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VASCULITIS (LR ESPINOZA, SECTION EDITOR)

Damage Assessment in ANCA-Associated Vasculitis

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Abstract Antineutrophil cytoplasm antibody associated vasculitis has been transformed from life-threatening conditions to chronic relapsing long-term diseases as a result of significant advances in immunosuppressive therapy. Although mortality still occurs, it is much less frequent, with an average 5-year survival of over 70 %. In the setting of chronic conditions, it becomes increasingly important to monitor the burden of disease in terms of both active inflammation requiring immunosuppression and chronic damage (scarring) from vasculitis and its treatment and associated comorbidity. The damage that accumulates in patients with vasculitis does not respond to immunosuppressive treatment. It is important to distinguish disease activity from disease damage to prevent unnecessary immunosuppression, but it is equally important to recognize damage for what it is, so that it can be addressed appropriately. Damage is an inevitable consequence of long-term vasculitis for over 80 % of patients, which should not surprise us given the severity of the original illness. There is potential value in measuring damage as a means of providing prognostic information. Using a quantified score such as the Vasculitis Damage Index (VDI) allows us to predict mortality. Patients with at least five items of damage on the VDI score have substantially worse mortality (7- to 11-fold worse risk), as compared with those with lesser amounts of damage. These findings should be taken into context when planning the management of patients with vasculitis, as well as in clinical trials of vasculitis. Disease damage is an important surrogate for long-term outcome in vasculitis, and studies should be designed to limit the amount of damage accumulating as a result of therapeutic intervention, rather than simply controlling disease activity, as is currently the aim in recent randomized controlled trials in vasculitis. Furthermore, careful cataloguing of damage, as well as disease activity items, provides much greater detail in describing and observing the long-term natural history of primary systemic vasculitis in patients treated with immunosuppressive agents who survive their initial disease process.

Keywords Vasculitis · ANCA · Mortality · Damage · Organ failure · Hypertension · Prognosis

Abbreviations

AAV	ANCA associated vasculitis
ANCA	Antineutrophil cytoplasm antibody
BVAS	Birmingham Vasculitis Activity Score
DAS28	Disease Activity Score for 28 joints
GPA	Granulomatosis with polyangiitis (GPA)
HAQ-DI	Health Assessment Questionnaire Disability Index
LDIQ	Lupus damage index questionnaire
MPA	Microscopic polyangiitis
RA	Rheumatoid Arthritis
SDI	SLICC/SLE damage index
SHS	Sharp/van der Heijde Score
SLE	Systemic lupus erythematosus
SLICC	Systemic lupus international co-operating clinics
VDI	Vasculitis Damage Index

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Introduction

The term *antineutrophil cytoplasm antibody* (ANCA) associated vasculitis represents a group of uncommon inflammatory disorders associated with a substantial risk of early mortality if untreated [1]. Significant progress in managing the disease has been made since the introduction of cyclophosphamide and glucocorticoid therapy, and recent control trials demonstrate that for generalized ANCA associated vasculitis, mortality should be around 7 % or less at 18 months [2]. Mortality can rise to around 26 % for patients with severe disease, characterized by impending or actual kidney failure requiring dialysis [3]. Relapse is a frequent complication of surviving vasculitis, occurring in around 50 % of cases, more commonly in patients with granulomatosis with polyangiitis, as compared with microscopic polyangiitis [4, 5•], despite good control of the disease. However, many patients develop scarring in many organ systems, such as impaired renal function from loss of nephrons and/or chronic nasal destruction. These manifestations, while they may have originally been due to active vasculitis, are no longer a feature of active vasculitis but reflect the consequences of disease, its treatment, and comorbidity. Treatment, while beneficial on the whole, can result in scarring and lead to impairment of function (obvious examples of this include the development of hypertension or hyperglycaemia, in part due to high doses of glucocorticoid therapy, or haemorrhagic cystitis and/or bladder cancer from continued exposure to large doses of cyclophosphamide). In addition to these manifestations, patients with vasculitis, in common with patients with other chronic inflammatory diseases, are at greater risk of cardiovascular and cerebrovascular disease, which is not a direct result of vasculitis affecting vessels in these territories and may occur at an age at which atherosclerosis is unusual or less common [6]. The concept of all of these manifestations being measured as a burden of disease, representing scarring and irreversibility, has been used in systemic lupus erythematosus (SLE) and resulted in the development of the SDI/SLICC (systemic lupus international cooperating clinics) index [7]. We will review the potential and actual role of measurement of disease damage in ANCA associated vasculitis (AAV) and the importance of damage to patients with vasculitis.

Treatment of ANCA Associated Vasculitis

Several clinical trials completed in the last decade have demonstrated the benefit of cyclophosphamide as an effective treatment for generalized vasculitis associated with ANCA [2, 3, 8]. However, for patients with localized or early disease, methotrexate is an alternative effective substitute for cyclophosphamide [9]. In patients with severe vasculitis characterized by the presence of impending or actual renal failure and/or pulmonary haemorrhage, additional plasmapheresis, in addition to cyclophosphamide and steroid, appears to confer an advantage to kidney function, although it does not influence overall patient survival (26 % mortality), as compared with additional IV methylprednisolone [3]. Rituximab, a B-cell inhibitor is as effective as cyclophosphamide in controlling acute new or flaring vasculitis [10•, 11•]. All of these studies employed structured disease activity tools, which are variations on the Birmingham Vasculitis Activity Score (BVAS) [12], in order to define the primary outcome (achieving and/or maintaining remission). Although important, the results do not focus on the accumulating burden of damage suffered by these patients, as demonstrated in a large study of etanercept in granulomatosis with polyangiitis, where damage accumulation was noted even within the relatively short time span of the study (from an average of 1.3 items of damage at onset to 1.8 at the end), with 89 % of patients sustaining at least 1 item of damage by the first year of follow-up [13].

What Is Damage? How Much Occurs?

Although clinical trials frequently focus on disease activity, damage is a significant feature of systemic vasculitis. Importantly, long-term prognosis and quality of life are significantly affected by cumulative damage. A clear distinction between activity and damage is essential because it may help to avoid unnecessary exposure to cytotoxic medications [14]. It is the recurrence and persistence of disease activity that is largely responsible for long-term damage caused to patients with granulomatosis with polyangiitis (Wegener's), but not necessarily directly mediated by disease activity. In a longitudinal analysis of 158 patients with granulomatosis with polyangiitis, 86 % of patients had permanent damage as a consequence of disease, and 42 % had treatment-related damage [15]. The type of damage among these patients included end stage renal disease, chronic pulmonary dysfunction, hearing loss, saddle nose deformities, blindness, and death [15]. We define damage as the consequences of a diagnosis of vasculitis, occurring as nonhealing, irreversible scars. Furthermore, attribution to specific causes (active vasculitis or its treatment or comorbidities or infection) is less relevant, because damage measurement attempts to encompass the whole experience of illness. The principle applied is similar to that used in SLE with the SLICC index [7]. Table 1 lists the items in the vasculitis damage index, which is the most widely used tool for assessing damage. By definition, each item should have been present for at least 3 months or occurred at least 3 months ago (if it was a single discreet event, such as a stroke or myocardial

Table 1 Items recorded in the vasculitis damage index (*Adapted from:* Exley et al. [16]; with permission)

Musculoskeletal	**Peripheral vascular disease**
Significant muscle atrophy or weakness	Absent pulses in one limb
Deforming/erosive arthritis	Major vessel stenosis
Osteoporosis/vertebral collapse	Claudication >3 mths
Avascular necrosis	Minor tissue loss
Osteomyelitis	Major tissue loss
Skin/mucous membranes	Complicated venous thrombosis
Alopecia	**Gastrointestinal**
Cutaneous ulcers	Gut infarction/resection
Mouth ulcers	Mesenteric insufficiency/pancreatitis
Ocular	Chronic peritonitis
Cataract	Oesophageal stricture/surgery
Retinal change	**Renal**
Optic atrophy	Estimated/measured GFR ≤50 %
Visual impairment/diplopia	Proteinuria ≥0.5 g/24 hr
Blindness	End stage renal disease
Orbital wall destruction	**Neuropsychiatric**
Ear, Nose, Throat	Cognitive impairment
Hearing loss	Major psychosis
Nasal blockage/chronic discharge/crusting	Seizures
Nasal bridge collapse/septal perforation	Cerebrovascular accident
Chronic sinusitis/radiological damage	Cranial nerve lesion
Subglottic stenosis +/- surgery	Peripheral neuropathy
Pulmonary	Transverse myelitis
Pulmonary hypertension	**Other**
Pulmonary fibrosis	Gonadal failure
Pulmonary infarction	Marrow failure
Pleural fibrosis	Diabetes
Chronic asthma	Chemical cystitis
Chronic breathlessness	Malignancy
Impaired lung function	Other
Cardiovascular	
Angina/angioplasty	
Myocardial infarction	
Cardiomyopathy	
Valvular disease	
Pericarditis ≥3 months or pericardectomy	
Diastolic BP ≥95 or requiring antihypertensives	

infarction), in order to be recorded on the damage index. Inevitably these rules will lead to some concern over whether items can be defined as being truly irreversible if they appear to resolve, but we favor retaining irreversibility [16], demonstrating the burden of disease in individual patients. Figure 1 suggests how damage occurs as a complex interaction between disease activity, therapy, and comorbidity.

Why Is It Important?

Damage is defined as a nonhealing scar that will not respond to immunosuppressive treatment. The damage resulting from vasculitis itself or from treatment may ultimately prove more troublesome than disease activity to the individual patient [17]. It is important to separate damage from disease activity because this will help to rationalize therapy, thus avoiding unnecessary adverse effects of treatment. The standardized incidence ratio for bladder cancer was 4.8 in a study of 1,065 hospitalized GPA patients, of whom 110 had cancer [18]. The increased risk is directly related to the cumulative dose of cyclophosphamide [18]. The key to reducing damage is a better understanding of the disease state and, therefore, use of an appropriate therapy [19].

Damage and activity assessment tools enable the description of these two potentially coexisting disease states (active disease and scarring). Damage represents a chronic burden of disease for the patient; but for the clinician, damage represents the manifestations of vasculitis that do not merit prolonged immunosuppressive treatment. For example, acute renal failure, pulmonary haemorrhage, and acute respiratory failure are manifestations of disease activity that are well-recognized causes of early death [20]. Zycinska et al. showed that concurrent severe renal disease requiring dialysis and respiratory tract involvement carried the highest risk of death in the first year of diagnosis among patients with GPA [21]. The causes of death 5 years after diagnosis include renal failure (23.1 %), respiratory failure (15.4 %),

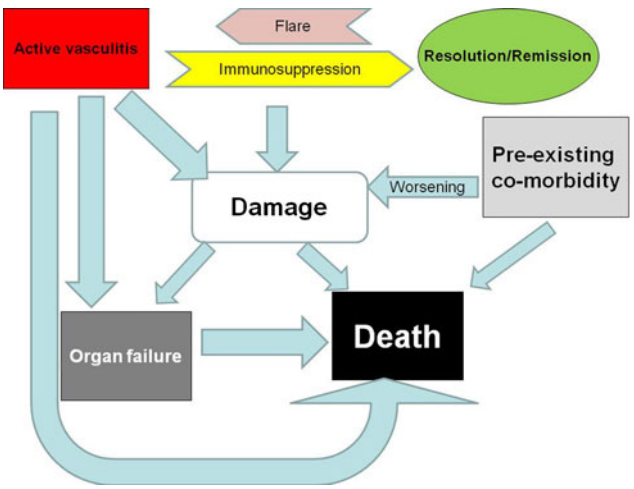

Fig. 1 Relationship between disease activity, therapy comorbidity and damage, organ failure, and death in vasculitis

myocardial infarction (15.4 %), and pulmonary embolism (15.4 %) [20].

How Do We Measure Damage?

The VDI is a comprehensive clinical checklist for recording the accumulation of damage in patients with systemic vasculitis. The initial index was developed from a cohort of over 100 patients, recording the nonhealing scars that occurred during the course of their disease and demonstrating that it was sensitive to change and was a useful predictor of survival (median damage score for nonsurvivors was 7, as compared with 4 for survivors) [16]. The VDI consists of a checklist, on a single sheet of paper. Each item is recorded if it occurred since the onset of vasculitis, has been present for at least 3 months, or occurred at least 3 months ago. Each item is given 1 point; for some items, such as myocardial infarction or stroke, it is possible to score 2 points because the item list includes a second or subsequent event. The list is divided into different body systems for convenience. Like disease activity measurement, it is necessary to record items depending on when they occur in relation to the diagnosis of vasculitis (but, unlike disease activity recording, not dependent on their specific cause). Any items that have occurred subsequent to the diagnosis of vasculitis can be considered damage items if they have persisted for more than 3 months. However, if items have been present before the diagnosis of vasculitis, they should be scored only if they have significantly deteriorated after the diagnosis of vasculitis was made. If the item is due to the consequences of vasculitis itself, such as impaired renal function from active nephritis, or if the item is due to a complication such as septicaemia or any other cause, such as drug toxicity, it does not matter. In other words, there is no attribution when it comes to recording damage. The items are recorded entirely on the basis of events occurring or being present persistently for 3 months after the diagnosis of vasculitis was made. Some items will definitely relate to previous disease activity, but that is not the case for all items. Other items might be definitely due to drug toxicity (e.g., osteoporosis or vertebral collapse) or possibly due to drug therapy (more uncertain for malignancy, because there is an increased risk of malignancy in patients with vasculitis per se, as well as the risk associated with taking cytotoxic drugs such as cyclophosphamide). The most effective way of completing a damage index form is to complete it in conjunction with a disease activity form (BVAS). This allows the observer to categorize the patient's problems into those relating to active disease and those relating to damage. It is often the case, in patients who have had disease for more than a few months, for there to be some damage items to record and, occasionally, to also have activity items recorded. Categorizing patients into whether or not they have active disease requiring immunosuppressive therapy should be based on a disease activity measurement (e.g., BVAS), whereas the damage score is a list of problems that accumulate as a result of the diagnosis of vasculitis and its subsequent treatments and any comorbidities. There is no direct relationship between current disease activity and disease damage; however, disease activity is a weak but significant predictor of subsequent damage (r=.2, p=.015, in a cohort of 180 patients with GPA) [13]. It is useful to document damage serially during follow-up; it is important to carry forward any items of damage previously recorded, because of the principle that damage items do not ever regress or improve, even though clinically the patient may appear to have recovered from the damage item in question. For example, if the patient has developed a leg ulcer which lasts at least 3 months, it would be recorded in the damage index permanently, even if the patient subsequently has treatment to heal the ulcer or a skin graft to cover the ulcer. Even though the problem has resolved, the damage item should still be recorded on the list at all subsequent damage assessments because it occurred and lasted for over 3 months. This can be difficult in practice, unless the previous record is to hand, due to errors of omission. We strongly recommend training to use the damage index and have developed a training program for this purpose. A Web site with more information on VDI, including forms and training advice, can be found at http://www.vasculitis.org.

Prognosis Based on Damage Measurement

The initial prognosis for patients with ANCA associated vasculitis has improved dramatically since the advent of treatment strategies such as cyclophosphamide and glucocorticoids [22]. On the basis of the VDI collected in a cohort of patients with systemic vasculitis from one center, a threshold of at least five damage items gives a 6.4-fold (confidence interval [CI}, 2.1–19) increased risk of future mortality [23]. A critical damage index score of at least 1 (based on severe items of damage) gives a 17.5-fold (CI, 2.3–136.1) increased risk of subsequent death. We speculate that a damage threshold may also predict organ failure, although we have not proven this yet. Figure 2 represents a schematic example of 3 patients developing increasing amounts of damage over time (some already have damage recorded at baseline, because patients, especially with GPA, have already developed scars at diagnosis).

How Does Damage Differ in Vasculitis Compared With Other Rheumatological Disorders?

The SLICC index for damage in SLE was developed to address the same issue of damage in multiple systems in

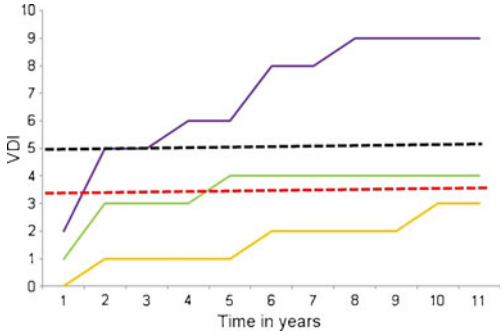

Fig. 2 Theoretical examples of 3 patients with low (shown in yellow), moderate (green), and high (purple) amounts of damage in vasculitis. Threshold for predicting mortality (black dotted line) is VDI >5; speculative threshold for organ failure is shown by red dotted line. VDI, Vasculitis Damage Index

SLE [7]. An item has to be present for 6 months in SLE in order to qualify as damage (whereas in vasculitis, the time is 3 months). A cohort of almost 300 patients with SLE followed over a 5-year period [24•] showed progressive increase in damage during a 5-year period. Damage in patients with SLE as measured using the SLICC index occurred in 6.3 % and 21.4 % of cases in one controlled trial of azathioprine versus ciclosporin [25]. Danila et al. reported that in 635 patients with SLE, around 20 % developed renal damage, 9 % had cardiovascular damage, around 8 % had pulmonary damage, and around 5.4 % had peripheral vascular damage; renal damage was predictive of death, but this depended on excluding poverty from the analysis, because this was the strongest predictor of death [26••]. A long-term cohort of 348 patients with SLE attending one center and followed over approximately 10 years demonstrated that 44.8 % had at least one item of damage as recorded by the SDI. The most common items of damage were musculoskeletal, neuropsychiatric, cardiac, and ocular features [27]. Cassano et al. reviewed 197 patients with SLE and documented the progressive increase in number of damage items over time from 0.52 in the first year to 2.46 by the 10th year, with particular involvement of the kidneys, neuropsychiatric manifestations, and cardiovascular and musculoskeletal features [28]. All of these figures suggest that damage is much more common in vasculitis than in SLE, although there are some differences in how damage is recorded in lupus, as compared with vasculitis, chiefly in the time frame, as well as allowing damage from comorbidity to be scored if it deteriorates in vasculitis patients. Swaak et al. reported two different mean values for the SLE damage index in a cohort of patients followed for 10 years: The mean SDI was 3.7 when comorbidity was included or 2.8 without including co-morbidity [29]. Stoll et al. evaluated the damage index in 141 patients with SLE, reporting a weak association with disease activity and global measures of health state; there was sufficient difference in the performance of the damage index to justify it being a separate end point for clinical studies [30].

In rheumatoid arthritis (RA), the extent of joint damage correlates with future functional ability. Rapid radiological progression (defined as an increase of 5 or more points on the Sharp/van der Heijde score) in the first year of treatment is associated with worse functional ability in later years (OR 4.6) [31]. The effectiveness of treatment with disease-modifying agents with or without biological agent should be measured using a structured score of disease activity such as the Disease Activity Score for 28 joints (DAS-28), but there are limitations: Some patients defined as having attained DAS-28 remission have significant residual synovitic joint counts [32]. Assessing damage as radiographic progression may be a more reliable target for treatment and prevention of irreversible joint damage and is recommended by the FDA as a surrogate marker of functional status [33]. Common imaging scoring systems are the Sharp score and its modifications by either van der Heijde or Genant, the Larsen score with modifications, and the Simple Erosion Narrowing Score [33]. Radiographs provide a permanent measure of damage in RA and the use of plain radiographs of hands and feet have been an integral part in the evaluation of the disease course and so are included in the common scoring systems [33]. However, in early RA, functional loss is related primarily to the extent of inflammation and disease activity, rather than damage [34]. With increasing disease duration, the cumulative effects of repeated flares in difficult-to-control disease results in more joint damage. In a cohort of 748 patients in reported remission, Aletaha et al. assessed the individual contributions of erosive damage and joint space narrowing to irreversible loss of function [35]. On univariate analysis, the disability index of the health assessment questionnaire (HAQ-DI) was worse in patients with joint space narrowing combined with erosive changes, as compared with erosions alone [35].

Conclusions

In the era of immunosuppressive therapy, long-term damage is now a major concern with regard to patient outcome in AAV. Damage has been an outcome in clinical trials of vasculitis, but never a primary outcome [2, 13]. Studies show that the accumulation of damage can start early; in GPA, an increasing VDI increases resistance to treatment, thus worsening survival [36]. Data from the Wegener's granulomatosis etanercept trial (WGET) demonstrated that the mean VDI (1.3) at study enrollment had increased at the end of the trial (VDI 1.8). This increase was due to damage that occurred despite (presumably optimal) therapy: Damage items included visual impairment, hearing loss, nasal blockade, pulmonary fibrosis, hypertension, renal insufficiency, peripheral neuropathy, gonadal failure, and

diabetes mellitus [13]. Among the 180 patients enrolled in the WGET, only 11 % had not sustained a single item of damage after 1 year of enrollment [13]. When adjusted for baseline VDI, the correlation between the baseline BVAS/WG and the VDI score at 1 year was moderate, r=.20, p=.015.

In a European cohort of 158 patients [2] with GPA and microscopic polyangiitis, damage progression was commonly observed. The mean score on VDI was 1.3 (95 % CI, 1.0–1.6) increasing to 2.5 (95 % CI, 2.1–3.0) at 18-month follow-up [2]. Kamali et al. found that patients with GPA who died had higher early VDI scores than did those who survived (1.33 vs. 0.42, p=.002) [37]. In a cohort of 50 patients with GPA, Kamali et al. demonstrated that age at time of diagnosis (OR 0.9 [p=.06]) and early VDI scores (OR 0.5 [p=.04]) were lower in survivors; furthermore, an early VDI score of above 5 was related to death with 98 % sensitivity and 56 % specificity (p=.004) by ROC curve analysis [38].

These findings echo the importance of recording early damage in patients with AAV. Exley et al. stressed the importance of severe damage occurring in the early stages of vasculitis [16]; the extent of damage is an early indicator of subsequent mortality. The continuing morbidity of patients with AAV, despite improved prognosis with aggressive therapy, requires accurate assessment of disease. Damage assessment tools are available that can serve as outcome measures in clinical trials, as well as a guide to better clinical management of the patient. Assessing both disease activity and damage is integral to managing patients with AAV.

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