Development of a Core Set of Outcome Measures for Large-Vessel Vasculitis: Report from OMERACT 2016

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Abstract

Objectives: Among the challenges in conducting clinical trials in large-vessel vasculitis (LVV), including both giant cell arteritis (GCA) and Takayasu's arteritis (TAK) is the lack of standardized and meaningful outcome measures. The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group initiated an international effort to develop and validate data-driven outcome tools for clinical investigation in LVV.

Methods: An international Delphi exercise was completed to gather opinions from clinical experts on LVV-related domains considered important to measure in trials. Patient interviews and focus groups were completed to identify outcomes of importance to patients. The results of these activities were presented and discussed in a "virtual Special Interest Group" using telephone and internet-based conferences, discussions via electronic mail, and an in-person session at the 2016 OMERACT meeting. A preliminary core set of domains common for LVV with disease-specific elements was proposed.

Results: More than 60% of experts agree with using common outcome measures for GCA and TAK, with the option of supplementation with disease-specific items. Following interviews and focus groups, pain, fatigue and emotional impact emerged as health-related quality of life domains important to patients. Current disease assessment tools, including the Birmingham Vasculitis Activity Score, were found to be suboptimal to assess disease activity in GCA and standardized assessment of imaging tests were felt crucial to study LVV, especially TAK.

Conclusion: Research on outcome measures in LVV continues to evolve to reach an OMERACT-endorsed core set of domains and outcome measures.

Introduction:

Several vasculitides fall under the definition of large-vessel vasculitis (LVV), including giant cell arteritis (GCA) and Takayasu's arteritis (TAK) (1). Clinical research in LVV has been hindered by the lack of standardized outcome measures (2). The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group leads efforts to develop and advance development outcome measures in vasculitis, including LVV. Leading up to and during the 2016 OMERACT meeting, a "virtual Special Interest Group" was conducted to discuss the current research findings and propose a preliminary core set of domains. The main discussion points were: a) results of the international LVV Delphi (manuscript submitted); b) findings of the qualitative studies in TAK (manuscript in preparation); and c) current work on LVV disease activity and damage measures (Abstracts at OMERACT). Following the discussion, a preliminary core set of domains common to LVV with disease-specific elements was proposed.

Methods/Results:

Delphi exercise:

Given the lack of international consensus on outcome measures to assess LVV, the LVV Task Force conducted an international Delphi exercise to obtain experts' opinions regarding important disease domains for the assessment of disease outcomes in LVV (manuscript submitted for publication). Key findings emerging from this exercise include: i) many domains were common to TAK and GCA but some were distinctly identified with one or the other disease; ii) patient global assessment (PtGA) was accepted as a tool to assess patient-reported outcomes (PRO) in LVV; iii) the majority of experts agreed to have a common outcome measure tool for both GCA and TAK but that such a measure also be supplemented by disease-specific items for trials of GCA and TAK.

Patient interviews/qualitative research:

Generic PRO instruments such as the 36-item short form health survey (SF-36) and PtGA have been previously examined in patients with LVV (3-6). However, these instruments often lack the granularity and ability to capture essential disease-specific domains that are of high importance to patients with LVV. The LVV Task Force has completed individual interviews and focus groups with patients in the United States and Turkey to identify key health-related domains that patients consider important in TAK. Thirty-one patients participated. The most common themes and domains that emerged were pain and discomfort, fatigue and low energy levels, and emotional impact; a manuscript detailing this work has been prepared. Similar qualitative

research is now being planned for patients with GCA to identify similarities and differences between the two diseases.

The OMERACT SIG group felt the results of these data about patient preferences should be combined with the results of the Delphi about physician opinions to form the basis of the draft core set of domains.

Assessment of disease activity:

There currently exists no clear definition of disease activity in LVV. Several disease activity assessment tools have been used in clinical trials of LVV. These tools often use a combination of clinical symptoms, cumulative glucocorticoid dose/duration and acute phase reactants. In terms of a single tool, The NIH criteria for active disease (7), the Birmingham Vasculitis Activity Score (BVAS)(8), the Disease Extent Index for Takayasu's arteritis (DEI.Tak)(9), and the Indian Takayasu's Arteritis Score 2010 (ITAS2010) (10, 11) have all been used in clinical research for TAK (12-14). A similar disease-specific tool does not exist for GCA and a recent study lead by investigators within the OMERACT Vasculitis Working Group found BVAS to have limited utility in GCA (19). A combination of clinical symptoms, glucocorticoids dose or duration, and/or BVAS has been used in clinical trials of GCA (13, 15-18).

Imaging has emerged as a promising diagnostic and critical tool to follow the disease course of patients with LVV. Imaging modalities for LVV include color duplex ultrasonography (20-22), computed tomography angiography (23, 24), magnetic resonance angiography (25-28), and 18F fluorodeoxyglucose positron emission tomography either alone or with computed tomography

(29-32). These modalities differ in terms of test characteristics, cost, exposure to radiation, and availability. While there have been tremendous advances in imaging technologies in recent years, there is a need for formal validation of imaging modalities for correlation with activity, damage, and outcome in LVV. There remain major uncertainties about the meaning of radiographic changes in arterial walls (thickening, enhancement, high signal) regarding disease activity and prognosis.

Assessment of disease damage:

Besides the Takayasu's Arteritis Damage Score, there have been no other disease-specific damage indices validated for LVV (33). While the Vasculitis Damage Index (VDI) has been used to assess damage in LVV (34, 35) this tool is non-specific, includes all-cause damage, and contains many items that are irrelevant to LVV. The OMERACT LVV Task Force recently completed validation studies of VDI and a new LVV damage tool called the Large Vessel Vasculitis Index of Damage (LVVID) in GCA and TAK. The results of these studies were discussed and presented as posters at OMERACT 2016 and will be published separately.

Data and insights expected from trials conducted recently/ongoing:

Despite the lack of standardized outcome measures, several randomized clinical trials of LVV have been conducted recently with various success. In particular, four major clinical trials examining the role of various biologic medicines are of interest: A randomized trial of abatacept for the treatment of LVV (AGATA: https://clinicaltrials.gov/ct2/show/NCT00556439), a phase 2 randomized trial of tocilizumab in GCA(18), a phase III randomized trial of tocilizumab in GCA

(GiACTA) (36), and a phase III randomized trial of sirukumab in GCA (SIRRESTA: https://clinicaltrials.gov/ct2/show/NCT02531633). Outcome definitions for these clinical trials are similar and use a combination of relapse-free survival, cumulative glucocorticoid dose/duration, physician global assessment, acute phase reactants, and patient-reported outcomes. Furthermore, using patients' symptoms and acute phase reactants as indicators of disease activity may prove suboptimal given the potential for ongoing inflammation in asymptomatic patients (7) and the lack of appropriate specificity and sensitivity of acute phase reactants (37, 38). Additionally, using a dichotomous outcome measure such as active disease versus remission may miss a scale of response that is not necessarily captured in relapse-free survival assessment. Finally, if the recently-studied biologic therapies prove to be highly effective as glucocorticoid-sparing agents in LVV, they may alter the need or approach to measure cumulative glucocorticoid dose/duration variable as an outcome measure.

The OMERACT SIG group recognizes that new measures of disease activity in LVV need to be developed that incorporate several approaches, including PROs and imaging. It is anticipated that analysis of data from recently-completed and ongoing clinical trials in GCA and TAK will help advance disease assessment in LVV.

Proposal of a preliminary core set of domains in LVV:

As previously mentioned, the majority of experts in LVV voted through the Delphi exercise to have common outcome domains and measures for GCA and TAK supplemented with disease-

specific elements. The benefits to having common measures include generalizability, ease of implementation, and potential applicability to other LVVs like idiopathic aortitis.

During the OMERACT LVV SIG the group proposed a preliminary set of core domains for use in clinical trials of LVV (Figure 1) that includes a core set of domains with additional disease-specific elements. This approach to domain selection is congruent with the OMERACT Filter 2.0 methodology, including the 2 major concepts of impact of health conditions and pathophysiologic manifestations, and the 3 mandatory core areas of death, life impact, and pathophysiological manifestations.

Summary and future research agenda:

Steady progress that has been made to develop a set of outcome measures useful in clinical trials of LVV. The Delphi exercise identified domains of interest and outcome measures for the assessment of LVV and highlighted the importance of having a common set of domains and outcome measures for GCA and TAK, supplemented with disease-specific elements. The qualitative research identified domains of importance to patients from their own perspectives. Validation studies of the current disease activity and damage tools including BVAS and VDI underlined the shortcomings of these assessment tools in LVV. A draft initial core set of domains were developed for LVV. The following future steps have been planned:

1- Publish the results of the Delphi exercise, qualitative studies in TAK, and analyses of damage assessment tools in LVV.
2- Initiate qualitative interviews with patients with GCA to identify key themes and domains of high importance to patients with GCA.
3- Determine the differences and commonalities between GCA and TAK regarding disease experience that can assist in identifying disease-specific domains of interest.
4- Consider whether there is a strong need to develop a disease-specific PRO for GCA and/or TAK.
5- Incorporate data on the utility of imaging modalities in GCA and TAK into the outcome development program for LVV.
6- Finalize a draft core set of domains and identify the best candidate tools to measure these domains.
7- Test the draft core set of outcomes in cohorts and trials.

It is the ultimate goal OMERACT Vasculitis Working Group LVV Task Force to develop an OMERACT-endorsed, internationally-recognized core set of outcome measures for LVV for use in clinical trials.

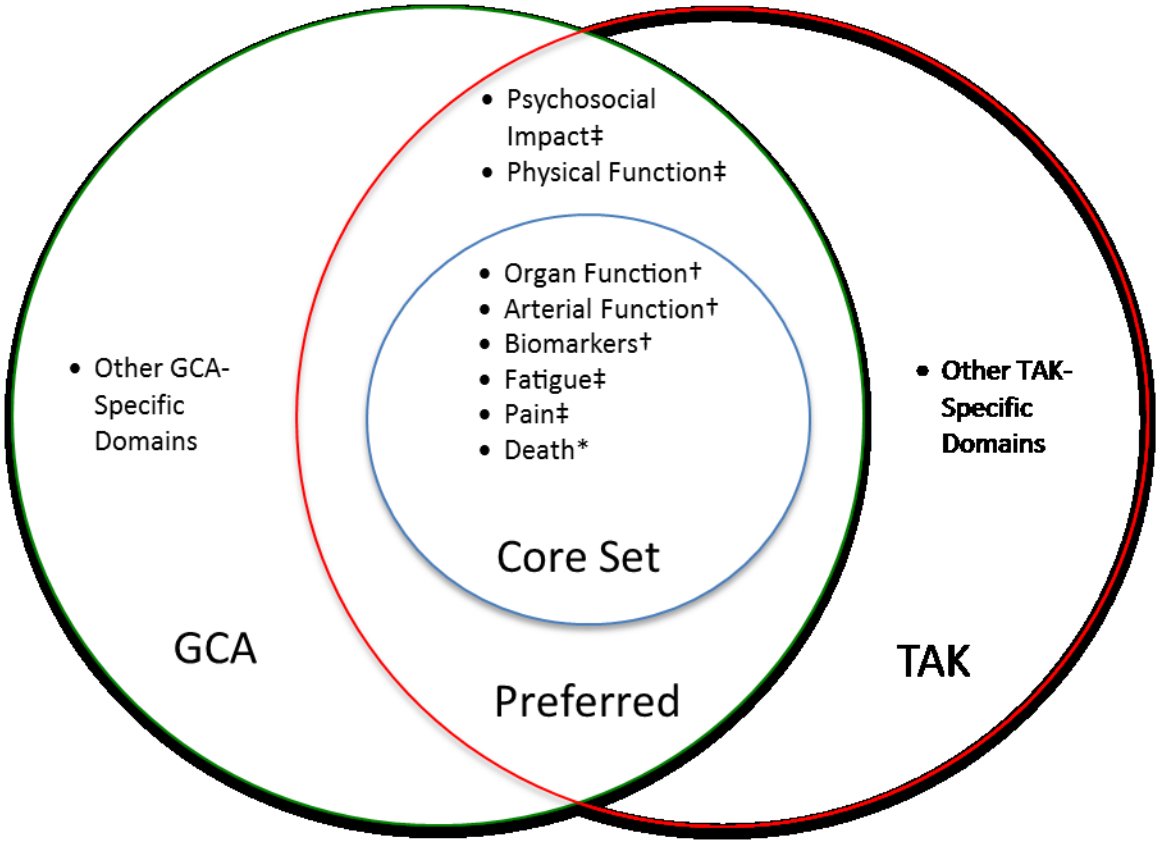

Figure 1. A draft core set (mandatory) and additional preferred domains i) common to both giant cell arteritis (GCA) and Takayasu's arteritis (TAK), and ii) separate disease-specific domains. The suggested core domains fall under the mandatory core areas of OMERACT filter 2.0: *Death, ‡life impact, and †pathophysiologic manifestations.

References:

1. Furuta S, Cousins C, Chaudhry A, Jayne D**.** Clinical features and radiological findings in large vessel vasculitis: are Takayasu arteritis and giant cell arteritis 2 different diseases or a single entity? J Rheumatol 2015;42:300-8.
2. Aydin SZ, Direskeneli H, Sreih A, Alibaz-Oner F, Gul A, Kamali S, et al. Update on Outcome Measure Development for Large Vessel Vasculitis: Report from OMERACT 12. J Rheumatol 2015;42:2465-9.
3. Yilmaz N, Can M, Oner FA, Kalfa M, Emmungil H, Karadag O, et al. Impaired quality of life, disability and mental health in Takayasu's arteritis. Rheumatology (Oxford) 2013;52:1898-904.
4. Akar S, Can G, Binicier O, Aksu K, Akinci B, Solmaz D, et al. Quality of life in patients with Takayasu's arteritis is impaired and comparable with rheumatoid arthritis and ankylosing spondylitis patients. Clin Rheumatol 2008;27:859-65.
5. Abularrage CJ, Slidell MB, Sidawy AN, Kreishman P, Amdur RL, Arora S**.** Quality of life of patients with Takayasu's arteritis. J Vasc Surg 2008;47:131-6; discussion 36-7.
6. Kupersmith MJ, Speira R, Langer R, Richmond M, Peterson M, Speira H, et al. Visual function and quality of life among patients with giant cell (temporal) arteritis. J Neuroophthalmol 2001;21:266-73.
7. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. Ann Intern Med 1994;120:919-29.
8. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM 1994;87:671-8.
9. 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.
10. 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.
11. Alibaz-Oner F, Aydin SZ, Akar S, Aksu K, Kamali S, Yucel E, et al. Assessment of Patients with Takayasu Arteritis in Routine Practice with Indian Takayasu Clinical Activity Score. J Rheumatol 2015;42:1443-7.
12. Hoffman GS, Merkel PA, Brasington RD, Lenschow DJ, Liang P**.** Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. Arthritis Rheum 2004;50:2296-304.
13. Henes JC, Mueller M, Pfannenberg C, Kanz L, Koetter I**.** Cyclophosphamide for large vessel vasculitis: assessment of response by PET/CT. Clin Exp Rheumatol 2011;29:S43-8.

14. Goel R, Danda D, Mathew J, Edwin N. Mycophenolate mofetil in Takayasu's arteritis. Clin Rheumatol 2010;29:329-32.

15. Mahr AD, Jover JA, Spiera RF, Hernandez-Garcia C, Fernandez-Gutierrez B, Lavalley MP, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. Arthritis Rheum 2007;56:2789-97.

16. De Silva M, Hazleman BL. Azathioprine in giant cell arteritis/polymyalgia rheumatica: a double-blind study. Ann Rheum Dis 1986;45:136-8.

17. Seror R, Baron G, Hachulla E, Debandt M, Larroche C, Puechal X, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicentre randomised controlled trial. Ann Rheum Dis 2014;73:2074-81.

18. Villiger PM, Adler S, Kuchen S, Wermelinger F, Dan D, Fiege V, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet 2016;387:1921-7.

19. Kermani TA, Cuthbertson D, Carette S, Hoffman GS, Khalidi NA, Koening CL, et al. The Birmingham Vasculitis Activity Score as a Measure of Disease Activity in Patients with Giant Cell Arteritis. J Rheumatol 2016;43:1078-84.

20. Sinha D, Mondal S, Nag A, Ghosh A. Development of a colour Doppler ultrasound scoring system in patients of Takayasu's arteritis and its correlation with clinical activity score (ITAS 2010). Rheumatology (Oxford) 2013;52:2196-202.

21. Schmidt WA, Blockmans D. Use of ultrasonography and positron emission tomography in the diagnosis and assessment of large-vessel vasculitis. Curr Opin Rheumatol 2005;17:9-15.

22. Karassa FB, Matsagas MI, Schmidt WA, Ioannidis JP. Meta-analysis: test performance of ultrasonography for giant-cell arteritis. Ann Intern Med 2005;142:359-69.

23. Prieto-Gonzalez S, Arguis P, Garcia-Martinez A, Espigol-Frigole G, Tavera-Bahillo I, Butjosa M, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. Ann Rheum Dis 2012;71:1170-6.

24. Prieto-Gonzalez S, Garcia-Martinez A, Tavera-Bahillo I, Hernandez-Rodriguez J, Gutierrez-Chacoff J, Alba MA, et al. Effect of glucocorticoid treatment on computed tomography angiography detected large-vessel inflammation in giant-cell arteritis. A prospective, longitudinal study. Medicine (Baltimore) 2015;94:e486.

25. Tso E, Flamm SD, White RD, Schvartzman PR, Mascha E, Hoffman GS. Takayasu arteritis: utility and limitations of magnetic resonance imaging in diagnosis and treatment. Arthritis Rheum 2002;46:1634-42.

26. Papa M, De Cobelli F, Baldissera E, Dagna L, Schiani E, Sabbadini M, et al. Takayasu arteritis: intravascular contrast medium for MR angiography in the evaluation of disease activity. AJR Am J Roentgenol 2012;198:W279-84.

27. Koenigkam-Santos M, Sharma P, Kalb B, Oshinski JN, Weyand CM, Goronzy JJ, et al. Magnetic resonance angiography in extracranial giant cell arteritis. J Clin Rheumatol 2011;17:306-10.

28. Klink T, Geiger J, Both M, Ness T, Heinzelmann S, Reinhard M, et al. Giant cell arteritis: diagnostic accuracy of MR imaging of superficial cranial arteries in initial diagnosis-results from a multicenter trial. Radiology 2014;273:844-52.

29. Fuchs M, Briel M, Daikeler T, Walker UA, Rasch H, Berg S, et al. The impact of 18F-FDG PET on the management of patients with suspected large vessel vasculitis. Eur J Nucl Med Mol Imaging 2012;39:344-53.

30. Soussan M, Nicolas P, Schramm C, Katsahian S, Pop G, Fain O, et al. Management of large-vessel vasculitis with FDG-PET: a systematic literature review and meta-analysis. Medicine (Baltimore) 2015;94:e622.

31. Umekita K, Takajo I, Miyauchi S, Tsurumura K, Ueno S, Kusumoto N, et al. [18F]fluorodeoxyglucose positron emission tomography is a useful tool to diagnose the early stage of Takayasu's arteritis and to evaluate the activity of the disease. Mod Rheumatol 2006;16:243-7.

32. Blockmans D, Bley T, Schmidt W**.** Imaging for large-vessel vasculitis. Curr Opin Rheumatol 2009;21:19-28.

33. Rajappa SM**.** Outcome of Vascular Interventions in Takayasu Arteritis Using the Takayasu Arteritis Damage Score. Arthritis and Rheumatism 2011;63:S588-S88.

34. Omma A, Erer B, Karadag O, Yilmaz N, Oner FA, Yildiz F, et al. Cross-Sectional Assessment of Damage in Takayasu Arteritis with a Validated Tool. Annals of the Rheumatic Diseases 2012;71:224-24.

35. Omma A, Erer B, Karadag O, Yilmaz N, Alibaz-Oner F, Yildiz F, et al. Remarkable Damage along with poor quality of life in Takayasu arteritis: cross-sectional results of a long-term followed-up multi-center cohort. Clin Exp Rheumatol 2016;In press.

36. Unizony SH, Dasgupta B, Fisheleva E, Rowell L, Schett G, Spiera R, et al. Design of the tocilizumab in giant cell arteritis trial. Int J Rheumatol 2013;2013:912562.

37. Salvarani C, Cantini F, Boiardi L, Hunder GG**.** Laboratory investigations useful in giant cell arteritis and Takayasu's arteritis. Clin Exp Rheumatol 2003;21:S23-8.

38. Kermani TA, Schmidt J, Crowson CS, Ytterberg SR, Hunder GG, Matteson EL, et al. Utility of erythrocyte sedimentation rate and C-reactive protein for the diagnosis of giant cell arteritis. Semin Arthritis Rheum 2012;41:866-71.