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Effectiveness of histocompatibility matching in high-risk corneal transplantation: a summary of results from the collaborative corneal transplantation studies

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Summary

The Collaborative Corneal Transplantation Studies (CCTS) were designed to evaluate the effect of donor-recipient histocompatibility matching and crossmatching on the survival of corneal transplants in high-risk patients. Corneas were allocated to the 419 patients in the double-masked Antigen Matching Study on the basis of HLA-A,-B and HLA-DR antigen match. ABO blood group compatibility was determined but not used for recipient selection. The 37 patients in the Crossmatch Study were randomly assigned to receive a cornea from either a positively or negatively crossmatched donor. All patients received topical steroid therapy according to a standard protocol. Matching for HLA-A,-B and HLA-DR antigens had no effect on overall graft survival, the incidence of irreversible rejection, or the incidence of rejection episodes. The positive group in the Crossmatch Study had fewer graft failures, rejection failures, and rejection episodes than the negative group; however, these differences were not statistically significant. The estimated proportion of eyes with failure from rejection by 3 years was 30% for the ABO-incompatible group and 16% for the ABO-compatible group (relative risk, 1.98; 95% confidence interval, 1.15 to 3.13). These studies demonstrate that, for high-risk patients who are immunosuppressed by topical steroid therapy: 1) neither HLA-A.-B nor HLA-DR antigen matching substantially reduced the likelihood of corneal graft failure; 2) a positive donor-recipient crossmatch did not increase the risk of corneal graft failure; and 3) ABO blood group matching may be effective in reducing the risk of graft failure from rejection.

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INTRODUCTION

More than 40,000 corneal transplants were performed in the United States in 1991, making the cornea one of the most commonly transplanted of human organs and tissues.[1] Corneal transplantation is also one of the most successful transplantation procedures, with two-year survival rates greater than 90% for initial grafts into avascular corneas.[2-5] However, when the patient is at high-risk for a graft rejection

because of vascularization of the recipient bed or previous graft failure, transplant survival is reduced to as low as 35%, with corneal graft rejection being the greatest cause of corneal transplant failure in humans.[6]

Early studies showed variable effects of matching HLA-A,-B antigens on the incidence of immunologic rejection episodes and graft failure.[2,7-9] More recent clinical studies indicated that HLA-A,-B antigen matching reduces graft reactions, while mixed results were reported for HLA-DR matching.[10-14]

Providing recipients with negatively crossmatched corneas had been reported to increase survival rates, but only in comparison to historical controls.[9-15] The few studies of the influence of ABO compatibility on graft survival have produced mixed results.[6,10-13]

If use of donor-recipient matching for corneal transplantation were instituted in the United States, it would radically change the practice of donor cornea distribution, substantially increasing the cost and waiting time for corneal transplantation. The cost of HLA typing of donor and recipients alone would be more than $4 million per year; establishing and maintaining a distribution network would entail additional costs. Thus, the Collaborative Corneal Transplantation Studies (CCTS) were designed and supported by the National Eye Institute to evaluate whether HLA antigen matching, donor-recipient crossmatching, or ABO compatibility, affects graft outcome in high-risk keratoplasty patients.

METHODS

The CCTS consisted of two trials.[16,17,18] The Antigen Matching Study (AMS) was designed to asess the effect of HLA-A,-B and HLA-DR antigen matching on corneal graft survival in patients who were at high risk for allograft rejection and who had *no* detectable lymphocytotoxic antibodies. The AMS was a prospective, double-masked, clinical trial of patients assigned corneas with different levels of HLA matching. All AMS patients received corneas from a negatively crossmatched donor. Comparison groups for data analysis were designated at the beginning of the study as 0 or 1 antigens mismatched (high match) versus 2 to 4 antigens mismatched (low match) for HLA-A,-B and as 0 antigens mismatched (high match) versus 1 or 2 antigens mismatched (low match) for HLA-DR antigens. Corneas were allocated without regard to ABO type. The intent was to compare graft survival in the ABO compatible and ABO incompatible groups for corneas allocated on the basis of HLA match.

The Crossmatch Study (CS) was designed to assess the effect of crossmatching on corneal graft survival in high-risk patients *with* detectable lymphocytotoxic antibodies. The CS was a prospective, randomized, double-masked clinical trial of patients assigned corneas from either positively or negatively crossmatched donors, designated as the positive and negative groups, respectively.

Time to irreversible corneal graft due to any cause was the primary outcome measure for both the AMS and the CS. Time to the first immunologic graft reaction, time to graft failure attributable to allograft rejection, and visual acuity were secondary outcome measures.

Candidates for corneal transplantation were screened at six clinical centers in the U.S. between May 1986 and September 1989. Eligibility criteria were designed to include patients with uncompromised immune systems who were at high risk for graft rejection. The study eye was required to have two or more quadrants of corneal stromal vascularization and/or a history of previous graft rejection. Patients who were

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The results of the HLA-A,-B, and HLA-DR typing and screening for lymphocytotoxic antibodies of all CCTS patients antigen typing and antibody screening results throughout the study. Donor corneas were allocated to the best-matched recipient through a computerized algorithm. The method of corneal allocation in the AMS increased the likelihood of patients receiving either a high HLA-A,-B match or a high HLA-DR match while limiting the waiting time to 18 months. The CS patients were randomly assigned to the positive or negative crossmatch group.

All patients were subject to a common set of examinations, treatments and evaluation procedures. A standard protocol for administration of postoperative medications and for recognition and treatment of immunologic allograft reactions was followed.[17]

RESULTS

A total of 419 patients were enrolled in the AMS and 37 patients were enrolled in the CS. Within the AMS, 137 (33%) of the 419 patients were in the HLA-A,-B high match group and 199 (47%) were in the HLA-DR high match group; 294 (70%) of the 417 patients having donors known blood group ABO were ABO compatible with their donors.

All patients had at least 18 months of follow-up for graft outcome after keratoplasty. Information on graft outcome was available through 2 years for 415 patients (91%), through 3 years 313 patients (69%), through 4 years for 184 patients (40%), and through 5 years for 62 patients (14%). Only 4% of all regularly scheduled follow-up visits were missed. Five percent of the AMS patients and 16% of the CS patients died during the follow-up period. Only 1% of the AMS patients missed their last two consecutive visits and were considered lost to follow-up. Patients could correctly explain their prescribed medication usage more than 95% of the time when questioned at each regularly scheduled visit.

Outcomes for HLA-A,-B Matching in the AMS

The incidence of overall graft failure was similar in the HLA-A,-B high and low match groups (Fig 1, p = .35). Thirty-seven percent of the grafts in the low match group and 33% of the grafts in the high match group had failed. Rates of graft failure due to rejection were 26% fot the low match group and 21% for the high match group (Fig 2, p = .34). The low and high match groups had similar rates of graft reaction (Fig 2, p = .38). Controlling for possibly confounding covariates, reduced the small observed benefit for a high HLA-A,-B match for each of the three outcomes.

Outcomes for HLA-DR Matching in the AMS

The HLA-DR high and low match groups had nearly identical rates of graft failure (Fig 3, p = .95). At 3 years after surgery, 24% of the grafts in the low match group and 25% of the grafts in the high match group had failed due to rejection (Fig 4, p = .60). The proportion of eyes having at least one graft reaction was similar between the HLA-DR comparison groups (Fig 4, p = .77). Controlling for possibly confounding covariates yielded adjusted estimated relative risks that were nearly identical to the unadjusted estimates.

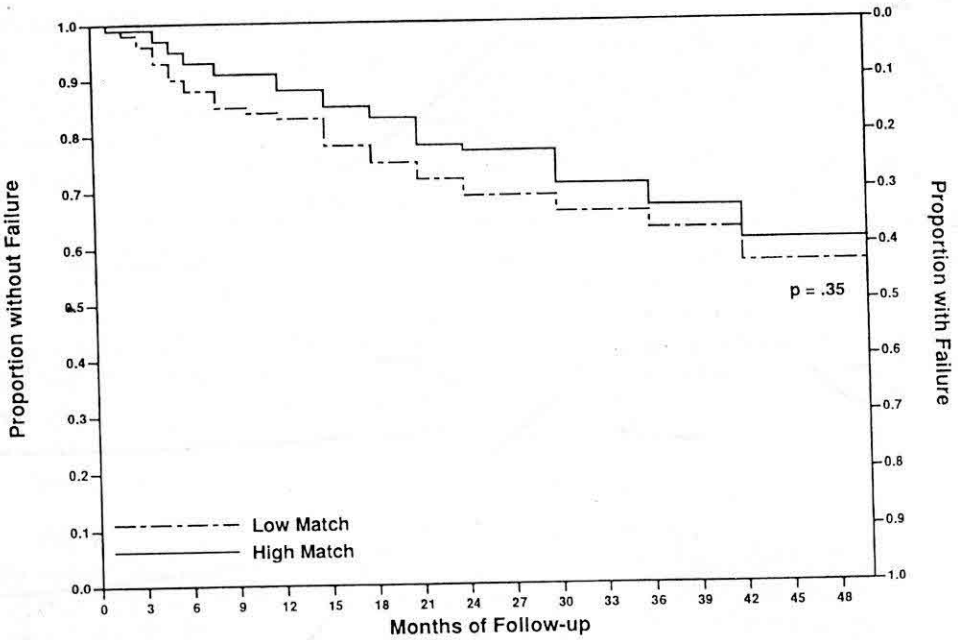

Fig 1. Any Graft Failure By Time and Match on HLA-A,-B
CCTS AMS

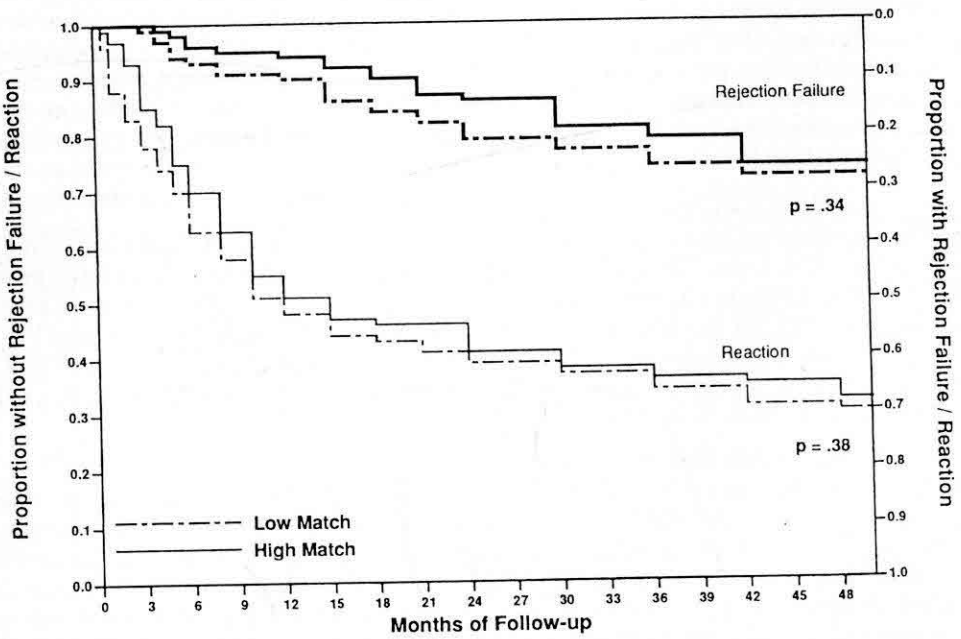

Fig 2. Reaction and Rejection Failure and Match on HLA-A,-B
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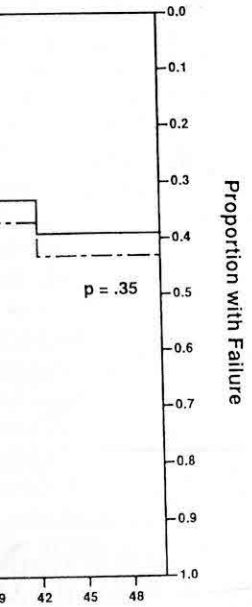

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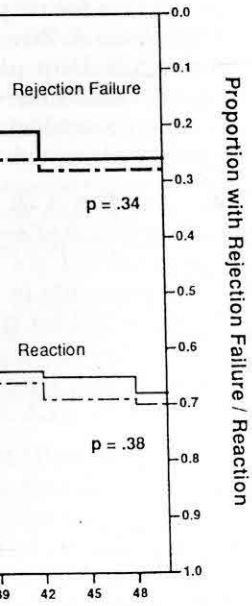

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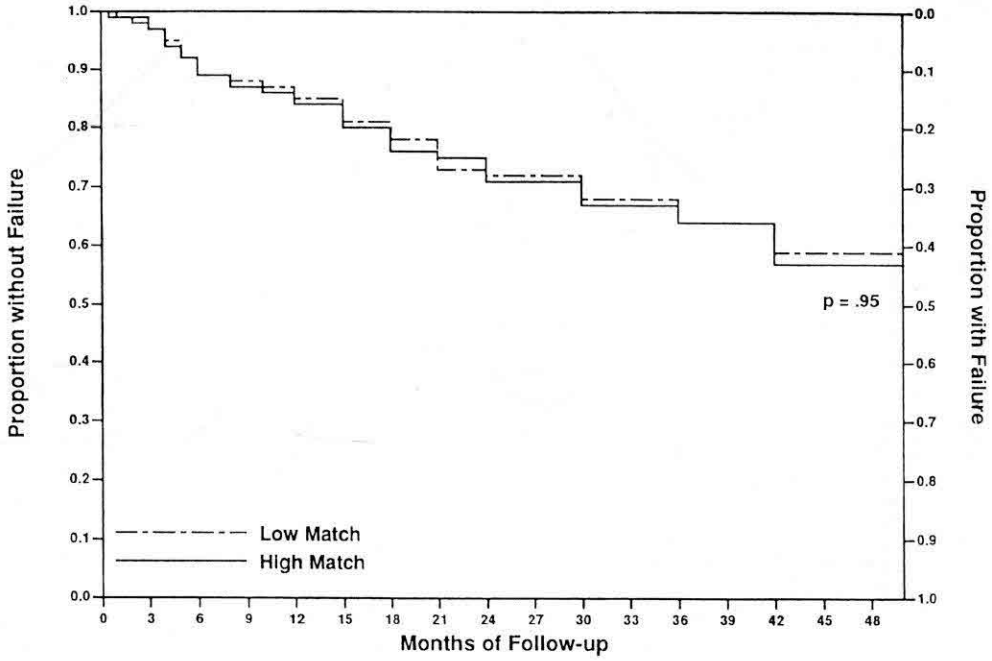

Fig 3. Any Graft Failure By Time and Match on HLA-DR
CCTS AMS

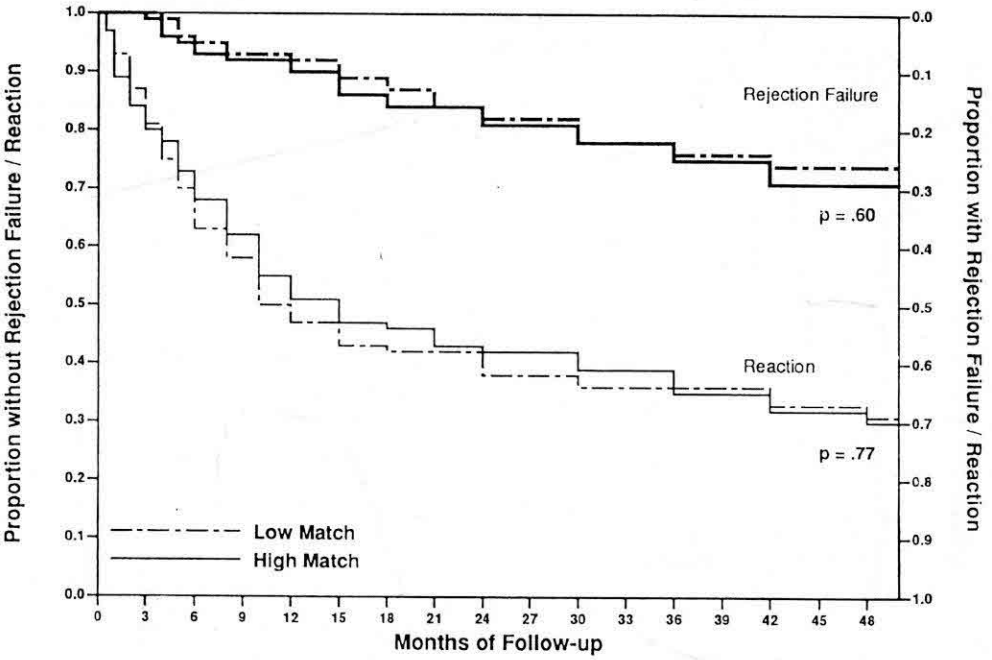

Fig 4. Reaction and Rejection Failure and Match on HLA-DR
CCTS AMS

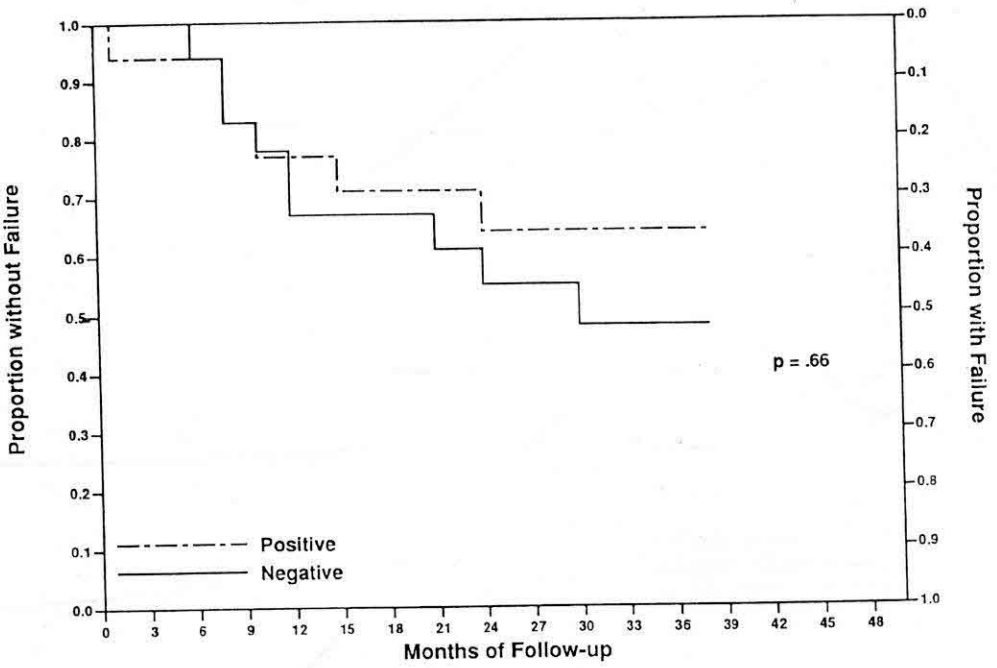

Fig 5. Any Graft Failure By Time and Crossmatch Group
CCTS CS

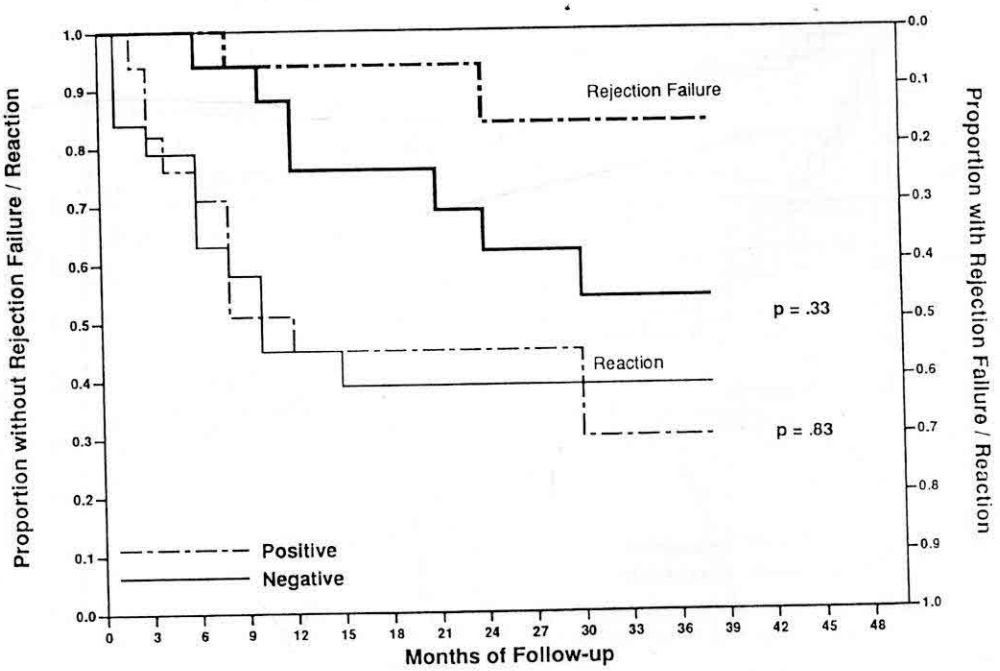

Fig 6. Reaction and Rejection Failure by Time and Crossmatch Group
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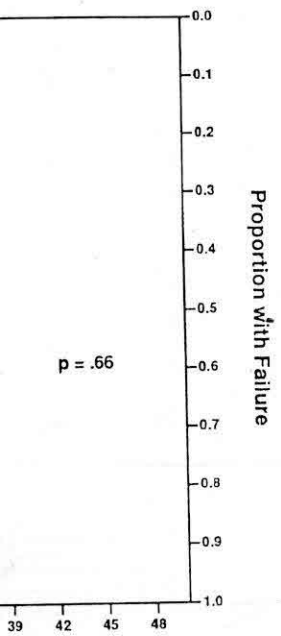

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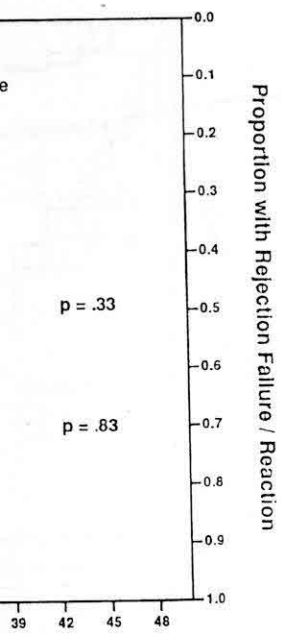

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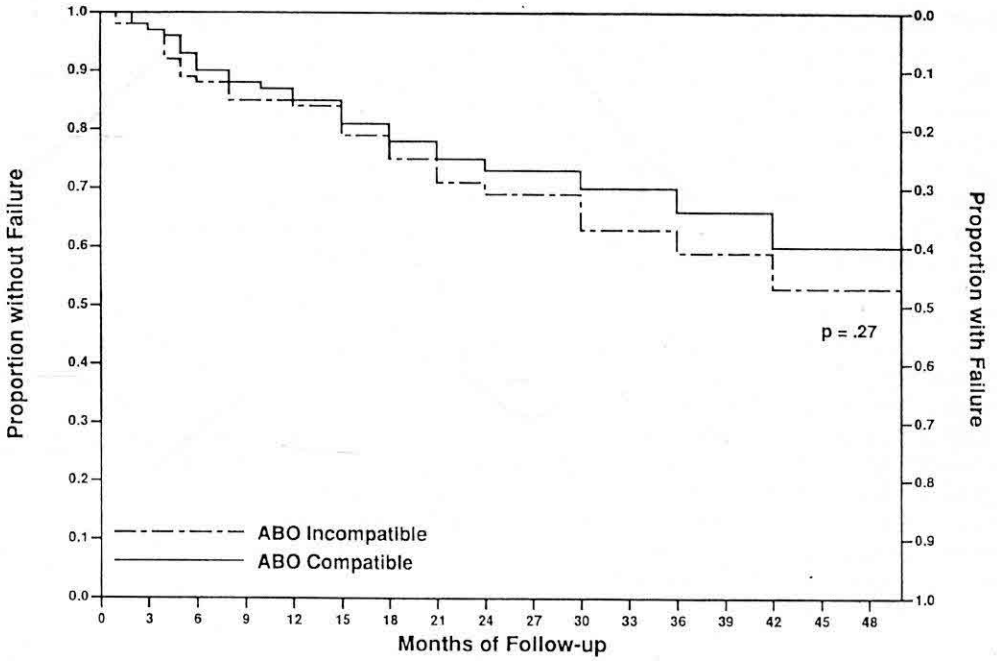

Fig 7. Any Graft Failure By Time and ABO Compatibility
CCTS AMS

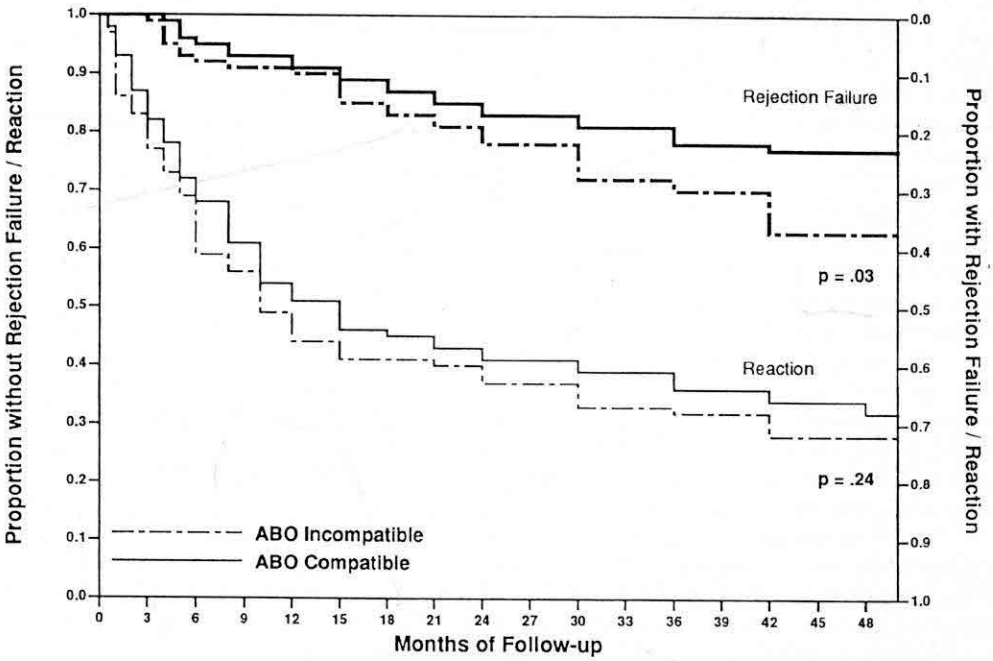

Fig 8. Reaction and Rejection Failure by Time and ABO Compatibility
CCTS AMS

Outcomes for the Crossmatch Study

The positive and negative groups had a similar incidence of overall graft failures (Fig 5, p = .66). Thirty-six percent of grafts in the positive group and 45% in the negative group had failed. The positive and negative groups also had similar rates of graft reaction (Fig 6, p = .83). Fifty-five percent of the positive group and 61% of the negative group had had a graft reaction. The rate of graft failure due to rejection was much higher in the negative group than in the positive group although it was not statistically significant (Fig 6, p = .33). At 2 years after surgery, 16% grafts in the positive group and 38% in the negative group had failed due to rejection.

Outcomes for ABO Compatibility in the AMS

The ABO incompatible group had more graft failures than the ABO compatible group (Fig 7, p = .27). Controlling for possibly confounding covariates increased the estimated benefit of ABO compatibility. Adjusted 3-year failure rate estimates were 41% for the incompatible group and 31% for the compatible group (p = 0.05). The ABO incompatible group had a slightly larger proportion of eyes with graft failure attributable to rejection (Fig 8, p = .03). At 3 years, adjusted rejection failure rate estimates were 30% for the incompatible group and 16% for the compatible group (p = .004). Sixty-eight percent of the incompatible group and 64% of the compatible group had had at least one reaction (Fig 8, p = .24).

DISCUSSION

The results of the CCTS were somewhat unexpected. At the inception of the Antigen Matching Study, it was hypothesized that increasing degrees of HLA-A,-B and/or HLA-DR matching would reduce the rate of graft reactions and failures. However, the CCTS found no evidence of a large beneficial effect of HLA-A,-B or HLA-DR donor-recipient matching on the rate of overall graft failure, the rate of failure due to rejection or the rate of reactions. Similarly, for the Crossmatch Study, it was hypothesized that, among recipients with detectable preoperative lymphocytotoxic antibodies, a positive donor-recipients crossmatch prior to keratoplasty would be associated with a higher rate of graft reaction and failure. In contrast, a positive donor recipient crossmatch prior to keratoplasty appeared, if anything, to correlate with improved graft outcome. At the very least, the inconsistency of these two reasonable hypotheses with the CCTS data underscores how little is actually known about the important factors that contribute to corneal allograft failure in high-risk patients.

The design of the CCTS differed from previous studies in way that may explain the apparent lack of effect of HLA matching and crossmatching on corneal graft survival. Notably, the postoperative topical immunosuppressive regimen used in the CCTS was more intensive than that used by the two most recent studies showing an effect of HLA matching on corneal graft survival.[10,14] A beneficial effect of HLA matching on graft survival may have been abrogated in the CCTS by postoperative steroids.

Any beneficial effect of ABO matching on graft survival has major implications for high-risk corneal transplantation. While ABO matching has been shown in several other organ transplantation studies to enhance graft survival, it has never been reported in corneal transplantation research. Matching donor and recipient for ABO compatibility would be relatively easy and inexpensive to implement; the testing is nor difficult, and approximately 70% of donor and recipient pairs would be compatible by chance. Compared to the logistical problems and expense of HLA matching (which

we conservatively estimate to be $4 million per years in the U.S. for high risk patients), providing ABO compatible donors may significantly improve the outcome of corneal transplantation at a relatively low cost.

The overall failure rate of 35% at 3 years after surgery in the CCTS was lower than expected for high-risk cases. Previous studies have indicated that corneal graft failure due to rejection can occur in up to 65% of eyes.[2] The patients included in the CCTS were high-risk as defined by stromal vascularization in at least two quadrants (82%) or previous corneal graft failure due to rejection in the study eye (70%). We had conservatively estimated before the CCTS began that the rate of corneal graft failure from rejection would be 45% at 2 years after transplantation, but our estimated failure rate from *all* causes was only 28% at 2 years.

We attributed the relatively high success rate in the CCTS to the use of intensive topical steroids postoperatively, close personal follow-up by the ophthalmologists and the study coordinators, excellent compliance and knowledge of the study medications by the patients, and the encouragement of the patients to report any unusual sign or symptom. Given the current state of knowledge of the mechanisms involved in corneal transplant failure, perhaps the most important conclusion to be drawn from the CCTS is that high-dose postoperative steroids, good compliance, and close follow-up are the keys to successful corneal transplantation in the high-risk recipient.

REFERENCES

1. *Activity Report, 1992.* Washington, DC: Eye Bank Association of America; 1992.
2. **Batchelor J. R., Casey, T. A., Gibbs, D. C. et al.:** HLA matching and corneal grafting. *Lancet.* 1976; 1:551-554.
3. **Völker-Dieben H. J. M., Kok-van Alphen C. C., Lansbergen Q., Persijn G. G.:** Different influences on corneal graft survival in 539 transplants. *Acta Ophthalmol.* 1982; 60:190-202.
4. Council on Scientific Affairs. Report on the Organ Transplant Panel: corneal transplantation. *JAMA.* 1988; 259:719-722.
5. **Price F. W., Whitson W. E., Marks R. G.:** Graft survival in four common groups of patients undergoing penetrating keratoplasty. *Ophthalmology.* 1991; 98:322-328.
6. **Nelken E., Nelken D., Michaelson I. C., Gurevitch J.:** Late clouding of experimental corneal grafts. *Arch Ophthalmol.* 1961; 65:584-590.
7. **Allansmith M. R., Fine M., Payne R.:** Histocompatibility typing and corneal transplantation. *Trans Am Acad Ophthalmol Otolaryngol.* 1974; 78:445-460.
8. **Ehlers N., Ahrons S.:** Corneal transplantation and histocompatibility. *Acta Ophthalmol.* 1971; 49:513-527.
9. **Stark W. J., Taylor H. R., Bias W. B., Maumenee A. E.:** Histocompatibility (HLA) antigens and keratoplasty. *Am J Ophthalmol.* 1978; 86:595-604.
10. **Boisjoly H. M., Roy R., Dubé I. et al.:** HLA-A,-B and -DR matching in corneal transplantation. *Ophthalmology.* 1986; 93:1290-1297.
11. **Völker-Dieben H. J. M., Kok-van Alphen C. C., Lansbergen Q., Persijn G. G.:** The effect of prospective HLA-A and -B matching on corneal graft survival. *Acta Ophthalmol.* 1982; 60:203-212.
12. **Völker-Dieben H. J. M.:** Factors which may influence corneal graft survival. In: *The Effect of Immunological and Non-immunological Factors on Corneal Graft Survival.* The Hague, The Netherlands: Dr W. Junk Publishers; 1984: 41-66.
13. **Völker-Dieben H. J. M., DiAmaro J., Kok-van Alphen C. C.:** Hierarchy of prognostic factors for corneal allograft survival. *Aust N Z J Ophthalmol.* 1987; 15:11-18.
14. **Sanfilippo F., MacQueen J. M., Vaughn W. K., Foulks G. N.:** Reduced graft rejection with good HLA-A and -B matching in high-risk corneal transplantation. *N Engl J Med.* 1986; 315:29-35.
15. **Foulks G. N., Sanfilippo F. P., Locascio J. A., MacQueen J. N., Dawson D. V.:** Histocompatibility testing for keratoplasty in high-risk patients. *Ophthalmology.* 1983; 90:239-244.

16. Collaborative Corneal Transplantation Studies Research Group. Design and methods of the Collaborative Corneal Transplantation Studies (CCTS). *Cornea*. 1993; 12:93-103.
17. Collaborative Corneal Transplantation Studies Group. *Manual of Operations*. Springfield, Va: National Technical Information Service; 1989. Publication NTIS PB 90-134925/AS.
18. Collaborative Corneal Transplantation Studies Research Group. Effectiveness of histocompatibility matching in high risk corneal transplantation. *Arch Ophthalmol*. 1992; 110:1392-1403.

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