Patient Related Outcome Measures

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REVIEW

Systemic vasculitis and patient-reported outcomes: how the assessment of patient preferences and perspectives could improve outcomes

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Abstract: The systemic vasculitides are a group of multisystem diseases, which can be life and organ threatening. High-dose immunosuppressants are required to control inflammation in vital organs, such as the kidneys, lungs, skin, joints, and eyes. Patients report a range of impacts on their health-related quality of life due to symptoms, irreversible damage, and the adverse effects of medications. The measurement of patient perspectives within clinical studies in vasculitis is essential to capture outcomes of greatest importance to patients. Validated generic, disease-specific and symptom-specific patient-reported outcomes available for use in patients with systemic vasculitis are reviewed here.

Keywords: patient-related outcomes, vasculitis, ANCA-associated vasculitis, large-vessel vasculitis, Behcet's syndrome, clinical trials

Introduction

The systemic vasculitides present clinically with inflammation in multiple regions of the body and can be life and organ threatening.[1–3] Randomized controlled trials with standardized, physician-derived outcome measurement of disease activity and damage have revolutionized the treatment of these diseases.[4–6] Systemic vasculitis is no longer invariably fatal, but patients can still suffer ongoing activity, organ damage that cannot be repaired, and adverse effects of immunosuppression.[7–9]

The impact of symptoms and side effects of treatment in systemic vasculitis can affect all aspects of health-related quality of life (HRQoL).[8,10,11] Systemic vasculitis affects people of working age[12] and those planning a family[13,14] or active retirement.[15] Patients also face the situation of having a rare autoimmune rheumatic disease,[16] which can be isolating, resulting in delays to get a diagnosis and treatment, and difficulties in navigating health care systems between different specialists.[16] Patients with vasculitis rank items of importance (in terms of symptoms and impact), differently to how their clinicians would rank those items.[17,18]

The Outcome Measurement in Rheumatology (OMERACT) initiative is an international collaboration of patients, researchers, clinicians, and methodologist to define core sets of outcome measurements for use in randomized controlled trials.[19] Stakeholder groups including the Food and Drug Administration and pharmaceutical companies also participate.[19] OMERACT has endorsed a core set of domains and outcome measures for use in clinical trials in ANCA-associated vasculitis (AAV)[20], large-vessel vasculitis[21], and Behçet's syndrome,[22] each set developed by the OMERACT Vasculitis Working Group. Measurement of disease activity levels and irreversible damage within clini-

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cal trials has been facilitated by physician-derived outcome measures, for example, the Vasculitis Damage Index.[23] In recent years, the patient perspective in systemic vasculitis has been a major focus for the vasculitis research community. A new disease-specific patient-reported outcome (PRO), the AAV-PRO,[24] has been validated; underpinning qualitative work in Takayasu's arteritis (TAK) and Behcet's syndrome has been performed;[25,26] and evaluation of alternative generic PROs including the Patient-Reported Outcome Measurement Information System (PROMIS) is underway.[27]

Measurement of HRQoL in vasculitis has mostly relied on the use of "generic" PROs, mainly the Short Form 36 (SF-36),[28] which is a well-recognized and validated outcome measure that allows comparison between patients with systemic vasculitis and other conditions.[28] As generic PROs were not designed for use in a specific disease, these measures can have reduced face and content validity in some settings.[29] This lack of specificity may reduce the ability to detect differences in disease states between patients and in the same patient over time.[29] Trials in AAV, for example comparing cyclophosphamide to rituximab, have not demonstrated a difference in SF-36 scores between arms, despite differences in the toxicities of the medications.[30] This may be due to a lack of sensitivity of the SF-36 or the high levels of glucocorticoids used in both trial arms. In a randomized trial of Avacopan (C5a receptor inhibitor) in AAV, patients not on glucocorticoids scored better on the physical domain of the SF-36.[31]

Disease-specific PROs should be developed with patient involvement throughout, in line with guidance from the US Food and Drug Administration on the development of PROs.[32] Good face and content validity is ensured by incorporating qualitative research with patients with the disease in question, to identify the full range of impacts of the disease and its treatment.[33] Questionnaire items are then based on the themes identified and are refined through piloting and cognitive interviews.[34] A survey including exploratory factor analysis[35] and Rasch analysis[36] can be used to identify the final structure of the PRO and to validate its measurement properties.[24,37]

This article describes the impact on HRQoL of living with AAV, TAK, giant cell arteritis (GCA), and Behçet's syndrome. Measurements of the patient perspective in the systemic vasculitides, through the complimentary use of generic and disease-specific and symptom-specific PROs, are also described.

AAV

AAV encompasses three multisystem diseases: granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis.[38] The AAVs are multisystem disorders resulting in inflammation and damage occurring in the kidneys, lungs, skin, ear nose and throat, eyes, and neurological system, and these manifestations can impact on HRQoL.[2,10]

Newly diagnosed patients with AAV have demonstrated impairments in HRQoL at entry into European Vasculitis Study Group trials[39], the Wegener's Granulomatosis Etanercept Trial,[41] and the French MAINRITSAN trial.[42] Physical functioning scores are the most affected, particularly in those with neurological involvement and older ages. Patients with AAV also report high levels of fatigue and rank this aspect as being of greatest importance to their overall HRQoL.[17,43] Survey data suggest that AAV-related fatigue is likely to be multifactorial and associated with pain, sleep disturbance, and higher levels of inflammation.[44] More than 40% of patients with vasculitis report symptoms of anxiety, and one-quarter report symptoms of depression, as measured by the Hospital Anxiety and Depression Scale.[9] Fifty in-depth qualitative interviews with patients with AAV-identified themes related to fear, anxiety, and stress in 70% of participants, while 50% of interviewees reported depression and 50% reported anger due to their disease or its treatment.[10]

Within the 2010 OMERACT core set for AAV, the OMERACT Vasculitis Group included the generic –SF-36 as the outcome measure to capture HRQoL.[20] They also identified the need for further work around capturing patient perspectives in AAV including exploration of alternative generic item banks and a disease-specific PRO.[45]

An international collaboration of patients and researchers from the United Kingdom, United States, and Canada formed a steering committee to oversee the development of a disease-specific PRO.[45]

Qualitative interviews with 50 patients with AAV from the three countries identified the following themes: symptom severity, and the impact of problems and limitations imposed by patients' AAV and treatment, on their work; domestic roles; family and social interactions (including activities and interests outside the home) and psychological state.[10] Underpinning themes were then recast as candidate questions for the new disease-specific PRO, and these questions were reduced and refined via piloting and cognitive interviewing.[24] A large-scale survey was then used to determine the ideal structure of the PRO, including domains and items, and to validate its measurement properties.[24] AAV-PRO domain scores distinguish between patients who self-report active disease vs disease in remission, has good construct validity, and is reliable and feasible to use.[24] It has good face validity due to having four patient partners on the steering committee and involvement of patients at each stage.[24]

The AAV-PRO questionnaire 29-item includes six subscales/domains: "Organ-Specific Symptoms", "Systemic Symptoms", "Treatment Side Effects", "Social and Emotional Impact", "Concerns about the Future", and "Physical Function". The domains provide a profile of the impact of AAV and its treatment on patients' everyday life.[24]

Each domain is scored separately to provide a profile of the overall impact of the disease and its treatment on HRQoL. Certain domains may be of interest in specific contexts; for example, the treatment and adverse effects domain may be important within therapeutic drug trials, but it would be important to collect the range of domain scores to identify the full impact on patients HRQoL and symptoms. In future, summary component scores may be derived, but this approach needs further investigation.

The AAV-PRO survey identified that women scored higher (ie, worse) on all six subscales.[24] Trends toward worse scores have been previously seen in female patients with AAV,[40] and HRQoL is reduced in other chronic conditions.[46,47] Younger people with AAV (<65) scored higher (worse) on the Social and Emotional Impact subscale of the AAV-PRO; this is also seen in other chronic diseases.[46,48] Younger age is a risk factor for fatigue and negative illness perceptions in AAV.[49]

The OMERACT Vasculitis Working Group gained endorsement by OMERACT for use of certain PROMIS domains and the AAV-PRO in clinical trials of vasculitis.[50] These instruments are complementary to each other. Both require further work to assess their validity in longitudinal settings, including their ability to discriminate between treatments of varying efficacy in the setting of a randomized controlled trial. Comparison of AAV-PRO domain scores with SF-36 domain scores in clinical studies of patients with AAV, to examine different aspects of construct validity, will also be an important validation step for the AAV-PRO.

GCA

GCA is caused by inflammation of the blood vessels around the head and neck, and elsewhere.[51] GCA frequently presents with severe headache, jaw claudication, systemic features including flu-like symptoms, fevers, and weight-loss, and polymyalgia rheumatica (inflammatory pain and stiffness in the hips and shoulders).[52] There is a risk of visual loss in 20% of untreated cases[52,53] and high-dose glucocorticoids are required to protect sight.[54,55] Glucocorticoids alone have been the only treatment available, but patients can suffer adverse frequent adverse effects including hypertension, diabetes, osteoporosis, psychiatric disturbance, and change in appearance.[56–59] A novel biologic medication, the interleukin-6-receptor inhibitor tocilizumab, appears to improve HRQoL at 1 year in patients with GCA;[60] this finding should be examined further but may be associated with the drug's glucocorticoid-sparing effect. The impact of GCA on patients' lives is due to a combination of symptoms (eg, visual disturbance, musculoskeletal symptoms and pain), adverse effects of glucocorticoids, and the disruption to normal life.[15] Patients fear blindness, have concerns about delay in diagnosis,[15] and rank losing sight in both eyes permanently', "having intense or severe pain" and "feeling weak, tired or exhausted" as key domains of HRQoL.[11] In patients with GCA, SF-36 scores do not correlate with visual loss or systemic complications, so generic PROs may be unable to differentiate between clinically important groups.[61,62] The OMERACT Vasculitis Working Group has, therefore, identified the development of a disease-specific PRO for GCA within their research agenda.[21,63]

At OMERACT 2018, qualitative work from patients with GCA in the United Kingdom and Australia was presented and included the following salient themes: "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".[64] These themes could be developed further into candidate questionnaire items for a disease-specific PRO for GCA.

The PROMIS is a bank of items, which have been generated from disease-specific PRO measures in a range of different diseases (examples include osteoarthritis, cancer, or asthma), to create generic item banks for particular domains eg, physical or mental health. Items within the PROMIS domains of Fatigue and Physical Function have been tested in patients with GCA and were found to be feasible to use, scores correlating with relevant SF-36 domain scores; but further validation work is needed.[27]

TAK

TAK is a systemic inflammatory condition that affects the large arteries, specifically the aorta and its major branches and the pulmonary arteries.[65] Symptoms can be systemic including weight loss, fever and fatigue, or due to vascular inflammation and occlusion, leading to pain, claudication and tissue loss.[65] Patients with TAK are diagnosed early in life. Patients with TAK have physical limitations and high levels of anxiety and depression compared with healthy controls;[66] scores are comparable to those from patients with ankylosing spondylitis and rheumatoid arthritis.[67] Younger patients and

those in remission have better HRQoL, while those requiring immunosuppression have worse HRQoL.[7]

The OMERACT Large Vessel Vasculitis Working Group identified the lack of a disease-specific PRO for TAK.[68] Qualitative research was performed through individual interviews and focus groups with patients with TAK from the United States and Turkey.[25] Salient themes identified included "Pain and Discomfort", "Fatigue and Low Energy Levels", and "Emotional Effects", and these themes could underpin the development of a disease-specific PRO for TAK.[25]

Behçet's syndrome

Behçet's syndrome affects a spectrum of various veins and arteries of different sizes[38]; patients can therefore present with a range of symptoms.[69] Oral and genital ulcers, nodular and papulopustular skin lesions, pan-uveitus, inflammatory arthritis and bowel disease, and a range of neurological disorders can occur.[69,70]

Oral and genital ulcers, neurological and ophthalmological involvement, joint pain, female sex, and high disease activity are specifically associated with worse HRQoL in patients with Behçet's syndrome; all patients have worse SF-36 scores compared with healthy controls.[8,71] Sexual function can be impaired in men and women.[72]

A systematic review of outcome measures used in Behçet's syndrome by the OMERACT Vasculitis Working Group revealed large variability in terms of outcomes, including PROs used across trials.[73] Generic measures to evaluate HRQOL in Behçet's syndrome include the EQ-5D,[73] but mainly the SF-36,[74]. Symptom-specific PROs have also been used in Behçet's syndrome, including the Oral Health and Related Quality of Life Scale[75] and the Arizona Sexual Experience Scale.[72] Psychological impact has most commonly been measured using Beck Anxiety Scale[76,77] and the Beck Depression Index.[78]

The review identified a validated disease-specific PRO, the Behçet's Disease Quality of Life Scale (BD-QoL),[37,77,79,80] which was developed in the United Kingdom and has undergone cross-cultural adaptation and validation in Korean and Arabic.[79,81] Item development was based on the qualitative work with patients with BD and included the following salient themes: "Relationships", "Emotions", "Limitations in Day to Day Activities", and "Self-Image".[37]

Conclusion

Patients with systemic vasculitides have different perspectives on their disease and its impact to their clinicians. It is important to capture the patient perspective accurately and reliably within clinical studies using validated outcome measures, which assess areas of greatest importance to patients. A limitation of PROs is that some aspects of a condition, which are objectively important to measure and very relevant to outcome (eg, blood pressure), may not be experienced by patients and therefore not represented. PROs are, therefore, complementary to physician-derived outcomes in terms of determining what matters most to patients with vasculitis, in relation to their disease and its treatment. Greater precision when measuring the impact on patients, for example, in terms adverse effects and fatigue, will facilitate targeted assessment of novel pharmacological and non-pharmacological interventions. There are advantages of using generic PROs, such as the SF-36, which facilitates direct comparison across diseases and, in some contexts, allows for unforeseen side effects to be detected; and the disease-specific PROs, such as the BD-QoL, which has fine-tuned, specific elements, with high face validity to patients with the disease in question. There is, therefore, a role for both.

The growing recognition of the importance of PROs in the assessment of vasculitis, and the availability of validated instruments to capture PROs in vasculitis may also mean that patients' perspectives will be incorporated into composite outcome measures in future trials.

Disclosure

JCR, PAM, and JD developed the AAV-PRO. The authors report no other conflicts of interests in this work.

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