Sir,

The use of combined intravenous pulse methylprednisolone and low-dose oral cyclosporin A in the treatment of corneal graft rejection: addendum to previous report

We reported earlier the successful use of combined intravenous pulse methylprednisolone and oral cyclosporin A in the treatment of acute corneal graft rejection.[1] In our study we found a success rate of 92% in reversing graft rejection, as compared with the 80% previously reported for treatment with intravenous pulse methylprednisolone alone.[2] The clinical anti-rejection effect of cyclosporin A may appear as early as a few hours after its commencement.[3] This occurred in the absence of significant serum levels of cyclosporin A, suggesting that even a low serum level of the drug may be effective. We therefore hypothesise that a lower dosage of cyclosporin A may produce similar anti-rejection effects. Systemic cyclosporin A is known to be associated with various systemic side-effects, including nephrotoxicity and hypertension.[4] A lower dosage may produce fewer side-effects. A prospective pilot study was therefore undertaken to investigate whether a lower dosage of oral cyclosporin A (2 mg/kg per day with no loading dose), when used with intravenous methylprednisolone in treating corneal graft rejection, would be as effective as the previous regime (loading dose of 15 mg/kg per day for 2 days, then 7.5 mg/kg per day for another 2 days, followed by a maintenance dose to achieve a trough blood level of 100–200 μg/l).[1]

A total of 9 patients with acute endothelial corneal graft rejection diagnosed at the Prince of Wales Hospital between January 1997 and September 1998 were recruited, with their informed consent. Inclusion and exclusion criteria were the same as in the previous study.[1] These patients were each given Sandimmun Neoral (Sandoz) at the low dose (2 mg/kg per day with no loading dose). The intravenous methylprednisolone and 1% prednisolone eye drops (Pred Forte, Allergan) were also given as previously described.[1] Six of the 9 patients (67%) had their acute rejection reversed (Table 1). In the remaining 3 patients whose rejection did not initially respond to the low-dose regimen, the cyclosporin A dosage was increased to reach a trough blood cyclosporin A level of 100–200 μg/l, i.e. the same as in the previous study.[1] Interestingly, amongst these 3 patients, 2 had their rejection reversed by the increased cyclosporin A dosage. Of the patients whose rejection initially responded to the low-dose regime, early recurrence of the rejection occurred in one (patient 9). The recurrent rejection was eventually controlled with our previous combined regime, returning a clear graft. The study was terminated after patient 9, in view of the apparently lower overall success rate of this low-dose regime in rescuing rejected grafts, and also the early recurrence of rejection in the last patient. No complications of cyclosporin A were encountered during the study period.

It appears that the lower dose of cyclosporin A, when used with intravenous pulse methylprednisolone in treating acute corneal graft rejection, is not as effective as our previous regime.[1] It is not clear why our low-dose regime was less effective. It could be due to too low an initial blood cyclosporin A level as a result of omission of the loading dose, or alternatively to too low a subsequent drug level as a result of the low maintenance dose. The fact that 2 of the 3 patients in this study whose rejection did not initially respond to the low-dose regime subsequently had their rejection reversed by the raised blood cyclosporin A level may point towards the latter as the cause. Before the availability of new information regarding the minimal effective dosage of cyclosporin A in the combined regime, we would recommend the one that we reported previously.[1]

Table 1. *Results of using combined pulse intravenous methylprednisolone and low-dose oral cyclosporin A in the treatment of acute graft rejection*

Patient no.	Sex/Age	Surgery to rejection (months)	Onset to treatment (days)	Outcome	Follow-up time (months)	Side-effects
1	M/61	45	2	Reversed	18	Nil
2	M/63	5	0	Reversed	8	Nil
3	F/52	3	2	Rejected[a]	8	Nil
4	F/74	33	7	Reversed	15	Nil
5	M/68	43	7	Rejected	23	Nil
6	M/74	5	7	Rejected[a]	8	Nil
7	M/46	45	0	Reversed	6	Nil
8	M/64	24	5	Reversed	5	Nil
9	M/44	2	4	Reversed	4	Nil
Mean	60.7	25.4	3.8	–	12.6	

[a]Corneal graft rejection eventually reversed by reverting to the higher cyclosporin dosage as described in the previous study.[1]

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Sir,

Hypopyon keratitis in corneal epithelial basement membrane dystrophy

Corneal epithelial basement membrane dystrophy (EBMD), also known as microcystic or map-dot-fingerprint dystrophy,[1–5] is a condition in which the attachment of basement membrane to the corneal epithelium is defective and may result in recurrent corneal erosion. Characteristically, the condition affects adults between the ages of 20 and 50 years, who present with corneal erosion often on waking. Although healing of corneal epithelium may take up to 6 weeks, secondary bacterial infection with hypopyon is uncommon. Three cases of EBMD with culture-positive microbial keratitis with hypopyon are presented and discussed.

Case reports

Case 1. A 34-year-old man with a known history of EBMD with characteristic 'maps' and 'fingerprint' lines presented with an acute episode of pain and was noted to have two areas of epithelial irregularity inferiorly on the right cornea, but no evidence of epithelial defect on fluorescein staining. He was treated with topical chloramphenicol and Voltarol (CIBA Vision) eye drops. Two days later he developed a small hypopyon with a central stromal infiltrate with thinned irregular epithelium but no obvious defect on fluorescein staining. Following corneal scrapes for microbiological analysis, he was treated with intensive topical and oral ciprofloxacin, mydriatic, and flurbiprofen as a non-steroidal anti-inflammatory agent. Corneal culture grew *Pseudomonas* species which responded to treatment. There had been no history of contact lens wear. At 5 months visual acuity had improved to 6/6 with a small off-axis corneal scar.

Case 2. A 44-year-old man presented with a small right-sided corneal erosion with underlying stromal infiltrate and small hypopyon. There was evidence of EBMD in the fellow eye characterised by fingerprint lines. He was treated with intensive topical and oral ciprofloxacin. Corneal cultures grew *Staphylococcus aureus* which responded to treatment. He was subsequently lost to follow-up.

Case 3. A 40-year-old woman with a history of recurrent erosion presented with a further episode in the left eye having traumatised the area with a mascara brush 5 months previously. She had been treated 10 years earlier for an infected erosion in the right eye which resulted in a central corneal scar. Examination showed a small central epithelial defect with a small hypopyon. Epithelial microcysts in the fellow eye suggested an underlying basement membrane disturbance. She responded to intensive topical and oral ciprofloxacin and received topical mydriatic and oral doxycycline. Corneal culture grew *Staphylococcus aureus*. At 3 months a fine residual scar was present and acuity was recorded as 6/5.

Comment

Recurrent corneal erosion is often associated with corneal EBMD.[1,5,6] Erosions may be subdivided into two groups: microform erosions where a small break occurs in the epithelium and macroform erosions with a larger break and loosely attached epithelium which is often associated with trauma. EBMD may be characterised by the presence of microcysts, subepithelial map-like patterns and whorled fingerprint lines.[2–5] Studies have shown an abnormal thickened basement membrane underlying an abnormal epithelium. The dystrophic epithelium produces aberrant basement membrane and adhesion

Fig. 1. *Case 1. Corneal epithelial changes.*