

THE EFFECT OF TOLERANCE TO NONINHERITED MATERNAL HLA ANTIGENS ON THE SURVIVAL OF RENAL TRANSPLANTS FROM SIBLING DONORS

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ABSTRACT

Background During pregnancy and nursing, a baby's developing immune system is intimately exposed to the mother's antigens. To determine whether this exposure is of clinical benefit to patients who later receive an allograft as an adult, we analyzed the outcome of primary renal transplantations from sibling donors.

Methods We retrospectively studied graft survival and rejection episodes in 205 patients who had received renal transplants at nine centers between 1966 and 1996 from sibling donors bearing maternal or paternal HLA antigens not inherited by the recipient. The sibling donors were categorized by analysis of family HLA-typing data.

Results In the multicenter analysis, graft survival was higher 5 years and 10 years after transplantation in recipients of kidneys from siblings expressing maternal HLA antigens not inherited by the recipient than in recipients of kidneys from siblings expressing paternal HLA antigens not inherited by the recipient (86 percent vs. 67 percent at 5 years and 77 percent vs. 49 percent at 10 years, $P=0.006$ for both comparisons). Paradoxically, there was a higher incidence of early rejection in the former group, suggesting that fetal and neonatal exposure to maternal antigens results in immunologic priming. Pretransplantation transfusions of donor blood reduced the incidence of acute rejection while preserving the beneficial effect of tolerance to noninherited maternal antigens on graft survival. Since 1986, new immunosuppressive drugs have lessened the short-term, but not the long-term, survival advantage of grafts expressing maternal HLA antigens not inherited by the recipient.

Conclusions In the transplantation of a kidney from a sibling donor who is mismatched with the recipient for one HLA haplotype, graft survival is higher when the donor has maternal HLA antigens not inherited by the recipient than when the donor has paternal HLA antigens not inherited by the recipient. (N Engl J Med 1998;339:1657-64.)

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DESPITE important advances in immunosuppressive therapy, rejection remains the leading cause of graft failure in recipients of renal transplants. Host T cells play a critical part in the rejection process, which involves the recognition of donor-derived histocompatibility antigens as well as the delivery of costimulation to the T cells.¹ In general, graft survival is optimal when the

donor is antigenically similar to the recipient, as is the case with an HLA-identical sibling donor or a fully HLA-matched cadaveric donor (i.e., matched with the recipient for antigens encoded at HLA loci A, B, and DR). This greater transplant survival is due to reductions in acute and chronic rejection in recipients with such donors.² However, because the HLA loci are highly polymorphic, well-matched donors are rare. Therefore, physicians who perform transplantations have long sought to exploit natural³ and artificially induced⁴ immunologic tolerance to foreign histocompatibility antigens as a means of improving the survival of antigenically mismatched grafts while reducing the need for long-term immunosuppressive therapy.

The introduction of maternal cells and antigens into the fetus during pregnancy gives rise to a form of tolerance to maternal histocompatibility antigens in adult life. For example, in one study, Rh-negative women whose mothers were Rh-positive were significantly less likely to form anti-Rh antibody during pregnancy with an Rh-positive fetus than were Rh-negative women whose mothers were also Rh-negative.⁵ A similar phenomenon in humoral immunity occurs with respect to the HLA system: about half the subjects exposed as adults to allogeneic HLA antigens during multiple blood transfusions were unable to form antibodies against one or more noninherited maternal HLA antigens, whereas their humoral response to noninherited paternal HLA antigens was not limited. The maternal influence, however, did not result in a uniform lack of immunologic responsiveness. For example, approximately 50 percent of the adult subjects had no deficiency in their humoral response to noninherited maternal HLA antigens,⁶ and there were no base-line differences in the response of cytotoxic T lymphocytes to noninherited maternal, as compared with paternal, HLA antigens.^{7,8}

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The immunogenetic basis of HLA-allele inheritance in the setting of renal transplantation from a living related donor is shown in Figure 1. If the mother has alleles *A* and *B* of the gene for an HLA antigen and the father has alleles *C* and *D* of the same gene, each offspring will receive one allele, *A* or *B*, from the mother, and one, *C* or *D*, from the father. If the offspring (for example, the female transplant recipient in this hypothetical family) receives allele *B* from her mother, then *A* is described as a noninherited maternal allele. Similarly, if she receives *D* from her father, then *C* is the noninherited paternal allele. However, she may have been exposed during fetal life to the product of the maternal *A* allele but not the paternal *C* allele, perhaps leading to tolerance to the corresponding HLA antigen. In the example in Figure 1, all four prospective donors would be expected to have the same degree of HLA-antigen mismatching with respect to the recipient at the HLA loci: one haplotype mismatch, or one mismatch each at HLA-A, B, and DR. In the case of graft donors *AB* (mother) and sibling *AD*, maternally induced tolerance to the *A*-encoded HLA antigen would be predicted to prevent increased graft loss due to acute and chronic rejection, which is the usual consequence of an HLA-antigen mismatch. A graft from the father or from sibling *CB* would presumably be subject to attrition caused by host responses to the paternal *C*-encoded antigens.

Given the universal nature of maternal antigens, it was hoped that tolerance to them might open new

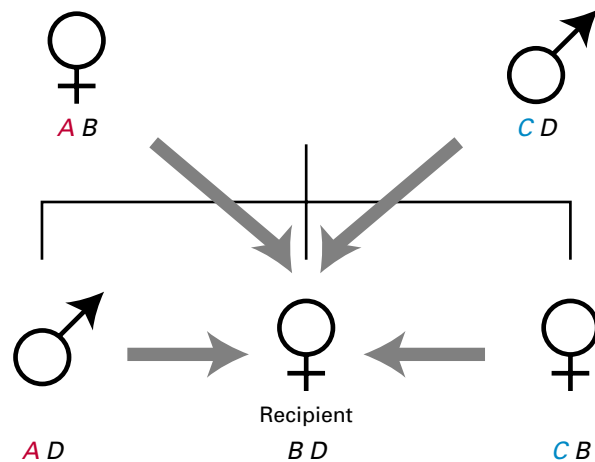


Figure 1. Hypothetical Case of Inherited and Noninherited Maternal and Paternal HLA Alleles in a Female Transplant Recipient with End-Stage Renal Disease.

Arrows indicate the potential sources of kidney transplants from living related donors (two parents and two siblings). All the potential donors have HLA antigens inherited by the recipient but also express either maternal antigens not inherited by the recipient (red) or paternal antigens not inherited by the recipient (blue).

avenues to improved transplant survival in humans.⁹ However, it was soon discovered that there was no difference between the survival of renal allografts donated by mothers and fathers; indeed, the father's kidney was found to have a slight short-term advantage.¹⁰ There was some question, however, as to whether the influence of exposure to maternal HLA antigens in renal transplantation was adequately assessed by comparing maternal donors with paternal donors, because of the problem of confounding covariates. These factors include the sex of the organ donor, previous sensitization of the donor (during pregnancy), and the presence in the donor of all the non-HLA as well as HLA antigens not inherited from the mother.

In the light of these considerations, we asked whether the presence in the donor of maternal HLA antigens that were not inherited by the recipient favorably influences the outcome of kidney transplantations between siblings in which the donor and recipient are mismatched for one HLA haplotype. In this model, the donor's sex, any previous sensitization of the recipient to the donor's HLA antigens, and the expression of all the HLA and non-HLA maternal antigens by the donor would not be expected to bias the results.

METHODS

Patients

We retrospectively analyzed graft survival in 94 patients who received a primary renal transplant from a living related sibling mismatched for one HLA haplotype at five transplantation centers in the Pacific Northwest region of the United States (Swedish Hospital, University of Washington Medical Center, and Virginia Mason Hospital — all in Seattle; Sacred Heart Hospital, Spokane, Washington; and Oregon Health Sciences University, Portland) and in a validation set of 111 recipients of renal transplants from siblings at four other transplantation centers in the United States and the Netherlands (the University of Wisconsin Hospital, Madison; the University of Leiden Hospital, Leiden; Dijkzigt University Hospital, Rotterdam; and Washington University School of Medicine, St. Louis). Of these 205 patients, 74 (36 percent) received their grafts from March 1966 through December 1985, and 131 (64 percent) received them from January 1986 through December 1996; 59 patients (29 percent) were conditioned with one to three transfusions of donor blood before transplantation, all after January 1980; 98 (48 percent) received their grafts without pretransplantation transfusions of donor blood; and transfusion status could not be determined for 48 transplant recipients (23 percent).

Patients requiring a renal transplant were selected for the study if serologic information on HLA haplotypes was available for at least one of their parents. The paternal or maternal origin of siblings' HLA antigens could then be determined, according to the parents' HLA-A and B types. In cases of uncertainty in haplotype identifications, serologic typing of the HLA-DR antigen was also included. In this way, each mismatched HLA antigen of each haplotypic sibling donor could be designated as a noninherited maternal or noninherited paternal antigen with respect to the recipient.

Immunosuppressive Regimens

All the recipients received immunosuppressive drugs to maintain long-term graft function. Before January 1988, several centers used a pretransplantation conditioning regimen for recipients of

transplants from living related donors with one HLA haplotype mismatch, consisting of transfusion of one to three units of donor blood over a two-to-six-week period before transplantation, either with¹¹ or without¹² concomitant azathioprine treatment. Post-transplantation immunosuppression before 1986 consisted of azathioprine and prednisone at most centers; beginning in January 1986 all patients were treated with cyclosporine as described elsewhere.¹³ Rejection was diagnosed on the basis of an increase in serum creatinine, confirmed by examination of a biopsy sample in most patients, and was treated primarily with bolus doses of glucocorticoids and, in cases of refractory rejection, with antilymphocyte globulin or (after 1982) muromonab-CD3 (OKT3).

The primary end point of the study was loss of the graft, defined as a resumption of dialysis, nephrectomy, or death. The incidence and timing of first episodes of acute rejection in the 86 patients who underwent transplantation at the University of Leiden Hospital and the University of Wisconsin Hospital were also analyzed.

Statistical Analysis

The rates of graft loss and rejection were estimated with the Kaplan-Meier product-limit estimator, and differences in these rates were evaluated by means of the log-rank test. Risk ratios were calculated by Cox proportional-hazards analysis, stratified according to center. Data on one patient who lost a graft (Dijkzigt University Hospital) were eliminated from the analysis because the hemolytic-uremic syndrome occurred 86 days after transplantation.

RESULTS

Effects of Noninherited Maternal Antigens

The base-line characteristics of the recipients of renal transplants from sibling donors expressing maternal or paternal HLA antigens not inherited by the recipient are shown in Table 1. There were no significant differences between the two groups in the incidence of single HLA-A, B, and DR mismatches; the age, sex, and race of the recipients; the proportion receiving transfusions of donor blood before transplantation; or the percentage of female or same-sex donors.

The retrospective analysis of 94 kidney transplants from living related donors in the Pacific Northwest included 37 from sibling donors expressing maternal HLA antigens and 57 from sibling donors expressing paternal HLA antigens not inherited by the recipient. A difference in graft survival between the two groups began to appear by the end of the first year (Fig. 2, left-hand panel). The overall graft survival at 10 years was 72 percent in the recipients of grafts from donors with noninherited maternal HLA antigens and 36 percent in recipients of grafts from donors with noninherited paternal HLA antigens ($P=0.06$). Analysis of the combined data for patients from all nine centers showed that graft survival was significantly higher when the sibling donor expressed maternal HLA antigens not inherited by the recipient (graft survival at 5 years, 86 percent, vs. 67 percent when the donor expressed paternal HLA antigens not inherited by the recipient; at 10 years, 77 percent vs. 49 percent; $P=0.006$ for both comparisons).

The relative risk of graft loss in patients receiving a kidney from a sibling who expressed paternal HLA

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	NO. OF TRANSPLANTATIONS WITH DATA AVAILABLE*	NONINHERITED ANTIGENS EXPRESSED BY SIBLING DONOR†		P VALUE‡
		MATERNAL	PATERNAL	
		percent		
No. of recipients	205	95	110	0.29
Recipient's age (yr)	139	28±10	31±10	0.11
Female sex	139	39	31	0.38
White race	106	96	100	0.23
Pairs with one HLA mismatch				
A	126	75	74	1.0
B	125	85	80	0.64
DR	116	80	75	0.51
Donor's sex				
Same as recipient's	119	42	45	0.85
Female	119	60	48	0.27
Received donor transfusions§	157	42	33	0.32

*Values are the numbers of transplantations for which the indicated information about the recipients and donors was available.

†All transplants were from sibling donors mismatched for one HLA haplotype and expressing either maternal HLA antigens or paternal HLA antigens not inherited by the recipient. Plus-minus values are means ±SD.

‡The P values were determined by Fisher's exact test for all characteristics except the number of recipients in each group (sign test) and the age of the recipient (rank-sum test).

§Values are the percentages of recipients who received one or more transfusions of blood from their sibling donors before transplantation.

antigens, as compared with maternal HLA antigens, not inherited by the recipient was similar among the study centers: at the University of Leiden Hospital, the risk ratio was 2.2 (95 percent confidence interval, 0.7 to 6.6); at the University of Wisconsin, the risk ratio was 2.2 (95 percent confidence interval, 0.5 to 9.0); for the combined Pacific Northwest centers, the risk ratio was 2.1 (95 percent confidence interval, 1.0 to 4.6); and for the combined data from the Dijkzigt University Hospital and Washington University School of Medicine, it was 1.9 (95 percent confidence interval, 0.3 to 10.5). Overall, the risk of graft loss was 2.1 times as great (95 percent confidence interval, 1.2 to 3.7) in recipients of kidneys from donors expressing noninherited paternal HLA antigens as in recipients of kidneys from donors expressing noninherited maternal HLA antigens ($P=0.009$).

Comparison with Transplants from HLA-Identical Siblings

The 10-year survival of kidney grafts from sibling donors expressing maternal HLA antigens not inherited by the recipient (77 percent) was better than that predicted for transplants from living related do-

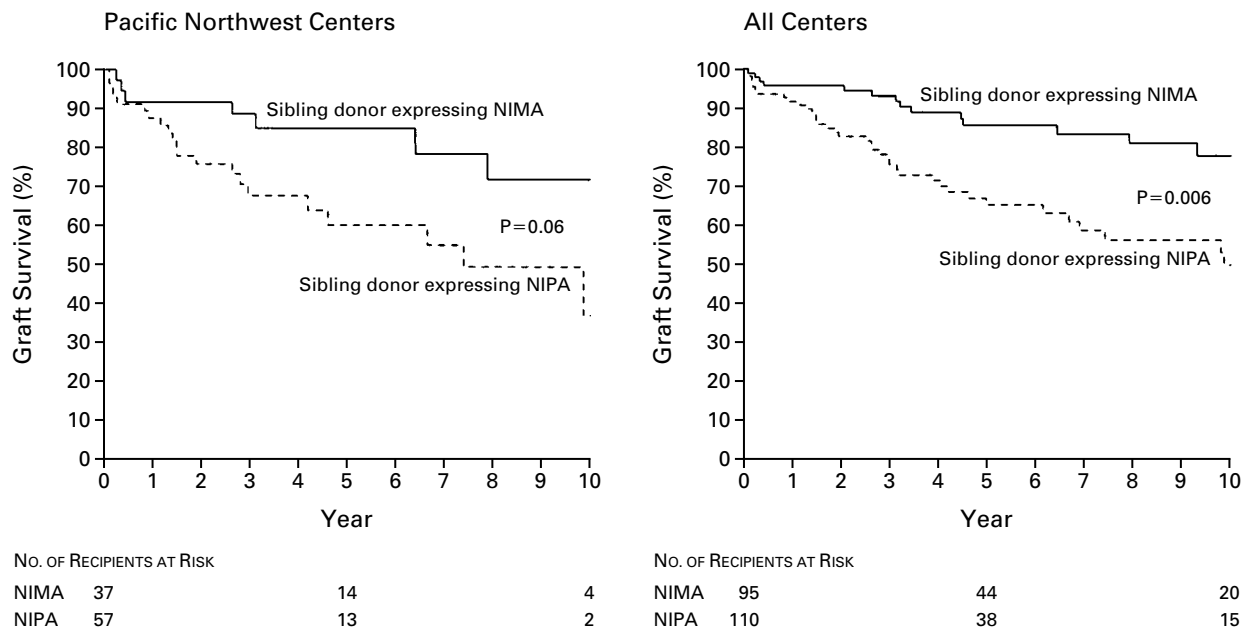


Figure 2. Graft Survival in Patients Who Received a Kidney Transplant from a Sibling Donor Mismatched for One HLA Haplotype. The donors expressed either maternal (NIMA) or paternal (NIPA) HLA antigens not inherited by the recipient. The left-hand panel shows results from five centers in the Pacific Northwest. The right-hand panel shows combined data from all nine centers. The numbers below the graphs indicate the numbers of recipients at risk for graft loss at the time of transplantation (0) and 5 and 10 years thereafter.

nors that differ in one HLA haplotype and was similar to results previously reported for transplantations between HLA-identical siblings.² We therefore compared the graft survival in 180 recipients of kidneys from siblings mismatched for one HLA haplotype at the five Pacific Northwest centers, the University of Wisconsin, and the University of Leiden Hospital with the concurrent results in the same centers over the same period (1966 to 1996) for 357 recipients of kidneys from HLA-identical sibling donors. The results indicate that the survival of grafts from donors mismatched with the recipient for one HLA haplotype and expressing maternal HLA antigens not inherited by the recipient was indistinguishable from that of grafts from HLA-identical sibling donors (risk ratio, 1.1; $P=0.80$) (Fig. 3). In contrast, a graft from a donor mismatched for one HLA haplotype and expressing noninherited paternal HLA antigens was significantly more likely to fail than was a graft from an HLA-identical sibling (risk ratio, 3.0; $P<0.001$).

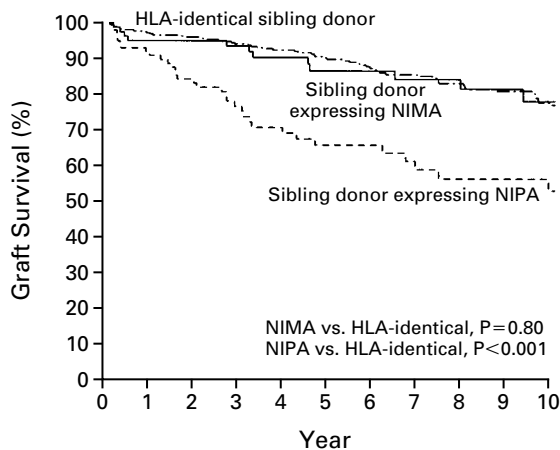
Effect of Changes in Immunosuppressive Regimens

To determine the effect of changes in immunosuppressive regimens, we chose as a demarcation point January 1, 1986, when cyclosporine was introduced into clinical use in recipients of kidneys from living related donors at the University of Wisconsin. The benefit of receiving a kidney from a donor expressing noninherited maternal rather than noninherited pa-

ternal HLA antigens in the group receiving transplants before 1986 was evident as early as 6 months after transplantation, and the difference in graft survival between the two groups was approximately 34 percentage points at 10 years (76 percent vs. 42 percent, $P=0.02$) (Fig. 4). Beginning on January 1, 1986, the early survival of grafts was markedly improved, and the benefit of receiving a kidney from a donor expressing maternal HLA antigens not inherited by the recipient did not become apparent until six years after transplantation. Nonetheless, the survival advantage at 10 years of grafts from donors expressing maternal HLA antigens not inherited by the recipient persisted (a 28-percentage-point difference) but was not statistically significant ($P=0.15$), perhaps because of the relatively small proportion of patients who were followed for more than 5 years (28 percent).

Evidence of a Priming Effect of Neonatal Exposure to Maternal HLA Antigens

In recipients of grafts from sibling donors mismatched for one HLA haplotype, we compared the time to a first episode of acute rejection between those whose grafts expressed noninherited maternal HLA antigens and those whose grafts expressed noninherited paternal HLA antigens. In the absence of transfusions of donor blood before transplantation (Fig. 5, left-hand panel), more than 80 percent of the recipients of grafts from donors expressing noninherited



NO. OF RECIPIENTS AT RISK

NIMA	81	41	18
NIPA	99	35	15
HLA-identical	357	235	119

Figure 3. Graft Survival in Recipients of Kidney Transplants from HLA-Identical Sibling Donors and Sibling Donors Mismatched for One HLA Haplotype.

Transplantations were performed at the five Pacific Northwest centers, the University of Wisconsin Hospital, and the University of Leiden Hospital. The donors mismatched for one HLA haplotype expressed either maternal (NIMA) or paternal (NIPA) HLA antigens not inherited by the recipient. The results in a concurrent series of transplantations from HLA-identical sibling donors at the same centers are shown for comparison. The numbers below the graph indicate the numbers of recipients at risk for graft loss at the time of transplantation (0) and 5 and 10 years thereafter.

maternal HLA antigens had a first rejection episode within two months after transplantation, significantly more than among the recipients of grafts from donors expressing noninherited paternal HLA antigens ($P=0.04$). This tendency toward earlier rejection was reduced by pretransplantation transfusions of donor blood ($P=0.56$) (Fig. 5, right-hand panel), and the beneficial effect of noninherited maternal HLA antigens on graft survival was preserved (data not shown).

DISCUSSION

Our study provides evidence that transplantation of kidneys from donors who express maternal HLA antigens not inherited by the recipient has a beneficial effect on the long-term survival of the graft. The benefit was evident to various degrees in patients at nine transplantation centers in the United States and the Netherlands who were treated with different immunosuppressive regimens and transfusion protocols and at different times. The 10-year survival of grafts from sibling donors mismatched for one HLA haplotype and expressing maternal antigens not inher-

ed by the recipient (77 percent) was not significantly different from the concurrent results obtained in the transplantation of kidneys from HLA-identical siblings. These findings support the hypothesis that cells and antigens of the mother modulate the antigen-specific reactivity of the fetal immune system and thereby induce a long-lasting form of tolerance to later antigen challenge in the adult.^{5,6} Together with the recent observation that a maternal effect can inhibit the development of graft-versus-host disease after cord-blood stem-cell transplantation from a sibling donor,¹⁴ our results indicate that a distinction can be made between favorable and unfavorable donor-recipient combinations in what was previously thought to be a homogeneous category of patients — those mismatched for one HLA haplotype with their donors.

Paradoxically, the maternally conferred survival benefit for kidney transplants from siblings was not associated with an absence of clinically diagnosed episodes of acute rejection. On the contrary, acute rejection occurred earlier in the recipients of kidneys from donors expressing maternal HLA antigens not inherited by the recipient, suggesting that the cellular immune response is primed by exposure of the fetus to the mother's antigens. This finding is consistent with the split nature of neonatal tolerance to noninherited maternal HLA antigens at the humoral as compared with the cytotoxic T-cell level. It also parallels the discordance between humoral and immunopathologic manifestations of immunity to Rh antigens in Rh-negative women who bear Rh-positive babies.⁵

Why was a maternally conferred survival benefit detected for kidneys transplanted from siblings, when a comparison of mothers with fathers as donors found no benefit associated with grafts from donors expressing noninherited maternal HLA antigens?¹⁰ There are several possible reasons. First, the comparison between mothers and fathers is hampered by sex restriction, because for reasons that are still unclear, the risk of graft loss is higher for kidneys from female donors than it is for kidneys from male donors¹⁵; infant recipients may be an exception to this pattern, since a tolerogenic effect of antigen exposure in utero can be evident in the case of a maternal kidney transplanted shortly after birth.^{16,17} Second, presensitization of the donor to the antigens of the recipient may cause the passenger leukocytes of the maternal kidney to initiate a low-level graft-versus-host reaction that may disrupt the tolerance mechanism in adult recipients.^{18,19} The possible additional roles of passenger leukocytes in the induction and maintenance of tolerance to organ allografts in general²⁰⁻²² and of tolerance to maternal kidney allografts in particular²³ are only beginning to be explored. Third, the shared HLA haplotype of the recipient and the kidney donor, which differs between parental and sibling donors who express the same HLA antigens not inherited by the

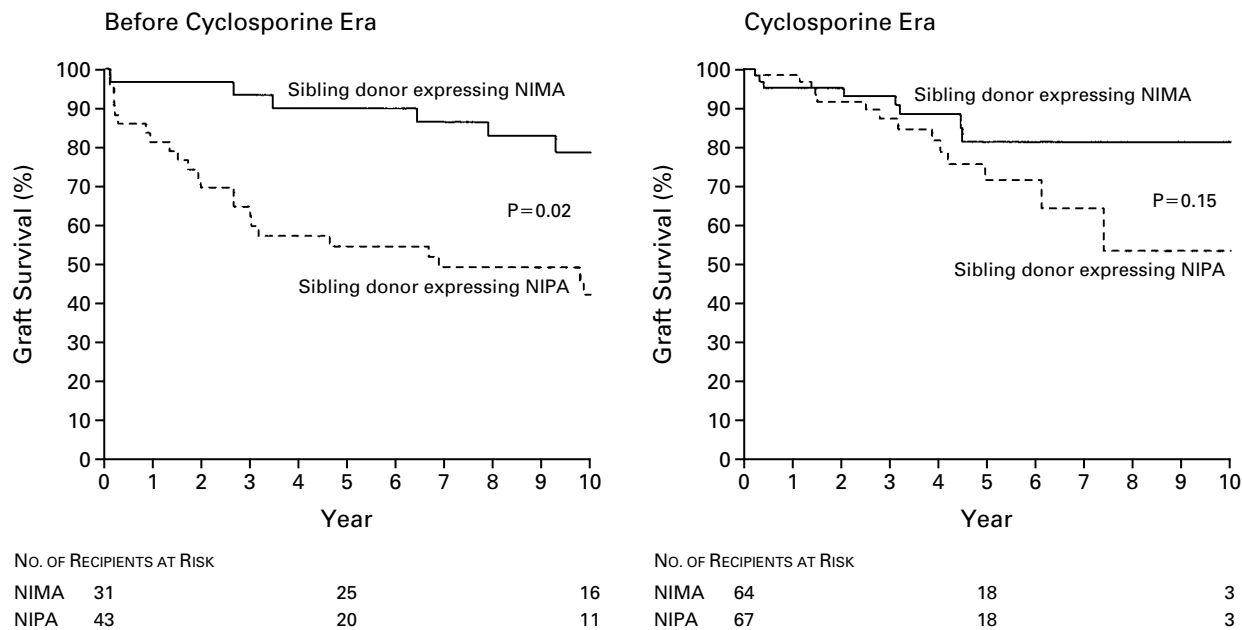


Figure 4. Effect of Immunosuppressive Regimen on Graft Survival in Patients Who Received a Kidney Transplant from a Sibling Donor Mismatched for One HLA Haplotype.

Results were analyzed according to whether the transplantation was performed before January 1, 1986 (left-hand panel), or beginning on January 1, 1986 (right-hand panel) (when cyclosporine was introduced into clinical use in recipients of kidneys from living related donors at the University of Wisconsin). The donors expressed either maternal (NIMA) or paternal (NIPA) HLA antigens not inherited by the recipient. The data shown are the combined results from all nine centers. The numbers below the graphs indicate the numbers of recipients at risk for graft loss at the time of transplantation (0) and 5 and 10 years thereafter.

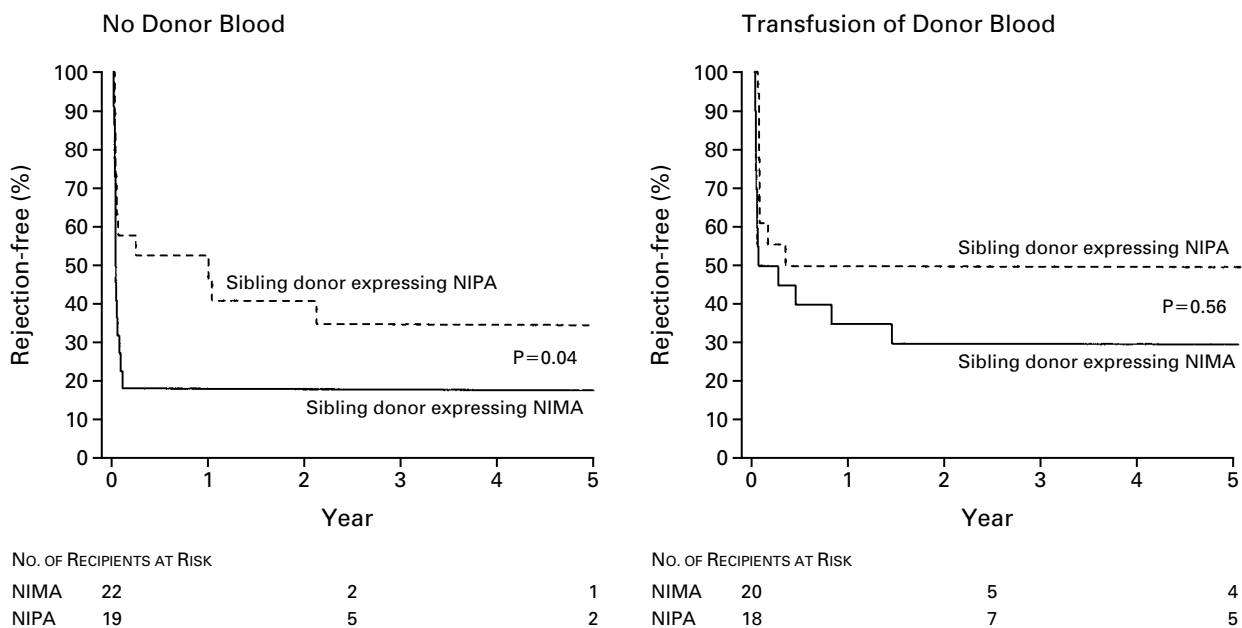


Figure 5. Effect of Donor-Blood Transfusion on the Rejection-free Interval in Patients Who Received a Kidney Transplant from a Sibling Donor Mismatched for One HLA Haplotype.

Results were analyzed according to whether the patients received no blood from the sibling donor (left-hand panel) or one to three transfusions of donor blood (right-hand panel) before transplantation. Donors expressed either maternal (NIMA) or paternal (NIPA) HLA antigens not inherited by the recipient. Data shown are from the University of Leiden Hospital and the University of Wisconsin Hospital. The numbers below the graphs indicate the numbers of recipients at risk for a first episode of rejection at the time of transplantation (0) and 2.5 and 5 years thereafter.

recipient, may be critical for the manifestation of maternally conferred tolerance.

The mechanism whereby exposure to maternal cells and soluble antigens during the fetal and early post-natal periods minimizes the consequences of a mismatch for an entire HLA haplotype remains unclear, but several possible mechanisms have been proposed. The formation of anti-HLA antibodies and related vasculopathy²⁴ may be prevented after transplantation by B-cell tolerance to noninherited maternal HLA antigens induced in the fetus⁶; regulatory cells, either of host^{9,25,26} or of donor^{23,27,28} origin, may be induced during fetal life and remain capable of being restimulated or reintroduced later in the adult recipient of the graft; and T_H2 memory cells may increase relative to T_H1 memory cells after exposure to maternal antigens presented by maternal or neonatal antigen-presenting cells.²⁹⁻³¹ The last mechanism could account for both the accelerated early acute-rejection response (memory T cells) and the resistance to late loss of the graft (T_H2 bias) in adult recipients of sibling-donated transplants expressing the same maternal HLA antigens encountered in utero. The attenuation of the early acute-rejection response in recipients of pretransplantation transfusions of sibling-donor blood expressing maternal HLA antigens that the recipient has not inherited parallels the suppression of donor-specific mixed-lymphocyte reactions in peripheral-blood T cells after donor-blood transfusion in this subgroup of patients.³² Taken together, these data are consistent with models in which the recall of antigen exposure in utero is essential for manifestation of the beneficial effects of blood transfusions on transplant survival.^{9,33}

The finding that noninherited maternal HLA antigens have a beneficial effect in sibling transplantation has immediate implications for the selection of a living kidney donor in cases in which only HLA-non-identical siblings are available. In addition, the selection of a donor expressing maternal HLA antigens not inherited by the recipient may provide an "acceptable mismatch" in cadaveric kidney transplantation,³⁴ in hematopoietic stem-cell transplantation,¹⁴ and (in future clinical trials) in the induction of tolerance in lieu of lifelong immunosuppressive therapy.

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