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Developing a composite outcome tool to measure response to treatment in ANCA-associated vasculitis: A mixed methods study from OMERACT 2020

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ABSTRACT

Objective: The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group aims to develop composite response criteria for ANCA-Associated Vasculitis (AAV).
Methods: The project follows the OMERACT approach for composite measures: (i) choose relevant domains; (ii) define high-quality instruments; (iii) decide on a scoring system approach; (iv) put through the OMERACT Filter 2.1 for validation.
Results: A systematic literature review of outcome measures used in clinical trials in AAV and an international Delphi exercise among patients with AAV and clinician-investigators with expertise in AAV have been completed to inform the candidate domains/instruments for the composite response criteria, which are the first two steps in the OMERACT approach for developing composite measures. Results of the systematic literature review and Delphi were presented at the OMERACT 2020 virtual workshop, and feedback was received on the next steps of the project, including the development of a scoring system approach.
Conclusion: The ultimate goal of this project is to develop validated composite response criteria for use in clinical trials of AAV.

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Introduction

ANCA-associated vasculitis (AAV) is a group of disorders characterized by inflammation of small- and medium-sized arteries. Previous work by the Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group [1] has included the development of a core set of domains and outcome instruments for use in clinical trials in AAV, which received endorsement at OMERACT 2010 [2]. This core set includes domains of disease activity, damage assessment, patient-reported outcomes (PROs), and mortality. Although PRO instruments were included in the core set, vasculitis disease-specific instruments were not available and became a subsequent focus of the Vasculitis Working Group. The Group developed both the AAV-PRO and tested the Patient-Reported Outcome Measurement Information System

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(PROMIS) for use in AAV, approaches that received endorsement by OMERACT [3,4]. However, these PROs have not contributed to the primary endpoint in RCTs in AAV published to date.

Clinical trials in AAV have used multiple instruments to define active disease or remission [2]. The most commonly used instrument for measurement of disease activity in AAV is the Birmingham Vasculitis Activity Score (BVAS) available in several versions [5-8]. BVAS has helped to advance the conduct of randomized controlled trials (RCTs) in AAV, but several challenges remain. BVAS provides a numerical score which is reduced in RCTs to a dichotomous variable representing active disease (BVAS>0) or remission (BVAS=0) [9-18]. The score is not linear (e.g. BVAS=12 does not indicate the disease is three times worse than BVAS=4); therefore, partial treatment response beyond the transition between active disease and remission (i.e., intermediate disease states) is not easily captured [19]. Patient input was not part of the development of BVAS. Since AAV is a multi-system disease with multifaceted impacts on patients, a composite response measure is likely to best capture the full spectrum of disease.

The goals of this project are to: 1) Develop an outcome tool that captures the full burden of illness across multiple domains and detects clinically important responses to treatment across intermediate disease states in AAV and 2) Develop, validate, and attain endorsement by the American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR), and OMERACT for new composite response criteria in AAV for use in clinical trials.

This report outlines the completed, current, and next steps in the development process for composite response criteria for AAV, illustrates the steps and challenges in developing composite measures for multi-system diseases, and summarizes the work leading up to and accomplished at OMERACT 2020.

Methods

The project to develop composite response criteria to assess response to treatment in AAV in clinical trials follows the OMERACT approach for composite measures: (i) choose relevant domains; (ii) define high-quality instruments; (iii) decide on a scoring system approach; (iv) put through the OMERACT Filter 2.1 for validation [1, 20, 21] (Fig. 1). The candidate relevant domains/instruments for a composite measure of response in AAV will be selected based on the OMERACT core set for vasculitis [2], a systematic literature review of outcome measures used in randomized controlled trials (RCTs) of AAV [22], a Delphi exercise among patients with AAV and clinician-investigators with expertise in AAV, and expert opinion. Steps to create a scoring system approach will include: i) creation of clinical vignettes from trial-level data, ii) virtual conferences with an expert panel, and iii) discrete choice experiments using the 1000Minds software system [23] to faciliate decision-making involving multiple criteria.

The project is led by a Steering Committee comprised of the authors of this article: two principal investigators (GT and PAM), two fellows (SM, the EULAR fellow) and (KQ, the ACR fellow), two patient research partners (GL and MBV), a biostatistician and OMERACT Technical Advisory Group member (RC), an epidemiologist expert in outcomes measures (BS), and additional experts in vasculitis from North America (CL and CP) and Europe (DJ and AM).

The OMERACT AAV Response Criteria Workshop was held on December 7, 2020 with two virtual sessions in the same day to allow more participants to attend. The rationale and outline of the project were presented to workshop participants, including an overview of composite measures, an overview of AAV, and limitations of existing measures of response in AAV [1]. To facilitate active discussion and obtain feedback regarding open or difficult issues in the development of composite response criteria for AAV from the OMERACT community of patients, clinicians, investigators, and methodologists, breakout sessions were conducted with several key questions discussed: 1) "How do we balance the perspectives of patients and physicians when selecting and weighting items for the composite instruments?"; 2) "How do we handle a large number of candidate relevant domains/instruments for a composite measure of response in AAV?"; and 3) "What are the major challenges for creating a composite outcome for a complex, multi-system disease?". Each breakout group included a facilitator and a scientific reporter.

Progress to date

Systematic literature review

A systematic literature review of outcome measures used as primary or secondary outcomes in RCTs of AAV (GPA and MPA) was

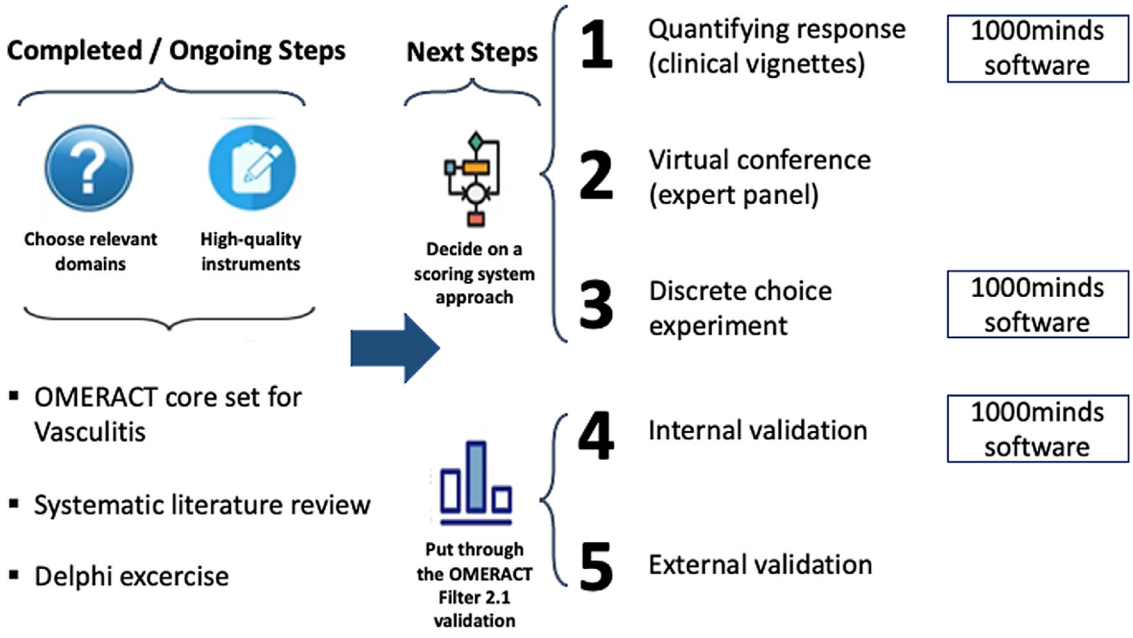

Fig. 1. Main steps in the development of composite measure for response criteria in ANCA-associated vasculitis.

conducted by searching Medline, Cochrane CENTRAL and ClinicalTrials.gov through April 30, 2019 and the results have been published [22]. Sixty-eight RCTs were identified. Outcome measures assessed in trials of AAV frequently included vasculitis-specific instruments for disease evaluation, but with variability in the definitions applied. A version of BVAS was the most widely used instrument for disease assessment. Definitions of single endpoint definitions for remission or relapse varied across RCTs. Damage was mainly assessed with the Vasculitis Damage Index and was a study outcome in 44% of the studies. Other outcomes assessed included: PROs (41%), drug exposure/safety (85%), and changes in biomarkers such as acute phase reactants or ANCA levels (35%). There was much heterogeneity in the timing for outcome assessment with the most frequent timepoints to assess response to treatment being 3, 6, and 12 months [22].

Delphi exercise

A 3-round online Delphi exercise using Delphi Manager software was conducted to reach consensus about which measures are considered by patients and physicians to be most important when assessing treatment response in clinical trials in AAV. Survey participants included international experts in AAV, recruited from the Vasculitis Clinical Research Consortium (VCRC) and European Vasculitis Study Group (EUVAS), and patients with AAV recruited from the Vasculitis Patient-Powered Research Network (VPPRN), the Vasculitis Foundation, and Vasculitis UK. The items included in the Delphi were based on the results of the systematic literature review and included items related to disease activity, patient-reported outcomes, organ damage, and adverse events. Participants rated on a scale of 1–9 the importance of each variable when assessing response to treatment in a clinical trial in AAV.

A total of 265 participants completed rounds 1–3 of the Delphi, including 176 experts in AAV and 89 patients with AAV. After completion of 3-rounds, 31 items were approved [≥70% participants rated the item as "critically important" (7–9)] and 0 items were rejected [≥70% participants rated the item of "limited importance" (1–3)] by both stakeholder groups. There were 16 additional items approved by either only patients or physicians. The most highly rated items related to disease activity included use of BVAS, extent of organ involvement, and global assessment. The most highly rated items related to patient-reported outcomes included global assessment, and changes in health-related quality of life measures. A fourth round is being conducted to rank items to help reduce and consolidate the list of approved items, and to finalize the domains and high-quality instruments for inclusion in the next steps of the development of this composite measure (Fig. 1).

OMERACT 2020 workshop

Eighty-one participants attended the OMERACT 2020 virtual workshop: 72 (89%) clinician/researchers and 9 (11%) patient research partners. During the workshop the Steering Committee presented the results of the systematic literature review and preliminary findings from the Delphi exercise, and an outline of planned methodology to develop composite response criteria in AAV, with the goal of obtaining feedback on challenges in the development of composite response criteria. Feedback from the eight breakout groups included strong endorsement of the importance of patient involvement and keeping both patient research partners and physicians involved in the project in parallel. The need for the composite response criteria to balance patient-reported outcomes and physician-based measures was also emphasized, and that items rated critically important by only one stakeholder group should still be considered. The main feedback for managing the large number of candidate relevant domains/instruments was to combine or group similar items from the Delphi to reduce redundancy and proceed with a fourth round of ranking, prioritizing items within a domain so that all domains are represented. To address the major challenges in creating composite response criteria, members of the breakout groups reflected on their experiences with composite outcomes in other rheumatologic diseases and highlighted the importance of incorporating different domains, separating toxicity from response, and avoiding inclusion of elements that will not respond to treatment.

Discussion

The first two steps in the OMERACT approach for composite measures for response criteria in AAV have been nearly achieved [i) choose

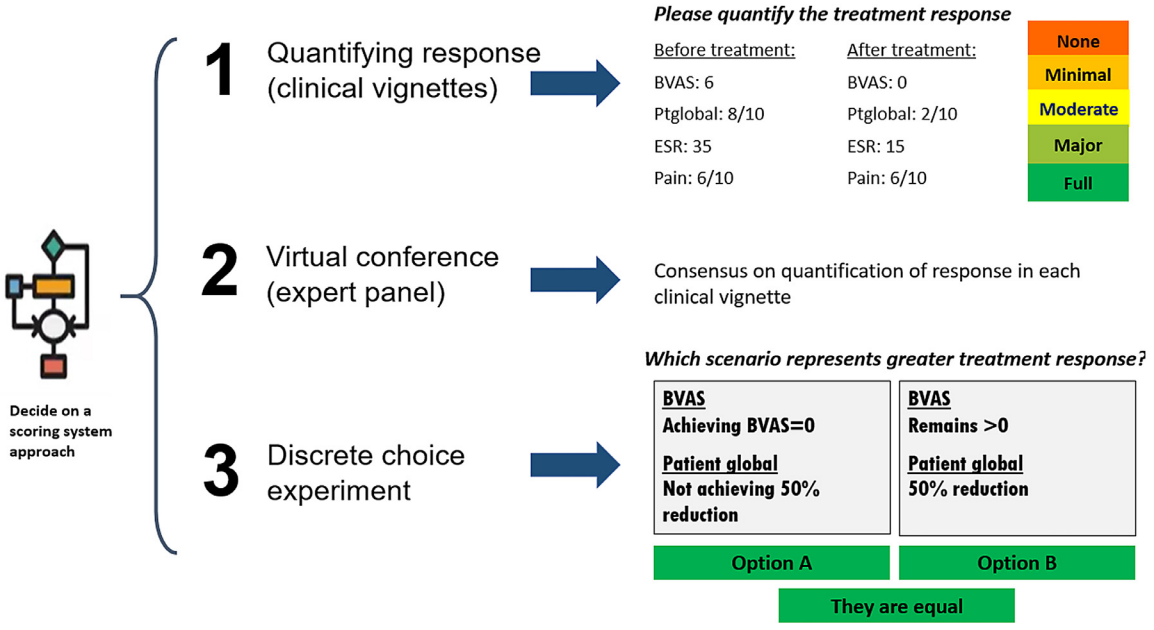

Fig. 2. Example of steps in the development of a scoring system for response criteria, including quantification of response, expert panel meeting, and discrete choice experiments.

relevant domains and (ii) define high-quality instruments], with the development of a core set of domains and outcome instruments for use in clinical trials in AAV [2], completion of the systematic literature review of outcome measures used in RCTs of AAV [22], and completion of the patient and physician Delphi exercise (pending results of the fourth round). During the OMERACT 2020 workshop, positive feedback about the progress of this project was received, and attendees provided suggestions on the final two steps in the OMERACT approach for composite measures [(iii) decide on a scoring system approach and (iv) put through the OMERACT Filter 2.1 for validation] (FIG. 1).

To decide on a scoring system approach, three additional steps are planned: 1) quantifying response using clinical vignettes, 2) virtual conferences with an expert panel, and 3) discrete choice experiments to faciliate decision-making involving multiple criteria (FIG. 2). Quantification of response will be conducted as an on-line exercise. Clinical cases will be presented and individuals will be asked to quantify treatment response in each case. The AAV Response Criteria Project Expert Panel will include experts in AAV and patient research partners to collect broader inputs and help ensure the development of a useful, feasible, and internationally accepted tool to assess response in AAV. At the Expert Panel conference, differences in responses among experts will be discussed, with a goal of reaching consensus on quantification of response in each clinical vignette. Finally, discrete choice experiments will be conducted through which the same expert panel will be presented with two scenarios and asked to assess which represents greater treatment response. This exercise will lead to numerical estimates for the relative importance of each criterion towards the overall composite response criteria (FIG. 2).

In the final step in the OMERACT approach for composite measures [(iv) put through the OMERACT Filter 2.1 for validation] (FIG. 1), internal validation will be performed using the same clinical vignettes and group of experts from prior steps, with quantification of response performed according to the new composite response criteria, rather than expert opinion. Agreement between expert opinion from earlier steps and the new composite response criteria will be calculated. External validation will involve using trial data to see how the new composite response criteria differentiate between treatment arms in RCTs. The ultimate goal will be to finalize validated composite response criteria for use in clinical trials in AAV.

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