Commentary

Corneal transplantation: how successful are we?

The cornea is one of a few relatively immunologically privileged sites within the human body.[1] Corneal transplant surgery is the most commonly performed allograft in the United Kingdom.[2] In terms of solid tissue allografts in humans, the cornea appears to be very successful with an overall first year survival rate as high as 90%.[3] Unfortunately, the long term reality is that the overall success rate diminishes to 74% at 5 years and 62% at 10 years[3] (Fig 1). In those eyes considered to be "high risk", especially those with corneal neovascularisation or ongoing ocular inflammation, the long term 10 year survival rate is less than 35%[4] (Fig 1). Of greater concern is that these survival rates have not improved over the past 10 years.[5]

The leading cause of corneal transplant failure is allograft rejection.[5][6] Table 1 illustrates the causes of corneal graft failure using data from the Australian Corneal Graft Registry (ACGR)[5] and the Corneal Transplant Follow-up Study (CTFS).[6] As one third of failures are due to irreversible rejection episodes, are ophthalmologists being unduly complacent about the management of such events? Furthermore, is this disappointingly poor and non-improving long term outcome seen with other solid organ transplants?

A review of the United Kingdom Transplant Support Service Authority (UKTSSA) audit data for the 1985–95 time period illustrates the following survival rates. For heart transplantation, the overall survival rate at 1 year was 75%, falling to 64% at 5 years.[7] The 12 month transplant survival rate has improved from 73% to 77% between the first and second 5 year periods of the 10 year audit review.[7] Liver transplantation was less successful with overall 1 year and 5 year survival rates of 65% and 55% respectively, diminishing to 44% at 10 years[8] (Fig 1). Nevertheless, the 1 year and 5 year survival rates dramatically improved from 51% and 40% in the 1985–6 cohort to 68% and 60% in the 1991–2 cohort.[8] This trend has continued with a 72% one year survival rate for the 1993–4 cohort.[8]

The most successful solid organ transplant is the kidney, which has similar overall survival rates to the relatively immunologically privileged cornea. The 1 year survival rate for the 1984–93 time period was 92%, only falling to 86% at 3 years and 80% at 5 years. The 10 year survival rate was 63% (95% confidence interval of 61% to 66%)[9]
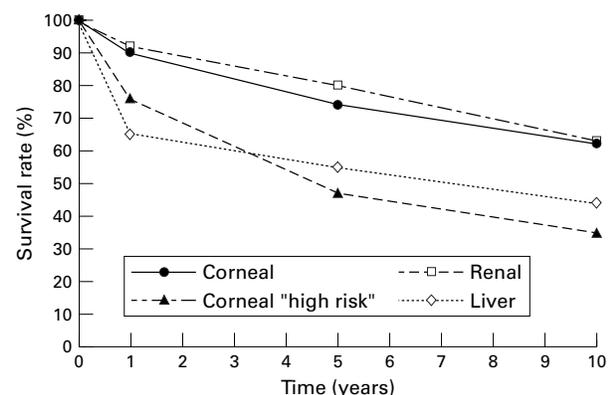
Table 1 Causes of corneal transplant failure

Cause of failure	ACGR[5]	CTFS[6]	Combined data
"Classic" rejection	32%	34%	32%
Endothelial decompensation	20%	17%	20%
Infection	14%	12%	14%
Primary technical	6%	13%	7%
Glaucoma	8%	0%	6%
Disease recurrence	0%	7%	1%
Others/unknown	20%	17%	20%
Number in series	985	201	1186

(Fig 1). This short and medium term survival rate has been sustained from the 1984–6 cohort to the 1990–3 cohort, despite an increase in the number of renal transplants by 50% to over 4300 during the latter period.

The data from the ACGR report[3–5] and the UKTSSA[7–9] highlight several important issues. Firstly, a lack of information on the outcome of UK corneal transplants beyond 18 months prevents a direct comparison with the Australian data. Secondly, for a relatively immunologically privileged site, the overall long term corneal transplant survival rates are only just comparable with those of the vascularised kidney (Fig 1). Thirdly, all other solid organ transplants have demonstrated improvements in survival rates over the past 10–15 years, unlike the cornea. Fourthly, for a similar period in time, "high risk" corneal transplantation survival rates are poor (Fig 1). So are there lessons to be learnt from those performing other forms of organ transplantation? Why do corneal allografts undergo immunological rejection episodes and fail, whereas other solid organ transplants survive long term in ever increasing numbers? Is the improved outcome in solid organ surgery the result of the use of appropriate immunosuppression, or are other factors such as tissue matching and transplantation by subspecialist surgeons playing a part in long term success?

As in other fields of transplantation, the knowledge of corneal graft rejection immunology has advanced at a phenomenal rate over the past 15 years. The major histocompatibility (MHC) molecules, both major or class I antigens (HLA-A and HLA-B) and minor or class II antigens (HLA-DR), have important parts to play in transplant immunology and rejection episodes.[10] HLA class I antigens are expressed in abundance on corneal epithelial, stromal, and endothelial cells,[11] while there is a relatively low indigenous expression of MHC class II molecules within the cornea, either on Langerhans cells in the epithelium or dendritic cells present within the stroma.[12]

Early studies[13–15] demonstrated a beneficial effect for HLA class I matching in the survival of corneal grafts, especially in high risk eyes. In one institution, long term 15 year survival rates of 80% were documented for high risk eyes matched for two or more HLA class I antigens.[15] The effects of class II matching have remained more controversial. One group has reported a significant positive effect for HLA-DR matching in high risk eyes, citing a 79% long term survival rate.[16] On the other hand, the UK based CTFS demonstrated an adverse effect in graft survival with HLA-DR matching.[14][17] A third study, the prospective multicentred American Collaborative Corneal Transplant Studies (CCTS),[18] has complicated the issue by not

Figure 1 Comparison of organ transplant survival rates over the same time period 1984 to 1996.

finding any beneficial or adverse effects for HLA matching, whether it be class I or class II antigens. The use of an intensive postoperative topical immunosuppressive regimen achieved a 65% three year survival rate, but probably prevented any effects of HLA matching from being observed. Despite the heterogeneity of these data, a meta-analysis of these comparatively small studies suggests a beneficial effect of MHC class II mismatching in high risk eyes, but only if the CCTS data are excluded.[19]

The importance of HLA matching and its effect on transplant survival has been demonstrated with other organs. In renal transplantation, the greatest success rate occurs with complete HLA class II (HLA-DR) matching[20–22] and this appears to extend into long term survival rates.[21 23] The UKTSSA audit data for renal transplantation[24] provide an in-depth analysis of HLA mismatches and their effects on graft survival. All cases of mismatching, whether MHC class I or II antigens, have adverse effects on graft survival. An additive effect is observed on the number of mismatches at each locus, with the most significant risk for failure being associated with the number of HLA-DR mismatches. A single HLA-DR mismatch has a significant 1.16 times increased risk of graft failure, increasing to 1.36 times for two HLA-DR mismatches.[24] The effect on graft survival does not appear to be limited to the first 3 months, but extends into the medium to long term, especially with two HLA-DR mismatches.[24]

A similar influence of positive HLA matching on heart transplantation survival rates has been demonstrated in a large collaborative study.[25] More recently, there has been a greater focus on HLA-DR matching. There appear to be significant short term advantages in graft survival and greater survival rates at 1 year with good HLA-DR matching compared with HLA-A or HLA-B matching.[26] In liver transplantation, the effects of HLA matching are still uncertain.[27] There is some evidence to suggest that positive crossmatching may have an adverse effect on graft outcome in the short term,[28 29] although further analysis involving greater numbers of transplants is awaited to confirm these findings.

The evidence from other solid organ transplantation suggests that HLA matching should have implications for long term graft survival rates, although the numbers of transplants evaluated in these studies are large when compared with the corneal data (Table 2). Perhaps this explains the lack of a significant effect in corneal transplantation, or has the CCTS[18] undermined the influence of HLA matching? The only real mechanism for clarifying the situation is to await the evidence from longer and larger prospective studies evaluating the role of HLA matching on corneal graft survival.

HLA matching represents one aspect of corneal transplantation immunology that needs to be addressed. In recent years, there has been a dramatic insight in demonstrating that the cornea is active in the maintenance of its relative immune privileged status.[30] Several immunological mechanisms have been demonstrated in mouse models suggesting the cornea participates in active immunomodulation. This includes the active expression of immunomodulatory cytokines such as interleukin 1a,[31] a chemoattractant for Langerhans cells,[32] which arguably act as the antigen presenting cell (APC) in the corneal graft rejection process. The topical application of interleukin 1a receptor antibody could potentially prevent the migration of Langerhans cells from the host into the donor tissue, thereby reducing the recognition by T cells through the indirect pathway.[33] Other studies have outlined the importance of the expression of cell surface inhibitors of immune effectors such as the Fas and Fas ligand.[34] These molecules are implicated in the process of immune tolerance by causing T cell apoptosis.[35] Subsequently, a lack of expression of the Fas ligand on the corneal endothelium can result in a greater risk of rejection.[36] A mechanism that stimulates the expression of this molecular complex may assist in preventing corneal graft rejection via immune tolerance.[36] Another important mechanism is the concept of anterior chamber associated immune deviation (ACAID).[37] It has been shown that antigens in the anterior chamber are detected by indigenous APCs. These pass into the general circulation via the trabecular meshwork and are carried to the spleen, thereby initiating an immune response lacking both T cell mediated delayed hypersensitivity and B cells secreting complement fixing antibodies.[38] Instead regulatory cytotoxic T cells and non-complement fixing antibodies are activated, creating a situation in which any inflammatory related immunogenic response is suppressed.[38] An activation of this mechanism before the exposure to a donor graft may prolong graft survival.[30 39]

One other potentially significant factor has also been alluded to in the 1996 ACGR.[40] In the analysis of patients undergoing corneal transplantation for keratoconus, surgeons performing more than 50 grafts per year retained a 98% nine year survival rate, compared with 86% for those performing fewer than 25 grafts per year (p = 0.003). Although the ability to manage the grafts in the postoperative period may partly account for this observation, there is undoubtedly an element reflecting the operative skill of the surgeon. As a consequence of "no stitch" phacoemulsification cataract surgery, the suturing skills of future ophthalmologists may not be as refined as those of ophthalmologists in the past. There may be a need to consider the role of the subspecialist corneal surgeon within each ophthalmic unit.

A reappraisal of the current situation is required. The acquisition of comparable data for other forms of transplantation occurring within the UK would be very beneficial for audit purposes. A clarification of the relevance and importance of the HLA antigens is essential. By utilising DNA tissue typing techniques[41 42] for HLA matching, current studies will hopefully resolve this issue in corneal transplantation. The advances in our understanding of corneal rejection immunology in the mouse need to be confirmed in the human. This knowledge needs to be applied in conjunction with the clinical evaluation of more specific therapeutic agents that modulate the immunological mechanisms of corneal graft rejection.[43–47] Finally, as with other disciplines within our specialty, such as vitreoretinal surgery, long term success may be better achieved by limiting corneal transplantation to subspecialist surgeons. By addressing these issues, it may be possible to improve overall corneal transplant survival rates by 5–10% per year and achieve better long term success with allografts in high risk vascularised corneas.

Table 2 Comparison of number of transplants evaluated in a variety of studies

Study	Tissue	Matching	Cohort	Number of transplants
Stark et al (CCTS)[18]	Cornea	DR	1986–7	419
Baggesen et al[16]	Cornea	DR	1988–90	51
Bradley et al (CTFS)[17]	Cornea	DR	1987–91	542
Opelz[21]	Kidney	DR	1988–91	3455
UKTSSA[24]	Kidney	A, B, and DR	1984–93	10 804
Opelz and Wujciak[25]	Heart	A, B, and DR	1985–92	8331

Follow up Study for giving permission to use the data which have been summarised in Table 1.

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