

Update on Outcome Measure Development in Large-vessel Vasculitis: Report from OMERACT 2018

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ABSTRACT. Objective. The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group seeks to develop validated outcome measures for use in trials for large-vessel vasculitis (LVV).

Methods. An international Delphi exercise conducted among investigators identified items considered important to measure active disease. In parallel, qualitative research with patients was conducted, including interviews and focus groups.

Results. Next steps prioritized by the group for LVV include (1) defining disease states (remission, flare, and patient-acceptable symptom state) and (2) selection of patient-reported outcome tools.

Conclusion. The ultimate goal is to develop an OMERACT-endorsed core set of outcome measures for use in clinical trials of LVV. (First Release May 15 2019; *J Rheumatol* 2019;46:1198–1201; doi:10.3899/jrheum.181072)

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Large-vessel vasculitis (LVV) is a rare set of diseases that mainly affect the aorta and its primary branches^{1,2}. The most common of the diseases are giant cell arteritis (GCA) and Takayasu arteritis (TA). Mainly because of the rarity of these diseases, there is no standardized protocol on how to monitor patients, when to repeat arterial imaging, or when to change therapy. This situation leads to significant variations in clinical practice.

In the last 5 years, the Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group has been developing a core set of domains in LVV. The working group recognizes the need to obtain final endorsement of the domains prior to selecting and/or developing associated outcome measurement instruments. Concurrently, the group has been conducting parallel projects to understand the perspectives of experienced physicians, investigators, and patients regarding outcomes of importance in LVV^{3,4}. The following work has been completed: a comprehensive literature review to assess the knowledge gap in this area³, an international Delphi exercise among clinicians and investigators to identify items considered important to determine active disease status in LVV⁵, and qualitative research with patients with LVV⁶. A draft set of core domains for LVV was proposed⁴. The group is currently working on 2 additional projects in LVV: (1) defining disease states [remission, flare, and Patient Acceptable Symptom State (PASS)] and (2) developing patient-reported outcome tools.

The projects outlined below are being pursued in line with OMERACT processes^{7,8}, and were presented at the OMERACT 2018 meeting at which feedback was obtained from meeting participants.

Defining Disease Status in Large-vessel Vasculitis

A simple definition of “active disease” in TA was proposed by Kerr, *et al* based on the presence of constitutional symptoms, new bruits, acute-phase reactants, or new angiographic features of arteritis¹. There are 2 other composite indices that were specifically developed for TA, DEI.Tak (Disease Extent Index–Takayasu) and ITAS2010 (The Indian Takayasu’s Arteritis Score 2010)^{9,10}, and proposed to help define disease states. DEI.Tak was based on the Birmingham Vasculitis Activity Score (BVAS) using the same 11 organ systems, some of which are not frequently affected in LVV; some weighting was applied to increase the effect of cardiovascular items. However, DEI.Tak was shown to have significant discrepancies with physicians’ judgments of activity¹¹. ITAS2010, a modification of DEI.Tak, has only 6 systems and is weighted even more heavily toward vascular items⁹. This modification modestly increased the agreement with physicians’ assessments, but still leaves substantial discrepancies between the 2 assessments¹². In GCA, only 1 study investigated BVAS in a prospective observational cohort of patients with GCA; it showed that most categories of the BVAS were not applicable in GCA, whereas many compo-

nents of active disease were identified in the “other” category, not contributing to the total BVAS¹³.

The randomized controlled trials involving TA and GCA conducted to date usually defined relapse and remission based on the presence/absence of signs and symptoms and/or acute-phase reactants (Table 1). These definitions were not obtained by a data-driven approach or using patients’ perspectives, but through expert opinion.

The disease states in LVV outlined above have not been well-defined, and definitions are not uniform across studies. The complexity of the disease makes it difficult to differentiate “activity” from “damage” to define remission or relapse. Further, disease states have not been studied from the patients’ perspective. PASS, the value beyond which patients can consider themselves well, has not been studied in LVV. PASS is independent of treatment decisions and purely reflects patients’ perspectives, and therefore could be a useful tool to understand patients’ perceptions of clinically meaningful disease states¹⁴.

The aim of our project is also to create a definition of disease states in LVV for use in clinical trials. To arrive at widely acceptable and feasible definitions, data elements will be preferentially used if they are considered important by physicians and patients, routinely identified in standard clinical practice, specific to disease activity (not damage), and not redundant with each other. The following steps will be carried out to achieve this goal: (1) a patient survey will be designed and implemented to receive patient input on items from the physician Delphi and new items considered relevant to disease states; (2) the features prioritized by patients, along with the results from the physician Delphi, will be reviewed during a meeting of key investigators and patients with the aim of reaching consensus on item reduction and selection for use; and (3) data will be collected from patients with LVV and their physicians within a multicenter longitudinal cohort, including the effect of each of the items on physicians’ judgments of remission, relapse, and change in therapy. Patients’ input on remission, flare, and PASS will also be collected and analyzed. These steps were discussed in the OMERACT meeting, with encouraging feedback from attendees including emphasizing that collecting data to develop a definition of different diseases will require significant input from the patients.

Patient-reported Outcomes in LVV

The OMERACT Vasculitis Working Group has highlighted the development of a disease-specific patient-reported outcome (PRO) measure for TA and GCA as one of the next steps in its research agenda^{4,15}. In TA and GCA, commonly used generic tools such as the 36-item Medical Outcomes Study Short Form-36 questionnaire (SF-36) do not distinguish between clinically important groups such as patients with and without visual loss or systemic symptoms^{16,17,18,19}.

An international collaboration has therefore been formed to develop disease-specific PRO measures.

As a first step in TA, 12 patients from the United States participated in semistructured, individual, in-person interviews and a total of 19 patients in Turkey participated in 2 focus groups⁶. The interviews and group sessions were recorded, transcribed, and analyzed with NVivo. A line-by-line review of narrative data was used to develop themes describing the effect of TA on patients' life. US patients were invited to free-list terms that they associated with disease states (active disease and remission). The Smith Salience Index was used to identify the most salient terms. Pain, fatigue, and emotional impact emerged as common themes. The most salient terms were pain/discomfort and fatigue/low energy levels during active disease, and pain/discomfort and emotional impact during remission. Outcomes were similar between the 2 countries. Current efforts are focusing on creating a disease-specific PRO tool for TA based on the results of the qualitative studies.

For GCA, the results of the first stage (qualitative interviews with 36 patients in the United Kingdom and Australia) were presented at the LVV Special Interest Group (SIG) session at OMERACT 2018. All patients had a confirmed diagnosis of GCA on temporal artery biopsy or ultrasound. Patients were purposely sampled to include a range of ages, sex, disease duration, and disease manifestations (specifically visual loss and large-vessel involvement). Initial overarching themes that emerged included "anxieties around getting a diagnosis of GCA," "description of symptoms related to GCA and its treatment" (including visual disturbance), "lack of bodily strength, stability, and stamina; difficulties with completing daily tasks," "difficulties with participating in social activities, work, and caring roles," "not feeling normal and impact on general perception of health," and "anxiety and fear of the future"²⁰. Key contextual factors around how patients experience GCA were also discussed, including the development of adverse effects and comorbidities, receiving support from family and friends, and self-management techniques such as maintaining physical activity. Discussions at OMERACT 2018 included the potential to expand the qualitative work into another geographic area by patients with GCA in Turkey, to ensure that the full range of themes of importance to patients is identified.

Themes are also being developed further into candidate questionnaire items for a disease-specific GCA PRO. Among the knowledge gained from the OMERACT conference was the importance of having questions that differentiate between patients in states of active disease and remission. In addition, identifying any background effect on health-related quality of life (e.g., symptoms related to glucocorticoid-related adverse effects or physical deconditioning because of the disease or treatment) was highlighted within the SIG. It was also decided to incorporate further prompts into the cognitive interview stage for the GCA PRO to ask patients to describe

the start of their disease, flares, and periods of remission. This qualitative work will be carried out as part of the cognitive interview stages in the United Kingdom and Australia and will be incorporated into the initial qualitative work planned in Turkey. The focus on flare will inform the development of the GCA PRO but could also be used to help define appropriate questions for the disease states patient survey planned (as outlined above).

Summary and Research Agenda

The OMERACT Vasculitis Working Group has suggested a preliminary core set of domains for LVV⁴, and has a new research agenda for the next 2 years:

- Achieve full endorsement of a core set of domains for LVV.
- Select and/or develop validated instruments for each domain in LVV.
- Advance PRO research in LVV by gathering more patient-derived data on disease-related quality of life issues, including regarding different treatment regimens, with an ultimate goal of developing an LVV-specific PRO instruments.
- Define disease states for use in clinical trials of LVV through data-driven methods that include input of all stakeholders.
- Work toward an endorsed core set of outcomes for LVV that include domains with matching validated outcome measures.

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