

Current Status of Outcome Measure Development in Vasculitis

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ABSTRACT. The conduct of randomized controlled trials for vasculitis, especially for the antineutrophil cytoplasmic antibody-associated vasculitides [AAV, granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis], has been greatly advanced by the development, use, and acceptance of validated outcome measures. Trials have subsequently provided the opportunity to validate and refine reliable, valid outcome measures for these multisystemic and relapsing rare diseases. The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group was formed in 2004 to foster development of validated and widely accepted outcomes in vasculitis using data-driven analyses, a dedication to building consensus, and adherence to, and guidance by, the principles of the OMERACT approach. This work led to the endorsement by OMERACT of the core set of domains and associated outcome measures for AAV. Next steps for the study of existing outcome tools in AAV include better definition of response criteria through development of more data-driven weighting of the elements of activity and damage assessment. The Working Group is now also embarking on a series of linked projects to develop validated patient-reported outcomes for use in clinical research in vasculitis. Additionally, the Working Group is studying how current methods of disease assessment and plans for new outcomes can be informed by the conceptual framework of the International Classification of Function of the World Health Organization. The success of the Group's work in AAV has also led to a formal process for developing outcomes for the large vessel vasculitides (Takayasu arteritis and giant cell arteritis) and Behçet disease. (J Rheumatol First Release Jan 15 2014; doi:10.3899/jrheum.131248)

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The idiopathic vasculitides represent a diverse group of disorders linked by inflammation of arteries. These diseases are often associated with organ- and life-threatening manifestations. The vasculitides are generally grouped by size of the predominant vessel involved^{1,2} with the main categories including small-, medium-, and large-vessel vasculitis and vasculitis with no predominant vessel size.

The past 20 years have seen the development of international research collaborations leading to the conduct of randomized clinical trials (RCT) for several types of vasculitis, including antineutrophil cytoplasmic antibody-associated vasculitis (AAV)^{3,4,5,6,7,8} and giant cell arteritis^{9,10}.

The conduct of RCT for vasculitis, especially for the AAV [granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis], has been greatly advanced by the development, use, and acceptance of validated outcome measures^{11,12,13,14,15}. The RCT have subsequently provided the opportunity to validate and refine reliable, valid outcome measures for these multisystemic and relapsing rare diseases.

The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group was formed in 2004 to foster development of validated and widely accepted outcomes in vasculitis using data-driven analyses, a dedication to building consensus, and adherence to and guidance by the principles of the OMERACT approach^{11,12,13,14,15}. The Working Group has been highly successful in both advancing the field of outcomes research in vasculitis and bringing together various investigative groups to function in a cohesive international collaboration. This work led to the endorsement by OMERACT of the core set of outcome measures for AAV¹⁵. Next steps for the study of existing outcome tools in AAV include better definition of response criteria and development of more data-driven weighting of the elements of activity and damage assessment.

A major deficiency in outcomes in vasculitis has been the lack of emphasis on incorporating patient self-assessment of disease and health, and including properly developed and validated measures of patient perspective into clinical research. The Vasculitis Working Group has directed a great deal of effort to diligently incorporating patients into the research process and studying patients' perspective on their disease. The Working Group is now embarking on a series of linked projects to develop validated patient-reported outcomes (PRO) for use in randomized clinical trials (RCT) in vasculitis. Additionally, the Group is studying how current methods of disease assessment and plans for new outcomes can be informed by the conceptual framework of the International Classification of Function (ICF) of the World Health Organization. The success of the Group's work in AAV has led to a formal process for developing outcomes for the large vessel vasculitides (LVV, Takayasu arteritis, and giant cell arteritis) and Behçet disease (BD).

We summarize the ongoing efforts of the OMERACT Vasculitis Working Group to refine outcome tools for AAV, develop PRO in vasculitis, understand vasculitis within the ICF framework, and start the process for core set development in LVV and BD. Each of these areas was addressed through the work preceding, during, and following the OMERACT 11 meeting.

ANCA-associated vasculitis. AAV, including granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss), are the forms of vasculitis for which there are the most high-quality clinical data on outcome measures and data from RCT. The OMERACT core set for AAV includes at least 1 validated outcome instrument for each of the major domains of disease: disease activity, disease damage, PRO/health-related quality of life (HRQOL), and mortality¹⁵. However, there remain important aspects of the core set that need substantive improvement, including development of PRO more representative of the patients' experience, defined response criteria for all outcomes, and improved weighting schemes for multiitem composite outcomes. Although these are rare diseases, clinical trials in AAV continue to be regularly conducted, providing excellent opportunities to collect data on existing measures and test new tools.

PRO in ANCA-associated vasculitis. The current standard measures of AAV have been developed by experts without input from patients and rely on physician-based assessments. The Working Group has been leading the coordinated international efforts to evaluate the unmet needs for PRO in AAV. Guided by OMERACT community input, the Group developed a research strategy, organized an investigative team, included patients as investigators, and will leverage its considerable research infrastructure to conduct a series of coordinated projects to advance the development of PRO in vasculitis. There is now a clear mandate from, and enthusiasm within, the vasculitis research community to embrace PRO as an important contribution to understanding of the burden of the disease on patients.

Patients with AAV experience disease-associated clinical manifestations that both substantially hinder their lives and are not adequately taken into account by either the traditional physician-based measures or standard HRQOL instruments used in current clinical trials of vasculitis¹⁶. The already-completed work on PRO conducted by the Working Group includes (1) in-person surveys of patients with vasculitis¹⁶; (2) a survey of vasculitis expert physicians¹⁷; (3) data from a large observational cohort and from a clinical trial on the use of the Medical Outcome Study Short Form-36 (SF-36)^{18,19}; (4) patient focus groups; and (5) an Internet-based survey. These studies have demonstrated that patients and physicians perceive and rate disease burdens from AAV markedly differently.

The SF-36 clearly captures other aspects of the disease not otherwise measured by the current standard AAV outcome instruments. The SF-36 is a valid “generic” measure of HRQOL, but as a consequence it is nonspecific and only modestly responsive to changes in the multiple domains of illness important to patients with AAV. Nonetheless, analyses of SF-36 data demonstrated that this PRO can discriminate between AAV disease states of importance and captures disease burden beyond the currently used standard physician-based measures¹⁹. Importantly, changes in SF-36 scores occur even during periods of clinical “remission,” implying that this PRO can provide new insights into the disease course in AAV.

Patients with vasculitis report that fatigue and other symptoms not included in clinician-based measures of AAV substantially affect their lives. A questionnaire study of 264 patients with vasculitis in 3 countries revealed, for example, that fatigue, a disease manifestation patients consistently reported as being of greatest importance, was among those aspects of AAV that physicians do not usually record or quantify¹⁶. Similarly, patients’ rankings of the importance of individual disease-specific manifestations, such as upper airway disease or renal impairment (both common problems in AAV), differed greatly from physician rankings of the same manifestation^{16,17}.

Patients also are concerned about the effect of their disease on their overall health. Preliminary data from formal focus groups of patients with AAV, conducted and analyzed by experienced qualitative researchers, consistently revealed that our patients experience a sense of permanent loss of the “fully healthy state” that severely affects their well-being, especially during periods of active disease (unpublished data).

The Working Group is conducting 2 related projects that directly address the unmet needs for PRO in vasculitis:

1. *Use of the Patient-Reported Outcomes Measurement System (PROMIS) for assessment of PRO in AAV.* This project will evaluate the feasibility and construct validity of instruments within the PROMIS to record important components of the disease experience among patients with AAV.

PROMIS is based on item-response theory and includes a growing set of instruments (both computer- and paper-based) to measure HRQOL within physical, mental, and social well-being domains (www.nihpromis.org). PROMIS instruments have the potential to consistently gather patient-identified domains of illness of importance in AAV. PROMIS is intended to provide clinical researchers with banks of psychometrically strong items intended to identify all aspects of self-reported health. Item response theory is the statistical framework for PROMIS and allows for using computer-adaptive testing (CAT) that involves study subjects being asked items of difficulty level guided by their response to previous items. This results in a higher precision and much less susceptibility to floor and ceiling

effects than most paper-based instruments of similar length. For most PROMIS item banks, several instruments (both CAT and paper-based) are available, and new instruments tailored to specific disease populations can be developed. The validation of PROMIS for vasculitis will be done in collaboration with patient partners as co-investigators and will use both qualitative data from patient interviews and quantitative data from longitudinal cohorts. Validation analyses will be conducted, and the most responsive PROMIS instruments will be tested within a RCT. The Working Group intends to optimize the use of PROMIS for disease assessment in vasculitis with respect to content, feasibility, and discrimination.

2. *Development of a disease-specific patient-reported outcome instrument in ANCA-associated vasculitis.* This project will create a disease-specific patient-based measure of disease burden in AAV through a comprehensive series of development steps that include focus groups, individual interviews, qualitative analysis, instrument drafting, cognitive testing, retesting, validation, and feasibility studies. This is a longterm project that will produce a validated instrument likely to be complementary to PROMIS and physician-based tools.

The Working Group has established an international collaboration to conduct these studies. The collaboration incorporates experts in vasculitis, qualitative research, biostatistics, and outcome measure development to conduct these overlapping projects related to PRO in vasculitis. The group also includes patients with AAV who are fully involved at every level of the research, including study design, implementation, and data analysis. Peer-reviewed funding has been obtained for these interrelated projects, including through grants from the US National Institutes of Health, the newly created US Patient-Centered Outcomes Research Institute, and the University of Oxford. These projects are also linked to the project on the ICF (see below) and all projects share common methodologies, investigators, and research resources.

Response criteria for ANCA-associated vasculitis. Most recent and current clinical trials in AAV include as their primary focus a dichotomous outcome of active disease or remission. However, validated and accepted response criteria are needed, even for remission. For example, what constitutes a “complete” or “partial” remission? How long must a patient be followed in a trial before a response is established? Also needed are intermediate outcomes to (1) gauge an early response that is meaningful and predictive of longer-term outcomes; (2) determine partial responses, for example, the transition from a severe disease to a state of low disease activity; and (3) measure more subtle changes even within a defined disease state, for example, improvement in upper airway symptoms in GPA. For outcomes other than disease activity, response may be a difficult construct to define. How can we measure response

for damage? Is lack of progression enough? For PRO or HRQOL measures, what is a meaningful response?

Definitions of response and establishment of minimal and major clinically important differences are needed for all the core domains and validated instruments in the OMERACT AAV core set. The work on weighting and scalability, as outlined below, will also help establish response criteria.

A goal of the Working Group is to apply OMERACT principles to establish validated response criteria for the outcome measures included in the core set and any new measures (such as new PRO) developed for AAV. Plans to work toward this goal include review of datasets from different international longitudinal cohorts and RCT of patients with AAV. Analyzing data on the individual items that make up the disease activity and damage assessment, including the range of item usage, the association between items and other major outcomes (e.g., mortality, relapse), will allow for exploration of the effect of changing weighting scores, or using subsets of items, to predict observed subsequent outcomes. Statistical modeling of these data could lead to more precise scoring systems and better response criteria.

Weighting of elements within composite outcome measures in ANCA-associated vasculitis. The measures of disease activity [various versions of the Birmingham Vasculitis Activity Score, (BVAS)] and disease damage (Vasculitis Damage Index and Combined Damage Index) for AAV provide single scores made up of the sum of many individual clinical items^{20,21,22}. While these measures have proved to be useful in RCT, there is a consensus that the scoring systems could be improved by redefining item weighting schemes. The versions of BVAS use item weights mostly defined by a small group of experts; the damage indices have no weights (simple sum of items). Further, these measures are all physician-based. Patient input is also important and should be used to inform the weighting system, particularly when it comes to assessing the importance of permanent damage.

The task of developing valid and data-driven weighting systems for these measures will be facilitated by the availability of data on longterm outcomes for several populations of patients enrolled in multiple RCT or longitudinal cohorts. The Working Group plans to analyze existing RCT data to explore which elements of the BVAS drive the discrimination between treatment arms and assign weights to the individual data elements. Such data-driven weights could result in a more discriminatory version of BVAS for use in clinical trials.

Application of the ICF to evaluate outcome instruments in vasculitis. The ICF is a general health model endorsed by the World Health Organization (WHO). The ICF describes health along 4 domains: body functions, body structures, activities and participation, and environmental factors^{23,24}.

The Working Group is applying the ICF to examine the spectrum of disease assessment/outcome measures for the study of vasculitis to identify areas of disease in need of further study and instrument development. Methods and steps for this initiative include conducting a structured literature review, collecting data from qualitative interviews, performing an expert Delphi exercise, and mapping these data regarding vasculitis outcomes and disease states to the ICF framework. This project will inform the PRO projects outlined above and will share use of data generated from the qualitative research conducted for the PRO projects. Advisers on this project include those in the OMERACT community and at the WHO have studied the ICF in the context of other rheumatic diseases.

Large vessel vasculitis. Although the many diseases that are classified under the term “vasculitis” share some common pathologic aspects and patients with these disorders are often cared for by physicians interested in many types of vasculitis, and the diseases are frequently studied as a group, it is increasingly recognized that the major subclasses of vasculitis have sufficiently different clinical courses and manifestations to necessitate separate approaches to outcome assessment. LVV, most notably Takayasu arteritis and giant cell arteritis, involves inflammation of the aorta and its major branches. LVV is treated primarily with high-dose glucocorticoids, and patients often have long periods of clinically seemingly inactive disease during which arterial damage progresses, highlighting the difficulty in determining the level of disease activity.

The Working Group has taken on the challenge to develop a core set of outcomes measures for LVV. A review of the literature demonstrated that not only are there no widely accepted or standardized outcome tools, but also there are not even broadly accepted definitions of important outcomes such as disease activity or response to therapy in LVV¹⁴. The steady adoption of routine use of ultrasound, angiography by means of computerized tomography, and/or magnetic resonance imaging into clinical practice and research has not yet led to standardized approaches to using these assessment tools in research.

The Working Group is advancing a research agenda that includes parallel projects to understand the perspectives and insight into outcomes of importance in LVV by expert and experienced physicians and investigators as well as patients. A Delphi exercise is under way to determine (1) experts’ consensus opinions on the disease domains and subdomains of importance to study in LVV; and (2) a preliminary set of outcomes and outcome instruments to capture data on the domains.

It is also essential to understand LVV from the patient perspective. Insight will be obtained through qualitative research methods, including focus groups and individual interviews, and analysis of existing data collected using established instruments, such as the SF-36 and PROMIS.

The goal of this work is to understand what domains of illness and health are important to patients and how the patient perspective of LVV can be captured for use in clinical research.

It is anticipated that the Delphi exercise, which includes participants from many countries and several medical disciplines, and the work exploring patients' perspectives of LVV, will help determine a research agenda for the international vasculitis research community to follow. The ultimate goal of this project is to establish a core set of domains and validated outcome measures for use in clinical research, including RCT in LVV.

Behçet disease. BD is another multisystem inflammatory disorder that is routinely classified among the vasculitides^{1,2}. Although there have been many clinical research studies in BD, including several multicenter clinical trials, there remains a huge unmet need to establish validated and well-accepted outcome measures for this complex disease. The need for a validated core set for BD is further enhanced by the growing interest in conducting clinical trials in this disease by large pharmaceutical companies, especially to test novel immune modulating agents.

The Working Group has agreed to advance work on outcomes research in BD. Using our experience in AAV and incorporating new members with content expertise in BD, we are now beginning the long process of establishing a research agenda with the ultimate goal of creating a core set of outcome measures for BD. The initial work includes a literature review to understand the current state of outcomes in the disease, a planned Delphi exercise to establish current consensus among experts in the field, and initial exploration of PRO and priorities. This work with BD is outlined in more detail in a companion article associated with OMERACT 11 reports²⁵.

The OMERACT Vasculitis Working Group continues to make steady progress on an expanding set of related research initiatives. The new projects regarding PRO in AAV and core sets for LVV and BD each provide excellent opportunities to apply the newly developed principles and advanced methodology of the OMERACT Filter 2.0 to guide development of outcome measures in vasculitis²⁶. These plans reflect the substantial input received during detailed discussions held during plenary and breakout sessions at the OMERACT 11 meeting from a wide range of members of the OMERACT community. The OMERACT Vasculitis Working Group will continue to work in an international, collaborative approach to advance these research projects in vasculitis.

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