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Delayed graft function does not influence long-term outcome in cadaver kidney transplants without mismatch for HLA-DRB1

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Abstract The currently study focused on the influence of delayed graft function on the long-term graft success rate in cadaver kidneys without any mismatches for HLA-DRB1. Donor-recipient HLA-DRB1 was determined by the significant two-locus linkages of HLA-B and -DRB1. The overall 5-year graft success rate was 88 % in an HLA-DRB1-compatible group, significantly higher than the 69 % in an HLA-DRB1 mismatch group ($P < 0.05$) and the 66 % in an HLA-DR mismatch ($P < 0.01$). Delayed graft function was observed in 182 of 223 transplants. This high incidence of 82 % is due to the fact that, in Japan, kidney procurement may only occur after cardiac arrest. The incidence did not differ in each group. The 5-year success rate for grafts with delayed function was 87 % in the HLA-DRB1-compatible group, again significantly superior to the 68 % in the HLA-DRB1 mismatch group and the 63 % in the HLA-DR mismatch cases ($P < 0.05$). There was, thus, no difference in graft success rate for each group, with or without delayed graft function. Consequently, we feel that delayed graft function has no impact on the long-term outcome in transplants without mismatches for HLA-DRB1.

Key words Delayed graft function, kidney transplantation · HLA-DRB1

Introduction

We have previously reported that HLA-DRB1-compatible transplantation (0 mismatches for HLA-DRB1) has an optimal graft success rate with both living related donors and cadaveric donors, and that this rate is comparable to that of HLA-identical siblings [4–6]. Yet, some authors have noted a correlation between delayed graft function and poor graft outcome in transplantation with cadavenic donors [2, 14]. The reason for this is that delayed graft function precludes a prompt diagnosis of a rejection crisis that may lead to impaired kidney function and, occasionally, to nonfunction. Najarian et al. [13] reported that delayed graft function had a sig-

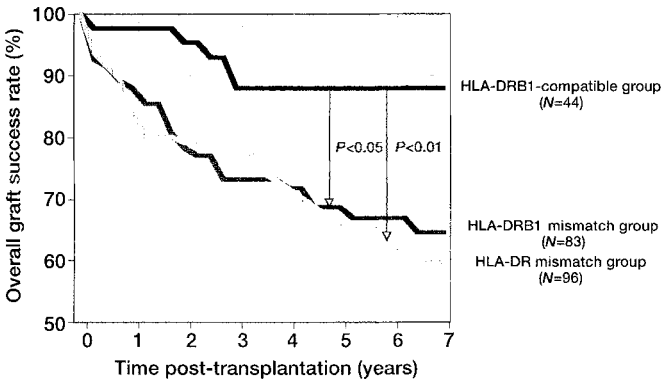

Fig. 1 The overall success rate for cadaveric donor transplants. Statistical significance was reached between the HLA-DRB1-compatible group and other mismatch groups ($P < 0.05$ and $P < 0.01$, as indicated)

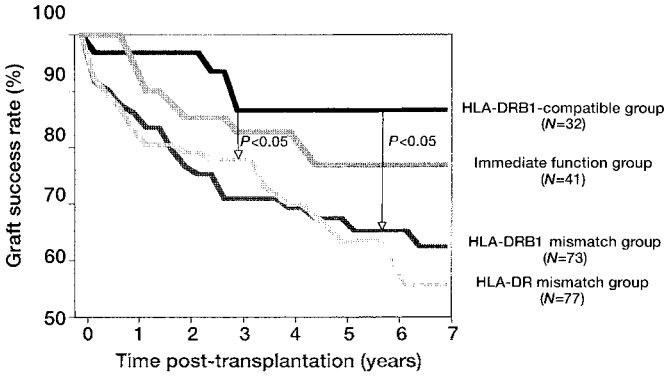

Fig. 2 The success rate for delayed and immediate graft function in cadaveric donor transplants. Statistical significance was reached between the HLA-DRB1-compatible group and other mismatch groups ($P < 0.05$)

nificant adverse effect on long-term cadaver graft outcome and that HLA matching had no influence on the outcome.

Our current study focused on the influence of delayed graft function on the long-term graft success rate in cadaver grafts without any mismatches for HLA-DRB1.

Materials and methods

HLA Typing and linkage disequilibrium study

Serotyping and genotyping were conducted for 916 unrelated Japanese patients using a standard microcytotoxicity assay [16] and a primer chain reaction with sequence-specific oligonucleotide probes [10]. Thirty HLA-DRB1 alleles were detected in this population. A linkage disequilibrium study of HLA-B and -DRB1 was performed on these data according to Baur and Danilovs' procedure [1]. Forty-three significant linkages were found using the chi-square test, as shown in a previous report [6]. Twenty-eight of the 30 HLA-DRB1 alleles were predictable with the serotyped HLA-B and -DR combination using significant associations, while the other two alleles – HLA-DRB1*0404 and HLA-DRB1*1402 – could not be determined in the linkage study. HLA-DR1 and -DR9 were assigned as HLA-DRB1*0101 and HLA-DRB1*0901 since no other types are detectable in the Japanese population [8]. The HLA-DRB1 of donor-recipient pairs was determined by these linkage disequilibria, as described previously [5, 6]. The positive predictive value was 93 % and the true positive rate was 76 % for this method, as evaluated previosly [6].

Kidney transplantation and success rate

A total of 223 grafts were transplanted using cadaveric donors in our four kidney transplant centers – Hyogo Prefectural Nishinomiya Hospital, Osaka University Hospital, the National Cardiovascular Center, and Social Insurance Chukyo Hospital – from 1983 to 1992. Immunosuppression consisted of cyclosporin A with azathioprine, mizoribine, and/or prednisolone. Any transplants involving tacrolimus or in the azathioprine era were excluded from this study. All grafts were followed up for at least 18 months. Kidneys were preserved by simple cooling with Euro-Collins (EC, $n = 200$) or University of Wisconsin (UW, $n = 23$) solution. Delayed graft function was defined as the need for hemodialysis after kidney transplantation due to oliguria under 500 ml/day. No exclusion was made for graft loss when the patient died with a functioning graft. The kidney graft success rate was computed in June 1994 following the Kaplan-Meier method. Statistical significance was evaluated with the Cox-Mantel test. The chi-square and Student's *t*-test were employed for evaluation of statistical significance in other cases.

Results

A total of 127 patients received kidneys from cadaveric donors without any mismatches for HLA-DR. The prognosis for 44 patients was made based on 0 mismatches for HLA-DRB1; these patients comprised the HLA-DRB1-compatible group. Eighty-three patients were categorized as the HLA-DRB1 mismatch group and comprised patients with one or two mismatches for HLA-DRB1 as well as patients for whom HLA-DRB1 could not be predicted. The remaining 96 patients were HLA-DR mismatch cases.

The overall graft success rate is given in Fig. 1. The 5-year rate was 88 % for HLA-DRB1-compatible cases, 69 % for the HLA-DRB1 mismatch group, and 66 % for the HLA-DR mismatch transplants. Thus, the HLA-DRB1-compatible transplants had a significantly higher success rate than did the other groups ($P < 0.05$ and $P < 0.01$, respectively).

Delayed graft function was observed in 182 of the 223 cases. This high incidence (81.6 %) is due to the fact that, in Japan, kidneys may be procured only after the cardiac arrest of the donor. Although nonfunction developed in seven grafts, the incidence was only 3.1 %. On the other hand, immediate function was seen in only 41 cases, or 18.4 %.

Table 1 Characteristics of transplants for each HLA-DRB1 matching grade

	HLA-DRB1 compatible group	HLA-DRB1 mismatch	HLA-DR mismatch	Statistical significance
No. of cases	44	83	96	
Recipient age	37.1 ± 8.7	37.7 ± 8.8	38.0 ± 8.9	NS
Male/female	22/22	46/37	68/28	$p < 0.05$*
Donor age	41.3 ± 15.2	41.0 ± 16.1	39.8 ± 18.0	NS
Warm ischemia time (min)	4.7 + 1.1	9.0 + 2.2	4.1 + 0.8	$p < 0.05$**
Total ischemia time (h)	7.8 ± 0.7	8.0 ± 0.5	8.0 ± 0.6	NS
Immediate function	12 (27 %)	10 (12 %)	19 (20 %)	NS
Delayed function	32 (73 %)	73 (88 %)	77 (80 %)	NS
Nonfunctioning kidneys	1 (2 %)	4 (5 %)	2 (2 %)	NS
Preservation fluids				
- Euro-Collins	36	78	76	$p < 0.05$***
- University of Wisconsin	8	5	10	
Duration of dialysis (days)	10.0 ± 1.1	9.9 ± 0.8	11.9 ± 1.1	NS

* $p < 0.05$ for HLA-DR mismatch group vs HLA-DRB1-compatible and mismatch groups; ** $p < 0.05$ for HLA-DRB1 mismatch group vs HLA-DR mismatch group; *** $p < 0.05$ for HLA-DRB1-compatible group vs HLA-DRB1 mismatch group

The incidence of delayed graft function and the background factors for each group are summarized in Table 1.There was little evidence that UW solution prevented delayed function in our series. The incidence was 78.3 % (18/23) in UW solution and 82.0 % (164/200) in EC solution. Warm and total ischemia times had an impact on initial graft function. The warm ischemia time was 3.2 ± 0.6 min (mean ± standard error) in the immediate function group and 6.7 ± 1.1 min in cases of delayed function ($P < 0.01$); total ischemia time was 6.5 ± 0.5 vs 8.2 ± 0.4 h, respectively ($P < 0.01$). No significant difference in total ischemia time was found within each HLA-DRB1 matching group. However, a statistically significant difference in warm ischemia time was observed between the HLA-DRB1 and HLA-DR mismatch groups ($P < 0.05$). Total ischemia time was 7.8 ± 0.7 h for the HLA-DRB1-compatible group, 8.0 ± 0.5 h for the HLA-DRB1 mismatch group and 8.0 ± 0.6 h for the HLA-DR mismatch group. Warm ischemia time was 4.7 ± 1.1 vs 9.0 ± 2.2 vs 4.1 ± 0.8 min, respectively.

Kidney function recovered after hemodialysis lasting 10.0 ± 1.1 days (mean ± standard error) in the HLA-DRB1-compatible group, 9.9 ± 0.8 days in the HLA-DRB1 mismatch group, and 11.9 ± 1.1 days in the HLA-DR mismatch group, except for the seven totally nonfunctioning kidneys. There were no significant differences in recipient or donor age, or in immediate or permanent nonfunction among the groups.

Aside from warm ischemia time, significant differences were found in recipient sex and preservation fluids. The male population was higher in the HLA-DR mismatch group than in the other groups. UW solution was used more in the HLA-DRB1-compatible group than in the HLA-DRB1 mismatch cases, though the incidence of delayed function did not differ.

The graft success rate for kidneys with delayed and immediate function is given in Fig. 2. For delayed function, the 5-year rate was 87 % in the HLA-DRB1-compatible group, 68 % in the HLA-DRB1 mismatch grafts, and 63 % in the HLA-DR mismatch cases. Thus, here also a significantly higher success rate was found for the HLA-DRB1-compatible group than for the other groups ($P < 0.05$). For kidneys with immediate function, the overall success rate was 79 %; it was 92 % in the HLA-DRB1-compatible group ($n = 12$), 80 % in the HLA-DRB1 mismatch group ($n = 10$) and 68 % in the HLA-DR mismatch cases ($n = 19$). The HLA-DRB1 matching effect on long-term graft survival was seen in the small group of kidneys with immediate function. Beyond that, no significant differences in the success rate for each group could be observed in this analysis whether or not function was delayed. The 5-year success rate was 87 % vs 92 % at 5 years in the HLA-DRB1-compatible group, while it was 68 % vs 80 % in the HLA-DRB1 mismatch group and 63 % vs 68 % in the HLA-DR mismatch group. Nonfunction developed at rates of 2.2 % vs. 4.8 % vs 2.1 % for each group, respectively. There was no significant difference in its incidence among the three groups.

Discussion

Our study revealed an extremely high incidence of delayed graft function – 82 % – compared to the 30 % reported in Europe and the United States [2, 14, 17], whereas the occurrence of permanent non-functioning

grafts – only 3 % of our cases – was similar to that of these reports. The high rate of delayed function was probably due to the non-heart-beating kidney donation and ischemia time. However, almost all of these kidneys recovered and functioned after 1 or 2 weeks on hemodialysis. Such a good rate of recovery might be related to our short ischemia times compared with other studies [2, 13, 14, 17].

In the literature, we find many contradictory reports about the effect of delayed function on subsequent graft survival. It seems plausible that delayed function should preclude appropriate diagnosis and treatment in case of early acute rejection or complications during the dialysis period, which are associated with reduced graft survival. Najarian et al. [13] showed that delayed function after cadaveric transplantation resulted in significantly decreased 1-year graft survival compared to immediate graft function. Ploeg et al. [14] recommended UW solution for kidney preservation because of its associated lower rate of delayed function, resulting in better graft survival. However, these analyses excluded hyperacute rejection and nonfunctioning grafts nor was HLA matching grade taken into account. In contrast, Kasiske et al. [9] demonstrated that the incidence and severity of post-transplant acute tubular necrosis had no correlation to chronic deterioration of graft function. Terasaki et al. [17] noted that in six-antigen match cases, there was relatively little adverse effect of delayed function on the 1-year survival rate.

In contrast, Gulanikar et al. [3] and Matas et al. [12] reported a significant effect of an acute rejection episode on 1-year and long-term renal allograft survival. Poli et al. [15] showed that patients without genomic HLA-DR mismatches were found in a significantly higher proportion in long-term survivors than in other categories, suggesting that positive selection occurred throughout the years after transplantation. In addition, Kobayashi et al. [11] demonstrated a significantly lower incidence of acute rejection of HLA-DRB1-compatible grafts than of incompatible grafts and 100 % graft survival for HLA-DRB1-compatible cadaver grafts.

Our previous studies revealed no difference in the graft success rate for living related and cadaver grafts [1–3] within the same HLA-DRB1 matching grade. The 5-year success rate for the two donor graphs was 96 % vs 92 % in the HLA-DRB1-compatible cases, 72 % vs 69 % in the HLA-DRB1 mismatch group and 72 % vs 67 % in the HLA-DR mismatch group [6]. There was no indication of any significant impact of delayed graft function on long-term kidney transplant outcome in these cases. Similarly, our current study clearly shows that delayed graft function does not influence the long-term success rate in cases without mismatches for HLA-DRB1.

Taken together, these findings have certain implications for the allocation of kidneys in the future with, no doubt, more of them going to HLA(-DRB1)-matched recipients. Total ischemia time will not need to be prolonged, since genotyping can be performed between the diagnosis of brain death and subsequent cardiac arrest, and the long-term results will be optimized.

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