Authors' Response to Public Comments on the
Project Plan for the ACR Vasculitis Guideline Project Plan (TAK, GCA, PAN, KD)

July 2018

Introduction

The American College of Rheumatology (ACR) is developing guidelines for the management of patients with Takayasu arteritis, giant cell arteritis, polyarteritis nodosa, and Kawasaki disease using the GRADE methodology. In this methodology, the literature search is based on PICO (Population, Intervention, Comparator, Outcomes) questions in which the populations of interest are defined and the outcomes (benefits and harms) of two interventions are compared. The PICO questions that will inform the literature search for these 4 vasculitides were developed by the ACR Vasculitis Guidelines committee and were posted for public comment on the ACR website March 27, 2018. The ACR Vasculitis Guidelines core oversight team reviewed the comments and address them below.

Public Comments on Takayasu's Arteritis (TAK) and Large Vessel Vasculitis (LVV)

We appreciate the comments and suggestions submitted by the rheumatology community regarding large vessel vasculitis (LVV) in general and Takayasu's arteritis (TAK) in specific. We recognize that other entities such as isolated aortitis and IgG4-related disease may be viewed as a large vessel vasculitides. However, we are using the 2012 Revised International Chapel Hill Consensus Conference nomenclature as our classification framework for these guidelines. This nomenclature system recognizes isolated aortitis as a single organ vasculitis, and IgG4-related disease has not been included thus far. Future nomenclature systems may include these entities as large vessel vasculitides and additional recommendations based on available evidence will have to be made.

With regards to disease activity, we believe that a clear definition and understanding of disease activity in LVV is yet to be developed but we agree that the Birmingham Disease Activity Score (BVAS) may not be an optimal tool to assess disease activity in TAK. We have included additional tools to assess disease activity in TAK, such as the National Institute of Health definition of active disease (1), Disease Extent Index-Takayasu (DEI-Tak) (2) and the Indian Takayasu's Activity Score 2010 (ITAS2010) (3) as additional tools to assess disease activity in TAK. We also recognize the important role of non-invasive imaging in the assessment of disease activity in TAK and have added PICO questions to address management of patients with apparent clinical remission but "active" disease on imaging.

As for the treatment of TAK, we have added biologics to the therapeutic armamentarium, such as abatacept, rituximab, and ustekinumab for the treatment of TAK as more studies describing their use is being added to the medical literature. While some studies may suggest that 7.5 mg of prednisone or equivalent and less should be considered "low-dose" glucocorticoids, we have kept 10 mg of prednisone or equivalent and less as a definition of "low-dose" glucocorticoids in congruence with other guidelines. We do agree however that the lowest possible dose of glucocorticoids should be aimed for to control disease activity in TAK. We have added questions to address management of renovascular hypertension and atherosclerosis in patients with TAK.

References:

1. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. Ann Intern Med 1994;120:919-29.
2. Aydin SZ, Yilmaz N, Akar S, Aksu K, Kamali S, Yucel E, et al. Assessment of disease activity and progression in Takayasu's arteritis with Disease Extent Index-Takayasu. Rheumatology (Oxford) 2010;49:1889-93.
3. Misra R, Danda D, Rajappa SM, Ghosh A, Gupta R, Mahendranath KM, et al. Development and initial validation of the Indian Takayasu Clinical Activity Score (ITAS2010). Rheumatology (Oxford) 2013;52:1795-801.

Public Comments on Giant Cell Arteritis (GCA)

Comments from the rheumatology community included whether the group should provide questions, analyses and recommendations for patients with LVV who do not neatly fit into typical diagnostic categories and those who have forms of LVV other than GCA and Takayasu's arteritis (e.g., IgG4-related disease, clinically-isolated aortitis, etc.). As discussed above, while these are important issues that deserve to be addressed, they are beyond the scope of the Committee's current charge and have been recently reviewed in detail by others (1-5).

Others questioned whether the committee should explore the utility of routine ophthalmology evaluation for all patients with GCA vs. only those who have visual symptoms, the utility of routine periodic large vessel imaging vs. imaging only by clinical indication, complications of biopsies and other diagnostic (e.g., imaging) procedures, the risks and benefits of increasing perioperative glucocorticoid therapy in LVV, and whether there is a role for statin therapy in patients with LVV. These questions will be addressed either through formal literature review based on PICO questions or expert guidance discussions.

Given the broad scope of the overall guideline effort, queries based on opinion or case reports will be deferred at this time.

References:

1. Stone JR, Bruneval P, Angelini A, Bartoloni G, Basso C, Batoroeva L et al. Consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology: I. Inflammatory diseases. Cardiovasc Pathol 2015;24:267-78.
2. Cinar I, Wang H, Stone JR. Clinically isolated aortitis: pitfalls, progress and possibilities. Cardiovasc Pathol 2017;29:23-32.
3. Svensson LG, Arafat A, Roselli E, Idrees J, Clifford A, Tan C et al. Inflammatory disease of the aorta: patterns and classification of giant cell aortitis, Takayasu arteritis and non-syndromic aortitis. J Thorac Cardiovasc Surg 2015;149(Suppl 2):S170-5.
4. Stone JH, Khosroshahi A, Hilgenberg A, Spooner A, Isselbacher EM, Stone JR. IgG4-related systemic disease and lymphoplasmacytic aortitis. Arthritis Rheum 2009;60:3139–45.
5. Perugino CA, Wallace ZS, Meyersohn N, Oliveira G, Stone JR, Stone JH. Large vessel involvement by IgG4-related disease. Medicine (Baltimore) 2016;95:e3344.

Public Comments on Polyarteritis Nodosa (PAN)

We agree and appreciate the importance of utilizing the most sensitive measure to determine the disease activity for polyarteritis nodosa (PAN) and other vasculitides. We acknowledge that the Five Factor Score (FFS) has been used to direct decisions about treatment in the presence of poor prognostic factors. However, the FFS was developed to assess disease severity and prognosis at the time of diagnosis. The FFS has not been validated as a clinical tool to measure disease activity, whereas Birmingham Vasculitis Activity Score (BVAS) has been validated as a disease activity tool and employed as such in clinical trials (1-3).

We recognize the importance of identifying deficiency of adenosine deaminase 2 (DADA2) as a specific entity within the framework of vasculitides. We plan to include introductory comments about the role of testing for DADA2 and have included a question regarding treatment in the revised PICO questions. We will discuss within the management guidelines manuscript the role of screening for possible infectious etiologies of medium/small vessel vasculitis (e.g., Hepatitis B, Hepatitis C and HIV) (4). We will also discuss the role of nerve and muscle biopsies in the diagnosis of PAN.

Per submitted suggestions, we will include "central nervous system involvement" in the "Severe Disease States #3" of the PAN management guidelines.

Public comments noted that some of the clinical trials in PAN have included mixed cohorts of PAN with microscopic polyangiitis (MPA) and/or eosinophilic granulomatosis with polyangiitis (EGPA), which influence outcomes and decision-making for treatment. We intend to address this concern in our literature review and within the management guidelines manuscript.

References:

1. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, Thibult N, Casassus P. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore) 1996;75:17-28.
2. Ribi C, Cohen P, Pagnoux C, Mahr A, Arène J, Puéchal X, Carli P, Kyndt X, Le Hello C, Letellier P, Cordier J, Guillevin L; French Vasculitis Study Group. Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: a prospective randomized study of one hundred twenty-four patients. Arthritis Rheum 2010;62:1186-1197.
3. Mukhtyar C, Lee R, Brown D, Carruthers D, Dubey S, Flossman O, Haal C, Hollywood J, Jayne D, Jones R, Lanyon P, Muir A, Scott D, Young L, Luqmani RA. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009;68:1827.
4. Samson, M, Puechal X, Devilliers H, Ribi C, Pascal C, Bienvenu B, Terrier B, Pagnoux C, Mouthon L, Guillevin L; for the French Vasculitis Study Group (FVASG). Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors. Autoimm Rev. 2008;13:945-953.

Public Comments on Kawasaki Disease (KD)

We appreciate the community's recommendations to include expertise outside of rheumatology (e.g., cardiology or infectious disease) and individuals outside of the United States. We have considered including these individuals at different times during the guideline development effort, including the initial formation of the voting and expert panels. However, the goal of this effort is to provide management guidelines for rheumatologists in situations where they are more likely to be involved in the management of Kawasaki Disease (KD) – for example, when glucocorticoids or other immunosuppressive agents are being considered, incomplete KD may be present, or non-cardiac manifestations may persist. As in other ACR guideline development efforts, rheumatologists outside of the United States have not been included given differences in practice patterns and availability of treatments between different countries.

In addition, there were suggestions for including disease assessment scores as outcomes, recommendations for long-term follow-up, and recommendations for management of adults with KD. In KD, disease-related outcomes and long-term morbidity are almost exclusively influenced by the extent of coronary artery involvement. Thus, more complex disease activity scores such as the BVAS or PVAS (1) are generally not necessary. Recommendations for long-term follow-up are generally based on the degree of coronary artery involvement, and thus have been provided by cardiologists (2).

Lastly, given the rarity and lack of data for the management of KD in adults, we have not formulated separate questions addressing KD in adults.

References:

1. Dolezalova P, Price-Kuehne FE, Özen S et al. Disease activity assessment in childhood vasculitis: development and preliminary validation of the Paediatric Vasculitis Activity Score (PVAS). Ann Rheum Dis 2013;72(10):1628-33.
2. McCrindle BW, Rowley AH, Newburger JW et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation 2017; Apr 25;135(17):e927-e999.