Treat-to-target in vasculitis: is this a sensible approach?

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Received and accepted on September 26, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 73): S149-S153.

Key words: vasculitis, ANCA, granulomatosis with polyangiitis, microscopic polyangiitis, Birmingham Vasculitis Activity Score, Vasculitis Damage Index, cyclophosphamide, rituximab

Competing interests: none declared.

ABSTRACT

It is possible to achieve substantial initial control of systemic vasculitis in the majority of patients. However the 'target' has shifted considerably over the last 20–30 years from keeping patients alive to maintaining good quality disease control, avoiding the development of comorbidities – either as a result of disease or treatment, and also preventing relapses. This expansion of potential targets that can be achieved in systemic vasculitis has arisen because we have more effective therapies, but more importantly we have developed a framework within which targets can be created reproducibly. In other words we have much clearer definitions of what constitutes clinical disease activity, relapse, remission and morbidity. These targets are based on simple clinical evaluation, limited laboratory assessments of patients that can be undertaken by any secondary care facility. As a result of this they remain at a clinical level and may not address the most important targets, which are curing disease and that would be the aspiration to move towards. The first step towards that is to move from clinically-based targets towards mechanistic targets based primarily around the pathophysiological drivers of disease. That in turn may lead to identification of specific targets that can turn off disease. The systemic vasculitides are heterogeneous and although for ANCA- associated vasculitis in the short term treatments are similar, the development of clear understanding of mechanisms and new targets may bring with it the promise of much more focused therapies that will address only individual targets and therefore personalise therapy for each individual condition and patient.

Introduction

The term systemic vasculitis describes a group of uncommon but not rare inflammatory diseases of blood vessels which can result in severe end organ ischaemia or failure, and be fatal in multi system disease if left untreated. The most severe forms are often associated with the presence of anti-neutrophil cytoplasm antibody (ANCA). As a result of current therapy, the acute mortality for these diseases has been reduced to between 6 and 26% (1-4). Unfortunately however, patients often experience recurrence of disease; in addition the manifestations of disease as well as its treatment are likely to lead to chronic scarring or damage (5). In large vessel vasculitis, such as Takayasu arteritis and giant cell arteritis, mortality is relatively low but the morbidity is relatively high. End organ ischaemia in GCA can lead to visual loss and in Takayasu arteritis to stroke or other end organ compromise from involvement of the great vessels (6).

Recognising and documenting the aspects of disease that represent activity (7) and damage (8) has been an important step forward in our ability to design studies to set and achieve targets in systemic vasculitis. These are not perfect tools and they do not work for all forms of vasculitis. However they have provided the basis for developing clinical trials which have then demonstrated effective control of disease for small vessel ANCA associated vasculitis in the first instance. Further work is required to develop suitable targets in large vessel vasculitis (9). More recent data suggests that prognostic tools may be available to anticipate future risk of relapse; this will be reviewed but remains speculative at present.

Does it make sense?

For the generalist, management of vasculitis might seem very straightforward; often involving large doses of glucocorticoid therapy for a relatively short duration. When this approach starts to fail, as it is inevitably will in the majority of patients with ANCA-associated systemic vasculitis, patients may be referred on for more specialist care to clinicians with an expertise in vasculitis (10). At this point the opportunity

arises to introduce more effective immunosuppressive therapy but often in the context of a patient who has already received large doses of glucocorticoid therapy. Therefore, we need to make allowances for the burden of toxicity associated with this approach.

Recent data from a study comparing rituximab with cyclophosphamide for anti-neutrophil cytoplasm antibody associated vasculitis (AAV) demonstrates the considerable problems of glucocorticoid therapy (3). Despite using rituximab, a specific monoclonal B-cell inhibitor instead of cyclophosphamide, a chemotherapy agent with significant toxicity, there was no significant difference in the number of adverse events in patients receiving either cyclophosphamide or rituximab. This was almost entirely attributed to the large doses of glucocorticoid therapy accompanying the immunosuppressive agents.

A number of considerations must be recognised in application of the concept of "treat-to-target" in vasculitis:

1. We must define what the target should be: is it mortality, or organ failure, or relapse, or damage, or impaired well being or functional impairment? All of these outcomes are important and require a careful standardised structured approach to define achievement of the target or not.
2. The treatment should be sufficient to reduce the disease burden to a pre-set agreed level. The ideal pre-set agreed level is complete absence of disease, resulting in long-term remission or cure. In the majority of patients with small vessel vasculitis, we can reduce mortality (11), achieve remission (10), but cannot maintain it in around half the patients (12) and cannot prevent damage (13). By contrast, it may be achievable in larger vessel disease, particularly giant cell arteritis. However, studies of patients undergoing aortic resection suggest that patients with previous episodes of GCA who subsequently develop aortic aneurysm (and there is a suggestion that the two are linked, epidemiologically) may continue to show active vasculitis on histology of the samples of aorta resected at the time of aneurysm repair despite the absence of any current symptoms (14). Furthermore, it has been suggested that about 20% of patients with GCA develop aortic aneurysms (15). Therefore, we cannot argue that the disease is cured, although no active features are detected at a clinical level.
3. We would use an agent or agents which specifically treat the disease by targeting the abnormal pathophysiology (3, 4); this is in comparison to the current situation where we use generalised immunosuppression (1, 16, 2, 17). In turn, we should be able to minimise undue toxicity to the patient.

Therefore, it does make sense to consider a more refined approach to the management of vasculitis and this will necessarily require more careful evaluation of patient responses to therapy in order to judge how much treatment to give, at what point, in what combination and for how long. We have only some of the answers to these questions based on studies up until now, but we should attempt to answer all of these questions using appropriate study designs over the next few years.

What are the targets in vasculitis?

Pathophysiological targets

Similar to an approach in inflammatory arthritis, we need to examine disease mechanisms and identify which aspects are vulnerable to attack by our current therapies. Moreover, we need to be selective about those therapies so that we minimise toxicity to the patient whilst maximising the therapeutic benefit.

We probably know most about the ANCA-associated vasculitides, where in the case of MPO ANCA there are good animal models demonstrating the pathogenicity of ANCA itself (18, 19). Furthermore, use of the B-cell inhibitor Rituximab has had a significant impact on the treatment of ANCA vasculitis especially for those who are ANCA positive. The situation is not quite so clear-cut in PR3 ANCA associated disease because there is currently no accepted animal model which clearly demonstrates the pathogenicity of PR3 ANCA (20, 21). The RITUXVAS (Rituximab *vs.* cyclophosphamide in ANCA-associated vasculitis) (3) and RAVE (Rituximab in ANCA-associated vasculitis) (4) studies were used as the basis for a successful FDA application for using rituximab in ANCA vasculitis (for PR3 ANCA and MPO ANCA related disease). B-cell inhibition had a significant benefit akin to but not superior to that achieved by using cyclophosphamide.

Other mechanisms involved in AAV include the complement pathway, especially C5 (22), and current studies are underway to assess the effect of complement inhibition in AAV. In virus associated vasculitis such as hepatitis B related polyarteritis nodosa, eradication of the virus appears to be the appropriate curative treatment and can be achieved with a combination of anti-viral therapy, with limited immunosuppression (23). Although hepatitis-C-related vasculitis has been treated with the same approach (24), it is more difficult to eradicate the target because of the re-emergence of Hepatitis C once the anti-viral therapy is stopped. A recent small randomised trial of rituximab compared to conventional immunosuppression (25) in cryoglobulinaemic vasculitis achieved comparable results, and was very well tolerated (over 60% remaining on rituximab compared to only 3% on conventional therapy after 12 months).

Serological markers as targets

A recent meta-analysis of ANCA titres in management of systemic vasculitis suggests that they are of very limited value in determining how long and how much to treat for (26). If ANCA does not disappear in patients who have achieved clinical remission using induction therapy with cyclophosphamide, the persistence of ANCA increases the risk of relapse if the patient is subsequently switched to azathioprine (27). Potentially, this could serve as a target in this setting *i.e.* the target is to ensure that the ANCA titre is negative before induction therapy is stopped. However, this approach has not been tested in adequate numbers in a controlled trial. Conversely significant rises in ANCA titre might occur during the course of the disease in 29% of patients without any clinical consequence (28).

An early study from 1990 (29) proposed to treat patients prospectively on the basis of rising ANCA titre with aggressive immunosuppression but this approach has not been validated in subsequent studies (30) because of the significant discrepancy between clinical disease activity levels and serological findings (*i.e.* ANCA titre). Conventional biomarkers of inflammation such as C-reactive protein and sedimentation rate are not reliable in systemic vasculitis because they could be influenced by the presence of concurrent infection which is not uncommon especially in GPA where upper airways disease may be associated with the colonisation of the upper and or lower respiratory tract, especially with *Staphylococcus aureus*.

Changes in renal function such as a rise in creatinine or a fall in creatinine clearance are an important target, which may indicate recurrence or worsening of underlying vasculitis, but equally may reflect damage. Further rises in creatinine may be influenced by poorly controlled hypertension which can be secondary consequences of previously active vasculitis rather than currently active disease. However a creatinine rise in the presence of active urinary sediment could be used as a target for increased treatment.

Imaging biomarkers of disease activity

There are no recognised effective imaging biomarkers in small vessel vasculitis that can be used to measure response to therapy that are applicable. There was some early interest in indium labelled white cell scans to localise active disease in the upper airways in patients with granulomatosis with polyangiitis – Wegener's (GPA) (31). More sophisticated development of CT scans and MRI scans has enabled more anatomical detail to be revealed to demonstrate both the presence of active granulomatous inflammation in GPA and the presence of damage particularly to bony structures. However this has not been quantified to allow a standardised approach to be applied, but this could be an area for development (32).

PET-CT scanning can be used to quantify the amount of aortic involvement in large vessel vasculitis both Takayasu arteritis and GCA (as well as the more indistinct condition of large vessel vasculitis) but there are problems of repeat procedures involving expense and radiation and only one or two studies demonstrating a clear treatment effect from immunosuppressive treatment (33-35). This is an expensive and potentially hazardous approach because of the large amounts of radiation required in relatively young often fertile individuals with Takayasu arteritis.

Ultrasound examination of accessible arteries in larger vessel vasculitis such as giant cell arteritis might potentially act as an intriguing and non-evasive way of evaluating treatment response. The presence of a halo around the temporal or axillary arteries may be an acceptable alternative to biopsy as a diagnostic test; the presence of a halo around the abnormal vessel provides 68% sensitivity and specificity 91% (36). This allows the possibility of ultrasound scanning of the same artery (otherwise it would have been removed by biopsy) so that the change in the appearance of halo could be used to measure the resolution of inflammation.

It is not clear if the rate of disappearance or intensity of the halo are potentially useful targets to monitor the effectiveness of existing and new therapies. In one small study of 13 patients resolution of the halo took an average of 21 days after initiation of treatment (37). However this has not been widely tested. It is possible that more invasive imaging such as PET CT scanning may provide quantitative information on response to therapy. This is yet to be tested formally, but could potentially offer a very effective solution to rapid early testing of new therapies in GCA.

Clinical evaluation tools to define targets

The simplest target is patient survival; whilst this might be somewhat redundant now for most forms of vasculitis, it does remain a significant issue for very severe disease especially ANCA positive patients presenting with renal failure or pulmonary haemorrhage. A recent trial suggested that despite aggressive treatment, around 26% of such patients would be likely to die within 18 months (2). However for the majority of forms of vasculitis, although mortality is still a problem despite current therapies (38), early mortality is much reduced compared to the historical observations of 80% of deaths in untreated cases (11, 39).

Therefore, more careful assessment of morbidity is used to distinguish between different treatments and also to determine if treatment is sufficient. Morbidity can be classified as morbidity reflecting disease activity, (Birmingham Vasculitis Activity Score – BVAS) (7), morbidity due to accumulating damage, (Vasculitis Damage Index – VDI) (5), or morbidity affecting patient functional performance and activities of daily living, which so far have not been well characterised in vasculitis apart from using very general scores such as the short form 36 (40).

The OMERACT group (Outcome MEasures in RheumAtology Clinical Trials) have recommended a set of evaluations to be used in trials in vasculitis (41) but these have not yet reached clinical practice. However, they do form the basis of a rational approach to standardise patients at diagnosis and evaluate and stage them for disease severity in order to select the most appropriate treatment protocol. Guidelines recommended by EULAR (10) and the British Society for Rheumatology (42) support this concept and suggest that regular monitoring of disease activity and damage will allow a clearer definition of patient progress.

In most of the European Vasculitis Study Group (EUVAS) studies, the prespecified end point has been to achieve remission of disease as defined by the absence of active BVAS items (43). In other words the treat-to-target concept has been applied for many years in the context of these studies (1, 44, 45). It would therefore seem sensible to use a similar approach in clinical practice since this has the strongest evidence base. There are some problems with the approach for patients who do not fully respond *i.e.* do not reach the pre-specified target of improvement or remission. The alternatives are to allow for a longer period of treatment in order to

allow for the target to be achieved *i.e.* give 6 months of induction treatment with cyclophosphamide as opposed to 3 months for example, or to accept a lesser target; an example of this would be a 50% reduction in the baseline BVAS, as used in a study of gusperimus in refractory GPA (46).

For individual patient care, it is possible to start with one set of targets and if they are not achieved, to consider offering a less ideal but more achievable target. But should disease activity be the main target for treatment? There is a link between disease activity and mortality (11, 7) but it is a relatively weak association; a stronger association with mortality is the accumulation of damage (47). Based on the VDI scores collected in a cohort of patients with systemic vasculitis, a threshold of at least 5 damage items gives a 6.4 (Confidence intervals 2.1-19) fold increased risk of subsequent death (47). A critical damage index score of at least 1 (based on severe items of damage) gives a 17.5 (confidence intervals 2.3–136.1) fold increased risk of subsequent death. Therefore measurement of the Vasculitis Damage Index as a surrogate for long-term mortality might be paving the way for using VDI as a future target, such as the avoidance of a threshold of damage in vasculitis.

Other potential targets are to prevent the development of co-morbidity: examples would be the avoidance of malignancy (there is a substantial risk of bladder cancer in patients treated with high doses of cyclophosphamide) (48), cardiovascular disease (49) and drug toxicity (50), all of which are significant events in the course of patients with ANCA vasculitis. Perhaps we should think of these as secondary rather than primary targets. The main aim is to bring patients into clinical remission by reducing their overall disease activity by controlling active inflammation, but at the same time avoiding the accumulation of damage either induced by the disease activity, complicating infection or drug toxicity or the emergence or worsening of co-morbidity. In ANCA-associated vasculitis, therefore, we would suggest that the targets have been defined and can be achieved.

Newer approaches

A recent study (51) has shown that genes in the interleukin-7 receptor pathway, T-cell receptor signalling and genes expressed by memory T cells can be used as predictors of subsequent relapse in patients with ANCA vasculitis. This raises the issue of prognostic targets allowing us to identify patients in advance who are likely to do badly. This resets the whole approach, because these targets appear to be independent of current clinical evidence of disease activity or any other known biomarkers. This data are preliminary and have not been confirmed to date. However, this approach might assist in biomarker discovery at much earlier phases of the disease, thereby creating a new set of targets which adds to the complexity of not only controlling current disease but also preventing future disease.

Conclusions

The treat-to-target concept remains relatively simple, but its application in vasculitis is complex because there is a need to achieve at many levels. However, by using a standard structured approach to patient evaluation and having pre-set targets in mind, response to treatment can be measured and it should be possible to implement an effective standardised approach to the care of all patients with ANCA vasculitis. All of these approaches require regular, careful characterisation of the patient's clinical state at the onset of treatment as well as during follow up, to determine whether or not a target has been achieved. In time, we aspire to a similar targeted approach in other forms of vasculitis.

Acknowledgements

I would like to thank Keri Fathers for administrative support.

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