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Clinical outcomes among renal transplant recipients with pre-transplant weakly-reactive donor specific antibodies

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Abstract

Background—Alloantibody can lead to antibody mediated rejection and graft loss in renal transplantation, necessitating an assessment of crossmatch compatibility. Within the past decade, more specific solid phase assays of alloantibody have been widely adopted, allowing virtual crossmatching based on unacceptable antigens, the threshold of which is determined by individual centers.

Methods—We examined the clinical outcomes of 482 patients transplanted 2007–2009 in a single center, focusing on 30 patients with weakly reactive donor specific antibody (DSA) determined prospectively prior to renal transplant.

Results—Compared with patients without DSA, patients with weakly reactive DSA do not have increased rates of antibody mediated rejection, cellular rejection, or graft loss despite conventional immunosuppression utilization.

Conclusions—Using the screening methodology and immunosuppression regimen we have applied to the patients with weak DSA allows them to be transplanted with equivalent outcomes as those without DSA, despite the overall higher-risk characteristics of the patients in the weak DSA group.

Keywords

renal; kidney; antibody; rejection; crossmatch; transplant

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Introduction

It has long been recognized that alloantibodies specific for a renal allograft can cause antibody-mediated rejection. This phenomenon can lead to graft dysfunction and eventual loss of the allograft (1, 2). Among patients awaiting a renal allograft, sensitization to HLA alloantigen is a significant barrier to transplantation. It has been estimated that in the United States alone, 30–40% of patients have significant levels of alloantibody that can potentially decrease the pool of HLA-compatible organs for those individuals or require desensitization prior to transplantation (3).

Alloantibodies, acquired as a consequence of pregnancy, blood transfusion, or organ transplantation, can be detected by a variety of techniques. These include complement dependent cytotoxicity, flow cytometry, and solid phase immunoassays such as single bead antigen assays.

Single antigen bead (SAB) immunoassay is a highly sensitive technique for the detection and identification of anti-HLA antibodies(4) By allowing for separate identification of both donor and recipient HLA expression, a virtual crossmatch can be completed with designation of unacceptable antigens, and organs can be allocated expeditiously(5) It is accepted practice to screen potential renal transplant candidates awaiting transplantation with quarterly solid phase immunoassay and report all detected HLA antibodies to the United Network for Organ Sharing (UNOS). By screening for known HLA specificities, virtual crossmatching also significantly decreases the likelihood of incompatible lymphocyte crossmatch, particularly among sensitized patients(3)

However, several significant issues remain undefined regarding the application of SAB assays in the virtual crossmatch. First, these assays are not strictly quantitative in nature, and there is not an accepted cutoff for mean fluorescence index (MFI) of anti-HLA class I and class II antibodies detected by the SAB assays that has been validated to have clinical immunological relevance. Each transplant center currently sets its own MFI threshold for unacceptable antigens, with most centers selecting an MFI cutoff between 3000–5000. Some centers choose higher or lower values, belying a lack of data in this area. A lower MFI cutoff value leads to a more stringent virtual crossmatch, with fewer recipient samples undergoing lymphocyte crossmatch at the time organ offers are made, but possibly a lower likelihood of an incompatible lymphocyte crossmatch that may ultimately preclude transplantation. A higher cutoff value would allow for more potential lymphocyte crossmatches, and defers the decision about whether an antigen is truly incompatible until the time of a lymphocyte crossmatch after an organ is offered. This strategy would be predicted to produce a higher rate of incompatible lymphocyte crossmatches and may preclude performing crossmatches in sensitized patients with an enhanced likelihood of compatibility, depending on the number of sensitized patients a center chooses to crossmatch for each donor.

The second major concern with the use of SAB assays is the lack of consensus about the clinical relevance of weak anti-HLA class I and class II antibodies detected by SAB assays. In addition, it is well known that some of these weak antibodies may be reactive to cryptic

epitopes on denatured HLA molecules on the particle beads used in the SAB assays. There are no validated criteria for what levels of MFI values of DSA are acceptably safe for transplantation. While it has clearly been observed that pre-existing HLA antibodies predict outcomes in kidney transplantation(6), it has also been observed that DSA with low MFI values is not a reliable predictor of the clinical outcomes of the allograft(6–14)

The purpose of this study is to determine the fate of renal allografts in terms of both graft function and survival when transplanted against weakly positive DSA detected by SAB technology while using standard approaches to immunosuppression.

PATIENTS AND METHODS

Appropriate permission was obtained from the institutional review board and single center, retrospective study was undertaken using a prospectively and uniformly applied clinical protocol. In our centers, single bead antigen assays were put into clinical use in 2005, and virtual crossmatching was begun by our organ procurement organization in 2009. Consequently, we selected a cohort of patients to include all 515 patients undergoing kidney transplants from 2007 to 2009 to allow for at least two years follow-up analysis. All patients were followed through 2011.

In the United States, UNOS allows for virtual crossmatching using recipient and donor HLA specificities identified by HLA typing. In this study, HLA typing of recipients and donors was performed using DNA based techniques and included HLA-A, -B, -C, -DRB1, -DRB3/4/5, and -DQB1. In addition, if the recipient had antibodies against HLA-DQA, or -DPB, typing for these loci was also performed to identify unacceptable HLA specificities used in the virtual crossmatch. Once identified, each potential recipient's unacceptable HLA antigens are entered into a computerized database called UNET. These data are then used at the time of organ allocation to perform virtual crossmatch against the same data acquired from the donor. Anti-HLA antibody testing was performed using Luminex bead assays including at least one determination by single antigen class I and class II bead assays. Assays were performed according to the instructions provided by the manufacturer except for the addition of dithiothreitol to sera for the purpose of reducing interference. Reactivity due to denatured epitopes and non-specific reactivity detected by the Single Antigen bead assays are rule out by a careful analysis of the specificity pattern of bead reactivity as well as constancy of reactivity among the different Luminex bead assays. DSA specificities included HLA-A, B, C, DRB1, B3, B4, and B5, DQA/DQB, and DP. However, UNET does not allow listing of HLA-DQA, and DP specificities. With the exception of DQA, DP, and allele-specific antibody, any DSA with MFI values greater than 3000, HLA specificities were listed in UNET as unacceptable.

Flow cytometry crossmatch (FCCM) for T and B cells were performed prospectively. FCCM was performed using a Beckman-Coulter FC500 (1024 channels). For sample preparation, cells were treated with Pronase 1mg/ml and stained with affinity purified F(ab′)_2 Goat Anti-IgG, Fcγ, 2.2 moles FITC per mole F(ab′)2 (1:160 dilution). In most cases, serum specimens used in the final crossmatch include a current serum draw within the last 30 days prior to transplantation. At our center, FCCM reactivity is expressed using a relative

ratio of Molecules of Equivalent Soluble Fluorescence (MESF) values of the tested sample over the negative control sample. The threshold used to define FCCM reactivity is as follow. Negative: fluorescence ratio less than 1.5; weakly reactive: fluorescence ratio in the range of 1.5–2.5; positive: fluorescence ratio high than 2.5. Prior to reporting, the FCCM results are reviewed for consistency with past and current anti-HLA antibody specificities, presence of autoantibodies or other potentially interfering substances.

HLA compatibility was determined at the time of the organ offer based on pre-transplant virtual crossmatch and FCCM prior to transplantation. 30 patients were transplanted with low-level HLA incompatibility due to weak DSA to a single HLA specificity (normalized MFI values in the range of 800–3,000); in all patients, the T and B cell FCCM was either negative or weakly reactive (Relative Fluorescence ratio in the range of 1.5–2.5). Antibodies detected by SAB assays with MFI values less than 800 were considered to be insignificant. Patients with a single DSA <3000 MFI and a negative or borderline crossmatch were transplanted except when a) the MFI values in the historic sera (in the preceding 4 years) were higher than 3000; b) a weak DSA <3000 MFI is against a repeat mismatch from a previous transplant.

Post-transplant DSA was defined relative to pre-transplant normalized MFI values and met both of the following criteria: 1) Increase in pre-formed DSA normalized MFI value of greater than or equal to 100% and 2) Increase in pre-formed DSA normalized MFI value of greater than or equal to 1000. Post-transplant DSA was followed at least up to one year in the Weak DSA group and was assessed one or more times in all of those cases. Post-transplant DSA was not assessed routinely for all patients in the No DSA group.

Immunosuppression was standardized among all patients. Immunosuppression was initiated in the operating room prior to reperfusion and consisted of 500mg intravenous solumedrol and 1.5mg/kg anti-thymocyte globulin (Thymoglobulin, Genzyme, Cambridge, MA). Steroids were rapidly tapered to minimal oral doses. Patients received a total of 4.5–7.5mg/kg of thymoglobulin induction therapy depending on their degree of sensitization and the presence of delayed graft function (DGF). All patients were started on mycophenolate mofetil and a calcineurin inhibitor on the day of surgery. In nearly all cases, the calcineurin inhibitor of choice was tacrolimus. In our institution, pre-transplant desensitization has been employed only on small cohorts within research protocols. These patients are not included in the present study.

Kidney allografts were biopsied for cause based on clinical evidence of impaired allograft function including rising creatinine over baseline, not achieving predicted baseline creatinine, or prolonged delayed graft function. New onset donor specific antibody was a trigger for biopsy in some cases. The diagnosis of rejection was based on the updated Banff 97 diagnostic criteria (15, 16). Acute rejections were divided into acute T-cell mediated rejection and acute antibody-mediated rejection. For acute antibody mediated rejection, the histology included acute tubular necrosis-like changes, capillary margination and/or thromboses, or arterial fibrinoid changes, with positive immunofluorescent C4d positivity. For acute T-cell mediated rejection, the three critical components are significant interstitial infiltration (>25% renal parenchyma affected), tubulitis, and arteritis. The borderline change

is diagnosed when there is mild to moderate interstitial inflammation, but only mild lymphocytic tubulitis is present. Chronic T-cell mediated rejection is based on presence of arterial intimal proliferation and interstitial fibrosis.

Statistical analysis was performed using Stata (StataCorp LP, College Station, TX). Continuous variables were analyzed using Student's t-test or Chi square test. Frequency data were analyzed using fisher's exact test. Results were considered statistically significant when p-values were less than 0.05.

RESULTS

The general characteristics of the study population are shown in Table 1. Of the 482 patients who underwent kidney transplantation in the total cohort, 30 were found to have weak DSA with MFI values in the range of 800 to 3000 – these constitute the Weak DSA group. The remainder of the cohort (n=452) had no detectable DSA, constituting the No DSA group. DSA with MFI value of 3000 was a contraindication to transplantation.

There were relatively more women in the Weak DSA group than the No DSA group, consistent with the known phenomenon of sensitization associated with pregnancy. The recipient ages were similar. The bulk of the patients in both groups were performed in the setting of kidney transplant alone, though a small number in both groups had kidney transplants performed in the setting of combined kidney-heart, kidney-liver, or kidney-pancreas. None of the patients in the Weak DSA group underwent combined kidney-pancreas transplantation.

The mean ages of the donors and recipients were similar for the two groups. There were more deceased donor and fewer live donor transplants in the Weak DSA group (p=0.05). The rate of transplants using organs from donation after cardiac death (DCD) was similarly low between the two groups. In the Weak DSA group there was one living related donors and two unrelated donors. Female sex and African American race were present to a greater degree in the Weak DSA group than the No DSA group, these differences reached statistical significance (p=0.05, p=0.01).

Table 2 compares the two groups for the presence of several additional features thought to contribute to poorer immunologic outcome and likelihood of rejection. A small number of patients in each cohort had positive antibody detection but MFI < 3000 in the setting of 0% calculated panel reactive antibody (CPRA). The 0% CPRA is based on a cut off value of 3000. This finding was similar between the two groups. 86.7% of the patients in the Weak DSA group had a positive CPRA, compared to only 19.9% in the No DSA group (p<0.0001). More of the Weak DSA patients had previous allotransplantation (30% vs. 12.2%, p=0.003).

Table 3 delineates measures of clinical outcomes between the two groups. The Weak DSA cohort had slightly higher rates of poor initial function (DGF), graft loss, indications for biopsy, and death within the study period, but none of these measures achieved statistical significance. The rate of rejection did not differ significantly between the two groups (Table 3). The rate of rejection of all types was 16.7% in the Weak DSA group compared to 11.1%

in the No DSA group (p=0.37). Neither the rates of acute cellular rejection (ACR) and antibody mediated rejection (AMR) differed between the two groups. The mean creatinine one year after transplantation was 1.34 in the Weak DSA group and 1.6 in the No DSA group (p=0.67). Medians were 1.23 mg/dl and1.30 respectively.

As post-transplant assessment of DSA was performed only when clinically indicated, these data are complete for 24/30 of the patients in the Weak DSA group. Among these patients, 19 of 24 (79%) patients had post-transplant DSA, 10 of which were classified as without de novo DSA (under MFI of 3000), none of these patients lost the graft or required biopsy for cause. The remaining 9 were patients with positive de novo DSA (MFI ≥ 3000). Among these 9, 3 required for biopsy for cause, and all three showed rejection. Two lost their grafts, and one died of PTLD. In the No DSA group, 34 grafts were lost in the follow-up period – of these more than 70% were due to patient death with a functioning graft. The majority of the remaining graft loss was due to rejection in this group.

Discussion

The current study aimed at determining the relevance of DSA with low MFI values. Final determination of HLA compatibility was made based on a prospective T and B cell FCCM using a well standardized FCCM assay and stringent cut off values; in all patients, the T and B cell FCCM was either negative or weakly reactive (Relative Fluorescence ratio in the range of 1.5– 2.5). To the best of the authors' knowledge, our study is the first to show that using predetermined HLA compatibility criteria, a weakly positive DSA of less than 3000 MFI by SAB assays combined with a negative or weakly reactive flow cytomatric crossmatch have no adverse effect on short-term renal function or rates of early graft rejection. When compared to the control group, those with low MFI DSA had similar early allograft function as measured by the rate of DGF and serum creatinine one year post-transplant.

Furthermore, the graft survival and overall survival was equivalent between Weak DSA and No DSA cohorts. This finding is especially striking given that the Weak DSA group had a higher CPRA than the No DSA group, and that a higher CPRA is generally thought to be associated with poorer transplant outcomes. The Weak DSA group demonstrated no greater rate of clinical rejection of any type and equivalent survival of both the patient and the graft compared to the No DSA group. The association between the presence of DSA and elevation of CPRA, taken together with the observations that the Weak DSA group has higher proportions of African Americans, women, and re-transplant recipients, suggests that the presence of DSA in these individuals represents actual immunologic sensitization. Additionally, it should be noted that the Weak DSA group contained only one live donor transplant, and as such this group would be predicted to have lower graft survival than the No DSA group that included 25% live donor transplants.

The question of the relevance of pre-transplant DSA detected by SAB assays has been the subject of recent reports. Three important papers from Lefaucheur et al. described their use of enzyme linked immunosorbent assay (ELISA) technology to detect DSA and concluded that the presence of DSA is related to an increased risk of AMR and eventual graft loss(6,

11, 15). The same group went on to show that pre-existing DSA portends worse outcomes, demonstrating 8-year graft survival of 61% among patients with pre-existing DSA compared with sensitized patients without DSA (93%) and non-sensitized patients (84%). The authors performed crossmatches using FCCM and CDC-CM, and initially acquired DSA information using ELISA at the time of the transplant. They subsequently performed SAB analysis on the retrospectively identified peak-reactive sera after all clinical decisions had already been made. These retrospective data, derived by applying newer techniques in a reverse fashion, while informative, do not address the interpretation of low-MFI DSA observed at the time of the organ offer, nor the clinical outcomes associated with such observation. It is not clear that the same clinical decisions would have been made years prior if more complete data were available making the interpretation of clinical outcomes more speculative.

A related report by Amico and colleagues in 2009 examined patients who underwent renal transplantation who had DSA detected by SAB assays followed by a negative CDC-CM. They reported that among 67 such patients, some 55% of those with DSA experienced AMR, and that those with AMR had 20% lower death-censored graft survival when compared to those without. Interestingly, however, they also reported that the remaining 45% of their cohort with pre-transplant DSA did not have any clinical or subclinical evidence of AMR on protocol biopsy(16)

A recent report by Caro-Oleas and colleagues approached the topic of the significance of the magnitude of MFI on renal outcomes. Their study population was stratified into four groups based on pre-transplant DSA MFI values. They found that for intermediate and high value MFI, there was no difference in overall graft survival. They did, however find a significantly lower rate of graft loss in the population with the lowest value MFI, <1500. However, individuals were included in this cohort who had both low MFI DSA as well as no DSA at all, therefore no specific conclusions can be drawn regarding the clinical outcomes of individuals with low MFI DSA as distinct from those without DSA(17)

In this study, the risk of anamnestic antibody rebound and AMR due to immunologic memory was minimized by a careful analysis of antibody profile in historic sera and a close inspection of potential weak DSA to repeat HLA mismatches in re-graft patients.

This is not to suggest that patients with positive pre-transplant DSA would not benefit from some form of desensitization, nor that these patients are not at risk of developing AMR. In our study, desensitization was not used but it is unclear if these patients are at higher risk for ABMR after a long term follow up.

A strength of our study is the uniformity of the clinical pathway for the low DSA group. The decision-making thresholds and laboratory methods used in assessing HLA compatibility were predetermined, standardized, and consistent. The patients were treated with typical immunosuppression protocols, and MFI cutoffs for acceptability were set in advance. Furthermore, it is important to point out that the methods for the laboratory assays and data interpretation used in this study are explicitly described and form a substantive basis for comparison. It will be important for future papers that address this topic to be clear on

defining the methods and criteria used for HLA compatibility so that meaningful comparisons can be made between data sets from center to center.

Despite the large population captured in this study, the small size of the weak DSA group represents a relative weakness. Our data also do not allow for any conclusions to be drawn about the fate of patients transplanted with higher MFI values of DSA (i.e. MFI>3000), as these cases would have been screened out by virtual crossmatch and do not come to transplantation in our center. It is generally agreed upon that these SAB assays are not truly quantitative, and that each center will need to set its own thresholds. The relatively short follow-up time is a limitation as well, but is mandated by the recent adoption of this technology and the prospective application of this technology to the clinical decision-making in this study. As more time elapses from transplant we will be able to make firmer conclusions about the long term impact of DSA development. Furthermore, as it is our center's practice to only perform biopsies when indicated by clinical expression of rejection or other injury, no protocol biopsies are performed. Several studies have pointed to the presence of subclinical antibody-mediated rejection in renal transplantation cases with positive DSA.(18–20) The present study was not designed to specifically address this question regarding the presence or absence of subclinical antibody mediated rejection. We note that 25% of the patients in the Weak DSA group did develop post-transplant DSA. We do not perform routine post-transplant DSA surveillance for the nearly 500 patients transplanted in the No DSA arm. However, the development of 25% post-transplant DSA at one year or more after transplant is within the expected range in prior published studies surveying primary kidney recipients (21). The Weak DSA group we describe here was at greater immunologic risk and the development of positive DSA at similar rates to the published data reinforces the overall favorable outcomes seen in the Weak DSA group.

Overall, this study sheds some light upon an area of donor specific antibody detection and the clinical relevance of these antibodies when detected with a low MFI. In contrast to the more retrospective studies reviewed above, we conclude that in cases where pre-transplant DSA is less than 3000 MFI and a flow crossmatch is below a well-defined standardized threshold, patients can be transplanted with standard immunosuppression techniques and without desensitization, with equivalent outcomes in the first two years as those without DSA. This is despite the lower rates of living donors and the higher immunological risk profile of the recipients in the Weak DSA group. We see no significant differences in cellular or antibody-mediated rejection in the Weak DSA group compared to the No DSA group while under our typical immunosuppression regimen. For further study we plan longer term follow-up of all patients transplanted with low MFI DSA to determine if they develop higher rates of chronic rejection or antibody mediated rejection at more remote times after transplant, which may impact longer-term outcomes.

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Table 1

Patient Characteristics By DSA Group

	Weak DSA (n=30)	No DSA (n=452)	p-value
Female Sex	63.3% (n=19)	39.4% (n=178)	**0.01**
African-American	53.3% (n=16)	34.1% (n=154)	**0.05**
Recipient Age (years)	49.6 ± 12.8	50.6 ± 13.6	0.75
Donor Type			
Deceased	90% (n=27)	73.4% (n=332)	**0.05**
DBD	87% (n=26)	69.2% (n=313)	**<0.01**
DCD	3.3% (n=1)	3.9% (n=19)	1
Living Donor	10% (n=3)	26.5% (n=120)	**0.05**
Related	3.3% (n=1)	15.7% (n=71)	0.06
Unrelated	6.7% (n=2)	10.8% (n=49)	0.34
Donor Age (mean)	35.2 years	39.8 years	0.1

Table 2

Pre-transplant Immunologic factors

	Weak DSA (n= 30)	No DSA (n = 452)	p-value
Weakly positive Ab's, 0% calculated CPRA	10.0% (n=3)	6.2% (n=28)	0.43
Positive CPRA	86.7% (n=26)	19.9% (n=90)	**<0.0001**
Prior renal allograft	30.0% (n=10)	12.2% (n=55)	**0.003**

Table 3

Clinical outcomes of renal transplantation based on DSA category

	Weak DSA (n= 30)	No DSA (n = 452)	p-value
DGF	36.6% (n=11)	25.4% (n=115)	0.20
Any rejection	16.7% (n=5)	11.1% (n=50)	0.37
Any rejection above borderline	13.3% (n=4)	7.1% (n=32)	0.26
Any ACR	13.3% (n=4)	10.2% (n=46)	0.54
Any AMR	3.3% (n=1)	2.2% (n=10)	0.51
Any graft loss within follow-up time	10.0% (n=3)	6.9% (n=31)	0.5
Patients biopsied post txp	26.7% (n=8)	19.4% (n=88)	0.35
Death within follow-up time	6.6% (n=2)	4.6% (n=21)	0.64
Mean 1 yr creatinine	1.34 ± 0.12 mg/dl	1.6 ± 1.6 mg/dl	0.67
Median 1 yr creatinine	1.23 mg/dL	1.30 mg/dL	