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The Effect of ABO Blood Incompatibility on Corneal Transplant Failure in Conditions with Low Risk of Graft Rejection

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Abstract

Purpose—To determine whether corneal graft survival over a five-year follow-up period was affected by ABO blood type compatibility in participants in the Cornea Donor Study undergoing corneal transplantation principally for Fuchs' dystrophy or pseudophakic corneal edema, conditions at low risk for graft rejection.

Design—Multi-center prospective, double-masked, clinical trial

Methods—ABO blood group compatibility was determined for 1,002 donors and recipients. During a five-year follow-up period, episodes of graft rejection were documented, and graft failures were

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classified as to whether or not they were due to immunologic rejection. Endothelial cell density was determined by a central reading center for a subset of subjects.

Results—ABO donor-recipient incompatibility was not associated with graft failure due to any cause including graft failure due to rejection, or with the occurrence of a rejection episode. The five-year cumulative incidence of graft failure due to rejection was 6% for recipients with ABO recipient-donor compatibility and 4% for those with ABO incompatibility (hazard ratio 0.65, 95% confidence interval 0.33 to 1.25, p=0.20). The five-year incidence for a definite rejection episode, irrespective of whether graft failure ultimately occurred, was 12% for ABO compatible compared with 8% for ABO incompatible cases (p=0.09). Among clear grafts at five years, percent loss of endothelial cells was similar in ABO compatible and incompatible cases.

Conclusions—In patients undergoing penetrating keratoplasty for Fuchs' dystrophy or pseudophakic corneal edema, ABO matching is not indicated since ABO incompatibility does not increase the risk of transplant failure due to graft rejection.

INTRODUCTION

The Cornea Donor Study (CDS) was designed to examine the effect of donor age on long term corneal transplant survival for a condition at moderate risk for failure, mainly Fuchs' dystrophy or pseudophakic corneal edema. The first in a series of papers looking at the five-year results of this study reported that five-year graft survival was not related to donor age.[1, 2] The CDS was also designed to examine other secondary parameters of controversial, uncertain, or unknown clinical importance that might influence graft survival. One such objective was an assessment of ABO blood group donor-recipient compatibility and graft outcome.

The role that ABO blood group donor-recipient differences play in corneal transplant success has been a source of uncertainty since it was first reported by Havener, et. al., in 1958.[4] Incorporation of this sub-study into the CDS stems from the Collaborative Corneal Transplant Study's (CCTS) finding that ABO blood type compatibility reduced the risk of graft failure in a high-risk population.[3] This finding was an unexpected secondary finding in the CCTS, which warranted corroboration by a second study. The CDS provided an opportunity to address this important question further, albeit in eyes at low risk for rejection rather than the high-risk population of the CCTS.

METHODS

The CDS protocol was approved by the institutional review boards at each investigational site and written informed consent was obtained from each participant. Details of the CDS protocol have been reported previously.[1, 5, 6] Briefly, subjects were between 40 and 80 years of age, with a diagnosed corneal condition associated with endothelial dysfunction that placed them at moderate risk of overall graft failure but low risk of graft rejection, principally Fuchs' dystrophy and pseudophakic corneal edema. Clinical investigators and subjects were masked to all characteristics of the donor corneal tissue, including age, endothelial cell density, and donor ABO blood type.

ABO and Rh information for the donor were obtained by the eye bank from either existing medical records, or from blood typing when this information was not available in existing records. Donor tissue was assigned to a CDS subject without knowledge of the recipient's ABO type. Recipients' ABO and Rh information were obtained from either patient report, existing medical records, or from a blood test when the ABO type was not identified from another source. Results among subjects with self-reported ABO did not differ from those with ABO from a documented source such as existing medical records or from a blood test.

Preoperative management, surgical technique, and postoperative care (including prescription of medications), were provided according to each investigator's customary routine. Visits throughout the initial 6 months after penetrating keratoplasty were left to each investigator's routine. Thereafter, the minimum follow-up visit schedule included a visit between months 6 and 12 and then annual visits through five years.

Graft Failure Definition

At each visit, graft clarity was assessed. The definition of graft failure, based on the definition used in the CCTS[3, 7], was a regraft or, in the absence of regraft, a cloudy cornea in which there was loss of central graft clarity sufficient to compromise vision for a minimum of three consecutive months. The date of graft failure was the date of the first examination at which the cornea was cloudy as part of the failure event. For cases in which the cornea was not documented to be cloudy prior to regraft, the date of regraft was considered to be the failure date. Further details of the graft failure definition have been reported.[1]

Graft Rejection Definition

Graft rejection episodes were classified as *definite* when an endothelial rejection line was present in a previously clear graft and *probable* when there was inflammation (stromal infiltrate, keratic precipitates, cells in the anterior chamber, or ciliary injection) without an endothelial rejection line in a previously clear graft. The regimen for treatment of graft rejection was at the investigator's discretion and it was not possible to standardize a definition of when one rejection episode ended and the eye might be at risk for another episode. Therefore, for analysis, eyes were classified as to whether they had no rejection episodes or at least one episode.

Endothelial Cell Density

A subset of subjects participated in the Specular Microscopy Ancillary Study evaluating the relationship between donor age and endothelial cell density (ECD).[2] ECD was determined at the Specular Microscopy Reading Center (SMRC). Details on standard procedures for donor cornea preparation, capture of specular microscopic endothelial images, and ECD determination have been previously reported.[8, 9] Only subjects with five-year specular images whose transplant was classified as a success at five years were included in the analysis to determine the relationship between ABO/Rh compatibility and ECD.

ABO and Rh Compatibility

The donor and recipient were considered to be ABO compatible when one of the following conditions was met: 1) recipient and donor had the same ABO type, 2) donor was type O, or 3) recipient was type AB. The donor and recipient were considered to be Rh incompatible when an Rh+ donor was paired with an Rh- recipient.

Of the 1,090 eligible subjects enrolled in CDS, 990 (91%) had ABO data available for both the recipient and donor. Additionally, 10 cases in which the recipient was missing ABO were analyzed as compatible, because the donor was type O, and 2 cases where the donor was missing ABO were analyzed as compatible because the recipient was type AB. Thus, a total of 1,002 donor-recipient pairs were analyzed for ABO compatibility.

Of these, 808 (81%) cases had Rh data available for both the donor and recipient. Additionally, 7 cases in which the recipient was missing Rh were analyzed as compatible, because the donor was Rh− and 98 cases where the donor was missing Rh were analyzed as compatible because the recipient was Rh+. Thus, a total of 913 donor-recipient pairs were analyzed for Rh compatibility.

Statistical Methods

The primary outcome was graft failure due to rejection. Secondary outcomes included the occurrence of a rejection episode (with or without subsequent graft failure) and graft failure due to any cause.

Five-year rates of graft failure due to rejection were calculated using cumulative incidence, treating other types of graft failures as competing risks.[10] Cumulative probabilities of graft failure due to any cause were calculated using the Kaplan–Meier method. Because rejection episodes were evaluated at annual follow-up visits, life-table methods were used to compute the cumulative probability of a first rejection episode. Separate analyses were performed for definite only and definite/probable episodes. Univariate Cox proportional hazards regression models were used to assess the association of ABO- and Rh-compatibility with rejection graft failure, graft failures from all causes combined, and the occurrence of a rejection episode. No significant deviations from the proportional hazards assumptions were detected.

Evaluation of ECD at five years was restricted to subjects without graft failure at that time. Of the 1,002 pairs with ABO data, there were 321 recipients without graft failure who had a five-year ECD value available. Rh data were available for 297 of these pairs. For 102 of the 321 recipients, a donor specular image was not submitted to the SMRC for analysis, so the baseline donor ECD determined by the eye bank was used instead. The five-year ECD values were not normally distributed. Therefore the five-year ECD and the five-year percent cell loss were compared by ABO/Rh groups based on ranks. For each variable, the rank scores were transformed to have a normal distribution (van der Waerden scores). The resulting values were used as the dependent variable in ANCOVA models adjusting for baseline ECD. Percent change from baseline to five years was defined as the difference divided by the baseline ECD. This value is expressed as a percentage with negative numbers corresponding to loss of cells.

All reported p-values are two-sided. A significance level of 0.05 (with corresponding 95% confidence intervals) was used for the primary analysis of associating rejection graft failure with ABO compatibility and 0.01 (with corresponding 99% confidence intervals) was used for the secondary analyses. Statistical analyses were conducted using SAS version 9.1 software (SAS Institute Inc., Cary, NC).

RESULTS

The characteristics of the cohort included in this study were similar to those of the full CDS study population reported previously.[5, 6] Sixty-four percent of the recipients were ABO compatible with their donor, 86% were Rh compatible and 54% were both ABO and Rh compatible. ABO/Rh compatibility did not vary by any recipient or donor demographics including self-reported race/ethnicity (data not shown).

As seen in Table 1, graft failure due to rejection was not impacted by ABO compatibility. The five-year cumulative incidence of failure due to rejection was 6% for recipients who were ABO compatible with their donor compared with 4% for recipients with an ABO incompatibility (hazard ratio 0.65, 95% confidence interval 0.33 to 1.25, p=0.20). The overall graft failure rate from any cause was 15% in the ABO compatible cases and 13% in the incompatible cases (hazard ratio 0.82, 95% confidence interval 0.57 to 1.19, p=0.30).

Results were similar for rejection episodes (Table 1). The five-year incidence for a definite episode was 12% for ABO compatible compared with 8% for ABO incompatible cases (p=0.09), and 10% vs. 11% for Rh compatible vs. incompatible cases, respectively (p=0.53).

In an exploratory analysis, there was no indication that Rh compatibility was related to failure due to graft rejection or to the occurrence of one or more rejection episodes (Table 2). Among recipients without graft failure by five years, there was no significant difference in percent cell loss between ABO compatibility groups. The median endothelial cell loss from baseline to five years was 71% in both ABO compatible and incompatible groups (Table 3).

DISCUSSION

A search for immunologic factors that reduce graft survival has led researchers to examine the cornea for the presence of markers capable of inciting a rejection reaction. Among those examined have been HLA group I and group II antigens, the ABO blood group antigens and Lewis antigen. Studies of these antigens have shown some interesting, thought provoking and controversial results.

The CCTS investigated, in a prospective study, the relationship between corneal transplant failure and HLA match-mismatch. CCTS patients were eligible if there were factors present which placed them at high risk for transplant rejection, defined by the presence of two or more quadrants of corneal stromal vascularization or a history of corneal allograft rejection. The CCTS showed that matching for HLA -A, -B and -DR had no significant effect on overall graft survival, the incidence of irreversible rejection, or the incidence of rejection episodes. A secondary portion of the CCTS, which looked at ABO compatibility, showed that those who received a cornea from a blood group ABO incompatible donor had an increased risk of graft failure due to irreversible graft rejection. The adjusted estimates of the probability of graft failure from all causes at three years after surgery were 41% in the ABO incompatible group versus 31% in the ABO compatible group (RR=1.43, 95% CI 1.00-2.06, p=0.05). The estimates of graft failure due to rejection were 30% and 16% respectively (RR=1.98, 95% CI 1.25-3.13, p=0.004). [3, 11]

Because this was an unexpected secondary finding in the CCTS, corroboration of this finding in a second study was felt to be important. If it were true that ABO-compatible transplants had a lower rejection rate than incompatible ones, then ABO matching should be added to routine eye bank protocol. The CDS provided the opportunity to further address this important question, albeit in a cohort at low risk for rejection rather than the high-risk population of the CCTS.

The CDS set out to answer a number of questions regarding the role of ABO antigens. The first was whether there was a true benefit to matching ABO blood group antigens when assigning donor tissue to recipients; and whether this benefit would extend to moderate-risk patients. The second, and natural extension of the first, was to determine if a benefit did exist, whether or not it was of a magnitude that would justify changing eye banking practices in the United States.

The mechanisms by which ABO antigen incompatibility might increase the incidence of graft rejection in the normally avascular donor cornea are not as obvious as the mechanisms for vascularized solid organs. One theory is that isohemagglutinins directed against ABO blood group antigens on the corneal epithelium may provoke inflammatory reactions involving complement activation and attraction of macrophages. This process may lead to increased expression of alloantigens and cellular adhesion molecules that promote T-cell mediated allograft rejection. A second theory is that since peptides, but not carbohydrates, are recognized by T-cell receptors for antigen, the polymorphic cytoplasmic enzymes that create A and B blood group carbohydrates, rather than the A and B substances themselves, may be the targets of T-cells. A third theory is that exposure to common microorganisms may induce T-cell independent antibody production activated by the incompatible A or B antigens presented on

the corneal graft. Serologic studies of IgM and IgG titers in recipients of both compatible and incompatible grafts have been observed. However, no pattern of increased risk associated with titer increases has been detected in these small series.[12, 13]

The expression of ABO antigens is not uniform in all corneal layers. In the normal cornea, ABO blood group antigens are expressed only on epithelial cells. Ardjomand, et. al.[14] demonstrated the up-regulation of A and B blood group antigens on keratocytes and endothelial cells in corneas obtained from patients undergoing corneal transplantation for herpetic keratitis and keratoconus. They postulated that the presence of pro-inflammatory cytokines in the keratitis specimens was a cause for the up-regulated antigens. They could not explain the up-regulation of ABO antigens in 3 of 11 cases of keratoconus without histopathologic evidence of inflammation. In this same study, specimens obtained from patients with pseudophakic bullous keratopathy and Fuchs' endothelial dystrophy showed no up-regulation.

Donor corneal epithelium often sloughs in part or in total during or following corneal transplantation resulting in the replacement of a variable portion of the donors' ABO blood group antigens in the early post-operative period. Evidence from Ardjomand, et. al.[15] disclosed that small nests of donor epithelial cells with intact ABO surface antigens remain around the sutures at one year. It is unknown how long these nests of cells actually survive. However, the presence or absence of donor epithelium at the time of penetrating keratoplasty, did not affect the likelihood of graft failure or reversible allograft reaction in a randomized prospective series published by Stulting, et. al.[16]

Before 1980, there were a few studies of ABO compatibility with varying results. In these studies, surgical technique, eye banking practices, and postoperative immunosuppression were much different from today's standards. Overall graft survival was markedly lower. In a study by Mehri[17] of 68 grafts, the overall failure rates were quite high (70% for ABO compatible grafts and 61% for ABO incompatible graft). There was no distinction made between failure rates in the low-risk and high-risk groups and the results were statistically similar. Allansmith retrospectively studied 150 patients and observed a failure rate 3% higher in the incompatible group. In an analysis stratified by prognosis, results indicated that those with ABO incompatible grafts were no more likely to fail than those with ABO compatible grafts.[12] Batchelor studied 100 high-risk corneal transplant recipients with known donor and recipient ABO blood group phenotypes and reported that ABO incompatibility had no effect on the rate of graft survival at one year.[18]

More recently, two large studies of histocompatibility matching of corneal tissue involved surgical, eye banking, and patient management methods that are closer to those used today. In each of the studies, only a subset of donor-recipient pairs had known ABO blood types. Results of a study by Volker-Dieben indicated that there were no significant differences in failure rates between ABO compatible and incompatible cases.[19] A later report from the same series that included additional cases also indicated that there were no significant differences.[20] Boisjoly did not report on graft failure but did report that the relative risk of ABO incompatibility for corneal allograft reaction episodes was 0.70 (95% confidence interval of 0.38, 1.32).[21] Thus, in the series that used techniques most comparable to those used today, ABO incompatibility was not identified as a risk factor for graft failure. Small sample sizes may have limited the power necessary to find a significant result. The populations studied were racially homogeneous and included a mixture of both low and high-risk cases.

Mechanisms that influence ABO incompatibility in high-risk patients would be expected to operate in the moderate-risk population of patients entered into the CDS study. However, given the high success rate in this group, the magnitude of the absolute risk imposed by ABO incompatibility would be expected to be lower in moderate-risk patients. Our data disclosed

that rejection related graft failure, defined as a cloudy cornea sufficient to compromise vision for three consecutive months or longer, was not impacted by ABO compatibility, Rh compatibility, or combined antigen incompatibility. ABO/Rh compatibility also did not affect endothelial cell loss after five years. While we still do not know why there is an accelerated loss of endothelial cells in donor grafts up to ten years post-operatively (as compared with normal, ungrafted patients), these data suggest that ABO/Rh match-mismatch does not play a role in these changes.

How applicable are these results to other groups of corneal transplant recipients? It is reasonable to expect that these results apply to other corneal transplant conditions at low risk for rejection, such as those with avascular corneal scars and keratoconus, but one cannot reasonably extrapolate these data to high-risk conditions. The difference between the CDS ABO incompatibility findings in low-risk patients and the CCTS's incompatibility findings in high-risk patients may relate to the up-regulation of ABO antigens.

Many basic questions remain regarding the different findings in these two groups: Is the inflammation associated with corneal transplantation itself sufficient to up-regulate these antigen markers on all donor corneas; and if so how long does this last? Is there an up-regulation of ABO antigens that is dependent on the underlying host pathology? When are these markers expressed, where in the tissue, and for how long? What influence do steroids or immune modulators such as cyclosporine have on these changes when used for intermediate and long term graft management? Ongoing research in these areas may answer some of these questions.

The CDS had a large sample size and thus there is reasonable confidence that the graft failure rate due to rejection is not substantially higher than we found. Due to the low event rate, it is possible that a true difference between ABO compatible and incompatible cases could exist but not have been detected in the study. However, even if this were true, the tight confidence intervals on the event rates indicate that such a difference would be unlikely to be clinically meaningful. The lack of association of Rh compatibility with graft rejection is not surprising since we did not have a pre-specified hypothesis that there would be an association.

In conclusion, we found that matching donor and recipient for ABO blood type did not influence the incidence of graft failure due to immunologic rejection or endothelial cell failure in a corneal transplant population at low risk for rejection. The slow, progressive loss of endothelial cells (but not failure) documented by Ing, et. al.[22] and by the CDS[2] also does not appear to be influenced by ABO compatibility.

APPENDIX

CORNEA DONOR STUDY INVESTIGATOR GROUP

Listed in order of number of patients enrolled in the Cornea Donor Study are the clinical sites with city, state, site name, number of patients in parentheses and names of the investigators ordered alphabetically that participated in the study as part of the CDS Investigator Group.

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Listed in order of number of patients enrolled in the Cornea Donor Study are the eye banks with eye bank name, city, state, number of patients in parentheses and names of the eye bank directors and coordinators who participated in the study during the enrollment phase (D=Director, C=Coordinator).

EYE BANKS

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Table 1

Five-Year Graft Failure Rate According to ABO Compatibility

	Overall N=1,002	ABO Compatible N=638	ABO Incompatible N=364
Rejection Graft Failure			
# Failures	44	32	12
Cumulative Incidence ± 95% CI*	5% ± 1%	6%± 2%	4%± 2%
Hazard ratio** (95% CI*)		0.65 (0.33, 1.25)	
P-value		P=0.20	
Definite Rejection Episode			
# Failures	89	64	25
Cumulative Incidence ± 95% CI*	11% ± 2%	12% ± 3%	8% ± 3%
Hazard ratio** (95% CI*)		0.67 (0.42, 1.07)	
P-value		P=0.09	
Definite or Probable Rejection Episode			
# Failures	226	151	75
Cumulative Incidence ± 95% CI*	26% ± 3%	27% ± 4%	25% ± 5%
Hazard ratio** (95% CI*)		0.86 (0.65, 1.13)	
P-value		P=0.28	

*CI=confidence interval. The 95% confidence interval is reported for the primary analysis of graft rejection due to ABO compatibility (this table) and the 99% confidence interval for the secondary analyses (Table 2).

**ABO incompatible group compared with ABO compatible group.

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Table 2

Five-Year Graft Failure Rate According to Rh and ABO/Rh Compatibility

	Overall N=913[a]	Rh Compatible N=788	Rh Incompatible N=125	ABO and Rh Compatible N=494	ABO Compatible/Rh Incompatible N=82	ABO Incompatible/ Rh Compatible N=294	Neither ABO nor Rh Compatible N=43
Rejection Graft Failure							
# Failures	40	33	7	22	6	11	1
Cumulative Incidence ± 99% CI*	5% ± 2%	5% ± 2%	6% ± 6%	5% ± 3%	8% ± 8%	4% ± 3%	3% ± 7%
Hazard ratio** (99% CI*)		1.33 (0.46, 3.89)			1.63 (0.50, 5.33)	0.82 (0.32, 2.12)	0.51 (0.04, 7.09)
P-value		0.49				0.51	
Definite Rejection Episode							
# Failures	80	67	13	45	10	22	3
Cumulative Incidence ± 99% CI*	10% ± 3%	10% ± 3%	11% ± 7%	11% ± 4%	13% ± 10%	8% ± 4%	7% ± 10%
Hazard ratio** (99% CI*)		1.21 (0.56, 2.65)			1.32 (0.54, 3.25)	0.80 (0.41, 1.57)	0.75 (0.16, 3.48)
P-value		0.53				0.58	
Definite or Probable Rejection Episode							
# Failures	203	172	31	111	23	61	8
Cumulative Incidence ± 99% CI*	26% ± 4%	25% ± 5%	28% ± 12%	26% ± 6%	30% ± 14%	25% ± 8%	23% ± 20%
Hazard ratio** (99% CI*)		1.14 (0.69, 1.88)			1.25 (0.69, 2.25)	0.90 (0.60, 1.36)	0.81 (0.32, 2.08)
P-value		0.51				0.55	

[a] Rh data missing for 89 donor-recipient pairs.

* CI=confidence interval. The 95% confidence interval is reported for the primary analysis of graft rejection due to ABO compatibility (Table 1) and the 99% confidence interval for the secondary analyses (this table).

** Rh groups: the hazard ratio is generated for the comparison of Rh incompatible with the Rh compatible group; ABO/Rh groups: the hazard ratio is generated for the comparison of each ABO/Rh group with the ABO and Rh compatible group.

Table 3

Endothelial Cell Density (ECD) in Eyes without Graft Failure at Five Years

	N	Baseline Endothelial Cell Density (25th, 75th percentiles)	Five-Year Endothelial Cell Density (25th, 75th percentiles)	% Change from Baseline to Five Years (25th, 75th percentiles)[b]	P-value[c]
Overall	321[a]	2692 (2481- 2887)	765 (570- 1267)	−71% (−77% to −54%)	
ABO Compatibility (N=322)					0.95
Compatible	196	2660 (2494-2878)	783 (565-1262)	−71% (−78% to −54%)	
Incompatible	125	2726 (2452-2904)	742 (574-1267)	−71% (−77% to −54%)	
Rh Compatibility (N=298)[d]					0.85
Compatible	251	2692 (2492, 2882)	758 (566-1282)	−70% (−78% to −53%)	
Incompatible	46	2684 (2438, 2938)	740 (580-1267)	−73% (−77% to −57%)	
ABO/Rh Compatibility (N=298)[d]					0.43
ABO and Rh Compatible	152	2687 (2508-2870)	781 (547-1289)	−70% (−79% to −54%)	
ABO Compatible/Rh Incompatible	30	2583 (2429-2842)	819 (607-1382)	−70% (−76% to −48%)	
ABO Incompatible/Rh Compatible	99	2700 (2448-2899)	742 (578-1212)	−71% (−77% to −52%)	
Neither ABO nor Rh Compatible	16	2866 (2542-3035)	701 (551-1102)	−75% (−80% to −64%)	

[a] Data are from an ancillary study that only involves a subset of CDS subjects; this analysis excludes subjects with a graft failure by five years.

[b] Percent change from baseline = ECD at five years minus ECD at baseline divided by ECD at baseline and multiplied by 100%. A negative number indicates loss of cells.

[c] ECD values not normally distributed; comparisons based on ranks. Rank scores transformed to have normal distribution (van der Waerden scores). P-values generated for % change from baseline to five years.

[d] Rh data missing for 24 donor-recipient pairs.