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Impact of HLA-A-B-DR Matching in Kidney Transplantation: Graft and Patient Survival During Five Years

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Objectives: A successful outcome of renal transplantation depends on various components, with one primary factor being donor and recipient ABO and human leukocyte antigen (HLA) compatibility. The primary aim of our investigation was to determine the impact of HLA-A-B-DR matching on overall and five-year graft and patient survival and to evaluate and improve kidney transplant outcomes. **Methods:** A total of 70 adult, immunologically low-risk, first-transplant recipients were enrolled in our retrospective study. HLA-A-B-DR typing was performed by the polymerase chain reaction sequence specific primer (PCR-SSP) method. **Results:** HLA compatibility was carefully matched before transplantation resulting in 81.4% renal transplants with 0-3 HLA mismatches (MM). Overall graft and patient survivals were 52 (74.3%) and 60 (85.7%), respectively, in 70 cases. Five-year graft and patient survivals were 23 (67.6%) and 29 (85.3%), respectively, in 34 cases. A significantly higher rate of graft and patient overall survivals were revealed in the 0-1 MM group compared with those in the 2-3 MM and 4-6 MM groups ($p = 0.030$ and $p = 0.015$, respectively). **Conclusion:** A highly statistically significant correlation of HLA matching enhancing kidney graft and patient survival rates was determined in our analysis. Better HLA matching was associated with better graft and patient survival. Despite the current era of potent immunosuppressive therapy and improved patient management, the data continue support organ sharing based on HLA matching in kidney transplantation.

Keywords: Kidney, Graft Survival, HLA-Antigens

Introduction

Chronic kidney disease (CKD) is relatively common in Mongolia. A recent report showed that 13.9% of the Mongolian population had proteinuria or an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 as calculated by the Modified Diet in Renal Disease equation [1, 2]. Renal transplantation is the preferred long-term therapy for most patients with end-stage renal disease. Renal transplantation provides better quality of life [3, 4], increases life expectancy [5], and is more cost-effective [6, 7] than either peritoneal dialysis or hemodialysis.

The outcome of kidney transplantation is determined by graft and patient survivals. A one-year kidney graft survival of 90-95% is observed in most recognized transplant centers. Recent reports have indicated the one, five, and ten-year adjusted deceased donor kidney graft survivals are 91%, 69%, 43%, whereas living donor graft survivals are 96%, 81%, 59% respectively [8]. Tumurbaatar et al. published data revealing Mongolian kidney transplant outcomes with a one-year graft survival at 80% and patient survival at 94% [9].

Successful outcomes of renal transplantation depend on several factors such as histocompatibility, immunosuppression, postoperative management and laboratory support system. Mismatches between donor and recipient at the human leukocyte antigen HLA-A-B-DR also reduce long-term graft survival in renal transplantation. Opelz et al. showed ten years following transplantation the graft survival rate of first cadaver kidney transplants with a complete mismatch (6 HLA-A-B-DR mismatches) was 17% lower than that of grafts with no mismatch [10]. Among first cadaver transplant recipients with positive antibody reactivity against >50% of the test panel, the difference in graft survival at five years between patients with 0 or 6 mismatches reached 30% [10]. In the current era of immunosuppression, HLA matching is offering better long-term graft outcomes to most patients [11, 12, 13-16].

Kidney transplantation has been conducted successfully in Mongolia since 2006. The donors are selected based upon HLA matching. However, there is currently no published data available on long-term graft and patient survival and the impact of HLA-A-B-DR matching on survival. The aim of our study was to determine the effect of HLA-A-B-DR matching on overall and five-year graft and patient survival. Our primary goal in evaluating kidney transplant outcome was to define the best methodologies to be initiated for improving the long-term survival results in Mongolian kidney transplantation.

Materials and Methods

1. Study subjects

This retrospective antigen matching study began in 2013 and 70 kidney recipients were enrolled who received transplants from August 2006 until January 2014. Follow-up monitoring was performed at the First Central Hospital of Mongolia. Inclusion criteria for study subjects included: (1) being first-time adult transplants, (2) having panel reactive antibodies at <30% from a random pre-operative test panel by the ELISA test method, (3) having no donor-specific antibody observed (Lifecodes Single Antigen Beads, Immucor, Norcross, GA, USA), (4) having negative serologic cytotoxic cross match test, and (5) being ≥5 years old at the time of transplantation. Since immunosuppression is an important factor influencing the outcome of transplantation, the cyclosporine mono-therapy group was selected for determining five-year survivals. Patient medical files were used to collect data on demographic and clinical characteristics regarding their transplant status, age at the time of transplantation, sex, primary kidney disease, donor status, date of transplantation, dialysis date and death date.

Prior to transplantation, HLA DNA typing using the polymerase chain reaction sequence specific primer (PCR-SSP) method was performed for all donor recipient pairs. Briefly, blood samples from participants were collected and the extraction of DNA was performed according to the Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA). DNA typing for HLA-A-B-DR was performed by the PCR-SSP method according to manufacturer's manual. HLA-A-B-DR SSP (Bio-Rad, Germany) two-digit, low-resolution typing results were collected retrospectively from HLA laboratory files. The transplant recipients were subdivided into three groups: (1) zero to one antigen mismatching (0-1 MM), (2) two to three antigens mismatching (2-3 MM), and (3) four to six antigens mismatching (4-6 MM). The results were analyzed in relation to graft and patient survival.

2. Immunosuppressant protocols

The renal transplant team used two different immunosuppressive protocols with Alemtuzumab (Campath-1H; anti-CD52 monoclonal antibody): (1) 20-30 mg preoperatively and (2) 20-30 mg on the fourth postoperative day as the induction therapy. Between August 2006 and December 2009, 34 patients (48.6%) received cyclosporine mono-therapy trough level aimed at 100-150 ng/mL. From 2010, 36 recipients (51.4%) received triple therapy: (1) prednisolone, (2) either cyclosporine or tacrolimus, and (3) either mycophelate mofetil (MMF) or imuran. HLA-A-B-DR mismatching impact on cyclosporine was determined for the mono-therapy group and also all 70 participants.

3. Statistical analysis

The Kaplan-Meier method was used to analyze the impact of HLA-A-B-DR on graft and patient survival. All tests were performed with the use of SPSS for Windows, version 17.0 software (SPSS, Chicago, IL, USA). A p-value of <0.05 was considered to be statistically significant.

4. Ethical statement

The study was approved by the Ethical Review Board of the Mongolian National University of Medical Sciences and was conducted under the Declaration of Helsinki guidelines for human subjects research.

Results

Kidney transplantation has been conducted successfully in Mongolia since 2006 and the kidney transplant team has performed in excess of 100 kidney transplants to date. The number of successful renal transplants has increased annually for the past five years and the growth of transplantation was determined and compared to previous years cases (Figure 1).

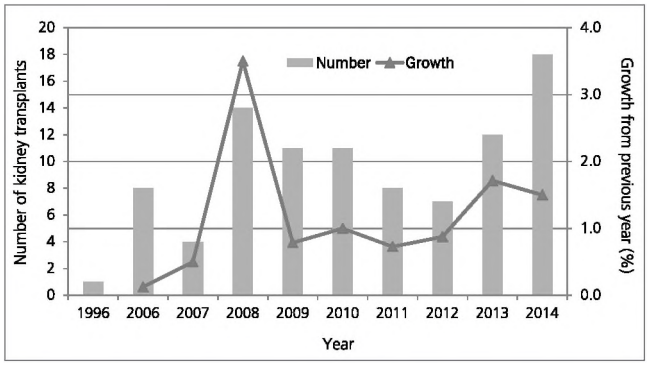

Figure 1. Number of kidney transplants performed per year and percent growth from year to year.

Overall graft and patient survivals were 52 (74.3%) and 60 (85.7%), respectively in 70 cases. Mean patient follow-up time was 39.6 ±25.9 months and mean kidney graft follow-up time was 36.6 ±23.7 months for 70 cases. The profile of the observed transplant recipients in this study is shown in Table 1. Recipient mean age at transplantation was 34.9 ±9.7 years. Male recipients numbered 54 (77.1%) and female recipients numbered 16 (22.9%). Primary causes of chronic kidney failure were glomerulonephritis (n = 68, 97.2%), diabetes (n = 1, 1.4%) and polycystic kidney (n = 1, 1.4%). The mean age of the donor at transplantation was 40.2 ±10.9 years. Living related donors numbered 63 (90%) and brain-dead donors numbered 7 (10%).

Table 1. Demographic and baseline characteristics

Characteristics	n (%)
(A) Recipients	
Mean age at transplantation (years)	34.9 ±9.7[f]
Sex	
Male	54 (77.1)
Female	16 (22.9)
Mean follow-up time after kidney transplantation (months)	39.6 ±25.9[f]
Mean kidney graft follow-up time (months)	36.6 ±23.7[f]
Underlying renal disease for kidney transplantation	
Glomerulonephritis	68 (97.2)
Diabetes mellitus	1 (1.4)
Polycystic kidney disease	1 (1.4)
HLA-A-B-DR antigen mismatch	
0 MM[a] (full matching)	5 (7.1)
1 MM	3 (4.3)
2 MM	18 (25.7)
3 MM	31 (44.3)
4 MM	9 (12.9)
5 MM	3 (4.3)
6 MM (full mismatching)	1 (1.4)
(B) Donors	
Mean age at donation (years)	40.2 ±10.9[f]
Donor type	
Living donors	63 (90)
Cadaveric donors	7 (10)
Immunosuppressive drug regimens	
Campath[b]+CyA[c] (in 2006-2009)	34 (48.6)
Campath+CyA/FK[d]+MMF[e]+Steroid (in 2010-2013)	36 (51.4)

[a]MM = mismatch [b]Campath = Campath-1H [c]CyA = cyclosporine A [d]FK = prograf, tacrolimus [e]MMF = mecophenolate mofetil, steroid/corticosteroid [f]Mean ±SD

The association between the HLA-A-B-DR antigen matching and kidney graft and patient survival was analyzed on the basis of retrospective PCR-SSP typing. Graft and patient survivals were computed with the Kaplan-Meier method. The result of HLA DNA typing showed that five transplants had a perfect six-antigen matching at HLA-A-B-DR. Of the 70 transplant recipients only one transplant was a complete 6-HLA antigen mismatch. There were 8 (11.4%) cases with 0-1 MM, 49 (70%) cases with 2-3 MM and 13 (18.6%) cases with 4-6 MM. The 4-6 MM group was found to have significantly lower three and five-year graft (71% and 35%, respectively, p = 0.030, Figure 2) and patient survivals (80% and 40%, respectively, p = 0.015, Figure 3) as compared to 0-1 MM (100%).

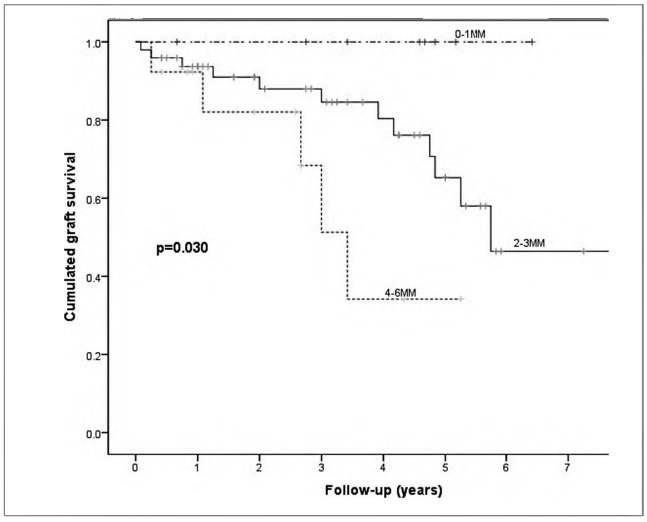

Figure 2. Kidney graft survival of transplant recipients with 0-1 MM for HLA-A-B-DR compared to those with 2-3 MM and 4-6 MM in 70 transplant recipients.

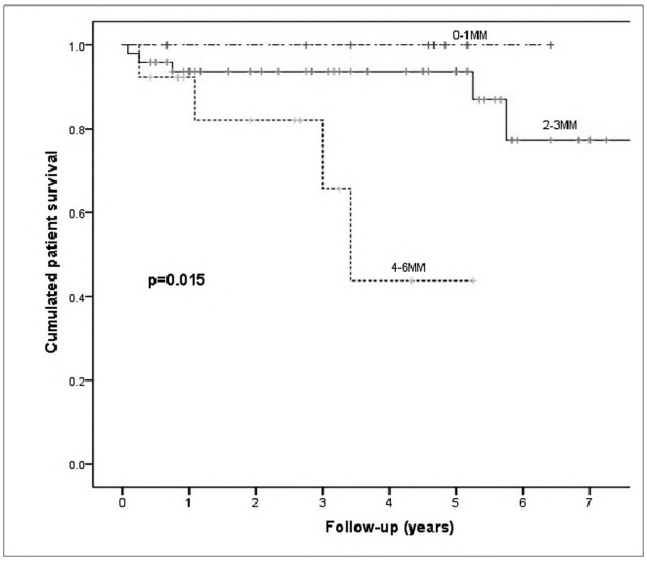

Figure 3. Patient survival of transplant recipients with 0-1 MM for HLA-A-B-DR compared to those with 2-3 MM and 4-6 MM in 70 transplant recipients.

Furthermore, the association of HLA matching, immunosuppressive therapy and long-term graft survival was analyzed. Campath-1H induction with the cyclosporine maintenance mono-therapy group, which had transplants between August 2006 and January 2010, were chosen for long-term survival analysis and HLA-A-B-DR matching effect. A similar pattern was observed to that mentioned above. Five-year graft and patient survivals numbered 23 (67.6%) and 29 (85.3%), respectively, out of 34 cases. The mean patient follow-up period after kidney transplantation was 58.7 ±20.1 months and the mean kidney graft follow-up period was 53.0 ±19.6 months for 34 cases. In the mono-therapy group, the 4-6 MM group was found to have a significantly lower three and five-year graft (75% and 30% respectively, p = 0.037, Figure 4) and patient survival (65% and 30% respectively, p = 0.001, Figure 5) compared to the 0-1 MM group (100%).

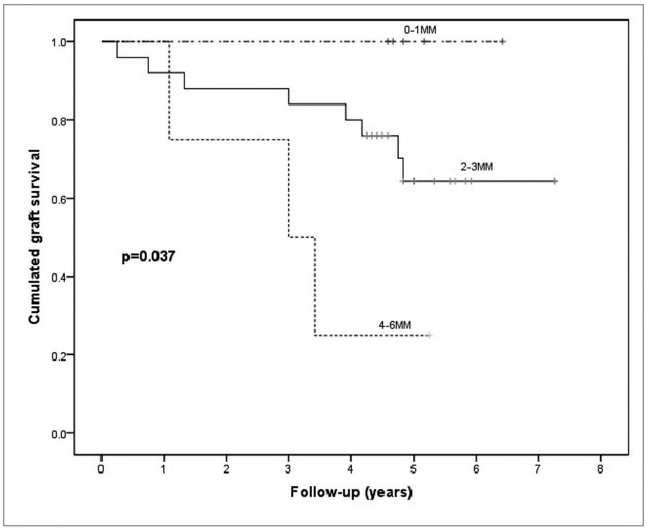

Figure 4. Kidney graft survival of transplant recipients with 0-1 MM for HLA-A-B-DR compared to those with 2-3 MM and 4-6 MM in 34 transplant recipients who were treated with cyclosporine mono-therapy.

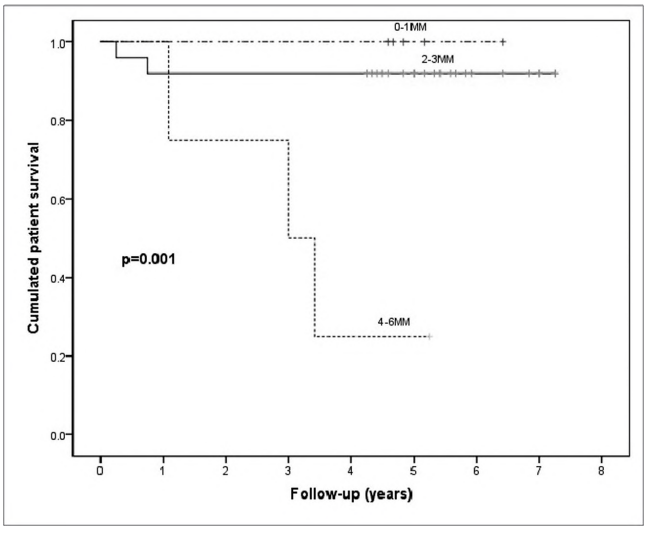

Figure 5. Patient survival of transplant recipients with 0-1 MM for HLA-A-B-DR compared to those with 2-3 MM and 4-6 MM in 34 transplant recipients who were treated with cyclosporine mono-therapy.

Discussion

The present retrospective study was the first long-term survival investigation based on HLA-A-B-DR matching for Mongolian

kidney transplantation. The study demonstrated that five-year graft and patient survival rates were lower when HLA-A-B-DR mismatches were >3 compared with results from well-established centers, for example 67% in USA [8, 17, 18]. Patients whose kidney graft failed stayed in hemodialysis treatment so there was not a difference between patient survival with or without cyclosporine mono-therapy. Most of the kidneys were harvested from living related donors (90%), who were relatively young female subjects. Because donors are selected based upon HLA matching, 81.4% of recipients were relatively well-matched. Our study also demonstrated the clinical relevance of HLA-A-B-DR matching by the DNA method for kidney transplantation. A highly statistically significant positive effect of HLA-A-B-DR matching on kidney graft and patient survival rates was found in our analysis. Our study is consistent with those of earlier studies in the literature in terms of the influence of HLA matching on graft and patient outcome [10, 19-22].

Since our study was retrospective and immunosuppressive therapy is a major factor in kidney graft outcome, we selected Campath-1H induction with cyclosporine mono-therapy group for the five-year survival analysis. The antigen matching effect also seemed more prevalent in this therapy group. However some clinicians support minimizing HLA antigen mismatching in kidney transplantation because of the introduction of efficient immunosuppressive therapy. Graft survival seemed lower with more mismatching, however this could be center dependent or immunosuppressive dependent. We could not find Campath-1H induction with cyclosporine mono-therapy graft survival five-year results in the literature.

Our study has conclusively shown that HLA antigen mismatching, adversely affects kidney graft survival in both short and long-term post-transplant survival. Methodologies used in HLA compatibility testing have improved over time, becoming more sophisticated. Historically, serology and cellular-based assays such as the mixed lymphocyte culture and complement dependent lymphocytotoxicity assay were used to determine HLA antigens. We used DNA-based PCR-SSP. The method was cost effective and suitable for living relative kidney transplantation. However we enrolled all the cases at the beginning of kidney transplantation and a limitation of this study was a low number of subjects. Survival analysis takes long time follow-up so for future research it could be better to evaluate kidney graft function by glomerular filtration rate and biopsy proven acute rejection as a follow-up one year after kidney transplantation.

In conclusion, we found a highly statistically significant correlation of HLA matching enhancing kidney graft and patient survival rates. Better HLA matching was associated with better graft and patient survival. Despite the current era of potent immunosuppressive therapy and improved patient management, the data continue support organ sharing based on HLA matching in kidney transplantation. Longitudinal cohort studies are needed in the future to exhibit an improved transplantation outcome.

Conflict of Interest

The authors state no conflict of interest.

Acknowledgements

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