American College of Rheumatology (ACR)
Vasculitis Guideline

Large Vessel Vasculitis (giant cell arteritis and Takayasu arteritis) and Medium Vessel Vasculitis (non-hepatitis-related polyarteritis nodosa and Kawasaki disease)

Public Comments

The ACR Vasculitis Guideline public comment was posted on the ACR website March 27, 2018. The announcement was e-mailed to the Practice Guidelines Subcommittee, Quality of Care Committee and ACR Board of Directors, and was included in multiple ACR publications and on ACR social media platforms. ***Twenty one (21)*** *responses were received via the online form;* ***two (2)*** *responses were received via email. The public comment period closed on April 27, 2018.*

RESPONSES RECEIVED ONLINE:

- **Name:** Paul Phillips
- **Institution:** SUNY Upstate Medical University
- **Position:** Emeritus Professor
- **Disclosure (optional):** Nothing to disclose

Comment:
Excellent plan, looks very complete.

- **Name:** Erick Adrian and Zamora Tehozol
- **Institution:** Medical Care and Research
- **Position:** Rheumatologist (Erick); Investigator (Zamora)
- **Disclosure (optional):** I am working with Roche and Lilly (Erick)

Comment:
I think we can add some statements to the Disease Related Outcomes and Activity: Paragraph 201, page 8, we can add, a burst or an intense increase in activity, because pulse therapy in a sensitive vessel could be and incorrect approach. Paragraph 221, page 9, ITAS 2010, is a Validated Score to maximize the relationship with activity, BVAS isn't reliable, and isn't sensible to follow up patients. Paragraph 488, page 20, Five Factor Score, is more sensible to change than BVAS in PAN, so, it's incorrect to think that BVAS could replace other index measures.

- **Name:** Ronald Laxer
- **Institution:** The Hospital for Sick Children, University of Tornoto
- **Position:** Professor of Pediatrics and Medicine
- **Disclosure (optional):** Nothing to disclose

Comment:
It is great that you are including Kawasaki disease in this project. I strongly suggest that you include a pediatric cardiologist with expertise and an international reputation on your expert committee. Drs. Sundel and Kim are eminently credible in Kawasaki disease, but had worked together in the same institution for many years, that may introduce bias in the voting. You might also consider someone with expertise in pediatric Takayasu disease (e.g., Steve Spalding, Cleveland Clinic).

- **Name:** Susa Benseler
- **Institution:** University of Calgary (Canada)
- **Position:** Deputy Head Research, Section Chief
- **Disclosure (optional):** Nothing to disclose

Comment:
It appears to be a fairly straight forward systematic literature review the group is proposing. The large vessel vasculitis groups appears to be a simple and very standardized task. The group has decided it would be worthwhile - some members are authors on the European vasculitis management papers (Merkel for aduls, others for SHARE).

My thought: Takayasu is a really rare condition and partnered efforts with Europe, INDIA and SOUTH AFRICA, where far more patients are seen, may be an opportunity. We are all aware of the limited TAK literature. Medium size vasculitis is capturing PAN - a disease not uncommonly found to be DADA2 and Kawasaki disease, a systematic inflammatory illness, which results in blood vessel inflammation in 20% of kids and aneurysms in3% - many have additional large vessel aneurysms (IVIG treated).

In peds we don't necessarily lump them - not sure this is great idea. The classification efforts by EULAR for medium size vessel vasculitis were perceived lukewarm. I would suggest separating these illness due to their very different nature.

Also please consider: For the latter there are several recommendations proposed by the AHA regarding diagnosis, treatment and monitoring. Not sure this separate lit review is great for partnership with other subspecialists. I can't find a peds ID or cardiologist (Newburger, McCrindle, others) on the list. I worry this will impact negatively on the uptake of the proposed recommendations. In many centers, rheum plays a very limited role in the care of kids with KD.

- **Name:** Arthur Brawer
- **Institution:** Monmouth Medical Center
- **Position:** Director of Rheumatology
- **Disclosure (optional):** Nothing to disclose

Comment:
For GCA, I offer the following: Lines 318 & 319 (disease state) - night sweats, fever, weight loss, anemia, headaches, and elevated ESR are not discriminating features. I refer you to two unique peer-reviewed published studies: (a) Open Access Rheumatology, Research and Reviews on April 1, 2016 by Arthur E. Brawer, M.D. (the natural course of PMR without corticosteroid treatment), and (b) International Annals of Medicine (April 2018) - Anarthritic Rheumatoid Arthritis... (by Dr. Brawer).

Line 332 (therapy) - in the absence of visual disturbances, TIA, or stroke, and in the presence of a classical biopsy (not one with inflammation of the vasa vasorum alone), corticosteroids should be withheld and patients should be treated solely with tocilizamide. There exists an army of elderly patients

with devastating side effects caused by corticosteroid treatment, and rheumatologists have forgotten the time-honored dictum of "do no harm."

Lines 379 & 381 (Dx and Bx) - biopsy should be 1.5 to 2cm, and classical findings should be mandatory.

Lines 383 thru 421 (treatment) - the knee jerk response of starting steroids prior to biopsy in an uncomplicated case of suspected GCA has arisen out of insecurity and nervousness, and is unfounded (especially if one takes the time to educate the patient). Prior to my two published prospective studies referenced above, five decades have elapsed without anyone questioning "traditional concepts." If you have bacterial endocarditis, show me the blood cultures. If you have GCA, show me the biopsy. The movement in rheumatology away from definitive pathological diagnosis is, in my opinion, very poor medical practice (e.g., MRI in DM instead of muscle biopsy; labs in SLE with DPGN instead of renal biopsy; ANCA in Wegener's instead of open lung biopsy). The same trend is happening with ancillary testing in GCA so as to avoid a biopsy - this is, in my opinion, absurd, and creates havoc when treatment goes awry.

For PAN, I offer the following: Lines 465 thru 478; and lines 528 thru 539 (therapy) - in severe disease, corticosteroids in any dose accelerates the tissue ischemia and "drives" the disease. I refer you to two unique peer-reviewed published studies: (a) Cyclophosphamide Without Corticosteroids for Treatment...., in Journal of Clinical Rheumatology, Volume 18 (5), August 2012, pages 265-267, by Dr. Brawer; and (b) Corticosteroids: the Knee Jerk Response, by Dr. Brawer, August 10, 2016 in Current Medical Research and Opinion. There is no short term solution for a long term problem - support the patient with routine care and treat solely with either cyclophosphamide alone or Rituxan alone.

Line 503 (Dx testing) - for severe disease, if a renal and/or mesenteric arteriogram cannot be done, a tissue biopsy is essential (both gastrocnemius and sural nerve biopsies, done at the same time, are usually sufficient).

- **Name:** Peter Merkel
- **Institution:** University of Pennsylvania
- **Position:** Chief of Rheumatology
- **Disclosure (optional):** Nothing to disclose

Comment:
Note: I am already part of the guidelines process and have previously reviewed/contributed to some of this material. Nonetheless, I have a few additional comments to consider (which may be mentioned in the long document):

The Core Oversight Team has done a terrific and comprehensive job of addressing key issues for these complex conditions. For Takayasu's arteritis and giant cell arteritis: Consider advice to clinicians about cases that do not fall easily into current classification criteria (and/or wait for the new ACR/EULAR Criteria that will be forthcoming later this year). e.g. older person with apparent aortitis but no cranial

features. Consider how to follow and treat patients with "hot" PET scans who are otherwise asymptomatic. Right or wrong, these cases are happening. Consider specifically the role for peri-procedure/peri-operative glucocorticoids when patients undergo vascular procedures. By this I a mean use of, for example, high-dose glucocorticoids before and after a stent placement. This is somewhat different from thinking about post-procedure medium- and long-term management. For all vasculitides (perhaps except GCA): address treatment of children. Are there any data clearly demonstrating different responses to treatments? Other considerations in the treatment of children?

- **Name:** Susan Goodman
- **Institution:** Hospital for Special Surgery
- **Position:** Attending Physician
- **Disclosure (optional):** Nothing to disclose

Comment:
This is a well thought through project plan. Excluding common entities such as Hep B associated vasculitis leaves a gap in guidance, however.

- **Name:** Robert Lightfoot
- **Institution:** University of Kentucky
- **Position:** Professor of Medicine
- **Disclosure (optional):** Nothing to disclose

Comment:
Good luck with the steroid dose issues. At my university, we teach that steroids are what we all use "until the real medicine starts to work." Steroids always worked for GPA, but the patients went ahead and died until the steroid-sparing effects cytoxan were discovered by accident. I wouldn't waste too much time on determining the "correct dose" of steroids. "High enough" is the best starting dose, and always a taper thereafter while the "real medicine" is begun.

- **Name:** Anthony Sammel
- **Institution:** Prince of Wales Hospital (Australia)
- **Position:** Rheumatologist
- **E-mail Address:** tsammel@hotmail.com
- **Disclosure (optional):** Nothing to disclose

Comment:
In the methods section, it would be useful to include an assessment of fluorescein fundoscopic angiography as a supplementary diagnostic tool for patients with ophthalmic presentations of GCA. Reference: Hayreh. Am J Ophthalmol. 1998.125:509-20.

- **Name:** Rory Marks
- **Institution:** University of Michigan
- **Position:** Associate Professor
- **Disclosure (optional):** Nothing to disclose

Comment:
Are the guidelines going to include a background section indicating that there are multiple additional types of large-artery vasculitis other than TA and GCA? Guidelines restricted to these 2 conditions could tend to make clinicians force patients into one or other of these conditions and not consider other diagnoses. For e.g., other, not rare, conditions include: (i) Hyper-IgG4 aortitis. (ii) Idiopathic aortitis, many of which are diagnosed after routine Ao-aneurysm surgery, and many, after very careful selection, don't require any immunosuppression at all.

- **Name:** Haner Direskeneli
- **Institution:** Marmara University, Division of Rheumatology (Turkey)
- **Position:** Chief
- **Disclosure (optional):** Nothing to disclose

Comment:
In my opinion, for Takayasu's arteritis, PICO Question A1 is an outdated one. Invasive imaging is not accepted to be the first-line of diagnostic tool, except in cases for acute stent placement. The question should also clarify the use of imaging in diagnosis vs monitoring of TAK. A PICO question on long-term cardiovascular outcome monitoring could also be valuable (CV risk factor assessment) as long-term increased risk for CV diseases are reported for TAK (GCA ?).In surgical intervention questions for TAK, no question clearly embraces approaches to aortic involvement sufficiently.

- **Name:** Hajime Yoshifuji
- **Institution:** Kyoto University (Japan)
- **Position:** Assistant Professor
- **Disclosure (optional):** Nothing to disclose

Comment:
I have one question in the imaging assessments of Takayasu arteritis. Page 9, Line 225, CT angiogram and MR angiogram are described. However, contrast CT and contrast MRI for evaluation of arterial wall (e.g., Nakaoka, Int Heart J, 2013;54(6):405-11) are not described. Although angiogram and contrast imaging are similar, they are different in the point that angiogram evaluates patency of arterial lumen while contrast imaging evaluates inflammation of arterial wall. The project plan of guideline is wonderful.

- **Name:** Christian Pagnoux
- **Institution:** Mount Sinai Hospital (Canada)
- **Position:** MD
- **Disclosure (optional):** Speaker fees from Roche, and advisory board fees from Roche, GSK, Sanofi and ChemoCentryx

Comment:

The choice of the large and medium vessel vasculitides for this first ACR guidelines on vasculitis is a good and smart move, as this is a global unmet need for TAK, Kawasaki (and PAN). For GCA, there has been a large international initiative, if I am correct, thus this would sound less of a need now, and is possibly redundant, with some of the same persons having been involved.

The committees include some well-known experts, some with well-known disclosures and relationships with pharmas. I just wonder whether 8 adult rheumatologists and 4 pediatric ones is enough for the voting panel of such a huge and important initiative. In addition, though I do not know all the members, I wonder whether including non-US experts (Canada, Mexico and other) should be considered.

I have nothing to add on the methods, which are well articulated. GRADE system has been the one preferred over the past years. This entire bibliographic search and grading, though, will be redundant with what has been done by other groups. But I guess there is not much choice...

TAK: Definitions of adverse events for imaging will be very generic, not specifically for TAK. Needed? Why using BVAS only and not a disease-specific developed tool such as ITAS? Not sure there is much data and not sure that is an important question to study IV pulse vs high dose steroids in TAK. Similarly to GCA, some patients with TAK keep a high CRP, without clinical or radiological signs of active disease / progression. What to do with them? Importance of the management of renal and pulmonary involvements specifically to underline maybe. Importance of pregnancy, management of the disease before, during and after pregnancy, and counseling for pregnancy.

GCA: Definitions of adverse events for imaging will be generic, not specifically for GCA. Needed? Imaging: guidance needed on which tests to perform at diagnosis and then for follow-up (CXR+US abdo? echo? or CTA or MRA for everyone? or if clinical findings?) - part of 4.9 question maybe (unsure) - Important to individualize the treatment of patients with aortitis or aorta aneurysm (which follow-up, for how long; place of biologics, especially when aneurysm develops later on, when the disease appears to be in remission) - place of prophylaxis in GCA patients (osteoporosis, PJP also or not)

PAN: Definition: justify why mononeuritis multiplex or muscle disease are severe disease forms (not all subsets are severe: sensory vs motor, muscle pain vs florid myositis), because being classified as severe impacts on the treatment choices.- diagnosis: define the place of genetic testing (DADA2 and other)- diagnosis: though not covered here, important also to remind here that several lab tests are needed, especially HBV testing.

KAW: Disease assessment: no score? no BVAS here? or PedVas?- follow-up of patients: guidance on whether or not long term follow-up is needed (to detect and manage possible late cardiovascular complications, in adulthood)- need to mention incomplete KAW disease in adults as well maybe.- need to precise the duration of treatment with aspirin (and other treatments if given - steroids).

- **Name:** Eric Matteson
- **Institution:** Mayo Clinic
- **Position:** Faculty Member
- **Disclosure (optional):** I was the site PI for the GiACTA trial

Comment:
I have COI because of being on the expert panel. I think the questions are well formulated, although I am allergic to the use of "impact," because it is a noun synonymous with "collision." "Effect" is generally a better choice. I also think that the term "low dose" prednisone is fraught, because there is a big difference in long-term therapy (e.g., years) between say 4 or 5 mg/day and over 7.5 mg a day.

- **Name:** Ahmet Gul
- **Institution:** Istanbul University, Istanbul Faculty of Medicine (Turkey)
- **Position:** Professor
- **Disclosure (optional):** Nothing to disclose

Comment:
Thank you very much for asking my opinion on the plan. It is a very well planned study, and I have just a few comments: Most of the imaging studies would be descriptive, and their evaluation may not be easy by standard PICO questions because of their different content. In addition to inflammatory markers, it may be possible to find information on endothelial activation or regeneration markers in TAK. Regarding anti-TNF and anti-IL6 biologic treatments, it is possible to find data on IL-1 blockade, as well for the treatment of large and medium vessel vasculitis. For PAN patients, it is necessary to advise about a necessary work-up to rule out underlying conditions including the extent of genetic testing for the MEFV and ADA2 genes.

- **Name:** Yoshihiro Arimura
- **Institution:** Nephrology and Rheumatology, Kyorin University School of Medicine (Japan)
- **Position:** Professor
- **Disclosure (optional):** Nothing to disclose

Comment:
Thank you for your e-mail. I think your guideline is well-crafted. I would like to offer the following comments. In my opinion, "frequently relapsing" should be included in the definition for refractory of the disease state. Thus, I suggest that number four be changed as follows: 4. Refractory: persistent active and/or frequent relapsing disease despite an appropriate course of immunosuppressive therapy. Or, if possible, the question concerning "in patients with frequent relapsing TAK and GCA" should be

added to the list of questions for Treatment of PICO in TAK and GCA. For example, a fourteenth question could be added that reads as follows: 14. In patients with frequent relapsing TAK, what is the impact of glucocorticoid + biologic therapy vs. glucocorticoid monotherapy on disease-related outcomes and treatment-related adverse events?

I would like to provide the following references:

1. Nakaoka Y1, Isobe M2, Takei S3, Tanaka Y4, Ishii T5, Yokota S6, Nomura A7, Yoshida S7, Nishimoto N8. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study).Ann Rheum Dis. 2018 Mar;77(3):348-354. doi: 10.1136/annrheumdis-2017-211878. Epub 2017 Nov 30.

2. Villiger PM1, Adler S2, Kuchen S2, Wermelinger F2, Dan D2, Fiege V3, BÃ¼tikofer L3, Seitz M2, Reichenbach S4. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial.Lancet. 2016 May 7;387(10031):1921-7. doi: 10.1016/S0140-6736(16)00560-2. Epub 2016 Mar 4.

- **Name:** Rosa Maria Pereira
- **Institution:** University of Sao Paulo, School of Medicine (Brazil)
- **Position:** Professor
- **Disclosure (optional):** Nothing to disclose

Comment:
Congratulations for the protocol. Below some suggestions:

1. Page 9 - item 7, Surgical intervention: Include - Valvar replacement
2. Page 9 - D - item 1 Study-specified disease activity assessment : Include NIH, ITAS-A 2010
3. Page 10 - item i. Correct: Survey (instead of Surgery), Euroqol (instead of Euroquol)
4. Page 11- B. treatment - include: In patients with TAK what is the impact of statin use versus not using a statin on disease-related outcomes and treatment-related adverse events, and cardiovascular events?
5. Page 12- C. Surgical vascular intervention - include: In patients with TAK, what is the impact of performing surgical intervention while the patient has active disease versus delaying until the disease is in remission on disease-related outcomes and surgical intervention-related adverse events?
6. Page 15-E. treatment-related adverse events - include: vertebral and non-vertebral fractures.

- **Name:** Christian Dejaco
- **Institution:** South Tyrol Health Trust/Rheumatology Service (Italy)
- **Position:** Chair
- **Disclosure (optional):** Speakers and advisory board honoraria from Roche, GSK, Sanofi, BMS, AbbVie, Celgene, MSD, Lilly, UCB, Pfizer

Comment:
Consider also outcome prediction as part of your objectives in order to build subgroups. Particularly for use of expensive drugs it is important to identify groups at risk for unfavourable outcomes. Study types: It will be difficult to find RCTs on diagnostic procedures, are prospective studies on patients with suspected disease included in the "observational" set? Diagnostic studies should be appraised by the QUADAS-2 tool (which can be implemented in GRADE), prognostic studies (which I feel should be included) with the QUIPS tool. For diagnostics: How will the pre-test probability for the disease be considered? The value of any test strongly depends on the pre-test probability search. Takayasu: would not spare abatacept from the list of biologics and in GCA would also include TNFs (even when both are known to be not effective).

- **Name:** Maria Cid
- **Institution:** Hospital Clinic, University of Barcelona (Spain)
- **Position:** Senior Consultant/Associate Professor
- **Disclosure (optional):** I have received consultation fees from Roche, GSK and Abbvie

Comment:
Thank you very much for your effort. Overall, PICO questions seem very accurate and appropriate. I am afraid that, unfortunately, there will not be strong evidence for many of the questions: this underlines how much we need to learn and configures a busy research agenda! I have the following comments:

TAKAYASU ARTERITIS

1. Page 8 - There are no PICO questions regarding suitability of various imaging techniques for diagnosis, only for follow-up. In GCA, for instance, there are PICO questions regarding diagnosis - Regarding therapy, there is no evidence supporting dose and duration of IV pulses, but 5 day-duration is a very unusual practice
2. Page 9 – Low-dose prednisone should be considered below 10 mg a day and possibly below 7.5 mg/day in terms of long-term tolerability and side effects (see Strehl C et al Ann Rheum Dis 2016 and Van der Goes MC Ann Rheum Dis 2010 - Biologics: there are a few reports on rituximab and ustekinumab, perhaps they should be mentioned.
3. Page 10 - I am not sure SF-36 means Short form health surgery. I think it is survey.
4. Page 11 - Treatment: Regarding to glucocorticoids for active TAK the PICO question addresses high-dose versus low-dose glucocorticoids on disease-related outcomes and treatment derived adverse events. For active TAK, moderate dose glucocorticoids may need consideration, more than, perhaps, low-dose. - PICO question 8 considers glucocorticoid + biologic agent (specify?) vs

glucocorticoid monotherapy. In many existing studies, biologics are given as an add-on treatment over conventional immunosuppressive agents.

5. Page 12 - in PICO questions about limb/organ ischemia (intervention vs. immunosuppression), any specific question about reno-vascular hypertension or is considered sufficiently included in organ ischemia? - TAK patients develop prominent vascular remodeling and secondary atherosclerosis. Should a PICO question address concomitant use of angiotensin converting enzyme inhibitors, angiotensin II receptor blockers or statins?

GIANT-CELL ARTERITIS

1. Page 13 - As for TAK, I do not think 5-day duration pulse IV methylprednisolone is common. 3 days is more usual.
2. Page 14 - In patients with GCA, high-dose prednisone is usually given at a maximum dose of 60 mg. Regarding oral glucocorticoids in vasculitis in general, prednisolone is frequently used as an equivalent to prednisone in Europe and use of prednisolone instead of prednisone can be found in the reviewed literature. - Same comment as for TAK regarding definition of low-dose prednisone - Regarding biologics, in addition to those supported by randomized controlled trials (tocilizumab and abatacept), other biologics have been occasionally used and should be mentioned : rituximab, ustekinumab, IL-1 antagonists and jakinibs - Anti-TNFs , particularly infliximab and adalimumab, should be discussed to recommend against their general use, based on randomized controlled trials. Results about etanercept are inconclusive. - Patients with GCA develop limb vascular stenosis much more infrequently than patients with TAK and frequently have vascular co-morbidities. Evaluation of 4 extremity blood pressure may not be routinely feasible or reliable. -Perhaps the role of statins, ACE inhibitors or angiotensin II receptor antagonists should be discussed, since there are several low-quality evidence papers published.
3. Page 15 - As complication of the temporal artery biopsy transient palsy of upper facial nerve branches, affecting the forehead should be added. Hematoma is another complication.
4. Page 17 - When discussing about aspirin, some of the existing literature refers to anti-platelet or anticoagulant agents and drugs other than aspirin have been used. In PICO questions addressing Kawasaki, for instance, different anticoagulants or anti-platelets are considered. Probably the term “non-glucocorticoid immunosuppressive agents” is used to remark that glucocorticoids are also immunosuppressive. However, people usually refer to non-glucocorticoid immunosuppressive agents simply as immunosuppressive agents. Using the term non-glucocorticoid-immunosuppressive agents in the PICO questions results a little bit long and confusing. When addressing surgical interventions, I am not sure that “severe disease” is the best term. I would use, as in TAK, limb or organ ischemia. The reason I am remarking this is because one of the most frequent severe complications is anterior ischemic optic neuritis (AION) and, at present, AION is not treated with intervention. Severity may also arise from refractoriness.

POLYARTERITIS NODOSA

1. Page 19 - Polyarteritis nodosa (PAN) is becoming a rare and heterogeneous disease. Should we include some recommendation about HBV, HCV, HIV or ADA2 deficiency testing? In severe

disease, CNS involvement should be added. Same comment about 5-day duration of pulse IV methylprednisolone I made when discussing other vasculitis.
2. Page 20 - There are some reports about use of rituximab. Anti-TNFs are considered for treatment of polyarteritis nodosa due to ADA2 deficiency.
3. Page 22 - When discussing diagnosis, muscle biopsy is only considered in the setting of peripheral nerve involvement. Muscle biopsy may disclose PAN findings in the absence of nerve involvement and is a safe and useful procedure. When addressing PICO questions regarding treatment it would be necessary to take into account that some existing trials are performed on mixed cohorts of patients with microscopic polyangiitis or eosinophilic granulomatosis with polyangiitis (Churg-Strauss).

KAWASAKI

1. Questions raised seem fine to me. However, my personal experience in Kawasaki is very limited.

- **Name:** David Jayne
- **Institution:** University of Cambridge (United Kingdom)
- **Position:** Professor
- **Disclosure (optional):** Nothing to disclose

Comment:

It is always hard to know when to set the timeline for the literature search but DCVAS may report useful information for diagnosis over the next 12 months. Chapel Hill is an imperfect tool, I agree you have to use it, but may need some discussion on overlaps/incomplete diagnoses etc. It may be valuable to state that you are not writing guidelines for rarer forms of vasculitis - Cogan's, primary CNS, IgG4, DADA2, etc. I presume these are for adults not children. You have probably already considered involving non-expert clinicians, i.e. general internists, to test how easy the guidelines will be to navigate and understand. From a European perspective, great that you are not focusing on AAV right now as this was done by EULAR/ERA a couple of years ago. The EULAR process did have ACR representation, and it is good to have as much international alliance as possible. This has been a problem in lupus guidelines. Guidelines should have an in built expiry or renewal date as they will necessarily become progressively out of date.

- **Name:** Benjamin Terrier
- **Institution:** Cochin Hospital (France)
- **Position:** Associate Professor
- **Disclosure (optional):** Received consulting and speaking fees (Roche, LFB, Grifols, GSK)

Comment:

No particular comment. Impressive plan in which I will be glad to participate.

Large Vessel Vasculitis (giant cell arteritis and Takayasu arteritis) and Medium Vessel Vasculitis (non-hepatitis-related polyarteritis nodosa and Kawasaki disease)

Public Comments

RESPONSES RECEIVED VIA EMAIL:

- **Name:** Liesbeth Brouwer and Maria Sandovici
- **Institution:** University Medical Center Groningen (Netherlands)
- **Position:** Not provided
- **Disclosure (optional):** Nothing to disclose

Comment:
This is a great initiative and a tremendous amount of work to be done! We found the PICO questions appropriate. We however miss:

1. PICO questions regarding organisation of care around diagnosis and follow-up of these vasculitis patients.
2. Effects of glucocorticoids on imaging as diagnosis and follow-up tools (FDG-PET, ultrasound, MRI-MRA); this should be taken into account in the diagnosis and/or treatment part of the guidelines.
3. In addition, one small detail: GCA A3. Manifestation of cranial ischemia are not limited to visual symptoms; jaw or tong claudication are also signs of cranial ischemia.

Genentech
A Member of the Roche Group

American College of Rheumatology
2200 Lake Boulevard NE
Atlanta, GA 30319

Dear ACR Vasculitis Guideline Committee Members:

Thank you for the opportunity to comment on the American College of Rheumatology (ACR) Vasculitis Guideline Project Plan. We applaud ACR's efforts in developing this evidence-based clinical practice guideline for the treatment and management of systemic vasculitis, as well as facilitating an open source, transparent process for key stakeholders to provide input.

Page 2, Background: Lines 22-24

Consider including small vessel vasculitis in the scope for this project plan.

- Although the European League Against Rheumatism (EULAR) developed guidelines for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), there is still a need for US based clinical guidelines to help in treatment-making decisions for both pediatric and adult patients with small vessel vasculitis.[1,2] There are ongoing studies to validate new classification criteria and patient reported outcomes (PROs) to support ongoing guideline development for this population of patients with AAV.[3,4] A guidance in this rare disease which affects fewer than 200,000 patients in the US, would be useful for the US physicians, who often refer to ACR's educational resources.[5-8]
- Emerging clinical evidence is available for patients suffering from these conditions, including data for Rituxan® (rituximab), which is the only FDA-approved drug for the treatment of granulomatosis with polyangiitis/microscopic polyangiitis (GPA/MPA).[9-16] Additionally, the RITAZAREM trial will provide the largest trial dataset for the use of Rituxan as remission-induction therapy for patients with AAV comparing two remission-maintenance strategies following induction with Rituxan. It will also explore whether prolonged B-cell depletion leads to sustained treatment-free remission after discontinuation of immunosuppressive therapy.[17,18] Lastly, RAVER is an ongoing open-label real-world study of adult patients with GPA or MPA treated with Rituxan, aiming to characterize safety events in the observational registry.[19]

Page 13, Giant Cell Arteritis (GCA), Definitions: A. Disease States, #1-6: Lines 317-324

Consider adding active disease (newly diagnosed and relapsing/refractory) with comorbidities as a separate disease state and patient population.

- Patients with GCA have higher rates of selected comorbidities, including severe infections, polymyalgia rheumatica, visual disturbances, facial pain, osteoporosis, cardiovascular diseases, diabetes, cataracts and hypokalemia; several of these are related to corticosteroid use.[20,21]
- Approximately 80% of patients with GCA exposed to long-term corticosteroid use experience treatment-related adverse events (AEs), contributing to these comorbidities.[22] Controlling disease acute symptoms while minimizing glucocorticoid exposure in this patient population in which comorbidities are common, is necessary.

Page 14, Giant Cell Arteritis (GCA), Definitions: D. Disease-related Outcomes, #6. Patient Reported Outcomes: Lines 349-350

Consider all PROs as equally valuable, since each represents individual patient feedback.

Consider measuring Fatigue as a PRO.

- Fatigue is considered an important measure of disease burden in predicting outcomes in vasculitis.[23] In the exploratory analysis of the GiACTA phase III randomized, placebo-controlled trial which evaluated Actemra® (tocilizumab) in combination with a tapering course of glucocorticoids as compared with glucocorticoids alone, the combination therapy with Actemra

demonstrated greater improvements in health-related quality of life and fatigue as compared to those treated with prednisone alone.[24]

Page 18, Giant Cell Arteritis (GCA), PICO Questions: B. Medical Treatment, #20-23: Lines 425-436

Consider evaluating patients with relapsing or refractory GCA and the impact of glucocorticoids alone versus Actemra in combination with a tapering course of glucocorticoids on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events.

- GCA is a chronic and often relapsing disease, with approximately 50% and 80% of patients experiencing a relapse within one year to 5 years.[25] In the GiACTA trial, 53% of patients enrolled had relapsing disease.[26]
- If the initial glucocorticoids doses fail to control disease activity, they are usually increased and cumulative exposure highly correlates with treatment-related AEs.[22] Therefore, there is a need to prevent relapsing or refractory GCA and sustain disease remission using treatment options that reduce the steroid burden.

Specify the non-glucocorticoid immunosuppressive agents in questions 21 and 22.

Specify the immunosuppressive agents which will be escalated in patients with rising inflammatory markers in question 23.

Page 18, Giant Cell Arteritis (GCA), PICO Questions: C. Surgical Interventions, #24: Lines 439-441

Specify the immunosuppressive agents used in GCA patients with severe disease.

Please refer to the full Actemra and Rituxan prescribing information for complete product indication and safety information available at:

http://www.gene.com/download/pdf/actemra_prescribing.pdf
http://www.gene.com/download/pdf/rituxan_prescribing.pdf

We hope this information is helpful and we welcome the opportunity to provide clarification if there are any questions. Please contact me directly at (650) 438-7938 or tominna.lenore@gene.com.

Respectfully Submitted,

Lenore Tominna, PharmD
Managed Care Medical Communications
U.S. Medical Affairs, Genentech, Inc.

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