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

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Abstract

Objectives: The 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 i) defining disease states (remission, flare, and patient-acceptable symptom state); and ii) development of patient-reported outcome tools.

Conclusions: The ultimate goal is to develop an OMERACT-endorsed Core Set of outcome measures for use in clinical trials of LVV.

Introduction:

Large-vessel vasculitis (LVV) is a rare set of diseases that mainly affect the aorta and its primary branches (1, 2). LVV is comprised of several diseases, the most common of which are giant cell arteritis (GCA) and Takayasu's arteritis (TAK). Mainly due to 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 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 area (3); an international Delphi exercise among clinicians and investigators to identify items considered important to determine active disease status in LVV (5); and qualitative research with patients with LVV (6). A draft set of core domains for LVV were proposed (4). The group is currently working on two additional projects in LVV: 1) defining disease states (remission, flare and patient acceptable symptom state) 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 TAK was proposed by Kerr *et al.*, based on the presence of constitutional symptoms, new bruits, acute phase reactants, or new angiographic features of arteritis (1). There are two other composite indices that were specifically developed for TAK: DEI.Tak (Disease Extent Index in TAK) 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 impact of cardiovascular items. However, DEI.Tak was shown to have significant discrepancies with physicians' judgements of activity (11). ITAS2010, a modification of DEI.Tak, has only 6 systems and is weighted even more heavily towards vascular items (9). This modification modestly increased the agreement with physicians' assessments, but still leaves substantial discrepancies between the two assessments (12). In GCA, only one study investigated BVAS in a prospective observational cohort of patients with GCA which showed that most categories of the BVAS were not applicable in GCA, whereas many components of active disease were captured in the "*other*" category, not contributing to the total BVAS (13).

The randomized controlled trials involving TAK 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 utilizing patients' perspectives, but through expert opinion.

The definitions of disease states in LVV outlined above have not been well-defined and are not uniform across studies. The complexity of the disease makes it difficult to differentiate 'activity' from 'damage' to define remission or relapse. Furthermore, disease states have not been studied from the patients' perspective. Patient Acceptable Symptom State (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' perception of clinically-meaningful disease states (14).

The aim of this 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 utilized if they are considered important by physicians and patients, routinely captured 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 an aim of reaching consensus on item reduction and selection for use. 3) data will be collected from patients with LVV and their physicians within a multicenter longitudinal cohort, including the impact of each of items on physicians' judgements 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 received from meeting attendees.

Patient-Reported Outcomes in LVV

The OMERACT Vasculitis Working Group has highlighted the development of a disease-specific patient-reported outcome (PRO) measure for TAK and GCA as one of the next steps in their research agenda (4, 15). In TAK and GCA, commonly-used generic tools such as the 36-item short-form health survey (SF-36) do not distinguish between clinically important groups such as patients with and without visual loss or systemic symptoms (16-19). An international collaboration has therefore been formed to develop disease-specific PRO measures.

As a first step in TAK, 31 patients from the US and Turkey participated in semi-structured, individual, in-person interviews and focus groups (6). 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 impact of TAK 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 (SSI) 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 two countries. Current efforts are focusing on creating a disease-specific PRO tool for TAK based on the results of the qualitative studies.

For GCA, the results of the first stage, qualitative interviews with 36 patients in the UK 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. Initial themes that emerged included: “Anxieties around getting a diagnosis of GCA”, “Description of symptoms related to GCA and its treatment”, “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 co-morbidities, 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 the full range of themes of importance to patients is captured.

Themes are also being developed further into candidate questionnaire items for a disease-specific GCA PRO. The importance of having questions which differentiate between patients in states of active disease and remission, as well as capturing any background impact on HRQoL (e.g., symptoms related to glucocorticoid-related adverse effects or physical deconditioning due to the disease or treatment) was highlighted within

the SIG. It was 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 UK 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 LVV (4), 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 a 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 towards an endorsed core set of outcomes for LVV that include domains with matching validated outcome measures.

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