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ORIGINAL ARTICLE

Six-year outcomes in broadly HLA-sensitized living donor transplant recipients desensitized with intravenous immunoglobulin and rituximab

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SUMMARY

Desensitization with intravenous immunoglobulin (IVIG) and rituximab can improve transplantation rates in broadly sensitized kidney transplant recipients. However, long-term outcomes are lacking. Here we analyze long-term outcomes in living donor kidney transplant recipients desensitized with this regimen and compare them to low-risk recipients. Living donor kidney transplants that took place between July 2006 and December 2010 were considered retrospectively. The primary end point of the study was death-censored allograft survival at last follow-up. Secondary end points included patient survival, incidence of rejection, glomerular filtration rate (GFR), and proteinuria. There were 66 sensitized and 111 low-risk patients included. Average follow-up was 68 months. There was no difference in long-term patient or graft survival. The rate of rejection was similar in the groups with more early rejection in the sensitized group and more late rejection in the low-risk group. There was more antibody-mediated rejection in the sensitized group. Estimated GFR was similar during the follow-up period. Risk factors for rejection included a positive cross-match (HR: 2.4 CI: 1.35–4.40) and age (HR: 0.97 CI: 0.95–0.99). Desensitization with IVIG and rituximab has good long-term results with graft outcomes similar to non-HLA-sensitized patients despite higher immunologic risk.

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Key words
ABMR, desensitization, donor-specific antibodies, plasma exchange, transplant glomerulopathy

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Introduction

Living donor kidney transplantation is considered the best available therapy for end-stage renal disease (ESRD). The availability of a compatible living donor is a precious resource that cannot be lost. Unfortunately, many transplant candidates have a potential living donor who is human leukocyte antigen (HLA) incompatible. Sensitization to HLA antigens creates an immunologic barrier to successful transplantation with the subsequent need to remain on dialysis for years. This leads to a higher rate of morbidity and mortality, decreased allograft survival, and increased costs [1,2]. Desensitization therapies have bridged the HLA gap allowing those with incompatible living donors to undergo incompatible kidney transplantation.

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Combining high-dose intravenous immunoglobulin (IVIG) with rituximab (anti-CD20, anti-B cell) has improved transplant rates for this underserved population. Good short-term outcomes have been achieved with this approach [3,4]. However, long-term data examining the durability of this therapy are currently lacking. One retrospective, multicenter analysis reported inferior outcomes in patients with a positive cross-match at 5 years post-transplant [5]. However, the study did not report approaches to desensitization utilized by the individual centers. Here we report 6-year outcomes in broadly HLA-sensitized kidney transplant recipients who underwent a living donor kidney transplant after desensitization with IVIG and rituximab.

Patients and methods

Patient population

This observational, retrospective study included all living donor kidney transplants between July 2006 and December 2010. All patients had a minimum of 3 years follow-up. Both complement-dependent cytotoxicity (CDC) and flow cytometry cross-matches were performed by methods previously described [6]. Patients with an acceptable cross-match or donor-specific antibody (DSA) were included in the desensitized group. All nonsensitized (low-risk) patients undergoing a living donor kidney transplant during the same time period were included as a reference group. Those receiving a blood type incompatible transplant were excluded.

Desensitization and immunosuppression

Patients were desensitized prior to transplant with IVIG and rituximab as previously described [4]. Briefly, two doses of IVIG (2 g/kg, max 140 g) were administered 4 weeks apart with one dose of rituximab (1 g) given between the two IVIG infusions (Fig. 1a). Plasma exchange (PLEX) was utilized prior to transplantation for recipients that had a persistently high titer DSA and an unacceptable cross-match (Fig. 1b). A T- and/or B-flow cytometry cross-match <250 mean channel shifts (MCS) and a CDC cross-match negative at a 1:2 dilution were considered acceptable for transplantation. All nonsensitized patients received IL-2 receptor antagonists. All desensitized patients with a positive cross-match received lymphocyte depleting induction (alemtuzumab 30 mg subcutaneous × 1 dose). Desensitized patients with DSA but a negative cross-match received IL-2 receptor antagonist induction. All desensitized patients received lymphocyte depleting induction regardless of DSA status starting in 2008. An additional dose of IVIG was given to sensitized patients seven to 10 days after transplantation per protocol.

Maintenance immunosuppression for all patients consisted of a calcineurin inhibitor (primarily tacrolimus), mycophenolic acid, and corticosteroids. Target tacrolimus levels were initially 8–10 ng/ml in the low-risk group and 7–9 ng/ml in the desensitized group. Target trough levels were stepped down to 4–6 ng/ml over 12 months. Mycophenolic acid was started at 1000 mg twice daily in patients with interleukin-2 receptor antagonist induction and 500 mg twice daily in patients with lymphocyte depleting induction. All patients received antifungal prophylaxis for 1 month, anti-viral prophylaxis for 6 months, and pneumocystis jiroveci prophylaxis for 6 months.

DSA was defined as the presence of HLA antibody directed against donor antigen present at the time of transplant. Tissue typing was performed to determine HLA A,B,C, DR, and DQ. DSA analysis was performed on the Luminex platform (One Lambda Inc., Canoga Park, CA, USA) as previously described [6]. DSA was monitored in the desensitized group at the time of transplant then at months 3, 6, 9, 12, and annually thereafter.

End points and statistical methods

Demographic and outcome variables were collected for all patients via review of the electronic medical record.

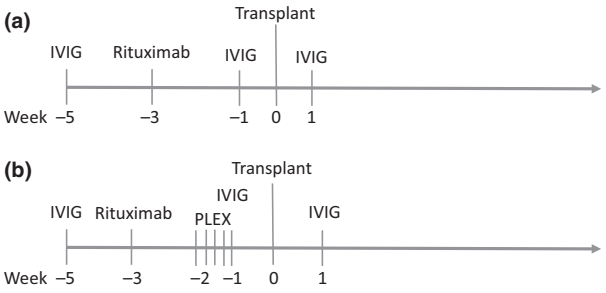

Figure 1 (a) Desensitization protocol without plasma exchange. Two doses of IVIG (2 g/kg, max 140 g) are administered 4 weeks apart with one dose of rituximab (1 g) given between the two IVIG infusions. Transplant occurs within 1 week of the last IVIG dose. An additional dose of IVIG is administered 1 week after transplant. (b) Desensitization protocol with plasma exchange. One dose of IVIG is administered followed a week later by rituximab. Five sessions of plasma exchange are performed every other day (1.5 plasma volume per exchange). A second dose of IVIG is administered immediately following the last plasma exchange session. Transplant occurs within 1 week of the last plasma exchange. An additional dose of IVIG is administered 1 week after transplant. There were no additional sessions of plasma exchange post-transplant.

The primary end point of the study was death-censored allograft survival at last follow-up. Secondary end points included patient survival, incidence of rejection, glomerular filtration rate (GFR), and proteinuria at last follow-up. Proteinuria was measured qualitatively and categorized as zero to trace, 1+, 2+, 3+, and 4+. GFR as estimated by the CKD-EPI equation was calculated each year after transplant for 5 years and at last follow-up in those with a functioning allograft. Categorical variables were analyzed using chi-square, and continuous variables were analyzed by independent samples *t*-test or Mann–Whitney. Survival was determined by the Kaplan–Meier product limit method with log-rank *P*-values. Cox regression was used to determine hazard ratios. DSA at the time of transplant was quantified using the DSA relative intensity score [7]. This scale assigns two points for each DSA with a mean fluorescence intensity (MFI) < 5000, five points for an MFI between 5000 and 10 000, and 10 points for an MFI ≥ 10 000. Biopsies were only performed for cause and not by protocol.

Results

Baseline group characteristics are detailed in Table 1. A total of 177 patients were included in the final analysis, 66 sensitized and 111 low-risk patients. The mean follow-up was 68 ± 15 months and ranged from 43 to 96 months. Two patients were lost to follow-up in the desensitized group, and three were lost to follow-up in the low-risk group. The sensitized group had longer follow-up, consisted more of women and were slightly older. There were no differences in race, cause of ESRD, diabetes, or HLA matching in the two groups. Fifty-three (80%) of the sensitized patients had a positive cross-match with 48 (73%) having either a T- or B-flow cytometry cross-match greater 200 MCS. The average T-flow and B-flow cytometry cross-match was 162 ± 75 MCS and 286 ± 88 MCS, respectively, in the 53 patients with a positive cross-match. The median class I and class II PRA for the sensitized patients were 45% (CI: 0–80%) and 71% (CI: 21–95%), respectively. Thirty-seven patients (56%) had a panel reactive antibody >80%. Thirteen patients (20%) received PLEX in addition to IVIG and rituximab as part of their desensitization protocol prior to transplant.

Characteristics pertinent to the sensitized patients grouped by the need for PLEX are summarized in Table 2. There were 33 patients (50%) in the sensitized group who had a previous transplant. Twenty-five patients had one previous transplant, five had two previous transplants, and three had more than two previous transplants. None of the patients in the low-risk group had a previous transplant. HLA antibody strength at the time of transplant was available for 41 patients that had single antigen bead testing (available at our center in 2009). Strong class II DSA (MFI > 10 000) was seen in 11/41 (27%) of the patients and strong class I DSA in 7/41 (17%) at the time of transplant.

Table 1. Baseline characteristics.

	Sensitized (*N* = 66)	Low risk (*N* = 111)	*P*-value
Length of follow-up, months	72.4	66.1	0.005
Age, years	46.5	44.6	0.031
Female, *n*(%)	43 (65)	32 (29)	<0.001
Race, *n*(%)			
White (non-Hispanic)	41 (62)	59 (53)	0.37
African American	6 (9)	10 (9)	
Hispanic	10 (15)	30 (27)	
Asian	6 (9)	10 (9)	
Other	3 (5)	2 (2)	
Cause of ESRD, *n*(%)			
Diabetes	9 (14)	23 (21)	0.699
Hypertension	11 (17)	12 (11)	
Glomerulonephritis	23 (35)	34 (31)	
Polycystic	6 (9)	13 (12)	
Other/Unknown	17 (26)	29 (26)	
HLA match	2.11	2.18	0.9
Time on renal replacement, days [SD]	785 [253–1358]	363 [0–794]	<0.001
Lymphocyte depleting induction, *n*(%)	44 (67)	3 (2.7)	<0.001

Transplant International 2016; 29: 1276–1285

Table 2. Immunologic characteristics and outcomes in desensitized patients requiring PLEX and those not requiring PLEX.

	No PLEX (n = 53)	PLEX (n = 13)	P-value
Prior transplant, n(%)	22 (41.5%)	7 (53.8%)	0.537
Negative cross-match, n(%)	9 (17%)	0	0.186
T-flow cross-match, n(%)	158 ± 71	175 ± 91	0.613
B-flow cross-match, n(%)	282 ± 89	300 ± 90	0.537
DSA RIS, mean ± SD	7.53 ± 7.1	18.2 ± 15.6	0.004
DSA RIS > 20, n(%)	3 (37.5%)	5 (62.5%)	.031
Patient survival, n(%)	51 (96.2%)	11 (84.6%)	0.064
Graft survival, n(%)	48 (90.6%)	10 (76.9%)	0.121
Rejection, n(%)	8 (15.1%)	12 (92.3%)	<0.001
GFR 1 year, mean ± SD	66.1 ± 20.8	56.7 ± 14.5	0.181
GFR 2 years, mean ± SD	64 ± 19.9	47 ± 11.1	0.023
GFR 3 years, mean ± SD	62.9 ± 22.9	56.1 ± 11.9	0.393
GFR 4 years, mean ± SD	61.3 ± 22.8	52.2 ± 12.3	0.283
GFR 5 years, mean ± SD	62.7 ± 25.9	53.8 ± 14.7	0.463
Last GFR, mean ± SD	63.9 ± 23.2	50.1 ± 13.4	0.075

PLEX, plasma exchange; CXM, cross-match; DSA RIS, donor-specific antibody relative intensity score; GFR, glomerular filtration rate (ml/min/1.73 m^2); SD, standard deviation.

Death-censored graft survival was 87.9% in the sensitized group and 88.3% in the low-risk group (P = 0.96) over a mean follow-up period of more than 5 years (Fig. 2). The causes of graft loss are displayed in Table 3. There were eight graft losses in the sensitized group and 13 graft losses in the low-risk group. The one patient in the low-risk group whose graft failure was due to chronic rejection had recurrent episodes of CMR leading to interstitial fibrosis and tubular atrophy without evidence of TG. One patient in the desensitized group whose graft failure was attributed to chronic rejection had multiple episodes of AMR with evidence of TG. The leading cause of graft loss was rejection in each group. Allograft rejection was the only predictor of graft loss (HR: 12.9 [4.37–38.42] P < 0.001). The following variables were not predictors of graft loss in the univariable analysis: sensitization status, previous transplant, positive cross-match, DSA, induction type, race, age, and sex (data not shown). Rejection remained the only predictor of graft loss in the multivariable model that also included positive cross-match (HR: 13.5 [4.47–40.9] P < 0.001). There was one graft loss in the low-risk group attributed to bleeding and no graft losses in the desensitized group related to bleeding.

There was no difference in patient survival in the sensitized and low-risk groups (Fig. 3). There were four deaths over the follow-up period in the sensitized group. The causes of death were as follows: cardiovascular event (2) and infection (2). There were 10 deaths in the low-risk group. The causes of death were as follows: malignancy (5), infection (3), and cardiovascular event (2). Age was the only predictor of patient survival in the univariable and multivariable analysis (HR: 1.05 [1.004–1.089] P = 0.03). Sensitization status, positive cross-match, rejection, induction, and diabetes status

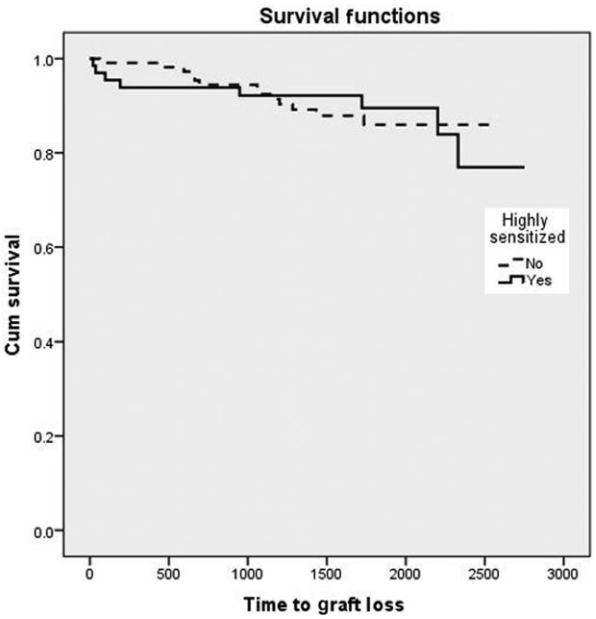

Figure 2 Kaplan–Meier curve showing overall allograft survival in the sensitized and low-risk groups. There was more early graft loss in the sensitized group, but long-term allograft survival was equal.

Table 3. Cause of graft loss.

Sensitized (N = 8)		Low risk (N = 13)	
Acute rejection	5 (62.5%)	Acute rejection	7 (55%)
CMR	1	CMR	2
AMR	4	AMR	5
Technical	1 (12.5%)	Recurrent GN	2 (15%)
Polyomavirus BK	1 (12.5%)	Polyomavirus BK	1 (7.5%)
Chronic rejection	1 (12.5%)	Chronic rejection	1 (7.5%)
		Technical	1 (7.5%)
		ATN	1 (7.5%)

CMR, cell-mediated rejection; AMR, antibody-mediated rejection; ATN, acute tubular necrosis.

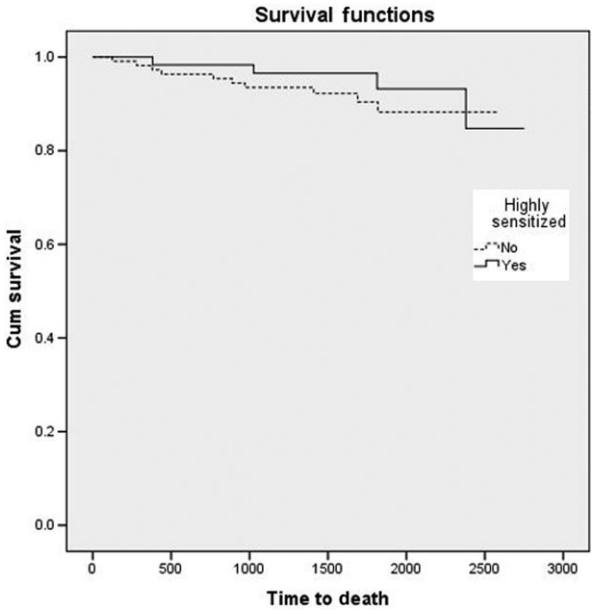

Figure 3 Kaplan–Meier curve depicting cumulative patient survival. There was no difference in patient survival in the sensitized and low-risk groups.

were not predictive of patient survival in this cohort (data not shown).

The incidence of allograft rejection was 30% in the sensitized group and 23% in the low-risk group (P = 0.18, Table 4). The median time to rejection was shorter in the desensitized group compared to the low-risk group (P = 0.004). A positive cross-match, B-flow cytometry cross-match >200 MCS, and age were predictive of rejection in the univariable analysis (Table 5). A positive cross-match and age remained predictors in the multivariable analysis (Table 5). There were 26 rejections in the low-risk group. Most of these rejections were cell-mediated (Table 4). Seven patients with rejection had documented nonadherence to their medical regimen and two patients had immunosuppression lowered or withdrawn due to infection. There were 19 rejections in the desensitized group. The majority of rejections in this group were antibody-mediated (Table 4). There was no documented noncompliance in this group of patients. Seventeen of the 19 patients (89%) who had a rejection episode within the desensitized group had a T- or B-flow cross-match >200 MCS compared to 31 of 47 patients (65%) who did not experience rejection in the same group (P = 0.06).

A subgroup analysis of the sensitized patients was completed to look for risk factors associated with rejection. Overall, there was no association with flow cytometry cross-match >200 MCS with rejection. However, separately, we found that a B-flow cross-match, but not a T-flow, >200 MCS was associated with rejection (P = 0.04). The strength of DSA at the time transplant was evaluated using the DSA relative intensity score in 42 patients that had this data available. A DSA relative intensity score >20 at the time of transplant was associated with rejection (25% vs. 8.8%, P = 0.04). Rejection was not associated with sex, age, diabetes, or previous transplant.

We compared characteristics and outcomes in the subgroup of sensitized patients that received PLEX prior to transplant and those sensitized patients who did not (Table 2). The rate of rejection in those requiring PLEX was 92% compared to 15% in those who did not (Fig. 4). Overall allograft survival was 77% in the group requiring PLEX compared to 91% without PLEX (P = 0.12). Patient survival was 86% in the PLEX group compared to 95% in those without PLEX (P = 0.06). The GFR at each year post-transplant was lower in the PLEX group, but this was only significant at the second-year time point (Table 2). The B- and T-flow cross-match at the time of transplant was similar in these groups as was the induction regimen, HLA mismatch, and PRA. However, the DSA relative intensity score was significantly greater in the PLEX group (18.5 vs. 7.2, P = 0.004) indicating the presence of stronger DSA.

GFR and proteinuria were evaluated annually and at last follow-up. There was no statistical difference in the degree of proteinuria in the two groups. Seventy-one percent of the sensitized patients had zero to trace protein at last follow-up compared to 77% in the low-risk group (P = 0.45). We looked separately at patients who had 2+ or more proteinuria at last follow-up. We found 12% of sensitized patients and 9% of low-risk patients to have this degree of proteinuria (P = 0.58). The GFR was not different in each group at every time point

Table 4. Results.

	Sensitized (n = 66)	Low risk (n = 111)	P-value
Patient survival, n(%)	62 (93.9)	101 (91.0)	0.431
Graft survival, n(%)	58 (87.9)	98 (88.3)	0.963
Rejection, n(%)	19 (28.8)	26 (23.4)	0.180
CMR Borderline	1	1	
CMR Banff 1	2	12	
CMR Banff 2	1	8	
AMR	15	5	
Transplant glomerulopathy, n(%)	11 (17)	4 (3.6)	0.004
GFR, mean ± SD	61.6 ± 22.4	61.4 ± 18.2	0.154
GFR 1 year, mean ± SD	64.5 ± 20.1	65.2 ± 18.8	0.712
GFR 2 years, mean ± SD	61.5 ± 19.7	60.7 ± 18.4	0.496
GFR 3 years, mean ± SD	61.7 ± 21.5	62.6 ± 18.2	0.195
GFR 4 years, mean ± SD	59.7 ± 21.4	61.2 ± 19.1	0.694
GFR 5 years, mean ± SD	61.5 ± 24.8	60.7 ± 17.2	0.063

CMR, cell-mediated rejection; AMR, antibody-mediated rejection; GFR, glomerular filtration rate (ml/min/1.73 m^2); SD, standard deviation.

Table 5. Predictors of rejection.

Variable	Hazard ratio	95%CI	P
Univariable			
Sensitization	1.486	0.829–2.663	0.188
Previous transplant	1.240	0.577–2.466	0.590
Positive cross-match	2.241	1.250–4.017	0.007
DSA only	0.830	0.201–3.423	0.796
Flow CXM > 200	2.158	1.192–3.904	0.011
T-flow > 200	2.094	0.750–5.846	0.158
B-flow > 200	2.158	1.192–3.904	0.011
Induction	0.558	0.304–1.026	0.06
African American	0.569	0.241–1.344	0.23
Diabetes	0.875	0.422–1.813	0.719
Age	0.977	0.957–0.997	0.023
Sex	1.170	0.647–2.117	0.603
HLA match	0.937	0.775–1.133	0.499
Multivariable			
Positive cross-match	2.442	1.355–4.400	0.003
Age	0.973	0.953–0.994	0.011

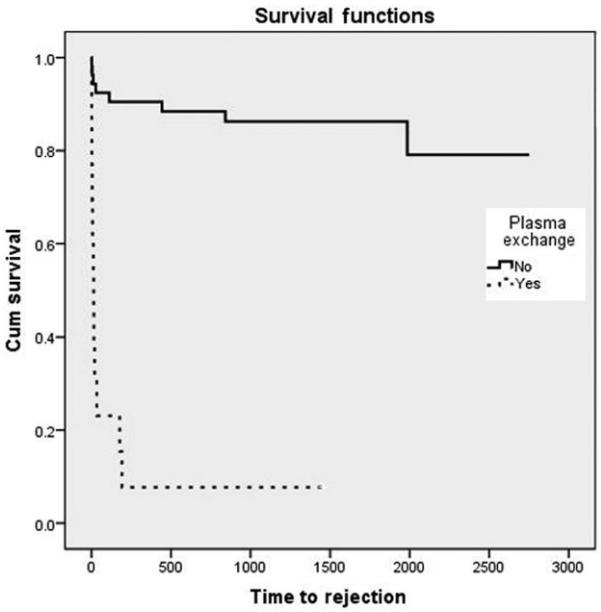

Figure 4 Kaplan–Meier curve showing freedom from rejection in a subgroup of sensitized patients receiving plasma exchange prior to transplant compared to sensitized patients who did not. There were statistically more rejection episodes in the group receiving plasma exchange.

measured (Table 4). The mean GFR was >60 ml/min in both groups at 5 years post-transplant. GFR declined from 64.5 to 61.5 (−3 ml/min) in the sensitized group and from 65.1 to 60.7 (−4.4 ml/min) in the low-risk group from year one until year five post-transplant. GFR at last follow-up (>5 years) was 61.6 ml/min in the sensitized group and 61.4 ml/min in the low-risk group. The incidence of transplant glomerulopathy was also determined in the groups. There were 11 cases (17%) identified in the sensitized group and four (3.6%) in the low-risk group (P = 0.004). Five of the eleven allografts (45%) in the sensitized group and two of four in the low-risk group (50%) ultimately failed during the following period.

The rate of polyomavirus BK and cytomegalovirus (CMV) infections was analyzed in the two groups. There were no differences in BK infection. Eight

patients (12%) in the desensitized group developed BK infection, two of whom had BK-associated nephropathy. Eleven patients (10%) developed BK infection in the low-risk group with one case of BK-associated nephropathy. There was one graft loss in each group due to BK-associated nephropathy. There was a trend toward more CMV infection in the low-risk group. Four patients (3%) in the desensitized group developed a CMV infection compare to 18 patients (16%) in the low-risk group ($P = 0.06$).

Discussion

Desensitization therapies have evolved over the last 15 years. Many studies demonstrating short-term outcomes have reported good efficacy, but long-term results are consistently lacking [1,3,8,9]. One previous study reported inferior long-term outcomes in living donor transplant recipients treated with a pretransplant regimen consisting of PLEX and low-dose IVIG without rituximab [10]. Here, we analyzed a sizable cohort of broadly sensitized living donor transplant recipients who underwent desensitization with IVIG and rituximab. This was a very high-risk cohort with 50% having a previous transplant and 73% with a strongly positive cross-match (Flow > 200 MCS). We were able to report outcomes with an average follow-up of almost 6 years ranging to as much as 8 years post-transplant. There were similar rates of graft survival and patient survival. There was more early rejection in the desensitized group; however, there was no statistical difference with long-term follow-up. Allograft function as measured by GFR and presence of proteinuria, both predictors of future graft survival, were also similar in the two groups. Based on this data, this approach to desensitization appears to be durable in the medium term without evidence of impaired allograft function compared to the low-risk group.

Short-term outcomes have shown the rate of rejection to be higher in HLA-sensitized patients [11]. We therefore expected the rate of rejection in the desensitized group to be greater in the long term as well. Indeed, in this study, we found rejection to occur earlier in the sensitized patients; however, the overall rate of rejection was similar in the long term due to more late rejections in the low-risk group. A higher rate of rejection is anticipated in HLA-sensitized patients given the greater immunologic risk of the transplant. Early antibody-mediated rejection occurs in sensitized patients via the activation of complement in the presence of DSA. This takes place earlier in the post-transplant period since time is needed to develop a more regulatory immune profile. The late rejection seen in the low-risk group seems to be driven by the higher rate of nonadherence. This is a difficult and frustrating problem for all transplant institutions. The rate of nonadherence was estimated at 22% in one study [12]. Those undergoing desensitization may be more likely to adhere to the medical regimen because their high-risk status and experiences with previous graft losses severely limit the possibilities for future transplantation. The type of rejection was also different in the two groups with more CMR in the low-risk group and more AMR in the sensitized group. The higher rate of CMR in the low-risk group is likely driven by the choice of induction agent at the time of transplant. All patients with AMR in the low-risk group had multiple *de novo* DSA while those with AMR in the sensitized group primarily had preexisting DSA. Factors predicting the risk for AMR in a similar group of sensitized patients were previously reported and include a DSA RIS > 17, positive cross-match, and previous transplant [7].

Reducing the rate of rejection is critical to improving long-term outcomes. Clearly, devising a strategy to improve adherence to the medical regimen will improve outcomes in all patients. However, in sensitized patients, a strategy must be undertaken to avoid or modify strong, deleterious complement fixing antibodies [13]. Our approach has evolved to address this issue. The availability of single antigen bead assays, which were unavailable at out center until 2009, provides a useful tool for analyzing DSA by determining characteristics that are likely to be deleterious. We avoid DSA with a MFI > 10 000 and those that are positive by the C1q single antigen assay. A major distinguishing feature of the PLEX group, who had worse outcomes, was the higher DSA relative intensity score. We therefore avoid transplantation if the recipient has a DSA relative intensity score >17. These data are consistent with other published studies that have associated DSA strength with outcomes [7,14]. In the early cohort, the B-cell flow cytometry cross-match was difficult to interpret in the presence of rituximab. Therefore, the final B-cell cross-match was often disregarded. The interpretation of the B-cell cross-match has improved now with the use of pronase in the cross-match and the availability of improved DSA assessment techniques. We can therefore better predict which positive B-cell cross-match is due to the presence of alloantibodies [15].

Allograft survival, patient survival, and allograft function were similar in the two groups as were the assessments of GFR and proteinuria at all the time points.

Transplant International 2016; 29: 1276–1285

This is of particular significance as declining GFR and increases in proteinuria are strong indicators of poor allograft outcome [16]. There was a higher incidence of transplant glomerulopathy in the sensitized group. The incidence ranges from 12% to 50% in various reports [17]. The presence of a positive cross-match and rejection is associated with the development of transplant glomerulopathy [18]. Although allograft survival was poor in both the sensitized and low-risk patients with transplant glomerulopathy, overall outcomes, including degree of proteinuria, GFR, and graft survival remained similar.

There is no established treatment for transplant glomerulopathy. Some approaches include raising overall immunosuppression and immune modulation targeting HLA antibodies with IVIG and rituximab [19,20]. We reported on a series of patients who received IVIG and rituximab for transplant glomerulopathy and found that clinical improvements were associated with the concomitant presence of microvascular inflammation scores and stabilization of interstitial fibrosis with tubular atrophy (IFTA) [21]. Close monitoring of DSA, a low threshold for allograft biopsy, and consideration of additional doses of rituximab post-transplant may assist in preventing and altering the course of transplant glomerulopathy.

Kidney paired donation programs have provided an alternative modality for transplanting HLA-incompatible pairs. These exchanges have gained popularity over the last 5 years through single center involvement in a number of registries. Success has been achieved for donor-recipient pairs with a high match power [22]. Factors that contribute to high match power include donor blood type O, recipient blood type AB, and recipients who are not broadly sensitized with low titer HLA antibody. One report placed the match rate of an O recipient with a non-O donor at 27% [23]. Patients with a cPRA of >80% are reported to be transplanted at a lower rate and likely to wait longer compared to patients with lesser degrees of sensitization [22,24,25]. All these factors must be accounted for when entering a broadly sensitized patient into a paired donation registry. A combination of desensitization and kidney paired donation has been used successfully for patients who are broadly sensitized with high titer DSA [26]. Outcomes reported here suggest that it may be beneficial to proceed with direct donation if there is an acceptable cross-match and a low likelihood of finding a match in the exchange. Another option may be to enter a donor/recipient pair into the exchange for a defined period of time and then proceeding with direct donation if a better match is not achieved through the registry.

A new kidney allocation system was implemented in the United States in December 2014. One provision in this new system is the awarding of significantly more points to registrants who are very broadly sensitized. This particularly applies to individuals with a cPRA > 95%. The retired allocation system provided four additional points for a cPRA > 80% while now a sliding scale is in play. Points are awarded starting minimally at a cPRA of 50% and exponentially growing to as many as 200 points for a cPRA of 100%. Early results show an increase in the number of very broadly sensitized patients receiving a kidney transplant in this new paradigm.

This system is in its infancy and it is not clear how it will affect the calculus for proceeding with an incompatible living donor transplant. Overall wait times should be decreased for this population although it is dependent on receiving a perfect or near perfect HLA match, which is still a rare event. We feel, in the current state, proceeding with an incompatible living donor transplant with an acceptable antibody profile, either via direct donation or through KPD, would benefit both the recipient and the allocation system as a whole by utilizing living donors and shortening wait times. Those individuals with a low match power will be more likely to receive a deceased donor kidney transplant with the revised allocation system based on the larger donor pool available to them.

We recognize the limitations inherent to this retrospective cohort. The selection of the low-risk group was based on what we consider to be the gold standard in kidney transplantation; living donor kidney transplant recipients with a negative cross-match and no DSA. This group was chosen to provide a frame of reference and perspective. Differences in the two groups apparent in this study are typical to the sensitized patient population. Multivariable models were used to account for most of these differences. Protocol biopsies were not performed in this cohort; therefore, subclinical rejection may go unrecognized.

The area of desensitization has been prolific over the last 10 years. The characterization of HLA antibodies has particularly evolved to the point where we can identify strong, complement fixing antibodies likely to be deleterious to renal allografts. The cohort presented in this study spans this time period and therefore a number of patients do not have well characterized DSA. However, a majority of patients did have this data available which was presented. It is not clear if the follow-up

observed, which averaged 6 months longer in the sensitized population, contributed to the outcomes reported here. This study was not designed to determine the effect of follow-up on outcomes. However, this variable deserves more attention in future studies.

Desensitization with IVIG and rituximab is shown to improve transplantation rates and to be cost-effective [2]. Outcomes reported here demonstrate excellent patient survival, allograft survival, and allograft function over the follow-up period. Prevention of early rejection in sensitized patients and late rejection in nonsensitized will improve overall outcomes. Avoidance of high MFI and complement fixing DSA is advisable. Kidney paired donation may be an option for patients who have a donor with an unacceptable cross-match and good match characteristics. Desensitization with IVIG and rituximab should be considered for living donor kidney transplant candidates who are broadly sensitized.

Authorship

JK: participated in research design, writing, performance of research and data analysis. SCJ: participated in research design and writing. PW: participated in research design and performance of research. RN: participated in research design and performance of research. JC: performance of research and data analysis. AP: performance of research and data analysis. RV: performance of research and data analysis. AV: participated in research design, writing, performance of research and data analysis.

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