvenile Systemic Lupus Erythematosus (jSLE): Rina Mina1, Michael Bennett2, Joseph M. Ahearn3, Joshua Pendi4, Jamie Eaton5, Nicole Wilson6, Prasad Devarajan7,8 and Hermine Brunner2.1Wexford, PA, 2Cincinnati Children’s Hospital Medical Center, 3Cincinnati Children’s Med Ctr, Cincinnati, OH, 4Cincinnati Children’s Hospital Medical Center, 5Cincinnati Children’s Med Ctr, Cincinnati, OH, 6University of Pittsburgh

Background: Preliminary data suggest that the Lupus Nephritis Renal Panel (LNRP), composed of transferrin, ceruloplasmin, acid-1-glycoprotein, neutrophil gelatinase-associated lipocalin, prostaglandin-D synthetase and monocyte chemotactic protein, is associated with worsening lupus nephritis in jSLE. Cell-bound complement activated products (CB-CAP) which consist of erythrocyte, reticulocyte and platelet-bound complement components (E-C4d, E-C3d E-IgBb, E-CRI, R-C4d, R-C3d, R-IgB and P-C4d) have been shown to reflect ongoing global disease activity in studies limited to adults with SLE.

Methods: Clinical, laboratory and biomarker data were collected from 12 jSLE patients during initial and follow-up visits. Levels of LNRP standardized to urine creatinine and CB-CAP were measured by enzyme-linked immunosorbent assay and flow cytometry respectively. Physician-rated change in patient’s disease course between visits (global/renal disease worsening: yes/no) served as the criterion standard.

Results: Using Wilcoxon Rank Sum Test and Spearman’s correlation, statistically significant association was seen between levels of specific urine biomarkers and the renal domains of disease activity indices and the criterion standard (see Table 1). Levels of urine biomarkers were seen to be elevated three months prior to renal worsening with the change in the biomarker level associated with the change in the renal disease activity scores. No significant correlation between extra-renal disease activity and urine biomarkers was seen. Of the CB-CAP, E-CRI, P-C4d and R-C4d were associated with current global/extra-renal disease activity. Traditional biomarkers for global and renal worsening correlated poorly with disease course and activity.

Correlation of Biomarkers with Disease Variables

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Disease variable</th>
<th>Concurrent validity</th>
<th>Predictive validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cereuloplasmin</td>
<td>Renal BILAG</td>
<td>0.61 0.02</td>
<td>Renal SLAM 0.70 0.02</td>
</tr>
<tr>
<td>Monocyte chemotactic protein</td>
<td>Renal SLAM</td>
<td>0.60 0.01</td>
<td>Extra renal BILAG -0.60 0.05</td>
</tr>
<tr>
<td>Transferrin</td>
<td>Renal SLAM</td>
<td>0.56 0.02</td>
<td>Renal SLAM 0.78 0.01</td>
</tr>
<tr>
<td>Prostaglandin-D synthetase</td>
<td>Renal SLAM</td>
<td>0.72 0.003</td>
<td>Renal SLAM 0.75 0.01</td>
</tr>
<tr>
<td>Acid-1-glycoprotein</td>
<td>Renal BILAG</td>
<td>0.66 0.01</td>
<td>Renal BILAG 0.66 0.03</td>
</tr>
<tr>
<td>Erythocyte complement receptor1</td>
<td>Total/Extra-renal BILAG</td>
<td>-0.53 0.02</td>
<td>Urine protein/creatinine -0.30 0.04</td>
</tr>
<tr>
<td>Erythocyte-factor Bb</td>
<td>Renal BILAG</td>
<td>-0.52 0.04</td>
<td>Creatinine clearance 0.63 0.02</td>
</tr>
<tr>
<td>Reticulocyte bound-C4d</td>
<td>Total/Extra-renal BILAG</td>
<td>0.72 0.04</td>
<td>Total/Extra-renal BILAG 0.89 &lt;0.0001</td>
</tr>
</tbody>
</table>

Legend: ¶ Only significant correlation shown ¶¶Urine biomarkers standardized to urine creatinine

Conclusions: LNRP is associated with renal disease activity and CB-CAP with extra-renal disease activity in jSLE. Further studies assessing the predictive properties of combining these biomarkers are in progress.

Disclosure: R. Mina: NIH, 2; M. Bennett: None; J. M. Ahearn: None; J. Pendi: None; J. Eaton: None; N. Wilson: None; P. Devarajan: None; H. Brunner: NIAMS-NIH, 2.

2107

Childhood Primary Angitis of the CNS: Identifying Disease Trajectories and Early Risk Factors for Persistently Higher Disease Activity. Tania Cellucci, Pascal N. Tyrrell, Suzanne Laughlin, Derek Armstrong, William Halliday, Shehla Sheikh and Susanne M. Benseler. The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Purpose: Childhood Primary Angitis of the CNS (cPACNS) is a devastating inflammatory brain disease. cPACNS comprises of distinct clinical subtypes at presentation. Disease courses of cPACNS have never been systematically studied. The aim of the study was to characterize and compare distinct disease activity trajectories in cPACNS and to identify early risk factors for persistently higher disease activity over time.

Methods: A single centre cohort study was performed including consecutive children diagnosed with cPACNS based on Calabrese criteria between December 1998 and June 2010. Patients had to be <18 years of age at diagnosis and have serial measures of disease activity as defined by physician global assessment (10 cm Visual Analogue Scale). Standardized clinical assessments, Pediatric Stroke Outcome Measures, inflammatory markers, and
neuroimaging characteristics were collected serially. Longitudinal data were analyzed using mixed effects models accounting for repeated measures and linear regression of slope parameter estimates over time.

Results: The study cohort consisted of 45 children: 21 males, 24 females, median age at diagnosis 9.8 years, and median follow-up 21 months. Diagnoses: 26 (57%) had angiography-negative cPACNS, and 19 (43%) had angiography-positive cPACNS. At diagnosis, children with angiography-negative cPACNS were more likely to be female (81% vs. 56%, p<0.001), present with seizures (85% vs. 10%, p<0.001), and have elevated levels of ESR (p=0.036) and CRP (p=0.046). Disease activity decreased significantly over time in all cPACNS patients (p<0.001). Distinct trajectories of disease activity over time were identified for each cPACNS subtype. Children with angiography-negative cPACNS had persistently higher disease activity and required a longer time to remission (p=0.046). Female sex and elevated inflammatory markers at diagnosis were not predictive of delayed remission. Seizures at diagnosis of cPACNS were found to be an early risk factor for persistently higher disease activity over time (p=0.016).

Conclusions: Distinct subtypes of cPACNS were found to have unique disease activity trajectories. In all children, disease activity improved significantly over time. However, children diagnosed with angiography-negative cPACNS and those presenting with seizures were at higher risk of remission failure, and persistently higher disease activity. Early recognition of this high-risk cohort may enable physicians to initiate targeted therapies and prevent long-term brain injury in children with cPACNS.

Disclosure: T. Cellucci: None; P. N. Tyrrell: None; S. Laughlin: None; D. Armstrong: None; W. Halliday: None; S. Sheikh: None; S. M. Benseler: None.

ACR Concurrent Abstract Sessions
Quality Measures and Innovation in Practice Management and Care Delivery

Wednesday, November 10, 2010, 2:30 PM–4:00 PM

2108

Predictive Validity of the New Preliminary ACR/EULAR Definitions for Remission in Rheumatoid Arthritis, David T. Felson1, Josef S. Smolen2, George A. Wells3, Bin Zhang4, Lilian H. D. van Tuyl5, Julia Funovits6, Maarten Boers6 and for the ACR/EULAR Commission To Redefine Remission in Rheumatoid Arthritis. 1Boston Univ Sch of Medicine, Boston, MA, 2Krankenhaus Lainz, Vienna, Austria, 3Medical University of Vienna, 4Univ of Ottawa Faculty of Med, Ottawa, ON, Canada, 5VU University Medical Center, Amsterdam, The Netherlands, 6VU University Medical Center, Amsterdam

Background: With remission in rheumatoid arthritis (RA) an increasingly attainable goal, there is a need for well-defined definitions of remission that is stringent but achievable and could be applied uniformly as an outcome in clinical trials.

Methods: A committee constituted from members of the American College of Rheumatology, the European League Against Rheumatism and the Outcome Measures in Rheumatology (OMERACT) Initiative guided the process and reviewed prespecified analyses from clinical trials of patients with RA. A stringent definition was requested including at least joint counts and an acute phase reactant, but excluding duration of state. As part of the search for a remission definition, trial data were analyzed to examine the ability of candidate measures to predict later good x-ray and functional outcomes (defined as change ≤0 in van der Heijde/Sharp scores and Health Assessment Questionnaire (HAQ) change ≤0 and HAQ score consistently ≤0.5 both during the 2nd year of respective trials). Likelihood ratios compared the proportion of patients in remission having the good outcome to the proportion of patients not in remission having the good outcome. To rank candidate definitions of remission, the p value from the logistic regression chi square test was used.

Candidate definitions of remission were downgraded when they led to values of core set measures which suggested disease activity incompatible with remission.

Results: Patients in a state of remission by several of the Boolean candidate definitions, as well as by traditional SDAI (≤3.3) and CDAI (≤2.8) definitions had an increased likelihood of both x-ray and HAQ stability (see Table 1).

Table 1. Predictive validity of candidate remission definitions for a good outcome in both x-ray and health assessment questionnaire

<table>
<thead>
<tr>
<th>Candidate remission definition</th>
<th>Prevalence of good outcome in patients: in remission</th>
<th>not in remission</th>
<th>LR(+)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJ28, SJC28, CRP, PtGA ≤1</td>
<td>66%</td>
<td>17%</td>
<td>7.2</td>
<td>***</td>
</tr>
<tr>
<td>TJ28, SJC28, CRP, PtGA ≤1</td>
<td>64%</td>
<td>18%</td>
<td>6.7</td>
<td>***</td>
</tr>
<tr>
<td>TJ28, SJC28, CRP, PtGA ≤1</td>
<td>64%</td>
<td>17%</td>
<td>6.8</td>
<td>***</td>
</tr>
<tr>
<td>TJ28, SJC28, CRP, Pain ≤1</td>
<td>67%</td>
<td>18%</td>
<td>7.5</td>
<td>***</td>
</tr>
<tr>
<td>TJ28, SJC28, CRP, Pain ≤1</td>
<td>65%</td>
<td>17%</td>
<td>6.5</td>
<td>***</td>
</tr>
<tr>
<td>SDAI ≤3.3§</td>
<td>56%</td>
<td>17%</td>
<td>4.8</td>
<td>***</td>
</tr>
<tr>
<td>SDAI ≤3.3§</td>
<td>38%</td>
<td>18%</td>
<td>2.2</td>
<td>**</td>
</tr>
<tr>
<td>SDAI ≤2.0</td>
<td>56%</td>
<td>20%</td>
<td>4.5</td>
<td>*</td>
</tr>
</tbody>
</table>

*P-value < 0.05; **P-value ≤ 0.01; ***P-value < 0.001
§New preliminary ACR/EULAR definitions for remission in RA

However, reaching remission according to SDA28, both at the traditional (<2.6) and a more stringent cut point (<2.0), was associated only with the likelihood of HAQ stability but not x-ray stability. Additional definitions were tested, including definitions that incorporated pain or patient global at remission levels and other variations, and results were similar. Apart from the SDA28 result, the analyses did not help to distinguish between definitions.

Conclusion: Based on these and other considerations, we propose that a patient be defined as in remission based on one of two definitions of remission. 1 When their scores on the following measures are all ≤1: tender joint count, swollen joint count, CRP (in mg/dL) and patient global assessment (0–10 scale). OR 2: when their score on the SDAI ≤3.3.

These new definitions can be uniformly applied and widely used in RA clinical trials. We recommend that one of these be prespecified in each trial as an outcome and that the results of both be reported. These definitions are currently ‘preliminary’ and are pending approval from the ACR and EULAR boards.

Acknowledgements: Some of the results were generated using clinical trial data provided by Abbott, Amgen, and Wyeth-Pfizer.

Disclosure: D. T. Felson: None; J. S. Smolen: None; G. A. Wells: None; B. Zhang: None; L. H. D. van Tuyl: None; J. Funovits: None; M. Boers: None; for the ACR/EULAR Commission To Redefine Remission in Rheumatoid Arthritis: None.

2109

Three Physician-Assigned Global Estimates for Inflammation, Damage and Non-Inflammatory Symptoms/Fibromyalgia Help To Clarify Overall Physician Global Estimates of Status in Patients with Different Rheumatic Diseases, Martin J. Bergman1 and Theodore Pincus2. 1Arthritis Medicine, Boston, MA, 2Boston University School of Medicine, Boston, MA.

Purpose: To analyze the capacity of three physician-assigned global estimates for inflammation, damage and non-inflammatory symptoms/ fibromyalgia to clarify the overall physician global estimate of status in patients with various rheumatic diseases, and for these global estimates to serve as surrogates for a quantitative physical examination.
Methods: All consecutive patients in a rheumatology setting in Pennsylvania, with any diagnosis, were assigned four global estimates by a rheumatologist, including overall global status, and 3 additional global estimates for inflammation, damage to any organ (e.g., joint, kidney) and non-inflammatory/fibromyalgia symptoms. The overall estimate was on a scale of 0–10, while the other 3 scales were scored 0–3, which were recoded to 0–10 for comparison with the overall global score. Consecutive patients were classified at first visit in 7 categories: rheumatoid arthritis (RA) (n = 40), osteoarthritis (OA) (n = 56), fibromyalgia (FM) (n = 14), systemic lupus erythematosus (SLE) (n = 9), spondyloarthropathy (n = 21), gout (n = 26) and other (n = 64). Mean scores were compiled in the 6 specific disease categories; the “other” patients were not analyzed.

Results: The overall physician global estimate ranged from 2.00 to 4.36, highest for patients with FM (4.36), followed by RA, spondyloarthropathy, OA, gout, and SLE. Physician global estimates for inflammation ranged from 0.50 to 4.53, highest for RA, followed by spondyloarthropathy, gout, SLE, and OA and FM. Physician global estimates for joint damage ranged from 0.37 to 3.83, highest for OA, followed by RA, spondyloarthropathy, and <1.0 (on the recoded 0–10 scale) for OA and FM. Physician global estimates for non-inflammatory/fibromyalgia symptoms ranged from 0.37 to 5.13, highest for FM (5.13), followed by spondyloarthropathy and RA, and <1.0 for OA, gout, and SLE. One of the 3 more-detailed global estimates was within 1 unit of the overall global estimate for all 6 diseases studied: for inflammation in RA, SLE, spondyloarthropathy, and gout; for damage in OA; and for non-inflammatory symptoms/ fibromyalgia in FM.

Mean physician-estimated scores for overall global status, inflammation, damage, and non-inflammatory symptoms/fibromyalgia at first visit, in consecutive patients in 6 diagnostic categories

<table>
<thead>
<tr>
<th>Variable</th>
<th>RA</th>
<th>OA</th>
<th>Fibromyalgia</th>
<th>SLE</th>
<th>Spondyloarthropathy</th>
<th>Gout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>40</td>
<td>56</td>
<td>14</td>
<td>9</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Overall Physician global (0–10)</td>
<td>4.03</td>
<td>3.25</td>
<td>4.36</td>
<td>2.00</td>
<td>3.33</td>
<td>2.23</td>
</tr>
<tr>
<td>Inflammation (0–10)</td>
<td>4.53</td>
<td>0.57</td>
<td>0.50</td>
<td>2.23</td>
<td>4.17</td>
<td>2.27</td>
</tr>
<tr>
<td>Damage (0–10)</td>
<td>2.40</td>
<td>3.83</td>
<td>0.77</td>
<td>0.37</td>
<td>1.58</td>
<td>0.43</td>
</tr>
<tr>
<td>Non-inflammatory/fibromyalgia symptoms (0–10)</td>
<td>1.03</td>
<td>0.83</td>
<td>5.13</td>
<td>0.37</td>
<td>1.17</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Conclusion: Physician global estimate scales for inflammation, joint/organ damage and non-inflammatory symptoms/fibromyalgia can clarify an overall physician global estimate. These detailed physician global estimates may be regarded as a quantitative summary of the physical examination. Limitations include the absence of longitudinal data, including disease flares. Nonetheless, in view of the importance of physical examination in clinical decisions in rheumatic diseases, these scales may supplement laboratory tests, which often are the only quantitative data in patient records, to assess and monitor patients with rheumatic diseases over long periods.

Disclosure: M. J. Bergman: Bristol-Myers Squibb, 2, 5; T. Pincus: Bristol-Myers Squibb, 2, 5.

2110

Rheumatologists on the Road: A Subspecialist’s Role in Caring for the Homebound. Ruchi Jain1, Suma Dasari1, Theresa Soriano2, Linda DeCherrie3 and Leslie Dubin Kerr1.1Mount Sinai Medical Center, New York, NY; 2Mount Sinai Medical Center

Background: In the next 20 years, the number of permanently homebound individuals in the United States will increase by 50% to reach 2 million. To address this problem, the Mount Sinai Visiting Doctors Program has proven to be a successful model as the largest primary care academic home visit program in the nation, serving over 1000 patients in New York City. Currently, there are no medicine subspecialty consult services in place for this rising subset of the population.

Our purpose in establishing a Rheumatology consult service within the Mount Sinai Visiting Doctors program was to provide a remedy to the unmet need for homebound patients with Rheumatologic diseases, and also to provide an educational opportunity for Residents and Fellows in community Rheumatology. Many of these patients were homebound by the very nature of their disease and social environment, and many had no care under a Rheumatologist.

Methods: Through electronic medical record, home-based primary care physicians sent consult requests to the Rheumatology Division. Initial assessments were made through the Routine Assessment of Patient Index Data 3 (RAPID 3) questionnaire.

Results: Over 6 months, 33 home visits were made; 25 as new consults and 8 as follow up visits. Reasons for referral included: management of a known connective tissue disease; a question of inflammatory arthritis; procedures including intra-articular injections, arthrocentesis and bursa drainage.

Demographics of patients (as of June 2010): 100% of consults were women, 40% of patients were Hispanic and 76% of patients were between the ages of 60–101. Twenty patients lived alone or with a home health aide, 5 patients lived with other family members. Fifty percent of patients had rheumatoid arthritis (RA). Osteoarthritis comprised 30% of patients seen. Treatment interventions included the following: addition of a disease modifying anti-rheumatic drug (DMARD) in 10 patients, 8 procedures, counseling in 7 patients and a change in the dose of existing medication in 4 patients. At initial evaluation, the average RAPID 3 score for patients with RA was 22.4, reflecting high severity of disease. One patient with psoriatic arthritis (PsA) on initial evaluation had a RAPID 3 score of 21 (high severity); after intervention the RAPID 3 score was 11 (moderate severity). One patient with diffuse scleroderma had a RAPID 3 score of 20.3 (high severity).

Conclusions: The ongoing, increasing number of consults and extent of disease on initial evaluation of these homebound individuals highlights the importance of a Rheumatologist’s role in the community. This initiative underscores a hidden, but growing population with current unmet needs. It also defines our role in patient advocacy consistent with our goals and beliefs as Rheumatologists, and as physicians.

Disclosure: R. Jain: None; S. Dasari: None; T. Soriano: None; L. DeCherrie: None; L. D. Kerr: None.

2111

Validation of Electronic Audiovisual Media Assessments of Patients with Rheumatic Diseases. Sarah McNamara1, Lorraine O’Neill2, John J. Carey2 and Robert J. Coughlan3.1N.U.I Galway University Hospitals, Galway, Ireland; 2N.U.I Galway University Hospitals, Galway, Ireland; 3N.U.I. Galway University Hospitals, Galway, Ireland

Purpose: Rheumatology centres often service remote or geographically dispersed areas where patients have significant access issues because of poor transport service or inclement climate. Our centre services such an area including inhabitants of several islands. The extensive availability of audiovisual communication via the Internet has introduced the possibility of ‘virtual’ assessment of patients living remote from their rheumatology centre. Studies in other diseases show such technology offers promise with obvious advantages for the patient such as saved travel time and cost. There are no published studies comparing the quality of information gained through remote contact to that gained in conventional face to face clinical encounters for patients with rheumatic diseases. The purpose of this study was to assess the validity of the information collected from a virtual patient visit (e-clinic) using “off the shelf” web based technology.

Methods: This study was approved by the local I.R.B. We planned to evaluate 20 patients referred to our centre with ‘possible early arthritis’ from different primary care centres (PCC) in our region for this pilot programme. An initial assessment using ‘Skype®’ or ‘iChat®’ was performed using ‘laptop’ computers by an experienced rheumatologist (RJC). A follow-up assessment was scheduled within 2 weeks for a face to face encounter in the rheumatology clinic by the same rheumatologist (RJC). Clinical features and diagnosis were compared using both methods.
Results: 5 PCC agreed to participate. 19 (95%) of subjects completed both assessments. Diagnostic agreement was 100% for both assessments (Rheumatoid Arthritis, Osteoarthritis, Tendonitis, Carpal Tunnel Syndrome). Agreement was ≥90% between both assessments for the following clinical features: joint swelling, restricted motion, Heberden’s nodes, tendonitis.

Conclusion: Web-based “off the shelf” technology can be used to accurately assess patients referred with ‘possible arthritis’ to rheumatologists. Support for further studies and development of audiovisual media for assessment of patients with rheumatic complaints is warranted.

Disclosure: S. McNamara: None; L. O’Neill: None; J. J. Carey: None; R. J. Coughlan: None.

2112 WITHDRAWN

2113 Quality of Care in Patients with Systemic Lupus Erythematosus. Jinoos Yazdany1, Laura Trupin2, Chris Tonner1, Gabriela Schmajuk3, Joann Z. Gillis2, Pantelis Panopalis1, Laura J. Julian2, Lindsey A. Criswell3, Patricia Katz4 and Edward Yelin5. 1McGill University, 2National Jewish Medical Center, 3Stanford University, 4UCSF, San Francisco, CA. 5UCSF

Objective: We applied newly developed quality indicators (Qis) for systemic lupus erythematosus (SLE) to a large, community-based cohort of individuals to detect areas where health care quality is suboptimal and to identify groups at risk for lower quality care.

Methods: Data derive from a prospective study of individuals with SLE, the Lupus Outcomes Study (LOS). In 2009, 814 individuals participated in the eighth annual survey. Respondents were queried by telephone regarding receipt of care recommended in 13 (of 20) SLE Qis amenable to self-report, as well as their sociodemographic characteristics, health care utilization, disease activity and medication use. For each QI, we calculated the proportion of eligible participants who received recommended care. In addition, we conducted multivariate analyses in which the primary outcome was a global pass rate, defined as the percentage of times recommended care was received among all eligible individuals. In these analyses, respondents contributed one observation for each eligible service, and thus there were between two and twelve observations per respondent. We accounted for these repeated measures in our regression models through generalized estimating equations, adjusting for age, sex, race/ethnicity, education, and poverty status. After eliminating observations with missing data, a total of 794 (98%) participants remained.

Results: The 794 LOS participants were mostly women (92%); 48% were <55 years old; 36% were non-white; 14% had poverty level incomes; 42% had college degrees. They were eligible for 4,054 quality indicators (mean 5 ± 2 Qis/person, range 2–12 Qis). Qis with the highest rates of receipt included counseling regarding sun avoidance (90%), influenza vaccination in those receiving immunosuppressive medications (80%), and calcium and vitamin D supplementation in those taking glucocorticoids (84%) [Table]. Participants were less likely to receive counseling consistent with other Qis, including assessment of traditional cardiovascular risk factors (smoking, lipids, body-mass index, blood pressure, diabetes; 29%), and counseling regarding medication risks and contraception in women at risk for pregnancy initiating potentially teratogenic medication (40%). The global pass rate was 65%; younger age, nonwhite race/ethnicity, and low income were associated with lower global pass rates. In multivariate analysis, only younger age remained statistically significant.

Discussion: In this community-based cohort of individuals with SLE, receipt of recommended care varied significantly depending on the QI assessed. For some Qis, rates of receipt of recommended care were low, suggesting the need for targeted quality improvement. Younger individuals appear to be at risk for lower quality care.

Quality Indicator summary1, time frame (in last year unless noted) Number Eligible % Rec’d

<table>
<thead>
<tr>
<th>Quality Indicator</th>
<th>Description of SLE quality indicators.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun avoidance counseling, ever</td>
<td>814 99%</td>
</tr>
<tr>
<td>Influenza vaccination if taking immunosuppressive medications</td>
<td>508 80%</td>
</tr>
<tr>
<td>Pneumococcal vaccination if taking immunosuppressive medications, ever</td>
<td>508 69%</td>
</tr>
<tr>
<td>Bone mineral density testing if receiving prednisone ≥7.5 mg/day</td>
<td>145 56%</td>
</tr>
<tr>
<td>Calcium and vitamin D if receiving prednisone ≥7.5 mg/day</td>
<td>145 83%</td>
</tr>
<tr>
<td>Antiresorptive or anabolic agent in patients with osteoporosis receiving prednisone ≥7.5 mg/day</td>
<td>98 61%</td>
</tr>
<tr>
<td>Counseling regarding risks if initiating new medication</td>
<td>148 68%</td>
</tr>
<tr>
<td>Appropriate drug monitoring for NSAID, DMARD or glucocorticoids, varies</td>
<td>683 69%</td>
</tr>
<tr>
<td>Glucocorticoid management plan if receiving prednisone ≥10 mg/day for ≥3 months</td>
<td>51 65%</td>
</tr>
<tr>
<td>Management of hypertension if renal disease and consecutively elevated blood pressures</td>
<td>26 54%</td>
</tr>
<tr>
<td>ACE inhibitor or ARB if renal disease</td>
<td>180 49%</td>
</tr>
<tr>
<td>Assessment of traditional cardiovascular risk factors</td>
<td>814 29%</td>
</tr>
<tr>
<td>Counseling regarding risks and contraception if reproductive age woman initiating potentially teratogenic medication</td>
<td>25 40%</td>
</tr>
</tbody>
</table>

Disclosure: J. Yazdany: None; L. Trupin: None; C. Tonner: None; G. Schmajuk: None; J. Z. Gillis: None; P. Panopalis: None; L. J. Julian: None; L. A. Criswell: None; F. Katz: None; E. Yelin: None.

ACR Concurrent Abstract Sessions
Rheumatoid Arthritis - Human Etiology and Pathogenesis: Anti-CCP in RA Etiology and Pathogenesis

Wednesday, November 10, 2010, 2:30 PM–4:00 PM

2114 The Gene-Environment Interaction between HLA-SE and Smoking Plays an Important Role in Shaping the Reactivity of the ACPA Response to Several Citrullinated Antigens. Annemiek Willemze1, Diane van der Woude2, Wendim Ghidye Alemayehu3, René R. P de Vries4, Tom W. J. Huizinga5, Leendert A. Trouw6, and René E. M. Toes3. 1Leiden University Medical Center, Department of Medical Statistics, 2Leiden University Medical Center, Department of Rheumatology, Leiden, The Netherlands, 3Leiden University Medical Center, Department of Rheumatology, 4Leiden University Medical Center, Department of Immunohematology and Blood Transfusion

Objective: Rheumatoid arthritis is a complex genetic disorder. Human leucocyte antigen shared epitope (HLA SE) alleles are the strongest genetic risk factor for anti-citrullinated protein antibodies (ACPA) positive rheumatoid arthritis (RA). It has recently been postulated that a specific interaction exists between genotype, smoking and autoimmune to a peptide from enolase. We showed recently that this is not specific for citrullinated α-enolase, but also for a peptide derived from citrullinated vimentin. The aim of this study was to further expand these findings by investigating if gene-environment interactions affect the reactivity pattern to other citrullinated antigens as well.

Methods: The reactivity of 766 RA patients to cyclic citrullinated peptide (CCP) and to four citrullinated peptides derived from vimentin (cVim), fibrinogen (cFib), linear Enolase (cEnolase=Col1) and Myelin Basic Protein (cMBP=anti-SA) was determined by enzyme-linked immunosorbent assay (ELISA). The separate effects of the HLA SE alleles and smoking were assessed by logistic regression analysis. Biologic interaction was analyzed by investigating if the effects of the risk factors combined exhibited departure from additivity.

Disclosure: S. McNamara: None; L. O’Neill: None; J. J. Carey: None; R. J. Coughlan: None.
**Results:** The ACPA reactivity profile was affected by a significant biological interaction between the HLA SE alleles and smoking. Both the separate effects of HLA SE alleles and smoking, as well as their combined effects were present for anti-cVim, anti-cEnolase, anti-cMBP and anti-cFib. This effect was strongest for anti-cVim with an odds ratio (OR) of 41 (95% CI 14.7–118.5) in the anti-cVim-positive subset for smokers who were homozygous for HLA SE, compared to an OR of 6.2 (95% CI 2.4–16.1) in the anti-cVim-negative subset. For anti-enolase, this resulted in an OR of 40.0 (95% CI 11.4–135.2) in the positive subset and an OR of 10.1 (95% CI 4.2–24.2) in the negative group. Anti-MBP and Anti-cFib resulted in a more modest effect for interaction for smokers, who were homozygous for SE (see Table 1). Combining anti-cVim positive and anti-cEnolase positive patients that were homozygous for HLA SE and smokers, resulted in an even higher OR of 160.0 (95% CI 18.6–1373.0) compared to the anti-cVim negative and anti-cEnolase negative subset with an OR of 5.4 (95% CI 1.9–15.3).

Table 1. Interaction between HLA SE alleles, smoking and autoimmunity to various citrullinated peptides in RA patients

<table>
<thead>
<tr>
<th>HLA SE positive and smoker</th>
<th>HLA SE homozygous and smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCYP2−</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>CCYP2+</td>
<td>7.7 (4.7–12.4)</td>
</tr>
<tr>
<td>CCYP2+cVim+</td>
<td>18.0 (8.2–39.7)</td>
</tr>
<tr>
<td>CCYP2+cEnolase−</td>
<td>20.6 (7.9–51.4)</td>
</tr>
<tr>
<td>CCYP2+cEnolase+</td>
<td>5.4 (3.2–9.1)</td>
</tr>
<tr>
<td>CCYP2+cMBP+</td>
<td>11.7 (6.4–21.5)</td>
</tr>
<tr>
<td>CCYP2+cMBP−</td>
<td>4.1 (2.2–7.7)</td>
</tr>
<tr>
<td>CCYP2+cFib+</td>
<td>8.4 (4.8–14.7)</td>
</tr>
<tr>
<td>CCYP2+cFib−</td>
<td>6.0 (3.0–12.0)</td>
</tr>
<tr>
<td>CCYP2+cVim+cEnolase+</td>
<td>73.1 (9.8–544.8)</td>
</tr>
<tr>
<td>CCYP2+cVim+cEnolase−</td>
<td>3.9 (2.2–7.1)</td>
</tr>
</tbody>
</table>

**Conclusion:** The gene-environment interaction between the HLA SE alleles and smoking is not specific for citrullinated α-enolase or citrullinated vimentin, but rather extends to other citrullinated antigens as well. These findings indicate that gene-environment interactions play an important role in shaping the reactivity of the ACPA response by broadening the ACPA-recognition profile.

**Disclosure:** A. Willemze: None; D. van der Woude: None; W. Ghidley Alemayehu: None; R. P. de Vries: None; T. W. J. Huizinga: None; L. A. Trouw: None; R. E. M Toes: None.

**2115**

**Antibodies of IgG, IgA and IgM Isotypes Against Cyclic Citrullinated Peptide Precede the Development of Rheumatoid Arthritis, Heidi Kokkonen1, Mohammad Mullazehi2, Ewa Berglin2, Gøran Hallmans3, Göran Waderud4, Rolf Rönne5, Heike Rönnelid4 and Solbritt Rantapää-Dahlqvist2.** 1Department of Nutritional Research, Umeå University, Umeå; 2Department of Public Health and Clinical Medicine/Rheumatology, Umeå University, Umeå; 3Department of Virology, Umeå University, Umeå; 4Division of Clinical Immunology, Uppsala University, Uppsala

**Background and Statement of Purpose:** We have previously shown that the presence of anti-cyclic citrullinated peptide (CCP) antibodies precedes the development of rheumatoid arthritis (RA) by several years. In a recent study we also showed that individuals who later developed RA had significantly increased levels of several cytokines, cytokine-related factors, and chemokines. In this study we aimed firstly to investigate the presence and accumulation of ACPA subtypes over time and correlate this accumulation with the isotypes increased significantly until disease onset and where at diagnosis of RA 70%, 40% and 30%, respectively. IgA antibodies but not IgG were significantly associated with up-regulated chemokines. In smokers IgA anti-CCP antibodies appeared much earlier before onset of symptoms of RA vs. in non-smokers. Patients positive for all three anti-CCP antibody isotypes already before onset of symptoms had a higher radiographic score both at baseline and after 24 months of disease compared with pre-RA individuals with fewer or no anti-CCP2 isotypes before onset.

**Conclusion:** Anti-CCP antibodies of both the IgG and IgA isotypes pre-dated the onset of RA by several years, also, anti-CCP antibodies of both IgG and IgA isotypes predicted the development of RA, with the highest predictive value for IgG antibodies.

**Disclosure:** H. Kokkonen: None; M. Mullazehi: None; E. Berglin: None; G. Hallmans: None; G. Waderud: None; R. Rönne: None; S. Rantapää-Dahlqvist: None.

**2116**

**Epitope Spreading of the Autoantibody Response in the Pre-Clinical Phase Predicts Progression to Rheumatoid Arthritis (RA), Jeremy Sokolove1, Reuven Bromberg2, Kevin D. Deane2, Piyanka Chandra2, Leslie Derber3, Jess D. Edison4, William R. Gilliland5, Jill Norris5, V. Michael Holers1, and William Robinson1. 1Stanford Univ School of Med, Stanford, CA; 2Stanford University, Mountain View, CA; 3Stanford University, Univ of Colorado School of Med, Aurora, CO; 4University of Colorado Denver, Aurora, CO; 5University of Colorado Denver, Walter Reed Army Med Ctr, Washington, DC; 6Walter Reed Army Med Ctr, Potomac, MD

**Purpose:** Anti-CCP antibodies have been demonstrated in the preclinical phase of RA, however, the fine specificity of antigens targeted by these antibodies has not been well defined. Similarly, elevations in serum cytokines have been demonstrated in the preclinical phase of RA. We sought to determine the fine specificity of the ACPA response in the preclinical phase of RA, to demonstrate a pattern of epitope spreading, to correlate this spreading with the development of cytokine elevations, and to derive a profile of ACPA fine specificity which can predict the imminent onset of clinical RA.

**Methods:** We performed multiplex bead arrays using the Bio-Plex system to evaluate a panel of 36 putative RA associated autoantibodies and 48 cytokines/chemokines in serial serum samples collected prior to the development of clinical RA. Serum collected prior to clinical diagnosis of RA was obtained from the US Department of Defense Serum Repository. 81 subjects and matched controls were evaluated. Average number of specimens was 2.9 (range 1–4) with first sample obtained an average of 6.6 yrs before diagnosis (range 0.1–13.7 yrs). Results for antibodies or cytokines with a value 3 SD above the median value of matched controls controls were considered positive. Kaplan-Meier survival analysis was performed based on time to first positive test for each subject and hazard ratios calculated compared to controls. Significance Analysis of Microarrays was applied to compare paired samples pre- and post-anti-CCP seroconversion (CCP2 ELISA) and to compare all samples at the earliest and later timepoints. We evaluated the accumulation of ACPA subtypes over time and correlate this accumulation with (i) anti-CCP titer and (ii) cytokine elevations. We performed logistic regression analysis to identify markers which could predict imminent onset of clinical RA (defined as within 2 years of testing).

**Results:** Pre-clinical RA subjects displayed a time-dependent expansion of ACPA fine specificity. The timing of appearance of ACPA subtypes was similar to that of anti-CCP antibodies and there was a parallel rise in anti-CCP titer and number of ACPA subtypes during the preclinical period. A rise in several RA-related inflammatory cytokines was strongly associated with the expansion of the ACPA response. Finally, we identify a panel of markers...
consisting of autoantibodies alone, or autoantibodies in combination with serum cytokines, which is able to identify those subjects most proximate to onset of clinical RA.

**Conclusion:** The preclinical phase of RA is characterized by an accumulation of multiple autoantibody specificities targeting a variety of citrullinated epitopes. The pattern of accumulation likely reflects epitope spreading and is correlated with rise in anti-CCP titer and ultimately, preclinical inflammation as reflected by rise in RA-associated cytokines. Characterization of the breadth and fine specificity of ACPA enabled identification of individuals within 2 years of RA diagnosis. Identities of such individuals may provide the opportunity for preclinical interventions in imminent RA not previously possible with use of anti-CCP testing alone.

**Disclosure:** J. Sokolove: None; R. Bromberg: None; K. D. Deane: None; P. Chandra: None; L. Derber: None; J. D. Edison: None; W. R. Gilliland: None; J. Norris: None; V. Holers: None; W. Robinson: None.

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### 2117

**Citrullinated Epitopes within the Atherosclerotic Plaque: A Target for Anti-Citrullinated Protein Antibodies?**

**Jersey Sokolove,** Orr Sharpe, Matthew Brennan, Andrew J. Connolly, and William Robinson.

**1** Stanford Univ School of Med, Stanford, CA, 2Stanford University, Mountain View, CA, 3Stanford University

**Purpose:** Patients with rheumatoid arthritis have a significantly increased risk for cardiovascular disease (CVD) due to accelerated atherosclerosis. Atherosclerosis is an inflammatory process similar to that observed within the RA synovium. Notably, elevated risk of CVD is mainly limited to anti-citrullinated protein antibody (ACPA) positive patients. Given our recent observation that citrullinated fibrinogen (cFb) immune complexes co-stimulate macrophage TNF production we sought to determine if citrullinated epitopes, specifically cFb, are present in the atherosclerotic plaque where they could be targeted to form immune complexes thus inducing inflammation and accelerating atherosclerosis.

**Methods:** We performed a series of proteomic and immunohistochemical studies of atherosclerotic lesions obtained from non-RA patients at time of autopsy to evaluate for the presence and identification of citrullinated proteins. Lysates were prepared from atherosclerotic segments of human aortic arch and subjected to 1 and 2-D polyacrylamide gel electrophoresis (PAGE). Parallel gels were transferred to nitrocellulose and probed for the presence of citrulline modified proteins using an anti-modified citrulline antibody (Millipore) and fibrinogen. Spots from 2D gel corresponding to citrullinated peptides were identified by mass spectrometry. Atherosclerotic plaque and pulmonary artery lysates were immunoprecipitated with anti-fibrinogen antibody and subjected to immuno-blot with IgG purified purified from anti-cFb RA patients. Paraffin sections of human coronary plaque were examined by immunohistochemistry for the presence of citrullinated proteins, fibrinogen, human PAD4, and fibrinogen.

**Results:** Western analysis of 1 and 2-D PAGE demonstrated several citrulline modified proteins within atherosclerotic plaque lysate. Mass spectrometry as well as re-probing of the western blot membrane for fibrinogen confirmed the presence of cFb. Fibrinogen immunoprecipitated from atherosclerotic plaque lysate, but not pulmonary artery lysate, stained strongly with IgG purified from anti-cFb positive RA patients. Interestingly, several additional ACPA targets were identified from pre-cleared atherosclerotic lysates probed with ACPA+ IgG. Finally, immunohistochemistry demonstrated co-localization of (i) citrullinated proteins, (ii) PAD4, and (iii) fibrinogen within the coronary artery atherosclerotic plaque.

**Conclusion:** Citrulline modified proteins are prevalent within the atherosclerotic plaque. Specifically, the presence of citrullinated fibrinogen is confirmed to be present and targeted by RA patient derived IgG. This observation suggests that humeral targeting of citrullinated epitopes, specifically cFb, by ACPA within the atherosclerotic plaque could provide a mechanism for accelerated atherosclerosis observed in ACPA+ RA.

**Disclosure:** J. Sokolove: None; O. Sharpe: None; M. Brennan: None; A. J. Connolly: None; W. Robinson: None.

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### 2118


**1** Institute for Environmental Medicine, Karolinska Institutet, 2Karolinska University Hospital, Stockholm, Sweden, 3Reumatology Unit, Karolinska Institutet, Stockholm, Sweden, 4Reumatology Unit, Karolinska Institutet

**Background:** Risk factors for rheumatoid arthritis (RA), such as *HLA-DRB1* shared epitope (SE) alleles, *PTPN22* and cigarette smoking, associate with anti-CCP positive disease. By subdividing CCP positive patients based on reactivity to CEP-1, the immunodominant B cell epitope on citrullinated alpha-eno-lase, we have previously shown that SE, *PTPN22* and smoking mainly constitute risk factors for CEP-1 positive, rather than CCP positive RA. Here, we investigate 5 RA subsets, grouped based on reactivity to CCP, CEP-1 and a citrullinated vimentin peptide (CitVim), representing another anti-citrullinated protein/peptide antibody (ACPA)-specificity.

**Methods:** Antibodies were analysed in serum from 1027 RA patients from the Epidemiological Investigation of RA (EIRA), a Swedish population-based case-control study. An ELISA was set up for detection of anti-CitVim antibodies, using a biotinylated CitVim peptide (amino acid 60–70). One hundred and fifty healthy controls were used to determine the 95th percentile cut-off. A positive and a negative control and a standard of pooled anti-CCP positive serum were included on each plate. Anti-CCP was measured using the Immunoscan CCPplus kit (Euro-Diagnostica) and anti-CEP-1, using an in-house ELISA previously described (Mahlu et al, Nature Genetics, 2009). Different RA subsets were compared with regard to risk factors by calculating odds ratios (OR) with 95% confidence interval by means of logistic regression.

**Results:** Patients were divided into 5 subsets: CEP-1+/CitVim+ (41%); CEP-1+/CitVim− (15%); CEP-1−/CitVim+ (11%) (the majority of patients in these subsets were anti-CCP positive and not divided further based on CCP status); CEP-1−/CitVim−/CCP+ (18%) and CEP-1−/CitVim−/ CCP− (15%). SE, *PTPN22* and smoking each showed strongest association in the CEP-1+/CitVim+ subset, intermediate association in the single positive subsets and low association in the ACPA negative subset. The combined effect of risk factors showed a similar pattern, with an OR of 52 in the double positive subset, 16 in the CEP-1 single positive, 5 in the CitVim single positive, 6 in the CCP single positive, and 2 in the triple negative. Additionally, antibody levels were higher in CEP-1+/CitVim+ patients compared to single positive patients.

**Conclusion:** Our data show that the anti-CEP-1 and the anti-CitVim antibody response only partly overlap, and that SE, *PTPN22* and smoking predispose to the development of ACPA with multiple reactivities, rather than one single specificity. Interestingly, the CEP-1+/CitVim−/CCP+ subset still showed a strong association with SE (OR: 12), suggesting that other ACPA fine-specificities, for example citrullinated fibrinogen or collagen type II, could be found in this subset.

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### 2119

**Anti-CCP Positivity in Patients with Lung Disease but No Apparent Articular RA: A Pre-RA State?** Joshua J. Solomon, Allen Stevens, Mary Gill, Jennifer Brandorff, Jeffrey J. Swigris, Kevin Deane, Richard Martin, Roland M. du Bois and Arveh Fischer.

**1** National Jewish Health, 2University of Colorado

**Background and Objectives:** Anti-CCP positivity is highly specific for RA, and can be identified in patients prior to the development of articular manifestations of RA. Also, lung disease may be the initial clinical manifestation of RA, and as such patients with lung disease but no articular RA may have anti-CCP positivity, reflecting early RA-related immune dysregulation. For this study, we sought to identify and describe a patient cohort characterized by lung disease, with moderate-to-high anti-CCP positivity, in the absence of articular manifestations of RA.
Methods: Between January 2008 and January 2010, 2393 patients had an anti-CCP antibody test at our center using the INOVA CCP3.1 IgG/IgA ELISA kit. 312 patients had a positive anti-CCP (≥ 20 IU). Of these, we excluded those with a low-titer positive anti-CCP (20 IU–39 IU) (n = 63), patients in whom the anti-CCP was assessed due to joint disease (either with a pre-existing diagnosis of RA, or due to presence of joint symptoms of inflammation or synovitis on examination as determined by the treating physician) (n = 214), patients younger than 18 (n = 1), those without lung disease (n = 2) and all patients with other defined connective tissue diseases (CTD) (n = 18). Thus, the study cohort was comprised of 52 patients with a positive anti-CCP of at least moderate titer (≥ 40 IU) along with symptoms of respiratory impairment—without a prior diagnosis of RA, any other CTD, or presence of joint inflammation at initial testing for anti-CCP. All data were extracted by retrospective chart review.

Results:

Clinical characteristics of anti-CCP positive subjects with lung disease

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Median follow-up duration (d)</th>
<th>Median age (y)</th>
<th>Male gender</th>
<th>Smokers-Past</th>
<th>Smokers-Current</th>
<th>First degree relative with RA</th>
<th>Dyspnea/cough at presentation</th>
<th>Synovitis by history or exam at presentation</th>
<th>Median anti-CCP (IU)</th>
<th>RF positivity</th>
<th>Median RF (IU)</th>
<th>Development of articular RA during follow-up</th>
<th>Parenchymal lung disease</th>
<th>Airways disease</th>
<th>Parenchymal lung disease</th>
<th>Airways + Parenchymal disease</th>
<th>*Miscellaneous patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>458 (114–755)</td>
<td>68 (36–84)</td>
<td>22 (42%)</td>
<td>29 (57%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7 (17.5%)</td>
<td>52 (100%)</td>
<td>86.5 (40–235)</td>
<td>18 (37%)</td>
<td>148 (20–3650)</td>
<td>1 (2%)</td>
<td>17 (33%)</td>
<td>18 (35%)</td>
<td>13 (24%)</td>
<td>4 (8%)</td>
<td>*Includes one each of emphysema, vasculitis, sarcoidosis, and non-tuberculous mycobacterial infection</td>
</tr>
</tbody>
</table>

Conclusions: We have identified a cohort of patients, predominately former smokers, with lung disease, a moderate-to-high positive anti-CCP and no articular manifestations of RA. Within a median follow-up of 15 months, 2% of this cohort has already developed inflammatory arthritis. These findings suggest i) the lung is the site of initial RA-related immune dysregulation, and that such patients represent a pre-articular RA phenotype, ii) the lung in some cases is a pre-articular target of RA-related autoimmunity, or iii) in cases who never develop articular RA, anti-CCP generation may be a non-RA specific immune response, or that some factor prevents these patients from later developing RA-related articular disease. Prospective assessments of this unique cohort should help further our understanding of the etio-pathogenesis of RA.

Disclosure: J. J. Solomon: None; A. Stevens: None; M. Gill: None; J. Brandorff: None; J. J. Swift: None; K. Deane: None; R. Martin: None; R. M. du Bois: None; A. Fischer: None.

Background: Patients with SLE have an increased risk for cardiovascular disease (CVD). Traditional assessment of CVD risk profile is measured using Framingham Risk Score (FRS), but this may not capture all CVD risk factors in patients with SLE. An alternative tool to assess CVD risk is the Flow Mediated Dilation (FMD)

Objective: 1) To perform CVD risk assessment using FRS and endothelial flow mediated dilation (FMD) using high-resolution brachial artery ultrasound and 2) To determine association between endothelial function and FRS in women with SLE.

Methods: Our cohort consists of 173 females, ≥48 ACR criteria for SLE in whom the FRS and FMD were assessed as part of a study. Ten-year FRS was calculated on the basis of patients: age, smoking, systolic blood pressure (SBP), total cholesterol (TC) and HDL-cholesterol. Smoking, family history, SBP >130mmHg, serum TC >5.5 mmol/l and HDL <1.3mmol/l were considered as risk factors for CVD. Normal FMD was defined as a 6% to 15% increase in the post-cuff inflation diameter change of the artery. Abnormal FMD was defined as <6% increase in the post-cuff inflation diameter. Associations between FMD and FRS were assessed using linear regression analysis.

Results: The mean (SD) age was 43.6 (12.7) years, SLE duration was 8.9 (2.4, 18.6) and 23% (n = 77) were smokers. The mean SBP was at 121.9 mmHg (14.7) and 22.5% had elevated SBP. The mean (SD) serum insulin profile was as follows: triglycerides: 1.2 (0.6) mmol/l, total cholesterol: 4.7 (1.1) mmol/l, LDL-cholesterol: 2.6 (0.8) mmol/L, HDL-cholesterol: 1.7 (0.6) mmol/L, TC/HDL ratio: 3.0 (1.1), homocysteine:10.7 (4.3) mmol/L and CRP: 3.2 (6.2) mg/l. Abnormal serum levels were seen in 14.2% for TG, 21.2% for TC, 50.8% for LDL, 18.4% for HDL, 16.7% for homocysteine and 6.7% for CRP. The distribution of total CVD risk factors were as follows: 31% had 1, 44% had 2 – 4 and 25% had ≥5 risk factors. 44% (n = 76) were at low risk (FRS = 1–5%), 24% (n = 42) intermediate risk (FRS = 6–10%) and 25% (n = 35) at high risk (FRS = 11–20%) and 12% (n = 20) at very high risk (FRS > 20%). For each FRS risk the equivalent % FMD change and proportion of patients with abnormal FMD are reported in Table 1. Adjusted linear regression showed that for each increase of 1% in FRS one observes an average 0.24% decrease in FMD cuff change.

Table 1.  FRS, FMD cuff change (%) and proportion of abnormal FMD.

<table>
<thead>
<tr>
<th>Framingham Risk Score</th>
<th>Mean %FMD +/- (cuff change)</th>
<th>No of abnormal FMD/No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>10.1 +/- 8.2</td>
<td>30/76 (40%)</td>
</tr>
<tr>
<td>5-10%</td>
<td>9.4 +/- 6.7</td>
<td>14/42 (33%)</td>
</tr>
<tr>
<td>11-20%</td>
<td>8.8 +/- 8.9</td>
<td>17/35 (49%)</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>7.0 +/- 5.7</td>
<td>10/20 (50%)</td>
</tr>
</tbody>
</table>

Conclusion: FRS explains only a subgroup of patients with abnormal FMD, with approximately 40% of SLE patients with low FRS having abnormal FMD. Assessment of FMD in SLE may identify a subgroup of patients with endothelial dysfunction not identified by FRS. Following these patients prospectively may help to determine their actual CVS risk.

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Protection from Cardiovascular Events and Nephritis in SLE Correlates with Levels of IgM Natural Autoantibodies to Different Apoptosis-Associated Antigens. Caroline Gronwall1, Ehtisham Akhter2, Michelle A. Petri1 and Gregg J. Silverman1. Johns Hopkins University School of Medicine, Timonium, MD, 2Johns Hopkins University School of Medicine, Baltimore, MD, 1Univ of California San Diego, La Jolla, CA

Background: In murine models, we have reported that induction of high levels of IgM antibodies to phosphocholeline (PC), a phospholipid neo-determinant on apoptotic cells but not healthy cells, halts the progression of atherosclerosis in hypercholesterolemic mice (1), and can block in vivo and in vivo inflammatory responses to diverse agonists to TLR 3, 4, 7 and 9 (2) that is linked to the inhibition of central inflammatory signaling pathways.

Methods: To investigate for relationships between IgM antibodies to PC and other apoptosis-associated antigens with the clinical and laboratory features of SLE disease, we used standard ELISA to perform...
serologic surveys to PC, malondialdehyde (MDA) as well as cardiopin (CL) and β2 glycoprotein I (β2 gp I) in 95 SLE patients from the well characterized Hopkins Lupus cohort.

Results: In a pre-set series of analyses, for overall disease activity we found only modest inverse correlations with levels of IgM anti-MDA antibodies and the SLEDAI clinical disease activity index and Physicians global estimate (Pearson, P=0.01), but not with other IgM antibodies. Yet, patients without a history of past atherosclerotic cardiovascular (ASCVD) events (i.e., MI, CVA or TIA) had significantly higher IgM anti-PC levels (P= 0.00024, two-tailed t test) compared with past events, there was no relationship with a history of documented lupus nephritis. In contrast, patients without lupus nephritis had higher levels of IgM anti-β2 gp I (P=0.003) and IgM anti-CL (P=0.0001) than in those with lupus nephritis, while there was no association between levels of IgM anti-β2 gp I with history of ASCVD events (P=0.46) and only a trend for IgM anti-CL (P=0.051). IgM anti-β2 gp I levels by themselves did not correlate with other thrombotic events (P=0.3).

Patients with higher levels of IgM anti-MDA had modest associations with the absence of past ASCVD events (P=0.04) and the absence of lupus nephritis (P=0.04). Higher IgM anti-β2 gp I levels also correlated with lower C4 levels (Pearson, P=0.005), and a trend toward lower C3 levels (P=0.057). Otherwise there were no other significant associations with IgG anti-dsDNA or anti-CLq, or with C3 or C4, or ESR.

Conclusions: These findings support our hypothesis, based on murine studies and multiplex autoantibody microarray surveys of lupus twins (3), that some IgM autoantibodies are part of an evolutionarily conserved immune repertoire that provide homeostatic functions, which may protect from certain clinical features of autoimmune disease. Future studies will need to address whether these differences in antibody levels are present at earlier stages of disease development, which could provide valuable prognostic tools.

GJS is supported by grants from ALR, Arthritis Foundation, ACR REF Within Our Reach, NIAID R01 AI068063 and AI090118 and the Swedish Research Council (CG). MAP and the Hopkins Lupus Cohort are supported by NIAMS R01 AR43737 and the Johns Hopkins Univ GCRC M01-RR00052.

Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Mean NCP Score (95% CI)</th>
<th>p-value for trend, controlling for age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 (n = 30)</td>
<td>0.16</td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>45–55 (n = 39)</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55+ (n = 36)</td>
<td>0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 (n = 34)</td>
<td>0.18</td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>25–29 (n = 36)</td>
<td>0.21</td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>Anticardiolipin antibodies (aCL)</td>
<td>No (n = 37)</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes (n = 69)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Low C3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 51)</td>
<td>0.21</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Yes (n = 55)</td>
<td>0.26</td>
<td></td>
<td>0.068</td>
</tr>
<tr>
<td>Low C4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 63)</td>
<td>0.23</td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Yes (n = 43)</td>
<td>0.25</td>
<td></td>
<td>0.090</td>
</tr>
<tr>
<td>Current Prednisone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 69)</td>
<td>0.25</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>Yes (n = 36)</td>
<td>0.22</td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>Current Plaquenol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 21)</td>
<td>0.21</td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>Yes (n = 84)</td>
<td>0.25</td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Current Imuran</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 98)</td>
<td>0.25</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Yes (n = 8)</td>
<td>0.12</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Current Methotrexate (MTX)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 101)</td>
<td>0.22</td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>Yes (n = 5)</td>
<td>0.51</td>
<td></td>
<td>0.0029</td>
</tr>
<tr>
<td>Current Celleccept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 96)</td>
<td>0.24</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>Yes (n = 10)</td>
<td>0.20</td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Current Non-steroidal anti-inflammatory drugs (NSAIDS)</td>
<td>No (n = 62)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes (n = 43)</td>
<td>0.24</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Multivariable regression model to assess the joint association of predictors and the mean level of NCP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect on mean NCP score (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>0.08 (0.05, 0.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (per 5 unit change)</td>
<td>0.03 (0.00, 0.07)</td>
<td>0.049</td>
</tr>
<tr>
<td>History of Anticardiolipin</td>
<td>0.089 (−0.01, 0.17)</td>
<td>0.097</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.03 (−0.07, 0.13)</td>
<td>0.54</td>
</tr>
<tr>
<td>MTX ever</td>
<td>0.27 (0.07, 0.47)</td>
<td>0.0076</td>
</tr>
</tbody>
</table>

Conclusions: NCP is a better marker of immediate atherosclerotic risk than is calcified plaque. In our univariate analysis, low complement was associated with NCP. This is the only association with a marker of active lupus. Of the traditional CVRF- obesity- rather than hypertension- is strongly associated with NCP. Our results suggest that both active SLE (serologically) and traditional CVRF (obesity) contribute to NCP in SLE. The association with MTX is of concern, but should be replicated in larger studies and in multiple centers.

Disclosure: A. N. Kiani: None; J. Vogel-Clausen: None; M. Yew: None; L. S. Magder: None; M. A. Petri: None.

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Aspirin Response Is Impaired in Patients with Systemic Lupus Erythematosus. Vivian K. Kawai1, Ingrid B. Avalos2, Annette M. Oeser1, John Oates3, Ginger Milne4, Cecilia P. Chung4 and C. Michael Stein1. 1Vanderbilt University, Nashville, TN, 2Vanderbilt University, Brookline, MA, 3Vanderbilt University, Baltimore, MD, 4Vanderbilt University, 4VUMC 23rd Ave South Pierce, Nashville, TN
**Background:** Patients with systemic lupus erythematosus (SLE) have an increased risk of myocardial infarction, stroke, and other thrombotic events. Low-dose aspirin, used to prevent thrombotic events, irreversibly acetylates the platelet cyclooxygenase-1 (COX-1) enzyme and thus inhibits thromboxane A$_2$ (TxA$_2$) formation and platelet aggregation. However, some individuals do not respond adequately to aspirin—sometimes termed “aspirin resistance”. Although many lupus patients receive aspirin to prevent thrombosis, there is no information about platelet responses in this population. We examined the hypothesis that response to aspirin is impaired in SLE.

**Material and Methods:** We prospectively studied 34 patients with SLE and 36 age and sex-matched controls who received immediate-release aspirin 81 mg/day for 7 days with monitoring of adherence. Subjects did not take NSAIDs for 7 days before the study. As a measure of aspirin’s effect on its pharmacologic target, platelet COX-1, we measured concentrations of serum TxB$_2$ in patients and controls who were not receiving aspirin therapy at baseline, and after a week of aspirin therapy. Failure to suppress serum TxB$_2$ below 10 ng/ml is widely reported as a threshold for defining aspirin resistance; we compared the proportion of patients and controls with aspirin resistance. Continuous variables were expressed as median and interquartile range (IQR); McNemar and Wilcoxon rank sum tests were used to compare categorical and continuous data.

**Results:** The demographic characteristics of patients with SLE (n = 34, 82% female, age 41 [29–47 years] and controls (n = 36, 72% female, age 45 [33–55 years]) were similar. At baseline, median serum TxB$_2$ was similar in SLE (76.8 [39.0–134.8 ng/ml]) and controls (103.3, [30.6–130.3 ng/ml]) (P = 0.84). Aspirin suppressed serum TxB$_2$ production almost completely in controls to 1.5 [0.8–2.7 ng/ml] but had significantly less effect in SLE (3.1 [2.2–5.3 ng/ml]) (P = 0.002) (Figure). Aspirin resistance was present in 5/34 (15%) SLE patients and 0/36 controls (P < 0.001). Compared to those that were aspirin sensitive, the 5 aspirin resistant patients were more likely to have diabetes (P = 0.034), hypertension (P = 0.007), a history of smoking (P = 0.056), and a higher BMI (p = 0.055), but measures of disease activity (SLEDAI) (P = 0.96) and damage (SLICC) (P = 0.43) did not differ.

**Conclusions:** Patients with SLE are less responsive to aspirin than controls and resistance to the effect of aspirin on platelet COX-1 occurs. Obesity, diabetes, hypertension and a history of smoking were more common among lupus patients with aspirin resistance.

**Disclosure:** V. K. Kawai: None; I. B. Avalos: None; A. M. Ooser: None; J. Oates: None; G. Milne: None; P. C. Chung: None; C. M. Stein: None.

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**Figure.** Serum Thromboxane B$_2$ in patients with lupus and controls after aspirin treatment.

**Table.** CVE rates, in subgroups defined by SLE clinical characteristics

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Purpose: Patients with systemic lupus erythematosus (SLE) have a greater prevalence of atherosclerosis than the general population. This study was designed to identify risk factors for preclinical atherosclerosis in a predominantly African-American group of SLE patients.

Methods: Subjects with SLE but without a history of clinical cardiovascular events were enrolled. At entry, a Framingham risk factor history and medication list were recorded. Sera and plasma samples were analyzed for lipids, lupus activity markers, and total 25(OH) vitamin D (25(OH)D) levels. SLE Disease Activity Index (SLEDAI) and SLICC Damage Index scores were calculated. Carotid ultrasound measurements were performed to determine total plaque area (TPA) in both carotids as a validated measure of preclinical atherosclerosis that associates longitudinally with major cardiovascular events. Cases were defined as those with TPA values above that of age-matched controls from a population of 4272 patients in stroke and hypertension clinic. Descriptive analysis was performed on all variables between cases and controls. Associations between TPA and continuous variables were determined by correlation. Chi-square analysis was performed for ordinal variables against case or control status. Logistic regression analysis was performed to explore predictive markers. P values < 0.05 were considered significant. A nearest related neighbor machine learning model (NRN) to explore variables associating with elevated TPA in a nonlinear or collinear fashion.

Results: Fourteen of 51 subjects (27%) enrolled had elevated TPA compared to age-matched controls. 25(OH)D levels (16.6±3.2 vs. 22.6±1.8 ng/dl), SLEDAI scores (2.3±0.5 vs. 4.3±0.5), and anti-dsDNA antibody levels (34±18 vs. 136±59 IU) were significantly lower, while SLE disease duration (11.9±1.6 vs. 8.7±13 years) was significantly higher in cases. Age (r=0.58), C4 (r=0.36), and SLE disease duration (r=0.37) significantly correlated with TPA, while 25(OH)D levels significantly inversely correlated with age-adjusted TPA (r=-0.33). ACE-inhibitor use and a history of hypercholesterolemia were significantly associated with case status. Logistic regression models containing ACE-inhibitor use, 25(OH)D levels, and LDL levels had a diagnostic accuracy of 84%. Season of enrollment was not significant in the model. An NRN model was trained. Variables retained in the model as associating with abnormal TPA were hydroxylcholesterol, ACE-inhibitor, and statin use as well as 25(OH)D levels. This model resulted in a receiver operating characteristics area under the curve of 0.75 for discriminating cases.

Conclusions: This study demonstrates in SLE patients novel and previously described associations between lower atherosclerotic burden and factors that are known to restore endothelial function and reduce plaque in non-SLE populations. These associations provide a rationale basis for studying the effect of these therapies on endothelial function and vascular outcomes in patients with SLE.

Disclosure: R. L. Ravenell: None; D. L. Kamen: None; S. David: None; H. Bruce: None; A. Jonas: None; J. C. Oates: None.

ACR Concurrent Abstract Sessions
T Cell Biology and Targets in Autoimmune Disease
Wednesday, November 10, 2010, 2:30 PM–4:00 PM

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Dipyridamole Inhibits SLE T Cell Activation and Alleviates Nephritis in Lupus-Prone Mice. Vasileios C. Kyttaris, Zheng Zhang, Ourania Kampagianni and George C. Tsokos. Beth Israel Deaconess Medical Center

Background: SLE T cells provide help to B cells to produce autoantibodies and infiltrate tissues orchestrating local inflammatory responses. We have previously shown that SLE T cells are characterized by a robust calcineurin-mediated dephosphorylation of the transcription factor NFAT. Dephosphorylated (activated) NFAT translocates to the nucleus and activates a host of genes, including the co-stimulatory molecule CD154 that enhances antibody production by B cells, and several pro-inflammatory cytokines.

NFAT/calcineurin inhibition represents an attractive option for the treatment of various inflammatory diseases. Yet calcineurin inhibitors (cyclosporine A, tacrolimus) have significant side effects including nephrotoxicity. It was shown recently that dipyridamole inhibits the activation of NFAT without affecting total calcineurin phosphatase activity, potentially causing fewer side effects.

Methods: T and B cells were isolated from the peripheral blood of SLE and healthy individuals. The cells were incubated in the presence of dipyridamole (20µM or 50µM), or tartaric acid as control. T cells were activated with anti-CD3 and anti-CD28 antibodies. MRL/lpr lupus-prone mice were injected intraperitoneally with dipyridamole 50 mg/kg three times a week for 4 weeks. CD154 and cytokine production was measured with flowcytometry.

Results: Dipyridamole treatment of SLE T cells inhibited NFAT activation and decreased the expression of CD154 by 66±21% (p<0.0001, N=9). The production of IFN-γ decreased by 96±3% (p<0.0001, N=9), that of IL-17 by 74±29% (p<0.0001, N=9), and of IL-6 by 57±22% (p<0.0001, N=9). Moreover, dipyridamole inhibited the T cell directed production of immunoglobulin, including anti-dsDNA antibodies, in T/B cell mixed cultures. Activation of isolated B cells by anti-IgM was not affected by dipyridamole. Dipyridamole decreased significantly the expansion of T cells in vitro as assessed by CFSE staining.

Next, we treated MRL/lpr mice with dipyridamole. MRL/lpr mice have a very large number of CD4+CD45-CD8+ T cells (double negative T cells, DNT) that express high levels of NFAT. Treatment of these mice with dipyridamole decreased DNT proportion by 33% and prevented the emergence of pyuria. The dipyridamole treated mice did not develop skin lesions and were protected from early death (3/5 control-treated mice died by the fourth week of the trial as opposed to 0/5 in the dipyridamole treated group).

Dipyridamole treatment decreased the concentration of IL-6 in the serum (dipyridamole vs. control treated mice=364±52 vs. 5,280±206 pg/mL, p<0.0001). The percentage of CD3+ cells in the spleen decreased in the dipyridamole treated animals, primarily due to a decrease in DNT subpopulation (splenic DNT cells in dipyridamole vs. control treated mice= 47±2% vs. 67±2%, p=0.0045).

Conclusions: Inhibition of NFAT with dipyridamole results in decreased activation and expansion of lupus T cells, blocking at the same time T cell directed autoantibody production. Dipyridamole alleviates nephritis and prolongs survival of lupus-prone mice. Therefore we propose that dipyridamole is an attractive NFAT inhibitor that can be used in the treatment of SLE.

Disclosure: V. C. Kyttaris: None; Z. Zhang: None; O. Kampagianni: None; G. C. Tsokos: None.

2127

Defective T Cell Tolerance in Rheumatoid Arthritis Due to Increased B-Raf and K-Ras Expression. Pratima Deshpande1, Karnail Singh2, Mingcan Yu1, Guanglin Li3, Cornelia M. Weyand1 and Jorg J. Goronzy1. Emory University, Atlanta, GA, 2Stanford University, Stanford, CA, 3Stanford University School of Medicine, Stanford, CA

Background/ Purpose: Autoantibodies to common auto- and neo-antigens such as IgG Fc and citrullinated peptides are immunological hallmarks of rheumatoid arthritis (RA). Identified disease risk genes suggest that signaling pathways abnormalities are involved in RA pathogenesis. We have examined the hypothesis that defects in T cell receptor (TCR) signaling lower the activation threshold of RA T cells predisposing for a failure in maintaining tolerance.

Methods: TCR-induced signaling was compared in 65 patients with seropositive RA and 54 healthy controls by phospoepitope flow cytometry. The MAP Kinase Signaling Pathway PCR Array was used to screen for differentially expressed genes. SOS1, RasGRP1, DUSP5, DUSP6, K-Ras and B-Raf transcription was quantified by qPCR. Protein expression of B-Raf, C-Raf, K-Ras and N-Ras were compared by Western blotting and by flow cytometry. siRNA for K-Ras and B-Raf from Qiagen was used in silencing experiments. Co-localization of B-Raf or C-Raf with K-Ras or N-Ras in T cells from control and RA patients was examined by confocal microscopy. CD4 T cells from healthy HLA-DR4+ individuals were transfected with K-Ras or B-Raf cloned into the pIRE2-AcGFP1 vector. Cells were stimulated with 1 µM aa 65–77 native or R70Cit vimentin peptides.

Summary of Results: RA T cells responded to TCR stimulation with increased ERK phosphorylation compared to healthy controls of the same age.
Increased ERK responsiveness was a feature of all functional T cell subsets including naive T cells and did not correlate with disease activity. Increased expression of K-Ras and B-Raf in RA T cells, first identified in gene expression arrays of ERK pathway members, was confirmed by qPCR.

Methods: SKG mice were crossed with SLAP-deficient mice to generate Double SKG SLAP KnockOut (DSSKO) mice. Results: DSSKO mice do not develop zymosan-induced chronic autoimmune arthritis. This prevention of arthritis development is not due to significant alteration in thymocyte development or repertoire selection. Instead, regulatory T cells (Tregs), known to be critical in suppression of autoimmune arthritis, are increased in both SKG and DSSKO mice. This was accompanied by significant alteration in thymocyte development or repertoire selection.

Conclusions: Restricting ERK activity, in part by Rap-1 mediated inactivation of C-Raf is a more important mechanism to maintain energy to self-antigens or in the absence of costimulation. Expression of B-Raf that can bypass this pathway is low in T cells from healthy individuals. Naive and memory T cells from DSSKO mice expressed increased numbers of T cells responsive to low affinity and autoantigens. Our data suggest that B-Raf and K-Ras are promising targets to treat autoimmune diseases.

Disclosure: P. Deshpande: None; K. Singh: None; M. Yu: None; G. Liu: None; C. M. Weyand: NHI6, 2, NIAMS-NIH, 2, NIH, 2; J. J. Goronzy: NIAMS-NIH, 2, NIH, 2.

2128

SLAP Deficiency Enhances Both Number and Function of Foxp3+ Regulatory T Cells and Inhibits Chronic Arthritis in SKG Mice, Lisa K. Peterson1, Laura A. Shaw2, Anthony Joetham3, Shimon Sakaguchi1, Erwin W. Gelfand4, and Leonard Dragon4.

Background: Intrinsic defects in lymphocyte signaling have been implicated in the pathogenesis of rheumatoid arthritis. Manipulation of T cell function by altering TCR complex-mediated signaling could be a viable strategy to treat autoimmune diseases. However, the signaling networks required to eliminate or modulate the function of autoreactive T cells are not known, which is an obstacle in our capacity to manipulate autoreactive T cells. SKG mice have a point mutation in the zeta chain of the TCR complex. The same signaling chain of the TCR complex to which ZAP-70 binds. Thus, we specifically chose to create the Double SKG SLAP KnockOut (DSSKO) model because ZAP-70 and SLAP have opposing functions on the regulation of TCR complex mediated signaling. The combination of these two mutations provides a unique opportunity to determine how alterations in TCR complex-mediated signaling can modulate autoimmune disease in the context of a defined genetic background, uniform environmental conditions, and a well-characterized signaling disruption.

Methods: SKG mice were crossed with SLAP-deficient mice to generate Double SKG SLAP KnockOut (DSSKO) mice. Results: DSSKO mice do not develop zymosan-induced chronic autoimmune arthritis. This prevention of arthritis development is not due to significant alteration in thymocyte development or repertoire selection. Instead, regulatory T cells (Tregs), known to be critical in suppression of autoreactive T cells and prevention of autoimmunity, are increased in both the thymus and spleen of DSSKO mice. This was accompanied by inhibition of differentiation and/or expansion of Th17 cells, upon zymosan exposure, and suppression of chronic arthritis. Treg depletion and/or functional blockade unleashed the autoreactive Th17 cells and arthritis developed in DSSKO mice. In vitro suppression of effector T cell proliferation was also enhanced which demonstrated that DSSKO mice have increased numbers of Tregs with improved function.

Conclusions: These data show that DSSKO mice have enhanced development and function of Tregs, preventing the development of arthritis. Understanding how TCR complex-mediated signals influence Treg development, expansion, and function will advance our capacity to manipulate Treg biology. The long-term goal of these studies is to apply our findings to patients in a way that enhances Treg number and/or function to treat autoimmune disease.

Disclosure: L. K. Peterson: None; L. A. Shaw: None; A. Joetham: None; S. Sakaguchi: None; E. W. Gelfand: None; L. Dragone: None.

2129

The Role of BAFF in Promoting the Development of Cells and Th17-Mediated Disease. Xiaohui Zhou, Julie Wang, Jing Zhang, William Stohl, Song Guo Zheng, Tongji University Medical School, 2, USC Keck School of Med, Los Angeles, CA, 4, USC Keck School of Medicine, Los Angeles, CA.

Background: B cell-activating factor belonging to the TNF family (BAFF; BLyS) plays a critical role in promoting B cell maturation and survival and the development of autoimmune disorders. BAFF also affects T cell function through binding to one of the BAFF receptors, BAFF-R. BAFF-R targets the zeta chain of the TCR complex in SKG mice will prevent autoimmunity. To test this, we specifically chose to create the Double SKG SLAP KnockOut (DSSKO) model because ZAP-70 and SLAP have opposing functions on the regulation of TCR complex mediated signaling.

Methods: SKG and DSSKO mice were analyzed ex vivo for the surface staining of CD19, CD4, CD8, CD69, CD44, CD201,CCR6, CCR25 and intracellular staining of ROR-γt, IL-17, IFN-γ, IL-4 and Foxp3. IL-17A and IL-17F mRNA was determined by qPCR.

Results: The effect of BAFF in vitro differentiation of naïve CD4+ T cells into Th17 cells was assessed through stimulation with soluble anti-CD3/CD28 in the presence of IL-6 and TGF-β plus irradiated APC. We further detected the frequencies of Th1, Th2 and Treg cells in these mice. In addition, we evaluated the role of BAFF in the Th17 development in vivo using a Th17-mediated disease model, EAE.

Conclusions: This study suggests that BAFF may promote the development of autoimmune diseases through Th17 cell development and function in addition to its direct effect on B cell maturation and survival. These results implicate that manipulation of BAFF pathways has a beneficial role in treating Th17+ and/or Th1-mediated inflammatory diseases.

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2130

Activated Th17 Cells Drive Rheumatoid Inflammation and Are Resistant to Inhibition by Natural Antagonists of Their Development. Jan Leipe1, Mathias Grunke2, Claudia Dechant, Christiane Reinli, Hendrik Schulze-Koops3 and Alija Skapenko3, 1University of Munich, Munich, Germany, 2University of Munich, Munich, Germany.

Background: IL-17 has been identified as a new pro-inflammatory cytokine contributing to autoimmune inflammation in several animal models. Since the major source of IL-17 in human autoimmune diseases...
is still elusive, we analyzed Th17 cells, defined as a cell type producing IL-17, but not IFN-γ or IL-4, in patients with the prototypic autoimmune diseases, rheumatoid arthritis (RA) and psoriatic arthritis (PsA).

Methods: Th17 cells were analyzed ex vivo and in vitro by various methods e.g. multi-color flow cytometry, enzyme-linked immunosorbent assay (ELISA) and real-time PCR in well-defined cohorts of patients: active treatment-naive RA (n = 36) and PsA (n = 20) with very early disease, disease duration < 3 months), and patients with established RA (n = 21; disease duration 6 months to 6 years), disease duration < 3 months, responding or not responding to therapy. For control, patients with osteoarthritis (n=20) and age-matched healthy individuals (n=25) were analyzed.

Summary of the Results: Th17 cell frequencies and IL-17 production of CD4+ T cells from the peripheral blood of RA and PsA patients were significantly increased compared to controls. Importantly, Th17 cells frequencies strongly correlated with systemic disease activity in early (r = 0.91, p < 0.0001) and established (r = 0.72, p < 0.001) RA, and were reduced to control levels in response to clinically effective treatment. Th17 cells were specifically enriched in the inflamed joints of RA and PsA patients, and increased frequencies of synovial Th17 cells expressed the chemokine receptors CCR4 and CCR6 required for selective migration of Th17 cells into the joints. As molecular mechanisms underlying the pathophysiological Th17 cell activity in autoimmune arthritis, we identified an intrinsically elevated expression of the master transcription factor RORC, accompanied by increased Th17 cell differentiation, and a resistance of Th17 cells from the RA and PsA patients to the natural antagonists of their development, e.g. IL-4 and IFN-γ.

Conclusion: Together the data indicate an important role of Th17 cells and their effector functions in the pathogenesis of autoimmune arthritis, and provide the scientific basis for treatment approaches targeting Th17 cell functions.

Disclosure: None; M. Grunke: None; C. Dechant: None; C. Reindl: None; H. Schulze-Koops: None; A. Skapenko: None.

2131

Regulatory T Cell Recovery in HCV-Related Autoimmunity through IL-2 Therapy

Background: Patients with chronic HCV infection often develop autoimmune disease to modulate the homeostasis of Tregs. IL-2 therapy dramatically increases the percentage of Treg in HCV-vasculitis and was well tolerated.

Disclosure: D. Saadoun: None; M. Rosenzwajg: None; L. Musset: None; F. Carrat: None; D. Katzmann: None; P. Caouby: None.

ACR/ARHP Combined Abstract Session
ACR/ARHP Combined Orthopedics, Low Back Pain and Rehabilitation Abstracts: Hips and Knees: Focus on Function
Wednesday, November 10, 2010, 2:30 pm–4:00 pm

2132

Progressive Resistance Exercise in Women with Knee Osteoarthritis.

Renata Jorge1, Marcelo Souza2, Aline Chiari3, Anamaria Jones4, Imperio Lombardi, Jr5, Artur Fernandes6 and Jamil Natour7. UNIFESP, Sao Paulo, SP, Brazil, 8UNIFESP

Background: Knee osteoarthritis (OA) is a common musculoskeletal disorder. Recent guidelines for the management of knee OA emphasize the role of strengthening exercises. While most studies focus on the benefits of quadriceps strengthening, little is known about hip strengthening exercises in knee OA and also, about prescription in terms of intensity, duration, frequency and load.

Objectives: To assess pain, function, quality of life, walking endurance and muscular strength in women with knee OA who participated in a progressive resistance exercise program (PREP).

Methods: Eligible patients included women, age 40–70 years old with pain between 3 and 8 on a 10-cm pain scale. Of the 144 patients screened, 60 met the eligibility criteria and were randomized to the Experimental Group (EG) or Control Group (CG). Patients in EG participated in a 12-week PREP twice a week and CG remained on a waiting list for physiotherapy. The PREP consisted of strengthening exercises for knee extensors, knee flexors, hip adductors and hip abductors, all performed with 50% and 70% of the maximum amount of weight that can be tolerated for a given exercise (1 repetition maximum-IRM) using machines with free weights. The resistance was reevaluated every 2 weeks. Assessment for pain (VAS), muscle strength (IRM), walking endurance (6MWT), function (WOMAC) and quality of life (SF-36) were done at baseline, 6 weeks and 12 weeks by a blinded assessor.

Results: 29 female patients were randomly assigned to the EG and 31 to the CG. In the comparison between groups using ANOVA for repeated measures, we found better results for the EG with statistical difference for VAS (p<0.001), WOMAC (pain: p < 0.001; function: p < 0.001 and aggregate score: p < 0.001), some domains of SF-36 (physical function: p=0.002; physical role limitation: p=0.002 and pain: p=0.044) and on muscular strength (extensors: p<0.001; flexors: p=0.002 and abductors muscles: p<0.001). At 6 weeks, there was a significant statistical difference in the pain VAS (EG: 5.9; CG: 7.0; p=0.022), the WOMAC (EG: 30.9; CG:39.1; p=0.017); SF-36 physical component summary (EG:39.1; CG: 30.8; p=0.045) as well on muscular strength of knee extensors (EG:10.4; CG:5.7; p<0.001); knee flexors (EG:7.4; CG:5.2; p=0.003) and hip adductors (EG:29.2; CG:21.0; p<0.001). At 12 weeks, there was a statistically significant difference in the pain VAS (EG: 4.3; CG: 6.6; p<0.001); the WOMAC (EG:24.1; CG: 38.3; p<0.001); SF-36 physical component summary (EG:49.8; CG: 30.8; p<0.000); physical role limitation (EG:48.3; CG: 16.9; p<0.001) and pain (EG: 58.6; CG: 41.7; 0.006); as well on muscular strength of knee extensors (EG: 11.8; CG: 5.7; p<0.0001), knee flexors (EG: 8.6; CG: 5.3; p=0.000) and hip abductors (EG: 32.7; CG: 19.5; p<0.000)

Conclusion: A progressive resistance exercise program was effective in reducing pain and improving function, some domains of quality of life and strength in women with knee osteoarthritis at 6 weeks and 12 weeks after the intervention.

Disclosure: R. Jorge: None; M. Souza: None; A. Chiari: None; A. Jones: None; I. Lombardi, Jr: None; A. Fernandes: None; J. Natour: None.

2133

Reasons for Decline in Walking Despite Improvements in Knee Pain: The MOST Study


1Boston Univ. Schol of Med, Boston, MA, 2Boston Univ School of Med, Boston, MA, 3Boston University, Boston, MA, 4Boston University School of Medicine, Boston, MA, 5UCSF, San Francisco, CA, 6University of Alabama, University of Iowa

Method: This is the first study to report the use of IL-2 in human autoimmune disease to modulate the homeostasis of Tregs. IL-2 therapy dramatically increases the percentage of Treg in HCV-vasculitis and was well tolerated.

Disclosure: None; M. Rosenzwajg: None; L. Musset: None; F. Carrat: None; D. Katzmann: None; P. Caouby: None.

ACR/ARHP Combined Abstract Session
ACR/ARHP Combined Orthopedics, Low Back Pain and Rehabilitation Abstracts: Hips and Knees: Focus on Function
Wednesday, November 10, 2010, 2:30 pm–4:00 pm
Purpose: Reducing knee pain in persons with knee osteoarthritis (OA) is a key therapeutic goal of rehabilitation. However, recent studies have shown that improvements in pain do not necessarily result in improvements in function, and it’s not clear as to why this might be. We therefore evaluated factors associated with substantial declines in walking speed among persons who had meaningful improvements in knee pain.

Methods: The Multicenter Osteoarthritis Study (MOST) is a NIH funded longitudinal study of people who have or are at high risk for knee osteoarthritis. We included subjects who had meaningful improvement over 30 months in pain in either knee, defined as a 41% decrease in VAS pain with an absolute change of 20/100. We defined meaningful decline in walking speed as a decrease of 0.1 meters per second (m/s) during a 20 meter walk. Both values are based on previously published sources. We assessed changes in radiographic OA, comorbidities, widespread pain, and depressive symptoms over 30 months, and baseline knee strength as risk factors for decline in walking speed. To examine the association of risk factors with meaningful decline in walking speed we calculated risk ratios adjusted for age, sex, BMI, race, and baseline knee pain.

Results: Of the 465 persons with meaningful improvement in knee pain (mean (sd) age=63.7 (7.8), 67% female, BMI=31.3 (6.3), 82% White), 20% (91/465) had a meaningful decline in walking speed. More persons with a new onset of comorbidity had a decline in walking speed (32% (15/47)) compared with those with no comorbidity at baseline or follow up (17% (46/267)). Similarly, more persons with widespread pain at baseline and follow up had a decline in walking speed (24% (40/165) compared with those with no widespread pain at baseline or follow up (16% (22/139)). Adjusting for confounders, persons with new comorbidities and those with widespread pain had 1.8 and 1.7 times the risk of decline compared with those without comorbidities and widespread pain, respectively (RR 1.8 95% CI [1.1,2.9], 1.7 [1.0,2.9], respectively).

Conclusions: Improvements in knee pain do not guarantee positive changes in walking speed. Health providers should consider that onset of new comorbidities and pain in areas other than knee pain may increase risk of decline in walking speed despite improvement of pain in one or both knees.

Table. Association of risk factors for meaningful decline in walking speed among persons with meaningful improvement in knee pain.

<table>
<thead>
<tr>
<th></th>
<th>% (# decline/total #)</th>
<th>Adj Risk Ratio* [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None at 0 or 30m</td>
<td>20 (32/161)</td>
<td>1.0 [Ref]</td>
</tr>
<tr>
<td>Present at 0 and 30m</td>
<td>20 (55/275)</td>
<td>1.0 [0.6, 1.5]</td>
</tr>
<tr>
<td>None at 0, present at 30m</td>
<td>18 (4/22)</td>
<td>1.0 [0.3, 2.9]</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None at 0 or 30m</td>
<td>17 (46/267)</td>
<td>1.0 [Ref]</td>
</tr>
<tr>
<td>Present at 0 and 30m</td>
<td>20 (31/148)</td>
<td>1.1 [0.7, 1.7]</td>
</tr>
<tr>
<td>None at 0, present at 30m</td>
<td>32 (15/47)</td>
<td>1.8 [1.1, 2.9]</td>
</tr>
<tr>
<td>Wide spread pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None at 0 or 30m</td>
<td>16 (22/139)</td>
<td>1.0 [Ref]</td>
</tr>
<tr>
<td>Present 0m, none at 30m</td>
<td>20 (24/119)</td>
<td>1.1 [0.7, 1.7]</td>
</tr>
<tr>
<td>Present at 0m and 30m</td>
<td>24 (40/165)</td>
<td>1.8 [1.1, 2.9]</td>
</tr>
<tr>
<td>None at 0m present at 30m</td>
<td>12 (4/34)</td>
<td>1.0 [Ref]</td>
</tr>
<tr>
<td>Strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22 (31/141)</td>
<td>1.0 [Ref]</td>
</tr>
<tr>
<td>3</td>
<td>18 (19/106)</td>
<td>0.8 [0.5, 1.4]</td>
</tr>
<tr>
<td>4: Low</td>
<td>19 (22/116)</td>
<td>1.0 [0.6, 1.6]</td>
</tr>
<tr>
<td></td>
<td>8 (10/56)</td>
<td>1.0 [0.5, 1.9]</td>
</tr>
</tbody>
</table>

*Mutually adjusted for age, sex, BMI, race, baseline knee pain, and depressive symptoms. Higher risk ratios indicate greater risk of meaningful decline in walking speed.

Disclosure: D. K. White: None; D. T. Nelson: None; J. Niu: None; M. C. Nevitt: None; C. E. Lewis: None; J. Torner: None; T. Nevitt: None.

2135

Functional Benefits Following Dynamic Exercise in Patients with RA Taking Anti-TNFα Therapy Reflected in Lower Limb Function Tests but Not the HAQ. Angela Reid1, Audrey Brady2, Tara Cusack2, Catherine Blake3, Anne Barbara Monegy4, Douglas J. Veale5 and Oliver Fitzgerald6. 1Our Lady’s Hospice, Dublin, Ireland, 2Our Lady’s Hospice, 3St. Vincent’s University Hospital, 4St. Vincent’s University Hospital, 5University College Dublin, Dublin, Ireland.

Background: The medical management of rheumatoid arthritis (RA) has advanced with the introduction of biologic drugs including anti-TNFα therapy medication. Dynamic exercise is an important non-pharmacological therapy in RA and has been shown to improve function. The effect of dynamic exercise on function for people with RA on anti-TNFα medication has not yet been described. The purpose of this study was to investigate the effect of dynamic exercise, either on land or in water, on function in people with RA taking anti-TNFα medication.

Methods: A convenience sample of people with RA on anti-TNFα medication was recruited. Participants were randomised into one of 3 groups: a gym, a hydrotherapy or a control group. The gym and hydrotherapy interventions consisted of flexibility, strengthening and aerobic exercises. Exercise classes were undertaken for 1 hour, twice weekly for 8 weeks. The control group received no intervention. Participants were assessed by a blind assessor at baseline, 8 and 24 weeks. The primary outcome measure was the HAQ. Secondary measures of outcome included the 50ft Walk Test (50ftWT) and the Timed Chair Stand Test (TCST). Semi-structured interviews were conducted at 24 weeks to ascertain the exercise participation levels of individuals following completion of the study.

Results: Fifty one people (12 male / 39 female) with a mean age of 56 (± 10) years were recruited. The mean length of diagnosis was 14.1 (± 10.5) years and the mean length of time taking anti-TNFα medication was 2.9 (± 2.1) years. The 50ftWT improved significantly in both the gym and hydrotherapy groups at 8 weeks compared to the control group (gym p=0.02, hydrotherapy p=0.01). The TCST significantly improved in the gym group (p=0.02) when compared to the control group at 8 weeks. These improvements were not maintained at 24 weeks. No significant change was noted in HAQ scores. Of the 17 exercise group participants interviewed post-study, 3 had continued the exercise programmes between the eight and 24 week time-points. Reasons identified for failing to continue to exercise included lack of access to facilities and reduced motivation.

Disclosure: P. T. Rodrigues: Centro de Estudos em Reumatologia, 2; R. M. R. Pereira: None; J. M. D. Greve: None; R. Fuller: None.

2134


Introduction: The use of medial-wedge insole associated with ankle support produces a clinical improvement in osteoarthritis of the knee valgus, as described in our previously study [Arthritis Rheum 59(5): 603–608]. However, there are no data regarding the biomechanics effect of these orthoses.

Objective: To evaluate the foot plantar maximum vertical force in patients with OA in the lateral compartment of the valgus knee using medial-wedge insole associated with ankle support.

Method: A total of 42 feet of 21 women with bilateral knee osteoarthritis (ACR criteria), with valgus deformity ≥ 8 degrees were evaluated regarding clinical and biometrics data. Patients were assessed with: 1. standard shoes with medial-wedge insoles (controls); 2. with the medical-wedge insole without (8 mm medial elevation at rearfoot) and 3. with these insoles and neoprene ankle support. The system FSCANR 3.816 version, with flexible soles and 960 load sensors on the surface, was used to obtain the foot plantar vertical force. The acquisition of the measures took 8 seconds and the data was collected between seconds 2 and 6. The values were given in Newtons (N).

Results: The patients were 65.14 ± 10.24 years old; the mean disease duration was 9.3 years, the body mass index was 29.4 ± 4.1. The pain at rest was 5.57 ± 2.18 (range 2–8) by visual analogue scale, the degree of radiographic OA (Kellgren-Lawrence) was 2.62 ± 0.82, WOMAC index was 70.8 ± 11.2 and Lequesne 14.55 ± 3.19. The femoral-tibial angle was 169.38 ± 43.32 degrees. The maximum vertical force was significantly lower in the patients with the use of medial-wedge insoles compared to control (287.30 ± 89.28 vs. 347.42 ± 87.14 N, p= 0.003). Likewise, patients with the use of medial-wedge insoles and ankle support had a diminished vertical force compared to control (248.15 ± 99.77 vs. 347.42 ± 87.14 N, p<0.0001). The support promoted a further reduction in strength compared to the isolated use of the insole (248.15 ± 99.77 vs. 87.30 ± 89.28 N, p=0.03).

Conclusion: The use of medial-wedges insoles promotes a reduction in the maximum vertical force in osteoarthritis of valgus knee. This finding may explain the clinical improvement observed in our previous study probably by a more homogenous load distribution in the involved ankle and knee.

Disclosure: P. T. Rodrigues: Centro de Estudos em Reumatologia, 2; R. M. R. Pereira: None; J. M. D. Greve: None; R. Fuller: None.

Wednesday, November 10
### Table 1. Results

<table>
<thead>
<tr>
<th>Group (n = 17)*</th>
<th>Baseline</th>
<th>8 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gym</td>
<td>0.79 (0.51)</td>
<td>0.63 (0.48)</td>
<td>0.79 (0.61)</td>
</tr>
<tr>
<td>Hydro</td>
<td>1.07 (0.85)</td>
<td>0.99 (0.85)</td>
<td>1.03 (0.85)</td>
</tr>
<tr>
<td>Control</td>
<td>0.83 (0.55)</td>
<td>0.83 (0.59)</td>
<td>0.79 (0.56)</td>
</tr>
<tr>
<td>Gym</td>
<td>9.35 (1.97)</td>
<td>8.21 (1.86)†</td>
<td>8.6 (2.62)</td>
</tr>
<tr>
<td>Hydro</td>
<td>11.53 (3.87)</td>
<td>10.07 (2.05)†</td>
<td>10.24 (2.17)</td>
</tr>
<tr>
<td>Control</td>
<td>10.10 (3.36)</td>
<td>10.56 (3.34)</td>
<td>10.35 (2.60)</td>
</tr>
<tr>
<td>Gym</td>
<td>13 (5–19)</td>
<td>16 (10–32)†</td>
<td>16 (6–32)</td>
</tr>
<tr>
<td>Hydro</td>
<td>9 (6–23)</td>
<td>12 (8–23)†</td>
<td>12 (8–29)</td>
</tr>
<tr>
<td>Control</td>
<td>11 (5–20)</td>
<td>13 (6–22)</td>
<td>13 (0–22)</td>
</tr>
</tbody>
</table>

*Hydro Group n = 16 at 24 weeks. †p ≤ 0.05 one-way Anova, ‡p ≤ 0.05 Mann Whitney U Test.

### Conclusion

Participating in 8 weeks of dynamic exercise, either on land or in a hydrotherapy pool, improved function in this sample of people with RA on anti-TNFα medication as evidenced by the significant improvements in lower limb function tests at 8 weeks. This was not reflected by changes in HAQ scores. Access to facilities and support in terms of organised, suitable, supervised exercise classes may be necessary to enable this population to continue to engage in long term exercise.

**Disclosure:** A. Reid: None; A. Brady: None; T. Cusack: None; C. Blake: None; A. B. Mongey: None; D. J. Veale: None; O. FitzGerald: None.

### 2136

**Co-Morbid Pain in Hips, Low Back, and Non-Operative Knee Associated with Physical Function before and after THR.** Patricia D. Franklin,1 Wenjun Li,1 David C. Ayers,1 and Carol A. Oatis,1 1Arcadia University, Glenside, PA, 2Univ of MA Med Schl, Worcester, MA

**Introduction:** Older age, female gender, obesity, and poor emotional health are associated with poorer function before and after total knee replacement (TKR). In addition, medical co-morbidities are related to peri-operative adverse events. However, no research has documented the role of co-morbid pain in the low back, hips, and the non-operative knee on physical function before and after TKR. We evaluated the association of co-morbid low back, hip, and bi-lateral knee pain with function in TKR patients.

**Methods:** A prospective cohort of 130 consecutive, primary, unilateral TKR patients enrolled in a clinical trial reported demographic, pain, and function data before and at 6 months after TKR. Descriptive and multivariate analyses evaluated the associations among age, gender, BMI, emotional health (SF36, MCS), WOMAC pain score in both hips and both knees, and Oswestry low back pain and associations with (1) pre-op function (SF36, PCS) and (2) pre-post functional gain.

**Results:** Patients were 60% women with mean age=65, BMI=32.6, pre-TKR PCS=32.7. Before TKR, 52% reported mild or no pain in the non-operative knee, hips, and low back. Twenty (20) percent reported moderate/severe pain in one other joint or back, 13% in two locations, and 10% in 3 or 4 locations. Women reported moderate/severe pain more than men in the non-operative knee (34.5% vs. 11%); ipsilateral hip (28% vs. 15%); and low back (33% vs. 20%). After adjusting for age, gender, BMI, and MCS, greater pain in the surgical knee (p<0.000), contralateral hip (p<0.074), and low back (p<0.028) was associated with poorer function in TKR patients (r²=0.39).

**Conclusion:** In addition to pain in the surgical knee, co-morbid pain in the non-operative knee, hips, and low back explain much variation in peri-TKR function. Women report more non-operative joint pain than men at the time of TKR. These data suggest a need for a musculoskeletal co-morbidity score to assess total pain burden when evaluating TKR patient function before and after surgery.

**Disclosure:** P. D. Franklin: NIAMS-NIH, 2; W. Li: NIAMS-NIH, 2; D. C. Ayers: NIAMS-NIH, 2, Zimmer, 2; C. A. Oatis: NIAMS-NIH, 2.

### 2137

**Predictors of 12 Year Revision Risk Following Primary THR for Osteoarthritis in the US Medicare Population.** Jeffrey N. Katz,1 Elizabeth A. Wright,1 Akosha A. Nti,1 John Wright2, Henrik Malchau3, John A. Baron4 and Elena Losina5. 1Brigham and Women’s Hospital, Boston, MA, 2Brigham and Women’s Hospital, 3Brigham and Womens Hospital, Boston, MA, 4Dartmouth Medical School, 5Massachusetts General Hospital

**Introduction:** There have been no prior US national population-based studies of the risk of revision following primary total hip replacement (THR) for osteoarthritis (OA) with 12 year follow up and complete ascertainment of revision and mortality.

**Methods:** We used Medicare claims data to assemble a cohort of 51,347 patients ≥65 years old who had primary THR for OA in 1995–96. We followed this cohort in claims through 2008 and identified patients who had claims with ICD-9 codes indicating revision THR. We used Cox proportional hazard models to examine the association of age, sex, race, Medicaid eligibility (proxy for low income), comorbidity, and hospital Medicare THR volume on the risk of revision. We aggregated individual risk factors into a risk score and examined the effects of high individual risk score and THR volume in a Cox model.

**Results:** At the time of primary THR, the cohort had mean age 74, 63% were female, and 53% were operated upon by surgeons who performed fewer than 12 THRs per year in the Medicare population. Over 12 year follow-up, 27,955 patients died and 4,185 underwent revision THR. Factors independently associated with risk of revision THR included younger patient age (65–75 versus >75; HR 1.47, 95% CI 1.37, 1.57), male sex (HR 1.23, 95% CI 1.16, 1.31) and low annual surgeon THR volume (<12 cases/year; HR 1.23, 95% CI 1.13, 1.34). After adjusting for these factors, comorbidity, race, Medicaid eligibility and hospital volume were not associated with revision risk. We designated patients with both individual risk factors (male, younger age) as high risk, and those with 0 or 1 of these factors as lower risk. In a Cox regression model, low surgeon volume and high individual risk contributed independently to revision risk (Figure). We found no evidence for an interaction between individual risk and surgeon volume.

**Conclusions:** These first national, population based estimates of the 12-year risk of revision following primary THR confirm the risk associated with younger age and male sex and demonstrate that low surgeon volume is associated with revision risk in both high- and low-risk patients. The analyses are limited by our inability to adjust for patient weight or activity level with claims data. As THR is performed in increasingly younger patients, these findings underscore the need for further research on the risk of revision in patients < 65 undergoing primary THR.

**Disclosure:** J. N. Katz: None; E. A. Wright: None; A. A. Nti: None; J. Wright: None; H. Malchau: None; J. A. Baron: None; E. Losina: None.

### ARHP Concurrent Abstract Sessions

**Keep Working with Arthritis**

**2138**

**Too Young? Arthritis Is “Main Cause” of Disability for Millions of Working-Age U.S. Adults.** Kristina Theis,1 Charles G. Helmick,2 Jennifer M. Hootman3 and Matthew Braull. 1CDC, Atlanta, GA, 2Centers for Disease Control, Kennesaw, GA, 3Centers for Disease Control and Prevention

**Background:** Arthritis is well-established as a cause of disability, particularly among older adults. However, much less is known about its impact on working-age (18–64 years) adults. Using the most recent Survey of
Income and Program Participation (SIPP) data, we describe the prevalence and specific impacts of disability due to arthritis/rheumatism among working-age US adults.

Methods: SIPP is a longitudinal panel survey fielded by the US Census Bureau representing the civilian, non-institutionalized US population. Panel members undergo in-person interviews at 4-month intervals for a period of 2.5–4 years. Data presented here are cross-sectional findings from a disability topic module (fielded June–September 2005) of the 2004 SIPP panel. The disability module was administered to panel adults to identify self-reported disability (difficulty with ≥1 specified functional activities, activities of daily living (ADL), instrumental activities of daily living (IADL), selected impairments, use of an assistive aid, or limitation in ability to work around the house or at a job or business) and ascertain its “main cause.” Analyses weighted to population controls and incorporating sampling weights produced estimates and 95% confidence intervals (95% CI) of disability prevalence overall and by specific disability subcomponents for working-age adults overall and by age group (18–44 or 45–64 years) and sex for respondents identifying arthritis as the main cause of their disability. Statistical comparisons by age group and sex were significant at the 95% confidence level.

Results: At least 3.6 million working-age adults report arthritis as the main cause of their disability. Of these, 22.4% (95% CI 19.7–25.1) receive federal work disability benefits, 21.0% (95% CI 18.2–23.8) use assistive aids (e.g., cane), 17.7% (95% CI 15.4–20.0) have difficulties with ADLs, 20.9% (95% CI 18.3–23.5) with IADLs, 40.5% (95% CI 37.4–43.6) and 37.8% (95% CI 34.7–40.9) are limited in their ability to work around the house or at a job or business, respectively, and 89.9% (95% CI 88.1–90.7) have difficulty with specified functional activities, e.g., walking 3 city blocks (51.1%), lifting/carrying 10 pounds (32.9%). In absolute numbers, ~1.4 million report limitation in their ability to work at a job, 808,000 receive federal work disability benefits, and 740,000 require the use of cane, crutches, or a walker. The absolute number and % having difficulties with selected specified activities are significantly higher in those 45–64 compared with 18–44 year olds; yet, 743,000 younger adults report that arthritis disables them. Women comprise ¾ of the 3.6 million and ¾ to ¾ of those in all specific disability subcomponents.

Conclusion: Respondents in vulnerable pre-retirement years (45–64) and women at all ages, bear a substantial portion of arthritis disability and may be well-served by increasing reach of evidence-based programs that address these impairments. Women comprise about ¾ of all working-age adults with arthritis and were significantly more likely to report arthritis disability.

Disclosure: K. Theis: None; C. G. Helmick: None; J. M. Hootman: None; M. Braut: None.


Background: The impact of arthritis on employment is well-documented in many countries; however, little is known about its extent in working-age (18–64 years) adults in Australia. The aim of this study is to estimate the prevalence of arthritis and explore its links with age, gender, and labor force attachment in working-age Australians.

Methods: Data were obtained from the Household, Income, and Labour Dynamics in Australia (HILDA), a nationally representative survey of community-dwelling adults, with data collected by in-person interview and supplemented by a self-complete questionnaire. Data presented here are cross-sectional findings from HILDA 2007, the most recent time period in which arthritis status was ascertained. Participants reported an arthritis diagnosis by identifying arthritis from a list of conditions following: “Have you ever been told by a doctor or nurse that you have any of the long-term health conditions listed below?” Analysis was restricted to those with known arthritis status. Respondents estimated arthritis prevalence and the links with age, gender, and labor force attachment (categorized as employed, unemployed (actively seeking employment), or not in the labor force (all other dispositions, including discouraged job seekers). Weighted point estimates and 95% confidence intervals [95% CI], accounting for the complex survey design, were calculated for working-age adults overall and by age group (18–44 or 45–64 years) and sex.

Results: Arthritis affects 14.9% [95% CI 13.8–15.9] of working-age adults in Australia (1.6 million people) and was significantly greater in women (17.5% [16.1–19.0]) compared with men (12.1% [10.8–13.3]). Overall, employment was statistically significantly lower in those with arthritis compared to those without arthritis (57.7% [53.8–61.5] vs. 80.2% [78.9–81.5]). The same pattern of statistically significantly lower employment for those with arthritis vs. no arthritis holds for men (59.8% [53.9–65.8] vs. 86.6% [85.3–88.2]), women (56.2% [51.6–60.8] vs. 73.5% [71.6–75.3]), and both age groups. But the arthritis vs. no arthritis employment gap was much narrower for younger adults (70.9% vs. 81.6%) than for those in the older age group (54.5% vs. 77.5%). More than twice the prevalence of working-age adults with arthritis were not in the labor force compared to those without arthritis (40.6% [36.7–44.5] vs. 17.0% [15.9–18.2]). Unemployment was low and not significantly different between working-age Australians with and without arthritis.

Conclusion: Arthritis is common among working-age Australians, affecting approximately 1 in 7 potential workers. Employment is substantially lower among those with arthritis compared to those without for men and women across age groups; however, the increase in employment gap between the older versus younger age group suggests that employment is a greater challenge for individuals in middle age. Also, despite lower arthritis prevalence overall, men with arthritis appear to be more affected than women by low employment participation. The application of policy and public health interventions in combination may be needed to reduce the impact of arthritis on employment.

Disclosure: K. A. Theis: None; L. Busija: None; R. Willie: None; G. Elsworth: None; R. H. Osborne: None.

Association of Depressive Symptoms and Helplessness with Socioeconomic Status in People with Knee Osteoarthritis. Legh F. Callahan1, Jack H. Shreffler4, Kathryn Remmes Martin2, Brittia Schoster3, Jordan Renner2 and Joanne M. Jordan1. 1Chapel Hill, NC, 2Univ of North Carolina, Chapel Hill, NC, 3University of North Carolina at Chapel Hill, Chapel Hill, NC, 4University of North Carolina, Chapel Hill

Purpose: Individual and community socioeconomic status (SES) variables have been demonstrated to be associated with psychosocial outcomes in self-report and other types of arthritis, but these associations have not been examined in knee osteoarthritis to date. The purpose of this study is to evaluate associations between educational attainment, occupational status, and community poverty rate with depressive symptoms and perceived helplessness in people with knee OA.

Methods: A cross-sectional analysis was performed using data from 3085 people in the first follow-up evaluation (2000–2003) of the Johnston County Osteoarthritis Project. Depressive symptoms were measured with the 20-item Center for Epidemiologic Studies Depression (CES-D) on a scale of 0–60. Perceived helplessness was measured with the 5-item Rheumatology Attitudes Index (RAI) on a scale of 1–5. Educational attainment was dichotomized as high (e.g., professional, managerial, technical, sales) versus low (labor, service, farm, manufacturing) based on U.S. Census 2000 categories for self-reported occupation. Community poverty was defined from the U.S. Census household poverty rate for the block group in which the participant resided. Poverty rate was dichotomized as less than high school (HS) diploma or at least a HS diploma. Occupational status was dichotomized as high (e.g. professional, managerial, technical, sales) versus low (labor, service, farm, manufacturing) based on U.S. Census 2000 categories for self-reported occupation. Community poverty was defined from the U.S. Census household poverty rate for the block group in which the participant resided. Poverty rate was dichotomized as less than high school (HS) diploma or at least a HS diploma. Separate analyses were performed for those people having knee radiographic OA (rOA), defined as KL grade =/>2 in one or both knees, and for those with symptomatic knee OA (sOA) defined as KL grade =/>2 and with symptoms (pain or stiffness) in the same knee. Regression analyses were used to relate CES-D and RAI outcomes to all SES variables while controlling for age, gender, race, and BMI.

Results: Of the sample, 750 people had rOA. The average age was 67 years (45–94), 36% were African American, 58% had BMI ≥ 30, and 64% were female. 37% of the population had less than HS diploma, and 60% were in non-managerial occupations. The average CES-D was 6.9 (8.1), and the average RAI was 2.55 (0.71). Of those with rOA, 488 also met the definition of SOA. For people with knee rOA, CES-D scores were significantly higher for those with low educational attainment (β=2.04, CI = [0.77, 3.3]) and, independently, low occupational status (β=1.58 [0.33, 2.8]). RAI scores were significantly associated only with educational attainment (β=0.31 [0.19, 0.43]). Important covariates for CES-D were age ≥ 65 (β=−4.8 [−6.5, −3.2]) and being female (β=3.3 [2.1, 4.4]). Important covariates for RAI are being female (β=0.16 [0.05, 0.27]) and having BMI≥30 (β=0.25 [0.14,
0.37]). For people with knee OA, results generally paralleled those for ROA, except that CES-D was not independently associated with occupational status. Community poverty was not significantly associated with CES-D or RA in bivariate or multivariable analyses.

**Conclusions:** Low educational attainment is associated with higher levels of depression and feelings of helplessness in people with knee OA. Low occupational status may also play an independent role.

**Disclosure:** L. F. Callahan: None; J. H. Shreffler: None; K. R. Martin: None; B. Schoster: None; J. Renner: None; J. M. Jordan: None.

## 2141

### The Effect of a 6 Week Walking Program on Work Activity Limitations in Adults with Arthritis.

**Purpose:** To evaluate the effect of a revised 6 week walking intervention program, Walk With Ease (WWE), on work limitations among people with self-report arthritis.

**Methods:** While conducting an evaluation of the Arthritis Foundation’s (AF) Walk With Ease (WWE) community based walking program, pretest-posttest physical evaluations and self-report surveys were administered to 462 individuals. Of these, 94 were employed and answered a series of questions regarding the Workplace Activity Limitation Scale (WALS). This 12-item scale gauges physical activity limitations in working adults with arthritis. Participants answered individual WALS items by marking 0 (no difficulty), 1 (some difficulty), 2 (a lot of difficulty), and 3 (unable to do). Individual item scores were then summed and averaged to yield an overall WALS score which ranged from 0 (good) to 3 (bad) for each participant. At the 1 year WWE follow-up, 67 participants were still employed and retook the WALS. Pre-post t-tests were conducted for each individual WALS item and the overall WALS to determine whether participants significantly improved work limitations. Post-1yr t-tests were also conducted to determine if any improvements were maintained at 1 year.

**Results:** Employed WWE participants were on average 56 years old, 88% female and 61% Caucasian. Mean Body Mass Index was 32 and 81% had more than a high school education. Overall, 59% of participants improved their WALS during the 6 week program. In pre-post comparisons, the overall WALS significantly improved from a mean of 0.57 (SD = 0.34) to a mean of 0.47 (SD = 0.36), p < 0.001. Individual WALS items with significant improvement were: “Lifting/Carrying objects” (0.96 (SD = 0.72) to 0.71 (SD = 0.78), p < 0.001), “standing for long periods of time” (0.85 (SD = 0.77) to 0.6 (SD = 0.73), p = 0.01), “moving concentration” (0.34 (SD = 0.50) to 0.19 (SD = 0.40), p < 0.01), as well as “using hands” and “reaching” (both p < 0.05). Improvements shown at 6 weeks were maintained at one year in both the overall WALS (0.45 (SD = 0.31) to 0.43 (SD = 0.33)) and the 5 individual WALS items listed above.

**Conclusion:** After a 6 week walking program, working adults with arthritis showed significant improvement in overall work limitations. Improvements were primarily in lifting/carrying, standing for long periods of time and maintaining concentration while at work. One year after the walking program, work limitations improved were maintained. Walking intervention programs, such as WWE, should be considered by employers to improve the health and productivity of employees in both the short and long term.

**Disclosure:** B. L. Charnock: None; K. R. Martin: None; J. Shreffler: None; M. Altpeter: None; L. F. Callahan: None.

## 2142

### The Effect of Structural Deformities on Typing Styles of Touch Typists with Rheumatoid Arthritis.

**Purpose:** Rheumatoid arthritis (RA) may lead to severe fixed structural deformities of the hand and wrist that may change postures/motions during touch typing. Understanding the mechanism of hand motions during touch typing may provide insight into how people with RA can use their computer safely. This cross-sectional study examined the effect of structural deformities on the postures/motions of the hand/wrist during touch typing. We hypothesized that touch typists with RA with structural deformities would have significantly different typing postures/motions and speeds than those without structural deformities.

**Method:** A total of 33 subjects with RA were recruited from the University of Pittsburgh Medical Center (UPMC). Subjects were adults with RA, aged from 18 to 65 years, who self-reported being touch typists. Subjects’ posture/motions during typing were videotaped and rated for visual structural deformities (VSD) by a certified hand therapist. Typing postures/motions were rated by two trained raters using the Keyboard-Personal Computer Style Instrument (K-PeCS). Typing speed was calculated in words per minute. Based on the presence of any VSD, subjects were divided into two groups: 22 subjects with VSD and 11 subjects without VSD. Chi Square statistics and independent t-test were used to compare the K-PeCS items and typing speed between the two groups.

**Results:** The subjects were primarily female (88%), a mean age of 56.3 ± 8.8, and white (91%). Touch typists with VSD showed more fixed hand/wrist motions than those without VSD (Figure 1). Significantly more subjects with VSD showed whole hand motions to activate the keys rather than individual finger motions (i.e., no ulna deviation, no MCP hyperextension, straight finger joints, and use of 2 or less fingers). Significantly fewer subjects with VSD also used a wrist support. There was no significant difference for typing speed between the subjects with VSD (25.9 ± 13.0 wpm) and without VSD (27.7 ± 11.4 wpm) (p = .70).

**Figure 1.** Significantly different postures/motions during touch typing (*p < .05*).

**Conclusion:** Structural deformities can affect the typing styles of touch typists with RA. To compensate for inflexible hand movements, touch typists with VSD showed alternative typing strategies, such as “hunt and peck” style: moving whole hands rather than individual joints, floating the wrists, using fewer fingers, and keeping their fingers straight rather than curved. However these strategies may exacerbate existing problems by putting additional stress on already affected joints. Further evaluation by age should be considered.

Possible suggestions to ensure proper working posture include ergonomic keyboard, movable wrist support, or redesign of computer workstation.

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**Disclosure:** N. A. Baker: None; N. P. Gustafson: None; H. Shin: None; J. C. Rogers: None.

## 2143

### Formation of Solutions for Rheumatic Condition-Related Work Barriers by Occupational and Physical Therapists (OTs/PTs).

**Purpose:** Identification of patients’ rheumatic condition work barriers along with generation of solutions for barriers can reduce work disability. We have been exploring whether this type of intervention could be effectively provided by OTs/PTs. In a previous study 10 OTs/PTs had difficulty generating solutions for patients’ work barriers. To address this finding we used literature and expert opinion to develop an informational booklet containing possible solutions for a wide variety of barriers. In this study, we examined solution generation quality in a large sample of OTs/PTs and tested the effect of providing the solution booklet on quality of solutions generated.

**Methods:** Subjects were recruited from OT/PT professional associations. We developed and pre-tested 3 patient cases. Case information included a patient’s 3 most bothersome barriers, and subjects were asked to provide ≥3 solution for these 3 barriers. OT and PT subjects were then randomized to either receive (experimental=EXPM) or not receive (control=CTRL) the solution booklet to use as a resource. Three reviewers, blinded on subjects’ EXPM/CTRL and OT/PT status, rated the helpfulness of the solutions generated by each subject using a 5-point ordinal scale. Proportions of EXPM
and CTRL subjects giving solutions rated as probably or very likely helpful were calculated. Wilcoxon rank tests were conducted to examine differences in the solution helpfulness scores between the two groups.

**Results:** 113 subjects provided data, 55 OTs (26 EXPM/29 CTRL) and 58 PTs (24 EXPM/34 CTRL). To date we have evaluated data from 2 cases. The quality of solutions generated by CTRL subjects was good for 2 physical activity type of work barriers, with ≥75% giving probably/very likely helpful solutions. The helpfulness scores of solutions from EXPM subjects for these 2 barriers were not significantly better. For a vocational policy barrier and 35% for a vocational direction barrier. However, the quality of solutions given by EXPM subjects for these barriers was good with 86%, 76% and 82% respectively giving helpful solutions (p<.001 for all).

<table>
<thead>
<tr>
<th>Work barrier</th>
<th>Proportion giving helpful solutions</th>
<th>Median (interquartile range) score</th>
<th>Median (interquartile range) score</th>
<th>Proportion giving helpful solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical job activity barrier: prolonged standing</td>
<td>75%†</td>
<td>3.0 (2–4†)</td>
<td>4.0 (3–4)</td>
<td>45%</td>
</tr>
<tr>
<td>Medium (interquartile range) score‡</td>
<td>3.5 (1–4)</td>
<td>3.5 (1–4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work/home life barrier: attending children’s recreational event</td>
<td>22%‡</td>
<td>2.0 (1–2)</td>
<td>2.0 (1–3)</td>
<td>45%†</td>
</tr>
<tr>
<td>Cognitive work barrier: concentrating on work activities</td>
<td>45%§</td>
<td>4.0 (1–3)</td>
<td></td>
<td></td>
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<tr>
<td>Proportion giving helpful solutions</td>
<td>45%†</td>
<td>4.0 (1–3)</td>
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<td>&lt;.0001†</td>
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<tr>
<td>Median (interquartile range) score‡</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Proportion giving helpful solutions</td>
<td>35%§</td>
<td>4.0 (1–3)</td>
<td></td>
<td>&lt;.0001§</td>
</tr>
<tr>
<td>Median (interquartile range) score‡</td>
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</tbody>
</table>

**Table.** Helpfulness of Solutions Formed by Subjects Who Did and Did Not Receive Information about Possible Solutions

**Conclusions:** OTs/PTs not receiving supplemental information about potential solutions had only a modest ability to form helpful solutions for work barriers not related to physical work activities. However, providing information on ideas for solutions greatly enhanced the quality of solutions for other types of work barriers.

**Disclosure:** S. H. Allaire: None; J. J. Keyser: None; N. A. Baker: None; J. Niu: None; M. P. LaValley: None.

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**2145**

**Exome Resequencing in a Densely Affected Multigenerational SLE Pedigree.**

**Wednesday, November 10, 2010, 4:30 PM-6:00 PM**

**Genetics, Genomics and Proteomics: SLE**

**ACR Concurrent Abstract Sessions**

**Discipline:** Genetics, Genomics and Proteomics: SLE

**Title:** Exome Resequencing in a Densely Affected Multigenerational SLE Pedigree

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**Abstract:**

Systemic lupus erythematosus (SLE) is a complex auto-immune disease that has heretofore been the subject of intense genetic scrutiny. While genome-wide association studies in SLE have successfully identified approximately 30 new risk loci the low odds ratios of associated loci leave a substantial portion of the estimated heritability of SLE unexplained. By comparison, the high odds ratios of highly penetrant rare polymorphisms (e.g. TREX1, OR=25) suggest the possibility that some of the missing heritability of SLE may exist in the form of rare variants.

**Methods:** To begin to explore the role of rare variants in SLE susceptibility we resequenced the exome in a unique, densely affected multigenerational SLE pedigree with 7 affected individuals. A densely affected pedigree was specifically chosen with the assumption that rare variations conferring higher SLE risk are more likely to be represented in the family as opposed to the general population. The entire exonic region for the individuals within this family were captured through the use of the Agilent SureSelect sequence capture system and sequenced to 15x coverage using an Illumina GAIIx second-generation sequencer. Assembly of sequence to reference, variant calling, and other analyses were carried out using the CLC Genomics Workbench bioinformatics suite. Variants were verified with Illumina Omni1 Quad genotyping assays. Identified variants were screened using effect on protein function as determined by the SIFT algorithm.

**Summary:** Over 1700 coding variations were identified as shared between all case subjects within the family with approximately 40% encoding a nonsynonymous amino acid change. Of these amino acid changes approximately 7% are predicted to be damaging to the encoded protein. We have identified several nonsynonymous changes in proteins previously associated with SLE including NOTCH1 and TNP1.

**Conclusions:** We have identified a number of potentially rare variants that appear to preferentially segregate with case samples within a densely affected SLE pedigree. These variants, in some cases, are predicted to cause a nonsynonymous amino acid change which will damage the affected protein. Several of these damaging variants are within genes which have been previously associated with SLE while others are within associated pathways. We believe the identification of these variants may assist in the identification of causal variants as well as shed some light on missing heritability within recent GWAS studies.

**Disclosure:**

- G. Wiley: None; C. P. Lin: None; I. Adrianto: None; J. A. Kelly: None; K. L. Moser: None; K. M. Kaufman: None; J. B. Harley: None; C. Gray-McGuire: None; P. M. Gaffney: None.

**2146**

**Large-Scale Mapping of Systemic Lupus Erythematosus (SLE) Variants across Different Ethnicities Reveals That the IRF5-TNPO3 Region Is the Strongest Common Risk Factor.**

**Wednesday, November 10, 2010, 4:30 PM-6:00 PM**

**GC Genomics and Proteomics: SLE**

**ACR Concurrent Abstract Sessions**

**Discipline:** Genetics, Genomics and Proteomics: SLE

**Title:** Large-Scale Mapping of Systemic Lupus Erythematosus (SLE) Variants across Different Ethnicities Reveals That the IRF5-TNPO3 Region Is the Strongest Common Risk Factor

**Authors:**

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**Abstract:**

Genome-wide association studies (GWAS) have been extremely successful at identifying important SLE risk factors. Nevertheless, in spite of being more prevalent in African Americans, Hispanics and Asians, the majority of GWAS have been performed in Caucasians. Recent GWAS in Asians have been reported, but there is still a paucity of large-scale data on the genetics of SLE in non-European populations. As such, the specific genetic variants predisposing to SLE and their overlap with European ancestry risk factors are largely unknown. This study is aimed at elucidating the patterns of disease association across different ethnicities. We conducted a transethnic study called Lupus Large Association Study 2 (LLAS2) consisting of 8436 SLE cases and 7554 controls (1508 cases and 1270 controls and Hispanic and Native American ancestries (1679 cases and 1934 controls), Asian (1272 cases and 1270 controls) as well as in loci not previously implicated in SLE including NOTCH1 and TNP1.

**Summary:** We have identified a number of potentially rare variants that appear to preferentially segregate with case samples within a densely affected SLE pedigree. These variants, in some cases, are predicted to cause a nonsynonymous amino acid change which will damage the affected protein. Several of these damaging variants are within genes which have been previously associated with SLE while others are within associated pathways. We believe the identification of these variants may assist in the identification of causal variants as well as shed some light on missing heritability within recent GWAS studies.

**Disclosure:**

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With novel variants in haplotypes that are associated with susceptibility to SLE. These preliminary results suggest that identification of novel, potentially functional variants, in SLE-associated risk haplotypes will significantly improve our understanding of the functional changes that mediate disease susceptibility and ultimately lead to identification of the precise causal variants.

Conclusion: We have initiated a large-scale, targeted resequencing resource (REVEAL) to identify and disseminate novel functional variants in 86 regions of SLE susceptibility. Production sequencing is currently underway with a goal of completing the study by the end of 2011. Public access to the REVEAL data will parallel policies similar to the ENCODE project.

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Identification of a Novel Systemic Lupus Erythematosus Susceptibility Locus at 11p13 near CD44 in a Multi-Ethnic Study.

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Background: SLE is a chronic, heterogeneous autoimmune disorder characterized by inflammation, loss of tolerance to self-antigens and disregulated interferon responses. In this study, we sought to replicate a putative association at 11p13 from a genome-wide association (GWA) study not yet exceeding the stringent threshold for genome-wide significance (typically P<5×10^-8).

Methods: Genotyping was performed using Illumina iSelect technology. Stringent quality control measures were applied for Hardy-Weinberg proportions, proportion of missing genotypes and missingness between cases and controls. After quality control filtering, 3562 SLE cases and 3491 controls of European ancestry, 1527 cases and 1811 controls of African-American (AA) descent and 1265 cases and 1260 controls of Asian origin were included in the replication analysis. Logistic regression was implemented using PLINK under dominant, recessive and additive genetic models. Covariates for gender and population admixture were included. Stouffer’s weighted Ztrend scores were calculated for a meta-analysis between the GWA and replication results.

Results: Our GWA scan identified two SNPs in strong linkage disequilibrium (LD, r^2=0.94) located ~74kb telomeric to CD44 showing suggestive evidence of association with SLE in cases of European descent (rs2732552, P=0.004, OR=0.78, 95%CI=0.69–0.9334; rs837619, P=0.003, OR=0.78, 95%CI=0.675–0.9141). We observed independent replication at both rs2732552 (P=0.93×10^-8, OR=0.83, 95%CI=0.77–0.88) and rs837619 (P=7.7×10^-7, OR=0.83, 95%CI=0.77–0.90) in the European samples with a Mhet=1.82×10^-9 for rs2732552. The AA and Asian SLE cases also

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Targeted Resequencing in Systemic Lupus Erythematosus Genetic Risk Loci: Initial Results from the REVEAL (Resequencing Variants Enhancing Autoimmunity and Lupus) Resource.

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Background: Genetic predisposition is a potent element in susceptibility to SLE. Previous studies by the International Consortium for Systemic Lupus Erythematosus (SLEGEN) and others have associated more than 20 genomic segments with SLE susceptibility. These studies have localized causative genes into small genomic segments, but have not identified the precise genetic variations responsible for the functional changes that cause SLE. To elucidate the genetic lesions that are causative for SLE susceptibility, we have initiated deep sequencing studies of all of the genomic segments exhibiting suggestive or significant associations with susceptibility to SLE.

Methods: DNA samples for sequencing were obtained from the Lupus Family Registry and Repository (LFLR) at the Oklahoma Medical Research Foundation. Samples were ranked based on their content of SLE associated SNP haplotypes at defined susceptibility alleles and samples with the highest content of SLE-associated SNP haplotypes were prioritized for sequencing. Isolation of 86 SLE associated genomic segments was performed using either solid-phase microarray capture ( Nimblegen) or solution-based capture (Agilent SureSelect) followed by sequencing on the Illumina GAIIx platform. Custom software scripts were used to de-convolute multiplexed samples, eliminate redundant reads and assess for overall sequence coverage. Polished reads were aligned to the human genome reference (hg18) and variants (SNPs and deletion/insertion polymorphisms (DIPs)) were called using CLC Genomics Workbench Software (v4.0).

Results: We have completed sequencing of more than 100 SLE cases. Of the over 40 gigabases of total sequence reads aligning to the human genome in this study, 60–80% mapped to the targeted regions, yielding 35–45-fold average coverage. A comparison of 50 SNP genotypes previously determined in 5 samples with these sequences revealed concordance > 0.95. Further analysis of data from the first 32 European-American samples has revealed more than 2000 novel SNPs or DIPs in 2.9 megabases derived from 25 genomic segments showing significant associations with SLE. Our ongoing analysis of the organization of these polymorphisms, utilizing phylogenetic algorithms to network the SNP haplotypes formed in strong linkage disequilibrium with SNPs associated with SLE, has delineated multiple allele lineages
demonstrated association at rs2732552 (P = 5 x 10^-3, OR = 0.81, 95% CI: 0.70–0.94 and P = 4.1 x 10^-4, OR = 0.80, 95% CI: 0.70–0.91, respectively). The Asian SLE cases were associated with rs387619 (P = 0.001, OR = 0.85 95% CI: 0.70–0.91), but not the AA SLE cases, consistent with differences in the haplotype patterns between racial groups. The meta-analysis at rs2732552 for all 4 ethnic groups produced Pmeta=3.00 x 10^-13.

Conclusion: We have established genetic association with SLE to a haplotype near CD44. Imputation and trans-ethnic mapping focus the effect on a ~14kb haplotype in a region of strong regulatory potential that may influence expression of the centromeric gene CD44. This locus contains multiple regulatory sites that could potentially affect expression and functions of CD44, a cell-surface glycoprotein influencing immunologic, inflammatory and oncologic phenotypes. Further functional studies of this complex locus will be required to determine the precise variant(s) influencing SLE risk and to characterize the contribution to disease.

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Peripheral Blood Expression Signatures Reflect Current Lupus Activity and Likelihood of Future Flare. Carolyn Meyer1, Jason W. Bauer2, Thearikh Koeuth, Joseph Wilson3, Michelle A. Petri4, Peter K. Gregersen4, Timothy W. Behrens2 and Emily C. Baechler4, 1Timonium, MD; 2Genentech Inc., South San Francisco, CA, 3The Feinstein Institute for Medical Research, Manhasset, Manhasset, NY, 4University of Minnesota Department of Medicine, Minneapolis, MN

Background: Clinical management of patients with systemic lupus erythematosus (SLE) is complicated by the lack of biomarkers for evaluation of current disease activity and prediction of future flares. Type I interferon (IFN)-regulated genes and proteins are promising biomarkers for disease activity in lupus. However, many other pathways are likely to influence clinical activity. Here we used comprehensive gene expression profiling in blood cells to identify molecular signatures associated with current lupus activity and risk for future flare.

Methods: Illumina WG-6 BeadChips were used to compare expression profiles in blood cells of active SLE (SLEDAI≥2, n=36) vs. inactive SLE (SLEDAI≤2 and physician’s global assessment=0, n=96). Genes with t-test p<0.01 and average difference ≥25 were identified as differentially expressed. Hierarchical clustering was used to identify 10 molecular signatures of activity. Three genes from each signature, plus 16 other genes of interest, were then measured by TaqMan low density arrays (LDA) in longitudinally collected blood samples from additional SLE patients (Phase I, 443 visits from 100 patients). A subset of 23 genes selected from the Phase I study were then measured in 2 additional groups (Phase II, 816 visits from 194 patients; Phase III, single visits from 379 patients). GAPDH was used as a housekeeping control in relative quantification. Wilcoxon’s rank sum test identified transcripts that changed in paired visits before and during flare (increase in SLEDAI of ≥3 points; n=62 patients), or before and during attenuation of activity (decrease in SLEDAI of ≥3 points; n=73 patients). Logistic regression analysis identified transcripts associated with future flare (≤1 year).

Results: Among the activity signatures were clusters of translation-related genes, genes encoding MHC proteins, erythrocyte-related genes, granulocyte-related genes, and interferon (IFN)-regulated genes. Of the 23 genes selected for further study, 13 transcripts were differentially expressed between active and inactive SLE in both Caucasians (56% of subjects) and non-Caucasians (44%). However, 7 transcripts were markers for activity only in Caucasians, and 3 transcripts were significant only in non-Caucasians. In total, 28 individual analyses, 3 genes showed significant changes in expression from pre-flare to flare (CD93, ICAM3, and CXCR3), while HINT1 changed significantly with attenuation of activity. In Phase II, multivariate regression analysis of baseline transcript levels in 139 patients with a year of clinical follow-up (41 patients with flare, 98 with no flare), 3 transcripts showed significant ability to predict future flare: PECAM1 (p=0.0008), MX1 (p=0.01), and GPR183 (0.03 (model p=0.001)). We then tested the same genes in the Phase III validation samples. While GPR183 was not a significant predictor of flare in the Phase III data, both MX1 (p=0.001) and PECAM1 (p=0.07) were significant (model p=0.0008).

Conclusions: These results suggest that gene expression profiles in peripheral blood reflect changes in lupus disease activity and may have utility in predicting future lupus flares.

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The NALP3 Inflammasome Is Activated by Sodium Overload and Water Influx in Gouty Arthritis

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Background: One of the endogenous danger molecules of dying cells generated during apoptosis is monosodium urate (MSU). Precipitated MSU crystals in tissues and joints induce an inflammatory process with IL-1β induction after NALP3 inflammasome activation resulting in gouty arthritis. However, the exact mechanism of NALP3 activation is still elusive.

Purpose: Identification of the mechanism of NALP3 inflammasome dependent IL-1β production induced by MSU crystals.

Methods: The uptake of MSU was analysed by time lapse microscopy and cytofluorimetry. The plasma membrane integrity after ingestion of MSU was investigated by propidium iodide staining. Via REM-EDX the morphological and chemical structure of urate crystals was identified. The relative intracellular sodium concentration was analysed by Sodium Green fluorescence. The human IL-1β induction in presence of inhibitors of lysosomal acidification and of aquaporins in culture supernatants was quantified by simplex bead technology. Additionally, in an in vivo mouse experiment animals were treated i.p. with chloroquine following injection of MSU in generated ankle pouches. The IL-1β production in the pouch fluid was quantified by ELISA.

Results: Blood borne phagocytes ingest MSU crystals and substantially increase their side scatter (SSc) reflecting increased “granularity”. After the uptake of the crystals the cells swell shown by augmented forward scatter (FSc) and time lapse microscopy. Most of the phagocytes show an intact plasma membrane after ingestion of crystals. The treatment of phagocytes with MSU results in an induction of IL-1β production. Needle-shaped MSU crystals release sodium after treatment with acidic milieu and switch into barrel-shaped crystals. In swollen cells the intracellular sodium concentration of phagocytes after the uptake of MSU displays a markedly increased intracellular sodium concentration. Furthermore, the inhibition of lysosomal acidification and of aquaporins results in reduction of IL-1β production in in vitro and in vivo.

Conclusion(s): We suggest a novel model of NALP3 inflammasome activation after phagocytosis of MSU crystals: the phagocytes ingest crystals into endosomes resulting in fusion with acidic lysosomes. That induces a massive release of sodium from the MSU crystal and enhances the intracellular osmolarity. The hyperosmolarity of the cell is compensated by passive water influx through aquaporins following cell swelling. The latter reduces the intracellular potassium concentration below the threshold of NALP3 inflammasome activation. Finally, the decreased IL-1β production by treatment with inhibitors of lysosomal acidification or inhibitors of aquaporins supports our new model of inflammasome activation by MSU.

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Octacalcium Phosphate (OCP) Crystals Induce Synovial Inflammation and Cartilage Degradation

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Introduction: The presence of intra-articular basic calcium phosphate (BCP) crystals, including OCP, carbonated-apatite, hydroxyapatite and tricalcium phosphate crystals, is associated with severe osteoarthritides and destructive arthropathies such as Milwaukee shoulder. Although BCP crystals displayed, in vitro, mitogenic, anabolic and catabolic responses, their intra-articular effect was never assessed.

Objective: To determine the effects of OCP crystals in joints in vivo.

Methods: OCP crystals (200 µg in 20 µl PBS) were injected into the right knee joint (the contra-lateral knee joint injected with 20 µl of PBS serving as a control) of wild-type mice treated or not by the IL1R antagonist Anakinra or mice deficient for the inflammasome proteins ASC and NALP3. 4 days and 17 days after crystal injection, mice were sacrificed and knee joints dissected. Histological scoring for synovial inflammation and cartilage macrophages, neutrophils and T cells were performed. Technetium (Tc) uptake was measured at 6h, 1 and 4 days after OCP injection. Cartilage degradation was evaluated by Safranin O staining and VDIPEN immunohistochemistry.

Results: The intra-articular localisation of injected OCP crystals was evidenced by Von Kossa staining.

Conclusion: These data indicate in vivo that the intra-articular presence of OCP crystals is associated with cartilage destruction along with synovial inflammation. This is an interesting and new model of destructive arthropathy related to BCP crystals which will allow to assess new therapies in this disease.

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Quantitative Documentation of Tophus Volume Change Using Dual Energy Computed Tomography Scans

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Objective: Dual Energy Computed Tomography (DECT) scans provide obvious color displays for urate deposits and allow quantitative volumetric measurement of urate deposits in the articular and extra-articular structures. This report describes our recent experience on the potential utility of DECT scans to document changes in tophus volume in patients with tophaceous gout receiving urate lowering therapy.

Methods: This study included 12 consecutive patients with tophaceous gout who received urate-lowering therapy agents at our rheumatology clinic and underwent initial and follow-up DECT scans on at least one of the following four peripheral articular regions - elbows, wrists/hands, knees, and ankles/feet. The average interval between the two scans was 19 months (range, 11 – 29 months). Using a computer automated procedure to measure the apparent color-coded information of the urate deposits on DECT scans, we measured volumes of uric acid deposition in cm³ in initial and follow-up scans. The Wilcoxon rank-sum test was used to compare changes in tophus volume.

Results: All 12 patients (mean age, 67 yrs) with tophaceous gout who received urate-lowering therapy agents at our rheumatology clinic and underwent initial and follow-up DECT scans on at least one of the following four peripheral articular regions - elbows, wrists/hands, knees, and ankles/feet. The average interval between the two scans was 19 months (range, 11 – 29 months). Using a computer automated procedure to measure the apparent color-coded information of the urate deposits on DECT scans, we measured volumes of uric acid deposition in cm³ in initial and follow-up scans. The Wilcoxon rank-sum test was used to compare changes in tophus volume.
0.002) (See Table and Figure below). Total volumes from 10 patients reduced from 282.1 cm³ to 107.35 cm³ (67% reduction). Improvement of individual tophus volume in these 10 regions ranged from 41% to 83% (all p-values <0.05). In contrast, the two non-responders showed 36% increase in total tophus volume (total volumes from 157.74 cm³ to 246.19 cm³) with similarly increasing volumes in individual articular regions (range, 31% to 38% increase).

Table. Changes in DECT Urate Volume after Urate-Lowering Therapies among Ten Responders*

<table>
<thead>
<tr>
<th>Region of Tophus Deposition</th>
<th>No</th>
<th>Age/Sex</th>
<th>Hands &amp; Wrists</th>
<th>Elbows</th>
<th>Knuckles</th>
<th>Feet &amp; Ankles</th>
<th>Total Volume (Reduction %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Scan Follow-Up Scan</td>
<td>1</td>
<td>63/M</td>
<td>2.70 → 0.62</td>
<td>0.00 → 0.01</td>
<td>13.37 → 29.31</td>
<td>5.48 → 20.00</td>
<td>39.61 → 62.12 (68%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>81/M</td>
<td>2.45 → 0.33</td>
<td>0.41 → 0.41</td>
<td>8.41 → 0.72</td>
<td>12.67 → 0.93</td>
<td>20.97 → 39.09 (65%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>64/M</td>
<td>0.67 → 0.11</td>
<td>0.22 → 0.21</td>
<td>6.33 → 0.37</td>
<td>0.42 → 0.00</td>
<td>4.61 → 0.67 (66%)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>72/M</td>
<td>0.57 → 0.24</td>
<td>0.27 → 0.23</td>
<td>4.00 → 0.00</td>
<td>20.61 → 0.34 (96%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>75/M</td>
<td>36.37 → 6.25</td>
<td>18.58 → 10.37</td>
<td>57.56 → 5.29</td>
<td>10.86 → 14.14</td>
<td>31.35 → 12.05 (77%)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>67/M</td>
<td>1.75 → 0.37</td>
<td>0.27 → 0.11</td>
<td>0.36 → 0.19</td>
<td>NA</td>
<td>8.35 → 0.32 (37%)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>72/M</td>
<td>1.51 → 0.22</td>
<td>0.24 → 0.34</td>
<td>6.91 → 0.03</td>
<td>9.35 → 4.37 (57%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>84/M</td>
<td>0.02 → 0.00</td>
<td>0.06 → 0.07</td>
<td>NA</td>
<td>NA</td>
<td>0.60 → 0.38 (60%)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>64/M</td>
<td>NA</td>
<td>NA</td>
<td>0.32 → 0.35</td>
<td>NA</td>
<td>9.92 → 0.32 (62%)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>56/M</td>
<td>NA</td>
<td>NA</td>
<td>17.95 → 20.56</td>
<td>0.85 → 0.31</td>
<td>19.95 → 21.16 (66%)</td>
</tr>
<tr>
<td>Total</td>
<td>48.64 → 28.59</td>
<td>29.37 → 12</td>
<td>10.46 → 48.75</td>
<td>12.64 → 28.785</td>
<td>32.93 → 107.35 (67%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-values 0.008 0.03 0.002 0.03 0.002

Figure. A. The initial 30-DECT scan image of patient #4 (see Table) showing extensive urate deposits at the first metacarpophalangeal joint. B. The follow-up scan showing reduced MSU deposits after urate-lowering therapy (Arrows denote tophi that appear in red in color display and appear in gray in black/white display).

Conclusion: This study provides a proof of concept for the ability of DECT scan as a potentially sensitive, quantitative imaging tool in assessing tophus volume changes in patients with tophaceous gout. These data provide support for further prospective studies to examine the utility of DECT as a reliable imaging tool in following the response to urate-lowering therapy, through measurement of individual tophus volumes and total tophus burden in clinical care and trials.

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2153 Lead and Gout—Going, Going . . . Not Gone! Eswar Krishnan1, Bharathi Lingala1, James F. Fries1 and Vivek Bhalia1. 1Stanford Univ Medical Ctr, Palo Alto, CA, 2Stanford University, Palo Alto, CA, 3Stanford University

Background: Satellite gout, which characteristically follows the onset of chronic kidney disease and hyperuricemia is associated with whole blood lead levels >80 microgram (mcg)/dL, and has become rare over time. A whole blood lead level (BLL) ≤25 mcg/dL in adults or ≤10 mcg/dL for children has been considered “not elevated” by several authorities including the Centers for Disease Control. However, it is not known whether such “non-elevated” BLL can still cause hyperuricemia and gout.

Methods: We analyzed data BLL from the NHANES 2005–2007, a series of nationally representative surveys of the US population. We correlated BLL with serum uric acid (SUA) concentration and gout using appropriate sampling weights (SURVEYREG; SAS®). Participants with renal dysfunction were excluded. Geometric means were used to assess BLL due to skewed distribution. Gout was defined as self-reported physician diagnosis and/or use of gout medications (allopurinol and colchicine). Hyperuricemia was defined as SUA ≥7.0 mg/dL for men and ≥6.0 mg/dL for women.

Results: Prevalence of gout was 8-fold higher in the highest quartile of blood lead level compared to the lowest. The mean concentration of SUA was 5-fold higher with the highest quartile of lead (3.06 vs 0.57 mcg/dL p<0.001). After adjusting for the effects of age, gender, BMI, and ethnicity (variables that emerged statistically significant in bivariate regressions), the highest quartile of lead was associated with a ~2 fold increase in risk for hyperuricemia and gout.

Conclusions: In the era of decreased overt lead intoxication, “non-elevated” BLL remains a significant risk factor for hyperuricemia and gout. Further studies are needed to determine the utility of BLL for evaluating gout in clinical settings.

Table 1.

<table>
<thead>
<tr>
<th>Blood Lead Level (mcg/dL)</th>
<th>Range</th>
<th>Geometric Mean (mcg/dL)</th>
<th>Mean Serum Uric Acid Concentration (mg/dL)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.079</td>
<td></td>
<td>0.07 (0.05–0.08)</td>
<td>4.89 (4.03–4.95)</td>
<td>1.01 (1.01)</td>
</tr>
<tr>
<td>&lt;0.126</td>
<td></td>
<td>1.01 (0.99–1.03)</td>
<td>1.27 (1.20–1.34)</td>
<td>1.59 (1.58–1.60)</td>
</tr>
<tr>
<td>&lt;0.203</td>
<td></td>
<td>1.59 (1.58–1.60)</td>
<td>5.28 (5.22–5.33)</td>
<td>1.01 (1.01)</td>
</tr>
<tr>
<td>&lt;0.203</td>
<td></td>
<td>5.55 (5.48–5.62)</td>
<td>10.37 (10.36–10.38)</td>
<td>1.59 (1.58–1.60)</td>
</tr>
<tr>
<td>&lt;0.416</td>
<td></td>
<td>5.77 (5.70–5.85)</td>
<td>14.14 (14.13–14.15)</td>
<td>2.04 (2.03–2.05)</td>
</tr>
</tbody>
</table>

Disclosure: E. Krishnan: Ardea, 2, Savient Pharmaceuticals, 1, Takeda Pharmaceuticals North America, 5, B. Lingala: None; J. F. Fries: None; V. Bhalia: None.

2154 Increasing Gout Prevalence in the US over the Last Two Decades: The National Health and Nutrition Examination Survey (NHANES), Yanyan Zhu1, Bhavik Pandya2 and Hyon Choi1. 1Boston University of School of Medicine, Boston, MA, 2Takeda Pharmaceuticals International, Inc, Deerfield, IL

Objective: The prevalence of gout in the US more than doubled between the 1960s and 1990s, but it is unknown whether the increasing trend continued over the past 2 decades. To address this issue, we compared the prevalence of gout between National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES 2007–2008. We also compared the prevalence of hyperuricemia and mean serum urate (sUA) levels between the same time periods.

Methods: Using data from 5,707 participants (2,797 men and 2,910 women) aged 20 years and older in NHANES 2007–2008, we estimated overall, gender-specific, and age-specific prevalence of gout and compared it with data from 18,825 participants (8,816 men and 10,009 women) aged 20 years and older in NHANES III (1988–1994). Using the same data, we compared sUA levels between NHANES III and NHANES 2007–2008. The NHANES definition of hyperuricemia was sUA level >7.0 mg/dL in men and >5.7 mg/dL in women. During the NHANES survey, all participants were asked about a history of health-professional–diagnosed gout.

Results: The overall prevalence of gout among US adults was 3.9% (8.3 million adults) in 2007–2008 (Table). This gout prevalence was significantly higher than that in NHANES III (2.7%), with a difference of 1.2% (95% confidence interval [CI], 0.6 to 1.9). The difference was primarily due to increased prevalence among men and the elderly. Correspondingly, the
prevalence of hyperuricemia in 2007–2008 (21.4%) was significantly higher than that in NHANES III (18.2%), with a difference of 3.2% (95% CI, 1.2% to 5.2%). The mean sUA level significantly increased over the same time period (difference 0.15 mg/dl; 95% CI, 0.07 to 0.24 mg/dl).

Table. Overall, Gender-Specific, and Age-Specific Prevalence of Gout, NHANES III and 2007–2008

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall*</td>
<td>3.9 (3.3 to 4.4)</td>
<td>2.7 (2.3 to 3.0)</td>
<td>1.2 (0.6 to 1.9)**</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5.9 (4.7 to 7.1)</td>
<td>3.8 (3.2 to 4.4)</td>
<td>2.1 (0.8 to 3.4)**</td>
</tr>
<tr>
<td>Female</td>
<td>2.0 (1.5 to 2.5)</td>
<td>1.6 (1.3 to 2.0)</td>
<td>0.4 (−0.2 to 0.9)</td>
</tr>
<tr>
<td>Age Category (Yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–39</td>
<td>0.8 (0.4 to 1.3)</td>
<td>0.7 (0.3 to 1.2)</td>
<td>0.1 (−0.5 to 0.7)</td>
</tr>
<tr>
<td>40–59</td>
<td>3.5 (2.5 to 4.5)</td>
<td>2.6 (1.9 to 3.2)</td>
<td>0.9 (−0.2 to 2.1)</td>
</tr>
<tr>
<td>60–79</td>
<td>8.5 (6.4 to 10.6)</td>
<td>6.8 (5.8 to 7.9)</td>
<td>1.7 (−0.7 to 4.0)</td>
</tr>
<tr>
<td>80+</td>
<td>12.6 (10.1 to 15.1)</td>
<td>5.9 (4.7 to 7.2)</td>
<td>6.7 (3.9 to 9.4)**</td>
</tr>
</tbody>
</table>

*Adults aged 20 years and above. **p < 0.05; bold face indicates significance.

Conclusions: These findings from 2 separate nationally representative samples of US adults suggest that the prevalence of gout remains substantial and may have increased over the last 2 decades, particularly among men and the elderly. Correspondingly, the prevalence of hyperuricemia increased during the same period.


2155

Independent Impact of Hyperuricemia on the Future Risk of Hypertension: A Systematic Review and Meta-Analysis. Peter C. Grayson1,2, Seo Young Kim1,3, Michael P. LaValley2, and Hyon K. Choi3,4. 1Boston University School of Public Health, Boston, MA, 2Boston University School of Medicine, 3Boston University School of Public Health, Boston, MA, 4Brigham & Women’s Hospital, Boston, MA, 5Univ of British Columbia, Vancouver, BC, Canada

Purpose: A novel rodent model and a recent randomized trial of hyperuricemic adolescents with hypertension suggest a pathogenetic role of uric acid in hypertension, but it remains unknown whether these findings apply to adult populations where the larger disease burden exists. We conducted a systematic review and meta-analysis to determine if hyperuricemia was associated with incident hypertension, particularly in demographic subgroups.

Methods: We searched major electronic databases using Medical Subject Headings and keywords without language restrictions (through April 2010). Studies with data on incident hypertension related to serum uric acid levels were eligible for inclusion. We only included (1) prospective cohort studies without age restrictions; (2) at least 1 year of follow-up; (3) sample sizes of at least 100 subjects; and (4) inception cohorts free of hypertension. Hyperuricemia was eligible for inclusion. We only included (1) prospective cohort studies without age restrictions; (2) at least 1 year of follow-up; (3) sample sizes of at least 100 subjects; and (4) inception cohorts free of hypertension. Hyperuricemia was associated with an increased risk of incident hypertension, independent of traditional hypertension risk factors. Risk for future hypertension appears more pronounced in hyperuricemic younger individuals and women and appears diminished in US-based studies and studies conducted more recently.

Disclosure: P. C. Grayson: None; S. Y. Kim: None; M. P. LaValley: None; H. K. Choi: None.

Results: A total of 18 prospective cohort studies representing data from 55,607 participants and 13,025 incident hypertension cases were included. Hyperuricemia was associated with an increased risk of incident hypertension (unadjusted risk ratio (RR) 1.81, 95% confidence interval (CI): 1.55–2.07). When using adjusted values, the pooled RR was 1.41 (95% CI: 1.23–1.58) and there was high heterogeneity among included studies (21.75, p < 0.01).

For a 1 mg/dl increase in uric acid level, the pooled adjusted RR for incident hypertension was 1.13 (95% CI, 1.06–1.20). These RRs were significantly larger in younger study populations (p < 0.02) and tended to be larger in women (p = 0.06). Two studies suggested that the RR may also be larger among black individuals. Furthermore, later publication year and US-based studies were significantly associated with lower RR estimates (p-values < 0.02).

Conclusion: Hyperuricemia is associated with an increased risk for incident hypertension, independent of traditional hypertension risk factors. Risk for future hypertension appears more pronounced in hyperuricemic younger individuals and women and appears diminished in US-based studies and studies conducted more recently.

Disclosure: P. C. Grayson: None; S. Y. Kim: None; M. P. LaValley: None; H. K. Choi: None.

ACR Concurrent Abstract Sessions

Osteoporosis and Metabolic Bone Disease: Clinical Aspects and Pathogenesis

Wednesday, November 10, 2010, 4:30 pm–6:00 pm

2156

Effectiveness of Zoledronic Acid in the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis in Men and Premenopausal Women. K. Saag1, C. Roux2, J.-P. Devogelaer3, C.-S. Lau4, J.-Y. Reginster5, C. Bucci-Rechtweg6, G. Su7, P. N. Sambrook8 and D. M. Reid9. 1Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2Paris-Descartes University, Paris, France, 3Universite Catholique de Louvain, Brussels, Belgium, 4University of Aberdeen, Aberdeen, UK, 5University of Alabama at Birmingham, Birmingham, AL, 6University of Dundee, Dundee, UK, 7University of Liege, Liege, Belgium, 8University of Sydney, Sydney, NSW, Australia

Background: Bisphosphonates are effective in increasing bone mineral density (BMD) and reducing vertebral fracture risk in patients beginning or continuing glucocorticoid (GC) treatment. However, there are limited data available on the effect of bisphosphonates in men and premenopausal women receiving GC therapy. We studied 265 men, (mean age 56.4 years, mean femoral neck BMD T-score −0.8) and 195 premenopausal women (mean age 38.1 years, mean femoral neck BMD T-score −0.7) among patients enrolled in two arms of a double-blind, double dummy, 1-year study comparing the effects of zoledronic acid (ZOL) vs. risedronate (RIS) in patients either commencing GC treatment at a dose of at least 7.5 mg/day of prednisone or equivalent (prevention arm) or continuing long-term treatment of GC at that dose (treatment arm).

Methods: Patients received either ZOL 5 mg infusion at study entry or RIS 5 mg daily, along with calcium and vitamin D supplementation (1000 mg and 400–1200 IU, respectively). The primary endpoint was difference in BMD at the lumbar spine at 12 months. Secondary endpoints included changes in BMD at other sites (total hip and femoral neck), changes in bone turnover markers (BTM) (β-C-terminal telopeptides of type I collagen [β-CtX] and procollagen type I amino terminal propeptide [PINP]), and overall safety.

Results: The percentage change in BMD is listed in Table.
In the treatment subgroup, ZOL demonstrated a significantly greater reduction in serum β-CTX and PINP relative to RIS at all time-points for men and premenopausal women. In the prevention subgroup, ZOL demonstrated a significantly greater reduction in β-CTX at all time-points for men and premenopausal women, and in PINP at Month 3 (p = 0.0279) for men and at Month 3 (p = 0.0207) and Month 12 (p = 0.0160) for premenopausal women. Both treatments were well tolerated in men and premenopausal women, albeit with a higher incidence of influenza-like illness and pyrexia events post-infusion with ZOL.

Conclusion: In men receiving GC therapy, once-yearly ZOL infusion preserves or increases lumbar spine and total hip BMD within 1 year to a greater extent than daily oral RIS and shows a similar trend for femoral neck BMD compared with RIS in both treatment and prevention arms. In premenopausal women receiving GC therapy, once yearly ZOL or daily oral RIS preserves or increases BMD within 1 year with a significant increase in total hip BMD for ZOL compared with RIS in both treatment and prevention arms.

Table. Between-treatment comparison of percentage change from baseline in bone mineral density (BMD) for men and premenopausal women at 12 months (modified ITT population)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Zoledronic (n = 28)</th>
<th>Risedronate (n = 29)</th>
<th>p-value</th>
<th>Zoledronic (n = 28)</th>
<th>Risedronate (n = 29)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine BMD</td>
<td>2.46 (0.04)</td>
<td>-0.24 (0.00)</td>
<td><strong>0.0024</strong></td>
<td>2.46 (0.04)</td>
<td>-0.24 (0.00)</td>
<td><strong>0.0023</strong></td>
</tr>
<tr>
<td>Total Hip BMD</td>
<td>1.10 (0.84)</td>
<td>0.39 (0.66)</td>
<td>0.14</td>
<td>1.10 (0.84)</td>
<td>0.39 (0.66)</td>
<td>0.14</td>
</tr>
<tr>
<td>Femoral neck BMD</td>
<td>1.37 (0.78)</td>
<td>0.39 (0.66)</td>
<td><strong>0.0230</strong></td>
<td>1.37 (0.78)</td>
<td>0.39 (0.66)</td>
<td><strong>0.0232</strong></td>
</tr>
</tbody>
</table>

Background: FREEDOM was the pivotal 3-year Phase 3 study to establish the efficacy and safety of denosumab for the treatment of osteoporosis in postmenopausal women. The open-label extension of FREEDOM will evaluate the long-term (up to 10 years) efficacy and safety of denosumab. We report here first year results of this extension study, representing up to 48 continuous months of denosumab exposure.

Methods: Subjects enrolled in the extension study previously completed the FREEDOM trial. All subjects received subcutaneous denosumab (60 mg) injection every 6 months during the extension study and continued to take daily calcium (1 g) and vitamin D (≥ 400 IU) supplements. For those randomized to the denosumab arm in FREEDOM (long-term group), the data reported here reflect a total of up to 8 injections of denosumab. For those previously assigned to placebo (de novo group), the data are from exposure of up to 2 doses of denosumab for 12 months. Changes in bone mineral density (BMD) and bone turnover markers (BTM) over 12 and 48 months are reported for subjects enrolled in the extension. No formal statistical testing was planned for this interim report. P-values are descriptive.

Results: A total of 4550 (70.2%) subjects from FREEDOM were enrolled in the extension study: 2343 in the long-term and 2207 in the de novo group. The long-term group had a further 2.0% and 0.8% increase in lumbar spine and total hip BMD, respectively, during the 4th year of denosumab administration (P < 0.0001 compared to baseline BMD of the extension study; see Figure). The total increase over the 48 months treatment with denosumab in lumbar spine and total hip BMD was 12.1% and a 6.5%, respectively. The de novo group had a 6.0% and 1.7% increase in lumbar spine and total hip BMD, respectively, during their 1st year of treatment with denosumab in the extension study (P < 0.0001 compared to baseline BMD). The serum C-telopeptide (CTX) reduction profiles after denosumab initiation, and the increase in CTX levels at the end of the dosing period, were similar for the long-term and de novo groups. Adverse events (AEs) were reported by 70.4% and 67.9% of subjects in the long-term and de novo groups, respectively. Serious AEs were reported by 9.8% and 11.2% of subjects in the long-term and de novo group, respectively.

Conclusion: These results suggest that treating postmenopausal women with osteoporosis with denosumab for 48 months continues to significantly reduce bone resorption and further increase BMD. Long-term treatment decreases BTM with a similar pattern and to a similar degree as observed in the first year of treatment.

Disclosures: R. Chau布尔at: Amgen Inc., 5, Merck Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 2, 5, sanofi-aventis, 5, Pfizer Inc, 2, 5, 9, Sharpe & Dohme, Servier, and Roux; C. S903

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Percentage Change in BMD With Denosumab Treatment for 4 Years (Long-term) or 1 Year (De Novo)

Conclusions: These results suggest that treating postmenopausal women with osteoporosis with denosumab for 48 months continues to significantly reduce bone resorption and further increase BMD. Long-term treatment decreases BTM with a similar pattern and to a similar degree as observed in the first year of treatment.
IL-3 Inhibits Osteoclast Differentiation by Inducing of ID Expression.

Chang Hoon Lee1, Myeung Su Lee2, Yun Kyung Hong2, Jin-jeong Choi1, Min-Ho Whang1, Han-Bok Kwak1 and Jae Min Oh2. 1Anatomy, Wonkwang University, Iksan, Korea, Republic of; 2Rheumatology, Cha University Hospital, Sungnam, Korea; 3Rheumatology, Chonbuk University Hospital, 4Rheumatology, Presbyterian Medical Center, Chonju, 5Rheumatology, Wonkwang University Hospital, Iksan, Jeollabukdo, Republic of Korea, 6Rheumatology, Wonkwang University Hospital

Purpose: Interleukin-3 (IL-3) is produced in various pathological conditions and is thought to induce diseases, but it is unclear about its function under normal conditions and disease conditions associated with bone homeostasis. Here we examined the effect of IL-3 on osteoclast differentiation from mouse and human bone marrow macrophages (BMMs).

Methods: Human bone marrow cells were obtained from iliac crest marrow aspirates from healthy donors and multiple myeloma patients. BMMs were used as precursors for RANKL-induced osteoclast differentiation. RT-PCR and Western blotting were used to detect mRNA and protein expression.

Results: Although IL-3 can induce osteoclast differentiation from multiple myeloma bone marrow cells, IL-3 greatly inhibited osteoclast differentiation of mouse BMMs and human BMMs obtained from healthy donors. These effects of IL-3 were determined by treating at early time points (days 0 and 1). IL-3 inhibited the expression of c-Fos and NFATc1, the master expression of mouse BMMs and human BMMs obtained from healthy donors. These effects of IL-3 were determined by treating at early time points (days 0 and 1). IL-3 inhibited the expression of c-Fos and NFATc1, the master expression of IL-3-mediated inhibition of osteoclast differentiation was partially reversed by exogenous expression of c-Fos and NFATc1. Importantly, IL-3-induced inhibitor of DNA binding/differentiation (Id) 1, Id2, and Id3 expression and Id2 was sustained during course of osteoclast differentiation. Ectopic expression of NFATc1 in Id2-deficient BMMs completely reversed the negative effect of IL-3 on osteoclast differentiation.

Conclusion: We provide evidence that IL-3 inhibited osteoclast differentiation of hBMMs and mBMMs partly by inhibiting c-Fos and NFATc1 expression. Also, IL-3 can induce Ids expressions, which are involved in the inhibitory effect exerted by IL-3.

Disclosure: C. H. Lee: None; M. S. Lee: None; Y. K. Hong: None; J.-J. Choi: None; M.-H. Whang: None; H.-B. Kwak: None; J. M. Oh: None.

Raloxifene for Prevention of Glucocorticoid-Induced Bone Loss: A 12-Month Randomized Double-Placebo-Controlled Trial.

Chi Chiu Mok, Chi Hung To, Ling Yin Ho, Ka Lung Yu and Kwok Man Ma. Tuen Mun Hospital, Hong Kong, China.

Objectives: To study the efficacy of raloxifene in preventing bone loss in women receiving long-term glucocorticoids.

Methods: Postmenopausal women receiving glucocorticoids were randomized in a double-blind manner to receive either raloxifene (60mg/day) or placebo (one tablet/day) on top of calcium (1000mg/day) and calcitriol (0.25ug/day). Bone mineral density (BMD) and bone turnover markers (urine DPD/Cr, serum osteocalcin, P1NP and CTX) were assessed at baseline, month 6 and 12. New radiological fracture of the spine was assessed at month 12. The mean duration of menopause was 8.5 ± 2.5 years.

Results: 114 patients were recruited (age 53 ± 7.7 years; 29% patients naive to calcium and 75% patients naive to calcitriol). The underlying medical diseases were: SLE(51%), rheumatoid arthritis(33%), inflammatory myopathies(4%) and systemic vasculitides(4%). The duration and dose of prednisolone received by the participants was 62.2 ± 64 months and 6.7 ± 5.9mg/day, respectively. The mean duration of menopause was 8.5 ± 7.7 years and the body mass index (BMI) was 23.7 ± 3.5kg/m2. Pre-existing vertebral fracture was present in 65% (5) and adverse events (skin rash N=2, leg cramp N=1) was observed in raloxifene-treated patients (N=57). Conversely, BMD of the spine (−0.9 ± 0.4%; p=0.045) and hip (−0.8 ± 0.3%; p=0.01) dropped significantly in the placebo group (N=57). Three new fractures developed exclusively in the placebo-treated patients. All the bone formation and resorption markers dropped significantly in the raloxifene group but did not change significantly in placebo-treated patients.

Leg cramps were numerically more frequent in the raloxifene group but none of the participants developed arterial or venous thromboembolism. Other adverse events were not significantly different between the two treatment groups. Nine patients withdrew from the study because non-compliance to treatment (N=5) and adverse events (skin rash N=2, leg cramp N=1 and generalized aching N=1).

Conclusions: In postmenopausal women receiving long-term glucocorticoids, raloxifene is well tolerated and significantly increases spinal and hip BMD after 12 months’ treatment.

Disclosure: C. C. Mok: None; C. H. To: None; L. Y. Ho: None; K. L. Yu: None; K. M. Ma: None.
At multivariate analysis, low VITD values (F: 59.3, p<0.001) and the presence of an ARD (14.4, p<0.0003) were independent predictors for an increased PTH.

Conclusions: Patients with ARD have an impaired vitamin D metabolism evidenced by an increased PTH concentration for any plasma VITD range. Therefore, vitamin D supplementation to ARD patients should be targeted to reach full PTH suppression and not simply to obtain VITD concentrations considered optimal in other categories of patients.

Disclosure: P. P. Sainaghi: None; M. Bellan: None; G. Antonini: None; G. Bellomo: None; M. Pirisi: None.

2161

Bone Remodeling in Postmenopausal Women Who Discontinued Denosumab Treatment. Rachel B. Wagman1, Jaques Brown2, David W. Dempster2, Beiying Ding1, Ricardo Dent1, Javier San Martin1, Andreas Grauer3 and Jose R. Zanchetta1.

1Amgen Inc., Thousand Oaks, CA, 2Helen Hayes Hospital, West Haverstraw, NY, 3Instituto de Investigaciones Metabolicas, Buenos Aires, Argentina, 4Laval University Department of Medicine, Quebec, QC, Canada

Background: Denosumab is a fully human monoclonal antibody to RANKL which increases bone mineral density (BMD), reduces bone resorption, and decreases risk for vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis (Cummings et al. NEJM 2009). Transiliac crest bone biopsies from subjects with osteoporosis treated with denosumab for 1 to 3 years demonstrate low bone remodeling. The effects of denosumab treatment on biochemical bone-turnover markers (BTM) and BMD are reversible upon treatment discontinuation. However, the effects of denosumab discontinuation on bone histology and histomorphometry are not known. This study was designed to characterize the effects of denosumab therapy discontinuation on variables of bone histology and histomorphometry in postmenopausal women with low bone mass or osteoporosis. We report here interim bone remodeling results from a subset of subjects.

Methods: Subjects included in this study completed all denosumab doses in the phase 3 trial they were previously enrolled in, after which they received not more than 1 month of treatment for their osteoporosis. Transiliac crest bone biopsies were obtained for histology and histomorphometry evaluation for any plasma VITD at least 12 and <36 months after subjects completed the original trial. Fasting serum samples were collected to assess BTM levels at the time of tetracycline (TC) labeling. This study is ongoing with an expected enrollment of approximately 15 subjects. Data from 5 subjects are available and are reported here.

Results: Mean (SD) age for the 5 subjects at enrollment in the biopsy study was 59.6 (3.3) years. The first set of TC labeling occurred after a mean (SD) of 23.4 (2.7) months from denosumab discontinuation. All biopsies showed normal histology without evidence of pathology. Double TC labels were present in all biopsies, suggesting active remodeling. While osteoclast numbers increased, the other bone remodeling parameters were within the reference range. Both bone resorption and formation markers were similar to the subjects’ pretreatment baseline BTM levels.

Conclusions: These data demonstrate that bone remodeling returned to pre-treatment levels when postmenopausal women discontinued denosumab treatment. These results confirm that the effects of denosumab on reduction in bone turnover are reversible when therapy is discontinued.


ACR Concurrent Abstract Sessions
Rheumatoid Arthritis - Clinical Aspects: RA and Cardiovascular Disease

Wednesday, November 10, 2010, 4:30 PM–6:00 PM

2162

Longitudinal Predictors of Progression of Subclinical Carotid Atherosclerosis in Rheumatoid Arthritis. Jon T. Giles3, Wendy Post4, Roger S. Blumenthal5, Joseph Polak6, Michelle A. Petri7, Allan C. Gelber7, Moyes Szklo8 and Joan M. Batson1, 9Tsimmon, MD, 8Baltimore, MD, Johns Hopkins Univ, Baltimore, MD, Johns Hopkins University, Baltimore, MD, Johns Hopkins University, 9Tufts-New England Medical Center

Background: Coronary and extra-coronary atherosclerosis are increased in rheumatoid arthritis (RA) relative to controls; however, few longitudinal studies have explored predictors of change in atherosclerosis in RA patients.

Methods: Men and women with RA enrolled in ESCAPE RA, a cohort study of subclinical cardiovascular (CV) disease in RA, underwent bilateral B-mode ultrasonography of the common (CCA) and internal (ICA) carotid arteries at the first and third study visits, separated by an average of 3.2±0.3 years. Multivariate linear or Poisson regression, as appropriate to the outcome, were used to explore the associations of baseline and cumulative demographic, lifestyle, and RA disease and treatment characteristics with the average yearly change in maximal intima-media thickness (IMT) of the CCA and ICA, and incident or progressive carotid plaque (defined as newly identified plaque or progression in plaque stenosis). Baseline scans were reanalyzed concurrent with follow-up scans, to control for interpretive drift.

Results: A total of 158 RA patients [36% male; mean baseline age=59±8 years; median baseline RA duration=8.5 years; median baseline DAS28=3.6] underwent carotid scanning at both time points. CCA-IMT increased over time in 82% of patients (median yearly increase=16 μm; p<0.001) and ICA-IMT increased in 70% of patients (median yearly increase=25 μm; p<0.001). After adjusting for demographics, CV risk factors, and baseline IMT, baseline TNF inhibitor use was associated with a 37% lower rate of CCA-IMT progression vs.
non-users (14 vs. 22 μm/year; p=0.026: Figure, Panel A). The adjusted average yearly change in CCA-IMT was significantly higher for patients with earlier RA compared with those with longer duration disease (Figure, Panel B).

![Adjusted for age, gender, ethnicity, hypertension, diabetes, hyperlipidemia, exercise, smoking, body surface area, baseline maximum CCA-IMT, RA duration (where appropriate), and TNF inhibitor use (where appropriate).](image)

**Figure.** Adjusted yearly rate of change in CCA-IMT according to (A) baseline TNF inhibitor use and (B) RA duration.

For ICA-IMT, cumulative prednisone exposure was the only RA feature associated with progression [1.2 μm per year per gram increase in cumulative dose (95% CI 0.1, 2.4)] after adjustment. This rate was significantly lower in patients prescribed statins at baseline. Any plaque was identified in 104 patients (68%), with 13 of these (12%) demonstrating new or progressive plaque during follow-up. After demographic and RA disease activity (where appropriate), and TNF inhibitor use (where appropriate).

**Results:** We followed 599 RA patients for 3,085 person-years for ACS, and 6,525 person-years for CV mortality. We observed 66 new ACS, for an incidence of 2.1 per 100 person-years (95% CI 1.7, 2.7) and 120 CV deaths, for a CV mortality rate of 1.8 per 100 person-years (1.5, 2.1). The strength of association between plaque and ACS or CV death varied between cohort's age strata (Table). These findings did not change appreciably with adjustment for gender, CV risk factors or the ESR. Similar results were obtained with the IMT.

**Conclusion:** The ability of carotid ultrasound to predict CV events in RA varies with age. Plaque and IMT are most strongly associated with CV outcomes in younger RA patients. These findings may have implications for the early identification of patients at risk for CV events in RA.

**Disclosure:** I. Del Rincon: None; M. Sahai: None; D. H. O'Leary: None; D. F. Battafarano: None; A. Escalante: None.

### 2164

**Higher Prevalence, Extent and Severity of “Vulnerable” Coronary Plaque in Asymptomatic Patients with Rheumatoid Arthritis (RA).**

George A. Karpouzas1, Naser Ahmadi, Tae-Young Choi, Fereishte Hajsadeghi2, Silvia Munoz3 and Mathew Budoff2. 1Harbor-UCLA, Long Beach, CA, 2Harbor-UCLA, Long Beach, CA, 2Harbor-UCLA, Long Beach, CA, 3Harbor-UCLA, Long Beach, CA, 4UTHSCSA

**Background:** Higher incidence of myocardial infarctions (MI), sudden cardiac death, and worse survival after MI have all been reported in patients with RA. This risk exceeds traditional risk factors (RF) and insinuates accelerated atherogenesis in RA. We prospectively evaluated the presence, extent, total burden, and differences in the quality of coronary plaque in asymptomatic pts with RA compared to matched controls.

**Methods:** We report on the first 74 of 150 recruited pts with RA from a single center. Demographic, serologic, metabolic, Disease Activity Score (DAS28-3v-ESR), radiographic parameters and treatments are quarterly recorded. Pts underwent 64+ slice cardiac Computed Tomography Angiography (CTA); this non-invasive modality includes an initial non-contrast phase assessing coronary calcium, followed by a contrast scan that detects plaque with equal accuracy to conventional angiography, and is superior in the assessment of non-calcified, lipid-rich, non- obstructive or “vulnerable” plaque. RA pts were matched for age, gender, hypertension, diabetes, smoking, dyslipidemia and family history with controls undergoing CTA for evaluation of coronary arteriosclerosis. Individual coronary trees were evaluated for plaque volume and composition by standard methods (American Heart Association). Non-parametric tests were used for data analysis; regression models for plaque prevalence ratios (PR) and relative risk for plaque burden in RA vs. controls, adjusted for conventional risk factors were developed.

**Results:** The presence, extent, total burden, and differences in the quality of coronary plaque in asymptomatic pts with RA compared to matched controls.

**Conclusion:** The ability of carotid ultrasound to predict CV events in RA varies with age. Plaque and IMT are most strongly associated with CV outcomes in younger RA patients. These findings may have implications for the early identification of patients at risk for CV events in RA.

**Disclosure:** I. Del Rincon: None; M. Sahai: None; D. H. O’Leary: None; D. F. Battafarano: None; A. Escalante: None.
**Antibodies to b2-Glycoprotein-1 (b2GP1) IgA Are Highly Prevalent and Associated with Coronary Plaque in Asymptomatic Patients with Rheumatoid Arthritis (RA).**

**Methods:** We report on 74 recruited RA pts from a single center (table 1). Lupus Anticoagulant (LA), Anticardiolipin (ACL), and b2GP1 IgG, IgM and IgA were assessed by standard methods (DRVVT, Varelisa, and Bindazyme Elisa respectively). Positive (+) tests were confirmed 3 months later. Pts underwent coronary plaque evaluation with 64-slice multidetector Computed Tomography Angiography (CTA); this non-invasive modality includes an initial non-contrast phase assessing coronary calcium, followed by a contrast scan that detects plaque with high temporal and spatial resolution, and 3-dimensional volume of visceral adipose tissue (VAT) and clinical or subclinical atherosclerosis. Perivascular AT including epicardial (EAT), pericardial depots to predict non-calcified (NC), lipid-rich, “vulnerable” coronary plaque in asymptomatic pts with RA.

**Background:** B2GP1 is present in atherosclerotic plaque and b2GP1 IgA Ab have been associated with documented atherosclerosis, including myocardial infarction (MI). RA pts have higher risk of MI; however, the prevalence of b2GP1 IgA Ab in RA and their relevance to plaque characteristics are unknown. We evaluated prospectively the presence of b2GP1 IgA and its associations with coronary plaque prevalence, burden and consistency in asymptomatic pts with RA.

**Methods:** We report on the first 74 of 150 recruited pts from a single center (table 1). Lupus Anticoagulant (LA), Anticardiolipin (ACL), and b2GP1 IgG, IgM and IgA were assessed by standard methods (DRVVT, Varelisa, and Bindazyme Elisa respectively). Positive (+) tests were confirmed 3 months later. Pts underwent coronary plaque evaluation with 64+ slice cardiac Computed Tomography Angiography (CTA); this non-invasive modality includes an initial non-contrast phase assessing coronary calcium, followed by a contrast scan that detects plaque with equal accuracy to conventional angiography, and is superior in the assessment of non-calcified, lipid-rich, non-obstructive or “vulnerable” plaque. Coronary trees were graded in a standard fashion according to AHA. Non-parametric tests were used for data analysis; linear regressions between disease parameters and plaque, as well as relative risk regression models for plaque burden and consistency were constructed after adjustments for age, sex, classic coronary risk (CRF), RA duration and severity.

**Results:** B2GP1 IgA was highly prevalent in asymptomatic RA pts, by contrast to all other Ab classes and isotypes (p<0.0001). No differences in age, disease duration, or laboratory parameters were seen in (+) vs. negative (−) pts. The number of diseased arterial segments was not different in (+) vs. (−); however, the total plaque burden, and more importantly the NC/mixed plaque was significantly higher in the affected arteries of the b2GP1 IgA (+) ones (p=0.0001). In (40.5) b2GP1 IgA had the strongest correlation with NC/ mixed plaque burden than any other factors tested (p=0.003). After adjustments for all CRF, RA duration and severity (DAS28-3v), b2GP1 IgA (+) pts had a 47% higher plaque burden risk for total and 52% higher risk for “vulnerable” plaque (p=0.01 and 0.004 respectively).

**Conclusions:** B2GP1 IgA Ab previously reported in symptomatic pts with documented atherosclerosis, are highly prevalent in asymptomatic RA pts. They independently predict higher total, but more importantly higher vulnerable, NC plaque burden more robustly than the composite of classic CRF. As such, they may represent a useful screening test for “high-risk” plaque in asymptomatic pts with RA.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>b2GP1-IgA (−):</th>
<th>b2GP1-IgA (+):</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear Regressions (NC plaque burden)</td>
<td>r</td>
<td>r²</td>
<td>β (95% CI)</td>
</tr>
<tr>
<td>Cor: Risk (t)</td>
<td>0.37</td>
<td>0.14</td>
<td>2.9 (1.04–5.7)</td>
</tr>
<tr>
<td>B2 GP1 IgA</td>
<td>0.41</td>
<td>0.16</td>
<td>2.5 (1.2–3.3)</td>
</tr>
<tr>
<td>DAS28-3v</td>
<td>0.23</td>
<td>0.06</td>
<td>1.2 (1.05–3.7)</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.04</td>
<td>0.002</td>
<td>1.04 (0.31–1.2)</td>
</tr>
<tr>
<td>ESR</td>
<td>0.16</td>
<td>0.03</td>
<td>0.03 (0.00–0.07)</td>
</tr>
<tr>
<td>TNF psychotherapy</td>
<td>-0.25</td>
<td>-0.07</td>
<td>-1.63 (3.1–1.3)</td>
</tr>
<tr>
<td>Relative Risk Regression*</td>
<td>b2GP1-IgA (−):</td>
<td>b2GP1-IgA (+):</td>
<td>p</td>
</tr>
<tr>
<td>Total plaque burden score</td>
<td>1 (ref)</td>
<td>1.47 (1.06–4.76)</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-calcified/mixed</td>
<td>1 (ref)</td>
<td>1.52 (1.18–3.34)</td>
<td>0.004</td>
</tr>
<tr>
<td>Calcified</td>
<td>1 (ref)</td>
<td>1.09 (0.72–3.71)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, all traditional CRF, RA duration and DAS28-3v.

**Disclosure:** G. A. Karpouzas: None; N. Ahmadi: None; T.-Y. Choi: None; F. Hajsadeghi: None; S. Munoz: None; M. Budoff: None.

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**Increased Epicardial and Thoracic Pre-Aortic Fat Depots Predict “Vulnerable” Coronary Plaque in Asymptomatic Patients with Rheumatoid Arthritis (RA).**

**Methods:** We report on 74 recruited RA pts from a single center. Pts underwent VAT evaluation with 64+ slice multidetector Computed Tomography Angiography (MDCTA), with advantages of submillimeter collimation, high temporal and spatial resolution, and 3-dimensional volume of visceral adipose tissue (VAT) and clinical or subclinical atherosclerosis. Perivascular AT including epicardial (EAT), pericardial (PAT), thoracic pre-aortic (TAT) and subcutaneous (SAT) is metabolically active and a source of pro-inflammatory as well as anti-inflammatory cytokines with both paracrine and systemic effects. VAT volume and associations with coronary plaque burden and features in RA are unknown. We assessed the volume of these AT depots in asymptomatic patients (pts) with RA compared to non-RA matched controls for age, gender and all traditional risk factors undergoing evaluation for coronary artery disease. Additionally, we explored the ability of these diverse AT depots to predict non-calcified, lipid-rich, “vulnerable” coronary plaque burden in RA.

**Background:** There is increasing evidence of an association between volume of visceral adipose tissue (VAT) and clinical or subclinical atherosclerosis. Perivascular AT including epicardial (EAT), pericardial (PAT), thoracic pre-aortic (TAT) and subcutaneous (SAT) is metabolically active and a source of pro-inflammatory as well as anti-inflammatory cytokines with both paracrine and systemic effects. VAT volume and associations with coronary plaque burden and features in RA are unknown. We assessed the volume of these AT depots in asymptomatic patients (pts) with RA compared to non-RA matched controls for age, gender and all traditional risk factors undergoing evaluation for coronary artery disease. Additionally, we explored the ability of these diverse AT depots to predict non-calcified, lipid-rich, “vulnerable” coronary plaque burden in RA.

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views of the heart and its epicardial surface. Additionally, MDCTA detects coronary plaque with equal accuracy to conventional angiography, and is superior in assessing “vulnerable” plaque. Coronary trees were graded in a standard fashion according to American Heart Association (AHA). Non-parametric tests were used for data analysis; linear regressions between different AT depot volumes and vulnerable plaque, as well as relative risk regression models for AT volume risk and prediction of vulnerable plaque burden in RA pts were constructed after adjustments for age, sex, classic coronary risk (CRF), RA duration, and disease activity.

Results: Patients with RA had significantly higher volumes of EAT, PAT, TAT and SAT compared to non-RA matched controls (p<0.05 for all, table 1). RA subjects had 44% higher EAT and 49% higher TAT volume risk than non-RA controls after adjustments for age, sex, all CRF, and body mass index (p=0.001 and 0.005 respectively). Additionally, RA pts had significantly higher total coronary plaque burden (p=0.01), predominantly accounted for by “vulnerable” NC plaque (p=0.001). EAT and TAT where the strongest predictors of “vulnerable” plaque (p=0.001 for both) in asymptomatic RA pts. EAT volume change was the strongest predictor of presence and extent of such friable, high-risk coronary plaque after adjustments for age, sex, all CRF, body mass Index, DAS28-3v and disease duration (p=0.009), followed by TAT (p=0.01).

Conclusions: VAT tissue depots especially EAT and TAT are significantly expanded in asymptomatic RA pts compared to matched controls. They significantly predict the presence of “vulnerable” coronary plaque and remain its strongest determinants after adjustments for traditional CRF, anthropometric, and RA-specific features.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>RA (74)</th>
<th>Controls (74)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAT (cc)</td>
<td>109.9 ± 46.5</td>
<td>89.2 ± 38.5</td>
<td>0.001</td>
</tr>
<tr>
<td>PAT (cc)</td>
<td>47.9 ± 32.4</td>
<td>41.1 ± 29.5</td>
<td>0.04</td>
</tr>
<tr>
<td>TAT (cc)</td>
<td>157.9 ± 67.8</td>
<td>130.3 ± 56.1</td>
<td>0.01</td>
</tr>
<tr>
<td>SAT (cc)</td>
<td>53.9 ± 24</td>
<td>45.3 ± 29.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Relative Risk Regressions*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EAT (cc)</td>
<td>1.44 (1.09–1.96)</td>
<td>1.0 (Ref)</td>
<td>0.001</td>
</tr>
<tr>
<td>PAT (cc)</td>
<td>1.31 (1.07–2.15)</td>
<td>1.0 (Ref)</td>
<td>0.008</td>
</tr>
<tr>
<td>TAT (cc)</td>
<td>1.49 (1.11–2.03)</td>
<td>1.0 (Ref)</td>
<td>0.005</td>
</tr>
<tr>
<td>SC (cc)</td>
<td>1.22 (1.03–2.21)</td>
<td>1.0 (Ref)</td>
<td>0.03</td>
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</tbody>
</table>

RA cohort (n = 74)

Linear Regressions (NC plaque burden) $r^2$ β (95% CI) p

<table>
<thead>
<tr>
<th>Variable</th>
<th>RA (74)</th>
<th>Controls (74)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAT</td>
<td>0.42</td>
<td>0.18</td>
<td>1.72 (1.11–2.48)</td>
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<tr>
<td>PAT</td>
<td>0.27</td>
<td>0.08</td>
<td>1.41 (1.09–3.51)</td>
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<tr>
<td>TAT</td>
<td>0.46</td>
<td>0.21</td>
<td>2.18 (1.34–5.86)</td>
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<tr>
<td>SAT</td>
<td>0.19</td>
<td>0.04</td>
<td>1.25 (1.03–5.54)</td>
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RA cohort (n = 74)**

Relative Risk Regressions (NC/Mixed Plaque Score) $r^2$ β (95% CI) p

<table>
<thead>
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<th>Variable</th>
<th>RA (cc)</th>
<th>Controls (cc)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAT</td>
<td>1.0 (Ref)</td>
<td>2.68 (1.35–3.24)</td>
<td>0.009</td>
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<tr>
<td>PAT</td>
<td>1.0 (Ref)</td>
<td>1.54 (1.09–1.91)</td>
<td>0.01</td>
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<tr>
<td>TAT</td>
<td>1.0 (Ref)</td>
<td>2.36 (1.19–2.56)</td>
<td>0.01</td>
</tr>
<tr>
<td>SC</td>
<td>1.0 (Ref)</td>
<td>1.29 (1.01–1.93)</td>
<td>0.04</td>
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</table>

** Adjusted for age, gender, all CRF, BMI, DAS28-3v and RF duration.

Disclosure: G. A. Karpouzas: None; N. Ahmad: None; F. Hajsadeghi: None; T.-Y. Choi: None; S. Munoz: None; M. Bodiff: None.

2167

Citrullination Is Present in the Perivascular Interstitium of the Myocardium and Is Increased in Rheumatoid Arthritis Compared to Controls. Jon T. Giles1, Marc K. Halushka2, Fox-Talbot K. Mary4, Clifton O. Bingham5, Felipe Andrade6, Jin Kyun Park7, Antony Rosen8, Justyna Fert-Bober9, Jennifer van Eyk4 and Joan M. Bathon2. 1Johns Hopkins Univ, Baltimore, MD, 2Johns Hopkins University, Baltimore, MD, 3Johns Hopkins University School of Medicine, Baltimore, MD

Background: Myocardial dysfunction is increased among rheumatoid arthritis (RA) patients relative to controls. Autoimmunity against post-translationally modified (citrullinated) myocardial proteins may represent a pathophysiological link to both myocardial structural and functional abnormalities in RA patients.

Methods: Archived myocardial samples obtained during autopsy between 1995 and 2009 were assembled into four groups: RA; scleroderma; fatal myocarditis with no underlying rheumatic disease; and non-rheumatic disease controls. Records were adjudicated to confirm diagnosis. Samples were examined by immunohistochemistry for the presence and localization of citrullination using a commercial anti-modified citrulline antibody. A blinded cardiovascular pathologist graded average citrullination intensity, peak intensity, and average fibrosis for each case on a 0–3 scale. RA and control samples were further examined for the presence of peptidyl arginine deiminase enzymes (PADs 2 and 4) by immunohistochemistry.

Results: Myocardial samples from 17 RA patients were compared to those from 14 controls, 5 fatal myocarditis patients, and 9 scleroderma patients. The RA and control groups did not significantly differ by age, gender, race, or post-mortem interval. Citrullination was detected in the perivascular myocardial interstitium in each of the groups. Citrullination was not detected in the cardiomyocytes or endothelium. Average and peak citrullination were significantly higher in the RA group compared to the other groups, among which citrullination was equivalent (Figure, panels A and B). Myocardial fibrosis did not differ between the groups (Figure, panel C).

Myocarditis did not differ between the RA and control groups, and did not co-localize with citrullination. Rare, scattered PAD2 and PAD4 staining leukocytes were observed in both the RA and control samples. PAD2 and PAD4 staining was negligible within the cardiomyocytes and endothelium in both groups.

Conclusions: These data provided evidence for the first time that:
1) Citrullinated proteins are present in the myocardium, in general, 2) Higher levels of myocardial interstitial citrullination appear to be specific to RA, 3) differences in demographics, post-mortem interval, and histologic features did not account for higher citrullination in RA, and 4) While myocardial leukocytes were potential sources of PAD2 and PAD4 within the myocardial interstitium, these cells were not increased in RA at the time of death. Further investigation is centered on identifying the specific myocardial proteins that are targets for citrullination, determining whether citrullinated myocardial proteins are recognized by RA sera, and elucidating the consequences of interstitial citrullination on myocardial structure and function in RA patients.

Disclosure: J. T. Giles: None; M. K. Halushka: None; F.-T. K. Mary: None; C. O. Bingham: None; F. Andrade: None; J. K. Park: None; A. Rosen: None; J. Fert-Bober: None; J. van Eyk: None; J. M. Bathon: None.
**2168**

**ALD518 (BMS945429), a High Affinity Monoclonal Antibody Directed Against Interleukin-6, Reduces Disease Activity and Achieves Remission in Patients with Rheumatoid Arthritis and Inadequate Response to Methotrexate.** Philip Mease1, Vibeke Strand2, Levam Shalamberidze3, Aleksandar Dimic4, Richard Aranda5 and Jeff Smith6, 1Alder Biopharmaceuticals Inc., Bothell, WA, 2Bristol-Myers Squibb, Princeton, NJ, 3Institute of Rehabilitation and Treatment, Niska Banja, Serbia, 4Stanford University, Palo Alto, CA, 5Swedish Medical Center and University of Washington, Seattle, WA, 6TV. Tseliadaze Scientific Practical Centre of Rheumatology, Tbilisi, Georgia

**Background:** Interleukin-6 (IL-6) plays a key role in the inflammatory cascade in rheumatoid arthritis (RA). ALD518 (BMS945429) is an asialated, humanized, anti-IL-6 monoclonal antibody with a half-life of ~30 days. ALD518 binds to IL-6 with high affinity, preventing interaction and signaling mediated via soluble and membrane-bound IL-6R. Here, we report the impact of ALD518 on disease activity and DAS28 remission over 16 weeks.

**Methods:** Patients with active RA and an inadequate response to MTX were randomized 1:1:1:1 to intravenous ALD518 80, 160 or 320 mg or placebo during this 16-week, double-blind, placebo-controlled Phase II study. Patients received two IV infusions of ALD518 (Day 1 and Week 8), while continuing on stable doses of MTX. The primary efficacy endpoint was ACR 20 responders at Week 12. Disease activity was assessed via DAS28 (CRP) as a secondary endpoint, including mean change from baseline and DAS28-defined remission (score <2.6). Efficacy data were assessed for the modified intent-to-treat population. Safety was monitored throughout. P values for ACR responses are based on Fisher’s exact test and for DAS28 classes are based on chi-square tests.

**Results:** Of 127 randomized and treated patients, 116 completed the trial. At baseline, mean age was 52.3 years and RA duration was 6.8 years. Mean baseline DAS28 (CRP) scores were 6.3, 6.2, 6.1 and 6.1 in the ALD518 80, 160, 320 mg and placebo groups, respectively. Reductions in DAS28 score and the proportion of patients achieving Low Disease Activity State (LDA; DAS28 [CRP] ≤3.2), remission and ACR 20, 50 and 70 responses were rapidly achieved and greater than placebo for all ALD518 doses at each time point (Table). For all assessments, there was a trend toward greater responses with higher ALD518 doses.

<table>
<thead>
<tr>
<th>Time point</th>
<th>ALD518 80 mg (N=32)</th>
<th>ALD518 160 mg (N=34)</th>
<th>ALD518 320 mg (N=28)</th>
<th>Placebo (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28, mean reduction from baseline (see text)</td>
<td>2.0 mg/dL</td>
<td>2.5 mg/dL</td>
<td>3.2 mg/dL</td>
<td>0.6 mg/dL</td>
</tr>
<tr>
<td>LDAS (%)</td>
<td>10.0</td>
<td>23.5*</td>
<td>33.3*</td>
<td>26.1</td>
</tr>
<tr>
<td>DAS28-defined remission (%)</td>
<td>17.2*</td>
<td>21.2*</td>
<td>34.6*</td>
<td>3.3</td>
</tr>
<tr>
<td>ACR 20 (%)</td>
<td>50.0*</td>
<td>55.9*</td>
<td>71.4*</td>
<td>24.2</td>
</tr>
<tr>
<td>ACR 50 (%)</td>
<td>9.4</td>
<td>14.7</td>
<td>26.8*</td>
<td>3.0</td>
</tr>
</tbody>
</table>

**Conclusions:** In this Phase II study, the IL-6 inhibitor ALD518 resulted in rapid and significant improvements in disease activity sustained over 16 weeks of assessment in patients with RA and an inadequate response to MTX. ALD518 was well tolerated, with a safety profile consistent with the biology of IL-6 blockade.

**Reference:**


**Disclosure:** P. Mease: Alder Biopharmaceuticals, 5; Bristol-Myers Squibb, 2, 5, 8; V. Strand: Abbott Immunology Pharmaceuticals, 5; Alder Biopharmaceuticals, 5; Amgen Inc., 5; AstraZeneca, 5; Biogen Idec, 5; Bristol-Myers Squibb, 5, Canfiite Pharma, 5; CBio, 5; Centocor, Inc., 5; Cypress Biosciences, Inc., 5; Euro-Diagnostic; L. Shalamberidze: Alder Biopharmaceuticals, 2; A. Dimic: Alder Biopharmaceuticals Inc., 2; R. Aranda: Bristol-Myers Squibb, 1, 3; J. Smith: Alder Biopharmaceuticals, 1, 3.

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**2169**

**Efficacy and Safety of Ocrelizumab in Patients with Active Rheumatoid Arthritis Who Have an Inadequate Response to at Least One TNF Inhibitor: Results from the Phase III SCRIPIT Trial.** Paul P. Tak1, Philip J. Mease1, Mark C. Genovese2, Joel M. Kremer3, Boulou Harouei4, Yoshiya Tanaka5, Clifton O. Bingham6, Ali Ashrafzadeh7, Helen Travers7, Simon Safa-Leathers4, Sanjeet Kumar7 and Wolfgang Dummer8.

1Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, 2Genentech, San Francisco, CA, 3Genentech, 4Institut de Rhumatologie, Montréal, QC, Canada, 5Johns Hopkins University, Baltimore, MD, 6Roche, 7Seattle Rheumatology Associate, Seattle, WA, 8Stanford Univ, Sunnyvale, CA, 9The Center for Rheumatology, Albany, NY, 10U Occupa & Environ Hlth, Kitakyushu, Japan

**Purpose:** Treatment with rituximab has demonstrated clinical benefit in patients (pts) with rheumatoid arthritis (RA). This phase III study evaluated efficacy and safety of Ocrelizumab (OCR, a humanized anti-CD20 antibody) plus methotrexate (MTX) or leflunomide (LEF), in pts with active RA who had an inadequate response to ≥1 TNF inhibitor.

**Methods:** SCRIPIT was a randomized, double-blind and placebo (PBO)-controlled (DBPC) study. 840 pts with active RA (1987 ACR criteria; SJC ≥4, TJC ≥4, CRP ≥0.6 mg/dL and RF+ and/or anti-CCP+ and on stable MTX (7.5–25 mg/wk) or LEF (10–20 mg/day), were randomized (1:1:1:1) PBO, 278 OCR 2 × 200 mg, 285 OCR 2 × 500 mg). Pt baseline (BL) characteristics were well balanced between treatment groups (mean: age ~54 yrs, SJC ~17, TJC ~26, CRP ~2.8, DAS28 ~6.5 and RA duration 11.8 to 12.7 yrs). The DBPC period (48 wks) was comprised of 2 courses of 2 treatments each (Days 1, 15 and Wks 24, 26). All pts received 100 mg IV methylprednisolone premedication. Co-primary endpoints were ACR20 responses at Wks 24 and 48. Secondary endpoints included the change from BL in the total modified (van der Heijde) Sharp score (mTSS) at 48 wks and ACR50/70 responses at 24 and 48 wks.

**Results:** Key efficacy and safety data are shown in Table 1. Both OCR doses showed statistically significant (p<0.0001) improvements (vs PBO) in ACR20/50/70 at Wks 24 and 48. At Wk 48, statistically significant slowing of progression of joint damage (PJD) (change from BL in mTSS) was seen in OCR 500 mg dose group (62% inhibition, p=0.0020) but not in OCR 200 mg dose group (30% inhibition, p=0.2153) vs PBO. Frequencies of AEs, SAEs, and overall infections were comparable among the 3 treatment arms. Serious infections (SIs) were observed more through 16 weeks, serious AEs were reported in two ALD518 patients (both had significant increases in liver enzymes, and discontinued treatment). Increases in ALT >3x upper limit of normal occurred in 12, 6 and 29% of patients in the ALD518 80, 160 and 320 mg groups, respectively. Modest increases in total cholesterol were observed; mean levels at Week 16 were 6.5, 6.4 and 6.0 mmol/L in the ALD518 80, 160 and 320 mg groups, versus 5.4 mmol/L in the placebo group. Nine ALD518 patients had transient Grade II (five in the ALD518 80 mg group and four in the 160 mg group) and two had transient Grade III neutropenia (both in the 80 mg group). There were no serious infections or infusion reactions in any treatment group, and no evident immunogenicity.

**Conclusions:** In this Phase II study, the IL-6 inhibitor ALD518 resulted in rapid and significant improvements in disease activity sustained over 16 weeks of assessment in patients with RA and an inadequate response to MTX. ALD518 was well tolerated, with a safety profile consistent with the biology of IL-6 blockade.

**Reference:**


**Disclosure:** P. Mease: Alder Biopharmaceuticals, 5; Bristol-Myers Squibb, 2, 5, 8; V. Strand: Abbott Immunology Pharmaceuticals, 5; Alder Biopharmaceuticals, 5; Amgen Inc., 5; AstraZeneca, 5; Biogen Idec, 5; Bristol-Myers Squibb, 5, Canfiite Pharma, 5; CBio, 5; Centocor, Inc., 5; Cypress Biosciences, Inc., 5; Euro-Diagnostic; L. Shalamberidze: Alder Biopharmaceuticals, 2; A. Dimic: Alder Biopharmaceuticals Inc., 2; R. Aranda: Bristol-Myers Squibb, 1, 3; J. Smith: Alder Biopharmaceuticals, 1, 3.
frequently in OCR dose groups (5.1% and 4.3%) compared to PBO (2.5%). SIE rates were similar in both OCR and PBO groups outside Japan. Most common SIEs included pneumonias, cellulitis and urinary tract infections. Opportunistic infections in OCR-treated groups included 1 suspected Pneumocystis jiroveci, 2 de novo pulmonary tuberculosis, and 1 hepatitis B reactivation and none in PBO. There were no fatal infections during the DBPC period in any treatment groups.

Table 1. Efficacy, radiologic, and safety summary

<table>
<thead>
<tr>
<th>Placebo (n=277)</th>
<th>OCR 2 × 200 mg (n=277)</th>
<th>OCR 2 × 500 mg (n=282)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR20</td>
<td>24.5</td>
<td>43.0*</td>
</tr>
<tr>
<td>ACR50</td>
<td>9.0</td>
<td>21.3*</td>
</tr>
<tr>
<td>ACR70</td>
<td>2.9</td>
<td>7.6***</td>
</tr>
<tr>
<td><strong>Week 48</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR20</td>
<td>21.7</td>
<td>49.5*</td>
</tr>
<tr>
<td>ACR50</td>
<td>10.1</td>
<td>29.2*</td>
</tr>
<tr>
<td>ACR70</td>
<td>5.1</td>
<td>11.2***</td>
</tr>
<tr>
<td><strong>X-ray radiographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in mTSS Score, 24 wks</td>
<td>1.30</td>
<td>1.11</td>
</tr>
<tr>
<td>Mean change in mTSS Score, 48 wks</td>
<td>2.61</td>
<td>1.83</td>
</tr>
</tbody>
</table>

**Safety, %**

AEs 227 (81.9) 232 (83.8) 238 (84.4)
SAs 32 (11.6) 40 (14.4) 37 (13.3)
Infections 143 (51.6) 150 (54.2) 154 (58.2)
Serious infections (SIEs) 7 (2.5) 14 (5.1) 12 (4.3)
Infection-related rections, % 1st infusion 5.1 13.0 18.4
2nd infusion 5.8 4.1 4.0
3rd infusion 2.3 6.4 6.7
4th infusion 2.3 3.3 1.6
Serious AE disorder
Musculoskeletal 12 (4.3) 7 (2.5) 7 (2.5)
Cardiac 4 (1.4) 5 (1.8) 3 (1.1)
Injury 6 (2.2) 4 (1.4) 4 (0.7)
GI 1 (0.4) 1 (0.4) 0 (0.0)
Neoplasms 4 (1.4) 2 (0.7) 1 (0.4)
Blood/lymphatic 3 (1.1) 1 (0.4) 1 (0.4)
Serious infection rates
Total patient-years 246.03 247.63 254.92
Infections 9 17 16
Infections/100 pt-yrs 3.66 6.87 6.28
95% CI 1.67–6.94 4.00–10.99 3.59–10.19

**Safety sub-analysis**

<table>
<thead>
<tr>
<th>Placebo (n=37/240)</th>
<th>OCR 200 mg (n=36/241)</th>
<th>OCR 500 mg (n=38/244)</th>
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</thead>
<tbody>
<tr>
<td>Total patient-years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian/RO/W</td>
<td>33.67/212.36</td>
<td>33.16/214.47</td>
</tr>
<tr>
<td>Serious Infections</td>
<td>0.9</td>
<td>5/12</td>
</tr>
<tr>
<td>Serious Infections/100 pt-yrs</td>
<td>0.4/24</td>
<td>15/50</td>
</tr>
<tr>
<td>95% CI</td>
<td>0–1.9/9.0</td>
<td>4.90–15.19</td>
</tr>
<tr>
<td>1.94-8.05</td>
<td>2.89 – 8.97</td>
<td>2.50–8.95</td>
</tr>
</tbody>
</table>

**Conclusion:** Both OCR doses met the clinical primary efficacy endpoints. The reduction in PJD was statistically significant for 500 mg dose but not for 200 mg dose at 48 wks. The rate of SIEs was higher in both OCR doses compared to PBO; the increased rates appeared to be primarily driven by pts in Japan.

**Disclosure:** P. P. Tak: Genentech and Biogen IDEC Inc 2, 5, Roche, 2, 5, P. J. Mease: Genentech and Biogen IDEC Inc 2, 5, Roche, 2, 5, 8, M. C. Genovese: Genentech and Biogen IDEC Inc 2, 5, Roche, 2, 5, J. M. Kremer: Genentech and Biogen IDEC Inc 2, 5, S. Roche, 5, 8, Roche Diagnostics, 2, B. Harroun: None; Y. Tanaka: None; C. O. Bingham: None; A. Ashrafzadeh: Genentech and Biogen IDEC Inc 3, Roche, 1; H. Travers: Roche, 1, 3; S. Safa-Leathers: Roche, 1, 3; S. Kumar: Roche, 1, 3; W. Dummer: Genentech and Biogen IDEC Inc 3, Roche, 1.

**Background:** Osteopontin (OPN) is an extracellular matrix protein that is constitutively expressed in bone and epithelial tissues and upregulated in activated T cells, macrophages, synovioocytes and chondrocytes. OPN has diverse functions including chemotaxis, immunomodulation and activation of osteoclasts. High levels of OPN in serum, synovial fluid and tissue have been reported in rheumatoid arthritis (RA) patients, and OPN-blockade improves arthritides in animal models of RA. In this study, we assessed the safety, tolerability, pharmacokinetics, pharmacodynamics and initial efficacy of the humanized monoclonal antibody ASK8007 which binds to the SVVYGL epitope of OPN in patients with active RA receiving methotrexate (MTX), lefunomide (LEF) or sulfasalazine (SSZ).

**Methods:** In this combined first-in-man single dose escalation study (part A) and multiple dose proof-of-concept study (part B), patients meeting the American College of Rheumatology (ACR) criteria for RA who had been taking MTX, LEF or SSZ for 4 months with active disease were randomly assigned to receive either ASK8007 or matching placebo intravenously while continuing to receive MTX, LEF or SSZ. In Part A, patients were treated with a single dose of 0.3, 1.25, 5 or 20 mg/kg ASK8007 intravenously in four consecutive dose cohorts of 8 patients each. In part B, patients received 3 consecutive infusions of 20 mg/kg ASK8007 or matching placebo on day 1, day 8 and day 29. Safety monitoring, pharmacokinetic and pharmacodynamic analyses and clinical assessments were performed throughout the study. Synovial tissue was obtained at baseline and after 43 days of treatment, and was analyzed by immunohistochemistry and digital image analysis. The two co-primary efficacy endpoints were the change from baseline in the disease activity score evaluated in 28 joints (DAS28) and the change from baseline in the number of CD68 positive sublining macrophages in the synovium as assessed on day 43.

**Results:** ASK8007 was well tolerated up to the highest studied dose of 20 mg/kg in both parts of the study. No anti-ASK8007 antibodies were detected and no renal clearance of ASK8007 was observed. In part B, in the intention-to-treatment population, no difference was observed in the delta DAS28 between the ASK8007 treated patients (n=53) and the placebo-treated patients (n=16, P = 0.95). Results were similar for the per protocol population. In addition, no difference was observed in the delta CD68 positive sublining macrophages between the ASK8007-treated patients (n=9) and the placebo-treated patients (n=4, P = 0.61). Paired analysis also did not show a clear cut decrease in sublining macrophages within the ASK8007 treatment group. Although quantifiable ASK8007 concentrations were obtained in synovial fluid samples which indicates that it reaches the target site, there was also no effect of multiple doses of ASK8007 on the biomarkers for bone and cartilage metabolism and for inflammation in any of the matrices tested (blood, urine, synovial fluid and synovial tissue).

**Conclusion:** The results of this trial consistently show that blocking the extracellular matrix protein osteopontin is unlikely to be a feasible strategy for RA.

**Disclosure:** M. Boumans: None; J. Houbiers: Astellas Pharma, 3; P. Verschuuren: None; A. Ishikura: Astellas Pharma, 3; R. Westhovens: None; E. Brouwer: None; B. Rojkovich: None; S. Kelly: None; M. Den Adel: Astellas Pharma, 3; J. Isaacs: None; J. Gomez-Reino: None; G. Holtkamp: D. Gerlag and P. Tak. Astellas Pharma Global Development, the Netherlands and Japan, Leiderdorp, The Netherlands, Astellas Pharma Global Development, the Netherlands and Japan, 3Centre for Experimental Medicine and Rheumatology, Queen Mary’s School of Medicine, London, Department Rheumatology, University Medical Center Groningen, Groningen, The Netherlands, 2Department of Clinical Immunology and Rheumatology, Academic Medical Center / University of Amsterdam, Amsterdam, Noord-Holland, The Netherlands, 4Division of Clinical Immunology and Rheumatology, Academic Medical Center / University of Amsterdam, Amsterdam, The Netherlands, 5Musculoskeletal Research Group, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom, 6Rheumatology, Buda Charity Hospital, Budapest, Hungary, 7Rheumatology, Hospital Clinic Universitario, Santiago de Compostela, Spain, Santiago, Spain, 8University Hospital Leuven, Leuven, Belgium.
A R C 2 0 response rates demonstrated similar efficacy of tasocitinib between ALL MTX and non-MTX patients, as well as M12 and M24 patients (Figure 1). A R C 2 0 response rates at Month 24 were 81.8% and 77.8% for M24 MTX and non-MTX patients, respectively.

Conclusion: The safety profile of tasocitinib, regardless of background MTX use, was generally tolerable and manageable. Tasocitinib demonstrated sustained efficacy over 24 months in the treatment of RA. ACR response rates were similar in patients receiving tasocitinib monotherapy compared with patients on background MTX therapy.


2172

A Randomized Dose-Ranging, Placebo-Controlled Study of INCB028050, a Selective JAK1 and JAK2 Inhibitor in Subjects with Active Rheumatoid Arthritis. Maria W. Greenwald1, Rosanne Fidelus-Gort2, Rich Levy3, Jinyin Liang4, Kris Vaddi5, William V. Williams6, Robert Newton7, Swamy Yeleswarap7, Robert Flores8, Edward McKeever3, James Rodgers9, Stacey Shepard9, Pierre-Yves Berclaz10, Chin Hyok Lee11 and Mynica E. Luchi11, Desert Medical, Palm Desert, CA; Lilly Lilly & Company, 11; Incyte Corporation, Wilmington, DE; Incyte Corporation

Purpose: To characterize safety and efficacy of INCB028050 (050) in RA in subjects who had an inadequate response to any DMARD therapy including biologics.

Methods: Subjects with active RA (≥6 tender/≥4 swollen joints of 28), ESR≥28mm or CRP ≥7mg/L despite DMARD therapy were randomized to placebo (PBO) or 050 at once daily oral doses of 4mg, 7mg or 10mg with background DMARDs (excluding biologics). After 12 weeks subjects randomized to placebo were re-randomized to 7mg or 10mg for an additional 12 weeks (wks). The primary analysis was at the end of the 12-week PBO-controlled period. Subjects remained blinded to treatment assignment during the 24-wk treatment period. Subjects could be on stable doses of methotrexate (MTX), hydroxychloroquine, leflunomide, corticosteroids (<10 mg/day) and/or sulfasalazine. Results below are at Wk 12. The study was not designed to test for statistically significant differences between individual dose groups and placebo; p-values and significance levels are not displayed.

Results: The study enrolled 127 subjects, eighty percent women. Two subjects were randomized but not treated. One subject had no post-baseline assessments. Mean ages across treatment groups 54–58yrs. Mean disease duration ranged from 7–9 yrs. The proportion of subjects on background MTX ranged from 72–77%. The proportion of subjects who failed biologics in the past was 13%, 38%, 6% and 20% for the PBO, 4mg, 7mg and 10mg groups, respectively. Of the subjects who had failed biologics, 39% failed multiple biologics.

Response rates are expressed as mean % (also percent change from baseline for DAS28).

Wk 12 results

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>4 mg 050</th>
<th>7 mg 050</th>
<th>10 mg 050</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31</td>
<td>31</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>ACR20 (%)</td>
<td>32</td>
<td>52</td>
<td>59</td>
<td>53</td>
</tr>
<tr>
<td>ACR50 (%)</td>
<td>13</td>
<td>35</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>ACR70 (%)</td>
<td>3</td>
<td>16</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>DAS28 CRP Mean (%change)</td>
<td>5 (–19)</td>
<td>4 (–34)</td>
<td>4 (–32)</td>
<td>4 (–33)</td>
</tr>
<tr>
<td>DAS28 &lt; 2.6 (%)</td>
<td>16</td>
<td>23</td>
<td>25</td>
<td>17</td>
</tr>
</tbody>
</table>

Responses were observed as early as the first assessment (Wk2), demonstrating a rapid onset of action. Similar ACR responses were achieved with 050 regardless of background therapy or previous biologic experience. ACR20 responses for biologic experienced subjects was 33% and 43% for 4mg, 7mg and 10mg, respectively. ACR50 responses for biologic experienced subjects was 11% for PBO and 33%, 45% and 29% for 4mg, 7mg and 10mg, respectively.

The nature of treatment-emergent adverse events (TEAEs) was similar across groups. The frequency of TEAEs in PBO, 4mg, 7mg and 10mg 050 groups was 61.3%, 48.4%, 59.4% and 74.2%, respectively. One subject reported an unrelated serious AE (GI bleed). The most frequently reported TEAEs were headache (active 10.6% vs. 6.5% PBO), URI (active 5.3% vs. 9.7% for PBO) and diarrhea (active 5.3% vs. 6.5% PBO). At Wk 12, two cases of herpes zoster were reported (2.1% active vs. 0% PBO). Increases were observed in HDL and LDL, and HDL:LDL ratios tended to increase with therapy (active 10.06% vs. 0.41% PBO).

Conclusion: In this study, INCB028050 given once a day over 12 weeks was well tolerated and demonstrated clinically meaningful responses in subjects with inadequate response to DMARDs including biologics over 12 wks of treatment. All three doses tested were effective.

Disclosure: M. W. Greenwald: Novartis, R. Fidelus-Gort: Incyte, 1, 3; R. Levy: Incyte, 1, Infinity, 1; J. Liang: Incyte, 1, 3; K. Vaddi: Incyte, 1, 3; W. V. Williams: Incyte, 1, 3; R. Newton: Incyte, 1, 3; S. Yeleswarap: Incyte, 1, 3; R. Flores: Incyte, 1, 3; E. McKeever: Incyte, 1, 3; J. Rodgers: Incyte, 1, 3; S. Shepard: Incyte, 1, 3; P.-Y. Berclaz: Eli Lilly and Company, 1, 3; M. E. Luchi: Incyte and Company, 1, 3; C. H. Lee: Eli Lilly and Company, 1, 3; M. W. Greenwald: Incyte, 1, 3.
Conclusions: Consistent with the established IV abatacept profile, SC abatacept provides comparable efficacy and safety, with low immunogenicity and high retention rates; injection site reactions were few and mild. SC abatacept will provide additional treatment options for RA patients.

Disclosure: M. C. Genovese: Bristol-Myers Squibb, 2, 5, 8; J. A. Covarrubias: Bristol-Myers Squibb, 9, Lilly USA, LLC., 9, Pfizer Inc, 9, UNIDAT UNIMATLOGICA LAS AMERICANAS SCF; G. Leon: None; E. F. Mylser: Bristol-Myers Squibb, 6, Novartis Pharmaceuticals Corporation, 6, Roche, 6; M. W. Keiserman: Abbott Laboratories, 2, 5, Biogen Idec, 2, Bristol-Myers Squibb, 2, 5, Eli Lilly and Company, 2, Human Genome Sciences, Inc., 2, MSD, 2, 5, Pfizer Inc, 2, Roche, 2; UCB, Inc., 2; R. M. Valente: None; P. Nash: Centocor, Inc., 2, Schering-Plough, 8; J. A. Simon: None; W. Porawska: None; J. H. Box: Box Arthritis and Rheumatology of the Carolinas PLLC, 5, Bristol-Myers Squibb, 5; E. Nasonov: None; P. Durez: Bristol-Myers Squibb, 8, Schering, 8, Wyeth Pharmaceuticals, 8; R. Aranda: Bristol-Myers Squibb, 1, 3; R. Pappu: Bristol-Myers Squibb, 3; I. Delaet: Bristol-Myers Squibb, 1, 3; J. Teng: Bristol-Myers Squibb, 1, 3; R. Alten: Bristol-Myers Squibb, 2, 8.

ACR Concurrent Abstract Sessions
Sjögren’s Syndrome
Wednesday, November 10, 2010, 4:30 pm–6:00 pm

2174
Receptor-Mediated Small Interfering RNA Delivery in Sjögren’s Syndrome.
Kaleb M. Pauley, Adrienne E. Gauna and Seunghee Cha. University of Florida, Gainesville, FL.

Background: Sjögren’s syndrome (SjS) is characterized by xerophthalmia and xerostomia resulting from loss of secretary function due to immune cell infiltration in lacrimal and salivary glands. Current SjS therapeutic strategies employ secretagogues to induce secretion via muscarinic receptor stimulation. Based on our expertise on muscarinic type-3-receptor (M3R), we are utilizing ligands specific for MR to deliver siRNA into cells via receptor-mediated endocytosis, thereby altering epithelial cell responses to external cues such as pro-inflammatory or death signals while simultaneously stimulating secretion.

Methods: MR agonist carbachol was conjugated with siRNA targeting caspase-3. To test siRNA efficacy after conjugation, HSG cells were transfected with conjugate. To test conjugate efficacy, conjugate was added to HSG cells in culture. Quantitative RT-PCR and immunofluorescence were used to detect caspase-3 gene and protein expression, respectively. Carbachol functionality was assessed using intracellular calcium release assays. A FAM-labeled DNA probe was designed to target the antisense strand of caspase-3 siRNA and in situ hybridization was utilized to detect conjugate entry into cells.

Results: Transfection of conjugate into cells resulted in 80%-reduction in caspase-3 gene expression, confirming retained function of siRNA after conjugation. External conjugate treatment of HSG cells resulted in similar intracellular calcium release and induction of endocytosis as carbachol stimulation indicating that the carbachol portion of conjugate also retained function after conjugation. Using the FAM-labeled probe, conjugate uptake was visualized in HSG cells, indicating that the conjugate binds M3R and is taken into cells via receptor-mediated endocytosis as expected. In conjugate-treated HSG cells caspase-3 mRNA and protein expression was reduced 50% demonstrating the efficacy of our conjugate in siRNA delivery.

Conclusions: Both siRNA and carbachol portions of the conjugate were shown to retain function after conjugation, and external treatment of HSG cells with conjugate shows promising results. Further in vitro/in vivo studies are needed to optimize conjugate entry and test efficacy of conjugate in the prevention of cytokine-induced apoptosis. This therapeutic strategy can easily be manipulated to target different genes of interest while maintaining cell-type specificity, and has many potential clinical applications in the treatment of SjS. Supported by NIH grant T32DE007200 and Sjögren’s Syndrome Foundation Research Grant

Disclosure: K. M. Pauley: None; A. E. Gauna: None; S. Cha: None.
Structure and Antigenicity of the Ro/La RNP Particle. hY1 RNA Differentiates the Recognition of Epitopes in Systemic Lupus Erythematosus and Sjögren’s Syndrome. John G. Roussias1, Nikos C. Kyriakidès1, Stathis Kotsakis1 and Athanasios G. Tzioufas2. 1Department of Pathophysiology, Medical School, University of Athens, Athens, Greece, 2Medical School-Univ of Athens, Athens, Greece

Background: Ro/La RNP particle is targeted by autoantibodies in patients with Sjögren’s syndrome (SS) and systemic lupus erythematosus (SLE). Although the antigenicity of the components of the complex has been extensively studied, its overall 3D structure remains unknown. In contrast to Xeroderma pigmentosum, human Ro60 structure has not been solved. Two parts of the human La structure have been solved till now, one comprising the conserved La motif and its adjacent RNA recognition motif (RRM1) and another holding the C-terminal RNA recognition motif (RRM2), followed by a La motif and its adjacent RNA recognition motif (RRM1) and another. The human La structure have been solved till now, one comprising the conserved La motif and its adjacent RNA recognition motif (RRM1) and another holding the C-terminal RNA recognition motif (RRM2), followed by a C-terminal nuclear retention element (NRE). For hY1 RNA, only its secondary structure has been experimentally defined. The aim of this study was to determine the 3D structure of Ro/La RNP complex, evaluate the modeled structure experimentally and define its antigenicity.

Methods: Human Ro60 protein model was built by homology modelling from Xenopus Ro. 81% of human La was constructed by the assembly of its 3 parts: (i) 5–202 aa (La motif + RRM1), (ii) 203–224aa (linker region), (iii) 225–334 aa (RRM2 + NRE). hY1 RNA was built on the basis of its known secondary structure by a stepwise fashion. The whole Ro/La RNP complex was assembled and the structure was refined using extensive molecular dynamics calculations performed using the AMBER 9 software package. All peptides were antigenic epitopes on Ro60 and La antigens. ELISA experiments were performed using immobilized biotinylated synthetic hY1RNA analogue, recombinant Ro60 and La antigens and purified antibodies against specific epitopes or Ro60 and La autoantigens.

Results: Electrostatic analysis of the Ro/La RNP complex revealed that adjacent Ro and La autoantigens form a consecutively positively charged patch, interacting preferably with the negatively charged hY1 RNA molecule. More specifically, hY1 RNA binds to conserved amino acid residues located on the outside domain of the Ro60 doughnut and within the cleft formed between the La motif and an edge of the adjacent RRM1 of La. At this orientation, hY1-RNA completely masks epitopes 169–190aa of Ro60 and 145–164aa of La that were previously associated with SLE but not the SS related epitopes 211–232aa of Ro60 and 349–364aa of La. EMSA experiments demonstrated that the synthetic hY1-RNA analogue could form a complex with Ro60 and La autoantigens. In this regard, an ELISA assay was carried out, based on competition between synthetic-hY1 RNA and purified antibodies against specific epitopes on Ro and La autoantigens. It was found that Ro60 – hY1-RNA interaction was inhibited by anti-443–454, anti-anti-211–232 and anti-169–190 antibodies by 13%, 45% and 76%, respectively while La-hY1-RNA interaction was inhibited by purified anti-349–364, anti-301–320 and anti-145–164 antibodies by 10%, 43% and 97%, respectively. Moreover, EMSA experiments demonstrated that Ro60 and La interactions with hY1 RNA can also be inhibited by peptides corresponding to regions 169–190aa and 145–164aa of Ro60 and La autoantigens.

Conclusions: Our study demonstrates that the SLE related epitopes on Ro and La autoantigens are actually cryptotopes in Ro/La RNP three-dimensional structure masked by hY1 RNA. On the other hand, SS related epitopes are directly accessible by autoantibodies in Ro/La RNP structure.

Disclosures: J. G. Roussias: None; N. C. Kyriakidès: None; S. Kotsakis: None; A. G. Tzioufas: None.

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A Role of Autoimmune Response to M3 Muscarinic Acetylcholine Receptor in the Pathogenesis of Sjögren’s Syndrome Like Autoimmune Sialoadenitis. Maria Izuka1, Hiroto Tsukuboi2, Yumi Nakamura2, Naomi Matsuo2, Isoo Matsumoto2 and Takayuki Sumida1. 1Univ of Tsukuba/Inst Clin Med, Tsukuba City, Japan, 2Univ of Tsukuba/Inst Clin Med

Objective: Sjögren’s syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration of salivary glands, in which CD4 T cells play a prominent role. These infiltrating T cells play a crucial role in the generation of SS. Previous studies showed that autoantibodies and autoimmune-reactive T cells against M3 muscarinic acetylcholine receptor (M3R) were detected in patients with SS. In this study, to reveal the pathological role of M3R immune response in SS, we tried to induce SS like sialoadenitis by autoimmune response to M3R.

Methods: (1) C57BL/6J (M3R+/+) mice and M3R knockout (M3R−/−) mice were immunized intradermally with synthesized peptides encoding the extracellular domains of murine M3R (N-terminus, 1st, 2nd and 3rd extracellular loops) in CFA. On day 10, these mice were boosted with intradermal injection. Ten days after booster immunization, spleens were isolated, the immune response to M3R was examined in vitro, and then the spleocytes were transferred to Rag1 knockout mice (Rag1−/−) (M3R−/−→Rag1−/−). (2) Anti-M3R antibodies and the amount of saliva flow in M3R−/−→Rag1−/− mice were measured on day 0, 15, 45. (3) In M3R−/−→Rag1−/− mice, salivary glands were examined histologically by H&E staining and evaluated immunohistochemically using anti-Thy1, anti-CD20, anti-CD4 and anti-CD8 antibodies. Infiltrating lymphocytes derived from salivary glands were co-cultured with M3R peptides in vitro and cytokine (INF-γ, IL-17, IL-4) in the supernatant was measured by ELISA. (4) CD3+ T cells purified from M3R−/− mice immunized with M3R were transferred to Rag1−/− mice (M3R−/−→Rag1−/−) and salivary glands were examined by histological analysis. (5) The spleocytes from INF-γ+/−/M3R−/− mice immunized with M3R were transferred to Rag1−/− mice (INF-γ+/−/M3R−/−→Rag1−/−).

Results: (1) IL-17 and INF-γ were highly produced in spleocytes of immunized M3R−/−→Rag1−/− mice compared with M3R−/−→Rag1−/− mice. (2) In M3R−/−→Rag1−/− mice, anti-M3R antibodies were significantly increased and saliva flow were decreased. (3) On day 45, the sialoadenitis with remarkable mononuclear infiltration was observed and Thy1+CD4+ cells predominantly infiltrated in salivary glands of M3R−/−→Rag1−/− mice. IL-17 was preferentially produced from M3R reactive infiltrated T cells. (4) The moderate sialoadenitis with T cell infiltration was also detected in M3R−/−→Rag1−/− mice. (5) The obvious sialoadenitis was also observed in M3R−/−→Rag1−/− mice as well as M3R−/−→Rag1−/− mice.

Conclusion: These findings support the notion that M3R reactive Th17 cells might play a crucial role in the generation of autoimmune sialodenditis such as SS.

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2177

Δ4BAFF, an Alternate-Splice Isoform That Acts as a Transcription Factor To Enhance BAFF Production in Primary Sjögren’s Syndrome. Jacques-Olivier Pers, Gabriel J. Tobon, Laëtitia Le Pottier and Pierre Youinou. Brest University, Brest, France

Background: Elevated expression of ‘B cell activating factor belonging to the tumor necrosis factor family (BAFF), a potent B cell survival factor contributes to the expansion of low-affinity self-reactive B cells during the establishment of tolerance. However, mechanisms leading to BAFF over-expression in autoimmune settings, such as primary Sjögren’s syndrome (SS) or rheumatoid arthritis (RA) and in lymphoproliferation such as chronic lymphocytic leukemia (CLL) are not understood. To date, 3 transcriptional variants of the BAFF gene have been described, including Δ3BAFF, a truncated form that negatively regulates BAFF production. Herein, we examined the novel heterotrimers with full-length (FL) BAFF. Herein, we report the discovery and the role of a new transcript for BAFF due to the fact that exon 4 is spliced out.

Methods and Results: A 3' RACE-PCR was performed in B cells from SS patients and revealed another transcript with deletion of nucleotides 749 to 861 encoding the predicted exon 4. A new in-frame stop codon was artificially generated resulting in a truncated protein. A same alternate splice isoform was detected in mice. To assess the biochemical properties of the new variant of BAFF, RAMOS B cells were transiently transfected with pIRE52-EGFP-Δ4BAFF. Two bands at 21 and 17-kD prove to belong to 4BAFF protein in B cells from patients.

None; T. Sumida: None; H. Tsuboi: None; I. Matsumoto: None; T. Sumida: None.
cells from patients with CLL, in synovocytes from patients with RA or in epithelial cells from patients with SS.

**Conclusion:** We thus expand the view of BAFF gene regulation, which should contribute a better understanding of complex physiologic mechanisms involved in normal B cell survival, as well as in pathophysiology of autoreactive B cells. Our work introduces for the first time an entirely novel concept in biology suggesting that a human cytokine gene can be transcriptionally regulated by the activity of one of its own splice variants.

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**2178**

Local TACI-Ig Gene Therapy of the Salivary Gland of NOD Mice Reduces Auto-Immune Inflammation by Affecting the B Cell Compartment.

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**Background:** Sjögren’s syndrome (SjS) is characterized by inflammatory autoimmune exocrinopathy in which B cells and B cell-related factors are important. Some patients have benefited from the use of the pan B cell depleting agent rituximab, validating the B cell compartment as a therapeutic target. An alternative therapeutic approach could be to use the soluble receptor TACI, which binds BAFF and APRIL, factors important in B cell survival and activation. Overexpression of BAFF in mice leads to a SjS-like syndrome and BAFF and APRIL are aberrantly expressed in salivary glands (SG) of patients with SjS. Therefore, we evaluated the effect of blockade of APRIL and BAFF using local gene transfer of a gene encoding for a TACI-Ig fusion protein in the SG of Non-Obese Diabetic (NOD) mice that spontaneously develop a SjS-like disease.

**Material and Methods:** An adenovirus-associated virus serotype 2 (AAV2) vector encoding the TACI fusion protein was constructed by cloning of the extra-cellular domain of mouse TACI coupled to the Fc-part of mouse immunoglobulin (Ig) G1. Expression of this gene was driven by the CMV promoter. The TACI-Ig vector or a control vector expressing beta galactosidase (LacZ) was administered once locally into the SG of NOD mice at the age of 10 weeks. Stimulated saliva flow was determined 10 weeks post-vector delivery. Gene transfer was measured by QPCR and protein analysis of the transduced SG. Inflammation was assessed by quantitative immunohistochemistry as well as by analysis of Ig and cytokine levels in the SG and in serum.

**Results:** TACI-Ig was highly expressed following transduction of 293T cells, and media from transduced cells could block BAFF induced B cell proliferation in vitro. In vivo, retrograde canulation of mouse SG also resulted in stable transduction and expression of TACI-Ig as determined by QPCR and ELISA. No change in stimulated saliva flow was observed between TACI-Ig treated and control mice. However, TACI-Ig treated mice had reduced SG inflammation as determined by the number of inflammatory foci per cross sectional surface area of the SG (LacZ 3.8 vs TACI-Ig 2.6, p < 0.01) and pro-inflammatory cytokine levels (IL-2, IL-1β, IFN gamma) in the SG tended to be lower compared with control mice. Moreover, the numbers of B and plasma cells, were significantly lower (p<0.05) in the SG of treated mice, as well as IgG and IgM levels (50% and 41% reduction respectively, p<0.05). IgA levels did not change resulting in a significant improvement of the IgA/IgG ratio for the treated mice. Systemically, no significant changes in IgA levels did not change resulting in a significant improvement of the IgA/IgG ratio for the treated mice. Systemically, no significant changes in Ig-subtypes or cytokine levels were observed.

**Discussion:** The results presented here suggest that local B-cell targeted therapies may be beneficial in the treatment of SjS. The expression of a soluble TACI-Ig fusion protein in SG of NOD mice decreased autoimmune inflammation by reducing the number of B and plasma cells locally. The observed changes in IgG and IgM and the reduced IgG/IgA ratio levels suggest restoration of the balance of the mucosal immune system. When tested in patients with SjS, the timing of administration of the gene construct in the disease process may be critical in determining the outcome for salivary flow.

**Disclosure:** N. Roescher: None; J. L. Vosters: Dutch Arthritis Association grant [NR 07-1-406]; 2; M. Guadagnoli: None; J. P. Medema: None; G. G. Illei: None; J. A. Chiorini: NIH, 2; P. P. Tak: Arthrogen BV, Amsterdam, 9.

**ACR Concurrent Abstract Sessions**

**Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment - Biomarkers**

Wednesday, November 10, 2010, 4:30 PM–6:00 PM

**2179**

EBV-mir-Bart13 Downregulates Stim1, a Protein Involved in Calcium Signaling, in Human Salivary Gland Cells and May Contribute to the Pathogenesis of Sjogren’s Syndrome.

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**Background:** Loss of secretory function of salivary glands is one of the most important functional effects of Sjogren’s syndrome (SS), a chronic systemic autoimmune disease. Previous studies have reported the presence of Epstein Barr Virus (EBV) DNA in salivary glands of SS patients. MicroRNA profiling analyses in our laboratory have identified the EBV microRNA (ebv-mir-BART13) as significantly over-expressed in minor salivary gland biopsies of SS patients, when compared to the expression in minor salivary glands from non-Sjogren’s controls.

**Methods:** Using the RNA22 target prediction algorithm, we identified STIM1 3’UTR as a target of ebv-mir-BART13. Store-operated calcium entry (SOCE) and calcium release-activated calcium current (CRAC) are critical events for the replenishment of intracellular calcium stores and have indispensable roles in various cellular functions, including salivary secretion. SOCE is activated by the depletion of calcium in the endoplasmic reticulum (ER). STIM1, is a protein that has recently been identified as a critical molecular component of CRAC channels. STIM1, is suggested to be the ER-Ca2+ sensor protein regulating SOCE in a number of different cell types. Attenuation of SOCE current underlies salivary gland dysfunction in mice lacking transient receptor potential 1 (TRPC1). We hypothesized that ebv-mir-BART13 may contribute to the salivary gland dysfunction by down-regulating STIM1 and decreasing calcium influx in salivary gland epithelial cells.

**Summary of the Results:** To test this hypothesis, an expression plasmid was generated containing the 3’UTR of STIM1 downstream of the firefly luciferase coding sequence. The plasmid was co-transfected with ebv-mir-BART13 analogues and antagonists in HAS cells (human submandibular salivary gland cells). A 40% decrease in the intensity of the luciferase activity was observed 48 hrs after transfections, compared to controls, suggesting that ebv-mir-BART13 binds directly to the 3’ UTR of STIM1.

HAS cells were transfected for 24 and 48hrs, with ebv-mir-BART13 analog and the mRNA and protein levels of STIM1 were measured. The mRNA level was not affected by the presence of this viral miRNA. However, the protein level was dramatically decreased (over 70% decrease) both 24 and 48hrs after transfection, suggesting that the ebv-mir-BART13 exerts its effects on STIM1 not by degrading its transcript, but by repressing STIM1 translation. Functional Ca2+ assays through Thapsigargin-mediated depletion of the ER calcium in the ebv-mir-BART13 transfected cells showed a significant delay in the influx of calcium in the cytosol compared to controls.

**Conclusions:** Together, these functional measurements suggest that the presence of ebv-mir-BART13 in the salivary glands of SS patients might be, at least partially, responsible for the salivary gland dysfunction in those patients, by reducing the expression of STIM1, a critical member of the saliva secretion mechanism.

**Disclosure:** A. Gallo: None; M. Tandon: None; G. G. Illei: None; I. Alevizos: None.

**2180**

Striking Prevalence of Axial Spondyloarthritis in Primary Care Patients with Chronic Low Back Pain; a Cross-Sectional Study.

Lonneke van Hoven1, Jolanda Luine1, Huub Han2 and Angelique Weel3. 1Erasmus Medical Centre, 2Maasstadziekenhuis, 3Maasstadziekenhuis/Erasmus Medical Centre, Rotterdam, The Netherlands, 4Maassstadziekenhuis Rotterdam, Rotterdam, The Netherlands

**Background:** Chronic low back pain (CLBP) is one of the most common pain syndromes with unknown cause. Few studies however report that 5-7% is caused by Ankylosing Spondylitis (AS), a disease that until recently could be diagnosed 7–10 years after first presentation of symptoms. Since treatment of AS is most successfully in an early stage of the disease, the ASAS group
developed new criteria to diagnose axial Spondyloarthritis (aSpA) early. Early treatment requires early recognition and should therfore be done in primary care. Until now however, prevalences of aSpA in primary care patients with CLBP are missing.

**Purpose:** To determine the prevalence of aSpA in primary care patients with CLBP classified by ASAS criteria. To assess the diagnostic value of clinical tests commonly available to GPs and inflammatory back pain (IBP) questionnaires completed by patients themselves.

**Method:** In this cross-sectional study primary care patients with CLBP aged 19–45 years were identified from GP records by the International Classification of Primary Care code L03. All patients completed IBP questionnaires, (ASAS, Calin and Berlin) and underwent a complete history and physical examination by rheumatologist. Blood was drawn to assess HLAB27 and CRP. Sacroiliac joints (SIJ) were imaged by conventional radiography and MRI (Siemens Essenza). All images were scored by two experienced MSD radiologist, without any clinical information. Radiographic sacroilitis was defined by Modified New York criteria and MRI (T1, T2 and fat suppression series) evaluation followed ASAS recommendations. 3

**Results:** 364 patients (43% male, 36.3 yrs (sd 6.8), 9 yrs (sd 7.4) of symptoms) were evaluated. The overall prevalence of aSpA was 21.5 % (n = 77); using the ASAS criteria, n = 52 were diagnosed by the MRI criteria with one other SpA feature and n = 12 were diagnosed by a positive HLA B27 and two other SpA features. Based on the modified New York criteria we identified 6.6% (n = 24) of which 75% also fulfilled the ASAS criteria. Figure 1 shows the diagnostic value of characteristics available to GPs and IBP questionnaires. Highest post probability test were achieved for the diagnostic test HLAB-B27 and X-SIJ with respectively 68.3% and 75%.


Diagnostic value of clinical available tests in GP practice; Pretest 21.5%

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Post test** %</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36.4</td>
<td>55.8</td>
<td>18.1</td>
</tr>
<tr>
<td>BMI &lt; 25</td>
<td>31.2</td>
<td>61.3</td>
<td>17.8</td>
</tr>
<tr>
<td>Uveitis*</td>
<td>3.9</td>
<td>98.6</td>
<td>42.9</td>
</tr>
<tr>
<td>Crohn’s/coilitis*</td>
<td>3.9</td>
<td>99.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Positive family history*</td>
<td>22.1</td>
<td>92.0</td>
<td>42.5</td>
</tr>
<tr>
<td>Good response to NSAID*</td>
<td>76.5</td>
<td>52.5</td>
<td>33.1</td>
</tr>
<tr>
<td>Inflammatory back pain*</td>
<td>29.9</td>
<td>86.0</td>
<td>36.5</td>
</tr>
<tr>
<td>Peripheral arthritis*</td>
<td>13.0</td>
<td>93.7</td>
<td>35.7</td>
</tr>
<tr>
<td>Dactyliitis*</td>
<td>5.2</td>
<td>96.9</td>
<td>30.8</td>
</tr>
<tr>
<td>Enthesitis*</td>
<td>10.4</td>
<td>85.0</td>
<td>15.7</td>
</tr>
<tr>
<td>Psoriasis*</td>
<td>6.5</td>
<td>95.5</td>
<td>27.8</td>
</tr>
<tr>
<td>Any of*</td>
<td>40.3</td>
<td>74.7</td>
<td>32.3</td>
</tr>
</tbody>
</table>

**Diagnostics**

| CRP >10 mg/l | 11.7 | 95.8 | 42.9 |
| HLAB-B27 pos | 19.5 | 98.3 | 75.0 |
| X-SIJ | 36.4 | 95.5 | 68.3 |

**IPB Questionnaire**

| Calin | 85.7 | 27.2 | 24.0 |
| ASAS | 55.8 | 67.2 | 31.4 |
| Berlin | 79.2 | 34.1 | 24.4 |

**Conclusion:** In this cross-sectional study of primary care patients with CLBP the prevalence of aSpA based on the ASAS criteria is strikingly high. Additional ‘red flag’ symptoms determined by medical history and IBP questionnaires have modest diagnostic value. However, determine HLAB-B27 and X-ray of SIJ could help physicians in primary care identifying patients that should have accelerated referral to rheumatologist to start accurate treatment as early as possible.

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2181

Screening for Axial Spondyloarthritis in a Primary Care: Comparison of Two Strategies in a Multicenter Prospective Study. Denis Podddubny1, Janis Vahlidiek1, Inge Spiller1, Beate Buss1, Martin Rudwaleit1 and Joachim Sieper2. 1. Charité - Campus Benjamin Franklin, Berlin, Germany, 2. Charite Campus Benjamin Franklin, Berlin, Germany.

**Background:** The delay between first symptoms of axial spondyloarthritis (SpA) and the final diagnosis has been reported in different surveys to be still between 5 and 10 years. A major reason for such a delay in the diagnosis is the difficulty in identifying axial SpA patients among the large group of patients with chronic back pain in primary care. The current prospective randomized study was designed 1) to confirm the applicability of the established referral strategy [1, 2] in a multicenter study with rheumatologists not specialized in SpA and with primary care physicians, 2) to investigate whether this strategy can be improved by comparing it with a second strategy including additional screening parameters and asking for at least two parameters to be positive in case of referral.

**Methods:** Primary care physicians (n = 259) were randomly assigned either to strategy 1 or strategy 2 for referral of patients with chronic back pain (duration of more than 3 months), age of back pain onset <=45 years and no diagnosis of axial SpA to a cooperating rheumatologist (n = 43) for further diagnostic workup. According to strategy 1 suitable patients were referred if at least one of the following 3 screening parameters was present: HLAB-B27, inflammatory back pain (IBP), or sacroilitis detected by imaging. According to strategy 2, patients were referred if 2 out of 5 parameters were positive: the same 3 parameters from strategy 1 and additionally a positive family history of ankylosing spondylitis (AS) or a good treatment response to non-steroidal anti-inflammatory drugs. The final diagnosis of the rheumatologist was used as the gold standard.

**Results:** 560 consecutively referred patients were included in this analysis. Among 318 patients referred via the 1st strategy 41.8% (n=133) were diagnosed with definite axial SpA; AS in 61.7% (n=82) and non-radiographic axial SpA in 38.3% (n=51) of all axial SpA cases. Among 242 patients referred via the 2nd strategy, 36.8% (n=89, p>0.05 vs strategy 1) were diagnosed with definite axial SpA; similarly, AS in 61.8% (n=55) and non-radiographic axial SpA in 38.2% (n=34) of the SpA cases. The probability of the axial SpA diagnosis was clearly increased with the increase of the number of positive referral parameters. The most common referral parameter in both strategies was IBP but the best performance demonstrated HLAB-B27 in strategy 1 (with 57.7% of the referred with this parameter patients diagnosed as axial SpA) and sacroilitis by imaging in strategy 2 (axial SpA was diagnosed in 53.3% of the patients). The best combination of two referral parameters in both strategies was the combination of HLAB-B27 with sacroilitis by imaging with about 70% of the patients diagnosed as axial SpA.

**Conclusion:** The simpler referral strategy 1 confirmed it’s applicability in a multicenter study and demonstrated a slightly better performance in comparison to strategy 2. Therefore, strategy 1 can be recommended as an easy and reliable screening method for axial SpA on the primary care level.

**References**


Disclosure: D. Podddubny: None; J. Vahlidiek: None; I. Spiller: None; B. Buss: None; M. Rudwaleit: None; J. Sieper: None.

2182

Do the New EULAR/ACR Rheumatoid Arthritis Classification Criteria Identify Early Psoriatic Arthritis Patients? Laura C. Coates1, Philip G. Conaghan1, Paul Emery1, Michael J. Green3, Gamal Ibrahim1, Helen Makiiv1 and Philip S. Hellwell2. 1. Bradford Hospitals NHS Trust, UK; 2. Bradford, United Kingdom; 3. LIMM, Section of Musculoskeletal Disease, University of Leeds, UK, 4. York Hospitals NHS Trust, York, UK.

**Background:** The new ACR-EULAR classification criteria for rheumatoid arthritis (RA) have been developed to enable an early identification of patients with RA. They were tested during development in undifferentiated arthritis populations. The aim of this study was to investigate whether the new ACR/EULAR criteria for early RA are robust in excluding PsA and whether any patients would meet both these criteria and PsA classification criteria.

**Methods:** The new ACR/EULAR criteria for early RA and the Moll & Wright and CASPAR criteria for PsA were applied to cases of early PsA (less than 24 months symptom duration) early RA and other forms of
early inflammatory arthritis who were all disease-modifying anti-rheumatic drug naive. Gold standard diagnosis was confirmed by a consultant rheumatologist. All joints required for the ACR/EULAR criteria were assessed.

**Results:** 111 early PsA cases, 82 early RA cases and 29 other early arthritis controls (undifferentiated arthritis n=13, spondyloarthritides n=9, inflam OA n=4, crystal arthritis n=3) were recruited. The sensitivity of the ACR/EULAR criteria (score ≥6) in classifying early RA was 91%. The specificity for the criteria when considering all other diagnoses was 53%. When considering the specificity only for PsA, it was lower at 48%. When comparing classification criteria for RA and PsA, none of the PsA patients met the PsA criteria (either Moll&Wright or CASPAR), and only 1 of the other inflammatory arthritis patients fulfilled these criteria. The majority of PsA patients who met the RA classification criteria also met a PsA classification criteria.

<table>
<thead>
<tr>
<th>ACR/EULAR criteria components (%)</th>
<th>Early PsA (n=111)</th>
<th>Early RA (n=82)</th>
<th>Other controls (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovitis of at least 1 joint</td>
<td>92</td>
<td>96</td>
<td>83</td>
</tr>
<tr>
<td>1 large joint only</td>
<td>46</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>2–10 large joints</td>
<td>53</td>
<td>46</td>
<td>59</td>
</tr>
<tr>
<td>1–3 small joints</td>
<td>23</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>4–10 small joints</td>
<td>41</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>&gt;10 joints including 1 small</td>
<td>30</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>Neg RF and ACPA</td>
<td>94</td>
<td>20</td>
<td>79</td>
</tr>
<tr>
<td>Low positive RF or ACPA</td>
<td>4</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>High positive RF or ACPA</td>
<td>3</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Duration ≥6 weeks</td>
<td>99</td>
<td>98</td>
<td>83</td>
</tr>
<tr>
<td>Raised CRP or ESR</td>
<td>48</td>
<td>77</td>
<td>63</td>
</tr>
</tbody>
</table>

**Conclusion:** The new ACR/EULAR criteria are sensitive at identifying early RA but are not specific when considering psoriatic arthritis. The majority of PsA patients met the criteria due to high joint counts despite having negative immunology. The ACR/EULAR criteria must be used with caution in an early arthritis population particularly when patients have evidence of skin or nail psoriasis.

**Disclosure:** L. C. Coates: None; P. G. Conaghan: None; P. Emery: None; M. J. Green: None; G. Ibrahim: None; H. MakIver: None; P. S. Helliwell: None.

## 2184

**Suppression of Both DKK-1 and SOST in a Mouse Model of Ankylosing Spondylitis Implicates the WNT-Signalling Pathway in the Linkage of Inflammation and Bony Ankylosis in Spondyloarthristis.** Gethin P. Thomas1, Ran Duan2, Allison Pettit2, Tibor Giant1 and Matthew A. Brown2.

1Rush University Medical Center, 2The University of Queensland Diamantina Institute, 3The University of Queensland Diamantina Institute, 4University of Queensland Centre for Clinical Research

Ankylosing spondylitis (AS) is characterised by inflammation at entheses particularly in the spine and pelvis. Unlike in seropositive rheumatopathies in which erosion is the usual consequence of uncontrolled arthritis, in AS inflammation is followed by bony ankylosis. Although the inflammatory stages can be controlled medically, very little is known about the progression to the uncontrolled bone formation and no therapies are available that can slow this progression.

The proteoglycan-induced spondylitis model (PGISp) is a well-characterised mouse model of AS. Disease is induced by injections of a human proteoglycan extract, with axial inflammation evident after 9-weeks in the spine and sacroiliac joints. The resultant intervertebral disc destruction is followed by massive ectopic cartilage formation that eventually ossifies resulting in ankylosis, as demonstrated by toluidine blue staining and immunohistochemistry for collagen type I and osteocalcin.

To investigate the role of the Wnt-signalling pathway in this process, we studied the expression of two inhibitors of bone formation which act through the Wnt pathway, DKK-1 and SOST. Expression levels of both genes were significantly down-regulated in the spine and knee joints of PGISp mice. By week 12, DKK1 and SOST expression levels were reduced by 49% and 65% respectively in the spine, and by week 24 by 59% and 62% in peripheral joints, in PGISp compared with control mice (P<0.05).

We then undertook a microarray study comparing joints from control and PGISp mice. Unsupervised clustering clearly delineated between control and PGISp mice with 2600 genes being significantly differentially expressed between the two groups with 125 genes upregulated > 2-fold and 18 downregulated > 2-fold. In addition to genes involved in inflammation, and immune regulation, a significant over-representation of genes specifically involved in bone regulation including other members of the Wnt pathway was observed.
This study implicates the Wnt pathway as a likely mediator of the mechanism by which inflammation induces bony ankylosis in spondyloarthritis, raising the potential that therapies targeting this pathway may be effective in preventing this process.

Disclosure: G. P. Thomas: None; R. Duan: None; A. Pettit: None; T. Glant: None; M. A. Brown: None.

2185

Genetic and Clinical Correlates in African Americans with Ankylosing Spondylitis. Shervin Assassi1, Julie T. Dang1, Michael M. Ward2, Joel D. Taurog3, Michael H. Weisman4 and John D. Reveille5. 1Cedars-Sinai Medical Center, Los Angeles, CA, 2NIH, NIAMS, IRP, Bethesda, MD, 3Univ of Texas Health Science Center at Houston, 4Univ of Texas Health Science Center at Houston, Houston, TX, 5Univ Texas Health Sci Ctr, Houston, TX, 6U-Texas SW Med Ctr, Dallas, TX.

Background: There are few studies investigating disease characteristics of ankylosing spondylitis (AS) in African Americans (AA) because of the low prevalence of AS in this population. Furthermore, there are no previous studies, comparing disease severity between AA and white patients with AS.

The goal of this study was to compare clinical parameters in AA patients with AS to white patients and to examine associations of HLA-B, DRB1 and DQB1 alleles with AS in African Americans.

Method: Clinical data of 50 AA AS patients were derived from a cohort of 342 unrelated patients with AS. HLA class I and II alleles ascertained by DNA typing was performed on the AA AS patients as well as on 243 AA unaffected controls.

Results: AA AS patients had higher ESR, CRP, BASDAI, BASFI, and BASRI scores than white patients (Table). The difference in ESR, BASFI and BASRI remained significant despite correcting for disease duration, HLA-B27 status, gender, educational level and use of biologics. Despite higher disease burden, AA AS patients were less likely to be using biologic agents. This was especially pronounced in AA men with AS.

HLA-B27 negative African Americans with AS were older at disease onset, and had less frequently anterior uveitis compared to HLA-B27 positive AA patients.

HLA-B27 was present in 60% of AA patients, compared with 2% of AA controls. HLA-B*4001 (B60) was the only other HLA-B allele significantly increased among patients. Marginally significant increases were also seen in HLA-DRB1*1302 and DQB1*0501.

Conclusions: These data suggest that AA AS patients may have more severe disease than whites as well as a lower frequency of HLA-B27. Also, the association with HLA-B*4001 (B60) is seen in yet another ethnic group, in addition to whites and Asians.

Disclosure: S. Assassi: None; J. T. Dang: None; M. M. Ward: None; J. D. Taurog: None; M. H. Weisman: None; J. D. Reveille: None.

ACR Concurrent Abstract Sessions

Systemic Lupus Erythematosus - Animal Models

Wednesday, November 10, 2010, 4:30 PM - 6:00 PM

2186

Neutrophil Gelatinase Associated Lipocalin (NGAL) and Its Role in the Pathogenesis of Nephritis Induced by Pathogenic Antibodies. Rahul Pawar1, Simona Gindea2, Arlene T. Tieng2, Milena Pitashny2, Leil Herlitz2, Benjamin E. Levine2, Thorsten Berger5, Tak W. Mak3 and Chaim Putterman4. 1Albert Einstein College of Med, Bronx, NY, 2Albert Einstein College of Medicine, Woodmere, NY, 3Albert Einstein College of Medicine, Bronx, NY, 4Albert Einstein College of Medicine, 5Columbia-Presbyterian School of Medicine, The Campbell Family Institute for Breast Cancer Research, Toronto, ON, Canada

Background: Anti-dsDNA antibodies are instrumental in the pathogenesis of lupus nephritis, although the mechanism by which these antibodies contribute to kidney damage has yet to be determined conclusively. We had found that treatment of mesangial cells with pathogenic anti-dsDNA antibodies induced the expression of multiple proinflammatory mediators known to be associated with lupus nephritis. One of the most highly induced genes was NGAL (AKA Lipocalin-2). NGAL is upregulated in response to a variety of inflammatory, ischemic, and other insults to the kidney, and in fact is a sensitive and early urine biomarker in several types of human disease.

Purpose: To determine whether NGAL is expressed in the context of lupus nephritis, and investigate its role in the pathogenesis of renal injury induced by nephritogenic antibodies.

Methods: NGAL expression in serum, urine, and kidneys was analyzed serially in the MRL/lpr mouse lupus model. Nephrotoxic serum nephritis (NTS) was induced by passive transfer of preformed rabbit anti-mouse glomerular antibodies to C57Bl/6 wild type and NGAL deficient mice.

Results: With development of disease, MRL/lpr lupus mice displayed higher kidney NGAL expression than age-matched non-autoimmune mice. In addition, serum NGAL was significantly elevated in old MRL/lpr mice, as compared to young MRL/lpr, old MRL/+ and old BALB/c mice. Importantly, NGAL kidney expression in lupus mice significantly correlated with anti-dsDNA antibody titers and the renal pathology score. Significant elevations of kidney, serum and urine NGAL were observed as well in non-autoimmune mice following passive transfer of rabbit anti-mouse glomerular antibodies and induction of NTS.

To determine if NGAL upregulation is instrumental in antibody mediated nephritis, we compared the severity of renal damage in C57Bl/6 NGAL knockout and wild type mice following induction of NTS. We found that NGAL deficient mice had significantly attenuated proteinuria, and improved renal histopathology (decreased endocapillary proliferation and immune deposits) as compared to NGAL sufficient mice.

NGAL deficient mice display less kidney pathology following induction of NTS

Similarly, following NTS induction in non-autoimmune mice, NGAL injection significantly exacerbated nephritis (as assessed by increased proteinuria and more severe renal histopathology) and decreased survival. NGAL induced apoptosis via activation of caspase 3 and promoted the expression of inflammatory genes, in kidney cells in vitro and when injected to mice in vivo.

Conclusions: Nephritogenic antibodies upregulate kidney NGAL, which then appears to be instrumental in the pathogenesis of antibody mediated nephritis via promotion of inflammation and/or apoptosis. We are currently studying whether blocking NGAL may be a novel therapeutic approach for lupus nephritis.

Disclosure: R. Pawar: None; S. Gindea: None; A. T. Tieng: None; M. Pitashny: None; L. Herlitz: None; B. E. Levine: None; T. Berger: None; T. W. Mak: None; C. Putterman: None.

S917

Background: IFNα is a potent activator of innate and adaptive immunity, and it has been ascribed an important contributory role in SLE pathogenesis. It has previously been shown that administration of IFNα to pre-autoimmune NZB/NZW (NZB/NZW)1/F1 (BWF1) mice promotes rapid development of virulent SLE, whereas identical administration to non-SLE-prone BALB/c mice has no deleterious effect. Given the known importance of B cells and BAFF to SLE, we evaluated the dependence of IFNα-exaggerated disease on B cells and on BAFF in the BWF1-derived SLE-prone NZM 2328 (NZM) mouse model.

Methods: Fully congenic B cell-deficient NZM.JHD mice and BAFF-deficient NZM.BAFFKO mice were generated through the speed congenic approach. At 2–3 months of age (when autoimmunity had not yet developed in wild-type [WT] NZM mice), NZM WT, NZM.JHD, and NZM.BAFFKO mice were injected i.v. with 1–1.5 × 106 viral particles of either a recombinant adeno virus (Adv) vector containing murine IFNα subtype 5 under the control of the CMV promoter/enhancer (Adv-IFN) or the identical Adv vector lacking the IFNα insert (Adv-control). Mice were assessed for serum levels of SLE-associated IgG autoantibodies by ELISA; spleen lymphocyte phenotype by flow cytometry; renal immunopathology by routine histology, immunofluorescence, and immunohistology; severe proteinuria (>5-fold above baseline) in NZB/W F1 mice and to 3–6-mo-old BXD2 mice. In the present study, we determined if type I IFN can promote T-dependent antibody responses in BXD2 mice via its augmentation of the costimulatory function of MZ-P B cells.

Results: IFNα accelerates lupus in NZB/W F1 mice is associated with elevated serum levels of IgG2a and IgG3 anti-dsDNA antibodies, robust germline center formation and accumulation of large numbers of short-lived plasma cells in the spleen. SLE onset is associated with an increase in B cell TLR7 expression, increased levels of BAFF and IL-6, and induction of T cells expressing IL-21. Although IFNα drives IL-6 production and a polyclonal increase in serum levels of IgG in a T-independent fashion, autoantibody induction and the development of nephritis are both completely dependent on CD4 T cell help. However, neither CTLA4Ig nor anti-IL-21 prevented proteinuria onset despite inhibiting T cell activation, germline center formation, and production of IgG2a autoantibodies. This was due to failure to inhibit the generation of pathogenic IgG3 autoantibodies. In contrast, anti-4–1BB inhibited both IgG2a and IgG3 autoantibodies and prevented proteinuria onset. TACI-Ig did not prevent autoantibody formation, T cell activation or Ig deposition in the kidneys but still effectively delayed proteinuria onset by inhibiting renal chemokine production and preventing the activation of renal mononuclear cells. Remission could be induced with combination CTX/costimulatory blockade that depleted both IgG2a and IgG3 autoantibodies producing short-lived plasma cells thereby decreasing autoantibody deposition in the kidneys.

Conclusions: IFNα induces short-lived plasma cells that produce autoantibodies in a T cell dependent manner through both germlinal center and extrafollicular mechanisms. Prevention of germinal center formation is not sufficient to prevent SLE onset. Anti-4–1BB prevents both germinal center (IgG2a) and extrafollicular (IgG3) autoantibody formation and prevents SLE onset. Depletion of short-lived plasma cells produces the autoantibodies induces remission of disease. Surprisingly BAFF/APRIL blockade delays SLE without altering autoantibody or T cell activation; this is mediated via inhibition of the renal response to immune complex deposition but disease eventually ensues despite continuous treatment. These findings are relevant to interpreting results of recent clinical trials of biologic agents in SLE and suggest that the IFN signature confers a higher bar for therapeutic intervention.

Disclosure: Z. Liu: None; R. Bethunaickan: None; W. Huang: None; A. Davidson: Biogen Idec, 5, EMD Serono, 5, Medimmune, 5.

2189

Type 1 IFN-Dependent CD86hi Marginal Zone-Precursor B Cells Are Potent T Cell Costimulators in the BXD2 Mouse Model of Lupus. John S. Wang, Qi Wu, Ping-Ar Yang, Hao Li, Jun Li, John D. Mountz, and Hui-Chen Hsu.

Background: We previously showed that type I IFN producing plasma-cytoid dendritic cells (pDCs) upregulated the expression of CD69 on CD11c+CD21hiIgMhiCD23dim marginal zone precursor (MZ-P) B cells in the spleens of lupus prone BXD2 mice. This action promotes the follicular migration of antigen delivering MZ-P B cells directly to the germlinal centers (GC) in the BXD2 spleen. In the present study, we determined if type I IFN can promote T-dependent antibody responses in BXD2 mice via its augmentation of the costimulatory function of MZ-P B cells.

Methods: Confocal imaging was used to determine the location of pDCs, MZ-Ps and CD4 T cells in the spleens of BXD2 and BXD2-Ifnar–/– mice. H&E staining of spleen and kidney was used to determine the presence of IgGauto and IgG3auto cells in BXD2 and BXD2-CD86–/– mice. ELISA was used to determine serum levels of IFN-α, autoantibody, and NP-CCG- or NP-Ficol-induced anti-NP, antibody titers. The level of type I IFN transcripts in the peripheral blood was determined by quantitative real-time PCR. [3H]-thymidine was used to measure T cell proliferation.

Summary of the Results: There was increased clustering of pDCs located in the marginal sinus in the spleens of BXD2 mice, compared with B6 spleens. Consistent with this, RNA isolated from the peripheral blood of 3–6-mo-old BXD2 mice expressed >5-fold higher levels of Ifna1, Ifna4, and Ifna11, compared with those from B6 mice. Type I IFN receptor (IFNAR) deletion abrogated development of IgG2a and IgG3 cell formation and suppressed a T-dependent but not T-independent antibody response in BXD2 mice. Type 1 IFN signaling induced the expression of CD86, but not CD80, on CD11c+CD21hiIgMhiCD23dim follicular (FO), CD11c+CD21hiIgMhiCD23hi marginal zone, and MZ-P B cells. However, MZ-P B cells demonstrated the highest expression of CD86 and the highest capacity for T-cell costimulation with intact IFNAR. In BXD2, but not BXD2-Ifnar–/– mice, MZ-P B cells clustered at the intra-follicular T-B border, an important immunological junction where GC formation is initiated. Both IFNAR and CD86 deletion
suppressed GC formation, autoantibody production, and IgG deposits in the kidney.

Conclusions Reached: Our study proposes that type I IFN can offer a new avenue by which T-dependent autoantibody responses are generated in BXD2 mice. First, type I IFN is critical in bringing MZ-Ps to the T-B border in the FO interior at the pre-GC stage. Second, type I IFN significantly increases the levels of CD86 on MZ-Ps, providing potent costimulation to CD4 T cells. Because pDCs are systemically circulated between the peripheral blood and the spleen, the present study exhibit important pathogenic and mechanistic implication for the IFN signature in the peripheral blood of human lupus patients.

Disclosure: J. S. Wang: None; Q. Wu: None; P. Yang: None; H. Li: None; J. Li: None; J. D. Mountz: None; H.-C. Hsu: None.

Identification of a Genetic Locus on New Zealand Black Chromosome 1 Congenic Mouse That Leads to Increased Generation of T Follicular Helper and TH17 Cells. Nafiseh Talaei1, Yui-Ho Cheung2, Carolina Landolt-Marticorena3, Babak Noamani1 and Joan E. Wither. 1Toronto Western Research Institute, 2University Health Network, Toronto, ON, Canada, 3University of Toronto, 4University of Toronto, ON, Canada

Purpose: Genetic loci on the New Zealand Black mouse chromosome 1 have been linked to the development of glomerulonephritis (GN) and production of anti-nuclear antibodies. Congenic mice in which a NZB chromosome 1 (c1) interval, extending from 35–106 cM, produce anti-nuclear antibodies and develop mild glomerulonephritis (GN). By creating mice with smaller overlapping NZB c1 intervals, we found that at least 5 genetic loci modulate autoimmunity in this interval. Notably, mice with a 70–100 cM interval (c1(70–100 cM)) developed high titre anti-dsDNA antibodies and severe GN resulting in death of ~40% of mice by 8 months of age, whereas those with a smaller 96–100 interval (c1(96–100)) produced lower levels of anti-nuclear antibodies and lacked renal disease. A prominent feature of c1(70–100) mice was increased numbers of large germinal centers, which can be seen in mice with expansion of T follicular helper cells (TFH). The current study was undertaken to determine whether genetic loci on NZB c1 lead to expansion of TH17 and determine the cytokine profile of these cells.

Methods: c1(35–106 cM), c1(70–100 cM), and c1(96–100 cM) congenic and B6 control mice were aged to 4 months. The proportion and number of splenic TH17 cells was determined by flow cytometry. To evaluate cytokine production, splenocytes were stimulated with PMA/ionomycin for 24 h and the supernatant assayed by Cytometric Bead Array or ELISA. IL-4, IFN-g, or IL-17 producing cells were quantified by stimulating splenocytes with PMA/ionomycin for 24 h and examining intracellular cytokine expression by flow cytometry. Splenic sections were used to visualize the presence of TH17 and IL-17-producing CD4+ T cells in the germinal centers using immunofluorescence microscopy.

Results: The proportion of TH17 (CD4+ CD44hiCD26liCXCR5+) was significantly increased in c1(70–100) and c1(35–106) mice, with the highest levels seen in c1(70–100) mice. Splenocytes from all c1 congenic mouse strains demonstrated increased production of IL-21 and IL-17 following stimulation of PMA and ionomycin with the greatest increase seen in c1(70–100) mice and intermediate levels in c1(35–106) mice. Similar findings were observed for the proportion of IL-17-producing CD4+ cells. No differences were seen for production of IL-4 and IFN-g between B6 controls and congenic mouse strains, although c1(70–100) and c1(35–106) mice had increased proportions of IFN-g-producing CD4+ cells. Immunofluorescence microscopy confirmed the presence of increased numbers of TH17 cells in c1(70–100) and c1(35–106) mice, and revealed that the majority of IL-17 producing cells in c1(70–100) mice were located in the T cell zone and not the germinal center.

Conclusion: The findings suggest that a genetic polymorphism(s) on NZB c1 leads to expansion of TH17 and IL-17-producing T cells and that the levels of these cell populations are closely associated with the severity of disease.

Disclosure: N. Talaei: None; Y.-H. Cheung: None; C. Landolt-Marticorena: None; B. Noamani: None; J. E. Wither: None.

2191 Histone Deacetylase 9 Acts as an Epigenetic Switch in Aberrant CD4 T Cell Plasticity and PPAR-g Regulation in Systemic Lupus Erythematosus. Nilamadhab Mishra1, Kautil Yan1, Qiang Cao1, Christopher M. Reilly1, Jennifer Can1 and Benjamin A. Garcia1. 1Princeton University, 2Virginia Polytechnic Institute and State University and Edward Via College of Osteopathic Medicine, 3Wake Forest Univ Health Science, Winston-Salem, NC, 4Wake Forest University School of Medicine, 5Wake Forest Univ Health Sciences, 6Wake Forest Univ Health Sciences

Pharmacological inhibition of histone deacetylase (HDAC) activity provides a therapeutic benefit in murine model of SLE, but clinical efficacy remains to be established. Understanding the role of individual HDAC that plays in lupus pathogenesis may lead to development of isoform specific HDAC inhibitors for better tolerability and efficacy in lupus. To identify which HDAC play significant role in lupus disease we first surveyed HDACs in splenocytes, T cells, kidneys in MRL/lpr mice and human lupus CD4+ T cells. In this study, we report that HDAC9 is overexpressed in lupus prone MRL/lpr mice and human lupus CD4+ T cells compared to controls. To explore the role of HDAC9 in pathogenesis of lupus, we generated MRL/lpr mice with systemic HDAC9 deficiency by genetic deletion approach. We demonstrated that MRL/lpr mice deficient with HDAC9 have decreased lymphadenopathy, splenomegaly, serum levels of high-affinity dsDNA autoantibodies, proteinuria, immunocomplex deposit in kidney, glomerulonephritis and increased survival. HDAC9 deficiency resulted Th2 polarization, decreased DNT cells, ICOS positive T effector cells, plasma cells and increased regulatory T cells in MRL/lpr mice. This epigenetic switch of CD4+T cells as a result of HDAC9 deletion are due to changes in lineage specific master regulator transcription factors of CD4+ T effector and regulatory cells. HDAC9 deficient MRL/lpr mice have increased Fosp3, GATA3, and decreased Bcl6 expression. Increased expression of roquin, and miRNA101 contributed to the decrease expression of ICOS in HDAC9 deficient MRL/lpr mice. Upregulation of PPAR-g resulted decreased IFN-g, IL-12, iNOS, MCP1, CXCR3, CXCR4, CXCR5, CXCR6, and CXCR9 which resulted decreased inflammatory cells in kidney and peripheral tissues in HDAC9 deficient MRL/lpr mice. HDAC9 deficiency created changes in chromatin landscape selectively by increased site specific lysine histone acetylation in H3 (H3K9, H3K14 and H3K18) globally and locally in gene specific manner (IL-4, Fosp3, roquin and PPAR-g genes). Together, our results unveil an epigenetic switch regulatory role of HDAC9 in aberrant CD4+ T cell plasticity in MRL/lpr mice. Therefore, targeting HDAC9 by a specific inhibitor may provide therapeutic benefit in lupus, possibly, with fewer side effects.Finally, measurement of levels of different histone modifications particularly site specific histone acetylations (H3K9, K14 and K18) may provide a biomarker for selecting lupus patients most likely to benefit from HDAC9 inhibitors.

Disclosure: N. Mishra: None; K. Yan: None; Q. Cao: None; C. M. Reilly: None; J. Cann: None; B. A. Garcia: None.

ACR Concurrent Abstract Sessions
Systemic Sclerosis, Fibrosing Syndromes, and Raynaud’s - Clinical Aspects and Therapeutics
Wednesday, November 10, 2010, 4:30 pm–6:00 pm

2192 Long-Term Benefit of Mycophenolate Mofetil for Treatment of Diffuse Cutaneous Systemic Sclerosis. Elizabeth Le1, Fredrick M. Wigley1, Ami A. Shah1, Francesco Boin1 and Laura K. Hummers1. 1Johns Hopkins University, Baltimore, MD, 2Johns Hopkins University, Baltimore, MD, 3Johns Hopkins University

Background: No drug has been demonstrated to successfully control active diffuse cutaneous scleroderma, but immunosuppressive therapy, particularly if given at the early inflammatory phase of diffuse skin disease, could alter the natural course of the disease. In this observational study, we analyzed our Scleroderma Center’s experience using mycophenolate mofetil (MMF) for treatment of diffuse skin disease and compared changes in skin score with data from historical controls.

Methods: Scleroderma patients in our Center’s database started on MMF primarily for active skin disease were included in the analysis. Historical controls were obtained from 3 large multicenter randomized clinical trials (RCTs) of other medications (D-penicillamine (D-pen), Recombinant Human
Relaxin (Relaxin), and Oral Bovine Type I Collagen (Collagen Trials). Data from these 3 RCTs were pooled and analyzed irrespective of treatment assignments because none of the primary and secondary outcomes differed in the active agent groups compared with the placebo or control groups. The overall mean change in modified Rodnan skin scores (mRSS) at 6 months for the Relaxin group, and at 12 months for the D-pen and Collagen groups were compared to those of our MMF cohort at 6 and 12 months, respectively, using Student’s t-tests.

**Results:** Of 2571 patients in our database, 99 patients satisfied our inclusion criteria and were included in the primary analysis. Patients were mostly female (82%) of white (76%) or black (14%) race. The mean age at MMF initiation was 48.2 ± 11.2 years, and the mean scleroderma duration at MMF initiation was 21.8 ± 77.5 months with a median of 12 months (IQR 8–23). The median MMF dose was 3 grams daily (range 0.5–3 gm daily). The mean baseline mRSS of the MMF cohort was 12 months (IQR 8–23). The median MMF dose was 3 grams daily.

L. K. Hummers: None; M. Mehta: None; H. Wildman: None; S. Kloiber: None; K. A. Kirou: None; None; M. Crow: None.

**Disclosure:** R. F. Spiera: Bristol-Myers Squibb, 2, Novartis Pharmaceuticals Corporation, 2, United Therapeutics, 2, J. K. Gordon: None; J. Mersten: None; C. Magro: None; M. Mehta: None; H. Wildman: None; S. Kloiber: None; K. A. Kirou: None. None; None.

**S920**

**2194**

**Serious Complications and Mortality among 158 Patients with Systemic Sclerosis (SSc) in the Scleroderma Lung Study (SLS) Followed for up to 9 Years.** Daniel E. Furst1, Dinesh Khamana2, Philip J. Clements3, Keith Sullivan1 and Donald P. Tashkin2. 1Duke, Durham, NC, 2UCLA. 3University of California Los Angeles, Los Angeles, CA. 4University of California Los Angeles Medical School, Los Angeles, CA. 5University of California Los Angeles School of Medicine, Los Angeles, CA.

**Objectives:** To examine the mortality and serious complications of SSc in SLS patients, in up to 9 yrs f/u.

**Methods:** Pt’s: In 158 SSc patients (59% diffuse,41% limited), age: 47.9(1.0) yrs; dis dur:3.2(0.2) yrs;mRSS:14.7(0.9).All had alveolitis by lung HRCT of the lungs and/or BAL. FVC: 68.1(1.0) % pred;DLCO 47.2(1.1) % pred. Renal function was normal. They had entered the 1 yr, double-blind, study of cyclophosphamide vs. placebo and then underwent usual clinical care for the ensuing 4.7(1.8) yrs, thru 11/2009 or until death or loss to f/u.

**Results:** 72% of pt’s had complete or nearly complete data. Mortality data was available on 134 patients but complete date were available in 52 pt’s.5 yr mortality was 31.4- and 23.2%-Plac(p=0.92).Cancer caused death in 2 pt’s (colon and angiosarcoma) and occurred in 5 others (still alive) (breast, prostate, vulva, 2 unknown primary). 2 pts required total parenteral nutrition (2/108,1.8%),2 required dialysis(2/109,1.8%) and no pt’s underwent renal transplantation. 22 pt’s(32/109,20.3%) required at least intermittent oxygen therapy and 2 underwent lung transplantation (2/108, 1.9%).

**Conclusion:** Among SSc pt’s with alveolitis but generally moderate disease of moderate duration, mortality was surprisingly high over 9 yrs (27%). The need for oxygen occurred commonly (20.3%). Renal dialysis,TPN and lung transplantation were noted(1.8–1.9%). Cancers were not those usually associated with cyclophosphamide or immunosuppressive therapy, despite f/u for up to 9 yrs.

**Table 1. Demographics**

<table>
<thead>
<tr>
<th>Diffuse SSc</th>
<th>59%</th>
<th>mRSS (max: 51)</th>
<th>14.7 (1.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>47.9 (1.4)</td>
<td>Alveolitis</td>
<td>100%</td>
</tr>
<tr>
<td>Disease Duration (yrs)</td>
<td>3.2 (0.3)</td>
<td>FVC (% predicted)</td>
<td>68.1 (1.5)</td>
</tr>
<tr>
<td>DLCO (% predicted)</td>
<td>47.2 (1.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Objective: Scleroderma (SSc) is associated with functional disability and poor quality of life. This study examines the productivity of SSc outside and within the home in a large observational cohort.

Methods: 162 patients completed the Work Productivity Survey (Osterhaus, J., Arthritis Research and Therapy 2009) at baseline. Patients indicated whether or not they were employed outside of the home, how many days/month they missed work (employment or household work) due to SSc, how many days/month productivity was decreased ≥ 50%, and how many days per month where SSc interfered with work. Patients also completed other patient-reported outcome (PRO) measures (HAQ-DI, Functional Assessment of Chronic Illness Therapy (FACIT), and CESD). We developed binomial regression models to assess the predictors of days missed at home per month or days missed outside the home per month. The covariates included: type of SSc, education, physician global assessment, patient global assessment, HAQ-DI, FACIT-Fatigue and CESD.

Results: The average age of patients was 51.8 years, 81% were female, 69% were Caucasian, 51% had limited SSc, 41% had diffuse SSc, and 7% had overlap syndrome. Sixty patients (37%) were employed outside of the home, with a majority employed in non-manual work (68%). Employed patients reported missing 2.6 days per month of work (absenteeism), had 2.5 days per month productivity reduced by half (presenteeism), and had 2.2 days per month where SSc interfered with their work (Table). Of the 102 patients that were not employed outside of the home, 39.4% were unable to work due to SSc related health problems, 12.1% were homemakers, 28.3% were retired and 5.05% were students. Patients missed an average of 8 days of housework per month, had home productivity reduced by more than 50% in 6 days per month, and had 4 days where SSc interfered with household work.

In the regression models, patients with lower education and greater physician assessment of disease severity were more likely to miss work outside the home. Type of SSc (limited or diffuse) did not influence productivity but those with high HAQ-DI were more likely to miss work at home.

Table 1.

Productivity in the work place†

<table>
<thead>
<tr>
<th>Activity</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work days missed (absenteeism), mean (SD)</td>
<td>2.6 (6.3)</td>
</tr>
<tr>
<td>Days with work productivity reduced by ≥ 50% (presenteeism), mean (SD)</td>
<td>2.5 (6.1)</td>
</tr>
<tr>
<td>Days of SSc interference with work productivity, mean (SD)</td>
<td>2.2 (2.9)</td>
</tr>
</tbody>
</table>

Productivity at home

<table>
<thead>
<tr>
<th>Activity</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household work days missed, mean (SD)</td>
<td>8 (10.6)</td>
</tr>
<tr>
<td>Days with household work productivity reduced by ≥ 50%, mean (SD)</td>
<td>6 (9.7)</td>
</tr>
<tr>
<td>Days with family, social, leisure activities missed, mean (SD)</td>
<td>2.5 (5.5)</td>
</tr>
<tr>
<td>Days with outside help due to SSc, mean (SD)</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Days of SSc interference with household work productivity, mean (SD)</td>
<td>4 (3.4)</td>
</tr>
</tbody>
</table>

†Employed patients only. n = 60.

Conclusion: SSc has a major impact on productivity at home and at work. Nearly 40% of patients are disabled due to their SSc. Education, physician assessment and HAQ-DI were independent predictors of low productivity.

Disclosure: M. K. Singh: None; P. J. Clements: None; D. Furst: None; P. Maranian: None; D. Khanna: NIAMS-NIH, 2.
Background: Classification criteria for Systemic Sclerosis (SSc) are being updated as the previous ACR criteria did not regard all patients with limited cutaneous SSc, and did not include autoantibodies or nailfold capillaroscopy as items.

Objective: To select a set of items using Delphi procedures and the Nominal Group Technique (NGT) to be regarded for the classification of SSc.

Methods: Potential items for revising classification criteria for SSc were identified through two independent internet based consensus exercises, performed by the Scleroderma Clinical Trials Consortium (SCTC) and the EULAR scleroderma trials and research group (EUSTAR). The two first-round item lists were collated with removal of redundancies to a list of 168 items. This list was subjected to a Delphi procedure in three rounds using appropriateness scores on a 1–9 scale (1=completely inappropriate and 9=completely appropriate) and a consensus meeting using NGT.

Results: Round 1: 105 experts participated rating each of the 168 items. Items with a median score <3 were removed, resulting in a list of 102 items. Round 2: These items were again rated for appropriateness and subjected to a consensus meeting using NGT by European and North American SSc experts (n=16), resulting in 24 items. Round 3: The participants then individually scored each of the 24 items in a last Delphi round, using an appropriateness score (1–9) and by ranking their 10 favorites (top ranking 1–10). Items scored as relevant (70% of ratings in 7–9) were kept and ranked according to their top ranking while items scored as irrelevant (70% of ratings in 1–3 but less than 30% in 7–9) were discarded. This resulted in a list of 12 items that were kept (Table 1) and 12 ‘indecisive’ items, while no item was scored as irrelevant. The indecisive items were: Dermo, FVC, dysphagia, esophageal dilatation, reflex disease, telangiectasia, finger flexion contracture, tendon friction rubs, ANA, anti-PM/MSCL autoantibodies, PAH, puffy fingers, finger pulp loss, calcinosis and cardiomyopathy.

Table 1.

<table>
<thead>
<tr>
<th>Item</th>
<th>Appropriateness score (median)</th>
<th>TOP score</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive anti-topoisomeraser-I</td>
<td>9</td>
<td>73%</td>
<td>1</td>
</tr>
<tr>
<td>Presence of scleroderma</td>
<td>9</td>
<td>70%</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal nailfold capillary pattern</td>
<td>9</td>
<td>67%</td>
<td>3</td>
</tr>
<tr>
<td>Positive anti-centromere</td>
<td>9</td>
<td>62%</td>
<td>4</td>
</tr>
<tr>
<td>Positive anti-RNA polymerase III</td>
<td>8</td>
<td>43%</td>
<td>5</td>
</tr>
<tr>
<td>Finger tip ulcers or pitting scars</td>
<td>8</td>
<td>34%</td>
<td>6</td>
</tr>
<tr>
<td>Raynauds phenomenon</td>
<td>7</td>
<td>33%</td>
<td>7</td>
</tr>
<tr>
<td>Interstitial lung disease/pulmonary fibrosis</td>
<td>7</td>
<td>28%</td>
<td>8</td>
</tr>
<tr>
<td>Renal crisis</td>
<td>6</td>
<td>27%</td>
<td>9</td>
</tr>
</tbody>
</table>

Conclusion: The Delphi and NGT resulted in a set of items that will be assessed for their discriminative ability in a prospective study. Prospective data on SSc and ‘mimickers’ will be collected to yield further item reduction and development of new classification criteria for SSc.

Disclosure: J. Fransen: None; S. R. Johnson: None; A. Tyndall: None; M. Baron: None; M. Matucci-Cerinic: None; F. van den Hoogen: None; J. E. Pope: None; D. Khanna: None.

Antinuclear Antibody Screening in Systemic Sclerosis. Donna Rose Swistowski1, Nicole Sadding2, Victoria K. Shanmugam1 and Virginia D. Steen3. 1Georgetown University Division of Rheumatology, Immunology, and Allergy, Great Falls, VA; 2Georgetown University Division of Rheumatology, Immunology, and Allergy, Bethesda, MD; 3Georgetown University Hospital Department of Medicine, 4Georgetown University Medical Center, Washington, DC

Purpose: Scleroderma specific antinuclear antibodies (SScAB) are helpful predictors of disease manifestations, clinical course and outcome in scleroderma. Historically, immunofluorescence (IF) antinuclear antibody (ANA) testing was the gold standard method for ANA detection, and the American College of Rheumatology continues to recommend IF for evaluation of ANA. Many commercial labs have recently adopted newer, automated, non-immunofluorescence methods (NEW ANAs), such as EIA (enzyme immunoassay) or immunobead methods to evaluate for the presence of antinuclear antibodies. These new techniques rely on a limited panel of autoantigens in the assay.

The purpose of this study was to evaluate ANAs and SScAB results performed through commercial labs, using both NEW ANA detection techniques and traditional IF, in a consecutive cohort of scleroderma patients seen in the Georgetown Scleroderma Clinic over a one year period.

Methods: Between June 2008 and June 2009, 241 scleroderma patients were evaluated. Patient charts were reviewed for results of NEW ANA, IF-ANA, isolated nuclear ANA pattern (NuANA), and the SScAB profile including anticentromere (ACA), anti-topoisomerase (Scl-70), U1 RNP, and RNA polymerase III (Pol III) antibodies.

Results: The results of this study are summarized in Table 1. NEW ANA results were available in 58 patients with 28 patients (48%) testing negative. Of these 28 patients, 22 had either positive IF-ANA or a SScAB recorded: IF-ANA only (n=7), NuANA (n=6), Pol III (n=7), SSB (n=1), U1 RNP (n=1). In the patients with a positive NEW ANA (n=30) the NEW ANA successfully detected all patients with ACA (n=4), Scl-70 (n=13), U1 RNP (n=6), and SSA (n=1) antibodies. A positive NEW ANA additionally identified Pol III (n=1), NuANA with a + SSA (n=3), and nonspecific ANA (n=2). However, the NEW ANA failed to identify the NuANA, Pol III antibodies, and other IF-ANA patterns in a significant number of patients (20/22 vs. 6/30, p<0.0001).

The remaining 183 SSc patients did not have NEW ANA testing available. Of these patients, 156 (85%) had positive SScABs or an IF-ANA. ACA was present in 22.4%, Scl-70 in 25%, and U1 RNP in 9.6%. This accounts for 57% of patients who we predict would be identified with the NEW ANA assay. However, patients with other antibodies including Pol III (10.2%), NuANA (19.2%), and nonspecific ANA patterns (13.5%), account for 40% of the scleroderma patients in our population, and we predict these patients would not be identified using NEW ANA assays.

Conclusions: Immunofluorescence ANA should be performed in all patients in whom there is clinical suspicion for scleroderma. Physicians should remain skeptical of negative ANAs in patients with clinical evidence of scleroderma.

Disclosure: D. R. Swistowski: None; S. Sadding: None; V. K. Shanmugam: Dr. Shanmugam is supported by the American College of Rheumatology, Research and Education Foundation, Physician Scientist Development Award, 2; V. D. Steen: None.

ACR Concurrent Abstract Sessions

Vasculitis

Wednesday, November 10, 2010, 4:30 PM–6:00 PM

2197

Antinuclear Antibody Screening in Systemic Sclerosis. Donna Rose Swistowski, Nicole Sadding, Victoria K. Shanmugam and Virginia D. Steen. 1Georgetown University Division of Rheumatology, Immunology, and Allergy, Great Falls, VA; 2Georgetown University Division of Rheumatology, Immunology, and Allergy, Bethesda, MD; 3Georgetown University Hospital Department of Medicine, 4Georgetown University Medical Center, Washington, DC

Purpose: Scleroderma specific antinuclear antibodies (SScAB) are helpful predictors of disease manifestations, clinical course and outcome in scleroderma. Historically, immunofluorescence (IF) antinuclear antibody (ANA) testing was the gold standard method for ANA detection, and the American College of Rheumatology continues to recommend IF for evaluation of ANA. Many commercial labs have recently adopted newer, automated, non-immunofluorescence methods (NEW ANAs), such as EIA (enzyme immunoassay) or immunobead methods to evaluate for the presence of antinuclear antibodies. These new techniques rely on a limited panel of autoantigens in the assay.

The purpose of this study was to evaluate ANAs and SScAB results performed through commercial labs, using both NEW ANA detection techniques and traditional IF, in a consecutive cohort of scleroderma patients seen in the Georgetown Scleroderma Clinic over a one year period.

NEW ANA test results on 52 patients with corresponding ANA IF data or SScABs

<table>
<thead>
<tr>
<th>ACA</th>
<th>NEW ANA Positive (n=30)</th>
<th>NEW ANA Negative (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NuANA</td>
<td><em>(all + SSA)</em></td>
<td>6</td>
</tr>
<tr>
<td>Pol III</td>
<td>1</td>
<td>91%</td>
</tr>
<tr>
<td>ANA IF</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.0001.

Disclosure: D. R. Swistowski: None; S. Sadding: None; V. K. Shanmugam: Dr. Shanmugam is supported by the American College of Rheumatology, Research and Education Foundation, Physician Scientist Development Award, 2; V. D. Steen: None.

2198

Association between Vascular Physical Examination Findings and Angiographically-Detected Arterial Lesions in Subjects with Large Vessel Vasculitis. Peter C. Grayson, Gunnar Tomasson, David Cuthbertson, Simon Carette, Gary S. Hoffman, Nader A. Khalidi, Carol A. Langford, Carol A. Langford, Paul A. Monach, Philip Seo, Kenneth J. Warrington, Steven R. Ytterberg and Peter A. Merkel. 1Boston University, Boston, MA; 2Boston University School of Medicine, West Newton, MA; 3Boston University School of Medicine, Boston, MA; 4Boston University School of Medicine, Chicago, IL; 5Cleveland Clinic Foundation, Cleveland, OH; 6Cleveland Clinic Foundation, Pepper Pike, OH; 7Johns Hopkins Bayview Medical Center, Baltimore, MD; 8Mayo Clinic, Rochester, MN; 9Toronto Western Hospital, Toronto, ON, Canada; 10University of Hamilton, Hamilton, ON, Canada; 11University of South Florida

Purpose: The vascular physical examination (PE) to assess for pulses, bruits, and systolic blood pressure (SBP) readings is considered essential in the clinical evaluation of patients with large vessel vasculitis (LVV), including Takayasu’s arteritis (TAK) and giant cell arteritis (GCA). This study examined the relationship between findings on PE and angiographically-detected arterial lesions in subjects with established LVV.

Methods: 100 subjects (TAK=68, GCA=32) enrolled in a longitudinal, observational cohort underwent standardized PE and magnetic resonance
angiography of the aorta and its primary branches. Analysis was restricted to bilateral common carotid, subclavian, and axillary arteries. Sensitivity and specificity was calculated for the association between PE findings (absent pulse, bruit, and inter-arm SBP difference) and angiographic lesions defined as stenosis, occlusion, or aneurysm. To determine if PE findings accurately localized arterial lesions, a PE finding (e.g. left carotid bruit) was compared to angiograms findings in both the anatomically correlated vessel (e.g. left carotid artery) and in all vessels within the region (carotid or subclavian or axillary arteries).

Results: Participants were predominantly female (92%), Caucasian (87%), and had mean ages of 40 years (TAK) and 69 years (GCA). 67% had at least one PE abnormality: absent pulse (41%-TAK, 38%-GCA), bruit (54%-TAK, 28%-GCA), or ≥15 mmHg SBP difference (52%-TAK, 29%-GCA). Lesions in any of the carotid, subclavian, or axillary arteries were detected in 75% of subjects (92%-TAK, 59%-GCA). Individual PE findings had poor sensitivity (range 14–51%) and good-excellent specificity (range 72–98%) to detect arterial lesions. Sensitivity improved (range 52–71%) and specificity worsened (range 59–86%) if any of the 3 different PE maneuvers performed in combination were abnormal. Sensitivity worsened (range 6–30%) and specificity improved (range 88–100%) if 2 or more of the PE findings were abnormal or if individual PE findings were compared to regional vessels without imposing single vessel anatomical correlation.

Conclusion: In subjects with established LVV, vascular PE findings have low sensitivity but high specificity to detect arterial disease. Abnormal PE findings are highly associated with the presence of arterial lesions, but normal PE findings do not rule out the possibility of arterial disease. Even when considering PE findings in combination, sensitivity is still inadequate to rule out arterial lesions. Specificity improves when PE findings are evaluated in association with a broader region of arterial lesions rather than specific anatomically correlated vessel, suggesting that PE findings do not always accurately localize disease. While valuable in the assessment of arterial disease in LVV, the PE should not form the sole basis of assessment and should be supplemented by angiography.

Disclosure: P. C. Grayson: None; G. Tomasson: None; D. Cuthbertson: None; S. Carette: None; G. S. Hoffman: None; N. A. Khalidi: None; C. A. Langford: None; C. McClean: None; P. A. Monach: None; P. Seo: None; K. J. Warrington: None; S. R. Ytterberg: None; P. A. Merkel: None.

2199


Purpose: Giant Cell Arteritis (GCA) is a common vasculitis affecting adults. Studies have shown that incidence of GCA increases with age and is higher among women than men. Several previous studies have also reported a secular trend of increasing GCA incidence. However, these data may be confounded by birth cohort effects. The purpose of this study was to estimate the effect of age, birth cohort (birth year) and period (year of diagnosis) on the incidence of GCA in a UK general population cohort.

Methods: Incident cases of GCA between 1990 and 2008 were identified from The Health Improvement Network (THIN), an electronic medical record database of 6.3 million patients from general practices across the United Kingdom. Incident cases of GCA were defined by physician diagnosis of GCA and use of glucocorticoids in 1995–2008. An incident GCA case was defined as a subject aged over 50 years with first diagnosis of GCA following at least one year of enrollment in the database. Glucocorticoid use was defined as two prescriptions for oral glucocorticoids: the first within 6 months of GCA diagnosis and the second within 6 months of the first. Crude incidence rates were calculated as the number of new GCA cases divided by total person-years. Age- and gender-specific incidence rates of GCA were plotted, as well as relative incidence rates of GCA for age, birth cohort (birth year) and period (year of diagnosis), using age-period-cohort spline curves, based on Poisson-type likelihood. Incidence rate ratios were estimated for women compared with men and for later versus earlier birth cohorts, using proportional hazards models.

Results: Of 1.7 million subjects (men: 47.7%; women: 52.3%) aged 50–89 years old in 1995–2008, 2715 subjects developed incident GCA. The crude incidence rate was 1.3 and 3.0 cases per 10,000 person-years in men and women, respectively. The incidence rate of GCA increased with age until age 80, then decreased (Figure). For every 5-year age increment, incidence of GCA increased by 41% (RR: 1.41, 95% CI: 1.38–1.44). Incidence of GCA was 1.98 times higher in women than in men (RR =1.98, 95% CI: 1.82–2.16). Furthermore, the incidence was higher for later birth cohorts, with rate ratio of 1.49 per 1-year interval (95% CI 1.38–1.60). Incidence rate of GCA did not vary materially over the study period.

Conclusion: In this UK general population, there was a significant birth cohort effect on GCA incidence, independent of age and calendar year at diagnosis. After adjusting for the birth cohort effect, incidence rates and age-gender effects remained similar to those reported previously. This is the first study to demonstrate a birth cohort effect on incidence of GCA, suggesting the presence of risk factors to which individuals born more recently were exposed. Further research should aim to identify factors that contribute to these changes in GCA incidence.

Disclosure: M. Dubreuil: None; H. K. Choi: None; Y. Zhang: None; Y. Zhu: None.

2200

Identification of JAK1 as a Candidate Inflammatory Signalling Pathway by Genome-Wide Expression Profiling in Monocytes from Patients with Behcet’s Disease. Haner Direskeneli1, Joseph J. Boyle1, Fizil T. Ozdemir2, Vuslat Yilmaz2, Emel Eksioglu-Demiralp2, Dorian Haskard and Guher Saruhan-Direskeneli2.

Purpose: Behcet’s disease (BD) is a chronic, inflammatory disease of unknown etiology characterized by oral aphthae, genital ulcers, genital and ocular inflammation, and cutaneous papulonecrotic lesions. Behavioural genetics evidence suggests a genetic basis for BD, and several susceptibility loci have been identified. Further identification of BD susceptibility genes will help in elucidating the pathogenesis of BD and may lead to the development of novel therapeutic approaches. However, our understanding of the pathogenesis of BD is limited and a comprehensive understanding of this complex disease is required.

Materials and Methods: Mononuclear cells were isolated from peripheral blood of 28 patients with BD and 20 healthy controls. RNA was extracted and cDNA was synthesized from total RNA. cDNA was then used for real-time RT-PCR (Taqman®) and gene expression analysis was performed using the Genespring software (Version 10.0).

Results: Among 28792 transcripts analysed, in CD14+ monocytes, 1188 transcripts reached a significant difference level with a minimum 2-fold difference observed in 279 genes. In CD14+ lymphocytes, 2880 transcripts showed significant difference with at least 2-fold difference in 109 genes. In CD14+ monocytes of BD patients, oxyyster binding protein-like-8 (OSBPL8) (3.8 fold), cell-division-cycle-27 homolog (S. cerevisiae) (CDC27) (3.1 fold), myeloid/lymphoid or mixed-lineage leukemia-3 (MLL3) (3.1 fold), PHD finger protein-3 (PHF3) (2.9 fold) and BCL2-associated protein (BAX) (2.7 fold) had the highest expressions. However,
A Randomized, Controlled, Multicenter Phase III Study of the Efficacy and Safety of Rituximab (RTX) Monotherapy Versus the Best Available Treatment in Patients with Mixed Cryoglobulinemia Syndrome. Salvatore De Vita, Luca Quaruccio, Miriam Isola, Paola Masolini, Stefania Sacco, Ginevra De Marchi, Cesare Mazzaro, Patrizia Scala5, Marco Lenzi6, Mauro Campanini7, Salvatore Scarpato8, Antonio Tayn9, Maurizio Pietrgrande15, Clodoveo Ferri15, Maria Teresa Mascia15, Dario Roccatello15, Anna Linda Zignego15, Paolo Pioletti15, Armando Gabrielli15, Davide Filippini15, Oreste Perrella15, Sergio Migliarese13, Massimo Galli13, Giuseppe Ranieri Bonabbondio15, A.O. Maggiori and Medicina II Novara, Italy, 2Center for Systemic Manifestations of Hepatitis Viruses (MaSVE), Department of Internal Medicine, University of Florence, Italy, 3Center of Ricerche di Immunopatologia e Documentazione su Malattie Rare, Struttura Complessa a Direzione Universitaria di Immunologia Clinica, Ospedale S.G. Bosco, Torino, Italy, Department of Clinical Medicine, University of Bologna, S. Orosola-Malpighi Hospital, Bologna, Italy, 4Department of Infectious Diseases and Immunology, Cotugno Hospital, Naples, Italy, 5Department of Internal Medicine, Pordenone General Hospital, Pordenone, Italy, 6Department of Scienze Cliniche Luigi Sacco, Sezione di Malattie Infettive e Immunopatologia, Università degli Studi, Ospedale Luigi Sacco, Milano, Italy, 7Institute of Statistics, University of Udine, Udine, Italy, 8Internal Medicine Unit, Policlinico San Marco, Bergamo, Italy, 9Internal Medicine Unit, Saronno Hospital, Azienda Ospedaliera di Busto Arsizio, Saronno, VA, Italy, 10Internal Medicine, Donizetti Hospital, Monza, Italy, 11Internal Medicine, Università Politecnica delle Marche, Ancona, Italy, 12Nephrology Unit, Spedali Riuniti, Udine, Italy, 13Rheumatology Clinic, A.O. Niguarda Ca’ Granda Hospital, Milan, Italy, 14Rheumatology Clinic, Azienda Ospedaliero-Universitaria “S. Maria della Misericordia”, Udine, Italy, 15Rheumatology Clinic, University of Naples, Italy, 16Rheumatology Unit, Department of Internal Medicine, University of Modena e Reggio Emilia, Italy, 17Rheumatology Unit, Department of Internal Medicine, University of Modena, Italy, 18Nephrology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy, 19Rheumatology Unit, M. Scarlato Hospital, Scalfati, Salerno, Italy, 20Internal Medicine, Centre of Medical Genetics, University of Florence, Italy, 21Rheumatology Unit, Universita’ degli Studi, Ospedale Luigi Sacco, Milan, Italy, 22Department of Pediatrics, Rheumatology Unit, University of Messina, Italy

Objectives: This is the first randomized controlled trial comparing RTX with the best available treatments (i.e., cyclophosphamide, azathioprine, high-dose steroids, or plasma exchange) in MC patients with glomerulonephritis, or peripheral neuropathy or skin ulcers, where antiviral therapy failed or is contraindicated. The RTX 1 g x 2 treatment schedule was alternative to the standard hematologic regimen of 4 weekly 375 mg/m² infusions.

Discussion: None; J. J. Boyle: None; F. T. Ozdemir: None; V. Yilmaz: None; E. Eksioglu-Demiralp: None; D. Haskard: None; G. Saruhan-Direskeneli: None.

2201

A New Polymorphism of the Fibroblast Growth Factor (FGF)23 Gene: A Promising Predictor of Coronary Damage in Kawasaki Disease (KD). Fernando Falcini1, Laura Mass1, Francesca Franceschelli2, Gigliola Leoncini2, Serena Capannini3, Francesco La Torre4, Giuseppina Cacace5, Marco Matucci Cerinic6 and Maria Luisa Brandi7. 1Department of Biomedicine, Section of Rheumatology, Transplant Clinic, University of Florence, Florence, Italy, 2Department of Biomedicine, Section of Rheumatology, Transplant Clinic, University of Florence, Florence, Italy, 3Department of Internal Medicine, Metabolic Bone Diseases Unit, University of Florence, Italy, 4Department of Paediatrics, Rheumatology Unit, University of Messina, Italy

Background: Vascular endothelial cell damage is crucial in KD, acute systemic vasculitis complicated by arterial dysfunction. Intimal thickening and fibrosis are reported in KD coronary arteries. Several pts even timely treated with IVIG may develop coronary artery abnormalities (CAA) with risk of ischemic heart disease. Phosphatidins are new hormones involved in phosphate homeostasis and bone mineralization. FGF23, the master phosphatonin, acts through FGF1r present in vascular and heart tissues. FGF23 knockout mice develop ectopic calcifications and vascular and heart damage assuming that FGF23 contribute to the development of vascular injury.

Aims: 1.To measure the intact FGF23 serum levels in KD pts. 2.To assess the association between FGF23 levels and CAA. 3.To screen KD pts for FGF23 gene mutation looking at a possible role of FGF23 allelic variants in cardiac damage.

Patients: 95 KD pts (58 M, 37 F; mean age 30.5 mths) after informed consent entered the study. 30 age-sex matched healthy children acted as controls. All pts had received IVIG and ASA. In all, at baseline and at study entry lipid profile (cholesterol, HDL, LDL, tryglicerides) was evaluated.

Methods: Serum intact FGF23 level was measured, using an ELISA assay (Immunotopics Inc. San Clemente, CA, USA).Genomic DNA was extracted from peripheral blood and the 3 FGF23 exons, including the intron-exon boundary regions, were PCR-amplified and analyzed on ABI Prism 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA).

Results: KD pts have higher FGF23 serum levels than controls (72.5 ± 40SD vs 12.3 ± 3.2SD pg/ml. Student’s T Test: p=0.01).DNA analysis shows a new C insertion in the intronic region between nucleotide close to the exon 2 (nt382879: NM_020638.2:c.212-37_212-34insC).40SD vs 12.3 ± 3.2SD pg/ml. Student’s T Test: p=0.01).DNA analysis shows a new C insertion in the intronic region between 40 vs. 38.2 ± 5).

Conclusions: 1.From our preliminary data the segregation of FGF23 genotype with the CAA advocates a possible functional role of the new polymorphism in KD coronary artery injury. These data point to FGF23 gene polymorphism and serum FGF23 levels as two potential predictors of high
risk of CAA. So far, no individual genotype data are available for FGF23 gene polymorphism.

Disclosure: F. Falcini: None; L. Masi: None; F. Franceschelli: None; G. Leoncini: None; S. Capannini: None; F. La Torre: None; G. Calcagno: None; M. Matucci Cerinic: None; M. L. Brandi: None.

2203

Mepolizumab, a Humanized Anti-IL-5 Antibody, Has Steroid-Sparing Potential in Churg-Strauss Syndrome. Frank Moosig1, Kristina Butherus1, Bernhard Hellmich2 and Wolfgang L. Gross1, 1University Hospital Schleswig Holstein & Klinikum Bad Bramstedt, 2University of Tübingen & Kreiskrankenhaus Plochingen

Background: In Churg-Strauss-Syndrome (CSS), a condition closely related to the hypereosinophilic syndrome (HES), high doses of glucocorticoids (GC) are often needed to control activity despite additional immunosuppression. Currently, severe cases demand treatment with cytotoxic agents such as cyclophosphamide and 15–20% of patients are refractory to standard therapy. Therefore, new targeted therapeutic options are needed. Interleukin-5 (IL-5) is the major inductor of hypereosinophilia and eosinophils (EO) are believed to mediate organ damage. In HES, a steroid-sparing effect of mepolizumab has been demonstrated. Therefore, targeting IL-5 in CSS is reasonable.

Methods: In this phase II trial, we included 10 CSS patients with active disease (Birmingham vasculitis activity score [BVAS] ≥3) under standard therapy. After stopping previous immunosuppressive medication, except GC, 750 mg mepolizumab was administered IV every 4 weeks for a total of 9 infusions. GC were tapered, as feasible, without loss of disease control. Methotrexate was initiated after the last mepolizumab infusion.

Results: The initial median BVAS was 9 (range 4–15), the GC dose 20 mg/d (range 12.5–70 mg/d) and the EO count 205/µl (range 13–4867/µl). One patient was excluded from the study because of non-compliance after 3 infusions. All 9 remaining patients reached remission (BVAS 0 and GC dose <7.5 mg/d prednisolone). GC dose could be reduced in all 9 patients (week 32: 4.5 mg/d [range 4–12.5 mg/d]), BVAS and EO counts improved significantly (week 32: BVAS 0 (0±0), p=0.0057; EO 18/µl (range 4–64.8/µl), p=0.0059). No severe adverse events attributable to mepolizumab occurred and the overall safety profile was good. After stopping mepolizumab, 2 patients experienced major and 3 minor relapse during a follow up of 10 months (range 4–14 months).

Conclusion: This phase II trial strongly suggests that mepolizumab may be an effective and safe therapeutic option in refractory CSS and might offer benefits beyond its steroid-sparing potential.

ClinicalTrials.gov Identifier: NCT00716651

Disclosure: F. Moosig: None; K. Butherus: None; B. Hellmich: None; W. L. Gross: None.
2204
Perioclontal Disease Hampers Anti-TNF Treatment Response in Rheumatoid Arthritis. Cynthia Savio1, Gisele Maria Campos Fabry2, Ana Luisa Calich2. A novel focus on GI outcomes as an early primary endpoints. We used antibiotics Saad3, Jezelio Freire Carvalho3, Clovis Almeida Silva3, Eloisa Bonf4 and Jose Tadeu Tesseroli Siqueira3. 1Dentistry and Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil, 2Dentistry and Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil, 3Paediatric Rheumatology Unit, Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de Sao Paulo, 4Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de Sao Paulo.

Purpose: To evaluate prospectively the effect of anti-TNF therapy in periodontal disease and its possible association with rheumatoid arthritis (RA) treatment response.

Methods: Twenty RA (ACR criteria) patients were assessed before (BL) and after 6 months (6M) of anti-TNF treatment. A dentist performed systematic dental and facial examinations that included: orofacial clinical features, tooth decay (DMFT) index, periodontal assessment [plaque and gingivial bleeding index, probing pocket depth (PPD), cementoenamel junction (CEJ) and clinical attachment level (CAL)], Helkmans index and salivary flow. All patients were examined by a rheumatologist, blinded to dentist assessment, in order to evaluate: demographic data, clinical manifestations, drug use, disease activity (CRP, ESR, DAS 28) and quality of life (HAQ) parameters.

Results: The median age of RA patients was 50(27–70) years and 90% were female. The median disease duration was 11(2–43) years. Inflimaxin was used in 17(85%) patients, adalimumab in 2 and etanercept in 1. No differences were observed in the median of plaque and gingivial bleeding indices; PPD, CEJ and CAL comparing BL and 6M (p>0.05) in spite of a significant DAS28 reduction (5.55 vs. 3.98, p=0.008) and a trend to ESR (24 vs.13 mm/1h, p=0.071) after 6 months of therapy. Further analysis of the 9(45%) patients with periodontal disease (PD) at study entry revealed a lack of response with no significant differences in the disease activity parameters between BL and 6M (p=0.05). In contrast, patients without PD showed a significant improvement in disease activity [DAS 28 (5.5 vs. 3.8, p=0.01) and ESR (25 vs.12 mm/1h, p=0.05)] comparing BL and 6M, respectively. No differences were observed in the frequencies of orofacial complaints, alteration of mandibular mobility and clinical dysfunction indices and in the median of salivary flow after 6M in both groups (p>0.05). DMARDS use was similar comparing whole group at BL and 6M as well as comparing patients with and those without PD (p>0.05).

Conclusions: This study supports the notion that an underlying periodontal disease affects TNF blockers efficacy in RA patients. The possibility that a sustained gingival inflammatory state hampers treatment response in this patient group has high clinical interest, since this a treatable condition.

Disclosure: C. Savio: None; G. M. C. Fabry: None; A. L. Calich: None; A. C. M. Ribeiro: None; J. C. Moraes: None; C. G. Saad: None; J. F. Carvalho: None; C. A. Silva: None; E. Bonf: None; J. T. T. Siqueira: None.

2205
Safety without Borders: Upper and Lower Gastrointestinal Safety of Celecoxib in a Pooled Analysis of 52 Prospective, Randomised, Double-Blinded, Parallel-Group Clinical Trials. Gurkirpal Singh1, Ajith Manmatha, Armita Sehgal2, Alka Mithal2, Mark Sostek 1 and George Triadafilopoulos2.

1Astra Zeneca, 2ICORE, 3Stanford University, 4University of California Berkeley

Objectives: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the management of pain and inflammation associated with osteoarthritis, rheumatoid arthritis and other musculoskeletal disorders but they carry a risk for cardiovascular (CV) and gastrointestinal (GI) toxicity. Large outcome studies have found that high-dose naproxen is associated with GI toxicity but less serious CV toxicity than other NSAIDs and COX-2 selective inhibitors (Kearney et al. BMJ 2006;332:1302–1308). It is unclear whether lower doses of naproxen present a similar level of GI risk while maintaining a favourable CV safety profile.

Objectives: To examine the prevalence of hospitalisations for complicated gastroduodenal ulcers with Naproxen Is Dose-Dependent. Gurkirpal Singh1, Ajith Manmatha, Armita Sehgal2, Alka Mithal2, Mark Sostek 1 and George Triadafilopoulos2.

1Astra Zeneca, 2ICORE, 3Stanford University, 4University of California Berkeley

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Methods: We conducted a nested case-control study using data from MediCal, California (the largest Medicaid programme in the US, with more than 7 million participants per year). Patients were aged 18 years or older with physician-diagnosed arthritis and had received treatment with an NSAID or COX-2 selective inhibitor between January 1999 and June 2005. All hospitalisations for complicated gastric and duodenal ulcers were risk-set matched with 4 controls on the basis of age, gender and date of hospitalisation. Analyses were adjusted for potential confounders, co-medications, co-morbidities and over-the-counter use of NSAIDs, including aspirin.

Results: A total of 688,424 patients were included, contributing 2,665,611 person-years of observation time. Of these, 11,303 patients who were hospitalised due to complicated gastric or duodenal ulcers were matched to 45,212 controls (mean age 70.7 years, 35% male). Patient characteristics of users of different NSAIDs were similar, except for COX-2 selective inhibitors being prescribed to older patients with more GI risk factors, as expected. Multivariate-adjusted rate ratios (95% CI) for hospitalisation with different doses of naproxen compared with remote use (≥61 days prior to hospitalisation) were: 500 mg/day, 2.51 (1.61–3.92); 750 mg/day, 2.95 (2.34–3.73); and
1,000 mg/day, 3.1 (2.71–3.61). All rate ratios were significantly higher when compared with remote NSAID or COX-2 selective inhibitor use (p<0.001).

Conclusions: Although the risk of hospitalisation for ulcer complications with naproxen is dose-dependent, even low (equivalent to over-the-counter) doses are associated with a significant risk of serious UGI toxicity. Concomitant gastro-protective therapy should be strongly considered for high-risk patients, regardless of naproxen dose, in order to protect against complicated gastric and duodenal ulcers.

Disclosure: G. Singh: AstraZeneca, 2; A. Maniantlhrara: None; A. Schgal: None; A. Mithal: None; M. Sostek: AstraZeneca, 3; G. Triadafilopoulos: AstraZeneca, 5.

2207

Disappointing Responsiveness of the SF-6D to Improvement in Patients Receiving a First TNF-Blocker: Results of the DREAM Registry. Laurien Buitinga1, Louise M. A. Braakman-Jansen2, Erik Taal3, Wietse Kievit4, Henk Visser2, Piet L. C. M. Van Riel5 and Mart A. F. J. van de Laar6.

Background: For reimbursement of innovative but costly treatments results of cost-utility analyses are increasingly important. Preferences for health states (utilities) can be measured with instruments as the EQ-5D or SF-6D. Evidence about which measure can be used best to detect improvement in patients with Rheumatoid Arthritis is inconclusive [1].

Objective: To examine the responsiveness of the EQ-5D and SF-6D in patients with RA receiving a first TNF-blocker.

Methods: Data of 284 RA patients included in the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry starting a first TNF-blocker were used. The Wilcoxon Signed Rank test and standardized response mean (SRM) were calculated to measure internal responsiveness over 12 months and 95% CIs were estimated using bootstrapping. Receiver-operating characteristic (ROC) curves were used to assess external responsiveness and areas under the curves (AUCs) were calculated. Perceived health transition (item SF-36) and change in disease activity (DAS28) were used as external criteria. For the ROC curves, both criteria were dichotomized. Patients were classified as ‘responders’ (good and moderate) or ‘non-responders’, based on the EULAR28 response criteria, which takes into account the individual change in DAS28 and the level of DAS28 reached. Patients were classified ‘improved patients’ (perceived health much better or somewhat better than a year ago) or ‘non-improved patients’ (perceived health the same as a year ago, or somewhat worse or much worse than a year ago), based on their health transition score.

Results: According to the EULAR response criteria, 41.2% of the patients were good responders, 36.6% moderate and 22.2% non-responders. The EQ-5D scores slightly improved over 12 months (SRM(CI) 0.46(0.32 to 0.58)), whereas the SF-6D scores did not improve at all (SRM 0.02 (−0.10 to 0.13)). The EQ-5D was moderately able to correctly classify patients as ‘improved’ or ‘non-improved’ respectively ‘responder’ or ‘non-responder’ as the AUCs were 0.67 when using self-reported health transition and 0.72 when using disease activity as external criteria. The AUCs of the SF-6D did not differ from 0.5.

Conclusion: The EQ-5D was more responsive to improvement than the SF-6D. The SF-6D was poorly responsive to improvement in patients with RA receiving a first TNF-blocker. There is a need to reconsider the SF-6D as a valid utility measure in cost utility analyses in RA.

References:

Disclosure: L. Buitinga: None; L. M. A. Braakman-Jansen: None; E. Taal: None; W. Kievit: None; H. Visser: None; P. L. C. M. Van Riel: None; M. A. F. J. van de Laar: None.

ACR Concurrent Abstract Sessions
Epidemiology and Health Services Research: General Interest
Thursday, November 11, 2010, 9:00 AM–10:30 AM

2208

Multiple Medications Use in Adults with Chronic Disease, with and without a Musculoskeletal Condition. Gillian A. Hawker1, Ruth Croxford2 and Elizabeth M. Badley3.

Objective: To study the rate of common comorbidities and cardiovascular disease in ankylosing spondylitis (AS) patients compared with the general population seeking health care.

Methods: Sweden has a publicly funded health care system. All health care utilization is registered by the patients’ personal identifier in databases. We studied 1374 subjects (60% men) age ≥20 years, living in the county of Skåne, Sweden, who were registered with an AS diagnosis (ICD-10 code M45) in the Skåne Health Care Register at least once during 4 calendar years (2004 to 2007). We then recorded the occurrence of physicians’ diagnostic codes for a select number of comorbidities commonly associated with AS or

Conclusions: People with MSK conditions are almost twice as likely as adults with other chronic conditions to be using combinations of medications typically used to manage chronic pain, potentially increasing their risk for adverse drug effects leading to hospitalization and death.

Disclosure: G. A. Hawker: None; R. Croxford: None; E. M. Badley: None.

2209


Objective: To examine the responsiveness of the EQ-5D and SF-6D in patients with RA receiving a first TNF-blocker.
Cardiovascular disease or its risk factors. To obtain morbidity rates we calculated the person-time from the day after the first occurrence of the AS diagnosis within the study period until the first diagnosis of the disease or another censoring event (death/relocation). We then obtained standardized morbidity ratios (SMRs) by dividing the observed morbidity rate in AS patients by the expected based on the corresponding rate of the disease in the general health care seeking population of the county (761,210 inhabitants aged ≥20); an SMR >1 equals a higher rate of the disease among AS patients than in the general population of corresponding age and sex distribution.

Results: The highest SMRs were found for uveitis 26.06 (95% CI 21.97, 30.70) and inflammatory bowel disease 8.19 (95% CI 6.47, 10.22), Figure 1. Also, we found increased SMRs for ischemic heart diseases 1.83 (95% CI 1.53, 2.18), hypertension 1.70 (95% CI 1.51, 1.91), disorders of lipoprotein metabolism 1.34 (95% CI 1.04, 1.71), and diabetes mellitus 1.34 (95% CI 1.10, 1.62). Within the group of ischemic heart diseases we also evaluated acute myocardial infarction separately and although it is a relatively rare event the SMR was close to be significantly elevated; 1.43 (95% CI 0.97, 2.03), Figure 2. Further, the SMRs for psoriasis, osteoporosis, and atrioventricular blocks were also statistically significantly elevated.

Conclusion: Inflammatory diseases affecting the eye and the digestive system were the most notable comorbidities in AS patients, but the rate for cardiovascular disease was also higher indicating that AS is a chronic rheumatic disease with strong influence of comorbidities affecting the total burden of the disease.

Disclosure: A. B. I. Bremander: None; I. F. Petersson: None; S. Bergman: None; M. England: None.

2211
Elevated Maternal Serum Alpha Fetoprotein Predicts Reduction in RA Disease Symptoms during Pregnancy but Does Not Reduce Risk for Preterm Delivery. Don Nguyen1, Gretchen Bandoli1, Diana Johnson2 and Christina D. Chambers3. 1San Diego State University, 2University of California San Diego, San Diego, CA, 3University of California San Diego, University of California San Diego

Background: Mid-trimester elevated maternal serum alpha fetoprotein (MSAFP), a glycoprotein produced by the fetus, is associated with an approximately 3-fold increased risk of preterm delivery in otherwise normal pregnancies. Pregnant women with RA are at increased risk of preterm delivery, a risk that may be related to inflammatory disease activity or poor symptom control. It is suspected that the immunomodulatory effects of MSAFP represent a mechanism whereby disease symptom remission occurs in at least 1/3 of pregnant RA patients. However, it is not known if elevated MSAFP values in pregnant patients with RA are associated with the same 3-fold risk of preterm delivery as in the general population, or if high MSAFP values may lead to symptom remission and thereby reduce risk of early delivery in these patients.

Methods: The OTIS Autoimmune Diseases in Pregnancy Project, a North American-wide prospective cohort study of pregnancy outcome, enrolled 115 pregnant women with RA between 1999 and 2008 for whom mid-trimester MSAFP values were available from the obstetric record. Of these, 115 had one assessment of symptoms in the first half of gestation and 68 had a second assessment at 32 weeks' gestation, each consisting of 3 likert scale measures of interference with activity, pain, and global impact of disease based on the CLIN-HAQ and collected by maternal report. We examined the relationship between symptom scores at each time point and preterm delivery (<37 weeks' gestation), and symptom scores and elevated MSAFP (≥2.0 multiples of the median) using student’s t-tests. We also evaluated elevated MSAFP as a predictor of preterm delivery using logistic regression.

Results: A total of 19.8% of women in the sample delivered preterm and 5.8% of women had a documented elevated MSAFP. All 3 symptom assessments measured in the first half of pregnancy were significant predictors of preterm delivery (p <0.05). However, none of these same measures collected in the third trimester were associated with preterm delivery. Elevated MSAFP was associated with a non-significant 3-fold increased risk of early delivery (OR 3.32, 95% CI 0.69, 15.97). However, elevated MSAFP significantly predicted a reduction in symptom scores from early to late pregnancy on all 3 measures (p <0.05).

Conclusion: Elevated MSAFP does appear to be linked to reduction in symptoms over the course of pregnancy, but the immunomodulatory effect of MSAFP does not appear to contribute to a reduction in risk for preterm delivery, which approximates the increased risk reported for the general population. Women with RA who have poor symptom control in early pregnancy and/or elevated MSAFP are at increased risk of preterm delivery, but those with elevated MSAFP are less likely to see remission of symptoms as pregnancy progresses.

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2210
Elevated Maternal Serum Alpha Fetoprotein Predicts Reduction in RA Disease Symptoms during Pregnancy but Does Not Reduce Risk for Preterm Delivery.

Don Nguyen1, Gretchen Bandoli1, Diana Johnson2 and Christina D. Chambers3. 1San Diego State University, 2University of California San Diego, San Diego, CA, 3University of California San Diego, University of California San Diego

Background: The evidence base for an increased cardiovascular burden in inflammatory arthritis (as in diabetes, an established cardiovascular risk factor) is growing, but data from primary care records are rare. We sought to determine the prevalence of cardiovascular (CV) events in inflammatory arthritis, diabetes, hip- and/or knee osteoarthritis (non-inflammatory comparator) in a large primary care cohort. Data were analyzed using multi-level logistic regression analyses and corrected for I: age, gender, and II: age, gender, hypercholesterolemia and hypertension.

Methods: Data on CV morbidity (ICPC codes K75 (myocardial infarction), K89 (transient ischemic attack), and/or K90 (stroke/cerebrovascular accident) from patients with inflammatory arthritis (n = 1,343), diabetes (n = 11,784), osteoarthritis (n = 3,320) and controls (n = 158,439) were used from the Netherlands Information Network of General Practice (LINH), a large primary care cohort. Analysis was performed using multi-level logistic regression analysis and corrected for age, gender, and hypercholesterolemia and hypertension.

Results: Age and gender adjusted CV disease prevalence rates were significantly higher in inflammatory arthritis (OR 1.6 (95%-CI: 1.3–2.0) and in diabetes (OR 1.8 (95%-CI: 1.6–1.9), but not in osteoarthritis (OR 0.9

Disclosure: A. B. I. Bremander: None; I. F. Petersson: None; S. Bergman: None; M. England: None.
(95%-CI: 0.8–1.0). These results attenuated - especially in diabetes - but remained statistically significant after adjustment for hypertension and hypercholesterolemia: OR I.5 (95%-CI: 1.2–1.9) for inflammatory arthritis, OR 1.3 (95%-CI: 1.2–1.4) for diabetes, and OR 0.8 (95%-CI: 0.7–1.0) for osteoarthritis, respectively.

Table 1. Study characteristics

<table>
<thead>
<tr>
<th>IA</th>
<th>DM</th>
<th>OA</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td>1,343</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>59*</td>
<td>66*</td>
<td>51*</td>
</tr>
<tr>
<td>Female gender, %</td>
<td>64*</td>
<td>52*</td>
<td>68*</td>
</tr>
<tr>
<td>AMI, %</td>
<td>1.6*</td>
<td>2.7*</td>
<td>1.4*</td>
</tr>
<tr>
<td>TIA, %</td>
<td>1.6*</td>
<td>2.1*</td>
<td>1.7*</td>
</tr>
<tr>
<td>CVA, %</td>
<td>2.5*</td>
<td>3.6*</td>
<td>2.5*</td>
</tr>
<tr>
<td>Total CVD, %</td>
<td>5.4*</td>
<td>8*</td>
<td>5.3*</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>28*</td>
<td>48*</td>
<td>35*</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>7.6*</td>
<td>24*</td>
<td>10*</td>
</tr>
</tbody>
</table>

*p < 0.001 (compared to general population). DM, diabetes mellitus; IA, inflammatory arthritis; OA, knee- and/or hip osteoarthritis; AMI, acute myocardial infarction; TIA, transient ischaemic attack; CVA, cerebro vascular accident; CVD, cardiovascular disease.

Table 2. Multilevel logistic regression analyses for the association with CVD

<table>
<thead>
<tr>
<th>General population</th>
<th>IA</th>
<th>DM</th>
<th>OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude model</td>
<td>1.0</td>
<td>2.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.0</td>
<td>1.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.0</td>
<td>1.5</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*p < 0.001. Results as odds ratios (95%-confidence interval). DM, diabetes mellitus; IA, inflammatory arthritis; OA, knee and/or hip osteoarthritis.

Model 1: Adjustment for age and gender
Model 2: Adjustment for age, gender, hypertension and hypercholesterolemia

Conclusions: These results confirm an increased CV burden in inflammatory arthritis to levels similarly similar to diabetes. By contrast, lack of excess CV disease in osteoarthritis further suggests that the systemic inflammatory load is critical to the CV disease burden in inflammatory arthritis.

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2212

Impact of Age, Gender, Obesity, and Steroid Use on Quinolone-Associated Tendon Disorders. Barton Wise1, Christine Peloquin2, Hyon K. Choi3, Nancy E. Lane4 and Yuqing Zhang5. 1Boston Univ School of Medicine, Boston, MA, 2Boston University School of Medicine, Boston, MA, 3Univ of British Columbia, Vancouver, BC, Canada, 4Univ of California at Davis, Hillborough, CA

Background: Quinolone antibiotics are associated with an increased risk of tendinopathy, including tendon rupture. However, it is unknown whether certain characteristics predispose individuals to the adverse effects of quinolones. Identifying individuals who are more susceptible to these detrimental events has important clinical implications.

Methods: Using The Health Improvement Network (THIN) database, an electronic medical record database based on 6.3 million patients from general practices across the UK, we conducted a case-crossover study to assess whether the effects of quinolone use on the risk of tendon disorders vary by age, gender, obesity, and oral glucocorticoid use. For our primary outcomes, we examined Achilles tendinitis and tendon rupture at any site, to help ensure a high level of diagnostic specificity of end points. We identified patients with Achilles tendinitis or tendon rupture between 1986–2009 based on their electronic medical records. Subjects whose Achilles tendinitis or tendon rupture occurred within the first 2 years of entry to the THIN database were excluded. For each patient, we determined whether a quinolone and comparison antibiotic (trimethoprim, amoxicillin, nitrofurantoin) had been prescribed within 30 days prior to diagnosis of Achilles tendinitis and tendon rupture (case period) as well as the prescription of the same medications within 30 days one year prior to disease diagnosis (control period). We examined potential effect modifications according to age (<60 vs. ≥60 years), sex, obesity (BMI<30kg/m² vs.BMI ≥30kg/m²), and concurrent glucocorticoid use (yes vs. no) by adding an interaction term between quinolone use and each potential modifier in the conditional logistic regression model.

Results: We identified 29,312 cases of Achilles tendinitis and 7,740 cases of tendon rupture. Use of quinolone was strongly associated with an increased risk of Achilles tendinitis (OR=4.4, 95% CI: 3.3–5.8) and tendon rupture (OR=2.0, 95% CI: 1.2–3.4). No association was found between the use of other antibiotics and either outcome. The association with Achilles tendinitis was stronger among patients who were older than 60 yrs, non-obese, and who used oral glucocorticoids (p-values for interaction: <0.001, 0.01, and 0.03, respectively). The effect of quinolones appeared to be greater in women than in men although the interaction term was not statistically significant (see Table). Similar subgroup effects were observed in the associations with tendon rupture, except for the age group effect.

Conclusion: These findings from a large primary care population confirmed that quinolone use increases the risk of Achilles tendinitis and tendon rupture. These detrimental effects of quinolones appear to occur more often among women, elderly, non-obese patients, and individuals with concurrent use of glucocorticoids.

Disclosure: B. Wise: None; C. Peloquin: None; H. K. Choi: None; N. E. Lane: None; Y. Zhang: None.

2213

Bisphosphonate (BisP) Use May Be a Risk Factor for Osteonecrosis (ON) in Those Who Have Not Used Glucocorticoids (GCs): Data from the Health Improvement Network (THIN). Steven C. Vladi2, Hyon K. Choi1, Christine Peloquin1 and Yuqing Zhang5. 1Boston Univ School of Medicine, Boston, MA, 2Boston University School of Medicine, Boston, MA, 3Univ of British Columbia, Vancouver, BC, Canada

Background: BisP use has been linked to ON of the jaw in case reports. However, two epidemiologic studies suggested different conclusions about whether BisP use is associated with ON in general: one found that BisP use was associated with ON even after adjusting for GC use; the other found no association after adjusting for GC use and other factors. The latter suggests that GC use could be a strong confounder of any BisP-ON relationship. We therefore used data from THIN to investigate the association between BisP use and ON in persons who have not used GCs.

Methods: THIN collects anonymized patient data on over 3 million patients from a sample of primary care clinics throughout the United Kingdom. As all health information flows through the GP, THIN provides a complete patient record while an individual remains in a practice including medication prescriptions and refills. We created a cohort of subjects who had not been prescribed BisPs within the 1st year of entering a practice (new user exposure as 1) current (including the 30 days prior to index date), recent (31–180 days), and past (>180 days), and total dose (1–180 days, 181–360 days, >360 days), with no use as the reference in both cases. We used conditional logistic regression, adjusted for heavy alcohol use (ever, never), and tobacco use (current, past, never, missing), to calculate odds ratios for ON.
Results: We identified 608 persons with new ON (310 men, 298 women, mean age 52.7 yrs (sd 21.7)) and matched 2389 controls (51.6 yrs (sd 21.3) — 16 cases had fewer than 4 controls). 33 cases (5.4%) and 35 controls (1.5%) had at least one BisP prescription. Compared to never use the risk of ON was elevated in both current BisP users and recent users, but not in past users (see table). Compared to no use the risk of ON was elevated for all categories of total dose, with the peak from 181–360 days. The risk remained elevated after restricting the analysis to current users.

<table>
<thead>
<tr>
<th>Duration of use</th>
<th>Cases N (%)</th>
<th>Controls N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use (within 30 days)</td>
<td>24 (4.0)</td>
<td>21 (0.9)</td>
<td>6.1 (3.1, 12.0)</td>
</tr>
<tr>
<td>Recent use (31–180 days)</td>
<td>5 (0.8)</td>
<td>3 (0.1)</td>
<td>9.8 (2.2, 43.3)</td>
</tr>
<tr>
<td>Past use (&gt;180 days)</td>
<td>4 (0.7)</td>
<td>11 (0.5)</td>
<td>1.7 (0.5, 5.4)</td>
</tr>
<tr>
<td>1–180 days</td>
<td>10 (1.6)</td>
<td>13 (0.5)</td>
<td>2.5 (1.0, 6.2)</td>
</tr>
<tr>
<td>181–360 days</td>
<td>9 (1.5)</td>
<td>4 (0.2)</td>
<td>7.7 (2.3, 26.3)</td>
</tr>
<tr>
<td>&gt;360 days</td>
<td>14 (2.3)</td>
<td>18 (0.8)</td>
<td>2.7 (1.1, 6.8)</td>
</tr>
</tbody>
</table>

Conclusion: Though our analysis is limited by small numbers, BisP use appears to be a risk factor for ON even in those who have not used GCs. The risk appears highest with up to 1 year of use, suggesting that those who have not had ON within 1 year may be in less danger. After 6 months off drug, the risk approaches null. Given the high correlation between osteopenia/osteoporosis and BisP use, we cannot exclude that these findings are due to confounding by indication, though no relationship between low bone mass and ON is known.

Disclosure: S. C. Vlad: None; H. K. Choi: None; C. Peloquin: None; Y. Zhang: None.

ACR Concurrent Abstract Sessions
Genetics, Genomics and Proteomics: RA and Other Rheumatic Diseases

Thursday, November 11, 2010, 9:00 AM–10:30 AM

2214


Methods: After all data was quality filtered, 2,296 individuals with SSC and 5,171 healthy controls were analyzed for genetic associations with lcSSc, dcSSc, ACA positive and ATA positive subgroups. SNPs from each subphenotype with a corrected P value lower than 1×10<sup>−4</sup> were previously described in the literature were selected for replication. These associations were then analyzed in 9 replication cohorts from US and Europe comprising an additional 3,175 SSC patients and 4,971 healthy controls.

Results. Eighteen non-HLA SNPs were selected from the SSC GWAS analysis. Meta-analysis of all the cohorts (5,471 individuals with SSC and 10,143 healthy controls) showed a strong association of rs11642873 in the IRF8 gene (P = 5.42×10<sup>−12</sup>, OR = 0.75) and a suggestive but consistent association among populations, of rs12546074 in the GRB10 gene (P = 1.31×10<sup>−6</sup>, OR = 1.15) with the limited subtype of the disease. We also found a strong association of rs1047102 of the SOX5 gene (P = 1.04×10<sup>−7</sup>, OR = 1.36) with the ACA positive subgroup of patients. In addition to these phenotype dependent associations, we found rs11724804 in the DGKQ gene (P = 1.79×10<sup>−6</sup>, OR = 1.12), rs1868929 between the AMRC9 and PSMD1 genes (P = 3.27×10<sup>−6</sup>, OR = 1.27) and rs10275834 in the JAZF1 gene (P = 9.44×10<sup>−6</sup>, OR = 1.12) to be associated with SSC.

Conclusion: Outside of the HLA region, we have identified 3 new genes (IRF8, GRB10 and SOX5) associated with clinical manifestations of the disease, emphasizing the differential genetic component of each subphenotype of SSC. We also have identified 3 new genes associated overall with the disease: DGKQ (implicated in cell signal transduction), PSMD1 (the immunoproteosome subunit which loads immunogenic peptides for MHC transfer) and JAZF1 (a transcriptional repressor previously associated with SLE).

Disclosure: O. Gorlova: None; J.-E. Martin: None; B. Rueda: None; B. P. C. Koeleman: None; M. Teruel: None; L.-M. Diaz-Gallo: None; J. C. Broen: None; M. C. Vonk: None; C. P. Simeone: None; B. A. Alizadeh: None; M. H. J. Coenen: None; A. E. Voskuyl: None; A. J. Schuurenberg: None; P. L. C. M. van Riel: None; R. van ‘t Slot: None; A. Italiaander: None; R. A. Ophoff: None; N. Hunzelmanna; N. Ortego-Centeno: None; M. A. Gonzalez-Gaya: None; M. F. Gonzalez-Escrubano: None; P. Airo: None; J. van Laar: None; J. Worthington: None; R. Hesselstrand: None; V. Smith: None; F. de Keyser: None; F. Housiau: None; M. Mayes: None; R. Madhok: None; AF. Houssiau: None; J.-E. Martin: None; M. Beretta: None; P. K. Gregersen: None; S. Assassi: None; F. de Keyser: None; S. Arnett: None; T. Witte: None; L. Padykov: None; L. Klareskog: None; R. Sezard: None; B. A. Lie: None; A.-M. Hoffmann-Vold: None; P. Carrera: None; J. Varga: None; M. Hinchliff: None; A. T. Lee: None; P. Gourh: None; C. I. Amos: None; G. Riemekasten: None; A. Herrick: None; L. Beretta: None; K. P. Gregersen: None; S. Agarwal: None; S. Assassi: None; F. K. Tan: None; F. C. Arnett: None; T. R. D. J. Radstake: None; M. D. Mayes: None; J. Martin: None.

2215

Genetic Markers of Rheumatoid Arthritis Susceptibility in Anti-Citrullinated Peptide Antibody Negative and Shared Epitope Negative Patients. Sebastien Viatte1, Darren Plant2, John Bowes3, Anne Barton4 and Jane Worthington1. 1Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, 2Arthritis Research UK Epidemiology Unit, The University of Manchester.

Introduction: Recent genome wide and candidate gene association studies have identified over 30 confirmed single nucleotide polymorphisms (SNPs) predisposing to disease. Many of these studies have been undertaken exclusively or largely in samples from patients with anti-citrullinated peptide antibody (ACPA) (as assessed by anti-CCP status) positive RA and there is evidence that some genetic associations appear stronger in this subgroup than in ACPA negative patients. This differential association of susceptibility markers with ACPA positive/negative RA subsets or shared epitope (SE) positive/negative RA has led researchers to hypothesize that RA comprises a number of different diseases. However, due to the small numbers of seronegative or SE negative RA patients included in these studies, they lack sufficient statistical power to address the question currently. We aimed to...
undertake a thorough investigation of confirmed RA susceptibility loci in a large cohort of ACPA negative subjects with RA.

**Methods:** RA patients from 5 different large cohorts of patients originating from the UK were pooled together to reach a number of over 8,000 cases. The comparison group comprised 7000 healthy UK controls. Serologic data available for 5300 cases (3000 anti-citrullinated peptide antibody (ACPA) positive and 2300 ACPA negative patients) and data on SE carriage was available for 6400 patients (4500 bearing at least one copy, 1900 without any copies). This corresponds to the largest pool of ACPA-negative patients studied, to date. A set of over 40 SNPs mapping to 31 confirmed RA susceptibility loci was tested for association between controls and each of the 4 following subgroups: ACPA+, ACPA−, SE+, SE−.

**Results:** As expected, strong associations were observed between RA susceptibility SNPs and ACPA positive or SE positive patients. The emerging picture in the ACPA negative RA subset shows a differential association. A set of SNPs is associated with RA susceptibility, irrespective of the serologic status (eg. PTNP22, TNFAIP3), whereas other RA susceptibility SNPs do not show significant association with ACPA negative RA (eg. PRDM1, CD40). A similar picture characterizes the SE negative RA subset, though a higher number of RA susceptibility loci seem to be associated irrespective of the carriage of the SE.

**Discussion:** In the largest sample size studied, to date, we have shown that the strength of association, the effect size and the number of SNPs associated with disease appear to be smaller in SE negative RA patients compared to SE positive patient, and these effect sizes are even smaller in ACPA negative patients. This opens the question as to whether unidentified SNPs could preferentially and differentially confer susceptibility to ACPA/SE negative RA.

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2216

**A Signature of Aberrant Responsiveness of the Peripheral Immune System Predicts the 6-Month Risk of Infections in Rheumatoid Arthritis.** Megan L. Krause, John M. Davis III, Michael A. Strausbauch, Cynthia S. Crowson, Terry M. Therneau, Eric L. Matteson, Keith L. Knutson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN

**Purpose:** Patients with rheumatoid arthritis (RA) experience a high burden of infectious disease, which is a leading cause of mortality. Currently there are no biomarkers that stratify the risk of infections in these patients. We have recently shown that “signatures” of aberrant functional responsiveness of the peripheral immune system are associated with RA disease severity. We performed a pilot study to assess whether a blood-based immune signature could predict incident infections in patients with RA.

**Methods:** We designed a prospective, population-based cohort study of patients with RA. Infections were identified first by diagnosis codes and then validated by medical records review using previously published definitions. Peripheral blood mononuclear cells were isolated and stimulated with a panel of stimuli for both the innate and adaptive immune systems. Seventeen cytokine concentrations were measured via multiplex immunoassays. The stimulation panel included anti-CD3/anti-CD28, cytomegalovirus and Epstein Barr virus lysetes, CpG oligonucleotides, heat shock protein 60, phytohemagglutinin, phorbol myristate acetate with ionomycin, and Staphylococcal enterotoxins A and B. Mixed models were used to normalize log-transformed cytokine concentrations, adjust for assay effects, and to estimate and test for differences between the groups with and without incident infections. An immune signature score was created by selecting cytokine-stimulation combinations that were significantly different (p<0.05) between the groups. Logistic regression was used to test the association of a multi-cytokine prediction score and the risk of incident infections.

**Results:** In the six-month period following the index blood draw, 28 incident infections occurred among 267 patients with RA, 74.5% female, with mean age of 61 years and mean disease duration of 9.6 years. The only statistically significant variable at baseline that predicted infection was functional status defined by the Health Assessment Questionnaire (HAQ) disability index. Nine cytokine-stimulation combinations were significantly different between those with and without infection, including higher levels of TNFα, IFNγ, IL-17, IL-8, and GM-CSF and lower levels of IL-10 and IL-12 in response to various stimuli. The immune signature score was a statistically significant determinant of the 6-month risk of infections with an odds ratio of 4.0 (95% CI: 1.5 to 11, P=0.007) after adjusting for age, gender, HAQ, and use of disease-modifying medications.

**Conclusion:** This was one of the first studies to analyze ex vivo cytokine production and derive an immune signature that could help predict infection risk in patients with RA. The ability to predict infection risk could affect the choice of RA medications with their inherent immunosuppressive effects and the use of antibiotic prophylaxis. Reducing infection by preemptively altering therapy based on infection risk would have the potential to reduce morbidity and mortality for patients with RA.

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2217

**Homozygous 3.2kb Deletion in LEPREL1 (P3H2) Intron 1 Reduces Cyto- kine Production and Protects from Multiple Inflammatory Diseases.** Yohi Kirino1,2, Michael J. Ombrello13, Almuet Gul1, Kai Wang1, Akira Meguro2, Barbara Yang1,4, Massimo Gadina1,5, Fulya Cosan1,5, Nesilhan Abaci1, Katherine Sinimovich7, Peter K. Gregersen2,7, Phaedon Kaklamani8, Young-Hun Cho9, Dongskang Bang7, Hong-wei Sun10, Christopher Amos6, Massa Hamza11, Mitsuhiko Takeno12, Nobuhisa Mizukiz13, Hitodoshi Inokoz13, Shigeaki Ohno13, Yoshiaki Ishigatsu17, Hakon Hakonarson1, Daniel L. Kastner13 and Elaine Remmers14.

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**Purpose:** SNP genome-wide association studies (GWAS) are a powerful means to detect disease-associated variants, though it is difficult to detect rare or structural variants. Accumulating evidence has shown an involvement of gene copy number variation (CNV) in inflammatory diseases including systemic lupus erythematosus and psoriasis, suggesting that CNV analysis may be a promising means to identify novel disease-associated loci in rheumatic diseases. SNP marker intensity data from our previous Turkish Behcet’s disease (BD) GWAS (1215 cases and 1278 controls) revealed a common 3.2kb deletion in LEPREL1 intron1 (odds ratio (OR)=0.62, p=6.5×10−4), homzygous deletions of which appeared to protect individuals from disease (OR=0.62, p=6.5×10−4). This association of homozygous LEPREL1 deletion replicated in a Japanese BD collection (382 cases and 410 controls, OR=0.64, p=0.014). Independent BD collections showed trend toward protection from the disease (combined cases n=1821, controls n=2005, OR=0.63, meta analysis p=2.9×10−6). As the homozygous deletion in LEPREL1 was found to be common in both Turkish and Japanese populations, we sought to determine whether the deletion influences other inflammatory diseases, or in other ethnicities, as well. We found that patients with rheumatoid arthritis (combined cases n=1351, controls n=1659, OR=0.76, p=0.019), and type 1 diabetes (cases n=2214, controls n=2645, OR=0.82, p=0.038) were also protected from the disease, and trend towards protection in juvenile-onset Crohn’s disease and primary biliary cirrhosis was observed. A meta-analysis of these combined inflammatory diseases (cases n=6406, controls n=6309) supports our hypothesis that LEPREL1 has a role in inflammation (p=2.4×10−4).
LEPREL1, a prolyl 3-hydroxylase which is also called P3H2, is involved in type IV collagen modification. This gene appears to have additional functions. Although the protein is expressed in dendritic cells, and peripheral lymphocytes from individuals homozygous for this deleted region produce less LEPREL1 and inflammatory cytokines following exposure to stimulators of innate immunity. Our results offer new insights into the role an intragenic copy number variation plays in repressing development of inflammatory disease and reveal a novel modulatory mechanism for inflammation.

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2219

Discovery and Replication of JIA Predisposition Genes by Genome-Wide Association and Validation of Candidates in Fibroblast-Like Synoviocytes, Terri H. Finkel1, Haitao Zhang2, Benedicte A. Lie3, Edward M. Behrens1, Mara L. Becker2, Carol Wise3, Marilyn Pumar3, Emma Reusch4, Debra Shivers5, Berit Flata6, Øystein Forre7, Jane Munro10, Justine Ellis11 and Hakon Hakonarson. 1Center for Applied Genomics, The Children’s Hospital of Philadelphia, Philadelphia, PA, 2Children’s Hospital of Philadelphia, 3Children’s Mercy Hospital, Kansas City, MO, 4Children’s Hospital of Philadelphia, 5Department of Rheumatology, University Hospital, Rikshospitalet, Norway, 6Division of Genetics, The Children’s Hospital of Philadelphia, University of Pennsylvania, 7Division of Medical Genetics, Texas Scottish Rite Hospital for Children, 8Division of Rheumatology, Texas Scottish Rite Hospital for Children, 9Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, 10Division of Rheumatology, The Children’s Hospital of Philadelphia, 11Murdoch Childrens Research Institute, Royal Children’s Hospital, Melbourne, Australia

Purpose: Juvenile Idiopathic Arthritis (JIA) is the #1 cause of acquired disability in children. We recently identified TRAF1-C5 as a genetic locus associated with JIA, and have undertaken a comprehensive translational approach to elucidate its genetic contribution to this disease. Here, we identify single nucleotide polymorphisms (SNPs) associated with JIA by a genome-wide association (GWA) screen of a large well-phenotyped patient cohort. We validate expression of GW significant candidates in B cells and in synovial tissue from patients targeted by inflammatory arthritis. HFLS provide a readily available and renewable source of patient-derived tissues to examine JIA risk alleles/targeted by inflammatory arthritis. HFLS provide a readily available and renewable source of patient-derived tissues to examine JIA risk alleles/

Method: We use a GWA approach to identify risk alleles that associate with JIA in a discovery cohort of 1500 cases (diagnosed by revised ILAR criteria) recruited from greater Philadelphia and internationally (Stage 1). In Stage 2, we genotype an additional 1000 existing samples from well-phenotyped JIA cases recruited by other collaborating sites. This database is leveraged against matched samples from >10,000 genotyped controls. In parallel studies, we study allele-specific gene expression in:

1) genotyped lymphoblastoid cell lines (LCLs) from HapMap-CEU population samples and 2) primary HFLS established from synovial fluid samples obtained from a subset of the >200 JIA patients undergoing arthrocentesis each year at Children’s Hospital, obtained after informed consent.
Results: We have completed full genome genotyping of 1166 JIA cases and 8793 matched healthy controls using the Illumina HumanHap610Q BeadChip to track 600,000 polymorphisms, and have demonstrated significant associations of JIA to MHC loci, and to the non-MHC loci, PTTP22, IL2RA, and ANTXR2, as previously reported in inflammatory arthritides. We have also discovered GW significant associations within a locus encoding a novel chemokine receptor (CCR, discovery p-value = 4.32 x 10^-11; odds ratio = 0.66), for which replication is pending. We have demonstrated allele-specific effects on gene expression for significantly associated loci by assaying total RNA in genotyped LCLs from HapMap-CEU population samples, comparing individuals homozygous for risk vs. non-risk genotypes, and in primary HFLS established from JIA synovial fluid samples, analyzing allele-specific changes for our most significantly associated SNPs.

Conclusion: PTTP22, IL2RA, ANTXR2, and a novel CCR are associated with all forms of JIA, thereby potentially functioning as “master switches” predisposing to arthritis. The functional role of these genes is assessed for the first time in the disease-target tissue, HFLS, from children with JIA. HFLS are quiescent synovial lining cells that become highly proliferative and invasive in arthritis, and provide us with a renewable, druggable source of patient-derived cell types/tissues expressing our gene(s) of interest.

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ACR Concurrent Abstract Sessions
Imaging of Rheumatic Disease: Ultrasound
Thursday, November 11, 2010, 9:00 AM–10:30 AM

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High Frequency of Subclinical Ultrasound-Detected Synovitis in Juvenile Idiopathic Arthritis Patients with Clinically-Defined Inactive Disease
Silvia Magni-Manzoni1, Carlo A. Scire2, Angelo Ravelli2, Catherine Klersy3, Silvia Ross4, Valentina Muratore5, Chiara Visconti5, Stefano Lam1, Pietro Merli1 and Carlomaurizio Montecucco3. 1Dep.Pediatrics, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy, 2II Pediatric Unit, IRCCS Gaslini, Genova, Italy, 3Rheumatology Unit, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy, 4Scientific Dep, Fondazione IRCCS Policlinico S.Matteo, Pavia, Italy

Background: In children with juvenile idiopathic arthritis (JIA), it is unclear whether clinically-defined remission couples with absence of synovitis on imaging studies. Subclinical synovitis, as detected with US, has been found to be common in JIA.

Objectives: To investigate the frequency of US-detected subclinical synovitis in JIA patients with clinically-defined inactive disease (ID) and the role of US abnormalities in predicting a subsequent flare of synovitis.

Methods: The clinician established the presence of ID (active joint count = 0), physician’s global assessment on a 0–10 visual analog scale ≤ 0.5, and negative acute phase reactants) in 28 consecutive JIA patients. On the same day, a sonographer scanned independently 52 joints in each patient for synovial hyperplasia (SH), synovial fluid (SF), power Doppler signal (PDS), and tenosynovitis (TS). Patients were followed-up for at least 6 months; based on the subsequent disease course, they were classified having persistent ID at the last follow-up visit or a relapse of arthritis during the follow-up period (defined as a recurrence of clinically-defined active synovitis in 1 or more joints).

Results: The frequency of SH, SF, PDS, and TS in the 28 patients with ID was 75%, 71.4%, 32.1%, and 14.3%, respectively. Following the diagnosis of ID, 21 patients had persistent ID after a median of 12 months, whereas 7 patients experienced a relapse of arthritis a median of 6 months. The frequency of US abnormalities at the time of the diagnosis of ID in the 7 patients who had a subsequent disease flare was 100% for SH, 87.5% for SF, 14.3% for PDS, and 28.6% for TS. The main joint involved in the baseline US abnormalities were the knee and the wrist.

Conclusion: JIA patients with clinically-defined ID had a high frequency of US-detected synovial abnormalities, namely SH and SF. Of the US features, SH and SF may have a greater role in predicting a future relapse of synovitis, especially when detected in the knee and the wrist.

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2221
Ultrasoundography at the Onset of Early Arthritis Predicts Joint Erosions at One Year: Results of the ESPOIR Cohort Ultrasound Study
Thomas Funck-Brentano1, Frederique Gandjabekch2, Fabien Etcheepar3, Sandrine Jouss4, Cedric Lukas5, Voliaine Foltz6, Alian Saras7, Philippe Goupille8, Patrick Boumier4, Pierre Bourgeois3 and Bruno Faurel1. 1Amiens, 2Brest University Hospital, 3Immunohuematologie, Hospital Lapeyronie, Montpelier, France, 4Rheumatology Department, Pitié-Salpetrière Hospital, Paris 6 University, France, 5Tours University Hospital

Background: Ultrasoundography (US) has been shown highly sensitive to detect erosions at baseline, compared to conventional radiography (CR). However, only few longitudinal studies have investigated its capacity to predict future structural damage.

Objective: to assess the predictive value of US for future radiographic erosion on the same joint based on the ESPOIR cohort data.

Methods: ESPOIR is a nationwide early arthritis cohort that included between 2002 and 2005 813 early arthritis patients.

US was performed at baseline on 127 patients from the ESPOIR cohort in 4 centers at baseline. US characteristics: 10–13MHz linear array transducer; Power Doppler (PD): frequency of 8.3MHz and pulse repetition frequency of 750Hz. US was performed blindly from clinical and radiological findings. Targeted joints were MCP2&5 and MTP5 for erosion detection, MCP2 to 5 and MTP5 for synovitis (gray scale and power Doppler). CR of the hands, wrists and feet at baseline and one year were read by one investigator according to the van der Heijde modified Sharp score. Baseline US findings associations with joint erosions on CR at one year were tested in univariate analyses using two-by-two tables and Pearson’s chi-square tests. Predictive factors for joint erosion at one year by CR were tested in multivariate analysis including age, DAS28, CRP, ESR, positivity for Rheumatoid factor (RF) and anti-CCP and corticotherapy, using a mixed procedure.

Results: Patients characteristics at baseline were (mean ± sd or %): age 50.3 ± 12.2; Female 77.2%; DAS28 5.1 ± 1.3; number swollen joints 7.8 ± 5.6; number tender joints 7.3 ± 4.6; ESR 31.2 ± 24.0mm; CRP 19.8 ± 32.9 mg/l; Anti-CCP antibody positive 46.8%; Rheumatoid factor (RF) positive 35.4%. CR data at one year was obtained on 1184 joints that had mode B and PD evaluation and 708 joints for US erosions. CR erosions at one year: 105(9.8%) joints were erosive by CR on the 10 targeted joints. In univariate analysis, baseline PD positive synovitis and US erosions were associated with the presence of a CR erosive joint at one year. After adjustment for the clinical and biological variables, US erosions at baseline remained predictive of the presence of CR erosive joints at one year, independently from CRP and the presence of RF, also significantly associated (p < 0.001).

Table 1. Baseline US characteristics for the presence of CR erosion at one year:

<table>
<thead>
<tr>
<th>Prediction of future joint damage on X-ray at 1 year</th>
<th>X-Ray findings at year 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eroded joint</td>
<td>Non-eroded joint</td>
</tr>
<tr>
<td>US findings</td>
<td>Synovitis Joint with Doppler</td>
</tr>
<tr>
<td>(N = 1184)</td>
<td>196/1077</td>
</tr>
<tr>
<td>+ synovitis</td>
<td>30(4%)</td>
</tr>
<tr>
<td>US Erosion</td>
<td>Eroded joint</td>
</tr>
<tr>
<td>(N = 708)</td>
<td>29(5%)</td>
</tr>
</tbody>
</table>

* Adjustment for age, DAS28, CRP, ESR, positivity for Rheumatoid factor (RF) and anti-CCP and corticotherapy

When restricted to CR non erosive joints at baseline, these associations were maintained (PD synovitis: OR = 5.41[2.09–14.01]p < 0.001; US erosion: OR = 3.93[1.35–11.43]p = 0.012). When restricted on non erosive patients on baseline CR, US erosions became borderline significant (p = 0.052).

Conclusion: At the joint level, baseline US findings are associated with structural damage at one year. US is a reliable and useful technique to predict future erosions in early arthritis patients.

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CRP-Levels and Duration of Morning Stiffness as Predictors of Active Rheumatoid Arthritis as Verified by Ultrasound in Routine Clinical Practice. Christian Dejaco², Christina Dufner², Edith Wippfer-Freißmuth², Helmut Weiss², Winfried B. Graninger¹ and Michael Schirmer¹. ¹Department of Internal Medicine I, Medical University Innsbruck, Innsbruck, Austria, ²Department of Internal Medicine, General Hospital of the Elisabethinen Klagenfurt, Klagenfurt, Austria, ³Department of Internal Medicine, Hospital of the Barmherzige Brüder Marschallgasse Graz, Graz, Austria, ⁴Department of Radiology, General Hospital of the Elisabethinen Klagenfurt, Klagenfurt, Austria, ⁵Department of Rheumatology, Medical University Graz, Graz, Austria

Objective: To identify clinical and serological parameters predicting active disease as verified by ultrasound in rheumatoid arthritis (RA) patients from routine clinical practice.

Methods: Retrospective analysis of data from 149 consecutive RA-patients subjected to ultrasound (US) examination [mean disease activity score for 28 joints (DAS-28) 4.5 (standard deviation ± 1.3); mean age 63.7 (±13.4) years; 84.6% female; median disease duration 18 months]. Each patient underwent bilateral US assessment of wrists, metacarpophalangeal and proximal inter-phalangeal joints (=22 joints) for the assessment of synovial hypertrophy and/or effusion (SH/E) as well as synovial vascularity as determined by power Doppler (PD). According to Balsa A et al. sonographic remission was defined as the absence of PD-signals whereas presence of hypervascularisation indicated active disease[i]. The number of tender (TJ) and swollen joints (SJ), global assessment of disease activity on a visual analogue scale by the physician (VAS-phys) or patient (VAS-pt), C-reactive protein (CRP)-levels, erythrocyte sedimentation rate (ESR), duration of morning stiffness (MS), DAS-28, clinical disease activity index (CDAI), simplified disease activity index (SDAI) and health assessment questionnaires (HAQ) were recorded. This retrospective analysis was accepted by the local ethics committee.

Results: Sonographically detected hypervascularization was observed in 117 (78.5%) of the RA-patients. CRP, ESR and MS were higher in patients with sonographic signs of disease activity than in those with remission [CRP: median 0.8 (inter-quartile range 2.1) vs. 0.3 (0.6) mg/dl, p=0.01; ESR: 24 (39) vs. 14 (16) mm/1st hour, p=0.019; MS: 30 (115) vs. 12.5 (30) minutes, p<0.001, respectively]. TJ- and SJ-count, VAS-phys, VAS-pt, ESR, DAS-28, CDAI, SDAI and HAQ were similar among both groups. None of the parameters differed between those 10 patients without sonographic lesion and 112 patients with sonographic lesion. Using backward logistic regression analysis we found an odds ratio (OR) of 3.8 (1.6–9.1, p=0.003) for CRP >5.0mg/L (normal values 0–5.0mg/L) and an OR of 1.6 (1.1–2.5, p=0.024) for MS >30min (interaction between these parameters not significant) to predict active disease. The other clinical and serologic parameters showed no association with disease activity.

Conclusion: In routine clinical practice elevated CRP-levels and longer duration of MS alone are predictors of active RA as verified by ultrasound. This observation could be helpful for the development of referring strategies in the management of these patients.


Disclosure: D. A. Bong: None; J. Palau: None; I. Möller: None; E. Naredo: None.

2224

Clinic Based MSK Ultrasound in the Diagnosis and Treatment of Shoulder Pain—A Randomized Prospective Study. Aamir Saeed2, Mumtaz Khan, Siobhan Morrissey and Alexander D. Fraser1. 1Castleroberts, County Limerick, Ireland, 2Mid Western Regional Hospital, Limerick, Ireland

Introduction: Local corticosteroid injections are accepted by rheumatologists to be an effective option in the treatment of shoulder pain. Clinic based high frequency ultrasonography has been postulated to have a role in the diagnosis of shoulder pathology and guiding injections.

Aim: This randomized prospective study aims to assess whether clinic based MSK Ultrasound significantly improves the accuracy of diagnosis, treatment choices and positioning of injections in shoulder pain and if so whether this improves outcome.

Methodology: 100 consecutive patients with 125 painful shoulders were selected. Patients were randomized to receive either sonographic assessment and blind subacromial injection of 40 mg depomethone (Group 1, n = 66) or a sonographic assessment and guided injection of 40 mg depomethone (Group 2, n = 59). A blinded consultant rheumatologist performed all clinical assessments at baseline, 6 and 12 weeks including the hawkin kennedy test, supraspinatus tendon tenderness, patient and physician global visual analogue score for pain (0–10). All differences between clinical and ultrasound diagnosis for shoulder pain and incidental ultrasound findings for asymptomatic shoulders were recorded.

Results: 80 patients with 90 symptomatic shoulders (46 blinded and 44 guided groups) completed the study. Mean age 57.7 years, 65% female; mean patients with RTE due to radial nerve entrapment. The resistance may be related to the misdiagnosis rather than an actual lack of therapeutic response. We present, to our knowledge, the largest series of patients with RTE due to radial nerve entrapment in the radial tunnel. Radial tunnel syndrome is a pain syndrome characterized by point tenderness distal to lateral epicondylecty(LE) with radiation distally into the dorsal forearm due to compression of the deep motor branch of the radial nerve (posterior interosseus nerve or PIN) as it courses through the radial tunnel. With longstanding compression these patients may go on to develop motor findings.

Methods: Our study group consist of 23 patients, that were referred for evaluation of ongoing lateral elbow region pain unresponsive to conservative or invasive treatment. Evaluation consisted of thorough history and clinical examination. Ultrasound (US) examination of the elbow was performed by one of two experienced sonographers with a LOGIC E(Genelric Electric, Waukesha, Wisconsin) using a 12-7 MHz linear probe. In addition the radial nerve was examined from its origin to the wrist in both upper extremities. All patients subsequently underwent surgical exploration by the same hand surgeon with release of the compressive structures.

Summary of the Results: US findings included: positive “sonopalpation” in 19/23 patients at the proximal radial(proximal to Arcade of Frohse) and in 4/23 patients at the distal radial tunnel. The nerve was enlarged in relationship with the contralateral nerve, in the proximal tunnel in 9/23 patients and distal to the exit of the tunnel in 3/23 patients. No US changes were observed in 11/23 patients. In the 10 patients that underwent electromyographical testing only one was positive and in all 8 patients that had MRI there no evident changes of the PIN. At surgery all patients were found to have enlargement of the radial nerve. In 19/23 the enlargement was noted proximal to the Arcade of Frohse. In 3/23 patients the enlargement was noted distal to the exit of the nerve from the distal radial tunnel. In the final patient enlargement was evident throughout the entire course of the radial nerve between the two heads of the supinator muscle.

Conclusion: High resolution US enables us to visualize the peripheral nervous system and is an important part of the evaluation of entrapment neuropathies. This study is the most extensive report of radial tunnel syndrome and confirms the value of US in the diagnosis of this entity prior to the onset of motor weakness. US was able to localize the precise point of involvement by sonopalpation. US was helpful to the surgeon in localizing the area of entrapment and in planning the most appropriate surgical approach.

We also propose the following classification criteria for Radial Tunnel Syndrome: Type I- Radial nerve involvement in the proximal portion of the tunnel proximal to the arcade of Frohse; Type II— involvement of the distal portion as it emerges from the supinator heads; Type III – diffuse enlargement throughout its course between the supinator heads.

Disclosure: D. A. Bong: None; J. Palau: None; I. Möller: None; E. Naredo: None.

2223

Resistant Tennis Elbow (RTE) Due to Radial Tunnel Syndrome: Clinical Presentation, Sonographic Findings and Surgical Correlation. David A. Bong1, Jordi Palau1, Ingrid Möller1 and Esperanza Naredo2. 1Barcelona Sonanatomy Group, 2Hospital Universitario Severo Ochoa, Madrid, Spain, 3Instituto Puol de Reumatologia, Bruce, WI

Background: Tennis elbow is a commonly encountered problem in rheumatologic practice and it is frequently resistant to the standard treatment. The resistance may be related to the misdiagnosis rather than an actual lack of therapeutic response. We present, to our knowledge, the largest series of patients with RTE due to radial nerve entrapment in the radial tunnel. Radial tunnel syndrome is a pain syndrome characterized by point tenderness distal to lateral epicondyle(LE) with radiation distally into the dorsal forearm due to compression of the deep motor branch of the radial nerve (posterior interosseus nerve or PIN) as it courses through the radial tunnel. With longstanding compression these patients may go on to develop motor findings.

Methods: Our study group consist of 23 patients, that were referred for evaluation of ongoing lateral elbow region pain unresponsive to conservative or invasive treatment. Evaluation consisted of thorough history and clinical examination. Ultrasound (US) examination of the elbow was performed by one of two experienced sonographers with a LOGIC E(Genelric Electric, Waukesha, Wisconsin) using a 12-7 MHz linear probe. In addition the radial nerve was examined from its origin to the wrist in both upper extremities. All patients subsequently underwent surgical exploration by the same hand surgeon with release of the compressive structures.

Summary of the Results: US findings included: positive “sonopalpation” in 19/23 patients at the proximal radial(proximal to Arcade of Frohse) and in 4/23 patients at the distal radial tunnel. The nerve was enlarged in relationship with the contralateral nerve, in the proximal tunnel in 9/23 patients and distal to the exit of the tunnel in 3/23 patients. No US changes were observed in 11/23 patients. In the 10 patients that underwent electromyographical testing only one was positive and in all 8 patients that had MRI there no evident changes of the PIN. At surgery all patients were found to have enlargement of the radial nerve. In 19/23 the enlargement was noted proximal to the Arcade of Frohse. In 3/23 patients the enlargement was noted distal to the exit of the nerve from the distal radial tunnel. In the final patient enlargement was evident throughout the entire course of the radial nerve between the two heads of the supinator muscle.

Conclusion: High resolution US enables us to visualize the peripheral nervous system and is an important part of the evaluation of entrapment neuropathies. This study is the most extensive report of radial tunnel syndrome and confirms the value of US in the diagnosis of this entity prior to the onset of motor weakness. US was able to localize the precise point of involvement by sonopalpation. US was helpful to the surgeon in localizing the area of entrapment and in planning the most appropriate surgical approach.

We also propose the following classification criteria for Radial Tunnel Syndrome: Type I- Radial nerve involvement in the proximal portion of the tunnel proximal to the arcade of Frohse; Type II— involvement of the distal portion as it emerges from the supinator heads; Type III – diffuse enlargement throughout its course between the supinator heads.

Disclosure: D. A. Bong: None; J. Palau: None; I. Möller: None; E. Naredo: None.
shoulder pain duration was 18 weeks (14–22). Shoulder function tests (SFT), improved significantly from baseline in both groups at 6 and 12 weeks. However significantly greater improvements were noted at both time points in the guided versus the blind injection groups (Delta BL p<0.01 and p<0.05) respectively. Patient VAS scores and PGA for pain also improved significantly in both groups at 6 and 12 weeks but again improvements were significantly greater at both time intervals in the guided group p<0.05. 20 patients, 11 (19 shoulders) from blinded and 9 (16 shoulders) from guided group were excluded from study at 6 weeks either due to repeat injection or surgical referral. About 10% of asymptomatic contra-lateral shoulders significant pathology on ultrasonography ranging from shoulder impingement to full thickness tears. 8% of clinical diagnoses differed significantly from the ultrasound diagnosis and with clinical relevance.

**Conclusions:** Both blind and guided steroid injections are associated with significant improvements in shoulder function and pain when assessed at 6 and 12 weeks. Guided injections are more effective and should at least be considered in non-responders. 2 Clinically relevant differences between clinical and ultrasonographic diagnosis may occur and significant pathology may be identified in contra-lateral asymptomatic shoulders raising interesting insights into the historical pathophysiology of shoulder pain.

Disclosure: A. Saeed: None; M. Khan: None; S. Morrissey: None; A. D. Fraser: None.

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**Sonographic Needle Guidance and Cost-Effectiveness of Intraarticular Injections for Osteoarthritis of the Knee.** Natalia R. Chavez-Chiang, Wilmer L. Sibbitt, Suzanne Delea, Kye Park, Arthur D. Bankhurst, Philip A. Band and Hillary Norton. 1New York University School of Medicine, 2University of New Mexico, Albuquerque, NM, 3University of New Mexico, 4University of New Mexico HSC, Albuquerque, NM, 5University of NM Med Ctr, Albuquerque, NM, 6University of New Mexico, Albuquerque, NM

**Objective:** The present randomized controlled study addressed whether sonographic needle guidance affected the outcomes of intraarticular injection for osteoarthritis of the knee.

**Methods:** 94 non-effusive knees with osteoarthritis were randomized to injection by conventional palpation-guided anatomic injection or sonographic image-guided injection enhanced with a one-handed RPD (the reciprocating procedure device) syringe. A one needle, two-syringe technique was used. After intraarticular placement and synovial space dilation were confirmed by sonography, a syringe exchange was performed, and 80 mg of triamcinolone acetonide was injected with the second syringe through the indwelling intraarticular needle. Baseline pain, procedural pain, pain at outcome (2 weeks and 6 months), responders, therapeutic duration, reinjection rates, total cost, and cost per responder were determined.

**Results:** Relative to conventional palpation-guided methods, sonographic guidance for injection of the knee resulted in 47.7% reduction in procedural pain (p<0.001), a 41.7% reduction in pain scores at outcome (p<0.03), 107% increase in the responder rate (p<0.001), 51.6% reduction in the non-responder rate (p<0.001), a 35.5% increase in therapeutic duration (p =0.01), a 14.6% reduction ($48) in cost/patient/year, and a 58.8% ($593) reduction in cost/responder/year for a hospital outpatient (p<0.001).

**Conclusions:** Sonographic needle guidance improves the performance, clinical outcomes, and cost-effectiveness of intraarticular injections of the osteoarthritic knee.

Disclosure: N. R. Chavez-Chiang: None; W. L. Sibbitt: Apple, Inc, 1, 2, 5, Avanca Inc, 1, 2, 5, Avanca Medical Devices, 1, 2, 5, Avasca inc 1, 2, 5, Avasca Medical Inc 1, 2, 5, Becton Dickinson, 5, Celgene, 1, Ferring Pharmaceuticals Inc., 5, Intelligence Management Solutions, 1, S. Delea: None; K. Park: None; A. D. Bankhurst: None; P. A. Band: None; H. Norton: None.

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**ACR Concurrent Abstract Sessions**

**Innate Immunity and Rheumatic Disease (Oral)**

Thursday, November 11, 2010, 9:00 AM–10:30 AM
Identification of NLRP1 as a Systemic Sclerosis Susceptibility Gene: A New Clue for the Contribution of Innate Immunity in SSc Pathogenesis. Philippe Dieudé, Mickaël Guedj, Julien Wipff, Gabriela Riemekasten, Paolo Airo, Inga Mellechers, Marco Mattucci-Cerinic, Eric Hachulla, Catherine Bouilieu, Yannick Allanore and the GENESYS Consortium. 1Clinical Research Unit for Rheumatology, University Medical Center, Freiburg, Germany, 2Department of Rheumatology and Clinical Immunology, Charié University Hospital, Schumannstr. 20/21, D-10117, Berlin, Germany, 3Hôpitaux de Paris Cochin, Paris, France, 4Laboratoire Statistique et Génome, UMR CNRS-8071/INRA-1152/Université d’Evry Val d’Essonne, France, 5National Scleroderma Centre, Lille Cedex, France, 6Paris Descartes University, Department of Rheumatology A, Cochin Hospital, Paris, France, 7Paris Diderot University, Department of Rheumatology, Bichat Claude Bernard Hospital, APHP, Paris, France, 8Rheumatology and Clinical Immunology, Spedali Civili, Brescia, Italy, 9Saint Quentin Yvelines University, Laboratoire de Biochimie Hormonale et Génétique, Ambroise Paré Hospital, AP-HP, Boulogne, France, 10University of Florence, Firenze, Italy

Background: Recent evidence has highlighted a potential role of interleukin 1 beta (IL-1β) in systemic sclerosis (SSc). NLRP1 provides a scaffold for the assembly of the inflammasome that promotes the processing and maturation of pro-IL-1β. In addition, NLRP1 variants were found to confer susceptibility to autoimmune disorders.

Objective: To test for association the NLRP1 SNPs rs1002867, rs26706600, rs8182352, rs12150220, rs4790797 with SSc in the European Caucasian population.

Methods: NLRP1 SNPs were genotyped in 3227 individuals comprising a Discovery set (870 SSc patients and 962 controls) and a Replication set including individuals from Germany (532 SSc patients and 324 controls) and Italy (527 SSc patients and 301 controls), all individuals being of European Caucasian origin.

Results: Conditional analyses revealed a significant association only for the NLRP1 rs8182352 variant. Both the NLRP1 rs8182352 C allele variant and the CC genotype were found to be associated with SSc-related fibrosing alveolitis (FA+) in the combined population: OR 1.19 95% CI [1.05–1.36], P = 0.0065 and OR 1.43 95% CI [1.10–1.84], P = 0.0063, respectively. Significant differences were also found when the FA+ SSc patients were compared to the FA− SSc patients. 1

Conclusions: Our results establish NLRP1 as a new genetic susceptibility factor for SSc. This provides new insights into the pathogenesis of SSc, underlining the potential role of innate immunity in particular in the FA+ SSc sub-phenotype, which represents a severe subset of the disease.

Disclosure: P. Dieudé: None; M. Guedj: None; J. Wipff: None; G. Riemekasten: None; P. Airo: None; I. Mellechers: None; M. Mattucci-Cerinic: None; E. Hachulla: None; C. Bouilieu: None; Y. Allanore: None; and the GENESYS Consortium: None.

2227

MASP-1 and Pro-Factor D Proteins Are Present in Synovocytes and May Locally Activate the Complement Alternative Pathway To Induce Inflammatory Arthritis in Mice. Nirmal K. Banda, Minoru Takahashi, Magdalena J. Glogowska, Kazue Takahashi, Gregory L. Stahl, Teizo Fujita, William P. Arend and V. Michael Holers. 1Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women’s Hospital, Boston, MA, 2Department of Immunology, Fukushima Medical University School of Medicine, Fukushima, Japan, 3Department of Immunology, Massachusetts General Hospital for Children, Boston, MA, 4Division of Rheumatology, University of Colorado at Denver, Aurora, CO

Purpose: Mannose-binding lectin-associated serine proteases 1/3 (MASP-1/3) can cleave pro-factor D (pro-Df) into active factor D (Df), which is required for activation of the alternative complement pathway (AP). The AP is both necessary and sufficient for mediation of collagen antibody-induced arthritis (CAIA) in mice. We have recently shown that MASP/3 mice are resistant to CAIA due to a defective AP and MASP-1/3 protein is the predominant mechanism to cleave pro-Df in vivo. The objectives of this study were to examine whether MASP-1/3 not bound to mannose-binding lectin (MBL) or ficolins (FCN) can activate the AP, and if MASP-1 and pro-Df proteins are present in the joint.

Methods: Sera from wild type (WT), MASP-1/3−/−, MBL−/−/FCN A−/− and FCN A−/− C57BL/6 mice were used. CAIA was induced in WT and MASP-1/3−/− mice by injecting 4 anti-type II collagen (CII) mAb i.p. on day 0 and LPS i.p. on day 3. All mice were sacrificed on day 10. Sera from CAIA mice (with and without disease) and MBL−/−/FCN A−/− mice were analyzed in vitro for AP activation induced by anti-CII antibodies, zymosan and mannan.

Results: The sera of WT and MBL−/−/FCN A−/− mice, factor D existed exclusively in its active form, indicating that pro-Df is cleaved by MASP-1/3 in the absence of MBL or FCN. Conversely, sera from MASP-1/3−/− mice contained only pro-Df. There was no conversion of pro-Df to Df between day 0 (without disease) and day 10 (with CAIA) in MASP-1/3−/− mice. MASP-1/3 proteins are normally bound to MBL or FCN; however, we detected MASP-1/3 in the sera of MBL−/−/FCN A−/− mice which might be bound to an unknown protein. Anti-CII mAb, zymosan and mannann particles all induced C3b deposition and C3a and C5a generation in vitro using sera from MBL−/−/FCN A−/− and FCN A−/− mice under conditions where only the AP was active. These results suggest that MASP-1/3 is present in the circulation of MBL−/−/FCN A−/− mice and can initiate the AP of complement in vivo. IHC analysis showed the presence of MASP-1/3 in the synovium, but not on chondrocytes, in the knee joints of WT mice with CAIA. Pro-Df was found by IHC both in the synovium and on chondrocytes in the knee joints of MASP-1/3−/− mice without CAIA. These results indicate that MASP-1/3 protein is the predominant mechanism for cleavage of pro-Df in vivo and may activate the AP locally. Future studies will examine whether MASP-1 and pro-Df proteins are produced by the same cell in the synovium and whether conversion of pro-Df to Df occurs locally inside the cell or in the microenvironment.

Conclusions: MASP-1/3 protein predominantly cleaves pro-Df in vivo in CAIA. This study demonstrated that MASP-1/3, in the absence of MBL or FCN, can act locally in the knee joint and in the circulation to initiate the AP and inflammatory disease.

Disclosure: N. K. Banda: None; M. Takahashi: None; M. J. Glogowska: None; K. Takahashi: None; G. L. Stahl: None; T. Fujita: None; W. P. Arend: None; V. M. M. Holers: Taligen Therapeutics Inc., 1.
Mutated NLRP3 in Cryopyrin-Associated Periodic Syndromes Is Released from Restriction by CARD8. Sayaka Ito, Yukichi Hara, Yukio Shima and Tetsuo Kubota. Kyorin University, Tokyo Medical and Dental University, Tokyo, Japan, Tokyo Medical and Dental University

Purpose: NLRP3 in monocytes and other cell types plays a role in innate immunity as one of the intracellular pathogen recognition receptors, and its mutation is responsible for cryopyrin-associated periodic syndromes (CAPS). Once activated, NLRP3 forms a protein complex called the inflammasome with procaspase-1 and an adaptor protein ASC, leading to activation of caspase-1 and production of mature proinflammatory cytokines IL-1β and IL-18. Some experiments using cells expressing truncated NLRP3 indicated interaction between the NACHT domain of the NLRP3 and the FIIND domain of another adaptor protein CARD8, but involvement of CARD8 in NLRP3 inflammasome remains controversial. We herein aimed to clarify the role of CARD8 in NLRP3 inflammasome and its relevance to the pathophysiology of CAPS.

Methods: HEK 293 cells were transiently transfected with ASC, CARD8, procaspase-1, proIL-1β, and NLRP3 in wildtype or with CAPS-associated mutation. 24h later, whole cell lysates were provided for immunoprecipitation and western blotting. 48h after transfection, IL-1β in the cell culture supernatant was measured by ELISA.

Results: Wild type full-length NLRP3 was immunoprecipitated with CARD8, but interestingly, this interaction was inhibited by coexpression of ASC in a dose-dependent manner, suggesting that affinity between NLRP3 and ASC is higher than that between NLRP3 and CARD8. In contrast, NLRP3 with CAPS-associated mutation R260W or H11022 was unable to interact with CARD8. Cells expressing wildtype NLRP3, ASC, procaspase-1 and proIL-1β spontaneously produced IL-β, and it was significantly suppressed by cotransfection with full-length CARD8. Cotransfection of the FIIND domain of CARD8 showed less, but still significant, suppressive effect on the IL-1β production.

Conclusions: CARD8 interacts with full-length wildtype NLRP3, and may prevent the NLRP3 inflammasome from unrestricted activation. Disability of CARD8 to interact with mutated NLRP3 may explain continuous release of IL-1β by monocytes from CAPS patients.

Disclosure: S. Ito; None; V. Hara; None; Y. Shima; None; T. Kubota; None.

Complement Component C5 Plays a Central Role in Osteoarthritis. William Robinson, Andrew L. Rozelle, Tamsin M. Lindstrom, Reuben Gobezie, V. Michael Holers, David M. Lee and Qian Wang. Menlo Park, CA, 2Brigham and Women’s Hospital, Boston, MA, 3Tokyo Medical and Dental University, Tokyo, Japan, 4Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, 5Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, 6Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, 7Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Background/Purpose: Osteoarthritis (OA) is characterized by the breakdown of articular cartilage and is generally believed to result from “wear and tear”. Although low-grade inflammatory responses are observed in OA, their contribution to its pathogenesis is unclear. We herein aimed to determine the role of sublytic MAC on chondrocyte gene and protein expression.

Results: Mass spectrometry analysis revealed the presence of multiple complement effectors and inhibitors in the synovial fluid of OA patients. ELISA analysis demonstrated elevated levels of C3a and C5b-9 in OA synovial fluids, indicating activation of the complement cascade. Furthermore, synovium derived from OA patients was found to express complement components, whereas synovium from healthy individuals expressed only slight mRNA expression. We herein found that mice deficient in the central complement component C5 are protected against the development of degenerative arthritis, as assessed histologically and by gait analysis. Wild-type mice treated with an anti-C5 antibody were similarly protected. Moreover, the MAC (cell-bound form of C5b-9) was detected on chondrocytes derived from OA patients, and deposition of sublytic MAC on chondrocytes derived from OA cartilage induced the production of matrix–degrading enzymes, cell cycle regulators, inflammatory mediators, and complement components.

Conclusions: Our results suggest that local dysregulation of complement in synovial joints plays a critical role in the development of OA. Further, we demonstrated a critical role for the complement component C5 in the pathogenesis of experimental OA.

Disclosure: W. Robinson: Synostics, 1; A. L. Rozelle: None; T. M. Lindstrom: None; R. Gobezie: Synostics, 1; V. Holers: None; D. M. Lee: Synostics, 1; Q. Wang: None.
IL-10, in TLR2/4 condition. Unaltered response of TLR2/4 macrophages to IL-1 as control excluded a non-specific effect.

These findings indicate an important regulatory function of TLR2 in macrophage FcγR response with remarkable consequences for arthritis expression. A protective role of TLR2 in immune-complex driven arthritis beyond its previously-described role in promoting regulatory T cell function may provide a relevant therapeutic intervention for the future treatment of RA.

Disclosure: S. Abdollahi-Roodsaz: None; M. I. Koenders: None; F. A. J. van de Lou: None; W. B. Van Den Berg: None.

2231
A Novel Role of Endothelin-1 in Linking Ro60-sRNA Immune Complexes to Cardiac Fibrosis in Congenital Heart Block, David Alvarez-Carbonell1, Jiri Zavadil2, Rosana Abellar3, Franck Barrat4, Robert Clancy5 and Jill Buyon1. 1Columbia University Medical Center, 2Dynavax Technologies, 3New York University School of Medicine, 4New York University School of Medicine, New York, NY, 5New York University School of Medicine

Passively acquired anti-Ro associated congenital heart block (CHB) likely results from pathologic crosstalk between inflammatory and fibrosing pathways eventuating in scarring. The target, Ro60, complexed with uridine rich ssRNA induces TLR7-dependent macrophage production of supernatants capable of trans-differentiating human fetal cardiac fibroblasts. This study addressed the molecular components responsible for the TLR-dependent profibrogenic effects. In seeking the link between an inflammatory response of macrophages and the profibrotic effect on fibroblasts, a microarray analysis of fibroblasts transfected with either ETa or ETb siRNA, but not scrambled siRNA, also revealed ET-1/2/3 antibody staining but not isotype control in the septal region in areas showing calcification, fibrosis, and mononuclear cell infiltrates (not seen in an age-matched fetal heart). In conclusion, these data suggest that macrophage secretion of ET-1 may be one mechanism linking TLR inflammatory signaling to subsequent fibrosis and provide new insight in considering therapeutic for CHB.

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2232
Mucosal Associated Invariant T Cells Contribute to the Pathogenesis of Arthritis. Asako Chiba, Ryohsuke Tajima, Yusei Miyazaki, Takashi Yamamura and Sachiko Miyake. Department of Immunology, National Institute of Neuroscience, NCNP

Background: MR1-restricted mucosal associated invariant T (MAIT) cells are a subset of innate lymphocytes which express an invariant TCRαβ chain (Vα 19-Jα 33 in mouse and Vα 7.2-Jα 33 in human) with a limited set of TCRβ chains. We previously reported the regulatory role of MAIT cells in experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis. To understand their role in animal models of arthritis, we generated MR1-/- DBA/1J mice and analyzed their disease susceptibility to collagen-induced arthritis (CIA). We also investigated if MAIT cells are involved in the effector phase of arthritis by using two animal models of antibody-induced arthritis (AIA). Finally we studied mechanisms by which MAIT cells modulate autoimmune responses.

Methods: To obtain MR1-/- DBA/1J mice, MR1-/-C57BL/6J mice were backcrossed to DBA/1J mice for ten generations. To induce CIA, MR1-/- DBA/1J mice or WT littermates were immunized intradermally with bovine type II collagen (CII) (150μg) in Freund’s complete adjuvant containing 250μg of H37Ra Mycobacterium tuberculosis on day 0 and CII in IFA on day 21. AIA was induced in MR1-/- C57BL/6J mice and WT controls by injecting either a serum i.p., or a mixture of type II collagen antibodies i.v. followed by lipopolysaccharide i.p. 19i T cells (mouse MAIT cells) were sorted from liver or spleen cells of Vα19TGR-Transgenic (Vα 19Tg) CD1d-/- mice by using anti-TCRβ and anti-NK1.1 monoclonal antibodies. In adoptive transfer studies, NK1.1+ TCRβ+Vα19i T cells sorted from Vα19TgTgCD1d-/- mice were injected i.v. into MR1-/- mice on one day before the induction of arthritis. Cytokine producing capacity of MAIT cells stimulated with or without anti-CD3mAb in the presence of various types of cytokines was evaluated by ELISA or cytokine bead assay kit.

Results: MR1-/- DBA/1J mice were more resistant to CIA compared to WT littermates, as demonstrated by clinical and histological scores of arthritis. CII specific antibody levels in the serum were reduced in MR1-/- – DBA/1J mice compared to WT controls. The severity of clinical and pathological features of AIA was reduced in MR1-/- mice compared to control WT mice. MR1-/- mice reconstituted with MAIT cells developed severe forms of arthritis to the similar level of arthritis in WT mice. IL-17 production by anti-CD3mAb-stimulated MAIT cells was highly augmented in the presence of IL-23. In addition, MAIT cells were activated and produced IL-17 upon IL-23 stimulation even without TCR stimulation.

Conclusions: MAIT cells contribute to the pathogenesis of arthritis. MAIT cells may be activated by cytokines which are abundant in inflammatory arthritis, and this may in turn amplify autoimmune responses.

Disclosure: A. Chiba: None; R. Tajima: None; Y. Miyazaki: None; T. Yamamura: None; S. Miyake: None.

2233 WITHDRAWN

2234
An Endothelium-Specific NF-kappaB Inhibitor Ameliorates Inflammatory Joint Diseases. Bettina Sehnert1, Harald Burkhardt2, Falk Nimmerjahn3, Johannes Wessel1, Agnes Machnik1, Dietmar Vestweber4, Jochen Zwerina5, Georg Schett5, Stefan Dübel3 and Reinhard Voll5. 1Georg-August-University of Göttingen, 2Johann Wolfgang Goethe University Frankfurt am Main, 3Technical University of Braunschweig, 4University of Erlangen-Nürnberg, Erlangen, Germany, 5University of Erlangen-Nürnberg, 6University of Münster

Background: Therapeutical strategies that systemically block nuclear transcription factor-kappaB (NF-kappaB)-signalling may cause serious side effects due to the important role of NF-kappaB in a variety of anti-inflammatory regulatory pathways, for instance in the central nervous system, the liver and the immune system. NF-kappaB is a key player in inflammatory disorders such as rheumatoid arthritis. Activation induces the expression of multiple mediators involved in the initiation and perpetuation of inflammatory processes. We developed a novel class of NF-kappaB inhibitors, designated as ligand-sneaking construct (LSC), that interfere with the NF-kappaB signalling

Disclosure: S. Abdollahi-Roodsaz: None; M. I. Koenders: None; F. A. J. van de Lou: None; W. B. Van Den Berg: None.
pathway selectively in endothelial cells. We have chosen this cell population, because of its essential role in the extravasation of leukocytes in inflammation.

**Methods:** The LSC is a multimodular recombinant protein that consists of three domains: 1) an oligopeptide specifically binding the cytokine-activated endothelium 2) the translocation domain of pseudomonas exotoxin A (ETA II) that facilitates the endosomai release of the construct into the cytosol and 3) the NEMO-binding peptide (NF-kappaB inhibiting effector domain) (5). The effectiveness of this ETA II construct (LSC1) on NF-kappaB activation was analysed in vitro by an NF-kappaB-luciferase reporter gene assay and EMSA. In vivo binding of LSC1 to the cytokine-activated endothelium was proven by using the Olympus OV100 whole-mouse imaging system. The therapeutic effect of LSC1 in vivo was investigated in the antigen-induced arthritis and the KBN serum transfer model.

**Results:** E-selectin mediated internalization of LSC1 inhibited the transcriptional NF-kappaB activity in E-selectin expressing cells (CHO_E cells). Additionally, EMSA indicated a reduced nuclear translocation of NF-kappaB p65 was strongly binding to the activated endothelium. By whole mount immunofluorescence microscopy of tissue specimens derived from cytokine-activated mouse skin, nuclear form of NF-kappaB p65 was strongly suppressed in mice pretreated with LSC1 but not in control mice that had received the MutNBP2 construct. In the mouse model of antigen-induced arthritis, we observed a reduced joint swelling after LSC1 treatment. Moreover, LSC1 leads to an amelioration of inflammatory joint disease induced by anti-glucose 6 phosphoisomerase (anti-G6P) mouse serum. Histological studies confirmed the clinical data.

**Conclusions:** We presented for the first time an endothelium specific NF-kappaB inhibitor that shows therapeutic potential to treat inflammatory joint diseases in different mouse models of arthritis. This proof of concept study can be employed for targeting other cell types and to interfere with distinct signalling pathways.

**Disclosure:** B. Schmert: None; H. Burkhart: None; F. Nimmerjahn: None; J. Wessels: None; D. Vestweber: None; J. Zwerina: None; G. Schett: None; S. Düb: None; R. Völ: None.

## 2235

### Citrullination of Mouse Collagen Breaks Tolerance and Induces an Inflammatory Arthritis in the Absence of Adjuvant.

Jordan P. Lacy, Michael J. Duryee, Carlos D. Hunter, James R. O’Dell, Ted R. Mikuls, Geoffrey M. Thiele and Lynell W. Klassen. University of Nebraska Medical Center

**Purpose:** Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that primarily affects the synovial joints. Anti-citrullinated protein antibodies (ACPA) are predictive markers of the disease and its severity. Previous studies have demonstrated that ACPA can be induced in mice following injection of citrullinated type II collagen (Cit-Coll) in the Freund’s complete adjuvant (FCA). Therefore, it was the purpose of this study to determine whether mouse Cit-Coll in the absence of adjuvant can break tolerance and initiate an inflammatory arthritis in DBA/1 mice.

**Methods:** Mouse type II collagen was citrullinated using peptidyl arginine deiminase (PAD) and injected into DBA/1 mice at a concentration of (100 μg) in the base of the tail weekly for 5 weeks. Control groups were immunized with PBS, collagen, and collagen FCA. Animals were evaluated weekly for inflammation of the joints and serum was collected for the presence of anti-collagen or modified collagen antibodies. At week 6, animals were sacrificed paws removed for histology and spleens collected. The CD3+ T cells were then isolated and proliferated against collagen, albumin, Cit-Coll or Cit-albumin. Supernatants from the proliferation assays were collected and assayed for the presence of cytokines.

**Results:** Following 6 weeks of immunization, a significant increase in inflammation was observed as assessed by paw thickness and scoring in the Cit-Coll mice compared to controls. An increase in serum antibodies to Cit-Coll and Cit-albumin was present. However, no significant increase in antibodies to collagen was observed. In contrast, the immune response to Cit-Coll was predominantly T cell as shown by the increase in proliferative response to collagen and Cit-Coll. Assessment of cytokines from the proliferation supernatants revealed increases in IL-6 and IL-23 following from Cit-Coll immunized mice. Finally, histological analysis of joints from these animals showed an increase in joint erosion in the Cit-Coll immunized mice.

**Conclusions:** These data support the observation that citrullination of proteins increases the risk of this erosive inflammatory disease. Also, that citrullinated mouse type II collagen immunized in the absence of adjuvant causes an increase in T-cell proliferation with minimal antibody response to native collagen. The T-cell cytokine responses generated an IL-6 and IL-23 profile indicating an autoimmune response. Also, joint erosion and inflammation is evident in the Cit-Coll immunized mice as determined by scoring, paw thickness, and histology. Thus, this report suggests that citrullinated self-proteins may result in the abrogation of tolerance and the induction of an autoimmune response.

**Disclosure:** J. P. Lacy: None; M. J. Duryee: None; C. D. Hunter: None; J. R. O’Dell: None; T. R. Mikuls: None; G. M. Thiele: None; L. W. Klassen: None.

## 2236

### Differentiation and Activation of Regulatory T-Lymphocytes in a TNF-alpha Transgenic Model of Arthritis, and the Impact of Passive or Active Anti-TNF Therapies.

Jerome Biton1, Luca Semerano2, Marie-Christophe Boissier3 and Natacha Bessis3. 1Neovacs, Paris, France, 2Paris 13 University, Bobigny, France, 3Paris 13 University and APHP, Bobigny, France

**Purpose:** TNF-alpha is a critical cytokine in rheumatoid arthritis (RA). We recently demonstrated the efficacy of active immunotherapy against TNF-alpha (TNF-K) in a human TNF-alpha transgenic (TTg) mouse model of arthritis. Studies with anti-TNF-alpha treatments in autoimmune diseases suggest that TNF-alpha and TNF-alpha antagonists might act through the involvement of T cells subset, namely CD4+ CD25+ FoxP3+ regulatory T cells (Tregs).

**Objectives:** In the present study, we aimed to better characterize the impact on the Treg population of 1) a TNF-alpha driven disease, specifically arthritis in TTg mice, and 2) active or passive anti-TNF-alpha immunotherapy in this same model.

**Methods:** First, untreated TTg mice were euthanized sequentially at the age of 7 weeks, 12 weeks, 24 weeks and 24 weeks. 7 week-old and 24 week-old C57BL/6 wild type ( WT) mice were used as controls. Subsequently, three groups of mice were used: TTg mice given three doses of TNF-K at 15, 16 and 19 weeks of age, TTg mice treated with infliximab and untreated TTg mice. Then half the mice in each group were euthanized at 24 weeks and the other half at 31 weeks. After each euthanasia, the percentage and number of Tregs and the percentage of proteins increases the risk of this erosive inflammatory disease.

**Results:** CD4+ CD25+ FoxP3+ regulatory T cells (Tregs).

**Conclusion:** TNF-alpha overexpression induced an initial decline in Tregs. Then, once chronic inflammation was established, the frequency and the number of Tregs cells slightly increased with time, although it remained lower than in WT mice. We also observed a progressive and dramatic increase in TNFR2 expression (65.8% to 88.6% at weeks 7 and 24, respectively, P<0.0001) and MFI on Tregs from LN during the course of arthritis. We also confirmed that TNF-K was as effective as infliximab in treating established arthritis in TTg mice. Compared to untreated mice, hTNF-alpha blockade with either infliximab or TNF-K resulted in an increased Tregs frequency both in 24 and 31 week-old mice. Our study also showed that hTNF-alpha blockade induces an up-regulation of CTLA-4 expression by Treg cells in LN, accompanied by an increased Tregs suppressive activity on CD4+ CD25+ effector T cell proliferation. Finally, in LN of infliximab and TNF-K treated TTg
In addition, bone marrow derived monocytes (BMDMs) of wt and resolution micro-CT and Fluoride/FDG-PET analyses were performed. To identify abnormalities in bone metabolism and bone structure high 14 wks old mice were stained with toluidin-blue and TRAP. To inflammation, cartilage degradation and number of osteoclasts, joints were scored for clinical parameters for 14 weeks. For quantification of interbreed with arthritic hTNFtg mice. All resulting genotypes were neutralization but also on Treg upregulation.

**Conclusion:** In this study, in a strictly hTNF-alpha dependent inflammation model, we show for the first time that TNF-alpha can have different effects on Tregs, depending on the duration of exposure and on disease phase. Our work also shows that TNF-alpha blockade either by TNF-K or infliximab could depend not only on TNF-alpha neutralization but also on Treg upregulation.

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### ACR Concurrent Abstract Sessions

**Systemic Lupus Enrythematosus - Clinical Aspects and Treatment**

**Thursday, November 11, 2010, 9:00 AM–11:00 AM**

#### 2237

**The TRAF6 Binding Molecule p62/SQSTM1 Controls Inflammatory Bone Destruction in hTNFtg Mice.** Adelheid Korb1, Marianne Niedermeier2, Anja Hillmann1, Susanne Bürgis1, George Kollias1, Sven Herrmann1, Thomas Pap1, Thomas Weide1, André Gessner1, and Herrmann Pavenstädt2. 1Department of Immunology, University Erlangen, Erlangen, Germany, 2European Institute of Molecular Imaging, University Muenster, Germany, 3Institute for Experimental Musculoskeletal Medicine, University Hospital Muenster, Muenster, Germany, 4Institute for Experimental Musculoskeletal Medicine, University Hospital Muenster, Muenster, Germany, 5Institute of Immunology, Biomedical Science Research Center, Vari, Greece, 6Institute of Microbiology - Clinical Microbiology, Immunology and Hygiene, University Hospital Erlangen, Erlangen, Germany, 7Institute of Medical Pathology, Department of Nephrology and Rheumatology, University Hospital Muenster, Muenster, Germany

**Background:** Activation of NF-kappaB via RANK is essential in regulating osteoclastogenesis. This process is enhanced by pro-inflammatory cytokines such as TNFalpha. P62/SQSTM1 directly modulates these pathways through complex formation with TRAF6, aPKCs and ubiquitin. However, the function of p62/SQSTM1 in regulating bone turnover under inflammatory conditions and specifically the role of the signal transduction domains of p62/SQSTM1 in this process is not known.

**Methods:** Mice carrying a mutant of p62 with functional ubiquitin-binding but defective signal transduction domains (p62aaΔ69-251) were interbred with arthritic hTNFtg mice. All resulting genotypes were scored for clinical parameters for 14 weeks. For quantification of inflammation, cartilage degradation and number of osteoclasts, joints of 14 wks old mice were stained with toluidin-blue and TRAP. To identify abnormalities in bone metabolism and bone structure high resolution micro-CT and Fluoride/FDG-PET analyses were performed. In addition, bone marrow derived monocytes (BMDMs) of wt and p62aaΔ69-251 mice were isolated and osteoclastogenesis was studied using an established osteoclast formation assay. To investigate the underlying signalling pathways, cells were treated with TNFalpha and RANKL at different time points, and the activation of MAPKs was studied by Western Blot analysis.

**Results:** Histology and in vivo PET/CT studies revealed an increase in bone metabolism and bone mass in the hind paws, knees and vertebrae of p62aaΔ69-251 mice, but the number and size of osteoclasts of p62aaΔ69-251 and wt animals showed only minor changes suggesting that under physiological conditions the lack of the signal transduction domains of p62 is compensated by regulatory mechanisms. Compared to wt cells, however, BMDMs of p62aaΔ69-251 mice showed a significantly increased osteoclastogenesis, especially when stimulated with TNFalpha. Crossing of p62aaΔ69-251 mice with hTNFtg animals resulted in a dramatic increase in the severity of joint damage in the hTNFtg/p62aaΔ69-251/wt mice as determined clinically, by histomorphometry and PET/CT analysis. This was accompanied by an increase in the number and size of osteoclasts in vivo. During osteoclastogenesis, BMDMs from p62aaΔ69-251 mice showed an enhanced TNFalpha-induced ERK1/2 and p38 MAPK phosphorylation compared to that of wt mice.

**Conclusion:** In summary, our data suggest that p62 plays a relevant role in regulating TNFalpha mediated joint damage. They indicate that the loss of the TRAF6 and aPKCs binding domains has essential consequences for osteoclastogenesis under inflammatory conditions.

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#### 2238

**Low Blood Concentration of Hydroxychloroquine Is Associated with Failure of Hydroxychloroquine Treatment in Patients with Proliferative Lupus: Results of a Prospective Study.** Camille Frances1, Anne Cosnes1, Pierre Duhaut2, Noël Zahra3, Boutros Soutou2, Saskia Oro1, Didier Bessis1, Jacqueline Chevrant-Breton1, Nadege Cordel1, Dan Lipkser4 and Nathalie Costedoat-Chalumeau5. 1Department of Dermatology, Hôpital Tenon, Paris, France, 2Department of Dermatology, Hôpital Tenon, Internal Medicine Department, French National Reference Center for SLE, Pitié-Salpêtrière Hospital (GHPS), Paris, France

**Introduction:** We have previously demonstrated that low whole-blood concentration of Hydroxychloroquine [HCQ] is a marker for and a predictor of disease exacerbations in SLE patients, and we proposed 1,000 ng/ml as the target [HCQ] (Costedoat-Chalumeau, Ann Rheum Dis, 2007). We studied for the first time, the relationship between [HCQ] and efficacy of HCQ in patients with cutaneous lupus.

**Methods:** Patients treated with HCQ for a cutaneous lupus were prospectively included in this multicentric study. Clinical status was determined by a dermatologist who was blinded for [HCQ]. Complete remission was defined by the disappearance of all cutaneous lesions, partial remission by an improvement of more than 50% of at least one lesion, and minor disease activity by other cases. At the end of the study, [HCQ] was measured by HPLC.

**Results:** We included 300 patients: 253 (84%) women and 47 (16%) men, median age 44 years [12–86]. Cutaneous lupus included discoid lupus (n=160), subacute cutaneous lupus (n=86), lupus tumidus (n=52), chilblain lupus (n=26), and panniculitis (n=16), and 41 patients had 2 or more associated forms. Most patients (83%) were treated with 400 mg/d of HCQ. Clinical status was complete remission (n=114), partial remission (n=86) or failure (n=100).

The [HCQ] was 758 ng/ml [50–2843] if complete remission, 692 [50–2843] if partial remission, and 569 [50–257] if failure, (p=0.007). [HCQ] was significantly lower in men (557 [50–1572] vs 801 [50–3057] in women; p=0.006) who more frequently reported poor adherence to HCQ treatment. [HCQ] was 850 ng/ml [50–1000] as the target [HCQ] (Costedoat-Chalumeau, Arthritis Rheum, 2006). Very low [HCQ] (i.e. [HCQ] < 200 ng/ml) is a marker for poor adherence to HCQ treatment. For complete remission (n=910), the median [HCQ] was 758 ng/ml [50–2843], which was significantly higher in patients with complete remission (910 [50–4000] vs 692 [50–2242] if failure, p=0.002). [HCQ] was 755 [212–2843] if partial remission and 692 [201–2242] if failure, (p=0.037). This remained true when analysis was performed after exclusion of non-adherent patients. There were 350 patients who had [HCQ] below 200 ng/ml and were considered as non-adherent. Thirty patients (10%) had [HCQ] below 200 ng/ml and were considered as non-adherent. There were 8 patients in complete remission group, 8 in partial remission group, and 14 in failure group. Number of self-reported omissions of HCQ was significantly higher (p=0.0001) in non-adherent patients. After exclusion of non-adherent patients, [HCQ] was 850 ng/ml [201–3057] in the remaining 270 patients. [HCQ] remained significantly higher in patients with complete remission (952 [224–3057] vs 755 [212–2843] if partial remission and 692 [201–2242] if failure, p=0.026).

In the whole group, [HCQ] was significantly correlated to BMI (p=0.02), weight (p=0.002) and height (p=0.05). There was no correlation between [HCQ] and cigarette smoking, daily dose of HCQ or number of omissions of HCQ.

**Conclusion:** In conclusion, low blood concentration of HCQ is associated with failure of HCQ treatment in patients with proliferative lupus. Higher blood concentration of HCQ is associated with better clinical status. Low blood concentration of HCQ is a marker for poor adherence to HCQ treatment.
exclusion of non-adherent patients (p = 0.01 and p = 0.016 respectively).

Comment: [HCQ] allowed detection of non-adherence to treatment in 10% of cases. Even after exclusion of non-adherent patients, low [HCQ] was associated with failure of HCQ treatment in patients with cutaneous lupus. Regular drug assaying and individual tailoring of treatment might help to improve the efficacy of HCQ treatment in patients with cutaneous lupus.

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Factors Associated with Low Blood Concentration of Hydroxychloroquine in 523 Patients with Systemic Lupus Erythematosus: Data from the PLUS Study, Nathalie Costedoat-Chalumeau, Lionel Galicier, Camille Frances, Olivier Aumaitre, Frederic Liote, Veronique Le Guern, Nicolas Lima, Amar Smali, J. Ninet, Laurent Perard, Du Le Thi Huong, Bouchra Asli, Catherine Grandpeix, Laurent Sailler, F. Ackermann, Thomas Papo, Benoit Brihaye, Olivier Fain, Jerome Stirmann, Moez Jallouli, Gaelle Leroux, Jean-Baptiste, History of the LE, F. Lucy of associated: antiphospholipid syndrome, values of C3, antinucleosome antibodies and anti-DNA antibodies, % of patients treated with immunosuppressive drugs, and mean daily dose of prednisone

Methods: Among the 509 included in the PLUS study, 523 patients who were treated with the same dose of HCQ (400 mg/d) were studied. [HCQ] was measured at the time of inclusion, and the patients were divided into 2 groups according to their [HCQ]: group A ([HCQ] < 750 ng/ml), and group B ([HCQ] ≥ 750).

Results: The following parameters were similar between group A (179 patients) and group B (344 patients): mean age and duration of SLE, current smoking status, activity of SLE, and SLE activity (p > 0.05). In multivariate analysis, factors associated with low [HCQ] were low level of platelets (p = 0.001), high clearance of creatinine (p = 0.001), absence of treatment with steroids (p = 0.003), poor adherence (p = 0.003), high BMI (p = 0.003), and SLE activity (p = 0.024).

Conclusion: This preliminary analysis confirms in a new set of patients our previously reported association of low [HCQ] with a higher SLE activity. [1] This was not expected given that patients included in PLUS study have used antimalarials (HR = 0.3 p = 0.001) and immunosuppressives (HR = 2.4 p = 0.02) and less likely to have used antimalarials (HR = 0.3 p = 0.001) at enrolment.

References:

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Mortality in a Multinational Inception Cohort of SLE. Murray B. Urowitz1, Dafna D. Gladman2, Dominique Ibanez2, Caroline P. Gordon2, Sang-Cheol Ba3, Ann E. Clarke, Sasa R. Bernatsky3, F. Jorge Sanchez-Guerrero4, John G. Hanly, David A. Isenberg5, Anisur Rahman5, Paul R. Fortin5, Daniel J. Wallace6, Ellen M. Ginzler7, Joan T. Merrill8, Graciela S. Alarcón9, Barri J. Fessler10, Ian N. Bruce11, Gunnar K. Sturfelt12, Ola Nived10, Kristjan Steinsson13, Munther A. Khamashta12, Michelle A. Petri12, Rosalind Ramsey-Goldman13, Susan Manzi14, Mary Anne Dooley15, Ronald V. Vollenhoven16, Cynthia B. Aranow4, Thomas Stoll17, Manuel Ramos12, Kenneth C. Kalunian18, Asad A. Zoma10, Guillermo Ruiz-Irastorza19, Peter J. Maddison20, Diane L. Kamen21, "S. Sam Lim22, and Christine A. Pesci21, 1West Hollywood, CA, 2Timonium, MD, 3Emory University, Atlanta, GA, 4Feinstein Institute, Manhasset, NY, 5Harmon Medical Research Hospital, East Kilbride, United Kingdom, 6Hanyang University Medical Center, Seoul, Korea, Republic of, 7Hospital Clinico I Provincial, 8Hospital de Cruces, Universidad del Pais Vasco, 9Instituto Nacional de Nutricion, Mexico City, DF, Mexico, 10Kantonsspital Schaffhausen, Schaffhausen, Switzerland, 11Karolinska University Hospital, 12Landspitalinn University Hospital, 13Manchester Royal Infirmary, Manchester, United Kingdom, 14Medical University South Carolina, Charleston, SC, 15Montreal General Hospital, Montreal, QC, Canada, 16North West Wales NHS Trust, Colwyn Bay, United Kingdom, 17Northwestern University, Chicago, IL, 18Oklahoma Med Research Foundation, Oklahoma City, OK, 19Queen Elizabeth II Health Services Center, Halifax, NS, Canada, 20SUNY-Downstate Medical Center, New York, NY, 21The Rayne Institute, London, United Kingdom, 22Toronto Western Hospital, Toronto, ON, Canada, 23UBA Rheumatology, Birmingham, AL, 24UCL Div of Medicine, London, United Kingdom, 25UCL Div of Medicine, 26UCSD School of Medicine, La Jolla, CA, 27University Hospital Lund, Lund, Sweden, 28University of Alabama, Oakland, CA, 29University of Birmingham, Birmingham, United Kingdom, 30University of Manitoba, Winnipeg, MB, Canada, 31University of North Carolina at Chapel Hill, Chapel Hill, NC, 32University of Toronto Lupus Clinic, Toronto Western Hospital, 33University of Toronto Lupus Clinic, Toronto Western Hospital, Toronto, ON, Canada, 34West Penn Allegheny Health System, Pittsburgh, PA

Background: A large multicentre multinational inception cohort was established to study risk factors for atherosclerosis (AS) in SLE. This study describes survival, mortality and causes of death during the first 10 years of observation of the SLICC inception cohort.

Methods: Patients enter the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). Clinical and laboratory features of SLE and comorbidities are gathered in a standardized protocol at yearly intervals. Deaths are recorded as they occur and the cause of death is determined according to the ICD9 code. Demographic and disease related factors present at enrolment were compared in patients who died and in survivors using descriptive statistics, Kaplan-Meier curve as well as life table analysis.

Results: Since 2000, 1593 patients have been entered into the cohort (89.4% female, age at SLE 34.6y, mean followup of 3.7 years). 30 patients have died during the course of follow-up. Survival was 99.6% at 1 year, 98.4% at 3 years and 97.5% at 5 years (figure 1). Causes of death included coronary artery disease (CAD) in 7, SLE in 9, infection in 1, from other causes and 4 unknown. Patients who were older at diagnosis, more often had CAD, and had higher SLICC/ACR damage index scores at enrolment and a decreased physical components score (PCS) of the SF-36 at enrolment. Patients who died were also more likely to have used corticosteroids (HR = 6.4 p = 0.01) and immunosuppressives (HR = 2.4 p = 0.02) and less likely to have used antimalarials (HR = 0.3 p = 0.001) at enrolment.
Conclusion: This multinational inception cohort of SLE patients demonstrates the improved survival noted among patients with SLE. Causes of death in the first 10 years of observation of the SLICC inception cohort with an average followup of 3.7 years include CAD, SLE and sepsis. Even early on in the course of SLE, CAD is an important cause of death. Older age, history of CAD, early damage and impaired physical function, use of corticosteroids and immunosuppressives are associated with mortality.

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Mycophenolate Mofetil and Hydroxychloroquine but Not Azathioprine Improve HDL Function in Women with SLE

Maureen McMahon1, Jennifer M. Grossman2, Jessica Gomez3, Lori Sahakian1, Weiling Chen1, John Fitzgerald2, Brian Skaggs2, Joan T. Merrill3, and Bevra H. Hahn4.

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Objective: Women with SLE have an unexplained increase in CAD compared to controls. Normal HDL protects against plaque by preventing oxidation of LDL and the resulting inflammatory response. Pro-inflammatory HDL (piHDL) are abnormal HDL that cannot protect LDL from oxidation. We previously reported that 45% of SLE women vs % of controls have HDL function remained relatively stable (1.07 ± 0.53) vs. 1.30 ± 0.77 at 6 weeks (p=ns), and 1.00 ± 0.99 at 12 weeks (p=ns). In addition, there was a trend towards a correlation between change in HDL function and improvement in SELENA-SLEDAI in all groups, (r=-0.367, p=0.09), although this did not reach statistical significance.

Conclusions: In conclusion, HDL function is significantly improved by therapy with mycophenolate mofetil, although not to normal levels. There was also improvement with hydroxychloroquine, but not with azathioprine.

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Screening for Cognitive Impairment in Systemic Lupus Erythematosus

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Purpose: Cognitive impairment is frequent in patients with systemic lupus erythematosus (SLE). In order to make an accurate diagnosis of cognitive impairment formal neuropsychological assessment is required which is not universally available. Our objective was to determine the accuracy of a screening questionnaire for the detection of cognitive impairment in patients with SLE.

Methods: Ambulatory patients with SLE and rheumatoid arthritis (RA) were studied at a single academic medical center. Each subject completed a self-report questionnaire of cognitive symptoms (CSI), which provides a total score and 4 subscale scores, and the hospital anxiety and depression scales (HADS). The SELENA and ACR/SLICC damage index were used to assess global SLE disease activity and severity respectively. In addition the Automated Neuro-psychological Assessment Metrics (ANAM) which is a computerized test battery that takes 45 minutes to administer was used to evaluate the cognitive performance of SLE and RA patients. ANAM measures reaction time and accuracy in Simple Reaction Time (SRT), learning and recall using Code Substitution subtests (CDS and CDD), working memory using the Mathematical Processing (MTH) and the Sternberg Memory Scanning (ST6) subtests, sustained attention using a Continuous Performance subtest (CPT), visual-spatial processing using the Matching Grids (MSG) subtest, and short-term visual memory using the Match to Sample subtest (MSP).Efficiency of performance on each subtest was examined by “throughput”, “inverse efficiency” or the number of impaired ANAM items. ANAM measures reaction time and accuracy in Simple Reaction Time (SRT), learning and recall using Code Substitution subtests (CDS and CDD), working memory using the Mathematical Processing (MTH) and the Sternberg Memory Scanning (ST6) subtests, sustained attention using a Continuous Performance subtest (CPT), visual-spatial processing using the Matching Grids (MSG) subtest, and short-term visual memory using the Match to Sample subtest (MSP). Efficiency of performance on each subtest was examined by “throughput”, “inverse efficiency” or the number of impaired ANAM items.

Results: Sixty-eight patients with SLE and 33 with RA were studied. Both groups were predominantly female (92.7% and 97.0%) with a mean ± SD age of 45.5 ± 13.4 and 49.8 ± 10.2 years respectively. SLE patients had significantly higher total CSI scores (33.6 ± 10.5 vs. 29.4 ± 6.8; p=0.041) and attention/concentration subscale CSI scores (15.7 ± 5.3 vs. 13.3 ± 3.4; p=0.016) compared to RA patients. There was a positive association overall between CSI scores and HADS anxiety (p<0.0001) and depression (p<0.0001). After adjusting for age and education, there was no significant association (p>0.05) between ANAM global and subscale scores and CSI scores in SLE and RA patients. The results were similar using either “throughput”, “inverse efficiency” or the number of impaired ANAM items.

Conclusion: The use of self-report questionnaires of cognitive symptoms does not reliably screen for cognitive impairment in SLE patients. The results obtained with such instruments are confounded by the presence of anxiety and depression.

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Autoantibodies as Biomarkers for the Prediction of Neuropsychiatric Events in Systemic Lupus Erythematosus

John G. Hanly1, Murray B. Urowitz2, Li Su3, Sang Cheol-Bae4, Caroline Gordon5, Jorge Sanchez-Guerrero6, Ann Clarke7, Sasha Bernatsky8, Archana Vasudevan9, Daniel I. Wallace10, Paul Fortier11, Daniel J. Wallace10, Mary Anne Dooley10, Ian Bruce11, Kristian Steenisson12, Munther Khamashta13, Susan Manzi14, Rosalind Ramsey-Goldman14, Gunnar Urowitz15, Li Su13, Sang Cheol-Bae6, Caroline Gordon26, Jorge Sanchez-Guerrero2243.

Purpose:
The presence of selected autoantibodies at enrollment predicted the occurrence of NP events using the ACR case definitions for 19 NP syndromes. These were categorized into diffuse/focal and central/peripheral NP events. Decision rules of different stringency (model A and model B) were used to determine the attribution of NP events to SLE and non-SLE causes. Plasma/serum samples were available from 1047 patients for the determination of the following autoantibodies in a central laboratory: lupus anticoagulant, IgG anticardiolipin, anti-β2 glycoprotein-I, anti-ribosomal P and anti-NR2 glutamate receptor antibodies. The association between the presence of autoantibodies and the risk of the first occurrence of NP events was examined by Cox regression.

Results:
The PFOA group reported significantly greater knee pain severity versus the Control group for the past 30 days, post-TUG and post-FFW. Results of the WOMAC indicated that the PFOA group had greater knee pain and stiffness and significantly less physical function in the past 48 hours. Both groups completed questionnaires regarding knee pain, stiffness, and function. All tests of function in this population are more sensitive than the FFW and have been shown to be reliable and valid in persons with PFOA. The best test of function in this population is the TUG as it is more sensitive than the FFW and has been shown to be reliable and valid in persons with PFOA.

Conclusion:
The detection of LA and anti-ribosomal P antibodies near the time of diagnosis of SLE is associated with an increased risk for intra-cranial thrombosis and lupus psychosis respectively.

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ARHP Concurrent Abstract Sessions
What a Pain Rheumatic Diseases Can Be!

Patellofemoral Osteoarthrosis in Middle-Aged Adults: What Are the Best Measures of Physical Performance and Pain for Use in the Clinic and in Research?

Purpose: Osteoarthritis (OA) of the knee is common in Western society. The prevalence of knee OA in adults in the US is estimated to be 23-33%, totaling more than 9 million adults. The patellofemoral (PF) compartment of the knee is frequently involved. Isolated PF OA is present in 24% of persons aged ≥ 50 years with knee pain; 40% have combined PF and tibiofemoral OA. The presence of PFOA is associated with pain and disability. Activities that stress the PF compartment are negatively impacted, and strong quadriceps contraction with a flexed knee can be particularly painful. This includes the task of rising from a chair, i.e., sit-to-stand. It is unknown if a physical performance test including sit-to-stand is a more sensitive test of function in persons with PFOA versus a test of ambulation. Clinicians need tests of physical performance, perceived function, and pain to measure the impact of disease in patients. One goal of this study was to examine the impact of PFOA on physical performance, perceived function, stiffness, and pain in persons with bilateral PFOA compared to healthy, painfree subjects without PFOA. A second goal was to determine the best clinical tests to quantify physical performance and pain.

Methods: Thirty-two adults, aged 40–65 years, underwent radiographic screening for PF and tibiofemoral OA; 15 remained after radiographic exclusions. This cross-sectional study compared 2 groups: subjects with bilateral, symptomatic, radiographic PFOA (PFOA) and age- and gender-matched asymptomatic subjects with no radiographic PFOA (control). There were 17 PFOA subjects and 15 control subjects. Subjects underwent radiographic analysis. Both groups completed questionnaires regarding knee pain, stiffness, and function. WOMAC andVAS data were analyzed with Mann-Whitney U-tests, P < 0.05; TUG and FEW results were analyzed with t-tests, P < 0.05.

Results: The PFOA group reported significantly greater knee pain severity versus the Control group for the past 30 days, post-TUG and post-FFW (VAS). Results of the WOMAC indicated that the PFOA group had greater knee pain and stiffness and significantly less physical function in the past 48 hours. The PFOA group required a significantly longer time to complete the TUG versus controls. No significant difference was found between the groups in time to complete the FFW.

Conclusions: The results of this study demonstrate that middle-aged adults with PFOA have significant functional deficits, greater knee stiffness, and greater knee pain versus painfree adults without PFOA. The TUG is more sensitive than the FFW to detect physical performance deficits in persons with PFOA. The best test of function in this population is the TUG as it is more sensitive than the FFW and has been shown to be reliable and valid in persons with OA. The TUG is simple, quick and requires less clinical space than the FFW. Clinicians should use the TUG, accompanied by a VAS rating of pain, to capture the impact of PFOA on an individual’s function and pain.

Disclosure: L. T. Hoglund: None; M. A. Lockard: None; J. Song: None; M. F. Barbe: None.
Differences in Muscle Strength and Pain Thresholds between Postmenopausal Women with and without RA. Ulrika Thoors, Christina H. Opava, Birgitta Glenmark, Eva Kosek, Ingrid E. Lundberg and Cecilia Friden. Karolinska Institutet, Stockholm, Sweden

Muscle weakness, in particular loss of muscle mass, pain and tenderness are common symptoms in rheumatoid arthritis (RA). This seems to be the case even when inflammation is well controlled and may result in increasing disability with increasing age. Increased pain and increased loss of muscle mass is also found among healthy women at the time of menopause. The aim of our study was to examine differences in muscle strength and pain thresholds between postmenopausal women with and without RA.

Ten postmenopausal women with early (<2 years) RA (median age 57.5, median BMI 24) and ten healthy women (median age 58.5, median BMI 25) were recruited for the study. All women were independent in daily living, had passed menopause and did not use hormone replacement therapy. The median DAS 28 score was 2.7 (range 1.3–4.0) and the median HAQ score was 0.57 (range 0–1) in the RA group.

Measurements of isokinetic muscle strength in knee flexors and extensors, grip strength, timed standing, pressure pain thresholds (PPT), supra threshold pressure pain rated as 4/10 and 7/10 respectively on a Borg CR-10 scale, and segmental and plurisegmental endogenous pain inhibitory mechanism during muscle contraction were assessed in all participants.

No significant difference in knee extensor strength was detected between the women with RA and the healthy ones. Participants with RA were significantly weaker in the knee flexors (p=0.01) and in grip strength (p=0.007), and they were slower in the timed standing (p=0.05). Compared to the healthy women, those with RA had increased sensitivity to threshold pain (p=0.007) and to supra threshold pressure pain at both levels measured (p=0.001 and p=0.004 respectively). PPTs increased at the contracting muscle as well as at a distant resting muscle during standardized static contractions in both groups alike.

Our results indicate that previously noted difference in muscular strength between women with and without RA is present in early disease, in patients with low disease activity and seems to remain even after menopause. Further, the women with RA have generalized alloynia and hyperalgesia, but no dysfunction of segmental and plurisegmental pain inhibitory mechanisms. The normal function of endogenous pain inhibitory mechanisms despite chronic pain in women with RA might contribute to the good effects of physical activity in this group of patients.

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Fibromyalgia Diagnosis Is Significantly Impacted by the Number of Tender Points Presented on Patient Physical Exam. Terence W. Starz, Robert J. Sanchez, Bruce Duncan, Kaite Ka, Elizabeth Pinner, Shera D. Gruen and Dennis C. Turk. Arthritis & Internal Med Associates, Pittsburgh, PA; Pfizer; Roger Green and Associates, University of Washington, Seattle, WA

Statement of Purpose: To evaluate whether the number of tender points (TP) in simulated case vignettes influenced the likelihood of primary care physicians (PCPs) and rheumatologists (RHEUMs) diagnosing fibromyalgia (FM).

Methods: 200 PCPs and 100 RHEUMs experienced in treating chronic pain were recruited from an online panel to review simulated patient cases. All simulated patient cases included chronic widespread pain (CWP) + varying degrees of painful TPs (3–4, 6–8, and 10–12) on physical examination and various constellations of other FM related-symptoms (Table 1).

Each physician evaluated 20 cases and was asked to provide a diagnosis. The primary outcomes of interest were the diagnosis of FM, which was based on groups that include descriptions of varying numbers of TP present on physical examination and symptoms, by PCPs and RHEUMs. Bivariate statistics were used to examine the association between TPs and symptoms. Logistic regression models were used to examine predictors of FM diagnoses.

Results: 300 physicians reviewed 6000 simulated patient case vignettes. The overall FM diagnosis rate was 35% for PCPs and 63% for RHEUMs. The rate of FM diagnosis for the PCPs did not change among the different constellation of symptoms; however, as the number of painful TPs increased, the FM diagnosis also increased (Table 1). Among the RHEUMs, there was no significant difference in the dx rate among the different constellations of patient symptoms for those experiencing 3–4 or 6–8 painful TPs. However, among those with 10–12 painful TPs, a significant difference in diagnosis (67%–84%, p = 0.004) among the different constellation of patient symptoms were seen. The FM diagnosis rate for RHEUMs also increased as the number of TPs increased (Table 1). After controlling for covariates, the odds of an FM diagnosis among PCP was significant for those experiencing 6–8 painful TPs (odds ratio 1.82, p <0.001) and 10-12 painful TPs (odds ratio 4.64, p <0.001). Among the RHEUMs, the odds of an FM diagnosis was significant for those experiencing 6–8 painful TPs (odds ratio 1.57, p <0.001) and 10–12 painful TPs (odds ratio 3.20, p <0.001). The presence of 3–4 TPs did not impact the likelihood an FM diagnosis.

Conclusion: Although not all simulated patient cases met the ACR FM diagnosis criteria, the diagnosis of FM by RHEUMs was consistently higher than the diagnosis by PCPs across the different patient TPs and symptom groups reporting evaluating simulated patients. Existing studies, which are describing widespread pain with or without other FM symptoms and a variable number of tender points on physical examination, the number of tender points is the most significant patient characteristic that leads both primary care physicians and rheumatologists to make the diagnosis of FM. Further analysis is needed to understand reasons behind misdiagnosis.


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Background: Pain is common in patients with systemic sclerosis (SSc), and severity levels are comparable to other rheumatic diseases. Patients with SSc report a number of painful symptoms. Existing FM tools used in SSc have a variety of pain assessment tools, including a single-item pain Visual Analog Scale (VAS), a pain numerical rating scale (NRS), and the longer 15-item short-form McGill Pain Questionnaire (MPQ-SF). OMERACT 6 reported that the pain VAS is valid to measure pain related to Raynaud’s phenomenon and digital ulcers in SSc, but has not been examined as a general pain measure. VAS and NRS measures have been shown to function similarly in other patient groups. Despite being longer, the MPQ-SF would be a potentially attractive measure if it were to demonstrate more robust validity characteristics than single-item measures or if it were able to differentiate between sensory and affective components of pain, as has been suggested in some patient groups. The objectives of this study were (1) to assess whether the MPQ-SF has stronger validity characteristics among patients with SSc compared to two single-item measures, the pain NRS and the Present Pain Index (PPI), a single Likert item, and (2) to determine whether the MPQ-SF differentiates meaningfully between sensory and affective components of pain in SSc patients.

Methods: Patients with SSc were recruited from the Canadian Scleroderma Research Group Registry. To assess convergent validity compared to the NRS and PPI, Pearson’s correlations, with 95% confidence intervals (CIs), were computed between the MPQ-SF, NRS, and PPI with other outcome measures, including the Center for Epidemiologic Studies Depression scale (CES-D), the Health Assessment Questionnaire – Disability Index (HAQ-DI), and the Mental and Physical Component Summaries (MCS and PCS) scores of the Short-Form 36 Health Survey Questionnaire. To assess the degree that the MPQ-SF differentiated between sensory and affective factors, confirmatory factor analysis (CFA) models were conducted using MPLUS, treating items as ordinal data. In addition, Pearson’s correlations with 95% CIs of sensory and affective factor scores with CES-D, the HAQ-DI, the MCS and PCS were calculated to test for differences between the sensory and affective correlations.
Differentiate sensory and affective pain fit similarly well (c2(54) = 234.2, P < 0.001; CFI = 0.96, TLI = 0.99, RMSEA = 0.06). Sensory and affective factor scores correlated similarly with other outcome measures.

Conclusion: The MPQ-SF did not improve on the PRNRS or PPI as a measure of pain in SSc. In addition, no evidence was found that the MPQ-SF provides substantively different assessment of sensory and affective pain. The PRNRS is a reliable and valid measure of pain in SSc, and is advantageous for use because of its brevity in administration and scoring.

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2248

Daily Electronic Reports of Pain and Activity Difficulties in Children with JIA Versus Children with Other Rheumatic Diseases. Mark Connolly1, Maggie H. Bromberg2, Kelly K. Anthony1, Lindsey Franks4, Karen M. Gil1 and Laura E. Schanberg2. 1Children’s Mercy Hospital and Clinics, Kansas City, MO, 2Duke University Medical Center, Durham, NC, 3Duke University Medical Center, Durham, NC, 4University of North Carolina at Chapel Hill

Purpose: To compare children with JIA vs juvenile rheumatic disease (JRD) across daily measures of pain and associated symptoms. The role of pain in predicting activity difficulty also was examined in both disease groups.

Method: Children participated in a larger study to evaluate pain and functional limitations using electronic reports on handheld computers. Children with polyarticular JIA (26) and children with JRD (15), aged 8–18 yrs, were recruited from a pediatric rheumatology clinic. For 7 days, children completed morning, afternoon, and evening reports of pain characteristics (pain locations on a body map, pain duration on a 4-point scale ranging from “just a few minutes” to “>4 hours”), pain intensity and unpleasantness on a visual analog scale (VAS), fatigue (VAS), and difficulty in school, social, and physical activities (4-point scale ranging from “not at all difficult” to “extremely difficult”). A pediatric rheumatologist provided a diagnosis and disease severity score. Independent sample t-tests were used to evaluate differences in patients’ average responses across all assessments between patients in both groups. Hierarchical linear modeling was used to evaluate whether activity difficulty increased at times of greater pain intensity, and whether this relationship differed in direction or magnitude as a function of diagnostic group.

Results: Children were predominantly Caucasian (81% JIA, 73% JRD) and female (85% JIA, 67% JRD). Children with JIA on average reported significantly greater pain intensity (m = 30.6 vs m = 9.1, P < 0.05), pain unpleasantness (m = 31.4 vs m = 9.8, SD = 20.6, P < 0.05), and pain duration (m = 1.7 vs m = 7, SD = 1.05, P < 0.05) than children with JRD. The JIA group experienced pain in more locations (m = 8 vs m = 3, P < 0.05), greater stiffness intensity (m = 30.7 vs m = 7.4, P < 0.05), and higher levels of fatigue (m = 43.6 vs m = 17.7, P < 0.05) across all days. Children with JIA on average reported comparably mild levels of activity difficulty relative to children with JRD (m = 0.4 vs m = 0.6, ns). However, results of hierarchical linear modeling suggested that activity difficulty increased reliably at moments of greater pain intensity for both groups with the magnitude of this relationship greater for children with JIA (β(240) = 3.2, P < 0.01).

Conclusions: Although children with JIA experience comparably mild difficulty in daily activity participation relative to children with JRD, pain appears to uniquely influence the extent of difficulty these children have participating in daily activities. Pain management should therefore be a focus of JIA treatment to enable children to participate as fully as possible in normative social, academic, and physical activities.

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2249

How Do Patients Approach Risk-Benefit Trade-Offs: A Qualitative Analysis Using a Think Aloud Protocol. Liana Fraenkel, Paul Falzer and Kristin Mattocks. Yale University, Newtown, CT

Purpose: Eliciting patient preferences and incorporating them into treatment strategies can be beneficial for treatment adherence, patient empowerment, and clinical outcomes. Despite the importance of incorporating patient preferences into treatment strategies, little is known regarding the factors that influence how patients evaluate risk-benefit trade-offs. The purpose of this study was to gain a more complete understanding of how patients approach trade-offs using a think aloud protocol.

Methods: Patients with chronic pain were randomly drawn from primary care and women’s clinics at a large medical center. Participants were video-taped as they performed an Adaptive Conjoint Analysis survey and were instructed to: “Think out loud as you answer the questions on the computer. Just say out loud everything that comes into your head. Remember there is nothing right or wrong to say.” Participants were reminded by the research assistant to say their thoughts aloud after silent periods of 15 or more seconds. Audio-tapes were transcribed and two analysts independently read and coded the transcripts using the constant comparative method.

Results: Ninety-eight transcripts were analyzed. Four themes emerged regarding how patients approach risk-benefit trade-offs: 1) Selection of a dominant attribute to guide decision-making: Some participants evaluated all risk and benefits against one dominant attribute: “When you are in pain and you want to get rid of it if you make that your top priority and worry about the side effects later.” 2) Leveraging values and worldviews: Many participants were influenced by personal values: “I am thinking... I have a son and I don’t want to leave him without me.” 3) Inference of personal experience: Personal experience with specific side effects had variable effects on risk aversion: “I have experienced nausea and dizziness and it is not a party. It really knocks you out and I want to avoid that if I can.” Vs. “The nausea and the dizziness and trouble thinking clearly that is not that big of a deal. I know what that is like and it is not that big of a deal.” 4) Use and manipulation of numerical information: Participants also varied significantly in their use of numbers: “The differences in pain and the improvement percentages were really close together and these were further apart being 3 out of 10 compared to 8 out of 10.” Vs. “Well, it is the percentage: 3 in 10 as opposed to 1 in 10 which is a little bit less risky.”

Conclusions: Our findings suggest that patients draw on a range of strategies and values to evaluate risk-benefit trade-offs. Understanding how patients approach trade-offs may enable physicians to better understand how their patients consider competing treatment options in clinical practice.

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test in a wet workshop at the 13th International Congress on Antiphospholipid Antibodies in Galveston, TX (April 13th, 2010).

Methods: An in-house method developed by B de Laat and colleagues that utilizes hydrophobic microtiter plates coated with recombinant domain I and a commercial kit (INOVA) were evaluated for the detection of anti-DI antibodies. Samples were also evaluated simultaneously in an IgG aβ2GPI (INOVA) for comparison purposes. Aliquots of 26 APS patients and 21 controls (14 from healthy individuals and 7 from patients with infectious diseases) were distributed to the participants/groups. For the two-step ASR assay, procedure was carried out as published (Blood 2004; 104:2783-2790). Five plasmas from APS patients and five controls were tested prior to the workshop and at the workshop. In addition, normal plasmas were ”spiked” with dilutions of various aPL monoclonal antibodies (MoAbs) IgG and IgM: a) HCAL and EY2C9 [Center for Diseases Control (CDC)]; b) AbbyD0545 and AbbyD03892 (Phadia); c) ”Sapporo” (INOVA). The workshop was open to all congress attendees who registered for this event.

Results: 18 out of the 26 APS samples were positive in the IgG aβ2GPI (INOVA) ELISA. Fourteen and 10 out of the 18 APS samples that were positive in the IgG aβ2GPI, were positive in the DI ELISA (INOVA) and in-house respectively. This discrepancy is likely due to the fact that the in-house method is not calibrated for serum samples. All the samples that were positive in the DI ELISA (either in-house or INOVA kit) had evidence of thrombosis. All the APS plasmas had the IgM and IgA MoAbs (Phadia, INOVA and CDC) as well as the IgG INOVA MoAb reduced significantly the ASR anticoagulant activity. All negative plasmas were negative in the A5R.

Conclusions: In this workshop, the A5R showed to be a sensitive and specific new mechanistic assay for aPL antibodies. Samples tested in the DI assays, which were tested single-blinded, appear to correctly identify a subset of “pathological” aβ2GPI antibodies. Both assays appear to be promising assays for detecting patients at risk for thrombosis.


2251


Background: The standardization of tests used in the diagnosis of Antiphospholipid Syndrome (APS) [anticoagulant (aCL) and the anti-β2glycoprotein I (aβ2GPI)] is still a matter of debate and concern. One important topic of discussion is whether to use monoclonal (MoAbs) or polyclonal antibody preparations for the calibration and/or quality control of these assays. However, the proper cross-validation and evaluation of the available preparations is lacking.

Objective: to evaluate the performance of all MoAbs and polyclonal antibody calibrators for the detection of aCL and aβ2GPI antibodies (IgG, IgM) at a wet workshop at the 13th International Congress on Antiphospholipid Antibodies.

Methods: Monoclonal standards G2 and M3 for IgG, IgM aCL [Louisville APL Diagnostics, Inc. (LAPL)], MoAbs IgG and IgM: a) HCAL and EY2C9 [Center for Diseases Control (CDC)]; b) AbbyD0545 and AbbyD03892 (Phadia); c) “Sapporo” (INOVA) were distributed to the groups for evaluation. All serum and calibrator preparations were from the same lot and were tested in the following aCL and aβ2GPI IgG and IgM assays: QUANTA LITE™ (INOVA), TheraTest, Phadia, Bio-Rad (ELISA PhD™ Ix and Multiplex BioPlex™ 2200), in the aPL ELISA® [an assay that utilizes a mixture of negatively charged phospholipids and β2GPI (LAPL)] and in a new chemiluminescent assay HemosIL® AcuStar Antiphospholipid assay panel [Instrumentation Laboratory, IL]). Calibrators and kits were assayed as per the manufacturers’ instructions. The workshop was open to congress participants who registered for the event and the groups evaluated the calibrators at least on two occasions.

Results: All groups reported values of the polyclonal aPL calibrators within the expected range including the new chemiluminescent and the multiplex assays. Excellent correlation and linearity was observed with two monoclonal preparations (AbyD0545 IgG and IgM and Sapporo INOVA IgG and IgM). As expected, AbbyD3092 showed negative results in various tests (this antibody has aCL activity only). The “Sapporo” and the “CDC” monoclonal antibodies, although originally derived from the same hybridoma sources showed apparent different concentration, specificity and presentation (liquid affinity purified IgG for the Sapporo and freeze-dried hybridoma supernatant for the CDC). A large variability of the results of the CDC MoAbs was reported by the groups at this workshop when tested at the same final concentration (HCAL from 8.2 to 75.3 GPL units for IgG aCL and 20.9 to 424.5 Units for IgG aβ2GPI; EY2C9: from 30.4 to 145.3 MPL units for IgM aCL and from 0 to 520.4 Units for IgM aβ2GPI). Participants reported difficulties with the reconstitution of the CDC MoAb freeze-dried material, indicating problems with the stability and variability between vials of the preparations. Those included not only differences among any given assay but also within the same test, run in more than one occasion.

Conclusions: The LAPL polyclonal and the Phadia and INOVA monoclonal preparations are suitable sources for calibration of aCL and aβ2GPI assays. Based on results obtained at this wet workshop, the use of the CDC MoAbs is questionable and not recommended at this time.


2252

Comparative Evaluation of Different Immunoassays for the Detection of Antiphospholipid Antibodies: Report of a Wet Workshop during the 13th International Congress on Antiphospholipid Antibodies. Ricardo Forastiero*, Elizabeth Papalardo*, Kerrie Morin†, Catherine Quirbach†, Gabriella Lakos‡, Carlos Mattias‡, Roger Albesa‡, Virginia Nelson‡, Zakera Shums‡, Gary Norman*, Walter Binder*, Bruno Larida†, Maria Crisostomo*, Michael Watkins*, Hoang Nguyen*, J. Rand*, and Silvia S. Pierangeli*. Bi-Rad Laboratories, Hercules, CA, †INOVA Diagnostics, San Diego, CA, ‡Instrumentation Laboratories, Bedford, MA, §Phadia GMBH, Freiburg, Germany, ¶TheraTest Laboratories, Lombard, IL, ¶¶Univ of TX Med Branch, Galveston, Galveston, TX, §§Univ of TX Med Branch, Galveston, TX, ¶¶¶University of Favaloro, Buenos Aires, Argentina

Background: The performance and standardization of antiphospholipid (aPL) laboratory tests used in the confirmation of diagnosis of Antiphospholipid Syndrome (APS) is still a matter of debate and concern. Recently novel methodologies and platforms for the detection of aPL antibodies have become available, but proper inter-assay simultaneous comparisons have not been carried out. Objective: to evaluate the performance of different ELISAs and other new immunoassays for the detection of aCL and aβ2GPI antibodies (IgG, IgM) in a wet workshop at the 13th International Congress on Antiphospholipid Antibodies.

Methods: Aliquots of 26 un-identified APS serum samples (diagnosis according to Sapporo modified criteria) and 21 controls (14 from healthy individuals and 7 from patients with infectious diseases) were distributed to all participants/groups. All serum samples were evaluated in various aCL and aβ2GPI ELISAs, in the aPL ELISA® (an assay that utilizes a mixture of negatively charged phospholipids instead of cardiolipin, Louisville APL Diagnostics (LAPL) and in three fully automated methodologies: Hemo-IL® AcuStar Antiphospholipid assay panel, a chemiluminescent immunoassay panel on the ACL AcuStar™ (Instrumentation Laboratory (IL)) a fluoro-enzyme immunoassay (Phadia) and in the BioPlex 2200, random access, multiplex testing immunoassay system (Bio-Rad), using either an automated or “manual” platforms (see table). All kits were evaluated as per the manufacturers’ instructions and results were expressed in their respective units of measurement. The workshop was open to congress participants who registered for the event. Samples were evaluated in the different assays at least on two separate occasions.

Results: Clinical sensitivities and specificities and positive predictive values were calculated.
Although not all the assays reported the titters of aCL and aβ2GPI antibodies in the same units, the correlation of positive titers among the assays was excellent. All the healthy control samples were correctly identified by all groups as negative. Some of the aβ2GPI tests reported positive one of the infectious disease sample. All the assays, but in particular the AcuStar chemiluminescent immunoassay panel and the BioPlex2200 assays showed excellent intra-assay variation (<10 % CV).

Conclusions: All aCL and β2GPI tests showed excellent clinical sensitivities, specificities and positive predictive values and good agreement with respect to the levels of the IgG and IgM antibodies, regardless of assay type, or whether tests were done using automated or “manual” systems. New methodologies for the detection of aPL antibodies look promising and comparable to currently approved ELISA tests. This study validates current recommendations of the Sapporo revised criteria to use aCL and β2GPI for proper confirmation of diagnosis of APS.


2253

Elevated Cytokines and Chemokine Levels in Antiphospholipid Antibody (aPL)-Positive Patients. Vijaya L. Murthy, Shradhita Jatwani, Renan A. Aguilar-Valenzuela, Ellis D. Doan, Elizabeth Papalardo, Emilio B. González and Silvia S. Pierangeli. University of Texas Medical Branch, Galveston, TX

Background: Based on in vitro and animal studies, certain cytokines and chemokines such as tissue factor (TF), vascular endothelial growth factor (VEGF), soluble (s) E-selectin (sE-selectin) and tumor necrosis factor (TNF-α) have been shown to be associated with antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE). Here we examined the levels of cytokines/chemokines in aPL-positive patients with or without SLE, and compared them to controls.

Methods: Baseline sera/plasma of persistently aPL-positive patients [IgG/M Anticardiolipin antibody (aCL) > 40U, IgG/M anti-β2 glycoprotein-I antibody (aβ2GPI) > 20U, and/or positive lupus anticoagulant test] were obtained from an ongoing pilot intervention clinical study (clinical trials. gov #: NCT00764297). The biomarker levels of these 22 aPL-positive patients (primary APS: 8, APS with SLE: 8, asymptomatic aPL without SLE: 4 and asymptomatic aPL with SLE: 2) were compared to 22 matched healthy controls with no evidence of autoimmune, infectious, or inflammatory diseases. Interleukin (IL)-1β, IL6, IL8, TNF-α, VEGF, interferon inducible protein (IP)-10 and sCD40L were measured in serum using a Multiplex Assay (Millipore Milliplex™); titers of sE-selectin, and sTF were detected by ELISA. The Kruskal-Wallis test was used to compare the levels of biomarkers in aPL-positive subjects as compared to the controls. Spearman test was used to correlate the levels of the biomarkers in the different subgroups of patients.

Results: As compared to controls, we found an increase in the levels of IL-1β, IL6, TNF-α, IP-10, sCD40L and sTF in patients with APS. In a subgroup analysis, patients with aPL/APS and SLE (n=10) had significantly higher levels of TNF-α, IP10 and sCD40L as compared to aPL/APS patients without SLE (n=12) (p = 0.05, 0.029 and 0.05, respectively).

Conclusions: Our results underscore the importance of biomarkers in aPL-positive patients. This may help better understand the pathogenic mechanisms involved, and the development of targeted treatments.

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2254

The Involvement of CD36 in the Monocyte Activation by Antiphospholipid Antibodies. Masaru Kato1, Tatsuya Atsumi2, Kenji Oku3, Olga Amen1, Yuichiro Fujieda3, Kotaro Otomo3, Tetsuya Horita3, Shinsuke Yasuda3, and Takao Koike1,2. 1Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan, 2Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan, 3Department of Medicine II, Hokkaido University Graduate School of Medicine

Purpose: CD36, known as a scavenger receptor, is a transmembrane glycoprotein expressed on monocytes, macrophages, platelets and capillary endothelial cells. CD36 recognizes multiple ligands, including phosphatidylserine, and is a mediator of both atherogenesis and thrombosis. However, little data are available regarding the correlation between CD36 and thrombotic diseases. The purpose of this study is to investigate the possible involvement of CD36 in the pathophysiology of thrombosis in patients with antiphospholipid syndrome (APS).

Methods: This study comprised two sets of experiments. Firstly, a genomic polymorphism of CD36 was explored. Rs3765187, a single nucleotide polymorphism (SNP) linked to CD36 deficiency, was investigated by TaqMan PCR genotyping method in 795 Japanese, including 108 patients with APS, 265 with systemic lupus erythematosus (SLE) in the absence of APS, and 422 healthy subjects. In the second part of this study, the involvement of CD36 in antiphospholipid antibody (aPL)-induced tissue factor (TF) expression was examined using CD36 deficient mice or anti-CD36 antibody with the CD36 signal blocking property (FA6–152). Purified IgG from APS patients either anticaldrioglobin antibodies or phosphatidylserine dependent antithrombin antibodies positive (Pt-aCL and Pt-aPS/PT, respectively) and monoclonal aPS/PT (231D) were used in the experiments. The aPL-induced TF expression was tested by real-time PCR method on peritoneal macrophages from CD36 deficient mice or human peripheral blood mononuclear cells (PBMC) from healthy donors pretreated with FA6–152.

Results: The minor allele frequency of rs3765187 was less frequent in APS patients (2.8% p = 0.0001, compared with healthy subjects (10.2%). Pt-aCL, Pt-aPS/PT and 231D-induced TF mRNA expressions were not completely but significantly suppressed in peritoneal macrophage from CD36 deficient mice compared to wild type mice (WT).

Manufacturer Assay Method/Instrumentation Clinical sensitivity (%)(%) Clinical specificity (%)(%) PPV
Bio-Rad aCLGM Multiplex/BioPlex2200 100 95 0.95
Bio-Rad αβ,β2GPIGM Multiplex/BioPlex2200 100 95 0.95
Bio-Rad aCL GM ELISA/PBD 100 95 0.95
Bio-Rad αβ,β2GPIGM ELISA/PBD 100 91 0.92
IL Hemosil aCL GM Chemiluminescent/Acustar 100 95 0.95
IL Hemosil αβ,β2GPIGM Chemiluminescent/Acustar 100 100 1.0
INOVA QUANTA LITE™ aCL GM ELISA/manual 96 91 0.92
INOVA QUANTA LITE™ αβ,β2GPIGM ELISA/manual 88 100 1.0

Manufacturer Assay Method/Instrumentation Clinical sensitivity (%)(%) Clinical specificity (%)(%) PPV
Bio-Rad aCLGM ELISA/manual 100 100 1.0
Phadia Ella aCL GM ELISA/Phadia 250 100 100 1.0
Phadia Ella αβ,β2GPIGM ELISA/Phadia 250 100 95 0.95
Theratest aCL GM ELISA/Delix2 100 100 1.0
Theratest αβ,β2GPIGM ELISA/Delix2 100 95 0.95

Biomarker # Of aPL (+) samples elevated above cut-off points(%) Means of aPL positive samples Means of controls p
IL1b 16/22 (73) 7.65 0.35 <0.0001
IL6 17/22 (77) 42.15 0.71 <0.0001
IL8 9/22 (41) 27.44 40.87 0.1763
TNF-α 22/22 (100) 14.71 0.46 <0.0001
VEGF 12/22 (54) 208.78 113.59 0.9778
IP-10 22/22 (100) 683.43 106.7 <0.0001
sCD40L 21/22 (95) 1070.19 24.67 <0.0001
sTF 16/16 (100) 449.59 13.05 <0.0001
sE-selectin 3/16 (19) 20.78 42.04 0.0006

Conclusions: Our results underscore the importance of biomarkers in aPL-positive patients. This may help better understand the pathogenic mechanisms involved, and the development of targeted treatments.

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FA6–152 dose-dependently inhibited Pt-aCL, Pt-aPS/PT and 231D-induced TF mRNA expressions in human PBMC from healthy donors.  

**Conclusion:** The SNP linked to CD 36 deficiency was less frequent in APS patients, suggesting that CD36 insufficiency is protective for developing APS. The deficient or suppressed CD36 function significantly reduced aPL-induced TF expression in vitro. Taken together, scavenger receptor function may be essential in the thrombotic pathophysiology in APS patients. CD36 is a new potential therapeutic target of the affected patients.

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### 2255

**Potential Protein Targets for the Treatment of the Antiphospholipid Syndrome with Statins and Hydroxychloroquine.** Anastasia Lambrianides1, Silvia S. Pierangeli1, Katie Bell1, Wendy Heywood1, David S. Latchman3, David A. Isenberg1, Anisur Rahman1 and Ian Giles1. 1Univ of TX Medical Branch, Galveston, TX, 2University College London, London, UK, 3University College London, London, UK.

**Introduction:** A major mechanism of hypercoagulability in the antiphospholipid syndrome (APS) is antiphospholipid antibody (aPL)-mediated up-regulation of tissue factor (TF) on monocytes. Recent attention has been focused on other therapeutic tools for the APS to ameliorate the risk of the hemorrhagic complications associated with the use of anticoagulant drugs currently used for treatment. Statins have been shown to modify the function of endothelial cells and platelets by decreasing the expression of adhesion molecules, inhibiting TF expression and down-regulating inflammatory cytokines after treatment with aPL. Similarly, hydroxychloroquine (HCQ) has been shown to reduce the extent of thrombosis in an animal model of injury-induced thrombosis in APS and reversed aPL-induced platelet activation. Using proteomic analysis, our aim was to identify the effects of simvastatin and HCQ significantly altered the expression/modification of proteins in monocytes treated with IgG from patients with vascular thrombosis (VT).

**Methods:** IgG was purified from 7 patients with the APS who had experienced VT but no pregnancy complications and 7 healthy controls. A human monocyte cell line was treated with 100 μg/ml IgG for 6 hours. In some experiments, cells were pretreated with simvastatin (5 μM) or with HCQ (1 μg/ml) The cell extracts were examined by fluorescence 2D difference gel electrophoresis (DIGE).

**Results:** We have identified that there are 24 proteins showing significant differences in expression in monocytes treated with IgG from patients with VT in the presence of simvastatin – the majority with decreased expression between 2.1 and 5.2 fold. Furthermore, there are five proteins with altered protein expression patterns in monocytes treated with IgG from patients with VT in the presence of HCQ – four proteins with decreased expression between 2.1 and 2.3 fold and one protein with increased expression 2.6 fold.

**Conclusion:** Our findings demonstrate, for the first time, that statins and HCQ significantly altered the expression/modification of proteins in monocytes. These proteins may be critical targets that might be involved in the pathogenesis of the APS and supports the possibility that statins and HCQ may offer an alternative nonanticoagulant therapeutic approach for treating the APS.

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### 2256

**Irreversible Physical Disability in Rheumatoid Arthritis (RA) Is Determined by Cartilage Damage Rather Than Bone Destruction.** Josef S. Smolen1 and Daniel Aletaha2. 1Medical University of Vienna, Austria, 2Medical University of Vienna and Hietzing Hospital, Vienna, Austria.

**Background:** RA is characterized by joint damage leading to irreversible disability (assessed by health assessment questionnaire [HAQ]). Joint destruction is comprised of cartilage and bone damage, consequences of distinct pathogenetic mechanisms. They are evaluated by joint space narrowing (JSN) and erosion (ERO) components of the Sharp score. We aimed to determine the contribution of cartilage and bone damage to irreversible disability.

**Methods:** We evaluated data from randomized controlled clinical trials (ASPIRE, ATTRACT, DE019, ERA, Leflunomide, PREMIER, TEMPO). We extracted patients who were in stringent remission by the simplified disease activity index (SDAI≤3.3) to eliminate the activity-related component of disability. In these patients, we determined the residual HAQ at the time of remission (irreversible disability) and the JSN and ERO scores at baseline. We then compared effects of ERO and JSN on residual HAQ (across tertiles using ANOVA, and in regression models).

**Results:** Mean residual HAQ in remission increased across tertiles of JSN and ERO (ERO: 0.21, 0.25, 0.35 JSN: 0.19, 0.24, 0.39; p<0.001 for both). In patient groups formed according to JSN tertiles, increasing ERO scores did not lead to an increase in irreversible HAQ (for example, mean residual HAQ in the middle JSN tertile: 0.24, 0.24 and 0.23 for 1st, 2nd and 3rd ERO tertile, respectively; p=ns). In contrast, within each ERO tertile, increasing JSN was associated with an increase in residual HAQ (Figure 1). This relationship was maintained when adjustments for residual disease activity, age or disease duration were done (data not shown).

**Conclusion:** Irreversible physical disability is primarily mediated by cartilage and not bony damage, suggesting that therapeutic attention should be given to interference with cartilage destruction.

**Acknowledgement:** We thank Abbott, Amgen, Centocor, Sanofi-Aventis and Pfizer-Wyeth for providing us with data of their clinical trials and Farideh Alasti for statistical support.

The Impact of Body Weight on the Progression of Radiographic Joint Damage in Rheumatoid Arthritis Patients. Axel Finch1, Almut Scherer1, Anne Lubbeke-Wolff1, Hans Schwarz2 and Cem Gabay3. 1SCQM Foundation, Switzerland, 2Univ Hosp of Geneva, Geneva, Switzerland, 3University of Geneva, Switzerland, 4University of Geneva, Switzerland, 5University of Geneva, Switzerland, 6University of Geneva, Switzerland

Background: Obese individuals experience elevated levels of circulating pro-inflammatory cytokines. While obesity might be associated with an increased risk of developing RA and with impaired quality of life, the role of obesity on the progression of RA disease severity is not well established.

Objective: To examine if obesity is associated with more radiographic joint damage progression.

Methods: This is a prospective cohort study of the Swiss RA cohort (SCQM-RA) including all patients with available Body Mass Index (BMI) and complete sets of radiographs of the hand and feet. Patients were categorized according to the WHO BMI categories as “underweight” (BMI < 18.5), “normal weight” (BMI ≥ 18.5, < 25), “overweight” (BMI ≥ 25, < 30) and “obese” (BMI ≥ 30, < 35). The primary outcome of this analysis is the progression of ERO over time. Joint erosions (ERO) were assessed in 38 joints of hands and feet with a validated scoring method (Ratingen score, expressed in % of the maximum score) by a single experienced reader, blinded to clinical information. The evolution of ERO is analyzed using regression models for longitudinal data, adjusting for potential confounders.

Results: The mean BMI of the 4852 RA patients included was 25. The groups were similar for most disease characteristics, but for baseline radiographic damage, which was significantly higher for underweight patients.

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>N patients (%)</td>
<td>219 (5%)</td>
<td>2418 (50%)</td>
<td>1473 (30%)</td>
<td>742 (15%)</td>
</tr>
<tr>
<td>Age [yrs]</td>
<td>52</td>
<td>54</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Disease duration [yrs]</td>
<td>6.1</td>
<td>4.3</td>
<td>3.7</td>
<td>3.4</td>
</tr>
<tr>
<td>% Female</td>
<td>94</td>
<td>81</td>
<td>66</td>
<td>73</td>
</tr>
<tr>
<td>% RF+</td>
<td>77</td>
<td>77</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>DAS28 (ESR) [0–10]</td>
<td>4.6</td>
<td>4.5</td>
<td>4.5</td>
<td>4.6</td>
</tr>
<tr>
<td>HAQ-DI [0–3]</td>
<td>1.05</td>
<td>0.96</td>
<td>1.01</td>
<td>1.17</td>
</tr>
<tr>
<td>ERO score [% of max]</td>
<td>10</td>
<td>6.2</td>
<td>5.8</td>
<td>5.4</td>
</tr>
<tr>
<td>Estimated ERO rate at baseline [%/yr]</td>
<td>2.1</td>
<td>1.6</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>% Steroid</td>
<td>31</td>
<td>26</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>% Biologics</td>
<td>23</td>
<td>20</td>
<td>20</td>
<td>21</td>
</tr>
</tbody>
</table>

Patients were followed over a median duration of 4 years and assessed radiographically on average 3.3 times. After adjusting for baseline differences in prognostic markers of disease progression, underweight patients developed significantly more erosions over time than the other weight groups (p < 0.001).

Conclusion: Underweight was associated with more joint damage over time, probably reflecting uncontrolled disease and ‘rheumatoid cachexia’. Obesity and overweight was not associated with more rapid progression of radiographic damage in hand and feet joints.

Disclosure: A. Finch: None; A. Scherer: None; A. Lubbeke-Wolff: None; H. Schwarz: None; C. Gabay: None.

Clinical Rather Than Serologic Measures of Inflammation Determine Radiographic Progression in Rheumatoid Arthritis (RA). Daniel Aletaha1 and Josef S. Smolen. 1Medical University of Vienna, Austria, 2Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background: Disease activity in RA can be measured clinically by assessing joint inflammation, typically swollen joint counts (SJC), or systemically by evaluating the acute phase reactants, typically C-reactive protein (CRP). It has been suggested that both SJC and CRP contribute to progression of joint damage. However, since these measures are interrelated, it is not sufficiently clear, which of them is of primary relevance in driving radiographic changes. We aimed to determine the contribution of SJC and CRP to joint damage progression.

Methods: We evaluated data from methotrexate (MTX) monotherapy arms of recent randomized controlled clinical trials kindly provided by the respective sponsors (ASPIRE, ERA, Leffumonide, PREMIER, TEMPO). We pooled patients with complete clinical and radiographic data at baseline and 6, 9 and 12 months (n=871). In these patients, we determined the average SJC and average CRP levels from 6–12 months. We then dichotomised both variables into active and not active, where non active was defined as a mean SJC of <1 joint, or a mean CRP of <1 mg/dl. Radiographic progression was calculated based on the baseline and 12 months Sharp score readings. We cross-tabulated the mean radiographic progression in 2×2 tables according to activity/non activity of the two variables, SJC and CRP. We assessed the differences using the Wilcoxon two sample test.

Results: As shown in the Table, progression of joint damage in patients with mean CRP≥1 was higher if SJC were also active, and vice versa. If there was no joint activity (SJC<1), radiographic progression was unaffected by CRP status. However, if there was no serologic activity (CRP<1 mg/dl), SJC status still determined radiographic progression.

Table. Radiographic progression ± standard deviation (n) in accordance to SJC/CRP activity status.

<table>
<thead>
<tr>
<th></th>
<th>SJC active</th>
<th>SJC non active</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP active</td>
<td>4.6 ± 16</td>
<td>0.9 ± 5.9</td>
</tr>
<tr>
<td>CRP non active</td>
<td>2.0 ± 5.9 (n = 259)</td>
<td>0.7 ± 4.4 (n = 24)</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.0001</td>
<td>p = 0.146</td>
</tr>
</tbody>
</table>

Conclusions: Joint swelling rather than CRP contributes to progression of joint damage in RA.

Acknowledgement. We thank Abbott, Amgen, Centocor, Sanofi-Aventis and Pfizer-Wyeth for kindly providing us with data of their clinical trials and Fareideh Alasti for expert statistical support.


Coronary Atherosclerosis in Patients with RA and Acute Coronary Events: No Different Than in the Rest of Us? Marie E. Holmqvist1, Lennart T. H. Jacobsson1, Lars Alfredsson1, Stefan James4 and Johan Askling5. 1Karolinska Institutet, 2Karolinska University Hospital, 3Malmö University Hospital, 4University of Vienna, Austria, 5Malmö University Hospitals

The risk of ischemic heart disease (IHD) and the prevalence of atherosclerosis is increased in patients with rheumatoid arthritis (RA) compared to the general population. Based on individuals with clinical manifestations of IHD, few, and conflicting, studies that compare patients with RA and general population comparators with respect to extent of coronary artery disease (CAD) have been published.
Objective: To investigate whether angiographic patterns differ between patients with RA, known to be at increased risk of CAD, and the general population, at the time of clinical manifestations of acute CAD (unstable angina, ST-elevation myocardial infarction [STEMI], silent infarction and central chest pain).

Methods: RA patients diagnosed 1995–2006 with <18 months symptom duration at diagnosis included in the Swedish RA register were identified, n=6,919. For each patient, 5 sex/age/residential area/calendar time-matched general population comparators were identified, n=34,638. Participants were linked to the national Swedheart register, which includes information on indication for angiography and number of vessels with >50% stenosis for all subjects, and also presenting symptoms, status at admission and discharge diagnosis for all admitted to coronary care units (CCU). Relative risks (RR) and 95% CI were estimated using proportional hazards models. To compare the odds of different angiographic patterns, logistic regression models were fitted with RA (yes/no) as the independent variable, and extent of atherosclerosis classified according to the number of vessels with significant stenosis as the dependent variable.

Results: 218 (3.2%) patients and 737 (2.1%) controls underwent angiography due to any ischemic heart disease (stable and unstable angina, STEMI, silent infarction or central chest pain) after study entry, RR = 1.5 (95% CI 1.2, 1.7). Of those, 168 (77%) patients with RA and 534 (72%) comparators were investigated due to acute CAD. The proportion of patients with RA that underwent angiography due to STEMI was slightly higher, although not statistically significantly so, than in the population comparator (33% of the patients with RA and 26% of the comparators underwent angiography due to STEMI). There was no difference in the extent of atherosclerosis when patients with RA were compared to general population comparators.

Logistic regression modeling the risk of having significant stenosis in the below specified vessels comparing patients with RA who underwent angiography due to unstable angina, STEMI, central chest pain or silent myocardial ischemia to general population comparators who underwent angiography for the same reasons. Odds ratios (OR) and 95% confidence interval (CI) adjusted for age at angiography and sex.

<table>
<thead>
<tr>
<th>Patients with RA with outcome, n (% of all with angiography results)</th>
<th>Comparators with outcome, n (% of all with angiography results)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main artery* 13 (8.2)</td>
<td>30 (5.9)</td>
<td>1.4 (0.7, 2.8)</td>
</tr>
<tr>
<td>-LMA 0 (0)</td>
<td>1 (0.2)</td>
<td>-</td>
</tr>
<tr>
<td>-LMA + 1 coronary 1 (0.6)</td>
<td>4 (0.8)</td>
<td>0.7 (0.08, 6.8)</td>
</tr>
<tr>
<td>-LMA + 2 coronary 3 (1.9)</td>
<td>6 (1.2)</td>
<td>1.6 (0.4, 6.4)</td>
</tr>
<tr>
<td>-LMA + 3 coronaries 9 (5.7)</td>
<td>19 (3.8)</td>
<td>1.5 (0.7, 3.4)</td>
</tr>
<tr>
<td>1 coronary 47 (29.8)</td>
<td>162 (32.0)</td>
<td>0.9 (0.6, 1.3)</td>
</tr>
<tr>
<td>2 coronaries 37 (23.4)</td>
<td>110 (21.7)</td>
<td>1.1 (0.7, 1.7)</td>
</tr>
<tr>
<td>3 coronaries 26 (16.5)</td>
<td>90 (17.8)</td>
<td>0.9 (0.6, 1.4)</td>
</tr>
<tr>
<td>Normal coronaries 35 (22.2)</td>
<td>115 (22.7)</td>
<td>1.0 (0.6, 1.6)</td>
</tr>
</tbody>
</table>

* including all with afflicted LMAS regardless of status of other vessels. 10 patients with RA were missing if findings on angiography and 27 comparators.

Conclusion: These results confirm the increased risk of ischemic heart disease in RA, and further suggest that the angiographic pattern is similar among patients with RA and general population controls who develop acute CAD. This indicates that the increased risk of IHD/CAD in RA is not explained by more widespread atherosclerosis in those who develop acute IHD/CAD.

Disclosure: M. E. Holmqvist: None; L. T. H. Jacobsson: None; L. Alfredsson: None; S. James: None; J. Asking: None.

2260

Interleukin-6 Levels Are Associated with Elevated Ankle Brachial Index in Rheumatoid Arthritis. Cecilia P. Chung3, J. T. Giles3, Moyses Szklo5, Wendy Post2, Michelle A. Petri1, Roger Blumenthal4, Allan C. Gelber2, Russell Tracy6 and Joan M. Bathon4. 1CH-LMA 0 (0) 1 (0.2) –

Left main artery* 13 (8.2) 30 (5.9) 1.4 (0.7, 2.8)
-LMA 0 (0) 1 (0.2) –
-LMA + 1 coronary 1 (0.6) 4 (0.8) 0.7 (0.08, 6.8)
-LMA + 2 coronary 3 (1.9) 6 (1.2) 1.6 (0.4, 6.4)
-LMA + 3 coronaries 9 (5.7) 19 (3.8) 1.5 (0.7, 3.4)
1 coronary 47 (29.8) 162 (32.0) 0.9 (0.6, 1.3)
2 coronaries 37 (23.4) 110 (21.7) 1.1 (0.7, 1.7)
3 coronaries 26 (16.5) 90 (17.8) 0.9 (0.6, 1.4)
Normal coronaries 35 (22.2) 115 (22.7) 1.0 (0.6, 1.6)

Comparison of normal ABI (2.8 grams), p = 0.09. No statistically significant differences were observed in DAS28 (p = 0.89), CRP (p = 0.87), e-selectin (p = 0.63), or ICAM-1 (p = 0.63) between those with normal ABI vs. those with arterial incompressibility.

IL-6 concentration*

-<0.89 pg/ml
-0.91-1.43 pg/ml
-1.44-2.35 pg/ml
->2.36 pg/ml

*IL-6 concentration was categorized according to quartiles based on the whole dataset.

Conclusions: Patients with RA are at an increased risk of arterial incompressibility than control subjects. In patients with RA, higher concentrations of IL-6 are associated with a higher risk of arterial incompressibility.

Disclosure: C. P. Chung: None; J. T. Giles: None; M. Szklo: None; W. Post: None; M. A. Petri: None; R. Blumenthal: None; A. C. Gelber: None; R. Tracy: None; J. M. Bathon: None.

2261

Diagnostic Accuracy of the 2010 ACR/EULAR Used at Baseline after a 10 Year Follow Up in a Cohort of Patients with Recent-Onset Arthritis. Divi Corneé1, Sophie Varache2, Johanne Morvan1, Valerie Devauchelle-pense2, Jean-Marie Berthelot4, Sandrine Jousselou1, Catherine Le Cenaff1, Sylvie Hsoun3, Jean-Baptiste Thorel1, Antoine Martin1, Gerard Chales1, Pierre Youinou1 and Alain Sarbaux. 1CH Lorient, 2CH Morlaix, 3CH St Brieuc, 4CH Vannes, 5CH Brest, 6CH Brest, 7CH Nantes, 8CH Rennes.

Objective: We recently (EULAR 2010) evaluated the diagnostic accuracy of the 2010 ACR/EULAR and 1987 ACR criteria (unmodified and modified) by Liao et al. Ann Rheum Dis 2008:67:1557–61) for rheumatoid arthritis (RA) in a cohort of patients with recent-onset arthritis after a 2 year follow up. Our goal is now to verify the results after a ten year follow-up.

Methods: 164 patients with recent-onset arthritis of less than 1 year’s duration were prospectively included between 1995 and 1997 and followed inflammation in arterial incompressibility. Thus, we tested the hypothesis that arterial incompressibility is more prevalent in patients with RA than in control subjects and is associated with disease activity and markers of inflammation.

Methods: ABI, a reliable marker of peripheral and generalized subclinical atherosclerosis, was measured in 196 patients with RA enrolled in the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis (ESCAPE) study and in 1062 control subjects enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) study. Patients and control subjects were classified into three groups as follows: ABI > 0.9 and ≤ 1.3 (normal), ABI > 1.3 (incompressible), ABI ≤ 0.9 (obstructed). Demographic and clinical data were obtained and in patients with RA the disease activity score based on 28 joints (DAS28) calculated. Venous blood was drawn to measure the concentration of interleukin-6 (IL-6), C-reactive protein (CRP), e-selectin, and intercellular adhesion molecule-1 (ICAM-1).

Results: Arterial incompressibility was more prevalent in patients with RA (n = 27, 13.8%) than in control subjects (n=25, 2.4%), p<0.001. This association was independent of age, sex, and race (OR=7.5, p<0.001) and remained significant after adjustment for Framingham risk score, IL-6, fibrinogen and CRP (OR=5.8, p<0.001). RA patients with increased arterial incompressibility were more frequently male (66.7%) than those without (36.7%), p=0.005. Increasing quartiles of IL-6 concentrations were associated with higher prevalences of arterial incompressibility in patients (p for trend=0.04) but not in controls (p for trend=0.59). (Figure) The association between arterial incompressibility and IL-6 in RA patients remained significant after adjustment for HAQ (OR=1.9, p=0.04), but was attenuated after adjustment for DAS28 (OR=1.8, p=0.06). There was a trend towards higher cumulative doses of systemic corticosteroid use in patients with increased arterial incompressibility (median of 3.2 grams) compared to patients with normal ABI (2.8 grams), p=0.09. No statistically significant differences were observed in DAS28 (p = 0.89), CRP (p = 0.87), e-selectin (p = 0.63), or ICAM-1 (p = 0.63) between those with normal ABI vs. those with arterial incompressibility.

Conclusions: Patients with RA are at an increased risk of arterial incompressibility than control subjects. In patients with RA, higher concentrations of IL-6 are associated with a higher risk of arterial incompressibility.

Disclosure: C. P. Chung: None; J. T. Giles: None; M. Szklo: None; W. Post: None; M. A. Petri: None; R. Blumenthal: None; A. C. Gelber: None; R. Tracy: None; J. M. Bathon: None.
for 10 years. The diagnosis of RA was defined at follow-up completion as having a diagnosis of RA made by an office-based rheumatologist. All items of the unmodified and modified 1987 ACR criteria sets [criteria: 1-Morning stiffness≥1 hour, 2-Arthritis of three or more joint areas, 3-Arthritis of hand joints, 4-Symmetric arthritis, 5-Rheumatoid nodules, 6-Rheumatoid factor (positive), 7-Radiographic changes and 8-Anti-CCP antibodies (positive)] and of the ACR/EULAR 2010 criteria set (algorithm and scoring) were evaluated in each patient. Unmodified 1987 ACR criteria set were considered positive ≥4 of the 1–7 criteria, and the modified 1987 ACR criteria set for ≥4 of the 1–23–4–6–7–8 criteria (Liao 1) or ≥3/6 of the 1–23–4–6–8–8 criteria (Liao 2). We compared the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the criteria sets.

Results: At baseline, 60 of the 164 patients had alternative diagnoses better explaining the arthritis and 13 had erosions typical for RA; of the 91 remaining patients, 33 had more than 6 ACR/EULAR points (indicating definite RA), and 58 had fewer than 6 points. After 10 years, 9/13 patients with erosions and 25/33 with more than 6 points had RA. Sensitivity, specificity, PPV, and NPV of ACR/EULAR 2010 were 34/57 (59.6%), 95/107 (88.8%), 34/46 (73.9%), 95/118 (80.2%), respectively, i.e., better than both unmodified (34/57, 78/107, 34/63 and 78/111) and modified 1987 ACR criteria (47/57, 58/107, 47/96 and 58/68 for Liao2 and 37/57, 78/98, 37/66 and 78/98 for Liao1, respectively). After 10 year, of 9 patients who received biologics, 7 were detected by ACR/EULAR criteria. Similar results were observed for prediction of joint replacement.

Conclusions: ACR/EULAR 2010 criteria perform clearly better than the ACR 1987 criteria to predict a diagnosis of RA at 10 years. Much of the improvement was ascribable to the use of exclusion criteria.

Disclosure: D. Cornee: None; S. Varache: None; J. Morvan: None; V. Devauchelle-pensee: None; J.-M. Berthelot: None; S. Jousse-joulin: None; C. Le Henaff: None; S. Huang: None; J.-B. Thourel: None; A. Martin: None; G. Chais: None; P. Youinou: None; A. Sarau: None.

Table A. Mean (SD) Annualized Rate of Radiographic Progression by Treatment Increase up to Week 104 (n = 451)

<table>
<thead>
<tr>
<th>Predose increase (TCZ4)</th>
<th>Postdose increase (TCZ8)</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>336</td>
<td>346</td>
</tr>
<tr>
<td>Genant-modified Total Sharp Score</td>
<td>0.31 (1.07) 0.10 (0.52)</td>
</tr>
<tr>
<td>Erosion</td>
<td>0.20 (0.83)</td>
</tr>
<tr>
<td>Joint space narrowing</td>
<td>0.11 (0.53)</td>
</tr>
<tr>
<td>Data collected after study withdrawal are excluded</td>
<td></td>
</tr>
</tbody>
</table>

Table B. Safety up to Week 104 Before and After TCZ Dose Increase and by Pooled Treatment Groups

<table>
<thead>
<tr>
<th>Dose escalation group</th>
<th>Predose increase (TCZ4)</th>
<th>Postdose increase (TCZ8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>957c</td>
<td>983b</td>
<td></td>
</tr>
<tr>
<td>Exposure, PY</td>
<td>338.6</td>
<td>475.9</td>
</tr>
<tr>
<td>Serious AEs/100 PY</td>
<td>5.9</td>
<td>11.3</td>
</tr>
<tr>
<td>Serious infections/100 PY</td>
<td>0.9</td>
<td>2.7</td>
</tr>
<tr>
<td>n</td>
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ACR Concurrent Abstract Sessions
Rheumatoid Arthritis Treatment - Small Molecules, Biologies and Gene Therapy: Existing Biologies

Thursday, November 11, 2010, 11:00 AM–12:30 PM

2262
Tocilizumab (TCZ) Plus Methotrexate (MTX) in Rheumatoid Arthritis (RA) Patients (pts) Who Increased TCZ Dose from 4 mg/kg to 8 mg/kg: LITHE Radiographic and Safety Data. Roy M. Fleischmann, Ricardo Blanco2, Geraldo Castelar-Pinheiro3, Emma Vernon4, Christopher Mela5 and Janeiro, Brazil, 4Metroplex Clinical Research Center, Dallas, TX, 5Roche, de Valdecilla Cantabria, 3Hospital Universitario Pedro Ernesto, Rio de Janeiro, YRoche, Welwyn, United Kingdom

Purpose: Results of the TCZ clinical development program have shown that for most endpoints, the 8 mg/kg dose is more effective than the 4 mg/kg dose. In the US, TCZ 4 mg/kg has been approved as the starting dose with a subsequent escalation to 8 mg/kg based on clinical response. This analysis evaluated the effect of increasing the TCZ dose from 4 to 8 mg/kg on inhibition of radiographic progression and safety in the LITHE study.

Methods: RA pts with inadequate responses to MTX were randomly assigned to TCZ 4 or 8 mg/kg (TCZ4 or TCZ8) or placebo Q4W + MTX. From wk 16, blinded first-step rescue was allowed if pts had <20% improvement in SJC and TJC (eg, pts on placebo went to TCZ4, pts on TCZ4 or TCZ8 went to TCZ28). If <20% improvement persisted after 3 doses of blinded first-step rescue, pts received second-step rescue with TCZ8. At wk 52, pts were treated with open-label (OL) TCZ8 except those with ≥70% improvement in SJC and TJC, who could continue blinded therapy to wk 104. X-rays were taken at baseline and wks 24, 52, 80, and 104. Data were analyzed in pts whose dose increased from TCZ4 to TCZ8. Data from this TCZ dose-escalation analysis must be interpreted with caution because 78 pts who withdrew (44 for safety, 8 for insufficient response, 26 for other reasons) from the study before dose escalation are not included. In addition, criteria for dose escalation and/or dose continuation were based on efficacy results that were predetermined per study protocol. Safety data are provided for all randomly assigned pts who received ≥1 TCZ dose and who had at least 1 post-randomization safety assessment.

Results: Of 1190 pts (393, 399, and 398 randomly assigned to placebo, TCZ4, and TCZ8, plus MTX, respectively), 451 pts increased their dose from TCZ4 to TCZ8. In these 451 pts, annualized rate of progression of Genant-modified Total Sharp Score, erosion, and joint space narrowing slowed after the dose increased from TCZ4 to TCZ8 (Table A). Rates/100-patient-years (PY) of serious adverse events (AEs) and serious infections were lower than previously reported (Kremer et al, EULAR 2010) before dose escalation but increased to rates comparable to those of the TCZ pooled groups (TCZ4, n =597, includes pts who received TCZ4 as initial or rescue therapy; TCZ8, n =983, includes those who received TCZ8 as initial and/or rescue and/or OL therapy) after dose escalation (Table B). The low predose escalation event rates for the TCZ4 pooled groups are influenced by a selection bias—ie, pts who withdrew while on TCZ4 do not contribute safety data to the analysis of the switching group but continue to contribute to the rates in the TCZ8 pooled analysis.

Conclusions: For this analysis of pts who increased dose, the annualized rate of progression was reduced after pts increased their TCZ dose from 4 to 6 mg/kg; safety in these pts after dose escalation was comparable to that in the TCZ pooled groups.

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<td>Serious AEs/100 PY</td>
<td>5.9</td>
<td>11.3</td>
</tr>
<tr>
<td>Serious infections/100 PY</td>
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2263
Rituximab Treatment Induces the Expression of Genes Involved in Healing Processes in the Rheumatoid Arthritis Synovium. Ilse Guteierrez-Roelens, Christine Galant1, Iain Theate1, Rik J. Lories2, Patrick Durez2, Adrien Nzeusseu Toukapi3, Benoit Van den Eynde4, Frederic A. Housiaux5 and Bernard R. Lauwers6. 1De Duve Institute & Ludwig Institute for Cancer Research, Brussels Branch, 2Department of Musculoskeletal Sciences, Division of Rheumatology, Laboratory for Skeletal Development and Joint Disorders, Katholieke Universiteit Leuven, 3Department of Pathology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, 4Department of Rheumatology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain

Objectives: In previous experiments, we performed transcriptomic analyses on synovial biopsies obtained from anti-TNF resistant rheumatoid arthritis (RA) patients prior to (T0) and 12 weeks (T12) after initiation of rituximab therapy. We found that genes down-regulated between T0 and T12 were significantly enriched in immunoglobulin genes, and genes involved in chemotaxis, leucocyte activation and immune responses. By contrast, genes

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up-regulated between T0 and T12 were significantly enriched in transcripts involved in cell development and wound healing. We wondered whether up-regulation of the latter genes was a true effect of rituximab therapy, or whether the relative decrease in inflammatory cells and relative increase in resident synovial fibroblasts resulted in a biased appreciation of global gene expression profiles at T12.

**Methods:** Paired synovial biopsies were obtained from the affected knee of 20 anti-TNF resistant RA patients at T0 and T12. Fresh synovial biopsy tissue samples were fixed overnight in 10% formalin buffer and embedded in paraffin. Immunolabeling experiments were performed using the following antibodies: BMPR1A (Bone Morphogenetic Protein Receptor 1A), ME0X2 (Mesenchyme Homeobox2), LAMA4 (Laminin alpha 4), phospho-SMAD1/5 and phospho-SMAD3. Quantitative analysis of the antibody immunostained sections was performed using ImageJ software, according to the Digital Image Analysis process.

**Results:** BMPR1A, ME0X2 and LAMA4 are markers of mesenchymal cell differentiation. Immunolabeling experiments and digital quantification of the slides indicated that synovial expression of the three molecules is significantly induced by rituximab therapy in RA synovial tissue.

Up-regulation of these genes triggered us to investigate whether administration of rituximab resulted in synovial activation of TGF-β or BMP signaling. To explore this hypothesis, we performed phospho-SMAD3 (a marker of TGF-β activation) and phospho-SMAD1/5 (a marker of BMP activation) immunohistochemistry studies. No significant difference in phospho-SMAD3 staining was observed between T0 and T12. The phospho-SMAD1/5 signal significantly decreased between T0 and T12. These results indicate that synovial up-regulation of genes involved in healing processes is not associated with an increased TGF-β or BMP activity through its canonical signaling. To explore this hypothesis, we performed phospho-SMAD3 (a marker of TGF-β activation) and phospho-SMAD1/5 (a marker of BMP activation) immunohistochemistry studies. No significant difference in phospho-SMAD3 staining was observed between T0 and T12. The phospho-SMAD1/5 signal significantly decreased between T0 and T12. These results indicate that synovial up-regulation of genes involved in healing processes is not associated with an increased TGF-β or BMP activity through its canonical signaling.

**Conclusion:** Rituximab induces the expression of molecular markers of mesenchymal cell differentiation in the synovium. We did not find evidence of increased TGF-β and BMP signalling in the synovium at T12. Further studies are needed in order to investigate the possibility of increased BMP or TGF-β signalling at earlier time-points or the presence of alternative mechanisms of induction of mesenchymal cell differentiation.

**Disclosure:** I. Gutierrez-Roelens: None; C. Galant: None; I. Theate: None; R. J. Lories: None; P. Durez: None; A. Nzeusse Touskap: None; B. Van den Eynde: None; F. A. Housiaux: None; B. R. Lauwers: None.

**2264**

**Golimumab and Methotrexate Combination Therapy Significantly Improves Synovitis, Osteitis and Bone Erosion Compared to Methotrexate Alone—A Magnetic Resonance Imaging Study of Methotrexate-Naïve Rheumatoid Arthritis Patients, Mikkel Østergaard1, Paul Emery2, Philip G. Conaghan3, Roy M. Fleischmann4, Weichun Xu5, Elizabeth C. Hisa2, Anna Beutler1 and Mahboob U. Rahman1. 1Centocor Research and Development, Inc., 2; 9; 4Chapel Allerton Hospital, Leeds, United Kingdom, 4Chapel Allerton Hospital, Leeds, United Kingdom, 5Copenhagen University Hospital at Glostrup and Hvidovre, Hvidovre, Denmark, 6University of Texas Southwestern Medical Center, Dallas, TX

**Background:** In the GO-BEFORE trial, golimumab (GLM) improved signs and symptoms of RA, improved physical function, and slowed the progression of structural damage in patients who were methotrexate (MTX) naïve.

**Objective:** To evaluate the effect of GLM on the inflammation and structural damage detected by magnetic resonance imaging (MRI) in patients with RA who were MTX naïve.

**Methods:** Patients (n = 637) were randomly assigned to receive placebo (PBO) + MTX, GLM 100 mg + PBO, GLM 50 mg + MTX, or GLM 100 mg + MTX. A subset of study sites capable and willing participated in the MRI substudy. All patients from each substudy site were eligible for substudy participation (n = 318). GLM and PBO were administered via subcutaneous injection every 4 weeks. The primary comparison was between the PBO + MTX and combined GLM + MTX groups. MRI of the patient’s dominant wrist and metacarpophalangeal joints were obtained at baseline and weeks 12, 24, 52, and 104 using 1.5T MRI with contrast enhancement. Results through week 24 are presented here. Images were scored by two independent expert readers blinded to image time point or sequence, patient identity, or treatment group. Readers scored synovitis (0–21), bone edema (osteitis) (0–69), and bone erosions (0–230), using the Rheumatoid Arthritis MRI Scoring (RAMRIS) system; the average of each RAMRIS score provided by the readers was used in the analysis.

**Results:** Mean baseline RAMRIS bone edema and RAMRIS bone erosion scores were numerically slightly lower in the PBO than GLM groups. Significant improvements in RAMRIS synovitis, osteitis and bone erosions were observed at weeks 12 and 24 in the combined GLM + MTX groups relative to PBO + MTX (Table). Significant improvements in synovitis and bone edema were observed in both GLM + MTX dose groups at both weeks 12 and 24 versus the PBO + MTX group. Significantly less bone erosion progression was observed at week 12 for the 50 mg GLM + MTX group and at 24 weeks for both GLM + MTX doses. Comparison of radiographic data (using the van der Heijde modification of the Sharp score) within the MRI substudy patients (n = 318) showed no significant difference between the PBO + MTX and combined GLM + MTX groups (mean ± SD changes from baseline to week 28 of 0.92 ± 2.96 and 0.49 ± 3.23, respectively; p = 0.19), thus demonstrating MRI to be superior to x-rays in terms of sensitivity to changes in erosive progression.

**Conclusion:** Results of this MRI substudy of the GO-BEFORE trial demonstrated that patients who received GLM + MTX had improvements in inflammation (synovitis and osteitis) and improvements in erosions exceeding those observed with PBO + MTX as early as week 12 and continuing through week 24, confirming the clinical and radiological findings previously reported for the overall study population. MRI assessment was superior to x-ray in terms of sensitivity to change in erosive progression.

importance. Our objective was to investigate CRP kinetics during 14 weeks of IFX treatment to determine whether CRP can be used as a biomarker to guide dose optimization in RA patients.

**Methods:** This was a phase-IV, multicenter, observational study conducted in Europe. Adult patients with RA for whom treatment with IFX 3 mg/kg had been chosen per label were invited to participate. Patients were classified as good-responders (GR), moderate-responders (MR), or non-responders (NR) according to EULAR response at week 14. We built a statistical model to estimate mean (95% CI) CRP levels prior to each infusion by response group, and adjusted it for baseline CRP values and patient characteristics. We then analyzed CRP change among patients and CRP differences between groups. To confirm our results, we performed a similar analysis using data from the 3-mg/kg arm of the blinded randomized controlled ASPIRE study in early RA (St. Clair, 2004).

**Results:** 481 patients from the study were included in the analysis—79.8% female; mean age 53 (SD 13) years. Baseline mean DAS28 was 5.2 (SD 1.1). At week 14, 34.5% of patients were GR, 41.2% MR and 24.3% NR. CRP levels steeply declined in all groups from baseline to week 2. In the GR group, CRP remained stable at low levels during weeks 2 to 14. In the NR group, a CRP-rebound started at week 2 and reached near-baseline levels at week 14 (see figure; for clarity only GR and NR profiles are shown, CRP levels for MR were higher but close to those for GR).

Estimated CRP levels adjusted for baseline value and patient characteristics. Values at baseline are geometric means of original data. This rebound showed significant increases in CRP from weeks 2 to 6 and again from weeks 6 to 14 (P < 0.0001). Between-group differences were significant at weeks 6 and 14 for both GR and MR groups compared to the NR group. The confirmatory ASPIRE analysis included 277 patients who received IFX 3 mg/kg. At week 14, 27.4% of patients were GR, 46.9% MR, and 25.6% NR. CRP levels showed a similar pattern, with an initial improvement from baseline to week 2 in all groups and a significant increase in the NR group from weeks 2 to 14. Between-group differences were observed at weeks 6 and 14 for both the GR and MR groups compared to the NR group.

**Conclusion:** CRP kinetics during the first 14 weeks may help guide IFX treatment. Good response is characterized by stabilization of CRP at low levels, and non-response by a CRP rebound between weeks 2 and 14 during which time the infusion interval is increased. Studies of dose/frequency adjustments in non-responders to optimize therapy are needed.

**Reference:**

**Disclosure:** C. Meeuwisse: Merck Pharmaceuticals, 3, J. S. Smolen: Centocor, Inc., 2, 5, Schering-Plough, 2, 5, B. Boupnas: None, E. W. St Clair: None; M. U. Rahman: Johnson & Johnson, 1, 3; N. Vastesaeger: Merck Pharmaceuticals, 1, 3; W. van Duijnhoven: Merck Pharmaceuticals, 3, R. L. H. Nelissen: Merck Pharmaceuticals, 3, Schering-Plough, 3, R. Van Vollenhoven: Abbott Immunology Pharmaceuticals, 2, 5, 9, Merck Pharmaceuticals, 2, 5, 9, Pfizer Inc, 2, 5, 9.

2266


**Background and Purpose:** In the absence of clinical studies involving all agents, evaluating comparative efficacy of biologic therapies for patients with RA who failed an anti–tumor necrosis factor (anti-TNF) agent is difficult. Assessing comparative effectiveness of these interventions is challenging. We used meta-regression (MR) methods to estimate probability of clinical response for biologic therapies abatacept, adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, and tocilizumab, all in combination with methotrexate (MTX), for patients who failed prior anti-TNF therapy.

**Methods:** We updated earlier systematic reviews of biologic therapies in longstanding RA to identify relevant randomized controlled trials (RCTs) that reported American College of Rheumatology (ACR) response criteria. Prospectively, open-label studies were included. Dose-finding RCTs and safety studies were excluded. A hierarchical Bayesian mixed effects MR model was estimated (WinBUGS 1.4.3); adjustments for study-arm level heterogeneity included concomitant MTX, age, RA duration, baseline Health Assessment Questionnaire (HAQ) score, follow-up time, % failing prior anti-TNF therapy, and whether assigned treatment was a subsequent biologic. ACR responses in each arm were modeled simultaneously to reflect their nested nature (ie, patients with ACR70 also attain ACR50 and ACR20). Adalimumab, etanercept, golimumab, and infliximab were grouped for this analysis and overall efficacy for anti-TNF agents was compared with non-TNF biologics.

**Results:** The final dataset included 96 comparator arms from 32 studies. Covariate estimates indicated that prior anti-TNF agent failure was associated with a reduction in the log odds ratio (LOR) of ACR response for all treatments, but subsequent biologic treatment offset much of that reduction. Controlling for other factors, longer duration of disease and greater baseline HAQ score increased the LOR of ACR response for biologic relative to nonbiologic treatment. Likewise, longer follow-up decreased the LOR of ACR response. The table summarizes posterior mean predicted ACR response rates for patients with mean baseline HAQ score of 2.0, disease duration of 11 years, and at 6 months of follow-up.

<table>
<thead>
<tr>
<th>Placebo/None+MTX</th>
<th>anti-TNF+MTX</th>
<th>Anakinra+MTX</th>
<th>Abatacept+MTX</th>
<th>Rituximab+MTX</th>
<th>Tocilizumab+MTX</th>
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</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>27.4%</td>
<td>66.5%</td>
<td>49.9%</td>
<td>54.3%</td>
<td>64.1%</td>
</tr>
<tr>
<td>ACR50</td>
<td>12.0%</td>
<td>43.1%</td>
<td>27.7%</td>
<td>31.4%</td>
<td>41.5%</td>
</tr>
<tr>
<td>ACR70</td>
<td>4.8%</td>
<td>22.9%</td>
<td>15.0%</td>
<td>15.2%</td>
<td>22.3%</td>
</tr>
</tbody>
</table>

**Conclusions:** This MR analysis drew on a large body of clinical data and statistically controlled for heterogeneity to reliably estimate the relative treatment effects of a second biologic therapy in patients with RA who failed prior anti-TNF therapy. Patients treated with a second anti-TNF agent achieved comparable or superior clinical response compared with non-TNF agents. As such, for patients failing their first anti-TNF, a second anti-TNF agent should be considered an appropriate treatment option before switching to a non-TNF biologic therapy.

**References:**

**Disclosure:** A. Benedict: Abbott Laboratories, 2, United BioSource Corporation, 3; D. J. Vanness: University of Wisconsin, Madison, 3; S. Roy: Abbott Laboratories, 1, 3; M. A. Cifaldi: Abbott Laboratories, 1, 3.

2267

**Clinical and Radiological Efficacy of Biologics in Rheumatoid Arthritis Patients Naive or Inadequate Responders to Methotrexate: A Metaanalysis.** Pierreisnard Audrey, Issa Nahema, Barnetche Thomas, Richez Christophe and Schaeverbeke Thierry. Bordeaux University Hospital, Rheumatology Department, France

**Purpose:** Recently, an overview of Cochrane reviews comparing efficacy and safety of six biologics in rheumatoid arthritis (RA) was published. However, this study did not include tocilizumab, certolizumab and golimumab, and was not stratified based on previous methotrexate (MTX) use. Our objective was to perform a metaanalysis of all biologics available in RA into two situations: MTX naive patients and MTX inadequate responders.
In IR, the same OR was 4.79 (95% IC: 3.49,6,59). The NNT for ACR50 for etanercept were: 5 for MTX naive patients and 3 for IR; for adalimumab were: 7 and 3, respectively; for infliximab were: 7 and 4, respectively, and for abatacept were: 7 into the two groups; for rituximab were: 5 into the two groups; for golimumab as the confidence intervals for the risk comparisons of biologics head to head. In this study, we performed indirect comparisons using the number needed to treat (NNT) for ACR50 criteria. The primary radiological endpoint was the proportion of patients with no progression of total Sharp score at one year. Statistical analyses were based on odds ratio (OR) for efficacy. Using these combined estimates, we calculated the NNT for each product.

Results: 22 studies were included, 7 in MTX naive patients and 15 in IR. In MTX naive patients, biologics therapy showed significantly increased efficacy compared to MTX with OR for achieving an ACR50 response: OR: 2.11 (95%IC: 1.85, 2.41).

Conclusions: Response to biologic therapy in combination with MTX, compared to MTX alone was significant in IR and MTX naive group, but to a lesser extent in the MTX naive group. This difference could be explained by a relative efficacy of MTX in MTX naive patients. Interestingly, patients treated by anti-TNF therapy had significantly less radiographic progression than those with cellular therapy, in MTX naive patients.

Disclosure: P. Audrey: None; I. Nahema: None; B. Thomas: None; R. Christophe: Pfizer Inc; 5; S. Thierry: Abbott Laboratories; 5; Bristol-Myers Squibb; 5; Merck Pharmaceuticals; 5; Pfizer Inc; 5; Roche; 5.

ACR Concurrent Abstract Sessions Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment - Therapy Thursday, November 11, 2010, 11:00 AM–12:30 PM

2268 Outcome of an Education and Home Exercise Program for Ankylosing Spondylitis Patients: A Nationwide Randomized Study. Carlos Rodriguez-Lozano1, Xavier Juangla2, Juan Cruz-Martinez3, Andres Peña-Arribola4, Juan Mulero5 and Eduardo Collantes6.1 for the Spondyloarthropathies Study Group of the Spanish Society of Rheumatology (GRESSER), 2for the Spondyloarthropathies Study Group of the Spanish Society of Rheumatology (GRESSER), 3for the Spondyloarthropathies Study Group of the Spanish Society of Rheumatology (GRESSER), Hospital Ramón y Cajal, Madrid, Hospital Ramón y Cajal, Madrid.

Purpose: To assess the impact of a structured education and home exercise program on different outcome measures in patients with ankylosing spondylitis attended in daily practice.

Methods: Patients with ankylosing spondylitis (modified New York criteria 1984) aged 18–70 years participated in a 6-month nationwide prospective study, in which they were randomized to an education intervention (education group) or standard care (controls). The intervention included a 2-hour session in which professionals provided information about the disease and its management, and the implementation of a physical activity program at home. Patients received a printed leaflet and a fitness DVD to take home. All patients completed a diary card and received monthly remainder phone calls. Main outcome measures included a 0–10 cm visual analog scale (pain, global disease activity); Bath Ankylosing Spondylitis Disease Activity and Functional Index (BASDAI, BASFI); Patient Acceptable Symptomatic State (PASS); and quality of life (ASQoL). Data at 6 months were compared with baseline.

Results: A total of 622 patients (EG group 308, controls 314) participated (73% males, mean age 45 years, mean duration of disease 17 years). Regular medications included NSAIDs in 52% of patients and anti-TNF agents in 40%. Fifty-four percent of patients used to exercise regularly (mean [SD] 3.2 [3.3] hours/week). At baseline, both groups were well balanced (table). At 6 months, mean improvements in all outcome measures were statistically significant in both study groups except for ASQoL and patients in PASS condition, which were only significant in the education group. Between-group mean differences were statistically significant for ASQoL, BASFI, and percentage of patients changing from negative to positive PASS (table). Patients in the education group practiced more regular exercise than controls (P = 0.002) and increased their knowledge about the disease significantly.

Table. Outcome Measures at Baseline and after 6 Months

Variable Education Control Between-group difference (95% CI)
Baseline, mean (SD) Education Control Group Group
VAS global pain (0–10) 3.77 (2.59) 4.01 (2.67) 0.68* 0.47* 0.21 0.03 to 0.37
VAS nocturnal pain (0–10) 3.35 (2.83) 3.61 (2.99) 0.62* 0.52* 0.10 0.03 to 0.17
VAS patient activity (0–10) 3.98 (2.58) 4.17 (2.56) 0.68* 0.39* 0.29 0.03 to 0.56
BASDAI (0–10) 3.34 (2.27) 3.61 (2.26) 0.62* 0.24* 0.38 0.12 to 0.64
BASFI (0–10) 5.19 (2.54) 5.61 (2.62) 0.51* 0.21* 0.30 0.02 to 0.58
PASS positive) 58.9% 61.3% 2.4% 1.7% 0.7 17.5% to 11.8%

Conclusion: An education session and a structured exercise home program for patients with ankylosing spondylitis with relatively low disease activity improved physical function, quality of life and patients who were in PASS condition. Besides drug treatment, incorporating education and exercise in daily practice is feasible and reported substantial benefits.

Disclosure: C. Rodriguez-Lozano: None; X. Juangla: None; J. Cruz-Martinez: None; A. Peña-Arribola: None; J. Mulero: None; E. Collantes: None.

2269 SAPHO Syndrome Treated by TNF alpha-Blocking Agents. Report of 45 Cases. Gilles Hayem1,2,3, Romain Ben M’Barak4, Eric Toussirot3,4, Christian Combe3,4, Jean-Claude Berthelot5,6, Grégoire Cormier7, Anne Dubois7, Rose-Marie Javier7,8, Sylvain Lanot9, Marie-José Wattiaux10, Olivier C. Meyer11 and Daniel Wendling12.1 CHB Brive, France; 2CH La Roche sur Yon, France; 3CH Saint-Brieuc, France; 4CHU Besançon, France; 5CHU Bichat, Paris, France; 6CHU Bichat, Paris, Tunisia; 7CHU Marseille, France; 8CHU Nantes, France; 9CHU Strasbourg, France; 10Private Office, Paris, France; 11UC Lille, France.

Objectives: To evaluate the efficacy and safety of TNF-α-blocking agents in SAPHO syndrome.

Methods: A retrospective study was conducted by the “Club Rhumatismes et Inflammation” (depending from the French Society of Rheumatology (GRESSER)) to find and analyse all the case records from patients suffering from SAPHO syndrome, who had been treated with at least one of the three following TNF-α-blocking agents: adalimumab (ADA), etanercept (ETN), or infliximab (IFX). Demographic and clinical data were collected, including previous treatments and incident side effects. The efficacy of anti-TNFα
treatment was evaluated at last follow-up visit, based on the decrease of SAPHO syndrome-related symptoms, appreciated by each patient on a visual analogic scale (VAS). A score decrease of more than 80% was considered as a remission. An improvement comprised between 50 and 79% indicated a partial efficacy and a reduction less than 50% was interpreted as a lack of response.

Results: The case records of 45 patients (33F/12M; mean age 45) were available for analysis. The mean age at disease onset was 31 years (range 11–61). In all patients, SAPHO syndrome was previously considered as refractory to at least three of the five following types of treatments: non-steroidal anti-inflammatory drugs, corticosteroids, antibiotics (various regimens), synthetic disease modifying anti-rheumatic drugs (methotrexate or sulfasalazin), and bisphosphonates. Forty-four patients also had active cutaneous manifestations when TNF-\(\alpha\)-blocking agent was started. Thirty patients received ETN (25 mg biw or 50 mg qw SC; first biologic to be used in 17 patients; follow-up: 3–60 months). Remission was observed in 11 patients, and partial efficacy in 10. Twenty-two patients were treated with ADA (40 mg SC eow; first biologic in 7 patients; follow-up: 2 to 17 months). Remission and partial efficacy were registered in 12 and 2 patients, respectively. IFX was administered to 18 patients (5 mg/kg, infusions at week 0, 2 and 6, then every 8 weeks; first biologic in 12 patients; follow-up: 3–65 months). Remission and partial efficacy were noted in 5 and 5 patients, respectively.

The treatment with TNF-\(\alpha\)-blocking agents was stopped 11 times for a side effect, in 9 patients: 3 times with ETN (1 papillomavirus cutaneous and genital infection, 1 psoriasis vulgaris, 1 optic neuritis); 4 times with ADA (2 allergic reactions, 1 pyelonephritis, 1 hidradenitis suppurativa of the breast) and 4 times with IFX (1 psoriasis vulgaris, 1 flare of palmpoplantar pustulosis, 1 hidradenitis suppurativa of the breast and 1 periortitis).

Conclusion: TNF-\(\alpha\)-blocking agents seem to represent an interesting therapeutic option in refractory cases of SAPHO syndrome, without unpredictable side effects.

Disclosure: G. Hayem: None; R. Ben M’Barek: None; E. Toussrot: None; C. Comprie: None; T. Pham: None; E. Hovenveld: None; A. Martin: None; N. Balandraud: None; J-M. Berthelot: None; G. Cormier: None; A. Dubois: None; R-M. Javier: None; S. Lanot: None; M-J. Wattiaux: None; O. C. Meyer: None; D. Wendling: None.

Radiographic Findings after 5 Years of Infliximab Treatment in Patients with Ankylosing Spondylitis. Xenofon Baraliakos1, Frank Heldmann2, Desiree M. Van Der Heijde3, Joachim Listing4, Joachim Sieper2, Alessandra Oortwijn1, Rebecca Bolce 1 and Juergen Braun5. 1Centocor Inc, 2Charite Campus Mitte, Rheumatology, Berlin, Germany, 3German Rheumatism Research Center, 4Leiden University Medical Center, Meerssen, The Netherlands, 5Clinic Buch Rheumatologie, Berlin, Germany

Background: Anti-TNF therapy with infliximab significantly reduces inflammatory activity (clinical assessments, MRI) in patients with active ankylosing spondylitis (AS) but does not seem to have a major impact on radiographic progression over 2 years. Recent studies have indicated that patients where structural changes have already occurred show higher rates of radiographic progression as compared to those without occurrence of radiographic changes. The European Infliximab AS cohort (EASIC) has been started after the end of ASSERT and patients were treated with infliximab in a real-life setting for 5 years.

Objectives: To study the long-term effect of anti-TNF treatment with infliximab on the chronic AS related radiographic changes over 5 years.

Methods: Complete sets of radiographs of the cervical (CS) and the lumbar (LS) spine at baseline (BL) and after 2 (FU1) and 5 years (FU2) were available from 53 patients from EASIC. Images were mixed with images from different studies and scored blinded for time order and treatment by an experienced reader using the mSASSS.

Results: At baseline, the mean age was 42.4±7.9, 45/53 patients (85%) were HLA-B27 positive and 46/53 (86.8%) were male. The mean BASDAI was 6.3±1.3, the mean BASFI was 4.0±1.7 and the mean BASMI was 5.9±1.6. The mean mSASSS score at BL was 20.5±19.9 units and the number of patients with syndesmophytes in the cervical and/or lumbar spine was 31/53 (59%). Radiographic progression was observed in almost all patients, with a mean mSASSS change of 1.0±2.0 and 2.1±2.7 at FU1 and FU2, respectively, in the entire group (both p<0.05 as compared to BL). There were no differences between the CS and the LS.

Overall, there was a trend for more severe radiographic progression at BL for the group with syndesmophytes at BL, as compared to the group without. New syndesmophytes were found in 14/31 patients (45.2%) when BL syndesmophytes were present vs. 9/22 patients (40.9%) without. Similarly, the overall mSASSS progression at FU2 differed between patients with (2.4±2.7) and without (1.6±2.8) syndesmophytes at BL.

Conclusion: In constrast to RA, patients with AS show ongoing radiographic progression under anti-TNF treatment. Future studies with head-to-head comparisons with historical cohorts may indicate whether the velocity of this process of new bone formation is changed by this medication.

Disclosure: X. Baraliakos: None; F. Heldmann: None; D. M. Van Der Heijde: None; J. Listing: None; J. Sieper: None; A. Oortwijn: Centocor, Inc.; R. Bolce: Centocor, Inc.; J. Braun: None.
A Prospective Inception Cohort Study of the Clinical Presentation and Response to Treatment of Undifferentiated Spondyloarthropathy Versus Ankylosing Spondylitis and Psoriatic Arthritis. Jacqueline E. Paramarta1, Leen E. De Rycke2, Carmen A. Ambarus2, Paul P. Tak1 and Dominique L. Baeten2, 1Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, 2Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands.

Background: Ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are the best described and studied subtypes of spondyloarthritis (SpA). A significant proportion of SpA patients, however, does not fulfill the classification criteria for AS and PsA and are at risk to be diagnosed and treated late. The aim of this study was to assess whether patients with undifferentiated SpA (USpA) are different from AS and PsA in terms of patient characteristics, disease activity and response to treatment.

Methods: 175 patients presenting on a dedicated SpA outpatient clinic fulfilling the European Spondyloarthropathy Study Group (ESSG) criteria were recruited in a prospective inception cohort. Global assessment of disease activity visual analogue scale (VAS) patient and physician, Bath Ankylosing Spondylitis Disease Activity (BASDAI), 68 swollen and tender joint count, Schober, ESR and CRP were measured every 3 months. Parametric tests were used for normally distributed data and non-parametric tests for non-normally distributed data.

Results: The baseline demographic and clinical data are shown in Table 1.

Baseline demographics and disease activity

<table>
<thead>
<tr>
<th>USpA (n = 40)</th>
<th>AS (n = 74)</th>
<th>PsA (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age of onset (yrs)</td>
<td>31.7 (11.2–62.1)</td>
<td>36.5 (8.1–75.6)</td>
</tr>
<tr>
<td>Median disease duration (yrs)</td>
<td>1.3 (0.0–36.1)</td>
<td>4.2 (0.0–46.8)**</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>17 (42.6)</td>
<td>43 (68.1)</td>
</tr>
<tr>
<td>Inflammatory back pain (%)</td>
<td>35 (87.6)</td>
<td>72 (97.3)**</td>
</tr>
<tr>
<td>Peripheral arthritis (%)</td>
<td>25 (62.5)</td>
<td>26 (35.1)**</td>
</tr>
<tr>
<td>HLA-B27 positive (%)</td>
<td>17 (42.6)</td>
<td>49 (68.1)**</td>
</tr>
<tr>
<td>Sacroiliitis high grade (%)</td>
<td>1 (2.5)</td>
<td>74 (100.0)**</td>
</tr>
<tr>
<td>Sacroiliitis low grade (%)</td>
<td>18 (45.0)</td>
<td>0 (0.0)**</td>
</tr>
<tr>
<td>Positive family history for SpA (%)</td>
<td>20 (50.0)</td>
<td>23 (31.1)**</td>
</tr>
<tr>
<td>NSAIDs (%)</td>
<td>51 (77.5)</td>
<td>51 (68.1)</td>
</tr>
<tr>
<td>D-MARDs (%)</td>
<td>15 (25.7)</td>
<td>8 (10.8)**</td>
</tr>
<tr>
<td>Anti-TNF (%)</td>
<td>4 (10.0)</td>
<td>19 (25.7)**</td>
</tr>
<tr>
<td>VAS patient (mm) median (range)</td>
<td>62.5 (10–100)</td>
<td>50 (1–90)**</td>
</tr>
<tr>
<td>VAS physician (mm) median (range)</td>
<td>51 (4–90)</td>
<td>45 (0–90)**</td>
</tr>
<tr>
<td>BASDAI median (range)</td>
<td>5.3 (0.9–9.1)</td>
<td>6.0 (0.3–9.2)</td>
</tr>
<tr>
<td>BASDAI ≥ 4 (%)</td>
<td>27 (69.2)</td>
<td>45 (63.4)</td>
</tr>
<tr>
<td>SEC (68) median (range)</td>
<td>0 (0–8)</td>
<td>0 (0–26)**</td>
</tr>
<tr>
<td>TIC (68) median (range)</td>
<td>1 (0–34)</td>
<td>0 (0–16)</td>
</tr>
<tr>
<td>Schober (cm) mean (SD)</td>
<td>4.1 (1.1)</td>
<td>3.6 (1.2)**</td>
</tr>
<tr>
<td>Chest expansion (cm) mean (SD)</td>
<td>4.6 (1.4)</td>
<td>4.3 (1.5)</td>
</tr>
<tr>
<td>ESR (mm/h) median (range)</td>
<td>7 (1–64)</td>
<td>10.6 (2–61)</td>
</tr>
<tr>
<td>CRP (mg/l) median (range)</td>
<td>2.0 (0.1–5.9)</td>
<td>4.0 (1.0–38.0)</td>
</tr>
</tbody>
</table>

Conclusion: USpA displays an intermediate phenotype between AS and PsA, with only part of the patients representing pre-radiological axial SpA. Despite the atypical presentation and shorter disease duration, a large majority of USpA patients have high disease activity. The apparent efficacy of TNF blockers in this observational study, together with the emerging data of RCT in pre-radiological AS pleas for systematic assessment of novel treatments not only in AS and PsA but also in axial and peripheral USpA.

Disclosures: J. E. De Rycke: None; C. A. Ambarus: None; P. P. Tak: None; D. L. Baeten: None.

2273

Do Patients with Psoriatic Arthritis Who Present Early Fare Better Than Those Presenting Later in the Disease? Dafna D. Gladman1, Arane Thavaneswaran2 and Vinod Chandran2. 1Toronto Western Hospital, Toronto, ON, Canada, 2University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital

Background: Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis often seronegative for rheumatoid factor. Over the past few decades it has become clear that the disease is more common and more severe than previously appreciated. PsA causes deformities and joint damage leading to impaired quality of life and function and is associated with an increased mortality risk. It remains to be determined whether early diagnosis and treatment would alter the course of the disease. The aims of this investigation were (1) to determine whether patients presenting to a PsA clinic early in the course of the disease had less severe disease at presentation, and 2) whether disease duration at presentation predicts progression of joint damage.

Methods: Patients with PsA have been followed prospectively in a specialized clinic for 32 years. Patients were divided into those first seen within 2 years of diagnosis (group 1) and those seen with more than 2 years of disease (group 2). The two groups were compared with regards to demographics and disease characteristics at presentation to clinic. A multivariate analysis using a negative binomial model was conducted to determine whether patients with early disease had less progression of joint damage. The outcome variable was progression of clinical joint damage and the variables entered in the model were age, sex, group, clinical joint damage at first visit, NSAIDs at first visit, DMARDs at first visit, treatment with biologics at first visit, treatment with NSAIDs after the first visit, treatment with DMARDs, and treatment with biologics after the first visit.

The cohort included 40 USpA, 74 AS and 45 PsA patients. The age of onset (median 32 years; range 11–62), disease duration (1.3 years; 0–36), and proportion of male patients (42.5%) were lower in USpA than in AS and PsA. USpA patients had more axial and less peripheral disease than PsA, but less axial and more peripheral disease than AS. The presence of HLA-B27 (43%) and either high or low grade sacroiliitis (47.5%) were less frequent in USpA than in AS. Only 25% of the USpA patients fulfilled the ASAS criteria for pre-radiological AS, although it should be noted that MRI was not systematically performed. Half of the USpA group had a positive family history. Despite the atypical presentation, the baseline disease activity (VAS patient/physician and BASDAI) was higher in USpA than in the other groups. Upon initiation of TNF blockade in patients with high disease activity, we observed a significant and sustained decrease of the disease activity in USpA, which was similar in amplitude to the response in AS and PsA (Figure 1).

Conclusion: USpA displays an intermediate phenotype between AS and PsA, with only part of the patients representing pre-radiological axial SpA. Despite the atypical presentation and shorter disease duration, a large majority of USpA patients have high disease activity. The apparent efficacy of TNF blockers in this observational study, together with the emerging data of RCT in pre-radiological AS pleas for systematic assessment of novel treatments not only in AS and PsA but also in axial and peripheral USpA.

Disclosures: J. E. Paramarta: None; L. E. De Rycke: None; C. A. Ambarus: None; P. P. Tak: None; D. L. Baeten: None.
Thus patients in group 2 (late PsA) were older, had longer duration of psoriasis and PsA, more joint damage and were less likely to be treated with DMARDs, but had similar degree of psoriasis severity. Results of multivariate regression analysis on predictors for progression of joint damage are shown in Table 2. 

Table 2. Results of multivariate analysis on predictors for progression of joint damage in patients with PsA.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Rate of joint damage progression</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group (PsA &gt; 2 yr vs. PsA≤ 2 yrs)</td>
<td>1.62</td>
<td>(1.28, 2.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>(1.01, 1.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>1.15</td>
<td>(0.93, 1.42)</td>
<td>0.173</td>
</tr>
<tr>
<td>Clinical Joint Damage at 1st visit</td>
<td>1.03</td>
<td>(1.01, 1.05)</td>
<td>0.003</td>
</tr>
<tr>
<td>NSAIDS at first visit</td>
<td>1.04</td>
<td>(0.84, 1.30)</td>
<td>0.690</td>
</tr>
<tr>
<td>Biologics at first visit</td>
<td>0.89</td>
<td>(0.54, 1.45)</td>
<td>0.630</td>
</tr>
<tr>
<td>DMARDs at first visit</td>
<td>1.20</td>
<td>(0.95, 1.51)</td>
<td>0.130</td>
</tr>
<tr>
<td>NSAIDS after first visit</td>
<td>1.22</td>
<td>(0.89, 1.68)</td>
<td>0.230</td>
</tr>
<tr>
<td>Biologics after first visit</td>
<td>1.15</td>
<td>(0.90, 1.46)</td>
<td>0.250</td>
</tr>
<tr>
<td>DMARDs after first visit</td>
<td>1.52</td>
<td>(1.16, 1.99)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

After adjusting for age, sex, clinical joint damage at first visit and treatment, Group 2 has significantly more rate of clinical damage progression compared to Group 1.

Conclusions: Patients who present within 2 years of diagnosis have less severe disease at presentation than those presenting later in their course. Disease progression is more marked in those patients presenting with established disease of > 2 years duration. These results suggest that patients with PsA should be treated earlier in the course of their disease.

Disclosure: D. D. Gladman: None; A. Thavaneswaran: None; V. Chandran: None.

2274
Identification of cis-Regulatory Element Binding Differences in the C8orf13/BLK Promoter Region Linked with Risk of SLE. Ruifu Lu1, Nicolas Dominguez2, Susan Macwana2, Celi Sun2, Jennifer A. Kelly3, Kenneth M. Kaufman4, Carl D. Langefeld5, Marta Alarcon-Riquelme for BIOLUPUS Network6, Sang-Choel Bae7, Elizabeth E. Brown for PROFILE9, C. D. Langefeld: None; M. Alarcon-Riquelme for BIOLUPUS Network: None; S.-C. Bae: None; E. E. Brown for PROFILE: None; G. S. Gilkeson: None; T. B. Niewold: None; B. P. Tsao: None; N. Shen: None; K. L. Moser: None; J. B. Harley: None; S. Clem: None; C. Webb: None; J. A. James: None; S. K. Nath: None; P. M. Gaffney: None; J. M. Guthridge: None.

Purpose: Polymorphic haplotypes of the HIES-1 endogenous retrovirus influence lupus susceptibility. One of its gene products, HIES-1/Rab4 is overexpressed in lupus T cells and contributes to altered T cell activation via regulating endosomal recycling of cell surface CD4 and transferrin receptors as well as the CD3 zeta chain that transmits signals from the immunological synapse (IS). Increased production of nitric oxide (NO) has been linked to abnormal activation of lupus T cells and NO production has been localized to the IS. Here we investigated the role of HIES-1/Rab4 in compartmentalized production of NO.

Methods: Expression of proteins involved in NO production was investigated by RNA microarray and western blot analysis of negatively isolated T cells from 44 Caucasian female lupus patients and 23 age-matched Caucasian female controls. NO production was measured by flow cytometry.

Disclosure: R. Lu: None; N. Dominguez: None; S. Macwana: None; C. Sun: None; J. A. Kelly: None; K. M. Kaufman: None; C. D. Langefeld: None; M. Alarcon-Riquelme for BIOLUPUS Network: None; S.-C. Bae: None; E. E. Brown for PROFILE: None; G. S. Gilkeson: None; T. B. Niewold: None; B. P. Tsao: None; N. Shen: None; K. L. Moser: None; J. B. Harley: None; S. Clem: None; C. Webb: None; J. A. James: None; S. K. Nath: None; P. M. Gaffney: None; J. M. Guthridge: None.

2275
The HIES-1/RAB4 Lupus Susceptibility Gene Promotes Nitric Oxide Production in Human T Cells through Direct Interaction with Endothelial Nitric Oxide Synthase Interacting Protein. Tiffany N. Telarico1, Edward H. Doherty2, David R. Fernandez2, Adam Bartos3, Stephanie Oesc4, Werner Muller-Esterl2 and Andreas Perl1. 1SUNY, 2University of Frankfurt, 3Upstate Medical Univ, Syracuse, NY

Purpose: Polymorphic haplotypes of the HIES-1 endogenous retrovirus influence lupus susceptibility. One of its gene products, HIES-1/Rab4 is overexpressed in lupus T cells and contributes to altered T cell activation via regulating endosomal recycling of cell surface CD4 and transferrin receptors as well as the CD3 zeta chain that transmits signals from the immunological synapse (IS). Increased production of nitric oxide (NO) has been linked to abnormal activation of lupus T cells and NO production has been localized to the IS. Here we investigated the role of HIES-1/Rab4 in compartmentalized production of NO.

Methods: Expression of proteins involved in NO production was investigated by RNA microarray and western blot analysis of negatively isolated T cells from 44 Caucasian female lupus patients and 23 age-matched Caucasian female controls. NO production was measured by flow cytometry. The effect of HIES-1/Rab4 on NO production and expression of proteins involved in
NO synthesis was investigated by overexpression of a wild-type HRES-1/Rab4 and its dominant-negative form HRES-1/Rab4S27N. Direct interaction of HRES-1/Rab4 with potential binding partners was assessed by pull-down assays.

**Results:** NO production was increased in lupus T cells by 32% (p = 0.009). Expression of endothelial NO synthase (eNOS) interacting protein (NOSIP) was reduced by 61% in lupus T cells (p = 0.010). Over-expression of HRES-1/Rab4 suppressed NOSIP expression and shifted it to the cytosol, enhanced eNOS expression, and NO production while dominant-negative HRES-1/Rab4S27N had the opposite effects in human T cells. NOSIP was efficiently pulled down by HRES-1/Rab4-GST but not by GST alone in Jurkat cells and human peripheral blood lymphocytes.

**Conclusion:** The results indicate that over-expression of HRES-1/Rab4 promotes NO production through direct interaction with NOSIP and its targeting to the cytosol which may activate eNOS and modulate IS formation in human T cells.

**Disclosure:** T. N. Telarico: None; E. H. Doherty: None; D. R. Fernandez: None; A. Bartos: None; S. Oess: None; W. Muller-Esterl: None; A. Perl: None.

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**2276**

**Transcriptional Inflammatory Mechanism in Murine Lupus Nephritis: An Insight into Human Disease.** Tania C. Gonzalez Rivera, Celine C. Berthier, Viji Nair, Ramalingam Bethunaickan, Matthias Kretzler, Anne Davidson, and ERCB Consortium. 1Feinstein Institute, Manhasset, NY, 2University of Michigan Medical Center, Ann Arbor, MI

Despite advances in immunosuppressive regimens, lupus nephritis (LN) remains a significant cause of morbidity and mortality in lupus patients. Murine LN models have been used to study this heterogeneous disease but the failure of human trials to reproduce the results seen in mice has raised concerns whether these models truly reflect human disease. Using a transcriptional network comparison we aim to define similarities and differences between three LN murine models and human LN.

Affymetrix based expression profiles from prenephritic vs. nephritic kidneys from 3 LN mouse models (NZB/W, NZM2410, and NZW/BXSB, total n=40) and human renal biopsies from 15 living donors (LD) vs. 32 LN patients underwent disease model specific transcriptional network analysis (Bibliosphere).

Transcriptional networks were compared using the Tool for Approximate Large graph matching (TALE) to define cross-species conserved functional interactions. The NZM2410 model shared the highest number of nodes with human LN, followed by the NZB/W and the NZW/BXSB models (70, 46 and 37 major transcriptional network nodes, respectively). Pathway analysis of the 17 nodes shared by the human and murine models highlighted macrophage activation pathways (p=0.001).

To distinguish the components of the macrophage-specific signature that were due to an alteration in cell phenotype rather than to infiltration with increased numbers of cells per se, gene expression profiles of macrophages isolated from prenephritic and nephritic NZB/W kidneys were generated and compared with corresponding murine and human LN kidney profiles. A total of 406 transcripts were concordantly regulated between NZB/W kidney isolated macrophages and whole kidneys. Of those, 132 transcripts were regulated in the tubulointerstitium of human LN kidneys, consistent with macrophage-derived expression. This signature was used to define the transcriptional state of kidney resident macrophages in murine and human LN. Network analysis defined Stat3, Anxa2 and TIMP1 as major hubs in the transcriptional state of kidney resident macrophages in murine and human LN. Application of the MESH filter “macrophage activation” on the human and murine LN kidney profiles. A total of 37 major transcriptional network nodes, respectively. Pathway analysis of the 17 nodes shared by the human and murine models highlighted macrophage activation pathways (p=0.001).

**Conclusion:** Taken together our data suggest that during periods of high disease activity in SLE, complement activation negatively impacts the ability of RBC to flow through capillaries and thus potentially affects the delivery of oxygen to the tissues. Disruption of complement fragment deposition on RBC membrane may improve hemorrheology and alleviate vasculopathic phenomena often associated with SLE.

**Disclosure:** L. C. Ghiran: None; O. Kampagianni: None; M. L. Zeidel: None; S. S. Shevkoplyas: None; J. M. Burns: None; V. C. Kyttaris: None; M. L. Zeidel: None; S. S. Shevkoplyas: None; J. M. Burns: None; V. C. Kyttaris: None.

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**2277**

**SLE Serum Deposits C4d on Red Blood Cells, Decreases Red Blood Cell Membrane Deformability, and Promotes NO Production.** Ionita C. Ghiran, Ournania Kampagianni, Mark L. Zeidel, Sergey S. Shevkoplyas, Jennie M. Burns, George C. Tsokos, and Vasileios C. Kyttarisis. 1Beth Israel Deaconess Medical Center, 2Tuane University

**Background:** Systemic lupus erythematosus (SLE) is characterized by intravascular activation of the complement system and deposition of complement fragments (C3 and C4) on plasma membranes of circulating cells, including red blood cells (RBC). We have recently shown that deposition of complement fragments on RBC in vitro is associated with decreased deformability of the RBC membrane (Karnchanaphumatur P. et al, J Clin Invest 2009). We therefore hypothesized that exposure of RBC to immune complexes present in SLE serum leads to decreased RBC deformability via complement fragment deposition.

**Methods:** Serum and red cells were isolated from patients with SLE, and healthy controls. RBC from healthy 0Rh- individuals were incubated with SLE or control serum. We used flowcytometry to assess complement fragment deposition on RBC. RBC membrane deformability was measured by 2-D microchannel arrays. Protein phosphorylation levels were quantified by western blotting.

**Results:** Incubation of healthy donor RBC with sera from patients with SLE but not control sera led to deposition of C4 fragments on the RBC. These complement decorated RBC showed a significant decrease in their membrane deformability. Moreover, RBC from patients with SLE showed a significant decrease in their deformability as compared to healthy donors. As deformability depends on the calcium-mediated phosphorylation of skeletal proteins, we evaluated whether skeletal protein phosphorylation is altered after incubation with SLE sera. We found that sera from SLE patients triggered Ca++ influx in RBC that was followed by decreased phosphorylation of the cytoskeletal protein β-spectrin, and increased phosphorylation of Band 3. Furthermore, RBC membrane flickering, which has shown to be important for the progression of RBC through capillaries, was reversibly inhibited by SLE serum-induced complement fragment deposition on RBC membrane. Finally, the complement fragment decorated RBC produced significant amounts of nitric oxide (NO), an important mediator of immune function and vascular tone.

**Conclusion:** Taken together our data suggest that during periods of high disease activity in SLE, complement activation negatively impacts the ability of RBC to flow through capillaries and thus potentially affects the delivery of oxygen to the tissues. Disruption of complement fragment deposition on RBC membrane may improve hemorrheology and alleviate vasculopathic phenomena often associated with SLE.

**Disclosure:** L. C. Ghiran: None; O. Kampagianni: None; M. L. Zeidel: None; S. S. Shevkoplyas: None; J. M. Burns: None; V. C. Kyttaris: None.
Inhibition of JAK and PI3K tested abrogation of the antiangiogenic signature induced by interferon-alpha.

**Results:** Microarray data analysis revealed alterations in various molecules associated to IL-1 mediated signaling and of vascular endothelial growth factor-A (VEGF-A). Downregulation of IL-1β, IL-1 receptor-1 (IL-1R1) and VEGF-A and upregulation of IL-1R2 (decay receptor) were observed. This indicates a global downregulation of IL-1β function induced by type I IFNs. These abnormalities were more marked in the IFN-treated lupus EPCs/CACs than in the IFN-treated control cells, suggesting that lupus cells were more sensitive to IFN-α effects. Results were confirmed at mRNA and protein level. Treating lupus EPCs/CACs with IL-1β resulted in a significant improvement in their capacity to differentiate into a mature endothelium, therefore abrogating the deleterious effects of IFN-α. The beneficial effects from IL-1β are mediated, at least in part, by increases in EPC/CAC proliferation, decreases in apoptosis, and by preventing the skewing of CACs towards non-angiogenic pathways. IFN-α induces STAT2 and 6 phosphorylation in EPCs/CACs and JAK inhibition abrogates the transcriptional antiangiogenic changes induced by IFN-α in these cells. Immunohistochemistry of renal biopsies from patients with lupus nephritis, but not ANCA-positive vasculitis, showed this pathway to be operational in vivo, with increased IL-1RN, downregulation of VEGF-A and glomerular and blood vessel decreased capillary density, compared to controls.

**Conclusions:** Our study introduces a novel putative pathway by which type I IFNs may interfere with vascular repair in SLE through repression of proangiogenic pathways. IFN-α induces STAT2 and 6 phosphorylation in EPCs/CACs and JAK inhibition abrogates the transcriptional antiangiogenic changes induced by IFN-α in these cells. Immunohistochemistry of renal biopsies from patients with lupus nephritis, but not ANCA-positive vasculitis, showed this pathway to be operational in vivo, with increased IL-1RN, downregulation of VEGF-A and glomerular and blood vessel decreased capillary density, compared to controls.

**Disclosure:** S. G. Thacker: None; C. Berthier: None; D. Mattinzioli: None; M.-P. Rastaldi: None; M. Kretzler: None; M. J. Kaplan: None.

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**ARHP Concurrent Abstract Sessions**

**Rheumatoid Arthritis: From Clinic to Home**

Thursday, November 11, 2010, 11:00 AM–12:30 PM

**2279**

The Nurse’s Role in Treatment and Management of Patients with Rheumatoid Arthritis: A Delphi-Based Recommendation on Patient Unmet Needs. Jane E. D. Cottrell, Monique Jonas and Leeanna M. Bulinckx. Charité University Hospital, Berlin, Germany, Mount Sinai Hospital, Toronto, ON, Canada, PerCuro Clinical Research Ltd, Victoria, BC, Canada.

**Background:** Nurses serve many critical roles in the management and treatment of patients with rheumatoid arthritis (RA), including educating and counseling the patient and liaising between the patient and rheumatologist. Examining how these roles differ among practices can help clarify areas in which nurses can optimize patient outcomes. The objective of this Delphi project was to assess the role of rheumatology nurses in addressing the unmet treatment and management needs of the RA patient.

**Methods:** A modified Delphi method with two rounds of questionnaires was followed by an in-person meeting to explore issues on which consensus had not been reached. A steering committee of 3 nurses developed and refined the questionnaires. An international group of 12 nurses with extensive experience (clinical or research) with patients receiving biologic therapy for moderate to severe RA served as panelists and completed the questionnaires. Prior to the meeting, all responses were anonymous and confidential. Focal topic areas included the nurse’s roles as caregiver, provider of information, and assessor of disease status and treatment outcomes. Special attention was paid to understanding patient physical and emotional needs.

**Results:** In most European and Canadian practices/clinics, nurses spend substantially more time with the patient than the physician. In their interactions with patients, nurses initiate discussions about personal well-being and disease impact on quality of life—topics not always addressed by physicians due to time constraints or comfort level with these issues. Patients are more likely to discuss emotional and social issues related to their diagnosis with a nurse than a doctor and tend to expect the nurse to provide disease and treatment education to them and their families. The panelists agreed that it is critical to customize this information for each patient rather than provide written materials with no verbal explanation. The nurse is in a unique position to judge what level of support or education a patient may need at any given time. Although the benefits of support networks and peer-to-peer interactions were recognized, such interactions need not be limited to structured groups.

**While all panelists agreed that the doctor is more likely to recommend a particular therapy, the nurse has a critical role in educating the patient on efficacy, potential side effects, method and frequency of administration, product storage, and, if applicable, comfort with self-injection, including demonstrating proper device technique. Additionally, the nurse determines the patient’s readiness for and understanding of the treatment, monitors safety and progress, and coordinates care within a multi-disciplinary setting.**

**Conclusion:** The nurse’s role in the management and treatment of patients with RA is complex and diverse, yet vitally important to optimal care.


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**2280**

Self-Efficacy and Follow-Up with Nursing, Medical or Shared Care for Outpatients with Rheumatoid Arthritis. Jette Primdahl1, Lis Wagner2 and Kim Horslev-Petersen. 1King Christian X’s Hospital for Rheumatic Diseases in Graasten and University of Southern Denmark, Graasten, Denmark, 2Research Unit of Nursing, University of Southern Denmark, Odense, Denmark, 3University of Southern Denmark, Sønderborg, Denmark.

**Introduction:** Traditionally, people with rheumatoid arthritis (RA) are administered by scheduled medical consultations every 3–12 months. Treatment aims to control disease activity, but also to enable the patients to achieve perceived control over the disease and disease related problems. The latter may be reflected in the patient’s self-efficacy (SF) - the belief in one’s ability to carry out a task with a desired outcome.

**Aim:** To explore whether RA outpatients’ SF develops differently, depending on whether they have follow-up care in the form of nursing consultations, medical consultations or in a shared care setting with no planned rheumatologic consultations.

**Material and Methods:** Outpatients (n=287) with low active RA (Disease Activity Score, DAS-28 <3.2 and Health Assessment Questionnaire, HAQ < 2.5) from two Danish hospitals were randomized for one of the three types of follow-up care. The participants’ SF was measured by the Danish version of the Rheumatoid Arthritis Self-Efficacy questionnaire (RASE) and the Danish version of the Arthritis Self-Efficacy Scale (ASES). Data were collected at randomization, after three months and at one year. The relation between SF beliefs, outpatient setting, socio-demographic and disease related variables were explored in mixed models. A Wilcoxon signed-rank test was used to test the significance of differences.

**Results:** For both the RASE and the ASES the three outpatient settings varied significantly over time. During a one year follow-up, the RASE scores decreased in the medical group (mean diff. –5.30, SD 1.29, p=0.0002) and the shared care group (mean diff. –4.14 (SD 1.26), p=0.0002). Contrary to this, the participants in the nursing group maintained their SF beliefs at the same level (mean diff. -1.08 (SD 1.32), p=0.47). The RASE score at randomization and time were significant predictors for the development of the RASE scores the first year.

SF measured by the ASES was maintained at the same level in the medical group (mean diff. –17.73 (SD 23.54), p=0.48) and the shared care group (mean diff. –54.56 (SD 27.52), p=0.14), whereas a significant increase was seen in the nursing group (mean diff. 74.56 (SD 19.73), p=0.0001). Disease duration, HAQ, DAS-28 and ASES at randomization were significant predictors for the development of the ASES scores the first year. An increase of 1 in HAQ or DAS-28 at randomization predicted a significant decrease in the ASES of 48.28 (p=0.009) and 38.96 (p=0.002) respectively. No significant differences in disease activity or physical disability between the three outpatient settings were detected at any time.

**Conclusion:** Outpatients with stable RA, attending three nursing consultations during a one year follow-up stabilized or increased their SF beliefs depending on the questionnaire in use. This differed from medical consultations and shared care cohorts, where the patients’ SF beliefs decreased or did not change. The use of ASES as a response variable in longitudinal studies can be problematic because of its high correlation to disease activity and physical disability. The RASE, independent of disease activity and physical disability, confirmed the effect of nursing interventions.

**Disclosure:** J. Primdahl: None; L. Wagner: None; K. Horslev-Petersen: None.
Future Expectations and Worst Case Scenarios of Patients with Rheumatoid Arthritis: A Focus Group Study in Patients. Lauren Buitinga1, Louise M. A. Braakman-Jansen1, Erik Taal1 and Mart A. F. J. Van de Laar1. 1University of Twente, Enschede, The Netherlands, 2University of Twente, Enschede, The Netherlands, 3University of Twente, University of Twente; Medical Spectrum Twente, Enschede

Background: Rheumatoid Arthritis (RA) has a great impact on patients’ daily lives. Because of the unpredictable progressive nature of the disease, it is imaginable that people worry about the impact of their disease in the future. Many studies have shown the prevalent difficulties patients experience now. Little attention has been paid to future expectations and worst case future scenarios. Afterwards, the codes were discussed until agreement was reached about all codes. For categorization of the coded expressions, a distinction was made between body functions and structures, activity participation, environmental factors and personal factors, in line with the International Classification of Functioning, Disability and Health (ICF).

Methods: A qualitative focus group approach was used. Three heterogeneous focus groups of RA patients were composed on the basis of age group (18–40, 40–65, 65–80), gender and having a paid job or not. Eventually, 16 people participated. Transcripts were individually coded by three researchers, including the moderator and note-taker. Participants were asked about their past experiences and worst case future scenarios. Afterwards, the codes were discussed until agreement was reached about all codes. For categorization of the coded expressions, a distinction was made between body functions and structures, activity participation, environmental factors and personal factors, in line with the International Classification of Functioning, Disability and Health (ICF).

Results: This study revealed that people expected the impact of their RA to be the same or to deteriorate slightly in the future, also in relation to the process of aging. Most people expressed hope for the future and positive feelings because of continuously improving medication. However, also feelings of uncertainty and fears were expressed about the future course of the disease. A major concern was about becoming dependent on others. One of the focus groups particularly expressed concerns about becoming dependent on others with regard to self-care (e.g. toileting, bathing). Concerns were also raised about side effects of medication and losing mobility. For many participants, becoming dependent on others would be the worst imaginable RA-related future scenario, for one participant it would be even worse than dead.

Conclusion: In this study, dependency on others was the most prevailing RA-related worst case future scenario. Many participants expressed their concerns in relation to dependency side effects of medication and losing mobility. Although pain was a prevalent symptom in daily life, no future concerns about pain were raised. Most people in these focus groups also held a positive view of the future because of continuously improving medication.

Objective: To examine future expectations, and to reveal worst case future scenarios in patients with RA.

Methods: A qualitative focus group approach was used. Three heterogeneous focus groups of RA patients were composed on the basis of age group (18–40, 40–65, 65–80), gender and having a paid job or not. Eventually, 16 people participated. Transcripts were individually coded by three researchers, including the moderator and note-taker. Participants were asked about their past experiences and worst case future scenarios. Afterwards, the codes were discussed until agreement was reached about all codes. For categorization of the coded expressions, a distinction was made between body functions and structures, activity participation, environmental factors and personal factors, in line with the International Classification of Functioning, Disability and Health (ICF).

Results: This study revealed that people expected the impact of their RA to be the same or to deteriorate slightly in the future, also in relation to the process of aging. Most people expressed hope for the future and positive feelings because of continuously improving medication. However, also feelings of uncertainty and fears were expressed about the future course of the disease. A major concern was about becoming dependent on others. One of the focus groups particularly expressed concerns about becoming dependent on others with regard to self-care (e.g. toileting, bathing). Concerns were also raised about side effects of medication and losing mobility. For many participants, becoming dependent on others would be the worst imaginable RA-related future scenario, for one participant it would be even worse than dead.

Conclusion: In this study, dependency on others was the most prevailing RA-related worst case future scenario. Many participants expressed their concerns in relation to dependency side effects of medication and losing mobility. Although pain was a prevalent symptom in daily life, no future concerns about pain were raised. Most people in these focus groups also held a positive view of the future because of continuously improving medication.

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is low and moderate evidence that HB exercise programs have no deleterious effects (see Table I).

Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Functional ability</th>
<th>Aerobic capacity</th>
<th>Muscle strength</th>
<th>Self-reported pain</th>
<th>Disease activity</th>
<th>Radiological damage</th>
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<tbody>
<tr>
<td>Home-based program versus no intervention</td>
<td>+/+*</td>
<td>–</td>
<td>+/+*</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Brodin 2008</td>
<td>–</td>
<td>–</td>
<td>+*</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Home-based programs versus supervised programs</td>
<td>=</td>
<td>=</td>
<td>+**</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Van den Eude 1996</td>
<td>=</td>
<td>=</td>
<td>+**</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>Hansen 1993</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Huiss 2009</td>
<td>–</td>
<td>–</td>
<td>+**</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lemmey 2009</td>
<td>=</td>
<td>=</td>
<td>+**</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Home-based programs versus other home-based programs</td>
<td>=</td>
<td>=</td>
<td>+**</td>
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<td>–</td>
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<tr>
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<tr>
<td>O'Brien 2005</td>
<td>+#</td>
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<td>Stammart 1996, 1997</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Significant (p < 0.001) difference: ++
Significant (p < 0.05) difference: +
No significant difference: =
* In favor of home-based program
** In favor of supervised program
# In favor of the home-based program including strengthening and stretching exercises versus exercise programs with only stretching exercises.

Conclusion: HB exercise therapy is more effective with regard to functional ability and muscle strength than no exercise therapy. HB exercise therapy is less effective than supervised exercise with regard to aerobic capacity and muscle strength, but equally effective with regard to functional ability. When comparing different types of HB exercise programs, a combined program including strengthening exercises is more effective with regard to functional ability compared to a program without strengthening exercises. No detrimental effects were found in any of HB exercise programs. More research is needed with regard to the specific content and duration of HB exercise program.

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An Interactive Website Reduces the Information Need Regarding the Accessibility of Health Care Services in RA Patients. Jorit J. L. Meesters1, Ingeborg G. de Boer2, Marta Fiocco3 and Thea P. M. Vliet Vlieland4.
1Leiden University Medical Center, Leiden, The Netherlands, 2Leiden University Medical Center

Purpose: Sufficient knowledge about health care services is mandatory for effective self-management in RA patients (1). This study concerns the effects of an information intervention regarding the accessibility of 18 regional health care services on RA patients’ self-perceived knowledge and information need.

Methods: The intervention consisted of a weekly updated interactive internet site covering practical aspects of regional health care services for patients with rheumatic diseases, including an email helpline and a telephone helpline. The intervention also comprised an information kiosk with access to the aforementioned website in the outpatient clinic. Moreover, patients were invited to an information meeting in the hospital, and they received a set of information leaflets based on their individual needs.

A random sample of 400 RA patients from the outpatient clinic of our rheumatological department was asked to fill in a questionnaire before the internet site was launched (T1) and 24 months thereafter (T2) (pretest-posttest design).

The questionnaires concerned socio-demographic data, information need (yes/no), and the level of knowledge (insufficient/sufficient) regarding the accessibility of 18 regional health care services.

Results: 251 patients (response rate 63%) and 200 patients (50%) returned the questionnaire before and after the intervention, respectively, with 160 paired observations (112 females (70%), mean age 60.4 (SD 9.9)). Table 1 shows the percentages of patients reporting insufficient knowledge or an information need regarding the accessibility of a health care service (T1) and the changes in these percentages (T2-T1) (Mc-Nemar test). Only the results of the top 10 health care services (highest percentages insufficient knowledge at T1) are shown. At T1, the percentages of patients reporting insufficient knowledge were higher than those reporting an information need in all health care services.

Table 1 shows that there is a significant decrease of the patients who reported insufficient knowledge for 2 out of 10 health care services (in total: 2/18 services), and for information need 9 out of 10 health care services (in total: 15/18 services).

Table 1  Baseline (T1) respondents reporting insufficient knowledge and information need on the accessibility of health care services and changes (T2-T1)

<table>
<thead>
<tr>
<th>% Insufficient knowledge</th>
<th>SP</th>
<th>HN</th>
<th>SW</th>
<th>PS</th>
<th>OT</th>
<th>SM</th>
<th>PO</th>
<th>IG</th>
<th>HT</th>
<th>EC</th>
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<tbody>
<tr>
<td>T1</td>
<td>67</td>
<td>54</td>
<td>60</td>
<td>61</td>
<td>58</td>
<td>64</td>
<td>59</td>
<td>72</td>
<td>63</td>
<td>79</td>
</tr>
<tr>
<td>T2-T1</td>
<td>– 1</td>
<td>– 1</td>
<td>– 5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>– 1</td>
<td>– 12*</td>
<td>– 5</td>
<td>– 11*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% Information need</th>
<th>SP</th>
<th>HN</th>
<th>SW</th>
<th>PS</th>
<th>OT</th>
<th>SP</th>
<th>PO</th>
<th>IG</th>
<th>SE</th>
<th>HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>37</td>
<td>18</td>
<td>16</td>
<td>13</td>
<td>19</td>
<td>31</td>
<td>21</td>
<td>35</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>T2-T1</td>
<td>– 25*</td>
<td>– 15*</td>
<td>– 10*</td>
<td>– 9*</td>
<td>– 13*</td>
<td>– 19*</td>
<td>– 18*</td>
<td>– 19*</td>
<td>– 16*</td>
<td>– 9*</td>
</tr>
</tbody>
</table>

(*: significant difference, p < 0.05).


Conclusions: In RA patients an interactive internet site and the tailored provision of written information leaflets appear to decrease self-perceived information need on regional rheumatology health care services. The effects on self-perceived knowledge were limited. These findings suggest that supplying practical information about health care services should play a greater role in the treatment of RA patients. More research into the optimal strategies to inform patients is needed.

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Reference List

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