Adalimumab in high-risk penetrating keratoplasty: a case report

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ABSTRACT: A single case report of a 30-year-old Caucasian woman with four previous graft rejections, history of herpetic disease and neovascularization, who underwent a further penetrating keratoplasty. Immunosuppressors were additionally prescribed to prevent immune rejection. Keratoplasty was successfully performed but the initial immunosuppressive protocol had to be switched because of its side effects. Adalimumab was then introduced and maintained in monotherapy for 30 months. The corneal graft has remained clear so far, with no history of immune rejection while using this drug.

This is the first published report concerning the use of adalimumab for preventing graft rejection after high-risk penetrating keratoplasty. It seems to be effective in preventing corneal graft rejection in high-risk penetrating keratoplasty, and should therefore be considered for prophylactic therapy.

J Emmetropia 2015; 6: 163-165

Graft survival in corneal transplant can be compromised in several situations known as high-risk penetrating keratoplasty (PK), such as: previous graft rejection, corneal neovascularization, herpetic keratopathy, eccentric and large diameter of the graft approaching the vascular limbus, transplant in children, and other conditions that affect not only the transparency of the cornea, but also the ocular surface environment, as in the case of Lyell’s syndrome.

Where these are not present, graft survival for PK usually achieves 90% success in terms of transparency at 5-year follow-up, and treatment with corticosteroid drops (either with or without systemic reinforcement) is sufficient to prevent graft rejection.

However, when facing the prospect of a high-risk PK, a more active approach is required to avoid graft rejection and failure. The main weapon in the battle to keep the graft free from immune rejection in high-risk keratoplasty is to combine immunomodulators with the current corticosteroid therapy. The most commonly used drugs are: cyclosporine A (CsA), mycophenolate mofetil (MMF) and tacrolimus.

The recent introduction of new biological therapies has widened the range of therapeutic options for high risk PKs. Indeed, biologics that specifically target tumour necrosis factor alpha (TNF-α) are currently being evaluated to determine their efficacy in modulating corneal disease, because this cytokine can induce ocular inflammation. Furthermore, cellular constituents of the cornea also have a marked capacity to produce inflammatory cytokines, including TNF-α.

Adalimumab is a human monoclonal antibody that can bind TNF-α, inhibiting its biological effect. It has been used for childhood refractory uveitis and other inflammatory conditions of the eye with excellent results and relatively good safety. However, tuberculosis screening should be carried out before, during and after treatment, and it should not be used in patients with active infections; it is also contraindicated in demyelinating disease and moderate to severe heart failure.

CASE PRESENTATION

A 30-year-old pseudophakic woman was facing her fifth PK on the left eye due to previous graft rejection, limiting her sight to hand motion. Her right eye showed a clear corneal graft achieving best corrected visual acuity (BCVA) of 0.8 with contact lenses.
Her history revealed ocular inflammation at age 10 starting in the left eye and affecting her right eye some years later, with recurrent dendritic herpetic keratitis. Her first corneal transplant was performed in 2000 for the left eye, restoring clear media. Postoperative treatment included corticosteroid and antibiotic drops with oral aciclovir (400 mg bid) and systemic corticosteroids (deflazacort 30 mg bid). However, corneal graft rejection was detected at the two year follow-up, with a dense leukoma despite adequate treatment. A second PK was therefore carried out on the left eye in 2003, and in 2005, she underwent a PK on the right eye as well. A neurotrophic ulcer appeared in the left eye threatening perforation, which required an amniotic membrane patch and then a third PK in 2007 using the same postoperative protocol. While both grafts remained transparent, cataract surgery was performed for lens opacification in the right (2008) and, afterwards, the left eye (2009). Graft failure developed early after the left eye phacoemulsification, requiring a further keratoplasty (fourth) in 2010. Considering the previous history of rejection and failure, systemic immunosuppression was offered to the patient, but she refused as she wanted to conceive a baby. Unfortunately, another graft rejection developed in the left eye in 2012, two years after surgery. However, her right graft remains clear to date.

As keratoplasty for her left eye was considered high risk, keratoprosthesis or PK with systemic immunomodulation were offered. She had already given birth to her child and felt ready for a fifth PK, owing to the good results obtained with the previous procedures, as the grafts had stayed clear. Our clinic immunologists were then contacted to assist in the new treatment. Systemic immunosuppression with cyclosporine (100 mg bid) and mycophenolate mofetil (1 g bid) were introduced 4 weeks prior to corneal transplant, which was successfully performed in July 2012. The postoperative protocol included antibiotic and steroid drops, herpes prophylaxis and oral steroids. Surprisingly, two months after surgery, incipient graft rejection was detected in the right eye, but was successfully treated with steroid therapy. As the patient reported some weakness and myalgia attributable to CsA side effects, she was switched to adalimumab (40 mg every 2 weeks, subcutaneous), tapering MMF to 500 mg bid. The patient discontinued MMF the following month, as she was still feeling weak.

Currently, at 30 months after the last PK (Figure 1), the patient is on one steroid drop daily and topical valacyclovir ointment at night, as well as adalimumab (40 mg every 3 weeks). Corneal grafts are free from rejection, maintaining clearance up to 0.8 and 0.9 BCVA in the right and left eye, respectively. Only one episode of presumed herpetic epithelial (or neurotrophic) keratitis took place on her left graft, but it was able to be properly restored with no further episodes of immune rejection while using adalimumab. Only some general weakness has been reported, from which the patient can recover.

**DISCUSSION**

High-risk PK management can be challenging. Our patient had a history of herpetic disease, corneal neovascularization and four previous graft rejections (each additional graft increases risk by a factor of approximately 1.2)\(^9\), all of which diminish the probability of a further successful corneal transplant. In this scenario, different approaches should be considered, depending on the concurring factors, but the combination of immunomodulators has been shown to be effective in preventing graft immune rejection.

Systemic administration of CsA\(^8\) and MMF\(^9\) have already proven to be beneficial in preventing corneal graft rejection in high-risk patients. Nevertheless, the use of both systemic immunomodulators is limited by side effects such as nephrotoxicity, arterial hypertension, hepatotoxicity, gastrointestinal disorders and malignancy. When these front line drugs had to be discontinued in our patient’s case, other immunomodulators were considered.

Given that TNF-\(\alpha\) is an important angiogenic stimulus and is also involved in cell death during corneal graft rejection, biological therapies inhibiting TNF-\(\alpha\), such as adalimumab or infliximab, are being used in ophthalmology to control ocular immune and inflammatory processes. In this setting, TNF-\(\alpha\) is a clinically validated therapeutic target in the treatment of ocular inflammation\(^10\). It has also been reported that some TNF-\(\alpha\) haplotypes may increase the risk of corneal allograft rejection\(^11\).

According to the product labelling, a number of serious adverse events including infections, blood disorders and cancer may develop. However, our patient only reported some general weakness, allegedly due to adalimumab.
In this patient, the use of adalimumab seems to have been effective in preventing immune rejection in high-risk PK. To the best of our knowledge, this is the first time that adalimumab has been reported in relation to the prevention of graft rejection in PK.

REFERENCES