A link between the outcome of living unrelated kidney transplantation and HLA compatibility: a preliminary report

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Abstract

Introduction: Within the different variables affecting renal allograft outcome in the case of HLA matching, there is continued controversy. There are very few studies regarding this issue in grafts from living unrelated donors (LURDs). We aim to assess the impact of HLA compatibility on genetically unrelated renal transplantation.

Material and methods: Four hundred and one kidney grafts from LURDs were analyzed. The transplantation procedures were performed in Baqiyatallah hospital, Tehran, Iran, during the period between 1999 and 2002. HLA-A, -B and -DR loci were typed with PCR techniques both in donors and recipients. Based on the number of HLA mismatches, we grouped patients to Group I (0-4 HLA mismatches) and Group II (5-6 HLA mismatches). Three-year graft survival rates were compared in the study groups.

Results: From 358 pairs of donors and recipients, 242 (67.6%) had 0-4 and 116 (32.4%) pairs had 5-6 HLA-A-B-DR mismatches. The groups were not significantly different in terms of donor and recipient age difference, donor and recipient gender, ischemia time, follow-up time, and cyclosporine dose. Three-year graft survival was 83% for recipients with 0-4 HLA mismatches and 54% for those with 5-6 mismatches (p=0.001). Three-year graft survival was 83% and 54% for those recipients with 0 and 1-2 mismatches in HLA-A respectively (p=0.014), 77% and 64% for those with 0 and 1-2 mismatches in HLA-B respectively (p=0.029), and 74% and 62% for those with 0 and 1-2 mismatches in HLA-DR respectively (p=0.003). From the variables, including number of HLA mismatches, donor and recipient age and HCV infection, that significantly affect 3-year graft survival, all except donor age remained significant in the model.

Conclusions: Number of HLA mismatches, along with other variables including age of recipient and HCV infection, significantly affects survival of the allograft. If the result of this preliminary report is confirmed by future studies, the use of graft with a lower number of mismatches will be recommended for use, regardless of the type of allele.

Key words: HLA, HLA compatibility, graft survival, kidney transplantation, living donors.

Introduction

The rate of kidney donation by living donors varies worldwide [1], and it is the source of graft in about 20% of transplantations [2]. The main

region in the world that benefits from living donors for renal transplantation is probably the Middle East where about 85% of all transplant kidneys are donated by living subjects [3], and Iran has possibly the highest proportion among MESOT countries with up to 90% living donors [4, 5]. In Western countries, too, donation by living subjects has recently increased to become the main source of kidney transplants [6-8]. This is the case in the United States [2, 9], the world's wealthiest and most technologically advanced country, and it has been reported that living donors are often considered as the first source of kidney transplants in this country [9].

Living unrelated donors (LURD), the biggest source of transplant kidneys in Iran at nearly 80% of transplants [2, 5], are defined as living subjects who are genetically unrelated to their recipients [10]. The cause of such increasing interest among several countries in allocating transplant kidneys from LURDs is the possibility to diminish the time recipients spend on waiting lists for transplantation and to improve their survival [11, 12].

Iran with its high number of LURDs [5] is an appropriate region to examine the probable effect of HLA compatibility on graft survival. We assessed the impact of HLA compatibility between kidney recipients and their genetically unrelated donors – along with other demographic and clinical variables – on graft survival.

Material and methods

Four hundred and one primary kidney grafts from living donors with no blood relation to the recipients were studied. All transplantations were performed by one operation team in Baqiyatallah hospital, Tehran, Iran, during the 3-year period between 1999 and 2002. The transplant recipients included in this analysis had all undergone transplantation for the first time. The immunosuppressive regimen consisted of cyclosporine, mycophenolate mofetil and prednisolone for all transplant recipients. We used recommendations by the International Consensus Statement for comparison of cyclosporine 2 hours post dose (C2 level) in the study groups [13]. Since panel reactive antibody (PRA) levels in almost all patients were less than 10%, we did not analyze the effect of PRA on graft survival in this study.

HLA allele typing

Medium resolution allele typing for HLA-A, B and DRB1 loci was performed using PCR amplification followed by sequence-specific oligonucleotide probing (PCR-SSOP), (Dynal Biotech Ltd; Wirral, U.K.). Amplified sequences were hybridized to arrays of immobilized probes (35 probes for HLA-A, 56 for HLA-B, and 38 for HLA-DRB1).

HLA Mismatches

The number of HLA antigen mismatches was defined as the number of HLA antigens present in the donor but absent from the recipient. HLA-DR antigens were considered mismatched if broad HLA-DR antigens (HLA-DR 1 to 10) were present in the donor but absent from the recipient. If only one antigen was detected at any of the three loci (A, B, or DR), homozygosity at that locus was assumed. Based on the number of HLA mismatches, we grouped patients into Group I (0-4 HLA mismatches) and Group II (5-6 HLA mismatches) [14].

Statistical Analysis

Data analysis was conducted using SPSS version 11 for Windows. We used independent sample t-test and also x2 test to compare the groups by means of demographic and clinical variables. Multivariate (Cox proportional hazards and Bailey-Makeham) and univariate (Kaplan-Meier) methods were used to estimate the association of mismatches and graft survival. Three-year graft survival rates were computed according to the method of Kaplan and Meier. Log rank test was used to compare survival between study groups according to HLA mismatches. We could not assess the difference in outcome of subpopulations regarding the 0, 1-3 and 4-6 mismatches, because only 2 recipients had 0 mismatches, and a p-value less than 0.05 was considered statistically significant.

Results

Subjects: The mean age of recipients was 43.0±19.5 years (range, 18-60 years). Of 358 persons, 239 (66.7%) were male and 119 (33.3%) female. All subjects received their first kidney from a LURD.

HLA mismatches: From 358 pairs, 242 pairs (67.6%) had 0-4 HLA-A-B-DR mismatches and 116 pairs (32.4%) had 5-6. Three-year graft survival was 83% for those recipients with 0-4 HLA-A-B-DR mismatches and 54% for those with 5-6 mismatches (p=0.395).

HLA antigen data showed that the frequency of 2-antigen mismatches for each locus was 31% for HLA-A, 39% for HLA-B, and 55% for HLA-DR. Two (0.6%), 4 (1.1%), 40 (11.2%), 72 (20.1%), 124 (34.6%), 82 (22.9%) and 34 (9.5%) pairs had 0, 1, 2, 3, 4, 5, and 6 HLA-A-B-DR mismatches, respectively.

Some demographic and clinical data of the study groups are presented in Table I.

Graft Survival according to the number of HLA mismatches: Three-year graft survival was 83% for recipients with 0-4 HLA mismatches and 54% for those with 5-6 mismatches (p=0.001). Three-year graft survival was 83% and 54% for those recipients with 0 and 1-2 mismatches in HLA-A respectively (p=0.014), 77% and 64% for those with 0 and

Table I. Comparison of demographic and clinical data of study groups

	Group 1 0-4 HLA mismatches N=242	Group 2 5-6 mismatches N=116	Significance
Donor-recipient Age Difference	7.2±6.4	7.6±6.8	NS
Donor Gender (male)	201 (83%)	94 (81%)	NS
Recipient Gender (male)	162 (67%)	75 (65%)	NS
Recipient Age	43.6±19.0	42.8±17.2	NS
Ischemia Time	14.2±5.2	13.9±4.1	NS
Follow-up time of each group (months)	43.2±12.8	45.6±13.1	NS
Mean (SD) Cyclosporine (0-2 months) (ng/ml)	933±260	921±247	NS
Cyclosporine (2-6 months) (ng/ml)	881±256	871±243	NS
Cyclosporine (>6 months) (ng/ml)	745±197	750±181	NS

1-2 mismatches in HLA-B respectively (p=0.029), and 74% and 62% for those with 0 and 1-2 mismatches in HLA-DR respectively (p=0.003).

Variables affecting allograft survival: Donor and recipient age and HCV infection significantly affect 3-year graft survival. Multivariate analysis showed that the impact of recipient age, HCV infection and number of HLA mismatches – all except donor age – remained significant in the model.

Discussion

In this study, we showed that there was a better survival for allografts received from LURDs with higher compatibility in HLA-A-B-DR: HLA-A, HLA-B and HLA-DR. This effect remained significant in the model, beside the significant impact of recipient age and hepatitis C virus (HCV) infection.

Most studies regarding the impact of HLA compatibility on graft survival have addressed cadaveric transplant kidneys, and many of them have shown that the rise in the number of HLA mismatches will progressively decrease the chance of graft survival [14]. In the case of living donors, it has not been very clear whether or not HLA matching is a main determinant of the survival of transplanted kidneys. Some studies have reported that the outcome of kidney grafts from unrelated living donors is strongly influenced by HLA compatibility [15-17], and some have not [18-20]. In the study of Oien et al, human leukocyte antigen (HLA)-DR matching was a risk factor for early acute rejection episodes, but other HLA mismatch profiles did not significantly affect the transplantation outcome [21]. Mizutani et al in 2007 reported a link between increase in the strength of Anti-HLA-Specific Antibody and subsequent increase in serum creatinine levels of renal recipients [22].

Most who have reported the impact of HLA compatibility on graft survival have explained their finding with the immunological basis of chronic rejection. Recent studies have shown that indirect allorecognition pathways are important in the immunologic background of chronic rejection [23]. These pathways occur when the donor's alloantigens are processed by the recipient's antigen-presenting cells and the processed alloantigens are then presented to host CD4 T cells. Given that HLA class I antigen is the most abundant alloantigen on renal cells, the extent of HLA class I mismatch is thought to be associated with chronic rejection and kidney graft loss [24].

Most authors who have not found any correlation between HLA matching and living donors, have justified their findings with some theories, the most important of which is the fit-and-match hypothesis [9]. According to this hypothesis, in the case of living donors, while all donors are healthy and there is no activation of immunity, which activates by the process of death in the phase of cold ischemia in cadaveric donors considering that the process of death releases some cytokines that damage kidneys in deceased donors, HLA matching has little effect on grafts taken from living donors as compared to cadaveric donors [25].

In selecting LRDs, priority is given to the candidate who has the best HLA match with the recipient. For LURD transplants, however, HLA matching has been reported to not be very practical [5], and some transplantation protocols do not recommend HLA typing for living unrelated donors [26]. Some authors have recommended not allocating kidneys with respect to HLA matching, considering that finding a fully HLA-matched recipient for a given donor is not practical due to the allelic diversity of the loci [23].

We think HLA matching in LURDs should be considered important for two reasons. Firstly, if recipients and donors are registered at a data bank, allocating kidneys with respect to HLA matching will be possible. Secondly, although we are almost

unable to provide fully matched donors and recipients, we can lower the number of mismatches that seem to affect graft survival.

In the new immunosuppressive era, donor-recipient HLA mismatches are going to be neglected. This may be based mainly on the fact that the HLA difference in graft survival is thought to be overcome by utilisation of more potent immunosuppressives. This approach may add another risk of graft loss due to drug toxicity. Reminders of the positive impact of HLA compatibility on allograft survival may provide the opportunity to reduce immunosuppressive doses for those with low mismatch numbers. We should mention that in this retrospective study, as a limitation, we did not have access to important data including delayed graft function, acute cellular rejections and causes for graft loss.

Conclusions

In conclusion, our preliminary findings highlight that the number of HLA mismatches significantly affect survival of the allograft. The use of graft with a lower number of mismatches is recommended to be used, regardless of the type of allele.

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