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Editorials

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,[3,4] via the generation of autoreactive CD4+ T lymphocytes,[5-7] 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.[8-11] 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.[12,13] 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.[14-16] 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 oedema[19,20] 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 extractions[19,21,22] 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 Kaplan[24] 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 vitrectomy as there is some evidence that CD5+ B lymphocytes and TCR γδ 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 underlying 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 suppression 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 NSAIAs in the treatment of this condition is less clear but still offers the clinician a further choice in recalcitrant cases. Finally, vitrectomy is a treatment 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.

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