HHS Public Access

Author manuscript

Surv Ophthalmol. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Surv Ophthalmol. 2017 ; 62(6): 816–827. doi:10.1016/j.survophthal.2016.12.010.

Management of High-risk Corneal Transplantation

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Abstract

The cornea is the most commonly transplanted tissue in medicine. The main cause of corneal graft failure is allograft rejection. The incidence of graft rejection depends on the presence of high-risk characteristics, most notably corneal neovascularization. Although corneal graft has high success rates in the absence of these risk factors, high-risk keratoplasty is associated with low success rates due to a high incidence of immune-mediated graft rejection. To improve the survival of high-risk corneal transplantation, various preoperative, intraoperative, and postoperative measures can be considered. However, the key step in the management of these grafts is the long-term use of local and/or systemic immunosuppressive agents. Although a number of immunosuppressive agents have been employed for this purpose, the results vary significantly across different studies. This is partly due to the lack of an optimized method for their use as well as the lack of a precise stratification of the degree of risk in each individual patient. New targeted biologic treatments as well as tolerance-inducing methods show promising horizons in the management of high-risk corneal transplantation in near future.

Keywords

Cornea; graft rejection; high-risk; immunosuppression; neovascularization; transplantation

1. INTRODUCTION

In 1905, about half a century before the first successful solid organ (kidney) transplantation, Eduard Zirm performed the first human corneal allograft. Currently, more than 100,000 corneal transplantations are carried out annually worldwide[50] for various conditions such as

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Conflicts of Interest: none

keratoconus, bullous keratopathy, failed previous graft, and corneal scarring, dystrophies, or infections.[159]

Corneal immune privilege is a well-recognized phenomenon which explains the high success rates associated with corneal transplantation, with a 1-year survival rate of about 90%, and a 15-year survival rate of about 55% in avascular, non-inflamed host beds.[50,109] Despite advances in corneal surgery, optimal outcome is not achieved in all cases. This necessitates a better understanding of risk factors of the graft failure and the measures that can prevent such an outcome.

2. IMMUNOLOGY AND PATHOPHYSIOLOGY OF CORNEAL GRAFT FAILURE

The irreversible loss of refractive quality of the corneal graft is defined as graft failure, which can be immune or non-immune mediated.[121] Immune rejection remains the leading cause of graft failure, accounting for over half the cases of graft decompensation. Other reasons for corneal graft failure include glaucoma (10%), non-viral infections (10%), endothelial cell failure (8%), and viral herpetic infections (7%); the reasons for the remaining cases often go undetected.[121,147] The reported incidence of corneal graft rejection in different studies varies from 2.3% to 68%.[89,135] Overall, 30% of the transplanted corneas experience at least one episode of immune reaction and one third of these lead to eventual graft failure.[40,111] An avascular, non-inflamed corneal host, termed as low risk (LR) corneal transplantation, can expect a 5-year survival rate of 90% with only topical immunosuppression.[163] However, the survival rate dramatically decreases to below 35% in inflamed, vascularized host beds, so-called high risk (HR) corneal transplantation.[164,166]

Immune-mediated graft rejection is a complex interplay between lymphangiogenesis (afferent arm of the immune loop), hemangiogenesis (efferent arm of the immune loop), and inflammation, ultimately leading to loss of the privileged immune status. The avascular nature of the cornea, unique physiology of the anterior chamber recognized as Anterior Chamber Associated Immune Deviation (ACAID), low to absent expression of major histocompatibility antigens (MHC)-I and II in the cornea, quiescent corneal antigen-presenting cells (APCs), and presence of T cell apoptotic factors like Fas-ligand are some of the factors responsible for high survival rates of corneal allografts.[5,89]

Corneal transplant rejection involves an induction phase, which begins with the sensitization of the host to donor antigens and activation of corneal dendritic cells (APCs) which in turn sensitize and induce proliferation of T cells in the draining lymph nodes. The efferent phase, mediated by delivery of immune effectors to the graft site by blood vessels, is responsible for ultimately attacking the graft through a T cell dependent effector mechanism- both CD8+ and CD4+ Tcells which release inflammatory cytokines like interleukin (IL)-2, interferon (IFN)-γ, IL-4 and IL-10, subsequently resulting in graft rejection.[5,89]

3. RISK FACTORS FOR CORNEAL GRAFT REJECTION

The Collaborative Corneal Transplantation Study (CCTS) provided us with useful insights regarding various donor and host characteristics which lead to an increased risk of failure.[95] Some of risk factors for corneal graft rejection have been summarized below.

3.1. Donor Characteristics

Human Leukocyte Antigen (HLA) and ABO incompatibilities are the main donor factors that may affect graft survival. CCTS did not find any significant contribution to graft outcome from donor preservation methods, gender mismatch between recipient and donor, or the cause of donor death.[94] Time from death to enucleation, from enucleation to storage, and from storage to transplantation probably do not influence rejection rates, but may affect graft outcome.[1,152]

3.2. Host Characteristics

1) Host Bed Vascularity—Host bed vascularity is the principal risk factor for corneal allograft rejection. In a LR environment, the post-transplantation vascular sprouting is quickly inhibited, and the angiogenic privilege state of the cornea is restored. In a HR context, there is a loss of this angiogenic privilege and blood and lymphatic vessels invade the corneal graft, thus increasing the risk for allograft rejection. While clinically invisible lymphatics have a critical role in trafficking graft antigens to host T cells, corneal blood vessels are vital in delivering the immune effector cells to the graft site and driving immune rejection.[30,39] Both the extent and depth of corneal vessels directly correlate with the risk of allograft rejection; the more quadrants involved the greater risk of rejection (Fig. 1).[94,147,160] Khodadoust and associates classified the rejection risk based on the degree of host bed vascularization: avascular, mild (1–3 vessels), moderate (4–10 vessels) and heavy (>10 vessels). He realized that in the heavily vascularized group, 65% of grafts started to reject, and all finally failed despite a strong immunosuppressive treatment.[83] The CCTS defined “high risk cornea” as a cornea with two or more quadrants of deep stromal vessels prior to surgery.[148] According to the CCTS the presence of stromal vascularization in all four corneal quadrants doubles the risk of rejection, increases the severity of immune response against the graft, and reduces the time taken to reject the graft.[148] Once corneal rejection occurs, the difficulty of reversal also depends on the degree of corneal neovascularization.[49]

2) Pre-existing Local and Systemic Conditions—The risk of rejection is increased in re-grafts, particularly when two or more grafts have previously failed.[94] With comparable vascular beds, rejection rates are about 40% after the first graft, 68% after the second graft, and 80% after the third graft. CCTS recognized this risk to be 1.2 for each successive graft.[94] Plausible reasons include pre-sensitization, immune memory, and inflamed and vascular milieu from the previous surgical insults. Increased graft size and eccentric grafts are also associated with a higher risk for rejection due to increasing the access to the limbal vasculature.

Pre-existing diseases such as herpes keratitis, uveitis, atopic dermatitis, and eczema also increase the risk of immune reactions. Furthermore, ongoing active inflammation and infection at the time of surgery (so-called hot grafting) greatly predisposes to corneal allograft rejection and also to graft failure due to non-immunological causes.[94] Presence of ocular surface disease such as dry eye disease has also been shown to increase the risk of corneal graft rejection.[71] Clinical history of glaucoma, previous surgeries, particularly glaucoma surgery or previous anterior segment surgery other than penetrating keratoplasty, anterior iris synechiae, vitreous adhesions, and multiple surgeries at a time all raise the

rejection risk in the transplanted graft.[65,94,148,160] Presence of recipient lympho-cytotoxic antibodies due to a previous graft or corneal rejection, and blood transfusions may also increase risk of rejection.[98] Rejection during and after pregnancy is a common occurrence in all forms of transplantation, including corneal transplant recipients,[55] even though pregnancy is viewed as a state of relative immune suppression. On contrary, postpartum rejection episodes may be related to the reestablishment of a normal immune competence.[55,101]

Finally, it is important to diagnose limbal stem cell deficiency (LSCD) in patients who are candidates of corneal transplantation as this condition can result in ocular surface failure after the surgery.[68] Limbal stem cell deficiency is characterized by a loss of limbal palisades of Vogt, a late fluorescein staining of the cornea, chronic inflammation, irregular epithelium, recurrent erosion, persistent epithelial defect, and conjunctivalization, The clinical diagnosis may be confirmed by impression cytology which shows the presence of goblet cells on the cornea.[120]

3) Age and Sex—An increased risk of rejection is seen when the transplantation is performed in a young host bed.[106,131] This is due to a combination of a robust immune response and also due to difficulty in recognizing these episodes early due to inability to perform accurate examinations in this patient population in the office. Furthermore, it has been shown that corneal transplantation from a male donor to a female recipient is associated with a greater risk of rejection and graft failure compared with male to male matches.[155] However, not such an increased risk has been noted for female to male matches.[155]

4. MANAGEMENT OF HIGH-RISK CORNEAL TRANSPLANTATION

The purpose of this review is to highlight several management strategies of HR corneal transplantation, mostly evaluating the pre-, intra-, and post-operative measures to reduce the risk of an allograft rejection. It should also be noted that in patients with HR cornea, an alternative approach consists of the use of keratoprosthesis which is beyond this review article.

4.1. Preoperative Management

In HR corneal transplantation, preoperative measures are required to reduce the risk of rejection. An important practical approach consists of elimination or reduction of host corneal stromal neovascularization. Different modalities of treatment have been suggested for direct or indirect occlusion of corneal vessels, such as steroids,[60] radiation,[105] cystine,[35] cryotherapy,[60] sulfuric acid,[91] dextran,[91] conjunctival recession,[60] and laser treatment. Among these, laser treatment, using 577 nm yellow dye laser has been shown to be an effective modality for corneal vessel occlusion.[10,110] A long term efficacy is also achievable in fine needle diathermy before corneal grafting.[48] To reduce corneal neovascularization, an alternative and innovative approach has recently been introduced which includes the use of agents against Vascular Endothelial Growth Factor (VEGF), as discussed in greater detail below.

Another measure to improve the outcome of corneal graft in HR settings is donor-recipient antigen matching. The CCTS did not report any advantage from HLA class I or class II matching in corneal transplantation, while a modest benefit was detected from ABO antigen matching.[148] Although widely accepted in Europe, this strategy is still under evaluation in the United States. A benefit from major histocompatibility complex (MHC) matching has been reported from Canada,[22] Netherlands,[157] Germany,[81] as well as from the United Kingdom.[152] In patients considered to be of high risk for rejection, the improvement obtained with matching was in the order of 40% compared with those who were less well-matched.[81] For many patients, however, this may prolong the waiting time and delay the surgery. Sometimes these delays can be unacceptable considering the limited benefits from the process,[38] even if the delay could be assessed before surgery by considering the frequency of a given recipient's HLA antigens within the donor population.[21] Nonetheless, HLA matching in HR patients appears to have a beneficial effect as shown in more recent studies from Europe in which precise modern molecular methods of typing have been used.[81,156]

Kim et al.[84] proposed a preoperative use of corticosteroids 2 weeks before the transplantations. They revealed that the pretreatment with corticosteroids decreased the host bed neovascularization in both LR and HR corneal transplantation. The Bowman Club survey in the United Kingdom reported that 53% of the members routinely commenced preoperative treatment (monotherapy or a combination of 2 or more agents) in high risk cases. Topical dexamethasone (3 to 6 hourly, duration unspecified) was used by 33% of surgeons, oral prednisolone (40 to 80 mg for 2 to 7 days) by 22%, oral cyclosporine A (3 to 8 mg/kg, duration unspecified) by 14%, and single-dose intravenous methylprednisolone by 14%.[86]

Finally, as healthy limbal stem cells are necessary for survival of a corneal graft, special consideration should be given to the presence of LSCD. In patients with this condition, stem cell transplantation should be performed before cornea graft. For this, depending on each individual situation, autologous or allogeneic sources may be used from limbal or oral mucosal cells. One may also consider the use of keratoprosthesis as an alternative to performing both stem cell and corneal transplantation.

4.2. Donor Manipulation

It is well-known that depletion of class II-expressing "passenger" leukocytes in donor promotes the long-term survival of allografts by reducing immunogenicity in solid organ (e.g., heart and kidney) transplantation.[52,53,88] Simon et al.[138] discovered that prolonged storage of donor corneas prevented allograft rejection, particularly in HR corneal transplantation. However, preservation of corneal buttons requires a longer waiting time and can be detrimental to endothelial cells. Zhang et al.[164] reported that anti-CD45 antibody added to complement-mediated targeting of donor buttons was effective in depleting passenger leukocytes ex vivo within 1 day. This reduced the time required for storage. However, by this method only APCs of the donor would be suppressed, without any effect on host APCs, which would still be able to process donor MHC class II molecules expressed

by non-leukocyte populations. Thus, they did not find any significant effect of depletion of graft passenger leukocytes on corneal graft survival even in the HR setting.

Another field of research is also focusing on the ability of donor immature dendritic cells to play a fundamental role in transplant tolerance by perhaps activating regulatory T cells (Tregs).[33,56] Therefore, leukocyte depletion may have deleterious consequences in terms of Treg induction.

4.3. Intraoperative Considerations for High-risk Corneal Transplantation

Significant advances in instruments, suture materials, operating microscopes, medications, surgical techniques, adequate donor screening, and storage facilities have greatly improved the final visual outcome and survival of corneal transplantation.[115]

1) Type of Corneal Transplant—Penetrating keratoplasty, which is a full-thickness transplantation procedure, has been surpassed in its rates of graft survival, rejection reversibility, and visual and long-term surgical outcomes by selective lamellar keratoplasties that aim to only treat the affected corneal layer in patients suffering from single-layer pathologies such as endothelial dystrophies (e.g., Fuchs dystrophy).[23,59,117] Lamellar surgery is nowadays increasingly popular because of the reduced risk of immune rejection and intraoperative or postoperative complications.[148]

Deep anterior lamellar keratoplasty, where only stroma and epithelium are replaced,[50] boasts a 10-year stable graft survival rate of 99.3% with a small loss in endothelial cell density (11%).[140] Descemet stripping endothelial keratoplasty (DSEK) and Descemet membrane endothelial keratoplasty (DMEK) allow selective removal of the diseased Descemet membrane and endothelium. It has been demonstrated that endothelial keratoplasty has significantly lower rates of corneal graft rejection than penetrating keratoplasty.[6,119] For example, Anshu et al.[7] reported rejection rates of 18%, 12%, and <1% after penetrating keratoplasty, DSEK, DMEK, respectively. However, it should be noted that endothelial keratoplasty in HR setting has also a very low survival rate.[37,80] Furthermore, due to presence of neovascularization and scarring in many HR corneas, they are not suitable for endothelial keratoplasty alone and often require penetrating keratoplasty.

2) Suturing Techniques and Materials—Suturing technique is perhaps the area of greatest variation in corneal transplantation. Suturing technique (interrupted, continuous, or mixed) is not likely to be associated with the risk of rejection. But in high risk cases, such as children and hot eyes (infection and inflammation), the interrupted suture technique is more appropriate, as they have faster wound healing and sutures can be easily removed in cases of growth of new vessels or inflammation. In a Cornea Society survey 66% of respondents reported changing from their usual suturing technique in high risk cases, with changing to an interrupted suture technique in 88% of cases.[90] Regarding suture material, 10–0 monofilament nylon is considered superior to other suture materials. The suture knot is usually rotated into and buried just beneath the corneal surface in the donor stroma, because placing the knot in the host's stroma may attract vessels.[94,147,152]

4.4. Postoperative Prophylaxis

4.4.1. Topical Therapies

1. Steroids: Corticosteroids represent the principal medication in the management of corneal transplantation. They are readily absorbed across the ocular surface and high levels can be achieved in the anterior chamber. Prednisolone and dexamethasone are the most commonly used forms.[123] Loteprednol etabonate ophthalmic suspension was used by 9 to 11% of respondents at 2004 Cornea Society meeting survey in low-risk grafts but rarely for high risk grafts.[123] Furthermore, difluprednate, a novel strong synthetic steroid emulsion, has become widely accepted in the treatment of endogenous and postoperative inflammation as well as in high risk eyes.[74] High risk corneal allografts need to be more intensively treated and for a longer duration. Prednisolone acetate 1% or dexamethasone sodium phosphate 0.1% drops are given every two hours initially, slowly reduced over a period of 6 months to 1 year and a mild steroid, once daily, is maintained indefinitely for aphakic or pseudophakic cases.[123]

2. Cyclosporine A (CsA): Cyclosporine A (CsA) is a macrolide with a powerful immunosuppressive activity that modulates T cell function.[24] Cyclosporine A acts by binding to the intracellular protein cyclophilin, which inhibits the activity of calcineurin enzyme, blocking nuclear factor activation.[26] Cyclosporine A inhibits the IL-2 pathway, leading to a decrease in the synthesis and secretion of several pro-inflammatory cytokines such as IL-2, IL-4, IFN-γ, tumor necrosis factor-α (TNF-α), and thus results in an inhibition of helper and cytotoxic T cell differentiation. Systemic CsA is highly effective for prevention of immune rejection after solid-organ transplantation.[54,130] However, the systemic formulation is associated with the development of adverse events, such as hypertension, nephrotoxicity, hepatotoxicity and gastrointestinal toxicity among others.[27,58]

Topical ophthalmic CsA has been prescribed for years and has gained popularity among ophthalmologists to treat different immune diseases of the eye, including dry eye disease, vernal keratoconjunctivitis, and ocular graft-versus-host disease.[42,151,158] Although topical ophthalmic CsA has also been used for prevention of corneal graft rejection, its efficacy is a matter of controversy. Concentration of the drug for this purpose varies from 0.05% to 2% in the literature. Randleman and Stulting[123] reported that 48% of the respondents to the 2004 Cornea Society survey prescribed topical CsA for the management of high-risk grafts. In retrospective studies, Inoue et al. and Cosar et al. reported that in high-risk settings using a concentration of 2% of topical CsA resulted in improvement in rejection-free rates, but not in total graft survival rates; but, in a prospective study Belin et al. described improvements of both rejection-free and survival rates.[13,36,73] However, majority of other prospective studies have failed to demonstrate any benefit with the use of topical CsA for HR keratoplasty, regardless of the concentration used or risk setting.[25,75,114,118,150] In addition, some recent studies have shown that topical CsA does not add any advantage to the conventional treatment in managing high-risk grafts which have rejection.[13,36,73,75,165]

In conclusion, although topical CsA can be used in postoperative period in cases of steroid-induced glaucoma, allowing a reduction of topical corticosteroids,[13,14] its efficacy to reduce the risk of graft rejection in HR corneal transplantation is still questionable.

3. Tacrolimus (FK506): Tacrolimus, FK506, is a macrolide antibiotic, member of the calcineurin inhibitor family, with a potent immunosuppressive activity. Similar to cyclosporine, tacrolimus inhibits the initial phase of T-cell activation resulting in inhibition of T-cell signal transduction and IL-2 transcription. Additionally, cytokine release of TNF-α, IFN-γ, and other interleukins is also affected by tacrolimus.[136,145] Tacrolimus has been reported to have fewer systemic side effects than CsA, though that its immunosuppressive effect is 25–100 times more than that of CsA.[132]

Topical tacrolimus has been effectively used in inflammatory anterior segment diseases.[78] In addition, several studies have shown the ability of tacrolimus to penetrate in the cornea and also its efficacy in preventing corneal graft rejection in animal models.[15,64] Few case series have reported beneficial effect of topical tacrolimus in human HR corneal transplantation. Dhaliwal et al.[45] used off-label topical tacrolimus 0.03% ointment in 4 patients with HR corneal transplantation and did not have any rejection episode. In addition, Magalhaes et al.[93] retrospectively compared the combination of topical prednisolone 1% and tacrolimus 0.03% eye drops to prednisolone eye drops alone in HR corneal transplantation. They noted a significantly lower rate of irreversible graft rejections in the prednisolone plus tacrolimus group than in the prednisolone-alone group. Therefore, topical tacrolimus is worthy of further study as a second-line treatment in patients with high-risk corneal grafts.

4. Anti-VEGF: Vascular Endothelial Growth Factor (VEGF) mediators family, principally VEGF-A, is responsible for the angiogenic processes in corneal transplantation. Therefore, several anti-VEGF-A drugs have been evaluated for prevention and treatment of corneal neovascularization.[70,141] Recently, few studies have demonstrated the safety and promising results after off-label application of bevacizumab, a recombinant, humanized, monoclonal antibody against VEGF-A for corneal neovascularization in patients with penetrating keratoplasty. For this purpose, bevacizumab has been used as topical eye drops and/or though subconjunctival or intrastromal injections. The latter methods will be mentioned below in the section on “Subconjunctival Administration”. Bhatti et al.[17] employed topical bevacizumab 2.5% four times daily for 24 weeks in patients with HR corneal transplantation and noted a significant reduction in corneal neovascularization compared with the control group. Subsequently, the same group showed that subconjunctival injection of bevacizumab (2.5 mg/0.1 ml) was more effective than the topical application in reducing corneal neovascularization.[3,16] Other studies have used either subconjunctival injection or a combination of subconjunctival injection and topical application as discussed below.

4.4.2. Subconjunctival Therapies

1. Steroids: Immediate postoperative subconjunctival injections of methylprednisolone for routine prophylactic management have also increased in the Cornea Society survey in 2011 compared with the surveys in 1989 and 2004. Surprisingly, the usage of subconjunctival steroid preparations was noted to be higher in routine management of low-risk grafts (76%) than in high-risk grafts (54%); this may be related to the use of other topical and oral immunosuppressive agents in high-risk grafts.[82]

2. Anti-VEGF Agents: In addition to topical application which was mentioned above, subconjunctival injection of anti-VEGF agents, particularly bevacizumab (Avastin®), has been used to reduce corneal neovascularization and thus improve graft survival in HR corneal transplantation. Subconjunctival injections generate higher intraocular concentrations compared with systemic or topical administration of anti-VEGF-A.[26] In addition, it results in slower release of the pharmacological agent because anti-VEGF agents spread into the corneal stroma and remain there for several days to weeks.[31,43] Vassileva and Hergeldzhieva[153] showed the efficacy of subconjunctival, perilimbal, and/or intrastromal bevacizumab with a dose of 2.5 mg/0.1 ml per affected quadrant for reducing corneal neovascularization in HR keratoplasty. Furthermore, Fasciani et al.[51] showed the safety and efficacy of preoperative treatment of corneal neovascularization with bevacizumab before HR keratoplasty. Dekaris et al.[44] also found that 70% of HR grafts remained clear during 3 years of follow-up after combined subconjunctival and topical bevacizumab treatment.

Ranibizumab (Lucentis®) humanized anti-VEGF Fab antibody inhibits all forms of biologically active VEGF-A[28] and may be more effective in the treatment of the new vessels because of its smaller molecular weight (one-third of the full antibody) and possibly deeper penetration[57] and also because of its stronger binding affinity, compared with bevacizumab.[85,141] In addition, a combined modulation of hemangiogenesis and lymphangiogenesis by vascular endothelial growth factor (VEGF)-Trap R1R2 after normal-risk corneal transplantation has recently been shown to improve graft survival in a murine model of corneal transplantation,[40] but no study has been performed in humans.[47]

4.4.3. Intrastromal Therapies—In addition to topical and subconjunctival injection use of bevacizumab, intrastromal injection method has also been effective for treatment of corneal neovasculrization.[12,97]

4.4.4. Systemic Therapies—Systemic immunosuppressants may be administered on a prophylactic basis in HR corneal grafts to inhibit or regress corneal lymph- and hem-angiogenesis[39,92] and to prevent or reverse immune-mediated graft rejection. However, the morbidities associated with these medications may outweigh any improvement in graft survival and their usage is often based on surgeon judgment with a wide variability in the treatment use.[2]

1. Corticosteroids: A short course of systemic corticosteroids may be used postoperatively in patients with HR corneal transplantation.[82,123,124] However, no randomized clinical trial has been performed to assess the efficacy of this therapy. The Bowman Club Survey in the United Kingdom demonstrated that 44% of corneal surgeons use systemic immunosuppression including oral prednisolone for 1 day to 12 months postoperatively in high-risk cases.[86] In addition, the trend of using oral prednisolone or intravenous methylprednisolone and hydrocortisone administrations for routine management of corneal HR transplant has also increased during the past years though no consensus exists regarding dosage or duration.[123]

Numerous ocular and systemic side effects have been associated with systemic corticosteroids such as increased intraocular pressure, cataract formation, impaired wound

healing, systemic hypertension, osteoporosis, hyperglycemia, Cushing syndrome, and predisposition to opportunistic infections.[102] Therefore, new approaches, with alternative and less toxic immunosuppressive medications, have been explored. For example, it has been shown that intravitreal implant of dexamethasone can be used for treatment of corneal graft rejection in cases refractory to standard topical and systemic therapy.[154]

2. Cyclosporine A: Systemic CsA has been effectively used to prevent allograft rejection after solid organ transplantation.[54,130] Similarly, oral CsA has long been employed for prevention of rejection in HR corneal transplantation. However, there has been no consensus on the efficacy of this medication for such cases. Several studies have observed improved outcomes of HR corneal transplantation with oral administration of CsA.[103,127,142] For example, in a prospective study, Hill et al.[66] demonstrated a significantly higher rejection-free rate in CsA-treated corneal grafts (73%) compared with the untreated control group (49%). They also observed that 12 months of CsA treatment is associated with lower rejection rates compared with a shorter treatment period of 4 to 6 months.[67]

In contrast, many other authors have shown either no or only a limited efficacy of oral CsA for patients with HR corneal grafts.[72,116,129,137] For example, Poon et al. as well as Inoue et al. did not find a significant difference in rejection and failure rates between the CsA group and the control group.[72,116] Furthermore, in a randomized clinical trial by Shimazaki et al.,[137] there were no statistically significant differences in rates of rejection (30% and 16%) and failure (45% and 42%) between CsA-treated group and controls, respectively; however, all rejection episodes in the CsA group developed after discontinuation of the medication. Therefore, they speculated that oral CsA may postpone a rejection episode to a chronic clinical course, which is easier to be diagnosed and treated.[127,137]

These questionable effects of oral CsA on prevention of corneal allograft rejection may be partly due to confounding factors such as drug concentration, degree of corneal neovascularization, severity of primary host disease, duration of treatment, and occurrence of side effects.

Moreover, the variable results in CsA efficacy may also somewhat be explained by different medication dosages and blood levels in various studies. In most of studies, blood levels of 75 to 400 ng/mL have been maintained during the treatment period.[72,103,116,129] Due to its variable absorption, it is imperative to monitor the blood level of CsA as well as liver and renal function tests.[112]

Systemic CsA can be associated with significant side effects. These include hypertension, nephrotoxicity, hepatotoxicity, and gastrointestinal toxicity among many others.[67,72,103,129,137] Patients should be carefully monitored for these side effects during the systemic administration of CsA.

3. Tacrolimus (FK506): Oral tacrolimus has been used in ophthalmology to treat ocular immunologic disorders such as atopic keratoconjunctivitis, posterior uveitis, and chronic graft-versus-host disease.[129] Furthermore, because of its potent immunosuppressive effects,

several studies have employed systemic tacrolimus as a measure to prevent graft rejection in HR hosts in both animal and human studies.[87,139]

Joseph et al.[77] used systemic tacrolimus with a mean daily dose of 2.5 mg for 18–24 months in 43 patients with HR corneal transplantation. During a follow-up of 33.7 months, clarity of the graft was maintained in 65% of patients. Eight patients experienced rejection episodes while on tacrolimus, and this led to graft failure in 5 patients. In another study, Yamazoe et al.[161] used systemic tacrolimus in patients with HR keratplasty who developed graft failure despite treatment with systemic CsA. They observed significantly fewer graft rejection episodes and longer graft survival with tacrolimus than with CsA. Moreover, patients treated with tacrolimus tolerated the drug better than did those treated with CsA; however, still 20% discontinued tacrolimus treatment because of toxicity.

Therefore, it seems that tacrolimus can be an effective modality to prevent allograft rejection in HR corneal transplantation. However, the optimum length of treatment is still not known. In addition, it can be associated with side effects such as systemic hypertension, headaches, malaise and gastrointestinal upset.[77]

4. Mycophenolate Mofetil: Mycophenolate mofetil (MMF) is another systemic immunosuppressive agent which has been used safely and effectively after solid organ transplantation.[11] It is the pro-drug of the active substance mycophenolic acid (MPA), which inhibits the de novo synthesis of guanosine nucleotides, resulting in selective inhibition of T- and B-cell proliferation.[4]

In ophthalmology, MMF has been used to treat uveitis and HR corneal transplantation.[18,113,126] In a randomized, multicenter trial on 86 patients, Reinhard et al.[125] showed an immune reaction free rate of 89% in the MMF-treated group compared with 67% in the control group during the first year postoperatively. After a mean follow-up of 3 years in the same cohort, Birnbaum et al.[19] reported a reaction-free graft survival rate of 83% in the MMF-treated group and 64.5% in the control group. There was no statistically significant difference in graft failure between the two groups, although the percentage of graft failures as a result of rejection was noticeably higher in the control group (20% vs. 78%). Mycophenolate mofetil was relatively well tolerated. Mayer et al.[100] also used MMF in 10 patients with prior herpetic disease who underwent penetrating keratoplasty. They noted two mild rejections with no influence on endothelial cell density and no recurrence of herpetic disease. Moreover, due to synergistic effects of MMF with acyclovir,[108] this combination has been shown to be effective in improving the graft survival in keratoplasty after herpetic corneal disease.[96,100]

Safety and efficacy of CsA and MMF have been compared in few studies. In HR corneal transplantation, no statistical difference between CsA and MMF groups in terms of rejection episodes, graft survival, and occurrence of adverse events during a follow-up of 3 years.[126,128] Furthermore, in a retrospective study on 417 HR keratoplasties, Birnbaum et al.[18] have reported a significantly greater effect of MMF in preventing graft rejections when compared to the CsA group after 3 years of follow-up (72% vs. 60%, respectively), but with no significant difference in terms of graft survival (87% vs. 77%, respectively). However,

these results may be in part due to the patient selection, as the CsA group had more severely HR patients than did the MMF group. In terms of safety, MMF-treated patients presented a lower percentage of side effects than did the CsA-treated patients.[18] Comparison of MMF and tacrolimus has been performed in a murine study which showed that tacrolimus monotherapy more effectively reduced the risk of rejection than did MMF monotherapy.[143]

Broad and safe therapeutic range of MMF avoids the main side effects and also frequent checkups. Blood monitoring is generally unnecessary and is reserved for special situations, such as severe adverse events or treatment failure.[107] Therefore, MMF is more likely to be administered in patients with suboptimal compliance who fail to visit the ophthalmologist or general practitioner on a regular basis.[126,128] The most common side effects of MMF include infections, anemia, leucopenia, gastrointestinal disturbances, arterial hypertension, and hyperlipidemia.

5. Rapamycin (Sirolimus, Rapamune): Rapamycin is a bacterial macrolide which has antifungal and immunosuppressive properties.[134] Despite having a structure similar to that of tacrolimus, rapamycin is not a calcineurin inhibitor and thus not nephrotoxic. It acts by decreasing IL-2-mediated activation of T cells with a blood concentration range of 12–20 ng/mL.[134] Rapamycin has been shown to inhibit the growth factor-induced proliferation of fibroblasts, endothelial cells and smooth muscle cells, which are also beneficial in solid organ transplantation.[99]

Birnbaum et al.[20] showed a comparable efficacy in preventing immune reaction after HR keratoplasty between rapamycin and MMF both taken for 6 months. There was no immune reaction in either group during first 6 months, but with a 2-year follow-up reversible immune reactions occurred in 20–21% in both groups. Chatel et al.[29] also performed a prospective study on 6 patients with HR corneal transplantation. After 1 year of combination therapy with MMF and rapamycin, and then two years of rapamycin monotherapy, they had 3 rejections episodes with an irreversible failure in only 1 patient.

Broad spectrum of side effects following treatment with rapamycin, especially hyperlipidemia and arterial thrombosis, appears to limit its safe usage.[149]

5. NOVEL STRATEGIES FOR IMMUNOMODULATION IN CORNEAL TRANSPLANTATION

There is active ongoing research on finding new strategies to improve graft survival in HR corneal transplantation. Numerous immunoregulatory approaches have recently been evaluated in animal models with promising results in increasing corneal graft survival by inducing allotolerance (see below). Regulatory immune cells actively dampen the immune response against foreign alloantigens and induce allotolerance of corneal transplants.[5] Regulatory T cells (Tregs) and maturation-resistant tolerogenic dendritic cells (tolDCs) have been used in experimental models to induce tolerance and thus eliminate the use of immunosuppressive agents.[61,63,104] It has been shown that in vitro expansion of Tregs can also significantly promote allograft survival.[76] Our recent study demonstrated that systemic administration of low-dose IL-2 expands Tregs in vivo, enhances their function, and

ultimately promotes graft survival.[144] Administration of donor-derived tolerogenic DCs can also improve graft survival by increasing Treg frequencies.[62] Thus, therapeutic strategies aimed at amplifying Treg function are promising tools to induce allotolerance and promote graft survival.

In addition, antibody-based therapeutic agents are under development to modulate the rejection of vascularized organ allografts. The specific systemic treatment with intact antibody can certainly prevent or delay corneal graft rejection in experimental animals.[8] A wide variety of polyclonal, monoclonal, and recombinant antibodies have been tested targeting immune cell determinant or co-stimulatory molecules, such as IL-1 blockade,[41] leukocyte function antigen-1(LFA-1), very late antigen-1 and 4 (VLA-1, VLA-4),[69] CD40-CD154 pathway,[122] CD28 and CD3 (CD80 and CD86).[79] It has been reported as Cytotoxic T Lymphocyte Antigen 4 protein (CTLA4-Ig), a fusion protein acting on B7-CD28 binding, can also prolong corneal allograft survival after systemic injections in animal models by directly inhibiting T cell activation.[34] However, the efficacy of antibody therapy in humans is often limited by systemic side effects and by the development of anti-idiotypic and anti-isotypic antibodies in the recipient.[9] In addition, the blood-eye and blood-ocular surface barriers limit the access of whole antibodies into the eye. In fact, only few of these studies in experimental animals have been subsequently translated into clinical trials.[46,133]

Lately, there have also been novel approaches to immunomodulate alloimmunity that have focused on morpholine oligonucleoitides,[32] cell-specific gene therapy,[34] RNA interference,[146] and anti-VEGF therapy,[162] with promising experimental results.

6. CONCLUSIONS

Although corneal transplantation has high survival rates when performed in non-inflamed, avascular corneas, graft survival is significantly lower in HR keratoplasty due to a greatly increased risk of immune rejection. The management of HR corneal transplantation is challenging, and includes numerous preoperative, intraoperative, and postoperative measures. The key step in this management is the long-term use of local and/or systemic immunomodulatory agents. Although topical corticosteroids are almost universally utilized after keratoplasty, they are not adequate to prevent allograft rejection after HR keratplasty. For such cases, a variety of systemic immunomodulatory agents have been employed with variable success rates. Nonetheless, these medications can be associated with significant and often predictable systemic side effects. On the other hand, the optimal method of use as well as the dosage, frequency, and duration for these medications for individual cases of HR corneal transplantation have not been identified. This partly stems from the fact that the available criteria for defining HR keratoplasty may not be accurate. Developing a precise stratification of the rejection risk for each individual keratoplasty is the first step to have an individualized management strategy for optimal results in HR corneal transplantation.

In addition to currently available immunomodulatory agents, substantial research is underway to develop new strategies to reduce the risk of corneal allograft rejection. In addition to developing new targeted biologic treatments that block specific pathways implicated in transplant immunity, there are a number of tolerance-inducing protocols

including expansion of regulatory T cells through interleukin-2 therapy or use of tolerogenic APC that may hold promise in promoting corneal graft survival without the toxic side effects of systemic immunosuppressive medications.

7. LITERATURE SEARCH

This review was compiled using articles identified by searching the PubMed. The following keywords were used for the search: cornea, corticosteroids, cyclosporine A, failure, graft, high-risk, immunosuppression, keratoplasty, neovascularization, mycophenolate mofetil, rapamycin, rejection, tacrolimus, transplantation, and VEGF. All relevant articles in English were included. Those in languages other than English were considered if English abstracts were available.

Acknowledgments

Funding Source: Supported in part by NIH/NEI grant EY-12963 to RD.

ABBREVIATIONS

APC	Antigen-presenting cell
CCTS	Collaborative Corneal Transplantation Study
CsA	Cyclosporine A
DMEK	Descemet Membrane Endothelial Keratoplasty
DSEK	Descemet Stripping Endothelial Keratoplasty
HLA	Human Leukocyte Antigen
HR	High-risk
IL	Interleukin
IFN	Interferon
LR	Low-risk
MHC	Major Histocompatibility Complex
MMF	Mycophenolate Mofetil
TNF	Tumor Necrosis Factor
VEGF	Vascular Endothelial Growth Factor

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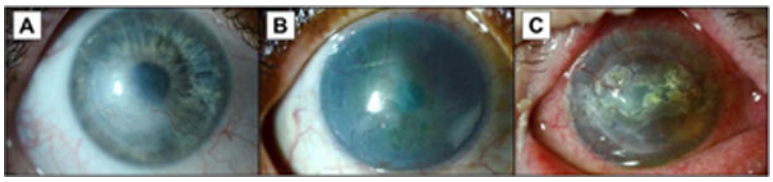

Fig. 1.

High-risk corneas with different degrees of corneal neovascularization: mild (A), in a patient with corneal scar after infectious keratitis; moderate (B), in a patient with longstanding bullous keratopathy; and severe (C), in a patient with the failure of the third corneal graft with associated ocular surface inflammation.