Assessment of Disease Activity and Damage for Clinical Decision Making in Vasculitis

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SUMMARY

The progress in many aspects of vasculitis has emphasised the need for detailed assessment to dissect the components of each individual case as it progresses and to use this to determine progressive therapeutic regimes tailored to the current disease status. Assessment of the extent of organ involvement and the degree of disease activity have obvious value in determining the need for initial therapy at disease presentation. The control of acute mortality has revealed a persistent morbidity, most clearly documented in patient self-assessment of their functional status. The high tendency to relapse also stresses the need for continuing assessment during long-term follow-up. Newer drugs may allow specific control of ongoing activity to be achieved at lower risk of toxicity. The problem of accumulating disease scars has not yet been solved although the detailed description of organ damage has revealed the important contribution which damage makes to later mortality. Finally, there are new techniques to look at the function of the endothelium itself — the important target tissue in vasculitis. These will hopefully provide opportunities to assess non-invasively the state of blood vessels and their potential to respond to further therapy.

Introduction

The concept of using careful assessment of the current clinical state both to determine the therapeutic regime required and to provide an estimate of longer term prognosis is not a new one but is only now being explored in detail. Wegener himself suggested that his syndrome originated as a local airways disease which later spread to a diffuse, multi-organ, lethal disease. This suggested that early therapy might be local and different in nature from that required for the systemic disease. Wegeners idea was soon developed into the ELK system — the first attempt at staging such disease. Such concepts will become increasingly important as therapy becomes more sophisticated, moving from blanket application of all that is available to flexible regimes carefully tailored to the current state of each individual. The long initial struggle to control the immediate life-threatening aspects of vasculitis has been largely successful — but at the expense of considerable morbidity from disease scars and drug toxicity. The advent of new drugs, plus increasing comprehension of disease mechanisms, suggests a brighter future. Experience with other autoimmune diseases indicates that better disease control is unlikely to come from a single panacea — or even a series of them. Advances will more likely come from application of a combination of drugs, each with

milder effects but aimed at a specific aspect of disease control and thus only applied to patients who have been shown by careful assessment to require this. Detailed disease assessment is now seen as a growth area with real potential for the transformation of the longer term outlook in vasculitis from one of chronic morbidity and relapse to one of rational long-term control of disease with minimal toxicity.

Disease extent

The relevance of disease extent has been studied in greatest detail in Wegeners by the Lubeck group, who have refined and extended the ELK concept, incorporating 11 items into a 21 point disease extent index (DEI) (1). This has been used in several therapeutic studies but its prognostic relevance and possible application to other forms of primary systemic vasculitis (1ºSNV) remain to be established. A simpler form of assessment of major organ involvement, the Five Factor Score (FFS) has however been shown to be applicable to the differentiation of poor prognosis disease, when applied at diagnosis or in an active stage of disease, in a spectrum of systemic vasculitis. It is thus a useful tool in deciding on the necessary therapy in individual cases (2). Renal impairment and GI involvement carry the most serious individual prognosis but the compound score is the simplest clinical tool.

Disease activity versus damage

One problem with any measure of disease extent is the need to distinguish between involvement due to current disease activity and that due to scars of pre-existing disease — ie damage. We have felt it important to devise indices which clearly distinguish between these two aspects. Although both are perceived by patients as part of the total disease burden, they have very different implications for treatment. Activity, representing the current load of inflammation directly relating to the disease process, indicates the need for specific drug therapy. In contrast, damage represents scars from disease, complications such as infection, and drug toxicity. These factors all require alternative approaches to therapy, such as rehabilitation, often with lowered dosage of specific anti-inflammatory drugs.

Activity

The first priority in disease assessment is to determine the degree of activity, especially systemic involvement, since this determines the immediate treatment need. In vasculitis, activity is defined as the degree of current active inflammation which can be directly ascribed to vascular disease. An activity score has to include items such as skin and mucus membrane lesions, non-specific systemic lesions such as fever, weight loss, etc.; together with assessment of major internal organs including, the heart, lung, kidneys and CNS. The Birmingham vasculitis activity index records 59 items in 9 organ-based systems (3). It can thus provide both a total score and an index of organ involvement (a disease extent measure). It has been validated, is sensitive to change and has been used in clinical trials ranging from cyclophosphamide regimes through to IVIg. It is incorporated into the VITAL scoring system used by the European Vasculitis study group (EUVAS) for their series of controlled trials. A high initial score was initially associated with an increased risk of mortality, an aspect which requires further study. More recently it has been shown to correlate well with the FFS when applied to active disease prior to therapy. Over 60 citations in the 7 years since the initial paper show that BVAS has additionally been used to assess the value of multiple clinical and research tests, ranging from T- or B-cell status to cytokines and markers of endothelial activation.

Damage

Chronic disease is frequently recognized by its characteristic scars — from the saddle nose of Wegeners to the joint erosions of RA. Despite this the detailed pattern and significance of disease scars in vasculitis has only recently received serious attention. However experience in other systemic autoimmune disease suggests that scarring is a most important factor in the longer term prognosis. Thus in the assessment of kidney involvement in SLE, features of damage such as fibrosis are better predictors of subsequent renal failure than any aspect of current inflammation. Development of a clinical index of damage in 1ºSNV was a harder task than that for activity but also turned out to provide a great deal of useful information on disease progression and prognosis. The vasculitis damage

index (VDI) was derived in Birmingham from consensus over items to be included between interested physicians, especially rheumatologists and nephrologists. It was honed by extensive discussion and group exercises among members of the EUVAS group. The VDI includes 64 items from 10 organ-based systems, together with evidence of drug toxicity (4). It has been validated, tested for reproducibility, and is easy to use in the clinic. The important factor is the additional information which this provides. Routine use of the VDI in follow-up established that damage is not a late complication but can occur surprisingly early. It is not necessarily progressive and actually more damage accumulates during the first 6/12 of follow-up than is seen in the same time interval after a subsequent flare of disease. Thus we commonly found accumulation of 2 to 4 (range 0-9) items of damage within 6/12, with less than 10% having no damage. The significance of such damage became very clear when severe disease (defined as subsequently fatal cases) was compared to milder cases. At the last examination, patients with severe disease had accumulated more items of damage than non-fatal disease (7v 4). Additionally the rate of damage accrual was faster in severe cases, as the mean disease duration at final testing was less than half of the 5 year follow-up in the non-fatal cases.

These data suggested that damage made a major contribution to disease severity. We tested this directly by evaluating the contribution of several aspects of damage to the relative risk of mortality in the whole group, using LOD scores (5). A total VDI score of ≥ 5 was associated with a 6 fold increased risk, which was early doubled in patients with a system score ≥ 3. The greatest relative risk of mortality (OR ≥ 17) was seen in those with critical organ damage in one or more systems. These data establish the importance of damage and the next task is to determine whether this can be used early on in disease as a predictor of subsequent prognosis. Our data on the total VDI scores showed that at 6/12 there was already greater damage detectable in patients with subsequent mortality. A prospective study is now needed to establish the sensitivity of the VDI in prediction and the time at which this is first clinically useful. What is already clear is that an important aim of future treatment must be to prevent damage due to scarring in 1ºSNV. This will most likely require different approaches than those used just to suppress disease activity.

Function

Full assessment of any chronic disease requires a measure of function, self-assessed by patients themselves, in order to understand the impact of the disease and their quality of life. There are advantages to using a generic rather than a disease specific measure. We have applied the widely validated Moss Index SF 36 which showed that both the physical role and the mental component were depressed in active disease. However, depressed scores persisted beyond the period of obvious disease activity. The assumption that this reflected the effects of damage was only partly supported by the data which showed a significant correlation of depressed physical function with severe damage but no overall clear relationship to the VDI. The psychological effects of an acute life-threatening disease such as 1ºSNV are clearly huge but the chief abnormality detected was in the physical function scores of the SF 36. It is, particularly the subscale corresponding to problems with work and socio-economic impact of the disease. This may reflect a requirement for further vasculitis therapy. For example the addition of TNFα blockade to standard therapy has been observed to markedly improve patient well-being. The prognostic significance of depressed function may well be greater than simply patient health perception, particularly if it reflects grumbling abnormalities at the vascular level (as discussed below). It will be important to establish whether depressed function predicts longer term outcome, in the same way that depressed HAQ functional scores have been shown to do in rheumatoid arthritis.

Endothelial dysfunction

There are two major problems with the current damage assessments. The first is that they have an in-built time lag, since they record scars after they have become established. This is too late to prevent problems — even though recognition may help to minimize their effects on function. An essential aim of future therapy must be to prevent scar formation. This requires prediction of lesions that may develop into scars rather than heal completely. That task may become easier when we address the second major problem of damage assessment — that we currently measure the

effects of altered blood supply on various organs but do not look at the direct effects of ongoing disease on the essential tissue, the blood vessels themselves. Techniques to do this are being actively developed by colleagues in cardiology to assess atheroma, which is also currently viewed as an inflammatory disease of blood vessels. These techniques can with advantage be applied to 1oSNV and offer the potential to detect endothelial cell dysfunction (ECD) before it represents fixed damage or even threatens tissue perfusion. We are using them to determine the reversibility of ECD by various therapeutic manoeuvres as well as to determine which lesions are at high risk of progressing to fixed damage.

ECD is seen in apparently well-controlled 1oSNV in the follow-up clinic. This has been detected in the brachial artery, a major muscular artery rarely involved clinically in these diseases. However it is not restricted to this site. It can also be detected by other techniques in small skin vessels — but is not restricted to 1oSNV syndromes classically viewed as small vessel disease. The initial assumption was that this represented an aspect of the damage we were currently assessing. However, further study revealed that ECD in acute disease may be reversible by aggressive therapy. This has so far been seen in a small number of cases after pulses of cyclophosphamide plus steroid or after TNF blockade. These data on reversibility suggest that ECD, in some cases at least, represents residual disease activity rather than fixed damage. The mechanisms for this remain to be determined but the concepts of Vallance and colleagues (6) that such dysfunction can follow both infection (LPS) and inflammatory cytokines (TNF) appear directly relevant to 1oSNV. Direct experimentation has shown that ECD can persist for days after only very brief exposure of a blood vessel to such challenge. The potential to progress to fixed damage has not been explored so far but the experience of accelerated vascular damage in organ transplants indicates the likelihood of this occurring. In addition detection of EC dysfunction may be of value in predicting relapse, since the impaired ability of such vessels to respond to physiological stimuli may enhance the risk of attracting further inflammation to that site.

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