Corneal Graft Rejection: A Review Of Literature And Recent Advances

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Corneal Graft Rejection: A Review Of Literature And Recent Advances

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Abstract

Immune rejections remain one of the most common causes of failure of penetrating keratoplasty. Epithelial rejection, chronic stromal rejection, hyperacute rejection and endothelial rejection constitute the different types of corneal graft rejection that might occur in isolation or conjunction. Various risk factors have been identified to increase the risk of graft rejections. With a recent advent in lamellar and endothelial keratoplasties, it is important to identify the patterns of rejection in these grafts. Corticosteroids remain the mainstay of prophylaxis and treatment of corneal graft rejection. The role of various immunosuppressive agents, systemic and topical, is being investigated and preliminary reports have shown some benefit. The successful management of corneal graft rejection involves understanding the immunopathogenesis of the same, prevention, early detection and prompt management.

Introduction

Corneal transplantation is the most commonly performed transplant procedure. In addition to the increasing number of corneal transplant procedures being performed worldwide, the recent years have seen an increasing trend towards component i.e anterior lamellar and endothelial surgeries. Although it is the most successful transplant procedure, the survival of the graft is under constant threat from a number of factors. Immune mediated rejection is one of the most common causes of failure of the transplanted tissue.1-5 This article discusses the risk factors, types, treatment and recent advances in the management of corneal graft rejections.

Definition and Incidence

Graft rejection refers to the immunological response of the host to the donor corneal tissue without regard to the effect of the response on graft survival. Corneal graft rejection can be defined as development of graft edema in conjunction with inflammatory signs in a graft that has been clear for at least two weeks in a primary graft and one week in a regraft. The reported incidence of graft rejection in literature varies from 2.3% to 65% depending on the risk factors of the recipients.6 The Australian Corneal Graft Registry reported the incidence of graft rejection to be 33%.7 In a retrospective study over 12 years, the incidence has been stated to be approximately 9-12%.8 Another retrospective study by Sangwan et al has reported an overall incidence of graft rejection to be 11.6% over a 15 month follow up period.9 The mechanisms responsible for immunological privilege of cornea include lack of blood vessels, lack of lymphatics, presence of blood-eye barrier, relative paucity of mature antigen presenting cells (APCs) in the central cornea, presence of immunomodulatory factors in aqueous humor, the constitutive expression of CD 95 L (Fas ligand) within the eyes.10,11 Anterior chamber immune deviation (ACAID) is another active regulatory process which has been speculated to be responsible for the immune privilege of the graft but it takes time to develop and may be insufficient to prevent active sensitization to the foreign antigen.12 This immune privilege may be lost by inflammation, development of corneal vascularisation, corneal lymphangiogenesis which induces alloimmunisation and subsequent graft rejection.

Risk Factors

FACTORS RELATED TO DONOR

ABO incompatibility: The Collaborative Corneal Transplant Study (CCTS) identified the ABO incompatibility to be a strong risk factor for graft failure.13 Similar results have been reported by a study by Borderie et al,14 stating that ABO compatibility may be effective in preventing irreversible
allograft rejection in high-risk recipients. However, the recent studies fail to support this evidence. According to the recent literature, ABO incompatibility does not increase the risk of transplant failure attributable to graft rejection. HLA incompatibility: Neither HLA-A,-B nor HLA-DR antigen matching were found to substantially reduce the likelihood of corneal graft failure by the CCTS. However, recent studies indicate that HLA typing has a role in reducing the rate of allograft rejection in both high- and low-risk patients. Tissue Storage: Tissue storage was found to have little influence on graft outcome in the CCTS. Similarly, no statistical difference in graft rejection rates was found between fresh and cryopreserved tissue in another study by Xu et al. However, it has been found that there is a higher graft survival after organ culture compared with graft survival after storage at +4 degrees C. It has also been reported that storage of corneal tissue may reduce the frequency of allograft rejection, especially in high-risk patients.

FACTORS RELATED TO THE HOST
Vascularisation: CCTS has defined vascularisation of the host bed in 2 or more quadrants extending at least 2 mm into the stroma as a risk factor associated highly with the rejection of the corneal grafts. The Australian Corneal Graft Registry Report 2007 has given a vessel ingrowth scale as follows: 0 – no vessel growth in any quadrant extending to graft-host junction, 1 - growth in 1 quadrant, 2 - growth in 2 quadrants; 3- growth in 3 quadrants, 4- growth in 4 quadrants. However, no distinction was made between superficial/deep; patent/ghost; single/multiple leash vessels. Graft failure and rejection risk increase with an increasing number of corneal quadrants affected by neovascularization before keratoplasty. Previously failed graft: Previously failed graft has been noted to be another high risk factor associated with graft rejection. The increased risk of the rejection episode in these cases can be attributed to host sensitization from the previous graft. Previous grafts may also be associated with host bed vascularisation which further increases the risk of rejection in such cases.

Herpes Keratitis: Cases with a preoperative diagnosis of herpetic keratitis are associated with high allograft rejection rates. In these cases, primary allograft rejection rates have been reported to be 29% in the first year and 46% in first 2 years. Histopathologic inflammation and neovascularization are known risk factors for corneal allograft rejection. Two-thirds of cases with clinically quiescent herpetic disease have been noted to harbor evidence of histopathological inflammation.

Technical factors: Large and eccentric grafts are associated with an increased rejection risk due to their proximity to the limbus. Suture loosening is one of the important risk factors for immunologic graft rejections. Longer operating times have also found to be associated with increased rejection of corneal grafts.

Other factors: The other factors associated with increased risk of graft rejection include young recipients and patients with history of atopic dermatitis. A previous anterior segment surgery, active inflammation and infection at the time of surgery, have been found to have a positive correlation with graft rejection.

Clinical presentation and types
Patients with corneal graft rejections present with symptoms of redness, watering, visual complaints and/or photophobia. The type of rejection episode can be classified as:

Epithelial Rejection: Being generally asymptomatic, the average period of onset is 3 months. This type of rejection is characterized clinically by an elevated, undulating rejection line and centrally progressing superficial epithelial infiltrate: Kaye’s dots. It is a self limiting episode but may be associated with other types of rejection.

Chronic stromal rejection: The average period of onset of such rejections is 6 weeks to 21 months. It can be recognized clinically by subepithelial infiltrates or donor tissue. It generally shows a positive response to steroid therapy. Underlying endothelial rejection should be ruled out.

Hyperacute stromal rejection: Presenting with circumlimbal injection, it is characterized by sudden onset of peripheral full-thickness haze in a previously clear graft. A stromal abscess like picture initially confined to the limits of the graft is noticed. A severe episode may lead to a persistent epithelial defect for a long time.

Chronic focal or endothelial rejection: The average period of onset is 8 months. Patients generally present with pain, redness or visual complaints. Clinical signs include conjunctival hyperemia, graft edema, keratic precipitates, Khodadoust line and anterior chamber reaction. Larger and eccentric grafts are more prone to develop endothelial rejection. Endothelial rejection is an emergency and needs emergent treatment to prevent the failure of the graft.

Graft rejection episode has been categorized by the CCTS on the basis of severity and devised guidelines for the management of such episodes.
Graft rejection in endothelial keratoplasty:
Lower rates of rejection have been reported following endothelial keratoplasty as compared to cases with penetrating keratoplasty. In a multicentric retrospective study of 199 deep lamellar endothelial keratoplasty (DLEK) and DSEK cases, the 2-year incidence of graft rejection episodes was 7.5%. Rejection episodes after endothelial keratoplasty have been reported to be less severe. This is evidenced by the high rates of reversibility and low rates of graft failure after the onset of rejection episode. One third of patients with graft rejection after endothelial keratoplasty are asymptomatic, and only about half of the patients complain of decreased visual acuity or irritation.

Graft rejection in lamellar keratoplasty:
As compared to penetrating keratoplasty, graft rejection has been noted less frequently in cases of lamellar keratoplasty. The reported rejection rates following anterior lamellar procedures range from 0% to 8%. Anterior lamellar keratoplasty avoids the risk of endothelial graft rejection. The patterns of rejection noted in such cases include isolated epithelial rejection, stromal rejection and combined epithelial and stromal rejection.

 MANAGEMENT
STEROIDS
Treatment of a rejection episode
Steroids form the mainstay of treatment of graft rejection episodes. While epithelial rejection and sub-epithelial infiltrates can be treated with frequent topical steroids; endothelial as well as combined endothelial and stromal rejections should be treated with systemic steroids. The distinction between treatment with topical vs systemic steroids can also be made on the basis of the severity of the rejection episode. Whereas mild episodes can be treated with topical steroids, severe rejection episodes require treatment with systemic steroids. Pulse steroid therapy is more effective than oral steroids for the treatment of a rejection episode. The graft survival rates have been found to significantly better for pulse methylprednisolone therapy. A single pulse is as effective as a double pulse repeated either at 24 or 48 hours after the initial dose. Intravenous dexamethasone has been found to be equally efficacious as methylprednisolone and thus may be used as an alternative in patients who are non-affording.

Various other routes have been tried for the delivery of corticosteroids for the management of a rejection episode. Subconjunctival, intracameral and intracorneal 48 routes have been found to be effective in the reversal of a rejection episode.

Prophylaxis
According to a survey analyzing the preferred practice patterns of ophthalmologists, topical steroids remain the mainstay for the prevention of corneal graft rejection. Topical steroids have been found to be equally efficacious to oral steroids; thus are an effective immune prophylaxis. Long term (12 months) topical steroids have a better rejection-free graft survival. Ross et al have reported that use of long term steroids (18 months) improves graft survival rate (hazard ratio: 1.5).

ROLE OF CYCLOSPORIN A (CSA):
CsA is a powerful immunosuppressive agent which binds to an intracellular protein called cyclophilin and inactivates calcineurin. The inactivation of calcineurin inhibits IL-2 and lymphokine production, thus limiting the activity if CD4+ and CD8+ lymphocytes.

Topical CsA has been used and studied extensively with regard to management of corneal graft rejection. Initial studies have documented evidence on the efficacy of the same in reducing the risk of allograft rejection. However, the current literature refutes these results. Recently, topical CsA have not been found to reduce the risk of allograft rejection in either 0.05% or 2% concentration. The role of oral CsA in the prevention of graft survival has been controversial. Although Hill et al had found significantly lower rejection rates with the use of long term (1 year) oral CsA in high risk keratoplasties, recent studies have found only a limited benefit of oral CsA in the prevention of corneal graft rejection. Whereas patients on topical regimes require monitoring of renal and liver function, oral CsA therapy requires therapeutic monitoring of its blood levels.

ROLE OF MYCOPHENOLATE MOFETIL (MMF):
MMF acts by inhibiting inosine monophosphate dehydrogenase required for proliferation of T- and B-lymphocytes. Randomized controlled trials suggest that oral MMF is effective in the prevention of allograft rejection in high risk keratoplasties. It has been found to be as efficacious as oral CsA in the
prophylaxis against graft rejections.64,65,66 The adverse effect profile is similar to that of CsA, however the omission of the therapeutic drug monitoring makes MMF economically superior as compared to CsA.

**ROLE OF TACROLIMUS (FK-506):**
With a mechanism of action similar to CsA, tacrolimus has been noted to be 10 to 100 times more potent than the latter. It inhibits calcineurin by binding to immunophilin or FK-506 binding protein (FKBP). Topical application of tacrolimus in the form of ointment67 or drops,68 has shown to be promising as a prophylactic agent against corneal graft rejection. Systemic tacrolimus has also been shown to be safe and effective in reducing rejection and prolonging graft survival in patients with high risk keratoplasty.69

**ROLE OF BEVACIZUMAB**
Bevacizumab has been used to induce regression of corneal neovascularisation.70 Majority of the studies document the decrease in corneal neovascularisation.71,72 However, the short term follow-up periods limit the clinical implications of these studies.

**NEWER AGENTS:**
Rapamycin/Sirolimus binds to FKBP and inhibits immunophilin activity. It also interferes with IL-2 induced signals. Oral rapamycin has been used alone73 and in combination with MMF74 and has been noted to have a benefit in prevention of corneal graft rejection. The role of basiliximab for immunosuppression is being investigated, the initial reports give conflicting results.75,76 Local gene therapy-mediated expression of the immunomodulatory cytokine IL-10,77 anti-lymphocyte monoclonal antibodies (anti CD52/CAMPATH-1H)78 are the new approaches being investigated in the management of corneal graft rejections.

**Outcome of corneal graft rejection**
The rates of reversibility of corneal graft rejection vary between 63% to 92%.9,42,79 The same depends on the interval between the onset of rejection episode and initiation of therapy. Shorter intervals have been found to have high reversibility rates. Delay of as short as one day in diagnosis and treatment of graft rejection results in significantly worse outcome.80 The risk factors for post rejection graft failure include increasing patient age, increasing donor age, preoperative diagnosis of bullous keratopathy and previously failed grafts.

**Summary**
Corneal graft rejection remains one of the most important factors limiting the outcome of corneal transplantation. Meticulous preoperative patient selection and patient education are important parameters for prevention and management of graft rejection. HLA matching has a role in increasing the survival of corneal grafts. The rejection patterns vary between penetrating and component keratoplasties. The role of corticosteroids in the prevention and management of the rejection reactions is unequivocal. Other immunosuppressive agents, topical and systemic, have shown some promise in the prophylaxis and treatment of corneal graft rejections. Experimental approaches, including the use of antibody based regimens and gene therapy are being developed and but are yet to see success in the practical management of rejection episodes.

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