Update on Outcome Measure Development for Large Vessel Vasculitis: Report from OMERACT 12

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ABSTRACT. ***Objective.*** The rarity of large vessel vasculitis (LVV) is a major factor limiting randomized controlled trials in LVV, resulting in treatment choices in these diseases that are guided mainly by observational studies and expert opinion. Further complicating trials in LVV is the absence of validated and meaningful outcome measures. The Outcome Measures in Rheumatology (OMERACT) vasculitis working group initiated the Large Vessel Vasculitis task force in 2009 to develop data-driven, validated outcome tools for clinical investigation in LVV. This report summarizes the progress that has been made on a disease activity assessment tool and patient-reported outcomes in LVV as well as the group's research agenda.

Methods. The OMERACT LVV task force brought an international group of investigators and patient research partners together to work collaboratively on developing outcome tools. The group initially focused on disease activity assessment tools in LVV. Following a systematic literature review, an international Delphi exercise was conducted to obtain expert opinion on principles and domains for disease assessment. The OMERACT vasculitis working group's LVV task force is also conducting qualitative research with patients, including interviews, focus groups, and engaging patients as research partners, all to ensure that the approach to disease assessment includes measures of patients' perspectives and that patients have input into the research agenda and process.

Results. The preliminary results of both the Delphi exercise and the qualitative interviews were discussed at the OMERACT 12 (2014) meeting and the completion of the analyses will produce an initial set of domains and instruments to form the basis of next steps in the research agenda.

Conclusion. The research agenda continues to evolve, with the ultimate goal of developing an OMERACT-endorsed core set of outcome measures for use in clinical trials of LVV. (First Release June 15 2015; J Rheumatol 2015;42:2465–9; doi:10.3899/jrheum.141144)

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Large vessel vasculitis (LVV) is a group of rare types of vasculitis that mainly affect the aorta and its branches. Giant cell arteritis (GCA) and Takayasu arteritis (TA) are the most common forms of LVV, although each disease is also rare[1,2]. There is evidence supporting the hypothesis that GCA and TA may not be distinct entities, but represent phenotypes within the spectrum of a single disorder[3,4]. GCA and TA may both present with similar clinical manifestations, as well as similar arterial histopathology revealing granulomatous inflammation.

Although there are many similarities between these 2 subtypes of LVV, they also have distinct features, most notably the demographics of affected populations. TA mostly occurs in women aged < 40 years and is more frequent in women from the Middle East and Asia, whereas GCA is mostly seen in people aged > 50 years with a strong predominance of white Europeans; there is also a female predominance in GCA[5,6].

As with most orphan diseases, the rarity of LVV is a major factor limiting the conduct of randomized controlled trials (RCT), and treatment choices in LVV are guided mainly by observational studies and expert opinion. Another reason for the lack of RCT for the treatment of LVV is the absence of validated and meaningful outcome measures for use in clinical trials[7,8]. What is required is an outcome measurement tool that passes the Outcome Measures in Rheumatology (OMERACT) filter of truth, discrimination, and feasibility[9].

The discussions held and progress made at OMERACT 12 (2014) by the Large Vessel Vasculitis Special Interest Group resulted from several years of work by the OMERACT vasculitis working group to assemble an international group of investigators and patient research partners to collaboratively develop data-driven validated outcome tools for clinical investigation in LVV. Given the absence of any well-accepted validated outcome measurement tools in both GCA and TA, the OMERACT meeting also included a discussion on whether 1 tool can be used in both diseases. Initially, disease activity assessment and patient-reported outcomes (PRO) were included in the agenda, and this report summarizes the progress that has been made on these domains as well as the group's research agenda.

Disease Activity Assessment in LVV

Despite many attempts to adopt standardized approaches to disease activity assessment in LVV, no one measure or set of measures has been accepted as valid and useful for clinical trials[7]. Many studies use a combination of clinical symptoms sometimes linked to changes in acute-phase reactants. In terms of a single activity measure, the Birmingham Vasculitis Activity Score (BVAS) is an index that has been developed and best validated for use in antineutrophil cytoplasmic antibody (ANCA) -associated vasculitis[10], but few studies of LVV have incorporated BVAS[11]. However, the differences in organ involvement in small- versus large-vessel vasculitis raise major concerns about using a common index for both classes of vasculitis[12]. BVAS includes many data elements that are unnecessary and unrelated to LVV and has few of the cardiovascular elements of prime importance to LVV. The Disease Extent Index-Takayasu (DEI-Tak) was created with the goal of better assessing the extent of the disease, rather than assessing disease activity[13]. DEI-Tak was derived from BVAS but includes a more detailed recording of cardiovascular findings. Nonetheless, the DEI-Tak includes rarely used items, is often incongruent with physician global assessments, and does not take into account imaging findings or acute-phase reactants[14]. The ITAS2010 (Indian Takayasu's Arteritis Activity Score 2010), an index modified from DEI-Tak, scores only clinical features newly present in the prior 3 months and has a weighting system with another version, the ITAS2010-A, that includes acute-phase reactants[15]. However, the correlation between ITAS2010 and physician global assessment is still insufficient, and the tool has not been widely adopted for use in research. No similar efforts have been made to develop a new single instrument for GCA.

Given the lack of consensus on definitions to assess disease activity in LVV, the OMERACT vasculitis working group's LVV task force initiated an international Delphi exercise to ask experts which disease domains and clinical manifestations should be used in disease activity assessment tools in TA and GCA (manuscript in preparation). Because there are variations in manifestations and prognosis depending on ethnicity, the Delphi exercise was disseminated to experts in several medical specialties, in many countries, and on several continents. The results of the Delphi exercise were discussed at OMERACT 12 and will be published separately; an extensive list of domains was produced, including constitutional symptoms, items related to major organ involvement, and a detailed assessment of the cardiovascular system and instruments of interest such as quality of life indices and different imaging methods to study in LVV. The Delphi exercise also indicated that a new tool for disease activity assessment is needed for LVV, with consideration to start with 1 tool to assess disease activity for both GCA and TA but to be open to developing 2 versions of an index if needed, because 67% of experts voted to have a common approach for both TA and GCA but to also develop additional disease-specific instruments for each disease. The OMERACT attendees agreed that the Delphi exercise was an important step in guiding the research agenda and building toward consensus and acceptance by the international vasculitis clinical research community.

PRO in LVV

It is now widely recognized that it is imperative to collect PRO within clinical trials of rheumatic diseases. The OMERACT vasculitis working group has previously demonstrated that patients with various forms of vasculitis report as

high priority several disease manifestations not collected by physician-based outcome measures used in clinical trials and that PRO can discriminate among different disease states in ANCA-associated vasculitis[16,17]. The OMERACT vasculitis working group's LVV task force recognizes that PRO would be included in the future core set and that a key component of the research agenda will be to develop and validate methods to capture the perspectives of patients with LVV.

Currently there are no disease-specific outcome tools available to assess patients' perspectives in LVV. General instruments, such as the Medical Outcomes Study Short Form-36 questionnaire (SF-36) and anxiety and depression scales have been tested in TA[18,19,20]. In GCA, 1 study found SF-36 scores to be comparable with the general population[21], and it has been suggested that domains of health-related quality of life that are important to patients with GCA might be poorly covered by generic instruments[22]. The OMERACT vasculitis working group began its work on PRO in LVV by conducting focus groups in Turkey and individual patient interviews in the United States with patients with TA in an effort to better understand what matters to patients. The preliminary results were discussed at the OMERACT 12 meeting and final analyses will be published separately. Patients with varied clinical experiences, disease durations, and exposures to therapies were included and asked open-ended questions about the effect of TA and the effect of therapies on the patients' quality of life. The patients with TA routinely reported as major aspects of their disease experience fatigue, other constitutional symptoms, extremity pain, limits to their physical activity and willingness to attend social events, and concerns about the longterm effects of their illness and therapy.

Because fatigue arose as a key domain of illness in TA and is repeatedly reported as important by patients with other vasculitides and systemic inflammatory diseases, the OMERACT vasculitis working group agreed to add fatigue as a domain in any preliminary core set for LVV and initiate further study of this area[17,23]. It was recognized that fatigue is a "state-specific" manifestation rather than being "disease-specific" and that a general index can likely be used to assess fatigue in LVV. In a preliminary study of 58 patients with TA from Turkey, the Multidimensional Assessment of Fatigue (MAF) score was high in patients with TA and comparable to scores among patients with rheumatoid arthritis and systemic lupus erythematosus. MAF was associated with anxiety, depression, and lower SF-36 subscores, but not with disease activity (Ilhan B, personal communication). However, the effect of fatigue on a patient's life may be different in a young person with TA compared to an older person with GCA. Therefore, further research is planned to understand the effect of fatigue in TA and GCA.

As part of the research agenda, more qualitative interviews and focus groups will be held for patients with TA, and a similar initiative will be planned for patients with GCA. The information and insight gained from this qualitative research will be compared and combined with the results of the international Delphi exercise to further inform the research agenda in developing a core set of outcomes for LVV.

Application of the OMERACT Filter 2.0 to Outcome Development in LVV

The OMERACT Filter 2.0 outlines 4 core areas for outcome measurement that describe the "impact of health conditions": death, life impact, pathophysiological manifestations, and resource use/economic impact[24]. The OMERACT vasculitis working group's LVV task force aims to identify the core domains within each of these areas. The overall goal is to develop a full core set of outcome measurements in LVV, either 1 for GCA and TA or 2 with modifications, that conforms to the OMERACT system. The OMERACT Filter 2.0 also brings into this process incorporation of adverse events and contextual factors, the study of both of which will further inform the process of core set development.

During OMERACT 2014 there was consensus to consider dividing the pathophysiological manifestations of LVV into 2 categories: systemic inflammation and vascular insufficiency. Examples of data elements of systemic inflammation include constitutional symptoms, acute-phase reactants, and arterial wall enhancement on imaging. Examples of data elements of vascular insufficiency include claudication, new bruit or loss of palpable pulse, and new arterial luminal occlusion on imaging. This categorization may help systematically assess signs, symptoms, and test results, inform a weighting system for data elements, and avoid duplicative measurements that are highly related to the same pathophysiological aspect of disease.

Additional Issues Regarding Core Set Development for LVV

One of the major difficulties in LVV is the differentiation between disease-related activity and disease-associated damage. Vascular stenosis may be due to active inflammation; however, it may also be a sign of scarring and resolution of fibrosis of a longstanding but no longer inflamed lesion. Some of the items proposed through the Delphi exercise may be clearly assigned to activity or damage. Damage is not a well-studied area in LVV and research will be needed to test the capacity for data elements and available vasculitis-associated damage indices to discriminate between activity and damage.

Time factors are also important when developing outcome measures because not only is LVV often a chronic relapsing and remitting disease, but also some manifestations, especially larger arterial lesions, evolve over long periods. Constitutional symptoms may be quite responsive to change and the response can be assessed quickly, whereas diagnostic imaging findings of stenosis may be associated with a more delayed response. Domains in an LVV core set to be used in

clinical trials need to be sensitive to change, and practical considerations regarding the feasible duration of studies need to be taken into account when choosing among outcomes of interest.

Resource use is highlighted in the OMERACT Filter 2.0 as an important consideration for core sets of outcome measures, and the LVV task force recognizes the need to consider costs when developing a draft core set. LVV occurs in all areas of the world including countries with markedly varying capacities to conduct expensive screening studies. Several of the imaging modalities highly rated as important by the Delphi process, including magnetic resonance imaging and positron emission technology, are extremely expensive, especially when used as serial measures of disease activity.

Research Agenda

As per the stepwise core set development approach associated with the OMERACT Filter 2.0, the LVV task force has already completed a comprehensive literature review, and has plans to incorporate input from patients, investigators, clinicians, and biopharmaceutical representatives. Contextual factors, and experience and data from clinical trials, will also be used to arrive at a draft core set of domains and instruments for additional testing in cross-sectional, longitudinal, and clinical trial cohorts.

Here are the next steps planned for the research agenda for the LVV task force.

- Complete the analysis of the Delphi exercise to produce an initial set of domains and instruments of interest derived from expert opinion
- Conduct additional interviews and focus groups with patients with TA and complete a qualitative analysis to derive key domains and themes of highest importance to patients with this form of LVV
- Initiate qualitative interviews with patients with GCA in a similar fashion as done with TA to derive key domains and themes of highest importance to patients with this form of LVV
- Determine the commonalities and differences between TA and GCA in patient perspectives on the burden of disease
- Determine what already-available PRO would be useful in LVV and consider development of a disease-specific PRO for TA and/or GCA
- Hold a conference including patients, investigators, clinicians, and biopharmaceutical representatives with the aim of achieving consensus on a draft core set of outcomes and candidate measures in LVV and consider response criteria in LVV
- Test the draft core set of outcomes and measures in cohorts and trials

Ultimate Goal: An OMERACT-endorsed Core for LVV

The OMERACT vasculitis working group has been seeking to develop a core set of validated outcome measures for use in clinical trials in large-vessel vasculitis. The research agenda initially included evaluating, validating, and/or developing disease activity assessment tools and PRO. Through the conduct of an international Delphi exercise, a list of items was identified clarifying physicians' perspectives on the important elements for the assessment of disease activity in LVV, including similarities and the differences for the assessment of both TA and GCA. Additional information is being collected from patients through focus groups and individual interviews, aiming to understand what really matters to patients.

REFERENCES

1. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. Ann Intern Med 1995;123:192-4.
2. Terao C, Yoshifuji H, Mimori T. Recent advances in Takayasu arteritis. Int J Rheum Dis 2014;17:238-47.
3. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Takayasu arteritis and giant cell arteritis: a spectrum within the same disease? Medicine 2009;88:221-6.
4. Grayson PC, Maksimowicz-McKinnon K, Clark TM, Tomasson G, Cuthbertson D, Carette S, et al. Distribution of arterial lesions in Takayasu's arteritis and giant cell arteritis. Ann Rheum Dis 2012;71:1329-34.
5. Kermani TA, Schafer VS, Crowson CS, Hunder GG, Gabriel SE, Matteson EL, et al. Increase in age at onset of giant cell arteritis: a population-based study. Ann Rheum Dis 2010;69:780-1.
6. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. Ann Intern Med 1994;120:919-29.
7. Direskeneli H, Aydin SZ, Kermani TA, Matteson EL, Boers M, Herlyn K, et al. Development of outcome measures for large-vessel vasculitis for use in clinical trials: opportunities, challenges, and research agenda. J Rheumatol 2011;38:1471-9.
8. Alibaz-Oner F, Aydin SZ, Direskeneli H. Recent advances in Takayasu's arteritis. Eur J Rheumatol 2014;1:24-30.
9. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for outcome measures in rheumatology. J Rheumatol 1998;25:198-9.
10. 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.
11. 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.
12. Direskeneli H, Aydin SZ, Merkel PA. Disease assessment in Takayasu's arteritis. Rheumatology 2013;52:1735-6.
13. Sivakumar MR, Misra RN, Bacon PA, for the IRAVAS group. The Indian perspective of Takayasu arteritis and development of a disease extent index (Dei.Tak) to assess Takayasu arteritis. Rheumatology 2005;44 Suppl 3:iii6-7.
14. 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 2010;49:1889-93.
15. 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 2013;52:1795-801.
16. Tomasson G, Boers M, Walsh M, LaValley M, Cuthbertson D, Carette S, et al. Assessment of health-related quality of life as an outcome measure in granulomatosis with polyangiitis (Wegener's). Arthritis Care Res 2012;64:273-9.

17. Herlyn K, Hellmich B, Seo P, Merkel PA. Patient-reported outcome assessment in vasculitis may provide important data and a unique perspective. Arthritis Care Res 2010;62:1639-45.
18. 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 2013;52:1898-904.
19. 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.
20. 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 6-7.
21. 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.
22. Hellmann DB, Uhlfelder ML, Stone JH, Jenckes MW, Cid MC, Guillevin L, et al. Domains of health-related quality of life important to patients with giant cell arteritis. Arthritis Rheum 2003;49:819-25.
23. Grayson PC, Amudala NA, McAlear CA, Leduc RL, Shereff D, Richesson R, et al. Illness perceptions and fatigue in systemic vasculitis. Arthritis Care Res 2013;65:1835-43.
24. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT Filter 2.0. J Clin Epidemiol 2014;67:745-53.