The treatment of chronic uveitic macular oedema

Is immunosuppression enough?

Chronic uveitis causes visual impairment in several ways including cataract formation, vitreous opacification, secondary glaucoma, and optic nerve inflammation. However, the predominant cause of visual loss in many forms of endogenous uveitis is macular oedema,1 which may or may not respond to successful control of the inflammatory response. Indeed, intractable macular oedema is the major cause of visual disability in intermediate uveitis, the disease entity with a rising incidence in westernised countries.2 Specific treatment of the macular oedema is therefore a parallel aim in therapy of chronic uveitis.

What is the immediate cause of the macular oedema? If this were known it could provide a target for therapy. Both human and experimental evidence in posterior uveitis supports an autoimmune theory in genetically susceptible individuals,3 via the generation of autoreactive CD4+ T lymphocytes,4 the response amplified via the cytokine network. An integral part of the inflammatory response is the breakdown of the blood-retinal and blood-aqueous barriers. The recruitment of inflammatory cells into the eye is dependent upon increasing blood-retinal barrier (BRB) permeability to cells which is characterised by morphological changes in the retinal vascular endothelium and the expression of adhesion molecules on activated endothelium for specific ligands on the activated lymphocytes.5,6 Specific targeting of therapy at these sites may reduce the incidence of macular oedema.

Presently, the treatment of chronic uveitis is dependent upon the severity of the inflammatory response, the presence of sight-threatening complications – for example, macular oedema, bilaterality of disease, and the general health of the patient.7,8 Treatment is aimed at suppressing the immune response with steroids (systemically or orbital floor) and/or cyclosporin A or azathioprine in steroid non-responsive or intolerant patients.9-16 However, the visual outcome (mainly due to persistent uveitic oedema) often betrays the best attempts at immunosuppression. Moreover, the side effects incurred with large doses of steroids often outweigh the benefits of attempting to control the macular oedema.

What other therapeutic options are therefore available? Farber et al in this month's issue demonstrate a reduction in chronic uveitic macular oedema and subsequent improvement of visual function by acetazolamide. They also use vitreous fluorophotometry to demonstrate a reduced fluorescence in treated patients, suggesting decreased leakage through the BRB. Previous to this report the data are somewhat conflicting. Cow et al 17 reported successful treatment with acetazolamide in a small number of patients, but Greux-Crosier et al 18 showed minimal benefit with the use of acetazolamide in 12 patients with uveitis. This may have been due to active choroiditis or retinal vasculitis at the time of treatment in patients who were not adequately immunosuppressed. Farber et al have pointed out that the long term use of acetazolamide has yet to be addressed, as it is not without side effects, but this should not detract from the encouraging results which they have shown with its short term use, particularly in the younger group of patients.

Prostaglandins have been implicated in the generation of persistent uveitic macular oedema2,5 and the benefit from treatment with systemic non-steroidal anti-inflammatory agents (NSAIAs) and topical NSAIAs – for example, diclofenac, have yet to be highlighted. Certainly NSAIAs reduce cystoid macular oedema in post-cataract extractions21-22 but the underlying pathogenesis of BRB breakdown is likely to be different from uveitis-associated macular oedema. Also, topical diclofenac has shown some benefit in the treatment of anterior segment signs of acute iritis,23 but these patients did not have any evidence of macular oedema, and this has yet to be assessed. Diamond and Kaplan24 have suggested both lensectomy and vitrectomy for cataract extraction in patients with chronic uveitis in whom they noticed a reduced rate of macular oedema after surgery. Certainly vitrectomy has a definitive role in treatment of chronic uveitis in aiding diagnosis, clearing optical media, and in treating secondary rhegmatogenous retinal detachments.25 The role of vitrectomy in the treatment of macular oedema is still controversial, particularly in patients with pars planitis, who one might expect to benefit the most.26 Macular oedema in the presence of persistent low grade vitreal inflammation may be an indication of vitreomcy as there is some evidence that CD5+ B lymphocytes and TCR y0 T cells are present in the vitreous in cases of autoimmune uveoretinitis.27 These cells are implicated in perpetuating autoimmune inflammation, perhaps by trapping and continually presenting antigen, despite adequate immunosuppression.

The choice of treatment is very much dependent upon the clinical findings in individual patients and as such in each case the predominant pathogenic mechanism for the macular oedema must be identified. The dysfunction of the BRB
leading to macular oedema may not be the mechanism in all
cases and the presence of active inflammation, macular or
choroidal ischaemia (as a result of active vasculitis), and
vitreoretinal traction may all contribute to the maculopathy.
Ultimately, therefore, successful treatment of persistent
uveitic macular oedema will be developed when the under-
lying pathogenesis is better understood. Future therapies
may be directed towards the prevention of lymphocytes
homing to the retinal vascular endothelium using antibodies
directed to specific adhesion molecules, or towards inhibiting
mediators of BRB damage – for example, histamine or
specific prostaglandins. However, it still appears that once
immune targeted damage has occurred, even with suppres-
sion of an active inflammatory response, the vessels behave
as though chronically damaged.

Current therapies for patients who do not respond to
tolerable doses of systemic immunosuppression include
acetazolamide, the dose of which in the long term could be
titrated against the patient’s response. Combinations of
acetazolamide and orbital floor steroids or low dose systemic
steroids may also show promise but as yet this has to be
documented. The role of NSAIDs in the treatment of this
condition is less clear but still offers the clinician a further
choice in recalcitrant cases. Finally, vitrectomy is a treat-
ment option in some patients with persistent oedema in
the presence of chronic vitreal changes, opacified media with or
without vitreoretinal traction at the macula. Our therapy
options are presently multifaceted and should be tailored for
each individual patient.

ANDREW D DICK

Department of Ophthalmology,
University of Aberdeen

2. Forrester JV. Uveitis. In: Davidson St, Jay B. eds. Recent advances in
4. Gery J, Mochizuki M, Nussenblatt RB. Retinal specific antigens and the
T-cell lines mediating experimental autoimmune uveoretinitis in the rat.
6. Lightman S, Towler H. Immunopathology and altered immunity in posterior
7. Charteris D, Barton K, McCartney A, Lightman S. CD4+ T-lymphocytes in
8. Dua HS, McKinnon A, McMenamin P, Forrester JV. Ultrastructural
pathology of ‘barrier sites’ in experimental autoimmune uveitis and experi-
9. Forrester JV, Liveridge, Dua HS. Resolution of local immune response by
10. Greenwood J. The blood retinal barrier in experimental autoimmune
Angiography with fluorescein-labeled dextrans in a primat model of uveitis.
12. Lightman SL. Use of steroids and immunosuppressive drugs in the manage-
14. Towler HM, Cliffe AM, Whitting PH, Forrester JV. Low dose cyclosporin A
15. Towler HM, Whitting PH, Forrester JV. Combination of low dose cyclosporin
20.
16. deVries J, Baarsma GS, Zaal MJW, Boen-Tan TN, Rothova R, Buitenhuys HJ,
et al. Cyclosporin in the treatment of severe chronic idiopathic uveitis.
17. Cox SN, Hay E, Bird AC. Treatment of chronic macular oedema with
18. Guey-Croiset Y, Othenin-Girard P, Herbert CP. Acetazolamide may be
sufficient for pseudophakic cystoid macular edema (CME) but not for uveitis-
induced CME. In: Dernouchamps JP, Verougstraete C, Casper’s-Velu L,
Tassignon MJ, eds. Recent advances in uveitis. Amsterdam: Kugler, 1993:
573–8.
19. Aj CV, Aj JS. Carbonic anhydrase inhibitors in ophthalmology. Surv Ophthal-
20. Mishima H, Manua K, Miyake K. The putative role of prostaglandins in cystoid
Effect on post-surgical inflammation and blood aequous humor barrier
23. Quentin CD, Behrens-Baumann W. Double-blind study on the efficacy of
prostaglandin synthesis inhibitor diclofenac and dexamethasone phosphate in
the treatment of iritis after topical application. Fortsch Ophthalmol 1987;
24. Diamond JG, Kaplan HJ. Encequintic and vitrectomy for complicated cataract
25. Koerner F, Merser J, Raggi I. Vitrectomy in 165 eyes with uveitis. In:
26. Dugal PU, Rando NA, Ozer S, Liggert PE, Smith RE. Fars plana vitrectomy
for intraocular inflammation-resistant cystoid macular edema unresponsive to
27. Liveridge J, Dick A, Cheng YF, Scott GB, Forrester JV. Retinal antigens
specific lymphocytes, TCR γδ T cells and CD5 + B-cells cultured from
The treatment of chronic uveitic macular oedema.

A D Dick

doi: 10.1136/bjo.78.1.1