Measuring disease activity and outcomes in clinical studies

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Untreated systemic vasculitis has an appalling prognosis. The pathogenesis is still being addressed, and we have no clear etiological agents defined in most cases of these uncommon but not rare diseases.[1,2] Our lack of understanding of pathogenesis has led to the widespread use of classification systems, which describe groups of patients with different forms of vasculitis in predominantly pathological and clinical terms using vessel size as the dominant classification.[3-5] These classification criteria are widely applied as diagnostic criteria, which is inappropriate since they do not serve this purpose well.[6] In many ways, however, this distinction between different forms of vasculitis has served as the empirical basis for different forms of therapy.[7] Large-vessel vasculitis is predominantly managed with steroid therapy alone, with the use of immunosuppressive drugs such as azathioprine or methotrexate only if there is resistance to steroids. By contrast, the small-vessel vasculitides, such as Wegener's granulomatosis involving the kidney, or microscopic polyangiitis with kidney and lung involvement, are primarily managed by the use of cyclophosphamide and steroids. Therefore, at the classification or diagnostic stage we are already making a distinction between diseases that we treat more or less aggressively. As a further refinement of this process, within each disease it is becoming increasingly apparent that there is a need to distinguish the pattern of involvement in each individual case and the current level of disease activity, which might require different levels of immunosuppressive treatment at any point in time.[8,9] This strategy leads to a more logical framework for addressing the need for appropriate immunosuppression. The concept that vasculitic diseases are a one-shot illness is no longer valid. We recognize that modern management has transformed the outcome for survival to a very high survival probability. However, survival is characterized by frequent episodes of reactivation of the original disease (in up to 50% of cases in some series) or persistent grumbling low-grade disease.[10,11] In addition, the chronic effects of disease scarring and drug toxicity take their toll and result in some cases in significant organ damage.[12] Accurate assessment of disease activity is therefore an essential part of the management of these complex diseases. We need to discriminate between appropriate levels of immunosuppression and also distinguish active disease from chronic scarring for therapeutic strategies to be more appropriate. Disease assessment may also offer the opportunity to predict future outcome and is increasingly of use in determining how aggressive to be at disease onset.[8] Therefore we must consider not only current levels of disease activity in their immediate context but also what they may be telling us of the likely future outcome. These are difficult tasks to expect any individual assessment to provide.

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PATHOLOGICAL AND SEROLOGICAL ASSESSMENT IN SYSTEMIC VASCULITIS

Histological evaluation is an important diagnostic step in systemic vasculitis. A recent study has suggested that the presence of tubular inflammation in kidney biopsies of patients with renal vasculitis is predictive of outcome[13]; in Henoch-Schönlein purpura, the presence of crescents, interstitial fibrosis, and of dense subendothelial deposits are all predictors of chronic renal failure.[14] Unfortunately, biopsies from other affected organs have not been shown to provide prognostic information. The role of repeated biopsies to assess disease activity or prognosis is limited by the morbidity of the procedure. In practical terms, it is difficult to justify serial biopsies to evaluate progress. Serological markers would be of importance in this regard; unfortunately, the ESR is very unpredictable and may be influenced by a number of factors including infection or chronic inflammation. Similarly, the C-reactive protein is a poor discriminator between infection and active vasculitis. Recent studies have suggested that procalcitonin levels may be a better discriminant between disease activity and infection in the setting of acute vasculitis.[15,16] The role of anti–neutrophil cytoplasmic antibody (ANCA) titers in measuring disease activity is still controversial. The ANCA pattern has been shown to predict the outcome in microscopic polyangiitis,[17] where the C-ANCA pattern has a higher risk of mortality associated with it than the P-ANCA pattern (3.78:1). However, this differential outcome has not been used as the basis of any published therapeutic studies so far. Although serial testing of ANCA has been correlated with disease activity,[18] there is still a con-

siderable overlap between normal variation in ANCA levels in these patients and disease activity, so that 29-43% of the ANCA rises may be in the absence of clinical disease activity.[19] Russell et al (2001) have suggested that antibodies to pro forms of ANCA are more closely linked to clinical disease activity.[20] It is possible that these ANCA rises are occurring on the basis of subclinical disease, but it would be difficult to justify therapy on the basis of rises in ANCA titer alone.

CLINICAL ASSESSMENT OF DISEASE ACTIVITY IN SYSTEMIC VASCULITIS

Clinical evaluation remains the gold standard for disease assessment in systemic vasculitis. It is perhaps the most natural system for clinicians managing these patients and has formed the basis for accurate assessment tools of disease activity, which have prognostic as well as practical importance on a day-to-day basis. Overall, however, each tool may contribute towards the evaluation of patients with vasculitis, and it is important to consider the evidence provided by a combination of clinical assessment, serologic assessment, and pathologic or radiologic assessment where appropriate. Together they allow better definition of vague terms such as relapse or remission, which can then be qualified in more objective evaluations.

Evaluation of disease for the purpose of clinical trials has been largely based on the use of clinical tools, both as measures of active disease and as prognostic discriminators. The five factor score has been used as a stratification process whereby patients with poor prognosis (ie, those with a score of 1 or greater) are scheduled to receive aggressive therapy, including cyclophosphamide, whereas patients with a good prognosis (ie, those with none of the 5 factors) are scheduled to receive steroids alone.[8,9,21] There has been more widespread use of the Birmingham Vasculitis Assessment Score (BVAS) in measuring disease activity during the course of the disease in clinical trials.[22] The European Vasculitis Group (EUVAS) have modified and used BVAS extensively in many of their clinical studies,[23-25] and the Wegener's Granulomatosis Etanercept Trial (WGET) investigators have developed a specific version of BVAS for use in a trial of etanercept therapy in Wegener's granulomatosis.[26] BVAS consists of a checklist of items that are predominantly based on clinical history and examination but supported by some laboratory investigation, such as serum creatinine and the presence or absence of blood or protein in the urine. BVAS has been applied to a variety of forms of vasculitis and shown to have biological validity and is highly reproducible. It aims to be objective by avoiding rating of abnormalities. It addresses the question of disease activity in the context of vasculitis and is designed to measure only those features that currently represent active vasculitic disease requiring therapeutic intervention. In other words, it attempts to record objectively the usual clinical decision-making process that forms the everyday practice of clinicians dealing with vasculitis. If an item is recorded on BVAS, the clinician recording it should be doing it with the conviction that the abnormality requires active therapeutic intervention. The distinction between what is new or worsening vasculitis activity as compared to a new event that does not represent active vasculitis (such as infection or side effects from treatment) is an important one and lies at the heart of the BVAS system. It is therefore heavily dependent on clinician expertise and judgement. In practice, these distinctions have to be made "on the spot" so that decisions on therapy can follow immediately. Therefore, the BVAS represents an intention-to-treat–based system of clinical assessment that is meant to be of direct practical value in the management of these patients.

The disease extent index (DEI) is applicable to Wegener's granulomatosis and has a high correlation with BVAS, but also includes an element of damage, therefore giving a cumulative assessment of disease.[27] The vasculitis activity index (VAI) is an analogue-scale measurement of organ activity in each of nine organ systems, and also includes indirect measures of activity, such as the sedimentation rate.[28] However, this does not allow for the detailed descriptions offered by either BVAS or DEI. It also suffers from the potential criticism of observer bias.

CLINICAL ASSESSMENT OF DISEASE DAMAGE IN SYSTEMIC VASCULITIS

Assessment of damage is important to distinguish from active disease. It may contribute significantly to the patient's overall state of health yet require very different management from that for activity. The vasculitis damage index (VDI) is an objective item list based on 11 organ systems, incorporating damage attributable to the disease as well as to its treatment.[29] Using the VDI, damage is detected surprisingly early, relating to the initial presenting episode.[12] In a cohort of 120 patients, one-third had already sustained damage before presentation to hospital. By six months, most patients had 2 to 4 damage items; only 5% had no damage items, while some patients had already accumulated up to 8 items. Damage was not restricted to a single organ system, since two-thirds of patients had two or more systems involved—a minority as many as six. This rate of damage accumulation was not maintained subsequently, and damage is not necessarily progressive in patients followed for up to 5 years.[30] This has implications for therapy, highlighting the need to control disease activity rapidly at presentation in the attempt to prevent early development of scarring. Damage is an important surrogate measure of outcome and is of predictive value in studies of systemic vasculitis. Therefore, the damage index may provide an important evaluation method for determining the success or failure of therapies in vasculitis. The systemic necrotizing vasculitis damage index (SNVDI) has been developed for specific use in polyarteritis and Churg-Strauss syndrome.[31] It is very similar to the VDI. Some aspects of damage are measured by the DEI, since it is an attempt to describe the overall spread of vasculitis throughout different organ systems in the individual patient.

PROGNOSIS IN VASCULITIS

Determining future outcome on the basis of current information would be of great value in systemic vasculitis. The DEI has been used to predict treatment responses in ANCA-positive patients with Wegener's granulomatosis where patients with low DEI levels (9 or less) favor better treatment response from pulse high-dose cyclophosphamide, whereas high DEI levels (above 9) benefit from

continuous oral standard-dose cyclophosphamide.[32] The ANCA pattern may be helpful in ANCA-positive microscopic polyangiitis, where mortality risk is higher (3.78-fold higher) for patients who have C-ANCA rather than P-ANCA.[19] BVAS and five factor score are of help in predicting mortality[9,22]; essentially, the higher the score, the greater the mortality risk. The VDI and its sub-scores (especially the critical damage index) are predictive of mortality. Comparing the VDI scores of a subgroup of patients who subsequently died with those who survived for at least a 5-year follow-up period, at the last available examination the fatal cases scored positive for significantly more items than the survivors, and this damage involved significantly more organ systems. It is also relevant that the final examination was at a mean of 2.6 years in the severe group but at 5 or more years in the others. In fatal disease, more items of damage, involving more organ systems, are accumulated at a faster rate than in non-fatal cases.[30] Patients who had a VDI score of greater than 5 carried a 6-fold increased risk of mortality. A system score of more than 3 nearly doubled that risk, while involvement of more than one item of critical organ damage carried a relative risk of 17.

CONCLUSIONS

The histologic, clinical, and serologic tools available in systemic vasculitis allow us to begin the task of stratifying patients according to outcome category as well as defining targets for improvement with different immunosuppressive regimens. Both of these aspects are essential in clinical trials of systemic vasculitis. Until we have pathophysiologically based evaluations, our clinical methods supported by laboratory tests remain the gold standard for management of these diseases and therefore also the gold standard for measurement tools in clinical studies.

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