Eye (2020) 34:1945–1946
https://doi.org/10.1038/s41433-020-0875-3

The ROYAL COLLEGE of OPHTHALMOLOGISTS

EDITORIAL

Conventional immunosuppression: the search for scientific evidence

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Received: 9 March 2020 / Accepted: 10 March 2020 / Published online: 27 April 2020

The management of uveitis has been an ongoing challenge, both because of the difficulties in establishing a definitive diagnosis and due to lack of management strategies determined by randomised clinical trials (RCTs). Once an infectious aetiology has been excluded, the treatment focus is on the control of inflammation, which is responsible for tissue damage and function loss.

Management usually involves the use of corticosteroids as first line therapy, but usually requires the addition of immunosuppressive agents.

Many strategies used in the management of uveitis are imported from experience in other areas of medicine, especially rheumatology. For many years, uveitis experts have been making use of unlicensed drugs to treat their patients, based mostly on experience-based evidence. So far, only two trials on conventional therapy have fulfilled the criteria for a Cochrane meta-analysis [1, 2], and both were related to the management of Behçet's disease. One was a double-masked trial of cyclosporin versus colchicine, which showed a significant reduction in disease severity and frequency of relapses for the patients treated with cyclosporin. The other was a controlled trial of azathioprine in Behçet's disease, which showed that azathioprine was useful in preserving visual acuity in patients with established eye disease.

In recent years, maybe as a consequence of the knowledge that uveitis is not as rare as previously thought, interest in developing specific therapies for uveitis has grown and this has resulted in recent RCTs for the development of new strategies. The Retisert implant (fluocinolone acetonide) was the first specific treatment for uveitis approved by the FDA, but not by the EMA, for the management of non-infectious posterior uveitis [3]. The 34-week safety and efficacy results of a 3-year study evaluating the implant showed that it significantly reduced uveitis recurrences, improved visual acuity, and decreased the need for adjunctive therapy in the studied patient population, but it was associated with frequent side-effects, especially the development of cataract and increase in intraocular pressure, with many patients requiring filtering procedure to control the intraocular pressure.

The HURON study was a 26-week trial designed to evaluate the safety and efficacy of two doses of dexamethasone intravitreal implant (DEX implant) for the treatment of non-infectious intermediate or posterior uveitis [4]. A single DEX implant significantly improved intraocular inflammation and visual acuity, with effects persisting for 6 months. The dexamethasone intravitreal implant was approved by NICE and is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults.

The safety and efficacy of an injectable fluocinolone acetonide implant (Fai) has also been assessed in a prospective, multicentre, randomised, doubled-masked, sham-controlled, 3-year, and phase 3 clinical trial. It demonstrated significant benefit in extending anti-inflammatory effect and reducing the likelihood of uveitis flares through 12 months [5]. The data of a 3-year study (unpublished) has confirmed the benefit of this strategy and showed a low incidence of pressure related problems.

The approval of Adalimumab for the management of non-infectious posterior uveitis was based on the outcome of the VISUAL trials, which demonstrated the efficacy and safety of this anti-TNFα biologic agent [6].

These new local and systemic options have added significantly to our arsenal to deal with visually threatening ocular inflammation, but they are not cheap, in terms of both costs and service burden. Little attention has been given to trying to establish the best uses of conventional therapy. These drugs have been used for a long time and do not represent a financial opportunity.

Clinical trials are expensive, time consuming, and old drugs are unlikely to be attractive outside an academic environment. For all these reasons, the work by Rathinam

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et al., is to be commended [7]. Proper evaluation of currently available conventional immunosuppressive therapies would explore cheaper and potentially quite effective therapies and needs to be encouraged. In their paper, "Effect of Corticosteroid-Sparing Treatment with Mycophenolate Mofetil vs. Methotrexate on Inflammation in Patients with Uveitis—A Randomised Clinical Trial" the authors compare the effect of two conventional immunosuppressive agents, methotrexate and mycophenolate. Mofetil, in achieving corticosteroid-sparing control of non-infectious intermediate, posterior and panuveitis. The patients were randomised at 1:1 allocation ratio and received treatment with the same regime for 6 months (primary outcome). This period was extended by another 6 months if the treatment was successful in controlling inflammation, but, in case of failure, they were switched to the other therapy for another 6 months. The results provided evidence that methotrexate was not inferior to mycophenolate mofetil, both for the 6-month primary outcome analysis and for the pre-specified 6-month secondary outcomes. A low level of adverse events was reported for both groups and, they were all related to elevated liver function tests. The findings showed that there was a difference in effect between the agents for the management of intermediate uveitis versus posterior and panuveitis, but the numbers were too small for further subgroup analysis. This issue needs to be addressed in further studies. The limitations recognised by the authors did not affect the conclusions.

Although the recently approved therapies do represent an important step in improving disease control, many patients may still benefit from some of the conventional options, leaving the new agents for those cases who fail to respond to the former. Therefore, an interesting strategy that should not be ignored is to define the main use and the relative efficacy of the conventional options versus the novel therapies especially in terms of health-economics. Further analysis of these older agents are required especially because in many countries results from such studies would provide important guidance for the clinicians.

Compliance with ethical standards

Conflict of interest Consultancy and Advisory Board for Allergan, Alimera, Boehringer Ingelheim, Abbvie, and Santen.

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