

Fibrosis

Postoperative fibrosis suppression

A L Schwartz

An alternative to intraoperative mitomycin C

The use of antimetabolites to modulate wound healing post-trabeculectomy has been a major advance in glaucoma filtering surgery. Initially, 5-fluorouracil and, more recently, mitomycin C, have been used to dramatically improve success rates in patients at high risk for trabeculectomy failure, reducing the need for postoperative glaucoma medications. However, the use of antimetabolites has been accompanied by an increased risk of complications, including early and late bleb leaks, hypotony, maculopathy, and endophthalmitis. An alternative treatment that could be applied after surgery to rescue those blebs that appear at increased risk to fail would be valuable, especially if it would obviate the need for mitomycin C.

Fuller *et al's* study in this issue of the *BJO* (p 1352) highlights a different approach to fibrosis suppression post-trabeculectomy. Their regimen involves the use of three agents taken orally: prednisone, a non-steroidal anti-inflammatory agent, and colchicine. They used these drugs in a series of 77 of 551 eyes that had undergone trabeculectomy between 1978 and 1998. In none of these operations was an antimetabolite used. All patients had either primary open angle glaucoma or exfoliation syndrome and only two patients had a previous trabeculectomy.

These 77 eyes were selected for antifibrosis treatment because of an exaggerated postoperative healing response with increased bleb vascularity, a Tenon's cyst formation with elevated intraocular pressure, or a reduction in bleb size with visible fibrosis and threatened bleb failure. The antifibrosis regimen was started, on average, 11 days after surgery; the range was 7–30 days. The best

response was in patients started within 2 weeks of surgery and six of the eyes required subsequent bleb needling. No cases of endophthalmitis, hypotony, maculopathy, late bleb leak, or serious systemic side effects from the postoperative regimen occurred.

Long term success rates are very impressive as defined by their criteria. Sixty nine of 77 eyes (89.6%) were classified as successful with an IOP of less than or equal to 21 mm Hg. The Kaplan-Meier probability of success was 0.91 at 8 years. This compares quite favourably with the 52% success rate at 4 years, reported by Ehnrooth *et al.*¹ However, today in a similar group of primary trabeculectomies, a pressure of 21 mm Hg post-trabeculectomy without consideration of disc and field status over time would not be classified a success by many ophthalmologists. The Advanced Glaucoma Intervention Study showed that patients required eye pressures less than 18 mm Hg for all follow up visits to prevent progressive damage.²

Fuller *et al* recommend that the oral medications be taken three times a day to be maximally effective. Given their potential side effects, the use of three systemic agents in an older age group population is somewhat worrisome. Dosages were tailored to patients' size, age, general health, and degree of possible bleb failure and they were reported to be well tolerated, with only seven patients requiring an oral histamine-2 blocker (ranitidine) to counteract gastrointestinal upset. One wonders why this regimen has not been more widely embraced.³

This series is noteworthy because of its unique therapeutic approach which may help to reduce the growing incidence of

complications associated with the use of mitomycin C. This regimen of fibrosis suppression has particular appeal in primary trabeculectomies. Bindish *et al* reported 123 eyes that underwent primary trabeculectomy with varying concentrations and durations of mitomycin C application.⁴ Their complications included hypotony (IOP <6 mm Hg) in 42.2% of eyes with a mean follow up of 26.1 months and hypotony maculopathy in 8.9% of eyes. It also could be used after mitomycin C trabeculectomy as adjunctive therapy to try to rescue a potentially failing filter if there were signs of early bleb failure.

For many eyes, this "exaggerated" healing phase may be part of an encapsulated bleb phase which responds well to conservative topical aqueous suppressant therapy.⁵ For others, it may represent a scarring process leading to bleb failure. We do not know how many of these blebs would fail and how many would function if this antifibrosis regimen was not initiated. A prospective randomised study comparing conventional postoperative topical therapy versus the antifibrosis regimen of postoperative prednisone, a non-steroidal anti-inflammatory, and colchicine would clarify its true benefit.

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Birdshot retinochoroidopathy

A bird in the hand . . .

A D Dick

Pathological correlate confirms clinical and experimental observations in posterior uveitis

Continuing our understanding of the basic pathobiology of non-infectious posterior segment intraocular inflammatory conditions has relied largely on experimental models of uveitis, such as experimental autoimmune uveoretinitis (EAU). Arguably such models are not well supported by human data in that there is still no definitive evidence of a role for retinal autoantigens in posterior uveitic conditions,^{1,2} despite us moving on to clinical trials of tolerance induction.³ On the other hand the models are useful. The pathological changes observed appear to explain what we may see clinically—namely, vitritis, retinal vasculitis, chorioretinal leucocytic infiltrates, and optic nerve head and macula oedema.^{4,5} As such we are able to discern common immune mediated processes that lead to inflammation, in particular T cell and macrophage behaviour, cytokine mediation of inflammatory response, and other immune regulatory mechanisms in play in the eye.⁶ To this end, preclinical studies of novel immune modulatory agents (a classic example being cyclosporin⁷) have now been successfully translated into clinical practice.⁸ There are caveats in our interpretations. Although in animal models the photoreceptors are the target tissue for retinal antigen specific autoreactive T cells precipitating the non-specific inflammatory process that follows,^{9,10} in humans there is little evidence that photoreceptors are primarily destroyed during posterior uveitis. Definitively, therefore, we require support of human pathological studies to confirm pathological processes we observe in experimental models. To date such an aim has been restricted because specimens have frequently been of end stage disease, which does not allow us to understand the evolution of ocular inflammation. Moreover, in humans non-infectious ocular inflammation represents a spectrum of conditions, the study of which may not permit an iteric approach to investigating pathology. We thus resort to modulating experimental models by varying antigen, antigen dose, species, and strain of animals used so as to mimic the spectrum of clinical non-infectious ocular inflammatory conditions, in particular Vogt-Koyanaga-Harada disease,

sympathetic ophthalmia, and birdshot retinochoroidopathy. These conditions demonstrate a significant HLA association with both MHC class II molecules in the former two¹¹ and MHC class I molecules in birdshot retinochoroidopathy,^{12,13} providing some relevance to the notion of an autoimmune pathogenesis. If we were to consider animal models as a true representation of posterior uveitis in humans and not just providing excellent experimental conditions to investigate general immunobiological processes and cell behaviour in the eye then we need more pathological information on specific uveitic conditions in order to translate our experimental findings more purposefully.

We require support of human pathological studies to confirm pathological processes we observe in experimental models

In this issue of the *BJO* (p 1439) Gaudio and co-workers have enlightened our understanding of an archetypical uveitis, birdshot retinochoroidopathy. Their clinicopathological description of “non-end stage” disease in an HLA A29 patient is timely. Birdshot retinochoroidopathy was initially described in patients with profuse retinal vascular leakage with resultant retinal, macular, and disc oedema^{14,15} with a poor prognosis over many years.¹⁶ The recently described animal model of spontaneous retinopathy in HLA-A29 transgenic mice¹⁷ supports the high specificity and sensitivity of HLA-A29 positivity in the diagnosis of birdshot retinochoroidopathy,^{12,13} and the increased relative risk of developing the disease when this allele is present. HLA-A29 Tg mice are characterised histologically by changes that are almost identical to those described in the report by Gaudio *et al*, including perivasculitis, vitritis, leucocytic infiltration of the optic nerve head, and choroiditis. More immunohistochemical information of, for example, cell phenotype, microglial activation, GFAP reactivity, and cytokine profile would have assisted in comparing findings with those of experimental models.

Why does HLA-A29 lead to increased susceptibility to develop birdshot retinochoroidopathy? Are we assisted by isolated clinicopathological reports in our understanding of the pathogenesis of uveitis? Reverting back to the animal model EAU, the most potent autoantigens that induce disease are soluble S-antigen (S-Ag) and interphotoreceptor retinoid binding protein (IRBP). Consequently, T cell responses in humans to these antigens have been studied extensively in a variety of uveitic conditions, and have been found particularly prevalent in birdshot retinochoroidopathy.¹⁸ There is now conceivably more relevance of S-Ag reactivity in uveitis. Firstly, there is biochemical evidence that two peptides from the carboxy terminus of S-Ag bind efficiently with the peptide binding motif of HLA-A29.¹⁹ Secondly, the previous clinicopathological report of birdshot chorioretinopathy exhibited strong T cell proliferative responses to S-Ag¹⁸ despite being no pathological features that truly paralleled the classic clinical features of birdshot during its evolution or paralleled the pathological observations in the HLA-A29 Tg mouse (the eye, however, was phthisical and frustratingly the patient was also HLA-A29 negative). Thirdly, although both reports show no conclusive evidence of photoreceptor involvement as seen during the development and end stage of inflammation in animal models, there was a significant granulomatous response in the outer retina in late stages of disease, which could be interpreted as targeting the photoreceptors. Clinically, end stage disease is highlighted by chorioretinal atrophy and reduced ERG responses but we still lack the definitive evidence to support the primary targeting of photoreceptors, as the clinical findings may be explained by vasculitis and ischaemia.

Finally, if we were to conclude that clinicopathological studies in uveitis or more pertinently birdshot retinochoroidopathy are represented well by animal models how, in the case of an MHC class I restricted disease, do we generate S-Ag specific CD4+ T cell activation and retinal inflammation? Historically the evidence for molecular mimicry, where infectious agents cross react with self determinants on, for example, HLA A29 is poor, despite isolated clinical reports.²⁰ The combination, however, of this current report and the generation of HLA-A29 Tg mice that demonstrate pathological features which strikingly resemble this present case offer an exciting future to develop our understanding of the pathogenesis of birdshot retinochoroidopathy and the role of retinal antigens, the results of which may then be translated to other uveitic conditions.

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C S Hoyt

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