What matters for patients with vasculitis?

Elaine Novakovich, Peter C. Grayson

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National Institutes of Health/NIAMS, Vasculitis Translational Research Program, Bethesda, MD 20892, United States

Correspondence:
Peter C. Grayson, National Institutes of Health/NIAMS, 10 Center Drive, Building 10, Rm 216G, Bethesda, MD 20892, United States.
peter.grayson@nih.gov

Summary

Advances in clinical care for patients with vasculitis have improved survival rates and created new challenges related to the ongoing management of chronic disease. Lack of curative therapies, burden of disease, treatment-related side effects, and fear of relapse contribute to patient-perceived reduction in quality of life. Patient-held beliefs about disease and priorities may differ substantially from the beliefs of their health care providers, and research paradigms are shifting to reflect more emphasis on understanding vasculitis from the patient’s perspective. Efforts are ongoing to develop disease outcome measures in vasculitis that better represent the patient experience. Health care providers who care for patients with vasculitis should be sensitive to the substantial burdens of disease commonly experienced by patients living with the disease and should strive to provide comprehensive care directed towards the medical and biopsychosocial needs of these patients.

The systemic idiopathic vasculitides are a group of rare diseases characterized by inflammation and necrosis of blood vessel walls with potential resultant organ- and life-threatening outcomes. The clinical spectrum of disease is often dependent on the size, number, and site of involved blood vessels [1]. Onset of vasculitis occurs throughout the age spectrum. Certain types of vasculitis, such as Takayasu’s arteritis, present in childhood or early adulthood. Other types of vasculitis, such as giant cell arteritis, are exclusive to later life. Advances in therapy have transformed vasculitis from a frequently fatal disease into a chronic illness. Physician-based measures for disease assessment have facilitated the conduct of successful clinical trials that have identified effective medical therapies and led to improved survival rates [2,3]. Despite these advances, patients with vasculitis continue to manage substantial burdens of illness. Treatment with potentially toxic medications, including glucocorticoids and other immune suppressants such as cyclophosphamide, is generally required to prevent fatal outcomes in severe cases. Although it is possible for most patients with vasculitis to achieve remission with therapy, the majority of patients experience disease relapse despite expert care, and relapses can be fatal. Across different types of vasculitis, the disease course is often chronic, relapse is common and
unpredictable, organ and tissue damage can accrue over time, new symptoms can occur late into the disease course, and the burdens of disease and treatment-related side effects can significantly impair psychological well-being and quality of life. The objective of this review is to describe disease burdens that are common to patients living with vasculitis. Research focused upon understanding vasculitis from the patient’s perspective, prioritizing issues relevant to patients, and development of patient-centered outcome measures in vasculitis is discussed.

**Material and methods**

A search of publications related to vasculitis and the burden of illness was conducted using the Medline (PubMed) library. The following search terms were used: vasculitis, granulomatosis with polyangiitis (Wegener’s), microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss), polymyalgia nodosa, Takayasu’s arteritis, giant cell arteritis, burden of illness, quality of life, health related quality of life, outcome, patient reported, self-reported, illness perceptions, patient education, employment, disability, psychological impact, physical impact, fatigue, depression, fibromyalgia, anxiety, unmet needs, sleep, reproductive health, pregnancy, fertility, genetics, medication adherence, and pain. Bibliographies of existing publications were reviewed. All abstracts were manually reviewed to identify studies of interest with focus upon prospective interventional or observational studies conducted within the last five years in larger study populations.

**Illness perceptions and educational needs**

Illness perceptions are the organized beliefs that patients have about their illness [4]. The validated revised Illness Perception Questionnaire (IPQ-R) [5] has been used to study patient-held beliefs about the symptoms that belong to vasculitis, the perception of the course of vasculitis, the overall understanding of the condition, and the degree of personal and treatment-based controllability of the disease. Among 692 participants representing 9 types of vasculitis, illness perceptions were strikingly similar across different forms of vasculitis and reflected strongly held beliefs about the substantial negative impact of disease on ability to function and emotional well-being [6]. Younger age, history of depression, active disease status, and poor overall health risk were risk factors for higher perceived burden of illness. Patient-held beliefs about cause of systemic vasculitis are highly variable, but altered immunity and stress are commonly agreed-upon causal beliefs [7]. Patients who hold certain causal beliefs, such as a belief that a change in the weather triggers relapse, tend also to report a higher degree of functional impairment, fatigue, and confusion about the condition. The majority of patients (90%) have specific beliefs about what caused their vasculitis and find discussions with their healthcare provider about their beliefs to be beneficial [7].

Patient educational and self-management programs can influence patient self-efficacy and health outcomes [8]. In a cohort of patients with vasculitis from the United Kingdom or the United States, information on diagnosis, prognosis, investigations, treatment and side effects was rated as extremely important [9]. Information on patient support groups and psychosocial care was rated as less important, and there were no major differences in rating of needs based on available clinical or demographic information. Patients with chronic conditions like vasculitis are encouraged to self-manage as much as possible and lack of effective patient education is a potential barrier to effective self-management [10]. Patients with vasculitis prefer to receive educational information about their disease from a knowledgeable healthcare professional with supporting written material rather than receiving information from the Internet or in a group setting [9,11]; however, most patient education materials for rheumatologic diseases are written at readability and suitability levels that do not support patient health literacy [12].

**Quality of life, fatigue, and patient outcome measures**

Several studies have examined health-related quality of life (HRQoL) in vasculitis, with particular focus upon the ANCA-associated vasculitides [13]. Despite advances in clinical management of vasculitis, HRQoL remains substantially reduced during both active disease and remission [14-19]. Approximately 20–30% of patients with vasculitis of working age report significant work disability [20-22]. Fatigue, depression, severe disease-related damage, and being overweight have been independently associated with risk for unemployment [20]. Over half of patients with vasculitis report that the circumstances of living with a rare chronic illness have negatively impacted friendships and social participation [23]. Interventions designed to help patients cope with the impact of vasculitis on HRQoL are needed. Patients with vasculitis frequently cite fatigue as one of the most burdensome symptoms of disease with significant negative impact on quality of life [24-26]. Despite a reported prevalence of severe fatigue in 2 out of 3 patients with vasculitis [6,27], the mechanisms underlying fatigue are poorly understood. Similar to other chronic illnesses, fatigue does not strongly correlate with disease duration or validated measures of disease activity, suggesting that psychosocial measures may in part mediate fatigue [6,28]. Fatigue has been associated with numerous clinical and biopsychosocial factors, including disease- and medication-related effects [29], patient-held illness perceptions [6], findings on functional magnetic resonance imaging [30], androgen deficiency [31], sleep disturbance [27,28], pain [27,29], female gender [27], dysfunctional coping strategies [27], and depression [28]. In other forms of chronic illness, non-pharmacological interventions [32] and cognitive
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behavioral therapy targeting cognitive factors contributing to fatigue [33] have demonstrated clinically significant and sustained reductions in fatigue. Similar approaches in vasculitis should be considered (box 1).

Lack of correlation between fatigue and existing physician-derived disease-activity indices in vasculitis highlights a need to incorporate patient-reported disease outcome measures in vasculitis. Physicians and patients with vasculitis may differ in their perspectives about the relationship of symptoms and disease activity [24]. For example, while physician-derived measures of disease activity do not correlate with fatigue, patient-reported disease activity status is strongly associated with degree of fatigue, suggesting that patients perceive fatigue to be a manifestation of active vasculitis [6,28]. Discordance between physician and patient perception of vasculitis activity is common, and change in patient-reported outcomes during remission may even precede periods of active disease as detected by physicians [34].

Efforts to develop patient-reported outcome measures (PROs) in vasculitis that sufficiently represent the patient perspective are ongoing. The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group has prioritized use of the Patient-Reported Outcomes Measurement System (PROMIS) for assessment of patient-reported outcomes in ANCA-associated vasculitis and development of a disease-specific patient-reported outcome instrument in ANCA-associated vasculitis [35]. The Patient-Centered Outcomes Research Institute (PCORI) recently launched the National Patient-Centered Clinical Research Network (PCORnet) to develop 18 patient-powered research networks (PPRNs), including a vasculitis-specific PPRN, that together will become a resource for integrating patient-generated data and electronic health information and conducting comparative effectiveness research [36]. These efforts will provide unprecedented opportunities for patients, clinicians, and researchers to work together to promote patient-centered outcomes research in vasculitis.

**Treatment and medication adherence**

Survival rates have improved across different types of vasculitis since the introduction of immunosuppressive therapy [37]. Despite improvements in the management of vasculitis, mortality remains increased compared to the general population in both the early and later stages of disease, highlighting an ongoing need for earlier diagnosis and targeted therapies [37]. The medications commonly used to treat vasculitis carry substantial risk for toxicity, including malignancy, infections, and other related side effects. High doses of glucocorticoids remain a mainstay of therapy for most types of vasculitis and are commonly associated with a wide range of potentially debilitating side effects. Minimizing glucocorticoid use is a high priority in vasculitis management, and algorithms to reduce the duration and total amount of glucocorticoid study are currently being investigated within ongoing clinical trials [38,39].

Advances in therapeutic options in ANCA-associated vasculitis (AAV) have outpaced advancements in other types of vasculitis. Currently, there are several therapeutic options for both the induction and maintenance phases of treatment in AAV [40–43]. Given the number of medications with proven efficacy at different stages of AAV, the identification of biomarkers that can be used to individualize treatment plans has become a high priority in AAV. The majority of patients with AAV will experience one or more relapses within five years of successful remission induction [44], and relapse can be life threatening [45]. There are few clinical or serologic predictors of relapse in AAV [46–49], and no predictor has been shown to reliably guide therapeutic decision-making [50]. Identifying biomarkers that predict clinical outcomes and novel therapeutics that induce durable remission is a high priority in AAV. In contrast to AAV, few randomized clinical trials have been conducted in other types of idiopathic vasculitis. In the large vessel vasculitides (giant cell arteritis, Takayasu’s arteritis) long-term glucocorticoid therapy is often required, and a lack of successful randomized clinical trials has limited the available adjunctive therapeutic options [51]. Glucocorticoid-related adverse events have been reported in 86% of patients with giant cell arteritis over 10-year follow up [52], highlighting the need for steroid-sparing therapies in this disease.

Patient survival in vasculitis is dependent upon medication adherence, yet the side effects commonly associated with treatment are burdensome to patients. Younger age, female sex, experience of side effects, and depression are associated with medication non-compliance in vasculitis [53]. Physician-directed instruction about medication use and potential adverse effects has a positive outcome on patient self-efficacy and

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**Box 1**

**Management of fatigue in vasculitis**

- Treatment of any underlying disease activity
- Review medication list for possible iatrogenic causes of fatigue
- Non-pharmacological interventions for fatigue include exercise, relaxation, counseling, education, rehabilitation, and energy conservation
- Patients may benefit from regular low to moderate impact aerobic exercise, progressively increasing in duration and frequency
- Energy-conservation strategies include: set priorities, pace self during tasks, planned rest periods and delegate less important tasks, plan high-energy activities at times of peak energy
- Practice good sleep hygiene including avoidance of stimulants (caffeine and nicotine), alcohol, long/late afternoon naps, and watching television in bed
- Encourage patients to discuss openly their disease/fatigue with family, friends and physicians, in order to improve their community support
improves medication adherence in vasculitis [54]. When initiating treatment in patients with newly diagnosed disease or monitoring patients with existent disease, providers should identify barriers to medication adherence and actively engage patients in shared decision-making regarding their treatment. Receipt of conflicting information about medications is reported by most patients with vasculitis and promotes poor medication adherence [55]. With the increase of information resources, whether valid or not, the presence of a supportive physician may counteract the negative effect of conflicting medication information [55]. Additional measures that increase medication adherence in the chronically ill population include: encouraging a family member or friend attend appointments, a notebook to document instructions or questions, rephrase and clarification of information, and offering contact number for questions between visits [56]. Few effective interventions have been identified that have a more positive impact than physician support and communication with their patients [57]. Therefore, health care providers caring for patients with vasculitis should frequently assess and discuss the patient’s experiences with medication-related issues throughout the course of disease management (box 2).

Reproductive health and genetics

Vasculitis can affect women of childbearing age; consequently, the impact of vasculitis on fertility and pregnancy outcomes is an important issue for patients living with the disease. Because of the relative rarity of pregnancies among patients with vasculitis, most of the data on reproductive health in vasculitis is limited to case-series and retrospective studies. An online survey of 350 women found a higher rate of pregnancy loss among women who conceived after a diagnosis of vasculitis compared to those who conceived prior to diagnosis (34% versus 22%), and only a minority of these women reported worsening of vasculitis during pregnancy [58]. A review of 214 pregnancies in Takayasu’s arteritis concluded that hypertension and/or pre-eclampsia occurred in 43% of pregnancies and 20% of infants had low birth weight [59]. Pregnancy outcomes vary across cohorts. An increase in pregnancy loss rates, pre-term birth, and a high level of vasculitis activity during pregnancy has been reported [60]. However, low rates of prematurity (9%) and disease relapse (occurring in only 1 out of 21 pregnancies) have also been reported in ANCA-associated vasculitis [61]. Many of the medications used to treat vasculitis are contraindicated during pregnancy and/or affect fertility. When caring for a patient with vasculitis who is seeking pregnancy counseling, several groups have made the following recommendations: contraception is essential until remission of disease has been achieved for a period of time, improved pregnancy outcomes correlate with established disease remission prior to conception, and preconception planning and close monitoring by a multidisciplinary team is needed during both the gestation and post-partum periods [59–63] (box 3).

Concerns about the heredibility of disease are common among patients diagnosed with vasculitis. Candidate and genome-wide association studies in vasculitis have identified polymorphisms that are unique to specific types of vasculitis and shared across other autoimmune diseases [64–69]. Despite the fact that genes probably play a role in susceptibility to some forms of vasculitis, it is unusual for vasculitis to occur in more than one member of the same family. Whole genome or whole exome sequencing approaches have been used to identify novel monogenic diseases in rare instances when there is familial clustering of vasculitis. Deficiency of adenosine deaminase 2 (DADA2) is a recently discovered autosomal recessive form of vasculitis that mimics idiopathic polyarteritis nodosa [70]. STING-associated vasculopathy with onset in infancy (SAVI) is a recently reported auto-inflammatory disease caused by gain-of-function mutations in

**Box 2**

**Strategies to improve medication adherence for patients with vasculitis**

- Time spent by health care provider to establish trust and support has significant impact on medication adherence
- Simplify medication regimen whenever possible
- Actively involve patient in treatment decision-making when possible to encourage self-management
- Encourage family member or friend to attend appointments in order to learn medication information
- Evaluate patient understanding of medication information through rephrase and clarification of material
- Suggest patient bring a notebook to document instructions or questions and maintain a log of medication schedule, when complex
- Provide contact information for questions between visits

**Box 3**

**Recommendations for pregnancy-related management in vasculitis**

- Preconception evaluation and counseling by vasculitis care provider and high-risk obstetrician
- Contraception is important until remission of disease is well-established
- Patient should be off treatment or on a stable therapeutic maintenance regimen that is safe to continue throughout pregnancy at the time of conception
- Close monitoring by a multidisciplinary team during the gestation and post-partum periods
- Comprehensive management of vasculitis disease activity during pregnancy and post-partum period
- Future research is essential to learn how further to improve management of pregnancy in vasculitis
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TMEM173 resulting in microthrombosis and cutaneous vasculitis [71]. Further application of both genetic and genomic approaches to the study of sporadic and familial cases of vasculitis could lead toward an improved understanding of disease pathogenesis in these conditions and ultimately toward discovery of curative therapies.

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