Editorial

Leflunomide versus methotrexate in Wegener’s granulomatosis

Wegener’s granulomatosis has major overlaps with other primary systemic vasculitides, especially microscopic polyangiitis, but also important differences [1]. Its cause is unknown, but it almost always involves the respiratory tract and is more common in cooler latitudes [2]. It typically pursues a protracted relapsing course resulting in chronic morbidity for the patient and an ever widening search for newer, safer therapies by their physician. Combination therapy with cyclophosphamide and corticosteroids, first introduced 35 yrs ago, revolutionized the treatment of Wegener’s granulomatosis and converted a frequently fatal disorder into a more chronic relapsing condition [3]. Subsequent clinical investigation has aimed to reduce drug-related toxicity, reduce relapse rates and recover organ function. In particular, the failure of short treatment regimens to induce prolonged disease control and the toxicity of long-term cyclophosphamide has driven the evaluation of alternative immunosuppressives for remission maintenance.

The terminology of remission and relapse has very different implications in vasculitis from its use in other disease, such as in cancer, and disease state definitions have recently been defined in a European League Against Rheumatism (EULAR) consensus report [4]. Remission has come to mean a state of disease control where symptoms and signs of active inflammation are absent after several months of high dose corticosteroids and cyclophosphamide or alternative immunosuppressive. Immunological markers, including anti-neutrophil cytoplasm autoantibodies (ANCA), and evidence of B and T cell activation often persist, and reduction or withdrawal of therapy is the most potent predictor of the return of overt disease [5–7]. Thus, remission is the suppression of the overt expression of vasculitis by ongoing therapy rather than the disappearance of the disease. The concept of remission has also been influenced by the desire to minimize cyclophosphamide exposure with short cyclophosphamide courses used to ‘induce remission’, and prolonged courses of a safer immunosuppressive to prevent ‘relapse’ [8].

Relapse or disease persistence is a greater problem in Wegener’s granulomatosis than in microscopic polyangiitis or polyarteritis nodosa [9]. This has been linked with the granulomatous nature of the inflammation, which is more refractory to therapy [9]. Also, to the role of upper respiratory tract infection, particularly with Staphylococcus aureus, in driving a dysregulated immune response, in association with damage to the respiratory epithelium caused by the disease [10, 11].

Both azathioprine and methotrexate have been studied for the maintenance of remission in Wegener’s granulomatosis and relapse rates of 10–30% a year reported, with one comparative trial finding no difference between them [8, 12-15]. A minority of patients are intolerant or develop severe reactions to these drugs, and long-term exposure increases the risk of opportunistic infection and malignancy. The consequences or relapse include loss of organ function, further exposure to cyclophosphamide and increased corticosteroid dosing. Leflunomide and mycophenolate mofetil are two newer immunosuppressives, initially introduced for rheumatoid arthritis and solid organ transplantation, respectively, which have attracted attention as potential superior alternatives. Current data with mycophenolate mofetil is non-randomized and largely from refractory patient groups, results have been variable and drug-related side effects relatively common [16, 17]. The German Rheumatic Diseases Network conducted a 20 patient pilot study with leflunomide and now report a randomized trial comparing leflunomide to methotrexate for remission therapy after 6 months of cyclophosphamide and corticosteroid induction treatment in ‘generalized’ Wegener’s granulomatosis [18].

The study aimed to demonstrate equivalence in the prevention of relapse, between leflunomide and methotrexate groups, in 145 patients over 2 yrs and was terminated after 54 patients had been recruited due to an excess of major relapses in the methotrexate group, seven vs one in the leflunomide group. The relapse rate with methotrexate was higher than in previous reports, from this study group and from others, and was attributed to the slow rate of increase of methotrexate dose and the oral route of administration. The majority of relapses involved the kidneys but it is not stated whether there were any differences in renal involvement at the time of diagnosis. The major relapses also tended to occur early in the trial, before the target dose of methotrexate 20mg/week had been achieved. Furthermore, this dose is at the lower end of the range of doses previously used in this condition [13]. The methotrexate dosing resulted in a low frequency of adverse reactions in this group with no severe reactions and half the total number of adverse reactions seen in the leflunomide group. In contrast, there were six severe reactions with leflunomide, a number which was the same as the excess of major relapses seen with methotrexate. The leflunomide dose of 30 mg/day was higher than the recommended dosing range in rheumatoid arthritis of 10–20 mg/day. As is so often the case, the efficacy of immunosuppression has to be balanced against its toxicity and if a major flare can be regarded as similar to a severe adverse reaction then there was no difference between the groups in this study.

Other factors than immunosuppressive dosing influence relapse rates [7]. Although the majority of patients were receiving prednisolone 5mg/day when methotrexate or leflunomide were started, this was tapered to zero within a few months. Also, prior steroid exposure had been considerably less than previous published regimens for ‘generalized’ disease [13, 19]. The contribution of maintenance steroid to relapse risk is unclear but there is an impression that protocols with prolonged steroids have lower relapse rates than those that withdraw steroids early [20]. ANCA positivity after induction therapy is related to relapse rate and was high in this study, 89% at randomization [6]. The trend for more patients under treatment with leflunomide to become ANCA negative during the trial reflects the association of ANCA with relapse and the higher efficacy of leflunomide in this study. Prolonged therapy with sulfamethoxazole/trimethoprim has reduced relapse rates in Wegener’s granulomatosis, probably by reducing respiratory tract infection [21]. Although no information on bacterial infection or antibiotic therapy is given in this report, infections were more common in the leflunomide group and were not obviously associated with infection.

Alternative strategies for prevention of relapse have included lymphocyte depletion and tumour necrosis alpha (TNFα) blockade. T cell depletion with CAMPATH 1-H (alemtuzumab) or antithymocyte globulin has led to sustained, treatment free, remissions in refractory patients [22, 23]. More recently, several preliminary studies have reported remissions of 6 months to several years after B cell depletion with rituximab [24, 25]. Etanercept, a soluble TNFα receptor was ineffective in preventing relapse in a large randomized study, and prolonged TNFα blockade appears to increase the risk of severe infection in this...
setting [20, 26]. Intravenous immunoglobulin has resulted in improvements in disease activity in Wegener’s granulomatosis and one study of Churg–Strauss angiitis reported a benefit of repeated dosing in maintaining remission [27, 28]. A newer immunosuppressive, deoxyspergualin, has been studied in active, refractory Wegener’s granulomatosis, and in a subgroup of patients from these studies only deoxyspergualin has been capable of avoiding disease flares [29].

Leflunomide can be added to the list of alternative immunosuppressive drugs for remission maintenance in Wegener’s granulomatosis. The dosing regimen used in this study led to severe drug reactions in 11% and the imbalance in drug-related toxicity between groups suggests dosing was not equivalent, thus the study does not give clear guidance as to whether leflunomide was superior to methotrexate. In addition to the need for more comparative data between immunosuppressives, the inter-patient variability in toxicity and efficacy of these agents indicates a need for new predictors of drug response.

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Acknowledgements

Funding to pay the open Access publication charges for this article was provided by ... The authors have declared no conflicts of interest.

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