

### Part 3: Newer therapies for ANCA-associated vasculitis

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This section of this Symposium report focuses on the therapeutic potential of newer agents for the treatment of AAV with the exception of rituximab and other forms of B-cell depleting therapy that are discussed in Part 2 of this report.

#### Newer anti-proliferative drugs

Deoxyspergualin is a novel anti-proliferative drug derived from *bacillus lat-erosporus* that suppresses lymphocyte and macrophage function and impairs neutrophil production (1). Studies in refractory ANCA-associated vasculitis and crescentic glomerulonephritis have demonstrated useful efficacy and in a murine model of spontaneous vasculitis, deoxyspergualin was superior to mycophenolate mofetil and as effective as cyclophosphamide in the control of vasculitis (2-5). A larger, multi-centre study of deoxyspergualin in 46 patients with refractory Wegener's granulomatosis has recently been completed (6). This study found a response rate of 90% with almost half of patients reaching a sustained full remission accompanied by significant reductions in prednisolone requirement. The improvement in disease activity was maintained after stopping deoxyspergualin during treatment with azathioprine. Deoxyspergualin has the potential to replace cyclophosphamide for the induction of remission in vasculitis without exposing patients to the fertility and malignancy risks of cyclophosphamide. Reversible leukopenia was frequent with deoxyspergualin and required close monitoring of blood counts.

*Mycophenolate mofetil* and *leflunomide* are licensed for the treatment of solid organ transplantation and rheumatoid arthritis respectively and are also under evaluation in vasculitis. Small studies in refractory vasculitis have reported a variable response to mycophenolate and a retrospective review in 53 patients with relapsing ANCA associated vasculitis found useful disease responses in over 50% of patients but dosing was limited by toxicity and subsequent relapse rates were high (7-9). A randomised comparison of leflunomide to methotrexate for remission maintenance

after cyclophosphamide induction was stopped early due to an excess of major flares in the methotrexate group (10). However, adverse events were more frequent in the leflunomide limb and the differences between methotrexate and leflunomide may, in part, have related to dosing. This study supports the use of leflunomide as an alternative drug for remission maintenance. Two studies are investigating the roles of mycophenolate mofetil for remission induction and maintenance therapy in vasculitis (11).

#### Intravenous immunoglobulin

Intravenous immunoglobulin as sole therapy was effective, in an open label trial, in arresting further deterioration in rapidly progressive glomerulonephritis associated with MPO-ANCA and reduced subsequent glucocorticoid and cyclophosphamide exposure (12). Previous studies have demonstrated a therapeutic effect of intravenous immunoglobulin in refractory disease, but this was not sustained, after a single course of therapy, for more than three months (13).

#### Tumor necrosis factor blockade

A rationale for tumor necrosis factor (TNF) blockade in the treatment of AAV has been based on the need for TNF priming before ANCA can induce neutrophil activation, on the presence of TNF and TNF receptor hyperexpression at sites of vasculitis, on the role of TNF in activating endothelial cells permitting leukocyte adhesion and on the triggering role of infection on vasculitic activity (14, 15). Blockade of TNF has led to resistance to vasculitis in animal models (16). Several uncontrolled studies pointed to a useful therapeutic effect of TNF blockade in giant cell arteritis, Takayasu's arteritis and ANCA associated vasculitis (17). A study with the 75kd soluble receptor, etanercept, was unsuccessful in preventing flares or reducing glucocorticoid requirements in Wegener's granulomatosis in a large, placebo-controlled trial (18). This study found an unexpected association of etanercept with malignancy, the significance of which remains unclear (19). A smaller

open label trial of infliximab suggested some short term efficacy in both new and relapsing ANCA associated vasculitis but longer exposure was associated with increased infection risk and disease relapse (20). Whether TNF blockade has a role in induction regimens or in refractory AAV disease has not been resolved and the current data argues against its routine use. It is also possible that different TNF blocking drugs have different potential in vasculitis. Perhaps of more concern has been recent reports of a secondary vasculitis developing in patients with rheumatoid arthritis receiving TNF blocking drugs (21, 22). Also, the different biological functions of TNF receptors suggests that blocking all TNF may well have negative as well as positive effects and more specific TNF receptor blockers might be safer and more useful.

### Lymphocyte depletion

Lymphocyte depletion with *anti-thymocyte globulin or alemtuzumab* (CAMPATH 1-H) has induced remission in over 80% of patients with refractory AAV but has been associated with a high rate of infections, most common in those critically ill or over 60 years of age (23-25). Immunosuppression-free remissions occurred but the majority of such patients relapsed within one year. Re-treatment with alemtuzumab appears safe and has led to further periods of sustained remission (26). Finally, early studies of *autologous stem cell transplantation* have led to prolonged disease control in previously refractory patients (27, 28). This procedure used high dose cyclophosphamide and anti-thymocyte globulin to ablate the immune system and autologous stem cell infusion to accelerate bone marrow recovery. Appropriate patient selection appears crucial to the success of this procedure avoiding excessive previous cyclophosphamide exposure and those with irreversible vital organ dysfunction (29). Of particular interest has been a report of allogeneic stem cell transplantation in a patient with Wegener's granulomatosis who developed acute myeloid leukaemia. Following successful transplantation, PR3-ANCA and evidence of vasculitis recurred, but

then subsided spontaneously and the patient remains well (28).

Important issues in the evaluation of newer treatments in vasculitis are: the time before a therapeutic effect becomes apparent, the duration of an effect and the need for concomitant therapy. Vasculitis frequently presents as a fulminant disease and lymphocyte depletion strategies may work too slowly to be effective on their own. In contrast, cytokine blockade may work quickly but the effect wears off and repeat dosing or an alternative therapeutic is required (20). The experience with placebo-controlled trials has indicated that the promise of early uncontrolled reports is often not fulfilled by randomised trials and emphasizes the need for large scale trials answering appropriate questions before the routine use of newer therapies can be recommended (18).

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