Reconsidering treatment options in childhood uveitis

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There is an urgent need for pre-existing guidelines to function as the basis for deciding the treatment in childhood uveitis

The expert panel producing guidelines in 2000 for the immunosuppressive therapy of ocular inflammatory disease specifically listed eight steroid-sparing agents. At the 2004 International Uveitis Study Group meeting in Venice, 10 different drugs were reported to be in use in patients with paediatric uveitis. Nearly 2 years on, there have been reports published of experience in paediatric uveitis using infliximab, etanercept and methotrexate. In the British Journal of Ophthalmology, Doycheva et al. describe the safety and outcomes with mycophenolate mofetil (see page 180).

Placebo-controlled trials or comparison between treatments are rare in the discipline of ocular inflammatory disease, and, when they do take place, rarely confirm the initial enthusiasm surrounding early reports of success. There are widespread concerns about the scarcity of drug trials specific for children. Trials are especially problematic in paediatric ocular inflammatory diseases as they are rare, the course of disease often runs into decades and many patients are concurrently treated for extracocular inflammatory disease. To understand how one can rationally choose between the wide range of treatments available, it is helpful to know how this large menu of drugs arose and on what basis drug effectiveness might be evaluated in paediatric uveitis.

Treatment has largely derived, second-hand, from the immunosuppressants developed for life-threatening conditions such as lymphoid malignancies, solid organ transplants and severe autoinflammatory diseases such as systemic vasculitis. The central role of T cells in transplant rejection, both in animal models of uveitis and in occasional pathological specimens of human uveitis, has resulted in medical ophthalmologists frequently using drugs first trialled in post-transplant regimens—in children these include steroids, antimetabolite or anti-proliferative agents (azathioprine and mycophenolate mofetil), calcineurin inhibitors (cyclosporin and tacrolimus), proliferation signal inhibitors (sirolimus and everolimus) and, more recently, a variety of monoclonal antibodies specific for cytokines thought to be relevant to disease immunopathogenesis.

Medical ophthalmologists have also been influenced by the development of those conditions most often associated with ocular inflammatory disease, such as the alkylation agent cyclophosphamide, which remains the first choice for the induction phase of systemic vasculitis, and methotrexate, which replaced gold, penicillamine and hydroxychloroquine for the treatment of both adult rheumatoid and juvenile idiopathic arthritis. Additional treatments useful in antibody-mediated autoimmune disease, such as pemphigoid, include intravenous immunoglobulin, plasmapheresis and, more recently, B cell specific monoclonal antibodies.
The proliferating menu of treatments reflects these various influences rather than arising from a consistent body of clinical trials specific for uveitis. Despite the years of investigation on animal models of uveitis we still await effective disease-specific treatment for uveitis and our treatment choices still rely heavily on the experience of other medical specialties. This would not matter if multisystem inflammatory disease responded to treatment in an equivalent way in each organ, and if the costs and benefits of treatment were equivalent for each patient with the same diagnosis. Unfortunately, patients with uveitis and systemic inflammatory disease often show a differential response in intraocular and extraocular sites to the same systemic treatment. In addition, medical ophthalmologists have to recalculate the therapeutic cost:benefit ratio for their patients who may be at no risk of extraocular disease and yet potentially bear considerable systemic costs from the monitoring and side effects of these potentially toxic treatments. This is especially true in children, in whom the physical and psychological costs of treatment may require as much consideration as their therapeutic efficacy.

Before advocating the value of aggressive immunosuppression in the treatment of childhood uveitis, it is important to learn from the experience of other doctors, and it is sobering to note that poor treatment compliance with immunosuppressive regimens during adolescence, which are similar to those occasionally administered in severe uveitis, is a major cause of graft rejection in paediatric patients undergoing transplant. The costs of non-compliance in chronic uveitis are somewhat lower, but the need to find treatments acceptable to the patient are equally pressing.

Mycophenolate mofetil is a logical choice to trial in paediatric uveitis. It is now a favoured alternative to azathioprine in post-transplant and vasculitis regimens; it has been used effectively in adult uveitis, and has the advantage of being an oral agent for children. The main complication is gastrointestinal upset. It is not known whether it is a more effective or more tolerable monotherapy compared with methotrexate in juvenile idiopathic arthritis.

Without comprehensive information about the outcomes of contemporary treatment, it is very difficult to assess the value of new treatments in uveitis. There will always be a wide range of complications at diagnosis in chronic painless childhood uveitis, as well as a wide range of possible outcomes that can take decades to evolve. In the absence of standardised definitions of treatment efficacy and disease progression, it is difficult to assume that reports of short-term disease control will readily translate into long-term patient benefit. There is a major problem in monitoring treatment effects in chronic uveitis—in many patients nothing much happens for very long periods, and disease fluctuates rather than entering either remission or developing significant relapse according to present definitions. Flare, cells, acuity and, more recently, optical coherence tomography findings may be measurable in many children, but it is not at all clear how changes relate to the efficacy of immunosuppressive treatment or long-term complications. The complexity of evaluating treatment efficacy is not helped by the fact that easily measurable complications such as loss of acuity, cataract, abnormal intraocular pressure and macular oedema may progress despite adequate immunosuppression or even, in the case of steroids, be caused by treatment.

The minimum information we require before changing treatments is to know the frequency with which patients respond. The end points of steroid reduction and change in relapse rate are provided in this paper. As there is little consensus on the initial treatment for most uveitis syndromes, we need the reassurance that patients receive appropriate initial treatments before we can interpret the relevance of treatment changes.

Early aggressive disease control is now advocated in a variety of chronic inflammatory disorders, and it may be time to reassess the long-advocated stepwise escalation of treatment in uveitis. Using familiar drugs, such as steroids and methotrexate, more appropriately at the onset of disease may reduce the later need for alternative immunosuppressants. We need further research to optimise initial treatments, as well as for expanding the repertoire of drugs used in case of treatment failure or side effects. We need to develop consistent treatment failure strategies so that treatment swapping or supplementation is determined by pre-existing guidelines, which can be modified, rather than by relatively arbitrary decisions of individual clinicians.

This is an exciting era for uveitis, with many new treatments becoming available. However, their long-term tolerability and safety are as important as their ability to achieve short-term disease control. These issues are of central importance in managing chronic childhood disease, where the mere administration of treatments such as frequent eyedrops, injections or regular blood monitoring may cause as much family disruption as any issues of drug toxicity. Doycheva et al have shown that mycophenolate mofetil can be a safe and effective treatment in this difficult group of patients.

It is not unusual for paediatric patients, when adults, to have profound disagreements with those involved in their childhood treatments. There are marked variations between patients, as well as between children and their carers, of the perceived costs of both treatment and the disease. There is no scientific process to value the costs of 5 years of methotrexate treatment or the benefits of cataract surgery in an amblyopic eye for the individual patient; we must develop tools similar to those developed by paediatric rheumatologists to incorporate patient preferences into our therapeutic decisions. However, it is clear that those involved in treatment decisions should be made aware of our uncertainties and that we all should continue to contribute to the collaborative work needed to improve our management.

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REFERENCES

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