Transpl Int (1998) 11: 82–88

ORIGINAL ARTICLE

Jacqueline M. A. Smits
Frans H. J. Claas
Hans C. van Houwelingen
Guido G. Persijn

Do noninherited maternal antigens (NIMA) enhance renal graft survival?

Received: 16 May 1997
Received after revision: 8 October 1997
Accepted: 19 November 1997

J. M. A. Smits (✉) · G. G. Persijn
Eurotransplant Foundation, P. O. Box 2304, 2301 CH Leiden, The Netherlands
Fax: +31 71 5790057

F. H. J. Claas
Eurotransplant Reference Laboratory, Department of Immunohematology and Blood Bank, University Hospital Leiden, Bldg 1, E3-Q, Postbus 9600, 2300 RC Leiden, The Netherlands

H. C. van Houwelingen
Department of Medical Statistics, University of Leiden, The Netherlands

Abstract To test the hypothesis that noninherited maternal antigens (NIMA) can modulate the alloreactivity of infant cells and provide protection for renal transplant recipients, a study of renal transplantations performed between 1980 and 1991 was undertaken. The survival rate of grafts with a mismatched antigen identical to the NIMA was compared to that of grafts in which the mismatched antigen was not identical to the NIMA. In the case of HLA-A mismatches, graft survival rates were significantly better for NIMA-mismatched transplants: 94% and 83% at 1 and 3 years, respectively, for single NIMA HLA-A mismatched transplants, and 83% and 67% when both HLA-A antigens were mismatched, compared to 76% and 68% (one non-NIMA HLA-A mismatch) and 67% and 45% (two non-NIMA HLA-A mismatches). Our results suggest that some class I NIMA-mismatched antigens are not harmful to renal transplant recipients.

Key words Noninherited maternal antigens, kidney transplantation · Acceptable mismatches, kidney transplantation · Immunological tolerance, kidney transplantation · Kidney transplantation, noninherited maternal antigens

Introduction

Due to the discordance between the number of patients registered for a kidney transplant and the number of kidneys available for transplantation, registries like Eurotransplant[a] are confronted with the phenomenon of "difficult-to-transplant" patients. Many of these patients are highly immunized, i.e. they have 85% or more panel reactive antibodies (PRA). They constitute around 6% of all newly registered patients. An analysis of the waiting list outflow has shown the chance for these patients to be transplanted within their 1st waiting year to be only half as high as that of nonimmunized patients (Smits et al., manuscript in preparation).

In order to enlarge the donor pool for these highly immunized patients, the "acceptable mismatch" scheme was developed [5]. In this context, it was observed that highly immunized patients formed antibodies significantly less often against the noninherited maternal HLA antigens (NIMA) than against the noninherited paternal HLA antigens (NIPA) [4]. This finding led to the idea of intrauterine-induced tolerance to the NIMA. If this induced tolerance were found to be long-lasting, it would imply that, in cases of renal transplantation, mismatched allografts had a different prognosis, depending on the NIMA character of the mismatched antigen. If the mismatched antigen was identical to the NIMA, the expected unresponsiveness to this mismatched antigen could result in a better graft survival rate than that of allografts in which the mismatched an-

[a] Eurotransplant (ET) is an international organ exchange organization in which donor hospitals, tissue typing laboratories, and transplantation centers in Austria, Belgium, Luxembourg, Germany, and The Netherlands collaborate.

Table 1 Example of the labels NIMA HLA-A, -B and -DR mismatch (MM) [*NIMA HLA-A MM = No* the mismatched antigen is not identical to the noninherited maternal antigen for antigens at the HLA-A locus (i.e., HLA-A2), *NIMA HLA-B MM = Yes* the mismatched antigen is identical to the noninherited maternal antigen for antigens at the HLA-B locus (i.e., HLA-B5), *NIMA HLA-DR MM = Irrelevant* no mismatched antigen at the HLA-DR locus]

Transplantation data	Phenotyping	NIMA HLA-A MM	NIMA HLA-B MM	NIMA HLA-DR MM
Patient	A1 A3 B8 B12 DR1 DR2			
Donor	A2 A3 B5 B12 DR1 DR2	No	Yes	Irrelevant
Mother of the patient	A3 A9 B5 B12 DR2 DR4			

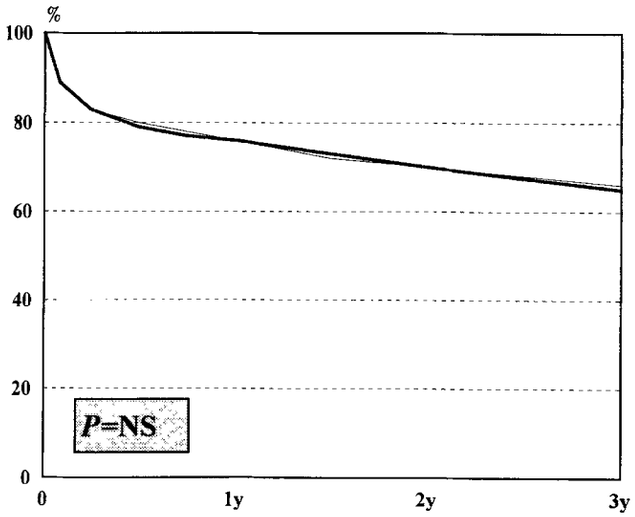

Fig. 1 Renal graft survival for the NIMA study population and the Eurotransplant (ET) population. — NIMA study population (n = 669); — ET data (n = Z 6762)

tigen was not identical to the NIMA. In order to test the hypothesis that the NIMA might play a protective role, a study was conducted using the Eurotransplant database.

Materials and methods

In this study, all cadaveric renal transplantations performed between 1 January 1980 and 31 December 1991 within the ET area and for which the HLA type of the mother was known (n = 669) were selected. Full house matched transplantations (zero mismatches for the HLA-A, -B, -DR loci) were excluded from the study. All donors and recipients were typed for HLA-A, -B, and -DR according to ET standards. The calculated number of mismatches was based on the HLA-broad antigens.

To evaluate the influence of a mismatched donor antigen that was identical to the NIMA (hereafter called a NIMA mismatch) compared to a mismatch of the same locus that was not identical to the NIMA, three new labels were defined. These labels indicated if the mismatch was of the same specificity as the NIMA. Table 1 shows an example of these three labels. Here, the patient's phenotype was A1 A3 B8 B12 DR1 DR2 and the donor typing was A2 A3 B5 B12 DR1 DR2; thus, the mismatched antigens were A2 and B5. The patient's mother had the following typing: A3 A9 B5 B12 DR2 DR4. The NIMA were A9, B5 and DR4. The HLA-B NIMA (B5) was identical to the mismatched antigen; therefore, the transplantation was labeld NIMA HLA-B mismatch = Yes. The other mismatched antigen, A2, was not identical to the HLA-A NIMA; therefore, NIMA HLA-A mismatch = No. As there were no mismatches on the HLA-DR locus, the study hypothesis was irrelevant in this setting.

In a previous study [6], we found that the immunogenicity of the mismatched donor HLA antigen was influenced by the recipient's HLA type. Certain specific donor/recipient combinations could be identified that were associated with a higher graft loss than others, the so-called taboo combinations. The data were reanalyzed after exclusion of these taboo combinations. Background characteristics were compared with the F test and the chi-square test. Graft loss was defined as return to dialysis, graft nephrectomy, or patient death, and survival probabilities were calculated by the Kaplan-Meier method.

Multivariate analysis, using the Cox model, was performed in two steps. First, the following prognostic factors for graft survival were modelled: HLA-A, -B, and -DR mismatch gradients, preservation solution [University of Wisconsin (UW), EuroCollins (EC), or histidine-tryptophane-ketoglutarate (HTK)], cold ischemia time, donor and recipient gender, donor and recipient age, number of transplant (first or retransplant), year of transplantation, and the percentage of PRA. In a second step, the three new labels were simultaneously entered and tested. All statistical corrections were made and possible NIMA effects could thus be tested when effects due to these previous factors were already taken into account.

In all Cox analyses reported, two-sided P values were given. A P value below 0.05 was considered significant. A Bonferroni procedure (multiplication of the P value by the number of factors) was not applied, as the data were analyzed in a regression model. For data handling, SAS 6.10 was used; statistical analyses were performed with SPSS 6.0.

Results

Descriptive statistics

Although the study population was not a random sample of the ET data set, the graft survival curves were not significantly different from those of the total population (Fig. 1). We therefore assumed that no selection bias had played a role. Table 2 shows the baseline characteristics of the study population (n = 669).

Table 2 Baseline characteristics of the study population (*25–75 p* 25th and 75th percentiles)[a]

Factor			
Recipient gender			
*	Male	380	(57%)
*	Female	280	(42%)
Recipient age (years)			
Median (25–75 p)		29	(21–37)
Highest % PRA			
*	0–5	197	(29%)
*	6–84	314	(47%)
*	85 +	144	(22%)
Donor gender			
*	Male	405	(61%)
*	Female	252	(38%)
Donor age (years)			
Median (25–75 p)		29	(18–42)
Donor cause of death			
*	Trauma capitis	314	(47%)
*	CVA	245	(37%)
*	Other	110	(16%)
Preservation solution			
*	EC	468	(70%)
*	HTK	25	(4%)
*	UW	109	(16%)
Number of transplant			
*	First transplant	502	(75%)
*	Retransplant	167	(25%)
HLA-A Mismatch gradient			
*	0	209	(31%)
*	1	317	(47%)
*	2	88	(13%)
HLA-B Mismatch gradient			
*	0	145	(22%)
*	1	362	(54%)
*	2	108	(16%)
HLA-DR Mismatch gradient			
*	0	335	(50%)
*	1	248	(37%)
*	2	29	(4%)
Cold ischemia time (h)			
Median (25–75 p)		26	(21–33)

[a] Not all information was available for every combination

Donor mismatch characteristics

The three labels (NIMA HLA-A, -B, and -DR mismatch) were defined in order to check the effect of a NIMA mismatch on graft survival. Each label has two levels, one reflecting the group of mismatches identical to the NIMA (NIMA mismatch) and one reflecting the mismatches that are not identical to the NIMA (non-NIMA mismatch). A NIMA HLA-A mismatch could be found in 51 transplantations (13%); 28 transplantations (6%) had a NIMA HLA-B mismatch, and 33 (12%) a NIMA HLA-DR mismatch (Table 3). As the labels could only be defined for mismatched transplantations, a third group containing transplants with zero mismatches or with a missing HLA-typing at that specific locus was defined ("Irrelevant group").

Table 3 Number of NIMA and non-NIMA HLA-mismatched *(MM)* antigen transplantations

NIMA HLA-A MM		NIMA HLA-B MM		NIMA HLA-DR MM	
Yes	No	Yes	No	Yes	No
$n = 51$ (13%)	$n = 354$ (87%)	$n = 28$ (6%)	$n = 442$ (94%)	$n = 33$ (12%)	$n = 244$ (88%)
Irrelevant $n = 264$		Irrelevant $n = 199$		Irrelevant $n = 392$	

The distribution of possible confounders, i.e., HLA mismatch and the percentage of PRA for NIMA and non-NIMA mismatched transplants, is shown in Table 4.

HLA-A locus

In the study population there were 51 transplantations where the HLA mismatch was identical to the NIMA. These NIMA-mismatched transplantations all had at least one mismatch at the HLA-A locus; 31% of these transplantations had no mismatch at the HLA-B locus and 55% had no HLA-DR mismatches. Transplantations in which the HLA-A mismatch was not identical to the NIMA had significantly more often a single HLA-A mismatch than the NIMA-mismatched transplantations ($P = 0.004$). This observation was not unexpected, as the chance of a NIMA HLA mismatch is higher when there are two HLA mismatches. The two groups did not differ significantly with respect to the HLA-B ($P = 0.8$) and -DR ($P = 0.8$) mismatches or to the percentage of PRA profile ($P = 0.9$).

HLA-B locus

Twenty-eight of our transplantations were performed with an HLA-B NIMA mismatch. These transplantations were not significantly different from those where the HLA-B mismatch was not identical to the NIMA with regard to HLA-A mismatches ($P = 0.6$), HLA-DR mismatches ($P = 0.5$), and percentage of PRA ($P = 0.8$). Significantly more single HLA-B mismatches were in the group of transplantations where the mismatch was not identical to the NIMA ($P = 0.03$).

Table 4 HLA mismatch and percentage PRA distribution for NIMA and non-NIMA mismatched (MM) antigen transplantations

Factor	NIMA HLA-A MM			NIMA HLA-B MM			NIMA HLA-DR MM		
	Yes, $n = 51$ (13%)	No, $n = 354$ (87%)	p-value	Yes, $n = 28$ (6%)	No, $n = 442$ (94%)	p-value	Yes, $n = 33$ (12%)	No, $n = 244$ (88%)	p-value
HLA-A mismatch									
0	–	–		13 (46%)	164 (37%)		10 (30%)	88 (36%)	
1	32 (63%)	285 (80%)	0.004	11 (39%)	213 (48%)	0.6	13 (40%)	123 (50%)	0.04
2	19 (37%)	69 (20%)		4 (15%)	65 (15%)		10 (30%)	33 (14%)	
HLA-B mismatch									
0	16 (31%)	96 (27%)		–	–		5 (9%)	52 (21%)	
1	27 (53%)	194 (55%)	0.8	17 (61%)	345 (78%)	0.03	14 (42%)	142 (58%)	0.02
2	8 (16%)	64 (18%)		11 (395%)	97 (22%)		14 (42%)	50 (21%)	
HLA-DR mismatch									
0	28 (55%)	197 (56%)		14 (50%)	235 (53%)		–	–	
1	19 (37%)	139 (39%)	0.8	14 (50%)	179 (41%)	0.5	28 (85%)	220 (90%)	
2	4 (8%)	17 (5%)		–	27 (6%)		5 (15%)	24 (10%)	0.3
?		1			1				
% PRA									
0–5%	18 (36%)	109 (32%)		7 (28%)	141 (33%)		8 (26%)	88 (37%)	
6–84%	25 (50%)	175 (51%)	0.9	12 (48%)	207 (48%)	0.8	18 (58%)	114 (48%)	0.5
85–100%	7 (14%)	60 (17%)		6 (24%)	85 (20%)		5 (16%)	37 (16%)	
?	1	10		3	9		2	5	
Not defined		$n = 264$			$n = 199$			$n = 392$	

HLA-DR locus

Transplantations where the HLA-DR mismatch was identical to the NIMA amounted to 12% ($n = 33$) in our study group. These transplantations had a significantly higher percentage of two mismatches at the HLA-A and HLA-B loci than transplantations where the HLA-DR mismatch was not identical to the NIMA (30% and 42% vs 14% and 21% for the HLA-A and -B loci, respectively). The HLA-DR mismatch distribution was not significantly different ($P = 0.3$), and no significant difference was seen between the two levels with regard to the percentage of PRA ($P = 0.5$).

Univariate analysis

Grafts in which the mismatched HLA-A antigen was identical to the NIMA had a significantly better survival rate (overall P value = 0.026) than those where the mismatched HLA-A antigen was not identical to the NIMA. Figure 2 shows the Kaplan-Meier curves stratified for HLA-A mismatches. Survival rates at 1 and 3 years for grafts in which the mismatched antigen was identical to the HLA-A locus were 94% and 83% for one HLA-A mismatched antigen and 83% and 67% when both HLA-A antigens were mismatched, compared to 76% and 68% (one non-NIMA HLA-A mismatch) and 67% and 45% (two non-NIMA HLA-A mismatches) for grafts in which the HLA-A mismatched antigen was not identical to the NIMA. No significant difference in graft survival between NIMA and non-NIMA mismatched antigen was seen for the HLA-B and -DR loci.

Figure 3 shows the survival rates of transplants with zero HLA-A mismatched antigens ($n = 209$) and of those with NIMA HLA-A mismatched antigens ($n = 51$; $P = 0.02$).

Taboo combinations

The observation that NIMA HLA-A mismatched antigen transplantations had a significantly better graft survival rate compared to non-NIMA HLA-A mismatched antigen transplantation could have been biased by the taboo effect, as more taboo donor/recipient combinations were found in the group of non-NIMA HLA-A mismatched antigen transplantations than NIMA HLA-A mismatched antigen transplantations (4.5% vs 2%, respectively). After excluding 17 taboo combinations (1 NIMA HLA-A mismatched and 16 non-NIMA HLA mismatched antigen transplantations), a significant difference in graft survival between NIMA and non-NIMA HLA-A mismatched antigen transplantations was still seen. Graft survival rates for the former ($n = 50$) were 90% and 81% at 1 and 3 years compared to 75% and 64% for the latter ($n = 338$; $P = 0.02$).

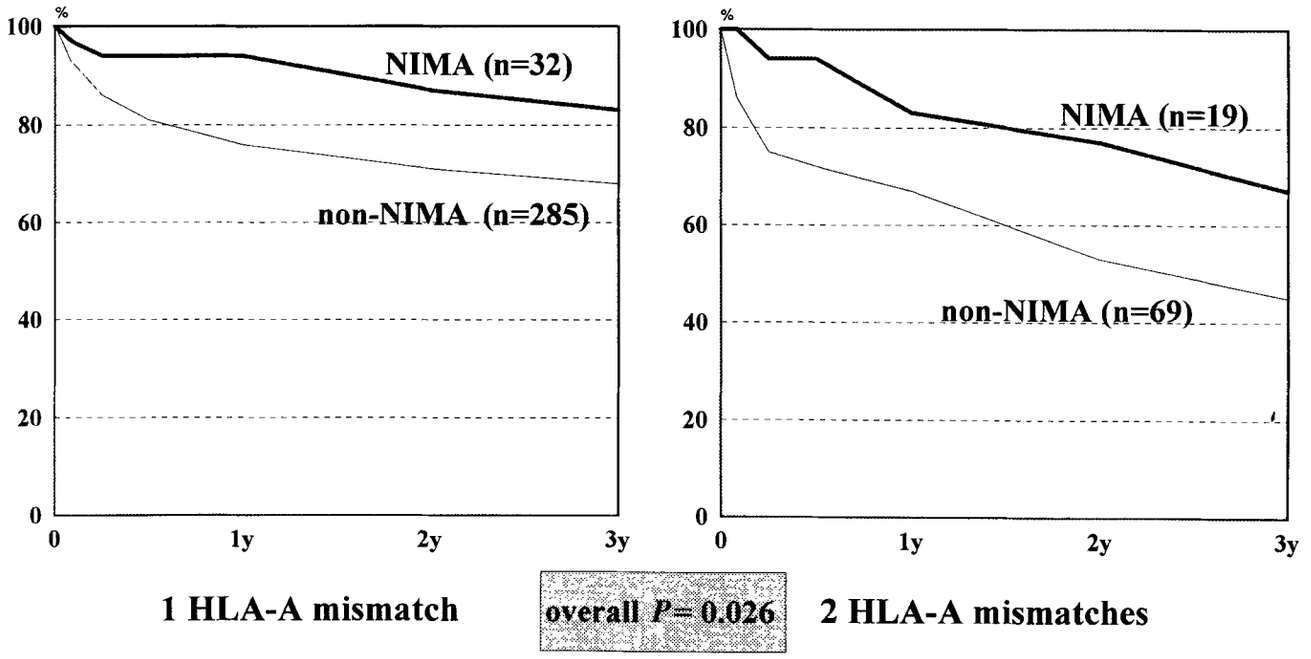

Fig. 2 Renal graft survival for NIMA HLA-A mismatched and non-NIMA HLA-A mismatched antigen transplantations stratified for the number of HLA-A mismatches

Table 5 Results of the multivariate analysis of the labels NIMA HLA-A, -B, and -DR mismatch after correction for confounding factors (*LCL* lower confidence limit, *UCL* upper confidence limit)

Label	Relative risk (95% LCL-UCL)	*P* value
NIMA HLA-A mismatch	0.53 (0.30–0.93)	0.03
NIMA HLA-B mismatch	1.49 (0.85–2.56)	0.2
NIMA HLA-DR mismatch	0.91 (0.50–1.67)	0.8

Multivariate analysis

The NIMA effect was tested after corrections for the following prognostic factors were made: HLA-A, -B and -DR mismatch gradients, preservation solution (UW, EC, or HTK), cold ischemia time, donor and recipient gender, donor and recipient age, number of transplant (first or retransplant), year of transplantation, and percentage of PRA. Table 5 displays the estimates of the relative risks and their 95% confidence intervals for the three NIMA labels: NIMA HLA-A mismatch ($P = 0.03$), NIMA HLA-B mismatch ($P = 0.2$), and NIMA HLA-DR mismatch ($P = 0.8$). Transplantations where the HLA-A mismatched antigen was identical to the NIMA had a relative risk of 0.53 of graft failure compared to transplantations where the HLA-A mismatched antigen was not identical to the NIMA. No significant interaction between the factor percentage of PRA and the factor NIMA HLA-A mismatch was observed (results not shown).

Discussion

The number of highly immunized patients waiting for a kidney transplant continues to grow. A special allocation scheme has been developed to increase the chance of finding a donor kidney for these patients. It is based on the definition of "acceptable mismatches", i.e., HLA alloantigens to which the patient has never formed antibodies, and it is aimed at selecting donors who have "acceptable" HLA-A and -B mismatches, but who are HLA-DR compatible. The finding that many of these mismatches are of the same specificity as the noninherited maternal antigens (NIMA) led to the idea of an intrauterine-induced tolerance to these NIMA. This study was undertaken in order to test the hypothesis that NIMA can modulate the alloreactivity of infant cells and provide long-term protection for renal transplant recipients.

In contrast to Pohanka et al.'s findings [11], this study shows that some class I NIMA can provide long-term protection after kidney transplantation. Transplantations performed with a mismatched HLA-A antigen that was identical to the NIMA were found to have a two times lower risk (RR = 0.53) of graft failure than transplantations where the HLA-A mismatch was not identical to the NIMA. Previous studies demonstrated that HLA-A mismatches have less influence on renal

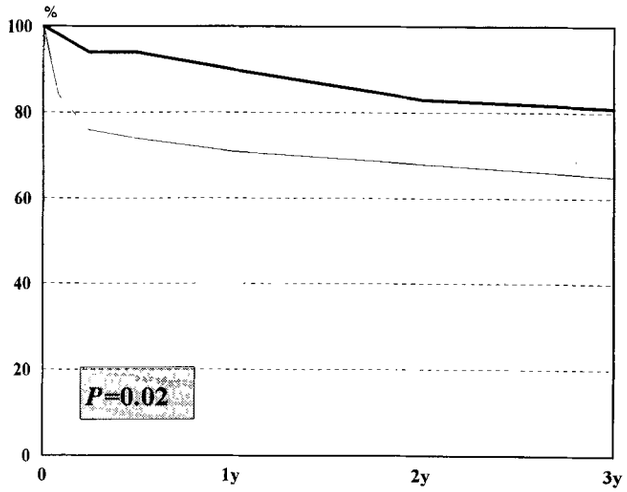

Fig. 3 Renal graft survival of NIMA HLA-A and zero HLA-A mismatched antigen transplantations. NIMA HLA-A MM ($n = 51$); zero HLA-A MM ($n = 209$)

graft survival than HLA-B mismatches [14]. In vitro it was also shown that the number of HLA-A-directed cytotoxic T-lymphocyte precursors (CTLp) is significantly lower than the number of HLA-B-directed CTLp [2, 12].

Thus far, the NIMA effect has only been demonstrated in highly sensitized patients [1, 7, 10, 11, 13]. Therefore, sensitization may play a role in revealing a latent non-responder status.

In light of these findings, we opted for a study design that allowed us to test the effect of NIMA mismatches in renal transplantation at each individual HLA locus. The present statistical model was built in such a way that we could correct for the percentage of PRA.

Although the effect was weak, this study showed that the risk of graft failure was significantly lower for NIMA HLA-A mismatched antigen transplantations than for transplantations where the HLA-A mismatched antigens were not identical to the NIMA. A possible explanation for this effect could be an imbalance of taboo mismatched transplantations between the two groups; however, after excluding these taboo transplantations, the NIMA effect could still be observed.

Figure 3 shows that NIMA HLA-A mismatched antigen transplantations have a statistically significantly better survival rate than those with zero HLA-A mismatches. A beneficial effect of HLA-A mismatching was reported by Bućin et al. [3], but the authors did not look for a possible NIMA effect. Our results seem to suggest that the effect of allosensitization due to the HLA-A mismatched donor antigen was not only neutralized, but that perhaps a form of (linked) suppression might have been elicited (H. Waldmann, personal communication).

Our findings are in agreement with the observation that a decreased antidonor mixed lymphocyte culture response was more often found when the donor transfusion products expressed NIMA than when they expressed the noninherited paternal antigens (NIPA) [1]. B-cell unresponsiveness against NIMA was observed in highly immunized patients [5, 7] and in patients who had received a donor-specific blood transfusion [1]. However, other studies could not demonstrate a NIMA effect: no difference in CTLp and helper T-lymphocyte precursor frequencies against NIMA and NIPA could be detected by limiting dilution analysis [13]. No difference in immunization against the NIMA and the NIPA in normal individuals could be seen at the humoral level by Pohanka et al. [11]. We also looked at the whole haplotype – as in the Pohanka et al. study – but we did not find a NIMA effect in our database.

It could well be argued that the elucidation of a NIMA effect can easily be hampered by the study design. A study needs the necessary power to detect an effect, i. e., the size of the study population should be large enough [8, 13] and the analysis of clinical end points, such as graft survival or rejection episodes, should include corrections for confounding factors. Pohanka et al. [11] did not report whether the mismatch distribution for the NIMA and the NIPA groups was comparable in quality (HLA-A mismatch versus HLA-DR mismatch) and quantity (1 versus 2 HLA mismatches), nor is it clear whether a correction was made for these possible imbalances. Testing the NIMA effect by comparing the outcome of maternal versus paternal grafts is also vulnerable to bias [9, 15], as it is impossible to correct for the fact that the propensity for graft loss from female donors is higher than from male donors [14].

Clinical as well as in vitro studies have indicated that HLA-B antigens are more immunogenic than HLA-A antigens. Therefore, one could assume that the induction of tolerance is also primarily caused by HLA-A antigens, as suggested by our data. This study focussed on a potentially protective effect of NIMA on long-term graft survival by looking at the separate loci (HLA-A, -B, and -DR). The results of the study are consistent with the hypothesis that NIMA can influence the immune repertoire of the offspring. The fact that a significant NIMA effect could only be detected at the HLA-A locus may suggest that it is soluble HLA molecules, rather than maternal cells, that act as the tolerance-inducing agents.

If the finding that some class I NIMA are not harmful in renal transplantation can be substantiated in further studies, the search for an acceptable donor for a patient with end-stage renal disease can be expanded by the identification of the NIMA.

Acknowledgements The donor hospitals, transplantation centers, and tissue typing laboratories collaborating within the ET organization are gratefully acknowledged for sharing their data. This study was supported by the Dutch Kidney Foundation.

References

1. Bean MA, Mickelson E, Yanagida J, Ishioka S, Brannen GE, Hansen JA (1990) Suppressed antidonor MLC responses in renal transplant candidates conditioned with donor-specific transfusions that carry the recipient's noninherited maternal HLA haplotype. Transplantation 49: 382–386
2. Breur-Vriesendorp B, Vingerhoed J, Van Twuyer E, De Waal LP, Ivanyi P (1991) Frequency analysis of HLA-specific cytotoxic T lymphocyte precursors in humans. Transplantation 51: 1096–1103
3. Bućin D, Ekberg H, Lindholm A, Persson H, Tufveson G, Albrechtsen A (1994) HLA-A incompatiblity associated with enhanced long-term renal graft survival in HLA-B, -DR mismatched transplants. Immunol Cell Biol 72: 455–460
4. Claas FHJ, Gijbels Y, Van der Velden-de Munck JJ, Rood JJ van (1988) Induction of B cell unresponsiveness to non-inherited maternal HLA antigens during fetal life. Science 241: 1815–1817
5. Claas FHJ, Gijbels Y, Van der Velden-de Munck JJ, De Waal LP, D'Amaro J, Hendriks GFJ, Persijn GG, Rood JJ van (1989) A selection of cross-match negative HLA-A and/or B mismatched donors for highly sensitized patients. Transplant Proc 21: 665
6. Doxiadis IID, Smits JMA, Schreuder GMTh, Persijn GG, Houwelingen HC van, Rood JJ van, Claas FHJ (1996) Association between specific HLA combinations and probability of kidney allograft loss: the taboo concept. Lancet 348: 850–853
7. Fluit L, Reekers P, Claas FHJ (1989) Are maternal antigens protective for antibody formation? Transplant Proc 21: 689
8. Hadley GA, Phelan D, Duffy BF, Mohanakumar T (1990) Lack of T-cell tolerance of noninherited maternal HLA antigens in normal humans. Hum Immunol 28: 373–381
9. Opelz G (1991) Analysis of the 'NIMA effect' in renal transplantation. In: Terasaki PI (ed) Clinical transplants 1990. UCLA, Los Angeles, pp 63–67
10. Phelan D, Hadley G, Duffy B, Mohanam S, Mohanakumar T (1991) Anti-idiotypic antibodies to HLA Class I alloantibodies in normal individuals: a mechanism of tolerance to non-inherited maternal HLA antigens. Hum Immunol 31: 1–6
11. Pohanka E, Cohen N, Colombe BW, Lou C, Salvatierra O Jr, Garovoy MR (1990) Non-inherited maternal HLA antigens and protection against sensitisation. Lancet 336: 1025–1028
12. Roelen DL, Bree FPMJ van, Beelen E van, Schanz U, Rood JJ van, Claas FHJ (1994) Cytotoxic T lymphocytes against HLA-B antigens are less naive than cytotoxic T lymphocytes against HLA-A antigens. Transplantation 57: 446–450
13. Roelen DL, Bree FPMJ van, Beelen E van, Rood JJ van, Claas FHJ (1995) No evidence of an influence of the non-inherited maternal HLA antigens on the alloreactive T cell repertoire in healthy individuals. Transplantation 59: 1728–1733
14. Thorogood J, Persijn GG, Schreuder GMTh, D'Amaro J, Zantvoort FA, Houwelingen JC van, Rood JJ van (1990) The effect of HLA matching on kidney graft survival in separate post-transplantation intervals. Transplantation 50: 146–150
15. Troche A, Prigoshin N, Ruiz SE, Ramirez JA, Ferraris JR (1994) The influence of noninherited maternal HLA antigens in pediatric renal transplants. Transplantation 58: 620–623