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 BrJ Ophthal (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 anti-fibrosis 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 anti-fibrosis 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 results 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. 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.

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.

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. 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. 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 anti-fibrosis regimen was not initiated. A prospective randomised study comparing conventional postoperative topical therapy versus the anti-fibrosis regimen of postoperative prednisone, a non-steroidal anti-inflammatory, and colchicine would clarify its true benefit.

References

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, despite us moving on to clinical trials of tolerance induction. On the other hand the models are useful. The pathological changes observed appear to explain what we may see clinically—namely, viritis, retinal vasculitis, choroidal retinoic cytokines, and optic nerve head and macula oedema. As such we are able to discern common immune mediated processes that lead to inflammation, particularly T cell and macrophage behaviour, cytokine mediation of inflammatory response, and other immune regulatory mechanisms in play in the eye. To this end, preclinical studies of novel immune modulatory agents (a classic example being cyclosporin) have now been successfully translated into clinical practice. There are caveats in our interpretations. Although in animal models the photoreceptors are the target tissue for retinal antigen specific autoimmune T cells precipitating the non-specific inflammatory process that follows, in humans there is little evidence that photoreceptors are primarily destroyed during posterior uveitis. Definitely, therefore, 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 clinical-pathological description of “non-end stage” disease in an HLA A29 patient is timely. Birdshot retinochoroidopathy was initially described in patients with diffuse retinal vascular leakage with resultant retinal, macular, and disc oedema with a poor prognosis over many years. The recently described animal model of spontaneous retinopathy in HLA-A29 transgenic mice supports the high specificity and sensitivity of HLA-A29 positivity in the diagnosis of birdshot retinochoroidopathy, and the increased relative risk of developing the disease when this allele is present. HLA-A29 Tg mouse are characterised histologically by changes that are almost identical to those described in the report by Gaudio et al, including perivasculitis, vitritis, leukocytic 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 clinical-pathological 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 found particularly prevalent in birdshot retinochoroidopathy. 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. Secondly, the previous clinical-pathological report of birdshot chorioretinitis exhibited strong T cell proliferative responses to S-Ag 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 choroidal 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 clinical-pathological 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. 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.
EDITORIAL

The “all online” BJO—why?

C S Hoyt

Online BJO

The “all online” BJO—why?

C S Hoyt

The “all online” BJO—why?

C S Hoyt

Dramatic changes have taken place at the British Journal of Ophthalmology over the past 6 months. Most readers have probably not noticed. However, all of our loyal reviewers and authors could not fail to do so. As of May 2002 the journal is now “all online”—for manuscript submission and review. We no longer process hard copy manuscripts in the review process. For most of our authors and reviewers this new “online” system has functioned smoothly and we have received many favourable comments about it. Regrettably, not all of our authors and reviewers have found the new system to their liking.

Why have we opted to go to an online submission and review process for manuscripts? First and foremost, when the system is fully established (with a few additional modifications) it will speed up significantly the peer review process. In fact, during the first few months of using the system the average time for completing a review of an original article was reduced to 21 days; the average time required for review, revision, and acceptance of an original article was only 27 days. For “letters to the editor” the process was even more efficient. Secondly, it allows us to routinely use reviewers throughout the world. Unfortunately, even in the 21st century sending hard copies of manuscripts by post is time consuming, costly and, for some countries, not always reliable. As a result, in the past the vast majority of our reviewers have resided in the United Kingdom or the United States. We hope this will not remain true in the future. Finally, it allows authors from countries that did not previously submit papers to the journal to do so. Already, we have received manuscripts for the “World view” column from authors in countries from which we had previously not received any manuscripts. The new online system should further our efforts to make the journal a truly international journal of ophthalmology—not only with regard to its editorial board but also to its authors, reviewers, and, most importantly, readers.

Our new online system, “Bench>Press,” was designed by HighWire Press, the same group that designed our website. Extensive research was conducted by HighWire before developing Bench>Press, but everyone involved realises it is a system in evolution. High-Wire has been extremely responsive to our recommendations for changes. The vast majority of these have come from the result of suggestions from our authors and reviewers. Minor additions and changes are likely to continue over the next several months. We welcome constructive criticism and suggestions that will help improve the system.

A new, more detailed set of instructions for using the system has been made available recently—please log on to our website—www.bjophthalmol.com, then click on “Submissions” and go to “For details on how to submit your manuscript online, via Bench>Press.” We hope these instructions will simplify the process for both authors and reviewers. Additionally, we are developing a problem solving page for users of BJO—http://bjomjournals.com/misc/problemsolver.shtml. Although we now believe these more detailed instructions should solve most problems authors and reviewers have experienced in the past, we urge users of Bench>Press not to hesitate in contacting our Bristol office (anne.williams@bristol.ac.uk) or our San Francisco office (choyt@itsa.ucsf.edu) if problems arise that cannot be solved with the aid of these new instructions.
It will undoubtedly take a bit more time for all authors and reviewers to feel perfectly comfortable with our Bench>Press system. Ultimately, we believe all authors and reviewers will find it quicker and more efficient than the old system of hard copy manuscripts. In the meantime we apologise for any frustration the system has caused any of its users. Rest assured even the editors have endured a few days (not many) of second thoughts. Yet, we will do everything possible to steer the transition smoothly forward until the online system is problem free. Moreover, we will attempt to minimise the drama involved in its use. We firmly believe the end product will be worth the effort.

Author’s affiliations
C S Hoyt, Editor, San Francisco, California, USA

New BJO online submission and review system

The Editors of British Journal of Ophthalmology are pleased to inform authors and reviewers of its new online submission and review system. Bench>Press is a fully integrated electronic system which uses the internet to allow rapid and efficient submission of manuscripts, as well as the entire peer review process to be conducted online.

Authors can submit their manuscript in any standard word processing software. Graphic formats acceptable are: .jpg, .tiff, .gif, and eps. (Nb. Multipage PowerPoint presentations are NOT acceptable.) Text and graphic files are automatically converted to PDF for ease of distribution and reviewing purposes. Authors are asked to approve their submission before it formally enters the reviewing process.

To access the system click on “SUBMIT YOUR MANUSCRIPT HERE” on the BJO homepage: http://www.bjophthalmol.com/, or you can access Bench>Press directly at http://submit-bjo.bmjjournals.com/.

We are very excited with this new development, it really is simple to use and should be a big improvement on the current peer review process. Full instructions can be found on Bench>Press and BJO online. Please contact Natalie Davies, Project Manager, ndavies@bmjgroup.com for further information.

Pre-register

We would be grateful if all British Journal of Ophthalmology authors and reviewers pre-registered with the system. This will give you the opportunity to update your contact and expertise data, allowing us to provide you with a more efficient service.

Instructions For Registering
1. Enter http://submit-bjo.bmjjournals.com
2. Click on “Create a New Account” in the upper left hand side of the Bench>Press homepage.
3. Enter your email address in the space provided.
4. Choose a password for yourself and enter it in the spaces provided.
5. Complete the question of your choice to be used in the event you cannot remember your password at a later time.
6. Click on the “Save” button at the bottom of the screen.
7. Check the email account you registered under. An email will be sent to you with a verification number and URL.
8. Once you receive this verification number, click on the URL hyperlink and enter the verification number in the relevant field. This is for security reasons and to check that your account is not being used fraudulently.
9. Enter/amend your contact information, and update your expertise data.
10. Please note: You only need to create a new account once. If you submit to another BMJ Publishing Group journal you can use the same email address and password.