

Commentary

Corneal transplantation for herpes simplex keratitis

While episodes of herpes simplex virus (HSV) epithelial keratitis can be treated effectively, recurrences may lead to corneal stromal scarring and decreased visual acuity. Consequently, herpetic stromal keratitis is a common indication for corneal transplantation in many published reports. However, there is a relatively high risk of graft failure in this patient group. The published literature on the management of herpetic keratitis by keratoplasty is difficult to interpret because diagnostic criteria are not standardised, duration of follow up is variable, and recipients of repeat grafts are included in many series. A rational basis for management of patients with visually significant herpetic keratitis awaits the resolution of certain key questions.

What is the comparative contribution of viral recurrence and allograft rejection to graft failure?

HSV has a natural ability to establish life long latency, a state in which the viral genome is not integrated, lytic viral genes are quiescent, and the metabolic functioning of the host cell is apparently undisturbed (reviewed by Cook and Hill¹). Reactivation of latent infection in the trigeminal ganglion and/or the cornea itself leads to recurrent disease. In one retrospective study of 72 first penetrating keratoplasties for herpetic keratitis, in the absence of any antiviral prophylaxis, the rate of recurrence following transplantation was 44% at 2 years.² However, graft failure in herpetic keratitis is most commonly attributed to allograft rejection. Cobo *et al* reported rejection to be the principal cause of graft failure in 64% and epithelial viral recurrence in 15%.³ Ficker *et al* reported these complications to lead to graft failure in 46% and 16% respectively.⁴ In the absence of pathognomonic signs such as a donor endothelial rejection line, a dendritic or geographic ulcer bridging the donor-recipient interface, rejection and viral recurrence can be impossible to distinguish clinically and may in some instances coexist. One of the major difficulties for the clinician is in differentiating stromal herpetic recurrence from early endothelial allograft rejection in a patient with localised graft oedema and subjacent endothelial precipitates. And, accordingly, it is difficult to interpret reported recurrence and rejection rates in published studies.

Two animal studies have provided information on different aspects of this question. Beyer and colleagues studied the incidence of viral recurrence following autograft transplantation in a rabbit model of herpetic keratitis,⁵ thus setting aside the influence of an allogeneic response and examining the effect of surgical inflammation on recurrence. All rabbits received post-transplant topical steroid, but a group receiving systemic aciclovir had a significantly lower incidence of virus shedding, epithelial ulceration, and stromal keratitis. Nicholls and colleagues studied HSV recurrence after allogeneic corneal transplantation in rats.⁶ Recurrence was found in graft recipients in both topical steroid and no treatment groups. The rejection process was found not to induce viral recurrence. However, incidence of recurrence was too low to allow investigation of the reverse effect—whether recurrence induces rejection. In summary, these two studies demonstrate that transplantation, possibly by trauma to corneal nerves, causes early

reactivation of virus at the site of latency and its release from nerve endings in the cornea.

Is corneal transplantation justifiable in patients with corneal opacity due to herpetic infection?

Transplantation may allow long term restoration of vision in some patients. In reported retrospective series, graft survival was 67%² and 66%³ at 2 years, and 71% at 5 years⁴ (in this study, topical antiviral therapy was administered with rejection therapy). Five year survival data from the Australian Corneal Graft Registry indicate that grafts in patients with a history of HSV which remain recurrence free following transplantation enjoy survival (83%) equivalent to those grafts in patients with no history of HSV keratitis: it is viral recurrence which has a major effect on graft survival (22% at 5 years, $p < 0.00001$).⁷ Information on antiviral prophylaxis is not provided in this report.

However, these reports answer the question only in part, indicating the proportion of patients in whom grafts remained transparent at the intervals given. In patients in whom transplantation is performed to improve vision, the most important measure of functional outcome is visual acuity, unaided or with preferred correction. The majority of patients with herpetic keratitis have a normal and usually emmetropic fellow eye, and will not be motivated to wear a correction for significant post-keratoplasty refractive error.⁸ Clinical experience and all published reports suggest avoidance of transplantation at the time of active viral disease, with the exception of impending or actual perforation. The acceptable recurrence free interval has not been determined. Until a randomised controlled trial is carried out, including examination of patient satisfaction, it will be difficult to decide on transplantation or not for the majority of patients with a normal contralateral eye.

What, if any, antiviral prophylaxis is appropriate in graft recipients with herpetic keratitis?

In several studies antedating the availability of aciclovir, topical antiviral therapy was not administered following transplantation because of the known ocular surface toxicity of idoxuridine and trifluorothymidine. Moyes and colleagues assessed the efficacy of prophylactic topical aciclovir after keratoplasty in a retrospective review. When compared with those who received no prophylaxis, patients treated with topical aciclovir had lower risk of viral recurrence (relative risk (RR) 0.44) and graft rejection (RR 0.43).⁹ There might be additional benefit in systemic, rather than topical, administration of antiviral therapy to increase drug levels in the anterior chamber and trigeminal ganglion. The only published prospective trial of oral aciclovir reported 22 patients randomised to receive either no prophylaxis or 800–1000 mg/day oral aciclovir, tapering over 1 year.¹⁰ No recurrences occurred in 14 eyes of 13 patients who received prophylaxis and but recurrence was observed in four of the other nine eyes.

The above data⁷ indicating that recurrence free grafts enjoy high survival rates, suggest that if routine antiviral prophylaxis following transplantation reduces rates of recurrence, it is likely to enhance graft survival. A placebo controlled study of oral aciclovir is at present in progress in

the Netherlands and its outcome is awaited with interest. For the present, a reasonable strategy would be oral acyclovir (or related agent) at 800 mg daily for 1 year following transplantation, and longer to accompany topical steroid if necessary. However, if prophylactic oral antiviral is to be used it is essential to confirm the presence of HSV in the recipient button by immunohistochemistry, in situ hybridisation, or other methods. Antiviral cannot be justified in the absence of such pathological confirmation, not least on account of cost and possible side effects. When treating episodes of possible allograft rejection, in view of the difficulty in differentiating stromal virus recurrence from rejection, it remains advisable to couple topical steroid therapy with topical antiviral therapy.

In patients with herpetic keratitis whose corneas are minimally vascularised (thus with reduced risk of rejection) and in whom recurrence is prevented, the prognosis for maintaining a transparent graft in herpetic keratitis is good. It is likely that it can be improved with antiviral prophylaxis. Key clinical issues remain those of allogeneic rejection and visual rehabilitation, as in all corneal graft recipients. However, for many patients with herpetic keratitis, the balance

of experience favours no surgery and further medical management on an as required basis.

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