

Progress Towards a Core Set of Outcome Measures in Small-vessel Vasculitis. Report from OMERACT 9

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ABSTRACT. The past decade has seen a substantial increase in the number and quality of clinical trials of new therapies for vasculitis, including randomized, controlled, multicenter trials that have successfully incorporated measures of disease activity and toxicity. However, because current treatment regimens for severe disease effectively induce initial remission and reduce mortality, future trials will focus on any of several goals including: (a) treatment of mild—moderate disease; (b) prevention of chronic damage; (c) reduction in treatment toxicity; or (d) more subtle differences in remission induction or maintenance. Thus, new trials will require outcome measure instruments that are more precise and are better able to detect effective treatments for different disease states and measure chronic manifestations of disease. The OMERACT Vasculitis Working Group comprises international clinical investigators with expertise in vasculitis who, since 2002, have worked collaboratively to advance the refinement of outcome measures in vasculitis, create new measures to address domains of illness not covered by current research approaches, and harmonize outcome assessment in vasculitis. The focus of the OMERACT group to date has been on outcome measures in small-vessel vasculitis with an overall goal of creating a core set of outcome measures for vasculitis, each of which fulfills the OMERACT filter of truth, discrimination, feasibility, and identifying additional domains requiring further research. This process has been informed by several ongoing projects providing data on outcomes of disease activity, disease-related damage, multidimensional health-related quality of life, and patient-reported ratings of the burden of vasculitis. (J Rheumatol 2009;36:2362–8; doi:10.3899/jrheum.090373)

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The vasculitides are a group of multisystem diseases involving inflammatory vascular pathology as well as other types of tissue inflammation. Vasculitis is often an organ- or life-threatening disease. Treatments for vasculitis include high doses of glucocorticoids in combination with immunosuppressive medications. The cumulative burden of disease for patients with vasculitis can be substantial, due to acute injury, persistent disease, recurrent flares, and drug toxicity.

The past decade has seen a substantial increase in the number and quality of clinical trials of new therapies for vasculitis, including randomized, controlled, multicenter trials^{1–6}. These trials have successfully incorporated measures of disease activity and toxicity. However, because current treatment regimens for severe disease effectively induce initial remission and reduce mortality, future trials will focus on any of several goals including (a) treatment of mild—moderate disease; (b) prevention of chronic damage; (c) reduction in treatment toxicity; or (d) more subtle differences in remission induction or maintenance. Thus, new trials will require outcome measure instruments that are more precise, better able to detect effective treatments for different disease states, and measure chronic manifestations of disease. Additionally, there are domains of illness in vasculitis not addressed in currently available outcome tools.

The OMERACT Vasculitis Working Group comprises international clinical investigators with expertise in vasculitis who, since 2002, have worked collaboratively to advance the refinement of outcome measures in vasculitis and create new measures to address domains of illness not covered by current research approaches. The group met during OMERACT 7 in 2004, during which the spectrum of outcome measures was reviewed and broad-ranging discussions identified several key areas of success, challenge, and controversy. These discussions led the group to propose an ambitious research agenda and were the basis for the ongoing international collaboration to advance and harmonize outcome assessment in vasculitis⁷.

The OMERACT 8 meeting in 2006 focused on specific domains that could be considered for inclusion in a core set, such as disease activity, disease-associated damage, and identification of new domains to explore, such as patient-reported outcomes. To collect data directly relevant to this research agenda, new projects were planned and developed⁸.

The OMERACT 9 meeting was preceded by evaluation of data from these new projects relating to domains of illness studied in vasculitis, including disease activity and damage assessment, as well as newer domains of importance identified at OMERACT 8, such as multidimensional health-related quality of life and patient-reported ratings of the burden of vasculitis. Although there is ongoing work in creating validated outcome measures for large-vessel vasculitis (e.g., giant cell arteritis and Takayasu's arteritis), the focus of the OMERACT group has been on outcome measures in small-vessel vasculitis. This focus is the result of a combination of the higher prevalence of small-vessel vasculitides and the availability of a large set of outcome data from randomized clinical trials for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) [Wegener's granulomatosis (WG) and microscopic polyangiitis]. However, many of the constructs and domains being studied in small-vessel vasculitis, as well as specific data elements, are also applicable to the study of large-vessel disease.

The overall goal of the OMERACT Vasculitis Working Group is to create a core set of outcome measures for vasculitis, each of which fulfills the OMERACT filter of truth, discrimination, and feasibility⁹, and to identify additional domains requiring further research; these additional domains may eventually contribute to, or complement, the core set. This article will (a) summarize the current status of the group's work in 4 key domains under consideration for inclusion into the core set; (b) report on the feedback from the OMERACT community of outcomes researchers, clinicians, patients, regulatory officials, biopharmaceutical industry executives, and government research administrators; and (c) outline both the current thinking about the levels of validation for the key domains of interest (Figure 1) and the updated research agenda (Table 1).

DISEASE ACTIVITY ASSESSMENT IN VASCULITIS

Disease activity is recognized as a central domain within the core set of outcome measures for clinical trials in systemic vasculitis. Development of disease activity assessment is more advanced than that of other domains in vasculitis. Measuring the degree of vasculitis disease activity has been achieved using structured clinical evaluation tools that catalogue abnormalities in multiple organ systems and derive numeric scores. The 3 main activity measurement instruments are the Birmingham Vasculitis Activity Score (BVAS)^{10,11} and its derivatives, the BVAS for WG (BVAS/WG)¹², and the BVAS 2003 (reviewed in Flossmann, *et al*¹³). For all 3 versions of the BVAS, demonstration of validity, sensitivity to change, and reproducibility has been made¹⁰⁻¹³ or is under way¹⁴, and all have met, to various degrees, the OMERACT filter of truth, discrimination, and feasibility⁹.

While BVAS and BVAS 2003 were designed as tools applicable in a wide variety of forms of vasculitis, BVAS/WG specifically focuses on WG. Other between-instrument differences are in the number and weighting of rated, "pre-specified" disease manifestations. Moreover, while all versions offer an option to include open-ended/free-text "other" disease manifestations, only BVAS/WG allows for scoring of such manually added items. However, the results of a comparative study on WG and microscopic polyangiitis suggested that BVAS, BVAS 2003, and BVAS/WG ratings are highly correlated with each other and with a physician's global assessment of disease activity¹⁵.

A recent study used data on BVAS/WG collected in a clinical trial of WG to examine various strategies for item selection and weighting to find the most appropriate methods for disease activity scoring¹⁶. This study concluded that the tool could be improved by omitting items that were rarely or never used, and by creating new items corresponding to disease manifestations frequently added in the free-text "other" section. A computational method generated a broader range of item weights compared to the expert opinion-based approach used in BVAS, BVAS 2003, and BVAS/WG.

The OMERACT Vasculitis Working Group recognizes that a number of challenges remain to be addressed in disease activity assessment of vasculitis. Although the various tools are conceptually quite similar, harmonization of disease activity assessment is a longterm aim, including using a single instrument designed based on data-driven item selection and weighting. Further, while all 3 instruments allow for separation of inactive and active disease, no cutoff values have been defined to differentiate between varying states of low, medium, or high disease activity. Finally, while the performance of these disease activity instruments has been evaluated extensively for WG and microscopic polyangiitis, there are only limited data available for other forms of vasculitis. Whether or not disease activity assessment tools should be disease-specific or remain universally applicable to all forms of vasculitis is still a matter of debate. Large datasets from completed and

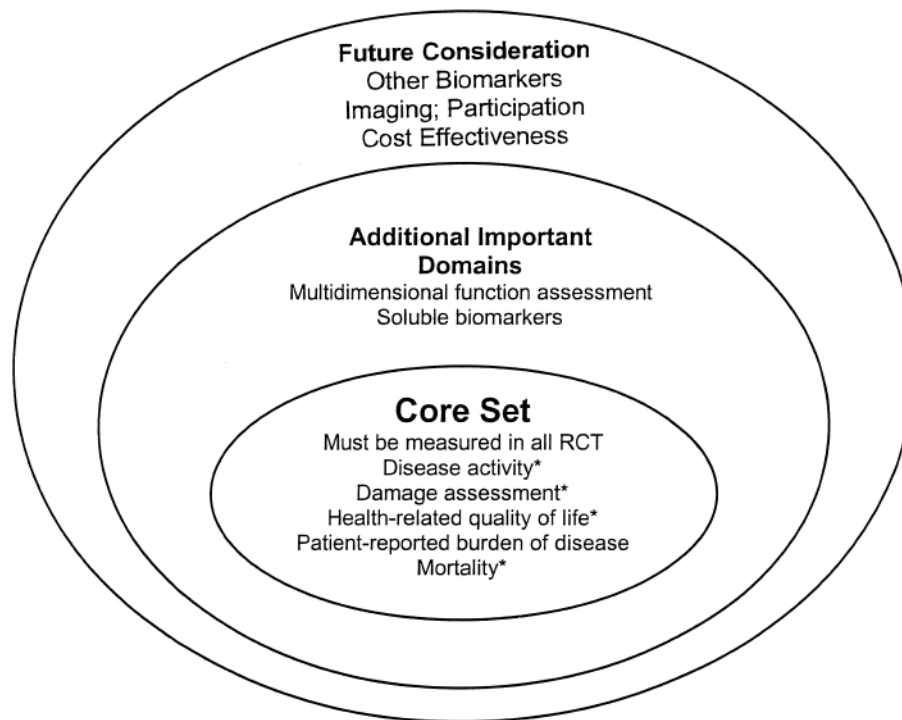


Figure 1. Domains of small-vessel vasculitis for study in clinical trials. *At least one instrument available for the domain has met the OMERACT filter⁹. RCT: randomized controlled trials.

ongoing clinical trials and longitudinal studies will allow investigators to address these areas of research, each of which was endorsed by OMERACT attendees as important additions to the research agenda.

DAMAGE ASSESSMENT IN VASCULITIS

While the patient perspective on the burden of disease is important, significant damage from vasculitis can be present that may not have immediate subjective consequences for the patient, and yet is important to document. The goals of treatment are at least in part to avoid the accumulation of such damage. Thus, a physician's perspective on damage is an additional key domain of interest in vasculitis. Damage denotes the consequences of vasculitis or its treatment that do not respond to immunosuppression¹⁷. For the patient, damage represents the chronic burden of disease. For the clinician, damage represents the manifestations of vasculitis that do not merit prolonged medical treatment.

The concept of damage is also an important outcome measure for clinical trials¹⁸. Because most vasculitis flares can be treated effectively in the short term, achievement of remission by itself may not be an adequate endpoint. Damage indicates the cost of achieving remission, aggregating the chronic morbidity that occurs after the disease flare has been treated. If 2 drugs both induce remission within 6 months of initiating therapy, the drug that also prevents the development of damage is superior. Damage thus represents a unique domain that

is not captured by other domains under study for vasculitis, including disease activity, quality of life, and other patient-reported outcomes.

The Vasculitis Damage Index (VDI) was developed to record the diverse forms of damage that can occur in association with all forms of systemic vasculitis¹⁹. The VDI serves to ensure that patients are assessed systematically for damage in a way that is both reproducible and analyzable, yielding a summary "damage score." The VDI performs well, but the OMERACT Vasculitis Working Group identified areas for reexamination, focusing on 3 issues related to damage assessment in AAV: content, weighting, and disease specificity⁷.

Content. Through expert consensus, the Combined Damage Assessment index (CDA) was developed and comprises 130 candidate items of damage⁸. The CDA is being applied to patients with WG or microscopic polyangiitis, and analysis of these data will help refine the index by identifying which items of damage should be included in future versions of the CDA.

Weighting. The VDI weights all forms of damage equally and thus each item contributes equally to the damage index score. To address the need for weighting, 50 experts in vasculitis were asked to rank items on the CDA using an 11-point Likert scale (from 0 to 10). These ranks will be used to create a candidate-weighting schema²⁰. Future studies will determine if the use of weights improves the correlation between the damage index score and other outcomes that correlate with damage, such as mortality and quality of life.

Table 1. Research agenda for the OMERACT Vasculitis Working Group.

Domain	Issue	Potential Solution
Health-Related Quality of Life (HRQOL)	Usefulness of the SF-36 as an outcome measure for AAV	Analysis of SF-36 from randomized controlled trials and observational cohorts
	Role of organ-specific instruments	Pilot such instruments in ongoing studies and compare to generic tool such as SF-36; evaluate addition of organ-specific tools to SF-36
	Individual domain vs composite scores	Evaluate scoring approaches in ongoing studies
	Potential use of HRQOL data for health economics assessment	Evaluate EuroQol-5D in ongoing studies
Patient-reported outcomes (PRO)	Item generation and selection	Patient focus groups PROMIS NIH Toolbox for certain items, such as fatigue, sleep Delphi exercise with patients with vasculitis
	Item reduction, item weighting, and overall revision of the instrument	
	Need for vasculitis type-specific instruments/modules	Pilot general vasculitis instrument and vasculitis type-specific instrument
	Validation of new PRO instrument	Use in randomized controlled trials
	Comparison of PRO and HRQOL	Compare PRO and HRQOL data within same patient cohort
Damage	Item selection	Compile items from data in ongoing studies
	Item weighting	Weighting informed expert rankings and trial data
	Need for vasculitis type-specific instrument	Comparison of VDI to AVID in ongoing studies; data from CDA
Disease activity	Weighting of items	Determine data-driven weights using global assessment scores, medium-term outcomes (3–12 months), physician treatment decisions, relapse risk, death
	Discrepancies between instruments	Harmonization, standardization of tools, new single instrument
	Definition of disease states (e.g., remission, relapse, low-disease activity, high-disease activity)	Longterm cohort studies
	Inclusion of other forms of vasculitis	Disease-specific evaluations; generic vasculitis instruments plus vasculitis type-specific modules

SF-36: Medical Outcomes Survey Short Form 36 Questionnaire; PROMIS: Patient-Reported Outcomes Measurement System; NIH: US National Institutes of Health; VDI: Vasculitis Damage Index; AVID: ANCA Vasculitis Index of Damage; CDA: Combined Damage Assessment.

Disease specificity. Because the VDI was designed to be broadly applicable to all forms of vasculitis, the instrument may not accurately record forms of damage specific to WG and microscopic polyangiitis. To test this hypothesis, the ANCA-associated Vasculitis Index of Damage (AVID) was developed²¹. AVID and the VDI are being applied simultaneously to 200 patients enrolled in a clinical trial, and these data should allow for testing of the hypothesis that, compared to the VDI, a disease-specific instrument has greater discriminant power for determining the overall prevalence of damage as well as changes in damage over time.

Feedback at OMERACT 9 reinforced the supposition that the concept of damage was indeed an important domain that should be considered for inclusion in the core set once an instrument has passed the OMERACT filter. Future work will include ongoing drafting and validation of a damage index.

MEASURING HEALTH-RELATED QUALITY OF LIFE IN VASCULITIS

The patient perspective has become increasingly recognized in OMERACT as an important aspect to be identified in

assessing disease outcomes. One such patient-reported outcome (PRO), health-related quality of life (HRQOL), has been identified by the OMERACT Vasculitis Working Group as a key domain of interest to measure in vasculitis that should be considered for core set inclusion. HRQOL is the component of a patient's quality of life that is thought to be attributable to their health status, rather than their education or socioeconomic status²². AAV has been transformed from a disease of almost certain mortality to one of chronic morbidity, thus making HRQOL an important outcome to assess. HRQOL of patients with AAV is likely adversely affected by disease activity, disease-related damage, and medication side effects. Measures of HRQOL may be influenced by many factors, and thus may serve as an overall measure of treatment efficacy. Importantly, HRQOL is only moderately associated with levels of disease activity or damage in longitudinal studies in other systemic inflammatory diseases^{23,24} and, therefore, should be considered for separate assessment.

The OMERACT Vasculitis Working Group has set goals of: (a) optimally defining which measures adequately assess HRQOL in AAV; (b) determining the best method to report

HRQOL scores to adequately reflect patients' experiences with vasculitis; and (c) assessing the factors, including therapies, that influence HRQOL in vasculitis. HRQOL in vasculitis has typically been measured to date using the generic Medical Outcomes Survey Short-Form 36 Questionnaire (SF-36)²⁻⁴. However, it is not clear that generic tools such as the SF-36 are able to measure important aspects of HRQOL in AAV with adequate precision and sensitivity. For example, patients with AAV may have manifestations such as fatigue and sino-nasal symptoms that influence HRQOL but are incompletely identified by a generic instrument such as the SF-36. Generic measures have been shown to be less responsive than disease-specific instruments in several clinical trials²⁵⁻²⁸. Thus, additional symptom- or disease-specific instruments may be necessary to improve our understanding of the effect of AAV and its therapies on HRQOL²⁹. Further, because AAV is a complicated multisystem disease, the reporting of individual domains of HRQOL are best reported separately rather than as composite scores. The addition of health utility scores such as the EuroQol 5D may provide important information for overall summaries of health that can be incorporated into health economic assessments^{30,31}.

The OMERACT 9 attendees agreed that HRQOL was an important domain meriting further research that could enable its inclusion as a core set domain. The optimal use of the SF-36 will be explored using data from previous clinical trials in North America and Europe as well as planned cross-sectional and longitudinal cohort studies. The role of organ- or symptom-specific tools (e.g., fatigue severity scores and sino-nasal symptom scores) will also be studied. The results of such studies will inform clinicians and researchers on the determinants of HRQOL and domains that may be particularly important measures of the efficacy of future therapies in AAV.

MEASURING PATIENT-REPORTED OUTCOMES IN VASCULITIS

Consideration of HRQOL as an important domain of interest contrasts with the historical approach of outcome assessment in vasculitis, which was primarily based on items that physicians considered relevant in terms of disease activity, disease extent, and damage. However, beyond HRQOL, little is known and published about the patient's perspective of burden of disease in systemic vasculitis. Despite the development and improvement of physician-administered instruments measuring disease extent, activity, and damage, there are no vasculitis-specific instruments covering patient-estimated burdens of disease. Because patients' subjective experiences are important, particularly in making treatment decisions, such patient-reported burden of disease should be included in the outcome measurement process. It was identified as an important component for measurement at the OMERACT 8 conference. Therefore the Vasculitis Working Group sought to develop an instrument that assessed the patient's view of the

burden of disease, a concept that was felt likely to be an additional domain separate from, but complementing, HRQOL.

After a systematic literature review, analysis of existing data, and input from a panel of physicians with expertise in the care of vasculitis, a questionnaire was developed to collect data regarding patients' view of vasculitis-related health outcomes or burden of disease. Several hundred patients with various forms of vasculitis from 3 countries in North America and Europe were surveyed with this preliminary instrument. Data included details on patient demographics, clinical data, and ratings on Likert scales of 40 vasculitis-related items as well as open text comments. Preliminary analysis revealed, perhaps not surprisingly, that patients' views of the vasculitis-related health outcomes differ substantially from physicians' views³².

The discussion and feedback at OMERACT 9 to this PRO project was extremely positive. The group felt that PRO was an important domain to be included in any proposed core set of outcomes in vasculitis. There was strong consensus to consider collecting data within focus groups of patients with various types of vasculitis to further identify and select items of importance. Another option is to utilize the Patient-Reported Outcomes Measurement System (PROMIS; <http://www.nihpromis.org>) to add additional items, particularly those regarding fatigue and sleep. It was also suggested that persons with specific organ manifestations may be best able to identify the specific burdens associated with those manifestations (e.g., renal failure). The possibility of conducting a patient Delphi process for item selection was also discussed. These steps could be informative for item reduction, item weighting, and overall revision of the instrument. Further consideration will also be given to whether vasculitis type-specific instruments/modules for this relatively heterogeneous group of diseases are needed for PRO assessment. Future work will include establishing whether such a PRO instrument provides additional information separate from, but complementary to, HRQOL instruments in vasculitis.

OTHER DOMAINS AND AREAS OF INTEREST

As future research sheds light on the utility of biologic/biochemical, imaging, or other biomarkers in vasculitis, these will need to undergo rigorous evaluation under the OMERACT filter to determine whether they should be included as core set measures. Further, as disease management focuses on limiting patient burden of disease, participation and function are additional important domains that will need to be put on the research agenda. As the core set is further developed, the group will also explore the utility of applying the principles of the International Classification of Functioning (ICF) for documenting the manifestations of disease³³.

SUMMARY

The OMERACT Vasculitis Working Group has made significant progress since its initial participation in OMERACT 7.

Based on the work to date, Figure 1 depicts a framework for the domains of interest identified as being important in vasculitis outcomes research. Through the OMERACT process, consensus has been reached to move forward with research on key domains and subsequently propose a core set of domains for inclusion in clinical studies of vasculitis (the inner circle in Figure 1). Table 1 outlines the specific research agenda for these domains. Other domains of interest are also felt to be important, but further work is required to determine whether such domains should be included in the core set, or whether they would complement the information obtained from the core set (the second circle in Figure 1). Finally, future research agendas will explore other domains, which may lead to additional useful outcome measures that may add to or complement the core set (the outer circle in Figure 1). The OMERACT Vasculitis Working Group plans to address the specified research agenda in Table 1 in an effort to have the initial 4 key domains, which were identified at OMERACT 8 and endorsed at OMERACT 9, evaluated through the OMERACT filter for inclusion in a core set of vasculitis outcomes at a future OMERACT meeting.

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