Sequential Bilateral Corneal Transplantation and Graft Survival

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• PURPOSE: To investigate graft survival and rejection following sequential bilateral corneal transplantation.
• DESIGN: Retrospective cohort study.
• METHODS: The study included patients with Fuchs endothelial dystrophy (FED), pseudophakic bullous keratopathy (PBK), or keratoconus who had undergone a penetrating keratoplasty (PK), endothelial keratoplasty (EK), or deep anterior lamellar keratoplasty (DALK) between 1999 and 2012. The main cohort included patients who had received a first transplant in both eyes for the same indication and a control cohort patients who had undergone a unilateral first corneal transplant. Main outcome measures were graft rejection or failure at 5 years.
• RESULTS: A total of 11 822 patients were included, of whom 9335 had a unilateral and 2487 bilateral corneal transplantation. For patients with FED ($P < .005$) and KC ($P = .03$) but not PBK ($P = .19$), a transplant in the second eye was associated with a 50% reduction in risk of graft failure within 5 years in the first eye (FED: hazard ratio [HR] 0.47, 95% confidence interval [CI]: 0.34–0.64; KC: HR 0.50, 95% CI: 0.24–1.02). For FED this was dependent on the type of transplant (EK: HR 0.30, 95% CI: 0.17–0.52; PK: HR 0.61, 95% CI: 0.42–0.88). We found no association between a transplant in the second eye and a rejection episode in the first eye (KC $P = .19$, FED $P = .39$, PBK $P = .19$).
• CONCLUSION: For FED and KC, a transplant in the second eye was associated with a reduced risk of graft failure in the first eye, independent of inter-transplant time. For FED this effect was pronounced following an EK in the first eye, where the risk of failure was reduced by 70%. (Am J Ophthalmol 2016;170:50–57. © 2016 Elsevier Inc. All rights reserved.)

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CORNEAL AND KIDNEY TRANSPLANTATION ARE THE most commonly performed types of transplantation.[1] The cornea differs from other tissues or organs in that it is a privileged site for transplantation owing to the absence of blood and lymphatic vessels, relative paucity of mature antigen-presenting cells, blood-eye barrier, and immunomodulatory factors within the eye.[2] Despite this, corneal graft failure is significant, with an overall 5-year graft survival of 71% (95% confidence interval [CI]: 69%–73%).[3] Corneal transplants fail predominantly from endothelial failure, as these cells do not divide and depend on survival of the donor endothelium. Corneal graft rejection and/or inflammation in the recipient are significant causes of endothelial failure.[4,5] Many of the risk factors associated with rejection are well recognized, including young recipient age, vascularization, sex mismatch, and previous rejection episodes.[6,7] In addition to donor- and recipient-related risk factors, graft survival is also dependent on the indication—for example, Fuchs endothelial dystrophy (FED), pseudophakic bullous keratopathy (PBK), and keratoconus (KC)—and the type of transplant—for example, penetrating keratoplasty (PK), endothelial keratoplasty (EK; Descemet-stripping endothelial keratoplasty [DSAEK] or Descemet membrane endothelial keratoplasty [DMEK]), or deep anterior lamellar keratoplasty (DALK).[8–12]

Although there is a significant increase in the rate of rejection in an eye receiving a second corneal transplant,[13] the effect of a transplant in the fellow or second eye on graft survival in either eye is unclear. This is an important question, because the common indications for corneal transplantation involve both eyes. Previous investigations have yielded conflicting results on the graft survival and rejection in patients undergoing bilateral corneal transplantation.[13–16] The UK Transplant Registry offers an opportunity to address these issues, particularly as completion of transplant outcome data are a requirement for all transplants registered with National Healthy Service (NHS) Blood and Transplant. In order to investigate whether a transplant in the fellow eye was associated with graft survival and rejection in the first eye, graft failure and rejection in patients who have had sequential bilateral and unilateral corneal transplants were compared, taking into account the indication and type of transplant.

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METHODS

IN A RETROSPECTIVE COHORT STUDY, DATA FROM THE UK Transplant Registry were provided by and analyzed in collaboration with NHS Blood and Transplant, which provided institutional board approval. In the UK Transplant Registry, blanket informed consent is obtained at the time of corneal transplantation from all patients, allowing the use of registry data for scientific purposes. The study cohort comprised patients over 18 years in the UK with FED, PBK, and KC (which are the main indications for corneal transplantation[11,17]) who had undergone either a PK, EK, or DALK between April 1, 1999 and March 31, 2012. The bilateral cohort included all patients who had received a first transplant in both eyes, where the indication was the same in both eyes and the transplant in the second eye occurred within the follow-up period for the transplant in the first eye (maximum of 5 years) and before graft failure in the first eye. A control cohort included all patients who underwent unilateral first corneal transplant for the same indication during the same period. Patients who underwent a transplant in the second eye beyond the follow-up period for the first eye or after graft failure in the first eye were also included in the control cohort. Patient and outcome data were collected at the time of the transplant and then at 1 year, 2 years, and 5 years post-transplant. All data were obtained from the UK Transplant Registry for corneas supplied through the UK corneal transplant service (CTS) eye banks.

• **POST-TRANSPLANT ENDPOINTS:** For the bilateral cohort, survival of the graft in either the first or second eye within 3 years of the time of transplant in the second eye was analyzed. In analyses comparing the bilateral and control cohorts, survival and time to rejection of the first eye graft within 5 years of the time of transplant in the first eye were the endpoints of interest. Survival times were censored for patients with a functioning graft at last follow-up. Time to rejection was censored for patients without rejection at last follow-up.

• **ANALYSIS:** Recipient and transplant characteristics of the bilateral cohort were summarized as counts and percentages. For the bilateral cohort, the median time between transplants in the first and second eye was defined as the inter-transplant time (ITT) and compared across indications using the Kruskal-Wallis test. Kaplan-Meier estimates of first and second eye graft survival from time of second eye graft were compared across ITT categories (<1 year, 1–2 years, >2 years) for each indication using the log-rank test. The association between ITT and first and second eye graft survival from time of second eye graft was further investigated using Cox regression. Nonlinear associations between ITT and first and second eye graft survival were assessed using the likelihood ratio test, comparing a linear form of ITT with the categorical form of ITT. In analyses comparing the bilateral cohort and the control cohort, survival and rejection-free rates for the first eye graft at 5 years post-transplant were estimated using the Kaplan-Meier method. The association between receiving a graft in the second eye and survival and rejection of the first eye graft was investigated using Cox regression. Because it was not known if and when a recipient would receive a transplant in the fellow eye at the time of the transplant in the first eye, a time-dependent indicator variable that changed from 0 to 1 at the time of the transplant in the second eye was used in the model, as shown in Figure 1. Regression analyses were performed separately for patients with FED, PBK, and KC, adjusting for the type of transplant (PK, DALK, and EK) as appropriate to that indication, low- or high-risk recipient

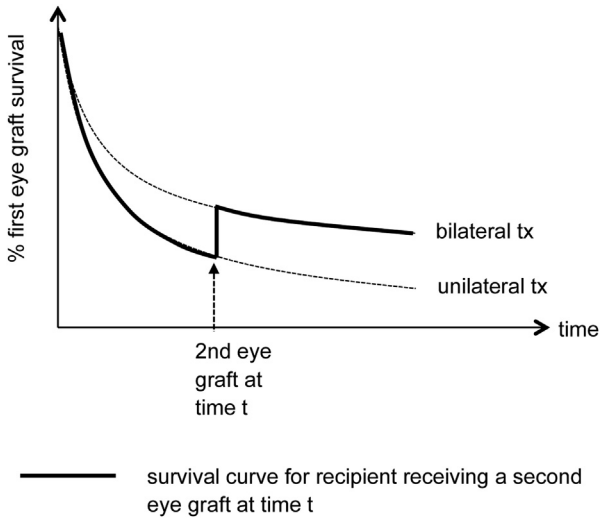

FIGURE 1. Schematic of graft survival in the first eye, illustrating a time-dependent Cox regression model. Estimated baseline survivor function before and following transplant in the second (fellow) eye shown. Recipients start on the baseline survivor curve (solid line). If a recipient never receives a transplant in their second eye, they remain on the bottom curve. At the time of the transplant in the second eye, the recipient "jumps" to the top curve, representing graft survival for the bilateral group. The vertical dotted line represents the median time to the transplant in the second eye, that is, the median time when the "jump" would occur. At the time of each graft failure in the cohort, the risk set includes only those patients who have survived to that time. This allows a direct comparison of patients with identical survival who had or had not received a second eye graft at that time. If the second eye graft for a particular recipient occurred after 1 such event, that recipient would be included in the "no second eye graft" category until the time of their second eye graft. The hazard ratio associated with the second eye graft is then interpreted as the hazard of graft failure for a recipient who received a second eye graft compared with one who did not, where the 2 recipients have the same values of all other covariates at that time.[18]

TABLE 1. Recipient and Transplant Characteristics of the Bilateral Cohort at the Time of the First Graft

Characteristic	Level	N (%)
Graft type	PK	1093 (69)
	DALK	134 (8)
	EK	357 (23)
Indication	KC	504 (32)
	FED	991 (63)
	PBK	89 (6)
Recipient sex	Male	748 (47)
	Female	836 (53)
Recipient age (y)	19–40	439 (28)
	41–60	220 (14)
	61–75	587 (37)
	>75	338 (21)
HLA-matched	No	1546 (98)
	Yes	38 (2)
High-risk	No	1123 (71)
	Yes	461 (29)
Other intraocular surgeries at time of graft	No	1071 (68)
	Yes	513 (32)
Complications at time of graft	No	1564 (99)
	Yes	20 (1)
Postoperative surgery prior to graft failure	No	1440 (91)
	Yes	144 (9)
Postoperative surgery prior to rejection	No	1451 (92)
	Yes	133 (8)
Time between first eye and second eye graft (y)	<1	322 (20)
	1–2	587 (37)
	>2	675 (43)

DALK = deep anterior lamellar keratoplasty; EK = endothelial keratoplasty; FED = Fuchs endothelial dystrophy; HLA = human leukocyte antigen; KC = keratoconus; PBK = pseudophakic bullous keratopathy; PK = penetrating keratoplasty.

Bilateral cohort defined as patients who underwent a transplant in the second eye within the follow-up period (maximum of 5 years) of the transplant in the first eye graft and prior to graft failure in the first eye graft.

(high risk defined as any ocular surface disease, corneal vascularization, or glaucoma at time of transplant), and, for KC and FED patients, postoperative intraocular surgery (predominantly cataract surgery) in either eye following the transplant prior to graft failure and/or rejection. Postoperative intraocular surgery was included as a time-dependent variable. Analyses were undertaken using SAS/STAT version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

A TOTAL OF 11 822 PATIENTS WERE INCLUDED, OF WHOM 2487 had undergone bilateral corneal transplantation within the study period. Of the 2487 patients with bilateral corneal transplants, 1584 (64%) had undergone transplants in both eyes within the follow-up period for the first eye and before graft failure in the first eye; 743 patients (30%) had a functioning graft in the first eye at last follow-up but received a transplant in the second eye beyond the known follow-up period for the first eye; 114 patients (5%) received a transplant in the second eye after having had a repeat transplant in the first eye; and 46 patients (2%) received a transplant in the second eye after graft failure in the first eye, but before or without a repeat transplant in the first eye. Therefore, 1584 patients were defined as bilateral recipients for the purpose of this study. Of these, the proportions receiving the same type of transplant in the second eye as in the first eye were as follows: EK, 98%, PK, 80%, and DALK, 78%. Follow-up data for the transplant in the second eye were missing for 59 patients (3.7%). For these recipients, only data for the transplant in the first eye were used. Recipient and transplant characteristics for the bilateral cohort are shown in Table 1.

Median ITT was higher for patients with KC (median 734 days, interquartile range [IQR] 503–1110 days) than for those with FED (median 616 days, IQR 378–981 days) and lowest for PBK (median 535 days, IQR 322–823 days) ($P < .0005$). We found no evidence of a nonlinear association between ITT and first and second eye graft survival for any indication ($P > .2$ in all cases) and hence a continuous linear form of ITT was used in all regression models. Graft survival in the first eye at 3 years from transplant in the second eye was higher for patients with KC (97.9%, 95% CI: 95.6%–99.0%) than for those with FED (92.4%, 95% CI: 89.5%–94.5%) and lowest for patients with PBK (74.7%, 95% CI: 60.1%–84.7%) ($P < .0005$). Importantly, however, within each indication first eye graft survival estimates were similar, regardless of ITT (KC $P = .16$, FED $P = .25$, PBK $P = .17$) (Figure 2). After risk adjustment, we found no association between ITT and graft survival in the first eye (KC $P = .14$, FED $P = .59$, PBK $P = .97$) (Table 2). Similar to the first eye, graft survival in the second eye at 3 years from transplant in the second eye was higher for patients with KC (94.6%, 95% CI: 91.8%–96.4%) than for those with FED (88.5%, 95% CI: 86.0%–90.6%) and lowest for those patients with PBK (75.3%, 95% CI: 61.4%–84.8%) ($P < .0005$). Again, within each indication, estimates of graft survival in the second eye graft were similar, regardless of ITT (KC $P = .80$, FED $P = .74$, PBK $P = .36$). After risk adjustment, we found no association between ITT and graft survival in the second eye (KC $P = .92$, FED $P = .07$, PBK $P = .38$) (Table 2).

For all 11 822 patients who received a first eye graft, the overall 5-year graft survival rates were 91% (95% CI: 90%–92%) for KC, 78% (95% CI: 76%–80%) for FED, and 53% (95% CI: 51%–56%) for PBK. The overall 5-year rejection-free rates were 83% (95% CI: 81%–84%) for KC, 87% (95% CI: 85%–88%) for FED, and 77% (95% CI: 75%–79%) for PBK. Analysis of first eye graft outcomes

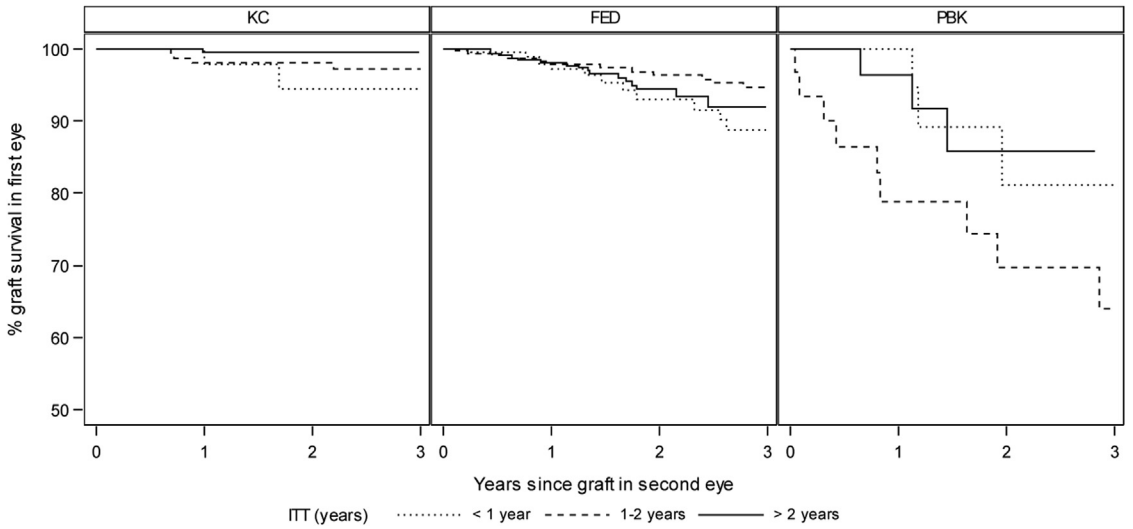

FIGURE 2. First eye graft survival, from the time of transplant in the second eye, by inter-transplant time (ITT) and indication for the bilateral cohort. Within each indication, graft survival in the first eye was similar for all categories of ITT (keratoconus [KC] $P = .16$, Fuchs endothelial dystrophy [FED] $P = .25$, pseudophakic bullous keratopathy [PBK] $P = .17$).

TABLE 2. Inter Transplant Time

Parameter	Transplants (N)	Graft Failure (N)	Hazard Ratio (95% CI) for Each Year Increase in ITT	*P* Value
Risk of graft failure in the first eye				
KC[a]	504	7	0.50 (0.19–1.31)	.14
FED[a]	991	40	1.11 (0.76–1.64)	.59
PBK[b]	89	15	0.99 (0.50–1.96)	.97
Risk of graft failure in the second eye				
KC[a]	489	22	1.02 (0.70–1.47)	.92
FED[a]	950	91	1.18 (0.99–1.40)	.07
PBK[b]	86	15	1.22 (0.79–1.87)	.38

CI = confidence interval; FED = Fuchs endothelial dystrophy; KC = keratoconus; PBK = pseudophakic bullous keratopathy.

Association between inter-transplant time and risk of graft failure in the first and second eyes within 3 years of transplant in the second eye described using Cox regression analysis. Separate models were created for each indication (KC, FED, or PBK).

[a]Adjusted for graft type, low or high risk, and postoperative surgery prior to failure.

[b]Adjusted for graft type and low or high risk.

for the whole study cohort indicated that, for patients with FED and KC, the risk of graft failure within 5 years in the first eye for patients who received a transplant in the second eye was half that of patients who did not receive a transplant in the second eye (FED: hazard ratio [HR] 0.47, 95% CI: 0.34–0.64, $P < .005$; KC: HR 0.50, 95% CI: 0.24–1.02, $P = .03$) (Table 3). By including an interaction term in each model (type of transplant in the first eye by second eye graft), we found that this effect was independent of the type of transplant in the first eye for KC ($P = .23$) but not for FED ($P = .03$, EK: HR 0.30, 95% CI: 0.17–0.52; PK: HR 0.61, 95% CI: 0.42–0.88). For patients with PBK we found no association between a transplant in the second eye and graft failure in the first eye, regardless of the type of transplant in the first eye (HR 0.69, 95% CI:0.42–1.14, $P = .61$). As an additional measure of how well the first eye graft was doing post-transplant, we also included post-transplant corrected logMAR visual acuity in the first eye as a time-varying covariate in each model. We still found that a transplant in the second eye was associated with a reduced risk of graft failure, although the confidence intervals are far wider owing to missing values of logMAR visual acuity (FED: HR 0.69, 95% CI: 0.45–1.04; KC: HR 0.49, 95% CI: 0.20–1.18; PBK: HR 0.76, 95% CI: 0.34–1.71). In addition, we found no association between a transplant in the second eye and the development of a rejection episode in the first eye, regardless of the type of transplant in the first eye (KC $P = .48$, FED $P = .11$, PBK $P = .85$) (Table 3). There were only a few cases of graft failure or rejection within 5 years of transplant where the type of transplant in the second eye was different from that for the first eye (KC: graft failure, 2 cases, graft rejection, 13 cases; FED: graft failure, 6 cases, graft rejection, 9 cases; PBK: graft failure, 1 case, graft rejection, 0 cases), so we were not able to estimate the effect of type of transplant in the second eye.

DISCUSSION

THE SUCCESS RATE OF CORNEAL TRANSPLANTATION IS affected by the indication and type of transplant,[17,19,20]

TABLE 3. Graft Failure and Rejection

Parameter	Level (Baseline)	Transplants (N)	Events (N)	Hazard Ratio (95% CI) for Graft in the Second Eye Compared With No Graft	*P* Value
Risk of graft failure in the first eye					
KC: Graft in second eye[a]	No	4104	285	1.00 (–)	
	Yes	504	7	0.50 (0.24–1.02)	.03
FED: Graft in second eye[a]	No	2966	540	1.00 (–)	
	Yes	991	47	0.47 (0.34–0.64)	<.01
PBK: Graft in second eye[b]	No	3168	984	1.00 (–)	
	Yes	89	15	0.69 (0.42–1.14)	.13
Risk of rejection in the first eye					
KC: Graft in second eye[a]	No	4104	546	1.00 (–)	
	Yes	504	58	0.72 (0.43–1.20)	.19
FED: Graft in second eye[a]	No	2966	277	1.00 (–)	
	Yes	991	78	0.85 (0.59–1.23)	.39
PBK: Graft in second eye[b]	No	3168	466	1.00 (–)	
	Yes	89	11	0.55 (0.20–1.47)	.19

CI = confidence interval; FED = Fuchs endothelial dystrophy; KC = keratoconus; PBK = pseudophakic bullous keratopathy.

Association between graft in the second eye and risk of graft failure or rejection in the first eye within 5 years of transplant in the first eye described using Cox regression analysis. Separate models were created for each indication (KC, FED, or PBK). Includes bilateral and control cohorts.

[a]Adjusted for graft type, low or high risk, and postoperative surgery prior to failure.

[b]Adjusted for graft type and low or high risk.

complications at the time of surgery,[21] and both donor[17,22,23] and recipient factors such as age, ocular surface disease, corneal neovascularization, and glaucoma.[22,24–26] The role of matching for human leukocyte antigen on graft rejection and survival is unclear.[27–29] Two of the main indications for corneal transplantation, FED and KC,[11,17] are bilateral conditions and, as such, many of these patients may undergo transplantation in both eyes. The effect of laterality and time order of bilateral corneal transplantation, however, has yielded conflicting results,[15,16,30,31] possibly owing to small single-center studies[15,30,31] or reliance on voluntary reporting.[16] In this study we used a large dataset from the UK Transplant Registry, including first and second eye grafts for 1584 recipients and first eye grafts for 10 238 recipients. Provision of follow-up data is a requirement of all surgeons undertaking corneal transplantation in the UK. One of the inherent weaknesses in studies using registry data is that the accuracy of the data will depend on the completeness and quality of the information that is collected. In the UK, the UK Transplant Registry was established to collect data nationwide in a standardized reporting format, which reduces errors owing to misclassification and misreporting. Despite the inherent weakness in this system there is a high return rate of 97% for the transplant record and high return rates of 86%, 84%, and 80% for the 1-, 2-, and 5-year follow-up forms, respectively (Jones MNA. Summary of form return rates—OTAG 15. NHS Blood and Transplant 29th Meeting of The Ocular Tissue Advisory Group. January 2016). In particular, for the bilateral cohort, there was a very high data return rate, with only 3.7% of follow-up data missing for the transplant in the second eye.

For all the included cases, the overall Kaplan-Meier estimates of graft failure and graft rejection in the first eye within 5 years was 24% and 17%, respectively, which is similar to previous reports.[19,20] The overall chance of corneal graft rejection was reduced after EK compared with PK in patients with a diagnosis of FED or PBK. Likewise, the chance of graft rejection was lower after DALK compared with PK in patients with a diagnosis of KC. Both of these findings are in concordance with literature.[4,9,32] In terms of other reported and known risk factors, the results of this and other studies confirm that the risks of corneal graft rejection and/or failure are associated with the indication and type of corneal transplant, presence of recipient risk factors such as age and inflammation, and intraoperative complications.[21,25,26] For patients who had undergone a corneal transplant in both eyes, however, for both FED and KC, the risk of graft failure in the eye that received the first transplant was reduced by 50% when the transplant in the second eye was carried out before failure of the transplant in the first eye. Importantly for patients with FED this association differed for each type of transplant in the first eye (EK: HR 0.30, 95% CI: 0.17–0.52; PK: HR 0.61, 95% CI: 0.42–0.88, $P = .03$). That is, the risk reduction was more pronounced if they had

undergone an EK in their first eye where the risk of failure was reduced by 70%, compared with a 40% reduction in risk if they had undergone a PK. Although the type of transplant in the first eye was considered, no adjustment was made for the type of transplant in the second eye owing to the small number of cases of graft failure or rejection where the type of transplant in the second eye was different from that for the first eye. The type of transplant, however, was usually the same for both eyes.

The different associations with graft survival between EK and PK may be related to the severing of corneal nerves in PK and the role of substance p secretion.[33] In a recent report of a mouse model studying the role of bilateral substance p secretion, it was noted that severing of corneal nerves in the process of unilateral recipient bed preparation abolished the corneal immune privilege in the opposite eye through a reduction in substance p.[33]

In contrast to FED and KC, we found no significant association between a transplant in the second eye and graft failure in the first eye for PBK patients. The absence of an association in patients with PBK may be explained by the generally poor graft survival for PBK.[34,35] For all 3 indications, however, we found no association between inter-transplant time and graft survival in either the first eye or the second. This would suggest that for FED and KC the improved survival of the graft in the first eye was independent of the time between transplants (within the 5-year period studied).

In contrast to graft failure, we found no significant difference in the risk of rejection following a transplant in the second eye compared with patients who did not receive a transplant in the second eye. This needs to be viewed with caution, as the definition and significance of a rejection episode would have been at the discretion of the reporting transplant surgeon. As opposed to the reporting of graft failure, low-grade inflammation and rejection may not have been evident or the patient may not have presented, so that episodes of rejection could have been missed. Such cases of low-grade rejection, however, would be expected to be at an increased risk of subsequent graft failure. Musch and Meyer[14] and Ozbek and associates[15] found no increase in rejection episodes after a transplant in the second eye, whereas Williams and associates[16] and Coster and Williams[13] found that a rejection episode in 1 eye was associated with an increased risk of rejection in the other eye. Tuft and associates[31] reported that a transplant in the contralateral eye was associated with an increased risk of rejection in the first eye that received a transplant. This conflicting evidence possibly reflects the design and length of follow-up in these studies, particularly as there is a higher risk of graft failure and rejection in the early postoperative phase, which then decreases over time.[16,36] There have also been case reports in the literature of bilateral corneal graft rejection occurring within 6 weeks to 1 year of the transplant in the fellow eye,[5,14,30] that were thought to have been initiated by the transplant in the second eye.[14,16] It has been suggested that this may be owing to systemic sensitization to mismatched tissue histocompatibility antigens present in 1 graft, some of which are also present on the graft in the contralateral eye.[16] This is supported by the finding in a rat model, where a second orthotopic corneal graft is rejected at an accelerated rate compared to the first graft.[37]

Despite the eye being a relatively immune-privileged site, it is not sequestered from the immune system. The phenomenon of anterior chamber–associated immune deviation (ACAID) has been described, in which introduction of foreign antigen into the anterior chamber of the eye results in suppression of the delayed-type hypersensitivity response to that antigen.[2] Although speculative, in sequential bilateral corneal transplantation, the first graft would potentially benefit from 2 initiations of systemically induced immune tolerance to human corneal tissue antigen, which may have contributed to the increased survival of the graft in the first eye in KC and FED. Steroid treatment has been shown to be associated with improved graft survival[38] and is likely to be an important factor in the findings of this study. Although the amount of steroid absorbed following topical administration is small, it is possible that the eye receiving the first transplant may have benefited from systemic absorption of postoperative topical steroid treatment to the second eye and thus receive additional immunoprotection.[39] Unfortunately, the duration and type of topical corticosteroid treatment in this study was not available to be included in the analysis. It may be hypothesized that first eyes of patients undergoing a second eye transplant remain on prolonged topical steroid treatment and clinical follow-up. First eyes might therefore benefit from earlier recognition and treatment of longer-term graft complications, including loose sutures or mild rejection episodes.

The present study may be subject to an inherent limitation resulting from patients with failed first grafts being more likely to receive a repeat transplant in the same eye, whereas patients with surviving first grafts may be more likely to receive a second eye transplant. In order to address this healthy-eye bias, we adjusted for factors known to be associated with graft outcome before quantifying the effect of having a second eye graft. We used postoperative intraocular surgery and visual acuity as measures of how well the first eye graft was doing post-transplant. This information, however, is only collected at 3 time points (at 1, 2, and 5 years post-transplant) and visual acuity is poorly reported at the point of graft failure. It is possible that we have not been able to accurately identify patients doing better in their first eye at the time of transplant in the second eye, since there are large periods of time between each point at which this information is captured. Reporting of measures such as postoperative intraocular surgery and visual acuity at more frequent intervals post-transplant may improve assessment of whether patients not doing as well in their first eye are less likely to have a graft in their

other eye. There may be other relevant factors that were not considered and that influence graft survival, such as type and duration of post-transplant steroid treatment. Clearly, these issues could be addressed in a prospective study.

There is little published to enable comparison to other paired organs. In cases of renal re-transplantation, Lucarelli and associates, although it was not the main purpose of their paper, found better renal function at 2 years follow-up and a reduced risk of acute graft rejection in patients without preliminary nephrectomy of the failed kidney transplant.[40] In spite of very high data return rates to the UK Transplant Registry, the proportion of first eye transplants lost to follow-up was 20% after 5 years, and the study may therefore be subject to a significant response-rate bias.

The main findings in this study are that for patients with KC and FED, a transplant in the second eye was associated with a 50% reduction in risk of graft failure in the first eye irrespective of ITT, and that for patients with FED the risk of failure was reduced by 70% if they had undergone an EK compared to a reduction of 40% if they had undergone a PK in their first eye. These results may have important implications for clinical practice. It is well established that repeat transplants in the same eye have a much higher risk of graft failure.[16] It is of note, therefore, that of the bilateral transplant recipients, only 2% received a transplant in the second eye after graft failure in the first eye and before undergoing a repeat transplant in the first eye. It is possible that patients with FED (particularly if undergoing an EK) or those with KC may benefit from a transplant in the second eye, if clinically needed, before the first transplant has failed, but a randomized study should be conducted to evaluate this.

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