Editorial

What place for the new biologics in the treatment of necrotising vasculitides

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Introduction

Biologics, including therapeutic antibodies and pooled immunoglobulin, offer great potential in vasculitis but their expense demands careful and thorough evaluation. The modern therapeutic era in vasculitis dates from the introduction of corticosteroids in the late 1940s, but it was combination therapy with immunesuppressives, especially cyclophosphamide, which led to a revolution in patient outcomes. A frequently fatal disease could now be controlled although prolonged medication was required to avoid relapse and increasing awareness developed of the early and late treatment-related complications (1). Further progress has been made by clinical trial networks developed in the 1980s and 1990s that have optimised and harmonised treatment regimens (2-4).

Biological therapies were introduced into vasculitis therapy in the late 1980s (5-7). Their clinical development in vasculitis has been slow, but in common with systemic lupus erythematosus (SLE), is now accelerating. They are increasingly used as rescue therapy on a compassionate basis but are likely to play a more major role in therapy in the future. The specificity of some biological agents enables pathogenetic and therapeutic studies to proceed in parallel. Post-genomic techniques are exploring therapeutic mechanisms and may produce a new classification based on predicted treatment responsiveness (8).

What are the problems with current therapy ?

Although high remission rates of 90% have been reported, remission is often delayed and remission sustained for more than six months occurs in less than 75%, and by five years, over 50% will have relapsed (4, 9,10). Also, conventional remission definitions imply the absence of overt disease on the background of continued therapy and many patients continue to have poor quality of life reflecting ongoing subclinical disease, irreversible damage or the effects of continued therapy (11, 12). In Wegener's granulomatosis the control of certain granulomatous features of disease, such as, retro-orbital granulomata is particularly difficult. The toxicity of therapy is almost universal with severe adverse-event rates ranging from 10-50% within the first year (9). Long-term therapy to prevent or treat relapses results in a high cumulative steroid and immune suppressive burden with important consequences for chronic morbidity and incapacity (1).

Thus the potential areas for new biologics to improve outcomes in vasculitis include the induction of earlier remission, minimising irreversible organ damage, the induction of sustained remission, reduction of steroid and immune suppressive exposure and improvement in patient function. Recent data is pointing to increased risks of cardiovascular disease and malignancy in vasculitis patients, addressing these risks will be a further challenge for newer therapies.

Which biologic agents have been used in vasculitis ?

1. IVIg

After the demonstration of a reduction in coronary artery aneurysm formation in the childhood vasculitis, Kawasaki disease, with pooled normal human immunoglobulin, its use in other vasculitis syndromes has become widespread despite the lack of any large randomised studies (13). There is uncertainty as to the therapeutic mechanism of IVIg in vasculitis with evidence for both non-specific anti-inflammatory and anti-cytokine effects and more specific correction of immunoregulatory defects (14). Three indications are emerging: as an addi-

tional agent for hard to control or relapsing disease, as an alternative agent when conventional immune suppression is contra-indicated, such as on the intensive care unit, in the presence of sepsis or in pregnancy; or as a component of induction therapy (15). Two uncontrolled studies have used IVIg alone as initial therapy, one in 'early systemic' vasculitis and one for rapidly progressive glomerulonephritis (16). The results in the latter group were surprising with reversal in the deterioration of renal function and partial normalisation of C-reactive protein and circulating cytokine levels (17). Further vasculitic indications with positive preliminary data include Henoch-Schönlein purpura, Churg-Strauss angiitis and vasculitic neuropathies (18-20).

2. Lymphocyte depletion

Polyclonal and monoclonal therapeutic antibodies designed to deplete T cells have led to treatment free remissions of varying duration in relapsing patients with Wegener's granulomatosis and other vasculitides (21, 22). Their use has been complicated by a high frequency of infections, related in part to previous high exposure to cyclophosphamide and corticosteroids, to the older age of vasculitis patients and to the presence of renal dysfunction. Re-treatment of subsequent relapse with the humanised monoclonal anti-CD52 antibody, CAMPATH 1-H, has been effective but is precluded after anti-thymocyte globulin by the development of an anti-globulin response. The duration of remissions appeared to be related to T cell, particularly $CD4^+$ T cell, levels and the typical prolonged $CD4^+$ T-cell suppression that follows CAMPATH 1-H probably explains the long remissions seen in some patients (23).

B cell depletion with Rituximab was first used with the aim of suppressing ANCA levels in a patient with relapsing Wegener's granulomatosis and persisting PR3-ANCA positivity (24). With experience from rheumatoid arthritis and experimental models a hypothesis has developed that T-cell autoreactivity is commonly B-cell dependent and the B-cell plays a role in autoantigen presentation or the provision of co-stimulatory support to T cells (25). T cell cytokines are promptly suppressed by Rituximab and Rituximab may well be effective in autoimmune scenarios without autoantibodies. Other indirect support for targeting the B cell comes from the presence of B cells at sites of active vasculitis, the association of B cell stimulating cytokines and B cell surface activation markers with disease activity and the preferential suppression of B cell activity by the effective vasculitis treatment, cyclophosphamide (26-28).

Rituximab targets the CD20 antigen which is expressed in a stable fashion on B cells but not plasma cells, causing cell lysis through Fcgamma RIII dependent mechanisms. A typical dosing of four, weekly infusions of $375mg/m^2$ reduces circulating B cells to levels undetectable by conventional methods. B cells then return after several months reaching pre-treatment levels by 9-12 months. It appears that sustained peripheral B cell depletion is required for a therapeutic effect but whether this effect is directly dependent on peripheral depletion or is dependent on B cell depletion in tissues or lymphoid organs is unknown. The B cell microenvironment including local B cell stimulating factor levels influence Rituximab cytotoxicity (29). Several, uncontrolled studies and many anecdotal reports observed disease remissions in relapsing and refractory patients with ANCA associated and other vasculitides (30-42).

B cell depletion has permitted reduction or withdrawal of immune suppressive and corticosteroid drugs important attributes of an ideal therapy. However, relapses occur in the majority and predicting relapse risk, and planning preemptive treatment, has become a crucial issue. B cell reconstitution is not closely correlated with flare but a rise in ANCA appears strongly predictive, and it is in this context, without the influence of concurrent immunesuppression, that ANCA monitoring may be particularly useful. Re-treatment with rituximab has been at least as effective as initial therapy but potential problems that may occur with repeat dosing include human anti-chimeric antibody (HACA) formation and hypogammaglobulinaemia. The role of concurrent immune suppression and corticosteroids is not clear: in rheumatoid arthritis, cyclophosphamide does not add to the therapeutic effect, however in vasculitis a treatment response may take several months and the more rapid response to cyclophosphamide may be required in more severe presentations.

3. Cytokine blockade

A rationale for blockade of tumor necrosis alpha (TNFα) has derived from the association of circulating TNFα levels with disease activity, from the presence of TNFα and TNFα receptors at sites of vasculitis, from the role of TNFα in priming neutrophils for ANCA mediated neutrophil activation and endothelial cells for neutrophil medicated cytotoxicity (43, 44). Furthermore, blockade of TNFα in two animal models has led to abrogation of vasculitis (45). Reduction of TNFα has also been considered to be a therapeutic mechanism of corticosteroids, IVIg and thalidomide in vasculitis therapy.

Preliminary compassionate use studies reported early efficacy of the chimeric anti-TNFα monoclonal antibody infliximab and the soluble 75kd TNFα receptor etanercept in patients with Wegener's granulomatosis, Takayasu's arteritis, giant cell arteritis and cryoglobulinaemic vasculitis (46-54, 55). By far the largest trial, the WGET study, examined the addition of etanercept to a standard corticosteroid/immunesuppressive combination for induction and maintenance therapy in new and relapsing Wegener's granulomatosis (4). No advantage of etanercept over placebo was seen in the primary end point, sustained remission, or in any other efficacy variables. There was no clear evidence that etanercept added to the safety risk of standard treatments with the exception of an increased number of malignancies in the etanercept group, which may have been due to chance, and was inconsistent with the absence of increased malignancy risk with TNFα blockade in rheumatoid arthritis and Crohn's disease (56, 57). The preliminary etanercept data that formed the basis of the

WGET study had reported clinical improvement when etanercept was added to a background of continuous immunesuppression for relapsing Wegener's granulomatosis but also found 'escape' of disease control with continued etanercept over the longer term (58). Thus it remains possible that etanercept has early, but not sustained efficacy in Wegener's granulomatosis but that this signal was lost in the WGET trial due to its co-administration with, generally effective, high dose induction therapy. Etanercept reduces the activity of circulating TNFα, but, in contrast to infliximab, does not bind to TNFα complexed with TNFα receptors, either in the circulation or in tissues. This difference in therapeutic mechanism has been proposed to explain the experience in inflammatory bowel disease, also associated with granulomata, when etanercept is ineffective whereas infliximab therapy is more successful (56).

An uncontrolled, prospective study of infliximab in ANCA associated vasculitis (Wegener's granulomatosis and microscopic polyangiitis) evaluated infliximab as an additional component of induction therapy in renal vasculitis and as an additional therapy to continuous immunosuppression in relapsing disease (50). For renal vasculitis, the addition of short-term, three months, infliximab was safe and appeared to induce more rapid remission and permitted more rapid steroid reduction than in historical studies. Infliximab also appeared effective and safe for relapsing disease over the first three months, but, of relevance to the WGET results, the benefit was not sustained despite continued infliximab and of greater concern, several severe infections were noted.

TNFα blockade may therefore have a role in induction regimens or the short-term control of relapsing disease when it has the potential to lead to more rapid disease control and reduce steroid dosage. As yet, there is no evidence that tissue damage, such as in the kidney, may be reduced by TNFα blockade or that TNFα blockade may be used in place of intravenous methyl prednisolone or plasma exchange in severe presentations. In addition to the possible differences in efficacy between etanercept and infliximab is the differential expression and biological roles of TNFα receptors in target organs and it is possible that specific TNFR1 or TNFR2 receptor inhibitors will be of more benefit.

Current evidence does not support the routine use of TNFα blockade in vasculitis but the large number of anecdotal reports in various refractory vasculitis scenarios suggest that TNFα blockade remains a therapeutic option to be considered. While accepting the weakness of existing data, tentative conclusions are that infliximab may be more effective than etanercept, that prolonged therapy may be less effective than short term therapy; and that TNFα blockade adds to the risk of severe infections especially with long-term use.

Early in its development in rheumatoid arthritis, the occurrence of anti-nuclear antibodies and systemic lupus erythematosus-like manifestations, and multiple sclerosis were reported with TNFα blockade. More recently, glomerulonephritis, cutaneous vasculitis, vasculitic neuropathy and ANCA associated renal vasculitis have occurred with both infliximab and etanercept in rheumatoid arthritis (59-63). Possible mechanisms for these reactions include an immune complex reaction between the drug and human anti-chimeric antibodies (HACA) or TNFα itself, or perturbation of cytokine networks leading to new autoimmune phenomena such as SLE (59, 64). Analysis of one case associated with infliximab failed to find anti-chimeric antibodies but reported a T cell predominant infiltrate and activation of Th1 associated cytokines.

The paradigm of prolonged TNFα blockade in rheumatoid arthritis, and the role of TNFα in a cytokine hierarchy, may not be transferable to vasculitis. This has implications for the transfer of other cytokine inhibitors evaluated in rheumatoid arthritis, such as the soluble interleukin 1 receptor antagonist (anakinra) or antibodies to the interleukin 6 receptor. Reversal of endothelial dysfunction with infliximab in vasculitis highlights potential benefits of TNFα blockade on cardiovascular risk (50, 65).

Evaluation of biologicals in vasculitis

At first sight, with remission rates of 90%, current treatment appears effective; more stringent end-points are required for biologics, including sustained and treatment free remission. There has been no standardisation of response criteria in vasculitis, which complicates the comparison of results from different trials.

The influence of concurrent steroid and immunesuppressive medication complicates the assessment of efficacy of biological agents, a particular problem for induction regimens in new patients. In contrast, previous and current treatments will exacerbate the risk of infection. Vasculitis involves multiple pathogenetic mechanisms and biologics may influence different pathways in different ways or have different effects in different sites; for example, intravenous immunoglobulin appears to be of particular use in vasculitic neuropathy while exacerbation of central nervous system autoimmunity has been a rare complication of TNFα blockade. Thus assessment of the effect of therapies on different pathways in parallel with clinical evaluation will be needed to understand therapeutic mechanisms.

Phase II trial evaluation should address the duration of therapeutic response to a biologic, dosing and dosing interval and concurrent therapy to enable appropriate end-point selection for phase III testing. Finally cost-effectiveness of expensive drugs will be required before routine use is supported by funding agencies and economic evaluation of vasculitis is in its infancy.

Conclusion

Existing studies clearly describe the outcomes and problems to be expected with current therapies and form a good comparator from which to judge the effectiveness of biologic therapies. There are major potential improvements to be made in both the effectiveness and safety of vasculitis therapy and the severity of the current consequences of vasculitis justifies invest-

ment in new therapies. A therapeutic rationale has developed for IVIg, cytokine blockade and lymphocyte depleting therapies and the pharmacodynamics of lymphocyte depleting therapies can be followed by lymphocyte subset analysis. Both IVIg and cytokine blockade are potential additional agents to standard therapy for induction regimens with short term effects in contrast to lymphocyte depletion which has potential as an alternative to current treatments for both induction and remission phases of treatment. IVIg is non-immunesuppressive and may protect against infective complications but cytokine blockade contributes to infective risk; T cell depletion has a high infective risk of particular relevance in elderly patients with renal impairment, however, B cell depletion may have little or no infective risk associated with its use.

Much of the initial experience with biologic agents comes from the management of relapsing or refractory vasculitis and this does not necessarily predict results that will be obtained with naive patients. Existing data with rituximab and IVIg is sufficient to support consideration as alternatives for relapsing disease but not for new patients. The situation with TNFα blockade is more problematic, certainly prolonged etanercept is ineffective for sustaining remission but whether short-term TNFα blockade may be beneficial either as a component of induction therapy or in relapsing disease, and whether infliximab or adalimumab are superior to etanercept is unclear.

These are exciting times in vasculitis therapy and it seems probable that the end of the era of steroid and immunesuppressive combination therapy is in sight not only with the use of agents discussed above but also with many other biological agents yet to be studied in vasculitis.

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