Patient education vital in reducing risk of corneal graft rejection

Defining corneal graft rejection as a specific tissue reaction of the recipient against the transplanted corneal graft that manifests as a reaction against all donor corneal cell layers or individual cell layers, Dr Allo said that the incidence of rejection is higher than commonly believed.

“The overall probability of having an episode of allograft rejection is between 21 per cent and 28 per cent for penetrating keratoplasty procedures, around eight per cent for deep anterior lamellar keratoplasty and less than five per cent for superficial lamellar keratoplasty.”

Focusing on allograft rejection in more detail, Dr Allo said that there are four principal types of graft rejection: epithelial, subepithelial infiltration, stromal and endothelial.

Epithelial rejection occurs in about 10 per cent to 15 per cent of cases and presents as an elevated, undulating line that is visible with staining. It often starts near a blood vessel at the graft-reipient junction, said Dr Allo, and an epithelial rejection line appears when the recipient epithelium replaces the donor epithelium. It may also progress to endothelial rejection if left unchecked.

More rare is subepithelial infiltration which is restricted to donor tissue and which presents with clinical features very similar to epidemic keratoconjunctivitis. It may often be a sign of low-grade immunological reaction, said Dr Allo.

He said that stromal rejection tends to be easily overlooked by the associated endothelial rejection and is characterised by a sudden onset of peripheral corneal haze and circumcorneal hyperaemia followed by destruction of the epithelial basement membrane and keratolysis.

Turning to endothelial rejection, Dr Allo said that it is the most significant and most frequent cause of graft failure, occurring in between 12 per cent and 44 per cent of cases, sometimes many years after surgery. It typically presents as increased corneal thickness, which is sometimes the only manifestation of the rejection, he added.

Other symptoms include keratic precipitates on the endothelium or grouped together in a “Khodadoust line” which tends to migrate from the peripheral cornea to the central cornea. While this line is often considered to be the classic hallmark of endothelial rejection, Dr Allo said that allograft rejection could occur without the presence of this line.

Lower risk with DALK

While deep anterior lamellar keratoplasty procedures avoid the risk of endothelial rejection, epithelial or stromal rejection may still occur for such patients, usually within 15 months postoperatively, said Dr Allo. In cases of epithelial rejection, a rejection line precedes or appears at the onset of stromal opacity.

Stromal rejection is characterised by symptoms such as stromal opacification, oedema, misty vision, discomfort, faint diffuse subepithelial opacity, punctuate epithelial erosions, folds in Descemet’s membrane and anterior chamber cells and flare, said Dr Allo. If the rejection is left untreated, progressive vascularisation with graft melting and final failure may occur.

After discussing the immunological bases of corneal graft rejection, Dr Allo said that there are three main approaches to reducing the risk of graft rejection.

The first approach is to decrease the recipient’s sensitivity by the reduction of antigen difference between the donor and recipient cornea using major histocompatibility complex (MHC) matching. While there is a lower rejection rate in normal and high-risk cases that are well matched for human leucocyte antigen (HLA), Dr Allo noted that one study found no significant beneficial effect for HLA class I and II matching in high-risk corneal graft recipients. The same study also demonstrated an increased risk of graft rejection in patients with lymphocytotoxic antibodies to HLA class I and II antigens.

The second approach entails reducing the clinical risk factors for graft rejection. While conceding that there is still much debate surrounding this issue, he identified corneal vascularisation, previous graft failure—especially from allograft rejection, and anterior synechiae as strong risk factors. Other possible risk factors include young recipient age, large or eccentric graft, HLA-mismatching, previous anterior segment surgery, concurrent virectomy with penetrating keratoplasty, concurrent intraocular inflammation, glaucoma, herpes simplex and chemical injury.

Unlike risk factors include donor-recipient sex or race disparity, prior blood transfusion or pregnancy and corneal preservation method, he said.

A third option to help prevent graft rejection would be reducing the recipient’s afferent or efferent immune response by pharmacological modulation.

“In patients without risk factors for immune reaction, a local postoperative treatment with corticosteroids is sufficient in most cases. However, high-risk patients for corneal graft rejection may need additional treatment in the form of other immunomodulatory substances such as immunosuppressant antimetabolites, immunosuppressant immunomodulators, antibody treatment and gene therapy,” he said.

Noting that these substances differ widely in their primary acting mechanisms and in their spectrum of side effects, Dr Allo discussed the advantages of current pharmacological approaches to graft rejection.

Corticosteroids remain the therapy of choice in cases of acute corneal graft rejection, said Dr Allo, and can be administered topically, subconjunctivally, perioricularly or by intravenous delivery. While they are effective in blocking T cell and APC derived cytokine and cytokine-receptor expression and decreasing inflammation, they are also associated with serious side effects and their use must be monitored closely.

Anti-metabolites gain popularity

Antimetabolites are becoming increasingly popular, in part because of the serious side effects associated with corticosteroids. Of these, Dr Allo cited azathioprine, which acts to inhibit purine synthesis necessary for the proliferation of cells, especially leucocytes and lymphocytes, and methotrexate, which inhibits the synthesis of DNA, RNA, thymidylates and proteins.

“High-risk patients for corneal graft rejection may need additional treatment in the form of other immunomodulatory substances...”

Immunomodulator agents used in graft rejection treatment include cyclosporine A, an immunosuppressive agent that lacks the myelosuppressive hazards of the antimetabolites, but which carries its own significant risks, including hypertension, renal toxicity, hepatotoxicity, and neurotoxicity. It should be employed only after a thorough medical evaluation, advised Dr Allo.

Another option is tacrolimus, which has been used successfully in liver and kidney transplantation and has also proven helpful in reducing rejection and prolonging graft survival in patients with high-risk keratoplasty, with a success rate of about 65 per cent, said Dr Allo. The main side effect of tacrolimus is hypertension, which is easily controlled with antihypertensive drugs.

Promising strategies for the future treatment of corneal graft rejection include antibody therapy and gene therapy, concluded Dr Allo.