Commentary

Short term immunosuppressive therapy and long term immunoregulation: promises and problems

Immune mechanisms are fundamental to the pathogenesis of many conditions which lead to severe visual impairment. For example, chronic uveitis is a significant and probably underestimated cause of visual handicap in the working population[1] and corneal graft rejection remains a significant cause of morbidity and failure to rehabilitate vision following initially successful surgery. Current treatment of inflammatory and immune ocular disease usually entails the long term use of immunosuppressive drugs with their inherent risks. Corticosteroids continue to be the mainstay of treatment for the majority of conditions but even at low dose there is a risk of metabolic abnormalities, osteoporosis, and iatrogenic glaucoma and cataract. Furthermore, a number of patients require 'steroid sparing' adjunctive therapy with drugs such as azathioprine, methotrexate, or cyclophosphamide which have their own inherent toxicities.

Systemic therapy, therefore, is often restricted to bilateral disease, or severe unilateral disease (often late in disease history), as one of the common restraints to immunosuppressive therapy in ophthalmology is the risk-benefit ratio in an otherwise 'well patient'. This is compounded by the scarce data on the natural history of posterior uveitides, and, in particular, the lack of diligently controlled trials to show any beneficial effect of immunosuppression. Moreover, it is difficult to recognise clinically the most appropriate time to commence therapy, with respect to combatting irreversible tissue damage and visual loss, in light of potential drug toxicity. The newer generation of immunosuppressive drugs, which includes cyclosporin A, FK 506, and mycophenolic mofetil,[2] appear more efficacious, and although no randomised controlled trials have been performed in uveitis, their beneficial effect in some patients is no longer questioned by clinicians who treat chronic inflammatory eye disease.[3] While each of these has a more focused immunosuppressive action chronic therapy is still required, usually in combination with corticosteroids, although they probably allow a reduction in the incidence of side effects compared with chronic high dose steroid therapy. However, there remains a subset of patients who are refractory to even the most aggressive regimens.

The 'biotechnology revolution' has provided numerous recombinant products with exquisite specificity for cells and mediators of the immune system. Examples are monoclonal antibodies (mAb) against T cells and cytokines, and soluble receptors with similar specificities (immunoadhesins).[4] These have facilitated progress on two fronts. Firstly, when used as disease probes they have greatly enhanced our understanding of immunopathological mechanisms and, secondly, they often prove to be effective therapeutic agents. For example, when an antagonist of tumour necrosis factor α (TNFα) was administered to rats previously immunised with soluble retinal extract, the onset of experimental autoimmune uveoretinitis (EAU) was delayed. While the degree of anterior chamber inflammation was only slightly reduced, there was much less irreversible retinal damage despite the presence of activated $CD4^+$ T cells.[5] In other experiments the disease was inhibited by mAb directed at $CD4^+$ T cells.[6] A possible conclusion from these experiments is that EAU is mediated by $CD4^+$ T cells which directly or indirectly lead to the accumulation of TNFα in the retina. Regardless of the exact interpretation, such experiments immediately suggest novel modes of intervention for patients with inflammatory ocular disease. Furthermore, using focused intervention, potent effects can be harnessed from relatively brief courses of therapy. For example, in a different model a 3 week course of mAb directed at $CD4^+$ or $CD8^+$ T cells not only reversed immunological rejection but also induced lifelong graft acceptance (tolerance) in mice that were actively rejecting foreign skin grafts at the time of mAb administration.[7] Of equal importance was the subsequent demonstration that, once tolerance is induced in such models, it is self sustaining via a process of 'infectious tolerance' in which potentially autoreactive T cells are tolerised as and when they develop.[8]

If equivalent effects could be harnessed in patients with autoimmune disease, this should provide for long term symptomatic relief from just a short course of 'immunomodulatory' treatment. Initial attempts to modulate human autoimmune disease in this way have provided only transient symptomatic relief but the animal data evolved from many rounds of well conducted and controlled research, and it is therefore naive to anticipate immediate success in patients.[9] In fact, three patients with refractory vasculitis have experienced long term disease remissions following mAb therapy. In one case this was achieved with two short courses of a pan-lymphocyte mAb, Campath-1H (C1H), and in the other combination therapy with C1H and an anti-CD4 mAb was required.[10] Importantly, in each situation successful treatment evolved using a iterative approach. Two further reports demonstrate the potential power of immunotherapy when applied to eye diseases. In the first, C1H therapy controlled aggressive retinal vasculitis which had proved refractory to all prior treatments.[11] In the second, C1H facilitated successful corneal transplantation in a patient with a prior history of recurrent graft rejection refractory to conventional immunosuppression.[12]

In all of the five cases referenced above, it was possible to wean conventional therapy to zero or very low levels following immunotherapy. While lymphotoxic mAbs such as C1H have resulted in long term peripheral blood lymphopenia (although no associated immunosuppression has been demonstrated), it is now apparent that equivalent effects are attainable with non-depleting reagents.[13] Even if these were immunosuppressive during the brief course (there is scant evidence to suggest this), the therapeutic index is high for any treatment which obviates the need for long term immunosuppressive drugs, and this should be a major stimulus for further research. At the basic level, we need to understand more about how the immunomodulatory agents operate.[14] In the clinic, not only is it important to institute well designed therapeutic studies but we must also try to understand more about our successes and failures. For example, vasculitis and eye disease may be particularly good targets for immunotherapy. In the former the vascular endothelium may provide a more accessible target for biological reagents than, for example, the

synovium of an arthritic joint. Similarly, the unique immunological environment within the eye may facilitate the re-establishment of regulatory immune circuits following therapy of ocular disease.

Our understanding of immune physiology and pathology is increasing exponentially with the promise of yet more novel interventions. The critical factor in immunotherapeutic research is to follow the rules that govern animal research; a logical, repeatable approach based upon knowledge of appropriate immunopathology. In the future we need to adhere to these principals in ophthalmology, and if we do, cures for autoimmune diseases may well follow.

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