Pre-transplant donor specific antibody and its clinical significance in kidney transplantation

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Summary

Background: **The traditional method for assessing HLA antibodies in recipient serum samples is the complement-dependent cytotoxicity testing (CDC). Recently, the highly sensitive microbead-based Luminex assay was introduced and can detect low levels of anti-HLA Abs.**

Objective: **To determine the impact of pre-transplant donor-specific HLA antibodies (DSA) detectable by Luminex, despite a negative CDC crossmatch, on the outcomes of kidney transplantation. The correlation and cut-off value of panel reactive antibody (PRA) and DSA was also evaluated.**

Methods: **Pre-transplant sera from 116 kidney transplant recipients with a negative CDC crossmatch were assessed for donor-specific HLA antibodies by using Luminex single antigen beads. The patients received kidney transplants at Ramathibodi Hospital between January 2003 and December 2007. The results were correlated with kidney graft outcomes.**

Results: **DSA were found in 24.1% (28/116) of all recipients. Of the twenty-eight DSA positive patients, four developed antibody-mediated rejection (AMR) (4/28 =14.3%). All these 4 patients had positive C4d staining in their biopsies. Of the eighty-eight DSA negative patients, two developed AMR (2/88 =2.3%). The AMR occurred more frequently in the DSA positive group than in the DSA negative group (14.3% versus 2.3%. The patient and graft survival were similar in both groups. The strength of pre-transplant DSA was not associated with the incidence of rejection episodes.**

Conclusion: **There was a higher incidence of AMR in patients with pre-transplant DSA despite a negative CDC crossmatch. However, pre-transplant DSA detected by Luminex had no statistically significant impact on delayed graft function, patient survival and graft survival.** ***(Asian Pac J Allergy Immunol 2012;30:48-54)***

Key words: *donor-specific antibodies, antibody-mediated rejection, Luminex*

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Introduction

Preformed antibodies directed against human leukocyte antigens (HLA) have a major impact on allograft survival and form a significant barrier in renal transplantation. Binding of these antibodies to HLA antigens on endothelial cells results in alloantibody-mediated tissue injury and subsequently allograft rejection.[1] Several laboratory tests are performed to reduce the risk of immunologic rejection in renal transplantation. Conventionally, the complement-dependent lymphocytotoxicity (CDC) crossmatch (XM) has been routinely used to detect preformed, donor-specific complement-fixing antibodies.[2] Since CDC-XM has been widely used, the incidence of hyperacute rejection has significantly reduced. However, antibody-mediated

rejection does occur in patients with a negative crossmatch result,[3] suggesting that the standard CDC assay lacks sensitivity in detecting clinically significant antibodies.

Recently, new technology using purified human leukocyte antigen (HLA) molecules coated on microbeads, Luminex single antigen beads, has been developed. Because of its high sensitivity, this new technique is able to detect very low levels of HLA antibodies (HLA Abs). Furthermore, it is able to determine antibody specificities more accurately.[4] The clinical significance of pre-transplant donor-specific antibodies (DSA) detected by Luminex testing, despite negative CDC-XM, would be useful for clinical decision making. The aim of this study therefore was to investigate the clinical outcomes of renal transplant recipients with pre-transplant DSA and negative pre-transplant CDC-XM, compared to those of patients without pre-transplant DSA.

Methods

Patients and Samples

A retrospective cohort study of recipients of kidney transplants at Ramathibodi Hospital, Mahidol University, Bangkok, Thailand was performed. Between January 2003 and December 2007, 334 both living and deceased donor kidney transplants were performed at our center. All kidney transplant recipients underwent CDC-XM testing with their donors, as well as testing for PRA by the CDC method with prolonged incubation times and had negative T-cell and B-cell CDC-XM at the time of transplantation. All recipients were followed up until June, 2009, with a median follow-up of 2.24 years.

From 334 kidney transplant patients, 272 patients had negative PRA and 62 had positive PRA by CDC assay in their pre-transplant sera. From 272 patients with negative PRA by CDC assay at pre-transplant, fifty-nine patients were randomly selected for inclusion in our study. From 62 patients with positive PRA by CDC assay pre-transplantation, 57 patients had pre-transplant sera available and were included. Stored pre-transplant sera from 116 (59 randomly selected from PRA negative group and 57 sera available from PRA positive group) patients were then tested for the presence of HLA Abs using the multiplex technology. The selection of study patients are detailed in Figure 1. We identified 28 recipient pre-transplant sera positive for DSA, despite negative pre-transplant CDC-XM and 88 recipient sera without pre-transplant DSA (control group).

The medical records of the study patients were reviewed to obtain their baseline characteristic and

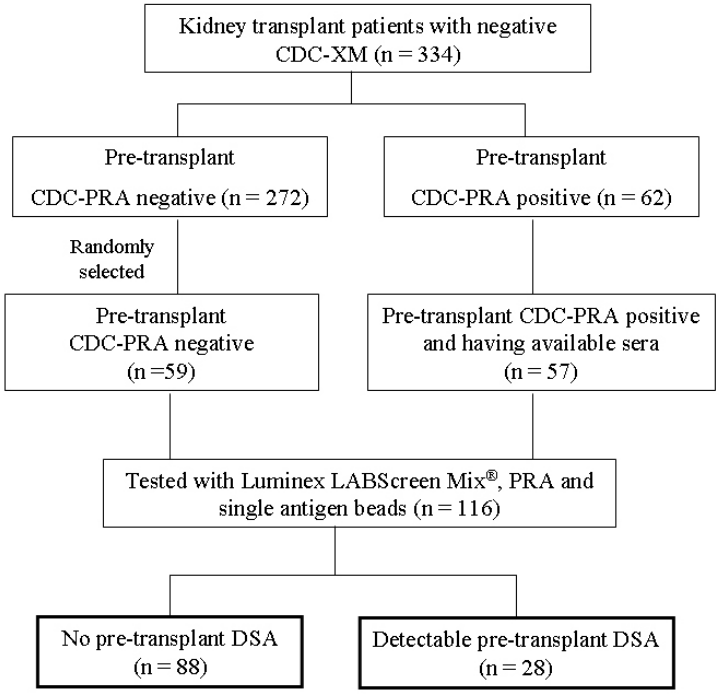

Figure 1. Selection of patients: Stored sera from 116 (59 randomly selected from PRA negative group and 57 sera available from PRA positive group) patients were tested for the presence of DSA by Luminex single antigen beads.

clinical outcomes. The following recipient variables were assessed: age of recipient at transplantation, sex of recipient, cause of end-stage renal disease and history of transplantation. Donor variables included the donor's source of kidney graft. Transplant variables included type of induction therapy, presence of delayed graft function (DGF), and initial immunosuppressive regimen.

This study was approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

Detection of DSA

Pre-transplant sera were tested for the presence of HLA Abs by LABScreen Single Antigen multiplex solid phase immunoassay (One Lambda, Canoga Park, CA) according to the manufacturer's instructions. In brief, multiplexed microbeads, each coated with a single antigen, were incubated with the patient's serum for 30 minutes and washed to remove unbound antibody. Anti-human immune-globulin antibody conjugated to phycoerythrin was added for 30 minutes and washed. Then the microbeads were examined for fluorescence by LABScan 100 flow analyzer (Luminex, Austin, Tx) and data were analyzed using HLA Visual software (One Lambda). The cut-off level was defined as a baseline normalized ≥500 mean fluorescence intensity units (MFI).

Definition of clinical outcomes

Biopsy-proven acute rejection was defined as a rejection episode which occurred within 6 months after renal transplantation. The diagnosis of acute cellular rejection and antibody-mediated rejection were based upon Banff 07 classification[5]. Delayed graft function was defined as the need for dialysis within the first week after transplantation.

Statistical analysis

Continuous variables were described as means (standard deviation, SD) and median (range) for data with normal distribution and non-normal distribution respectively. Categorical variables were described as proportion and Chi-square test was used to compare the difference between groups for continuous and categorical data respectively. Graft survival or patient survival was described by Kaplan-Meier survival analysis, using graft failure or death as the outcome of interest. A patient was considered as censored at the time of last contact if he/she was lost to follow-up, referred to The correlation and cut-off of PRA and DSA were determined by using a receiver operating characteristic

Table 1. Patient characteristics

Variable	All N=116	DSA-positive N=28 (%)	DSA-negative N=88 (%)	*p*-value
Age of recipient, mean (SD)	43.3 (12.6)	44.3 (11.9)	43.0 (12.9)	0.643
Sex of recipient				
Male	65 (56)	5 (17.9)	60 (68.2)	<0.001
Female	51 (44)	23 (82.1)	28 (31.8)	
Type of transplant donors				
Living donor	57 (49.1)	13 (46.4)	44 (50)	0.742
Deceased donor	59 (50.9)	15 (53.6)	44 (50)	
Age of donor, mean (SD)	37.3 (13.3)	38.1 (14.8)	37.0 (13.0)	0.800
Cause of ESRD				
Unknown	80 (68.9)	17 (60.7)	63 (71.6)	0.140
IgA nephropathy	13 (11.2)	5 (17.9)	8 (9.0)	
Diabetic nephropathy	11 (9.5)	1 (3.6)	10 (11.4)	
Lupus nephritis	4 (3.5)	2 (7.1)	2 (2.3)	
Focal segmental glomerulosclerosis	2 (1.7)	0 (0)	2(2.3)	
Congenital cystic disease	1 (0.9)	0 (0)	1 (1.1)	
Other	5 (4.3)	3 (10.7)	2 (2.3)	
Prior transplantation	8 (6.9)	6 (21.4)	2 (2.3)	0.003
HLA mismatch				
0	16 (13.8)	0 (0)	16 (18.2)	0.011
1-3	79 (68.1)	19 (67.9)	60 (68.2)	
4-6	21 (18.1)	9 (32.1)	12 (13.6)	
Pre-transplant PRA				
Negative	60 (51.7)	3 (10.7)	57 (64.8)	<0.001
Positive	56 (48.3)	25 (89.3)	31 (35.2)	
Cold ischemic time (hr), median (range)	0.67 (0.04,32)	17.2 (0.1, 28.3)	0.6 (0.04,32.0)	0.204
Induction				
None	73 (62.9)	12 (42.9)	61 (69.3)	0.010
Anti-thymocyte globulin	1 (0.9)	1 (3.6)	0 (0)	
Anti-CD25 monoclonal antibody	42 (36.2)	15 (53.6)	27 (30.7)	
Primary immunosuppression				
CsA/MMF/Pred	43 (37.1)	7 (25.0)	36 (40.9)	0.321
CsA/Aza/Pred	24 (20.7)	10 (35.7)	14 (15.9)	
CsA/Siro/Pred	4 (3.4)	1 (3.6)	3 (3.4)	
FK/MMF/Pred	21 (18.1)	5 (17.9)	16 (18.2)	
FK/Aza/Pred	5 (4.3)	1 (3.6)	4 (4.6)	
Other	19 (16.4)	4 (14.3)	15 (17.1)	

SD: standard deviation; ESRD: end stage renal disease; hr: hour; CsA: cyclosporine A; MMF: mycophenolate mofetil; Pred: prednisolone; FK: tacrolimus; Aza: azathioprine; Siro: sirolimus

(ROC) analysis. All analyses were performed using Stata statistical software, version 11.0 (Stata Corp., Collage station, Tx). *P* values <0.05 were considered statistically significant.

Results

Patient demographic and medical characteristics

Between January 1, 2003 and December 31, 2007, a total of 334 patients received renal transplants at our center. One hundred and sixteen patients were included in the study, as described above. All 116 patients had negative pre-transplant CDC-XM. The baseline characteristics of the 116 patients are shown in Table 1. There were no statistically significant differences between patients with or without DSA in terms of type of transplant donor and immunosuppressive regimens.

Correlation of DSA and Clinical outcomes

Among the 116 patients, 28 patients (24.1%) had pre-transplant DSA (DSA positive group). Identification of the antibodies showed that 10 patients (8.6%) had anti-HLA class I, 7 patients (6%) had anti-HLA class II and 11 patients (9.5%) had both anti-HLA class I and II in pre-transplant sera. Acute rejection episodes (any rejection within 6 months post-transplant) occurred in seven DSA-positive patients (7/28, 25%) and in thirteen DSA-negative patients (13/88, 14.7%). Although the percentage of patients with acute rejection episodes was higher in DSA-positive group than in DSA-negative group, it was not statistically significant (p =0.252). The percentage of patients with graft failure or death was also not statistically significant different between the DSA-positive and DSA-negative groups (Table 2). One-year and five-year survival were also analyzed using the Kaplan-Meier method. The analysis showed that the 1-year survival was not statistically different between the groups; 92.9% (74.4-98.2) in DSA positive and 96.6% (89.7-98.9) in DSA negative (Figure 2). Similarly, 5-year survival was not statistically different between both groups; 92.9% (74.4-98.2) in DSA positive and 92.7% (78.2-97.7) in DSA negative. In addition, rates of delayed graft function (DGF) were comparable between both groups (Table 2).

However, when we further subgroup the rejection episodes into cellular and antibody-mediated rejection, we found that antibody-mediated rejection (AMR) occurred more frequently in DSA-positive patients than in DSA-negative patients

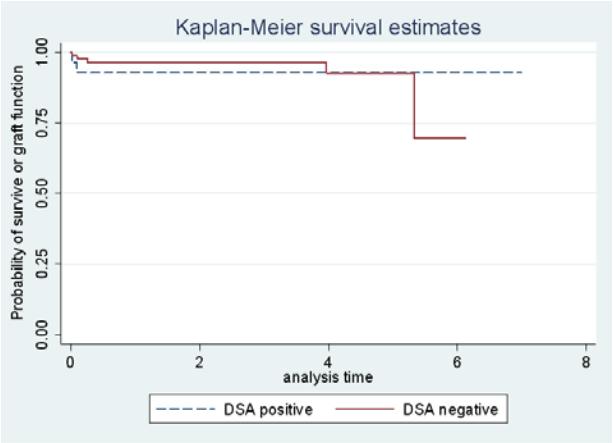

Figure 2. Kaplan-Meier survival curve, stratified by absence or presence of pre-transplant DSA detectable by Luminex assay. The survival was not statistically different between both groups (p = 0.9215).

(Table 2). Of the twenty-eight DSA positive patients, four developed AMR (4/28 = 14.3%). All these 4 patients had positive C4d staining in their biopsies. Of the eighty-eight DSA negative patients, two developed AMR (2/88 = 2.3%). These two patients also had positive C4d staining in their biopsies.

Correlation of DSA-MFI values and rejections

The analysis of the mean fluorescence intensity (MFI) of Luminex between DSA-positive patients with rejection (both acute and chronic rejections) and DSA-positive patients without rejection showed that the medians of MFI for both groups were not different. The pre-transplant DSA-MFI values of the eight patients with rejection episodes ranged from 1247 to 11654 (median 5685.9). In the twenty DSA-positive patients without rejections episodes, the pre-transplant DSA-MFI values range from 727.08 to 11744.56 (median 4555.6).

ROC analysis for optimal cut off point of PRA level

Since HLA-Ab identification with single antigen beads is very expensive, it is critically important for clinicians in resource-limited countries to evaluate how best to utilize this assay. Therefore, we determined the optimal cut-off point for PRA level (both PRA class I and II) by using Receiver Operating Characteristic (ROC) analysis in order to identify which sera should be further tested with Luminex single antigen beads. The analysis with ROC curve showed that PRA ≥ 10% resulted in the highest area under ROC curve (0.7861), with 78.57% sensitivity and 67.05% specificity (Figure 3).

Table 2. Comparison of clinical outcomes according to DSA status

	DSA-Positive N = 28 (%)	DSA-Negative N = 88 (%)	*p*-Value
Delayed graft function			
- Yes	8 (28.6)	24 (27.3)	0.89 (NS)
- No	20 (71.4)	64 (72.7)	
Graft failure or death			
- Yes	2 (7.1)	5 (5.7)	0.92 (NS)
- No	26 (92.9)	83 (94.3)	
Acute rejection			
- Antibody-mediated rejection	4 (14.3)	2 (2.3)	0.066 (NS)
- Cellular rejection	3 (10.7)	11 (12.5)	
- No	21 (75)	75 (85.2)	

NS = not significant

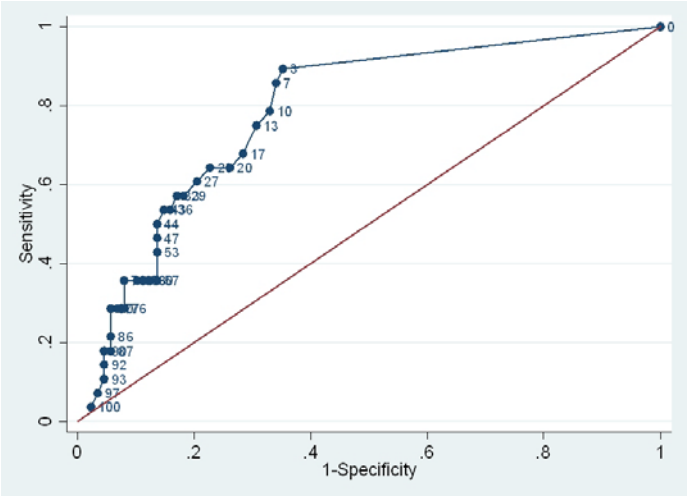

Figure 3. ROC analysis for the PRA cut-off value. The optimal PRA cut-off value for both PRA class I and II was 10%. The area under ROC curve was 0.7861.

Discussion

This study demonstrated the increased rate of antibody-mediated rejection (AMR) in patients with pre-transplant negative CDC-XM and pre-transplant DSA detectable by solid-phase immunoassay (Luminex). The 14.3% rate of AMR in DSA positive groups was higher than the 2.3% rate of AMR in the DSA negative groups. This is concordant with previous studies showing that pre-transplant DSA is associated with higher rejection rates.[6-7] Ishida et al. reported that 28 of a total of 125 patients (22%) were DSA-positive by FlowPRA microbeads, but negative by FCXM.[6] 16 of the 28 DSA-positive patients (57%) had biopsy proven antibody-mediated rejection. Further support for this notion comes from a study by Patel et al.[7] They evaluated sera from 60 transplant recipients and found that 20 patients had pre-transplant DSA detected by Luminex despite a negative FCXM. Of the 20 patients with DSA, 4 had AMR episodes (20%). The high rate of AMR in patients with pre-transplant DSA despite a negative crossmatch in their studies and our study confirms the clinical significance of the pre-transplant DSA identified by the new solid phase assay.

Although the presence of DSA in pre-transplant sera was associated with increased risk of AMR, it was not detrimental to graft survival or patient survival. This study demonstrated that the graft survival and patient survival were not significantly different between patients with DSA positive and DSA negative sera. In addition, the number of patients with acute rejection episodes and the rate of delayed graft function were similar in both groups. However, it has been shown that graft survival was significantly worse in patients with DSA than in those without DSA.[8] Nevertheless, several studies have confirmed our finding that there is no significant impact of pre-transplant DSA on long-term graft survival.[9-11] A study of 141 patients with negative CDC-XM and FCXM revealed that 16 of the 141 patients had DSA positive sera by Luminex and the 1-year graft and 5-year graft survival rates were not significantly different between the DSA-positive and –negative groups.[10] A recent study of 113 patients with negative CDC-XM sera also showed that the graft and patient survival were excellent in both the DSA-positive and –negative groups.[9] Similarly, the allograft function was comparable between DSA-positive and DSA-negative groups 4 years post-transplant.[12] Taken together, these data reveal similar graft survival in patients with or without pre-transplant DSA. Thus, the presence of pre-transplant DSA despite negative CDC or FCXM should not be considered as a contraindication to renal transplantation. It is worth mentioning that the impact of DSA detectable post-transplant on graft survival is different. A large patient cohort study showed that post-transplant detection of alloantibodies is associated with worse graft outcomes.[13-14]

Interestingly, a living-related kidney recipient in our study with rising titer of DSA post-transplant had a well-functioning graft. This patient with very low pre-transplant DSA titer (anti-DR13, -DR52 and -DQ6) was desensitized with plasmapheresis and intravenous immunoglobulin prior to transplantation.

Additionally, the anti-thymocyte globulin (ATG) was given for induction therapy. The DSA-MFI value of this patient was 4502 (anti-DR13, the highest of these DSA) before plasmapheresis. Afterwards, the MFI value decreased to 1247 on day 0 after plasmapheresis, however, it rebounded to 10491 on day 19 post-transplantation. Predictably, the kidney biopsy on day 18 post-transplantation showed positive C4d suggesting that antibody binding to the graft occurred, despite the absence of light microscopic abnormalities. Remarkably, this patient became DSA negative day 30 post-transplantation and hadnegative C4d staining in a kidney biopsy on day 90 and the serum creatinine level has remained stable at 0.9 mg/dL. It is possible that the patient was undergoing a state of accommodation. An experimental study has shown that pre-exposure of endothelial cells with a subsaturating concentration of HLA antibody conferred resistance to endothelial cells against complement-mediated lysis.[15] Incubation of endothelial cells with sub-saturating concentration of HLA Ab resulted in a significant up-regulation of the anti-apoptotic genes. In contrast, exposure of these cells to saturating concentration of HLA Ab leads to caspase-3 dependent cell death by apoptosis. This may explain why the grafts from several patients with DSA positive in our study continue to function well despite the presence of pre-transplant DSA.

It has been suggested that the strength of antibodies may be important in the sera of patients before transplantation[16]. However, we found that the mean concentrations of DSA-MFI, reflecting the amount of antibodies, were not different between patients with rejection episodes and without rejection. These data are consistent with tose from a previous study which showed that the rejection episodes could not been predicted from the value of pre-transplant DSA-MFI[9]. Recently, it has been shown that the DSA-MFI of peak serum predicted AMR better than DSA-MFI of current serum.[17] Together these data confirm that the strength of pre-transplant DSA does not correlate with the risk of AMR.

Patients who appear to be devoid of pre-transplant DSA may still be at risk of developing AMR. Indeed, 2 of 88 patients (2.3%) in the DSA negative group in our study developed AMR. Notably, one of these two patients had anti-Cw10 (reactive to HLA-Cw*03:02) and anti-Cw1 (reactive to HLA-Cw*01:02), while the other had major histocompatibility class I related chain (MIC) antibody. HLA-Cw and MIC are expressed on the cell surface of endothelial cells and thus are targets for humoral immunity associated with the rejection of kidney allografts. Several studies have addressed the significance of HLA-Cw and MIC antibodies in renal graft outcomes.[18-20] Couzi et al. reported that circulating anti-Cw antibodies were associated with acute rejection episodes and suggested that donor HLA-Cw typing should be performed to provide a high degree of accuracy for DSA identification by single antigen bead assay.[18] Zou et al. showed that MIC antibodies were associated with increased graft loss in renal allograft recipients.[20] More recently, Cox et al. demonstrated that MIC antibodies were significantly associated with acute rejection and graft dysfunction.[19] Unfortunately, HLA-Cw and MIC typing were not routinely performed in patients and kidney donors. We speculate that the AMR which developed in the two patients without DSA in our study may be induced by HLA-Cw antibodies and MIC antibody, respectively.

It is important to note that there is no consensus on the positive cut-off level for DSA. Others have suggested that a DSA > 2000 MFI should be considered positive.[9] In this study, however, a DSA with MFI > 500 was considered to be positive, following the recommendation of manufacturer. Using this cut-off value, the predictive value of a negative result (negative predictive value) for graft rejection was 86.1%. However, when the cut-off value was raised to 1000, the negative predictive value was increased to 90.4%, without decreasing the sensitivity of the test. Based on these findings, we suggested that the cut-off value of 1000 for DSA-MFI might give more valuable result in the context of clinical correlation. Some tissue typing laboratories in Europe used the new microbeads assay to determine antibody specificities in the sera of their patients on the waiting list.[21] However, this is not practical in resource-limited countries since antibody assay with single antigen beads is very expensive. We then analyzed the PRA cut-off level by using ROC curve in order to identify which serum should be further tested with Luminex single antigen beads. The ROC analysis showed that the optimal cut-off point for PRA level was 10%. This suggested that sensitized patients with PRA $\geq$ 10% should be subsequently detected for DSA.

In conclusion, donor-specific antibody detected by a highly-sensitive method prior to renal transplantation, despite negative lymphocytotoxicity crossmatch, was associated with a high rate of

antibody-mediated graft rejections. However, it was not detrimental to long term graft or patient survival. Detection of pre-transplant DSA by using this highly-sensitive method would be beneficial for identifying high-risk patients.

Acknowledgement

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