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ORIGINAL ARTICLE

Long-term outcome of highly sensitized African American patients transplanted with deceased donor kidneys

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Summary

Undertaking transplantation in highly sensitized African American (AA) patients as transplant recipients represents a unique challenge. We retrospectively compared the outcomes of AA with non-African American (NAA) patients who had panel reactive antibody >80% and received deceased donor (DD) kidneys by virtual crossmatch. Immunosuppressive regimen included basiliximab induction and tacrolimus, mycophenolate acid and steroids maintenance. Among 835 consecutive transplants from 1998 to 2007, 142 (17%) were sensitized patients including 89 (16.6%) AA and 53 (17.7%) NAA patients. The AA group had similar 5-year incidence of acute rejection as NAA group (21.4% vs. 26.4%, $P = 0.25$). Kaplan–Meier estimated graft survival at 1, 3 and 5 years were 91%, 85% and 82% in AA group, and 94%, 79% and 71% in NAA group ($P = 0.08$). The death-censored graft survival at 1, 3, and 5 years were 93%, 86% and 84% in AA group, and 96%, 83% and 78% in NAA group ($P = 0.11$). The 1, 3, and 5 years patient survivals were 93%, 88% and 85% in AA group, and 96%, 96% and 94% in NAA group ($P = 0.17$). Highly sensitized AA patients could be transplanted with DD kidneys at a similar rate as NAA patients, and they may not have a higher incidence of rejection or an inferior graft survival than NAA patients.

Introduction

The number of highly sensitized patients, which is commonly defined by a panel reactive antibody (PRA) >80%, is rapidly growing on the United Network for Organ Sharing (UNOS) waitlist [1,2]. These patients receive a priority of an additional four points, but they are still less likely to be transplanted or to have an extended waiting period [1,2]. Kidney-paired donation and/or desensitization can help patients who have an incompatible living donor [3–5]. For those without a living donor, desensitization with intravenous immunoglobulin (IVIG) may lower PRA level and improve transplant rate with deceased donor (DD) kidneys [6,7]. However, desensitization is associated with a high incidence of rejections, especially antibody-mediated rejection (AMR) [3–7]. The acceptable mismatch program within Eurotransplant (ET) has successfully transplanted many highly sensitized patients. Short waiting time and excellent graft survival were reported [8–10]. This innovative approach was adopted by the US transplant centers with virtual crossmatch to increase the transplant rate of DD kidneys in highly sensitized patients [11,12].

African American (AA) patients have been traditionally considered high risk for rejection and graft loss [13–15]. Their waiting time is usually longer than the non-African

American (NAA) patients. Therefore, undertaking transplantation in highly sensitized AA patients as transplant recipients may represent a unique challenge. There is no published paper examining their various outcomes. In this study, we summarize our 10-year experience in transplanting highly sensitized patients with a virtual crossmatch protocol. We retrospectively compare the long-term outcome of AA patients and NAA patients who had a peak PRA >80% and were transplanted with DD kidneys.

Materials and methods

Study population

This study was performed with an Institutional Review Board approved protocol. Our transplant center database was cross-referenced with a UNOS-requested database for all recipients transplanted with DD kidneys from January 1998 to December 2007 with known peak PRA ≥80%. Recipients were divided into an AA group and a NAA group. None of these patients was a part of any desensitization protocol.

Virtual crossmatch

Solid phase-based ELISA assay with LAT class 1 and class 2 trays (One Lambda Inc., Canoga Park, CA, USA) was used according to the manufacturer's protocol from January 1998 to September 2006 to identify HLA antibodies, and Luminex single antigen beads (One Lambda Inc.) were subsequently used, and the cutoff for Luminex assay was >2000 mean fluorescence intensity. The corresponding antigens were considered as unacceptable for that patient and were listed into the UNOS database. A patient would not be offered a kidney from a donor who expressed an unacceptable HLA antigen. Only those patients whose HLA antibodies were not donor-directed would appear on the match run. Our HLA laboratory required donor lymph nodes as the source of T and B lymphocytes. The final T- and B-cell crossmatches were negative in all patients by antihuman globulin-modified complement-dependent cytotoxicity. Flow cytometry crossmatch was added into our practice in 2001 and both T and B-cell flow crossmatches were also negative (channel shifts <40 for T-cell, and <100 for B-cell) before transplant.

Immunosuppression

All recipients received antibody induction with two doses of basiliximab and maintenance immunosuppression consisting of tacrolimus, mycophenolic acid and steroids. Intravenous methylprednisolone was administrated prior to reperfusion and tapered to 5 mg of prednisone by the 3rd month. Tacrolimus doses were adjusted to keep the 12-h trough levels between 10 and 12 ng/ml for the first 3 months, 7 and 10 ng/ml for the remainder of the first year, and 4 and 7 ng/ml thereafter. Each patient received either mycophenolate mofetil at 1 g or enteric-coated sodium mycophenolate at 720 mg twice daily.

Infection prophylaxis

All patients received sulfamethoxazole/trimethoprim for 1 year and clotrimazole for 3 months. CMV prophylaxis was given to seronegative recipients transplanted with seropositive donor kidneys (D+/R−) as well as the patients who received thymoglobulin for rejection. The regimen included IV ganciclovir during hospitalization followed by oral ganciclovir or valganciclovir for additional 3 months. CMV disease was diagnosed by positive CMV antigenemia or viral invasion in biopsied tissues. Treatment consisted of IV ganciclovir for 2–4 weeks, which was followed with oral ganciclovir or valganciclovir for additional 3 months.

Rejection

Rejection was presumed when patients had a sudden increase of serum creatinine by 20%, which was not explained by obvious causes. Kidney biopsy was performed and the severity of rejection was defined according to Banff criteria. Mild rejection (grade 1 or below) was treated with IV methylprednisolone. Thymoglobulin was used for steroid-resistant rejection, or as initial therapy for severe rejection (grade 2 or higher). AMR was diagnosed by positive c4d staining in peri tubular capillaries in addition to the tissue evidence of injury. Donor-specific antibody (DSA) was not routinely screened after transplant. Plasmapheresis, IVIG and thymoglobulin were used to treat AMR.

Outcome measures

Outcome measures included: (i) patient and graft survivals over 5 years, (ii) incidence of biopsy confirmed and treated acute rejection, (iii) post-transplant complications, (iv) quality of graft function as assessed by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation, and (v) etiologies of patient death and graft loss. Patient death included all mortalities from the time of transplantation. Graft loss was defined by primary nonfunction or loss of renal function requiring chronic dialysis. Death with a functioning graft (DWFG) was also counted as graft loss. Graft failure was excluded from the calculation of graft function.

Statistical method

Statistical analyses were performed using SAS version 9.1.3 software (SAS Institute Inc, Cary, NC, USA). Chi-squared or Fisher exact test was used for count data and *t*-test for continuous measures. Product-limit estimates of survival curves were generated by the Kaplan–Meier method and the survival difference was analysed by log-rank test. Multivariable logistic regression analysis with a stepwise variable selection was used for examining risk factors for graft loss and for rejection. A *P*-value <0.05 was considered statistically significant.

Results

A total of 835 patients, including 536 AA patients and 299 NAA patients received isolated DD kidney transplants during this 10-year study period. Some 142 of them (17%) were highly sensitized patients with peak PRA ≥80%, including 89 AA patients (16.6%) and 53 NAA patients (17.7%, $P = 0.72$). Median follow up was 6.8 years (range: 23.3–143 months) as of December 2009 and all patients were transplanted more than 2 years before this study. Table 1 summarizes the demographic characteristics of AA and NAA groups. There were 50 Caucasians, two Asians and one Hispanic patient in NAA group. There was no difference in gender, etiologies of renal failure, HLA mismatch, cold ischemic time, peak PRA, causes of sensitization, or donor factors between the two groups. As compared with the NAA group, the AA group was significantly older, had been on the wait-list for transplantation for a longer duration, and had a higher PRA value at the time of transplantation.

The immunosuppressive drugs, including the 12-h trough levels of tacrolimus, daily doses of mycophenolic acid and steroid were similar between AA and NAA groups at the first week, first month, 3rd month, 6th month and each year after transplant (data not shown). A similar percentage of patients (9% in AA and 11% in NAA) required modification of maintenance immunosuppression because of side-effects. Post-transplant medical events and surgical complications are summarized in Table 2. Delayed graft function (DGF) was similar, as was the incidence of CMV disease (12.4% in AA group and 7.6% in NAA group). The 5-year cumulative incidence of biopsy – confirmed and clinically treated acute rejection was not statistically different, 21.4% in AA group and 26.4% in NAA group. There were five episodes of AMR in AA group (5.6%) and four episodes in NAA group (7.5%). The time course of acute rejection was shown in Fig. 1. Surgical complications and graft functions (eGFR) were not different between the two groups (Table 2).

There was no statistical difference in graft survival by Kaplan–Meier analysis between the two groups (Fig. 2). The estimated graft survivals at 1, 3 and 5 years were 91%, 85% and 82% in the AA group, and 94%, 79% and 71% in the NAA group (log rank $P = 0.08$). The death-censored graft survival at 1, 3 and 5 years were not different between the AA group (93%, 86% and 84%) and the NAA group either (96%, 83% and 78%, log rank $P = 0.11$). The causes of graft loss were summarized in Table 2. Severe cellular rejection (vascular rejection) caused two graft losses in the AA group and one graft loss in the NAA group, while AMR led to one graft loss in the AA group and two in the NAA group. There was no significant difference in patient survival between the AA and the NAA groups (Fig. 3). The Kaplan–Meier estimated 1-, 3-, and 5-year patient survivals were 93%, 88% and 85% in the AA group, and 96%, 96%, 94% in the NAA group (log rank $P = 0.17$). The causes of patient death were summarized in Table 2. There were numerically more patient deaths (15.7%) in the AA group than in the NAA

Table 1. Demographic characteristics of African American (AA) and non-African American (NAA) groups (mean ± SD).

	AA ($n = 89$)	NAA ($n = 53$)	*P*-value
Recipient age	46.4 ± 13.1	41.5 ± 14.4	0.04
Gender (%)			
Female	60 (67.4)	30 (56.6)	NS
Male	29 (32.6)	23 (43.4)	
BMI (kg/m^2)	27.6 ± 7.8	26.9 ± 7.2	NS
Dialysis time (months)	50.6 ± 36.5	37.6 ± 33.9	0.04
Waiting time (months)	34.6 ± 21.6	26.5 ± 20.2	0.03
Causes of ESRD (%)			
HTN	49 (55)	24 (45.3)	NS
DM	20 (22.5)	14 (26.4)	
GN	12 (13.5)	9 (17)	
Others	8 (9)	6 (11.3)	
HLA mismatch	4.2 ± 1.8	3.9 ± 1.7	NS
Cold ischemic time (h)	17.1 ± 6.5	16.5 ± 6.9	NS
Peak PRA	93.6 ± 6.6	91.7 ± 6.4	NS
PRA at transplant	68.1 ± 24.0	56.0 ± 27.1	0.006
Causes of sensitization (%)			
Transfusion	6 (6.8)	12 (22.6)	0.08
Pregnancy	45 (50.6)	17 (32.1)	
Transplant	26 (29.2)	19 (35.9)	
Donor age	34.5 ± 15.2	33.2 ± 14.8	NS
Race (%)			
NAA	58 (65.2)	42 (79.3)	NS
AA	31 (34.8)	11 (20.7)	
Gender (%)			
Female	41 (46)	23 (43.4)	NS
Male	48 (54)	30 (56.6)	
BMI (kg/m^2)	25.5 ± 6.5	26 ± 7.1	NS

AA, African American; PRA, panel reactive antibody.

Table 2. Post-transplant events in African American (AA) and non-African American (NAA) groups (mean ± SD).

	AA (n = 89)	NAA (n = 53)	P-value
DGF (%)	22 (24.7)	11 (20.8)	NS
Acute rejection (%)	19 (21.4)	14 (26.4)	NS
CMV infection (%)	11 (12.4)	4 (7.6)	NS
Surgical complications (%)	14 (15.7)	9 (17)	NS
Bleeding	7	5	
Hematoma	2	1	
Lymphocele	3	1	
Wound infection	1	2	
Graft thrombosis	1	0	
Graft function			
eGFR at 1 month	50.5 ± 22.8	52.1 ± 28.3	NS
eGFR at 6 months	59.1 ± 21.6	58.9 ± 25.0	NS
eGFR at 1 year	61.8 ± 22.4	56.6 ± 20.7	NS
eGFR at 3 years	57.0 ± 23.2	55.4 ± 22.7	NS
eGFR at 5 years	46.5 ± 23.8	53.2 ± 24.8	NS
Graft loss (%)	18 (20.2)	16 (30.2)	NS
Causes of graft loss			NS
CAN	6	5	
DWFG	6	4	
Rejection	3	3	
Infection	2	3	
Others	1	1	
Patient death (%)	14 (15.7)	4 (7.5)	NS
Causes of death			NS
CVD	8	2	
Infection	4	2	
Malignancy	1	0	
Others	1	0	

AA, African American; CAN, chronic allograft nephropathy; DGF, delayed graft function; DWFG, death with a functioning graft; eGFR, estimated glomerular filtration rate.

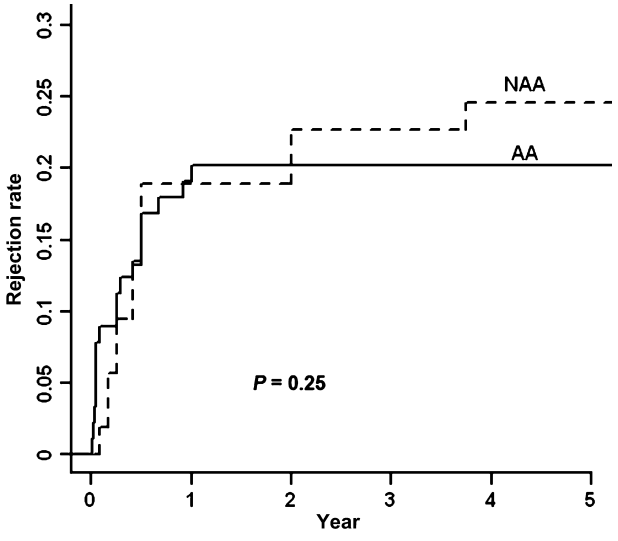

Figure 1 Cumulative incidence of biopsy-confirmed and clinically treated acute rejection between African American (AA) group and non-African American (NAA) group.

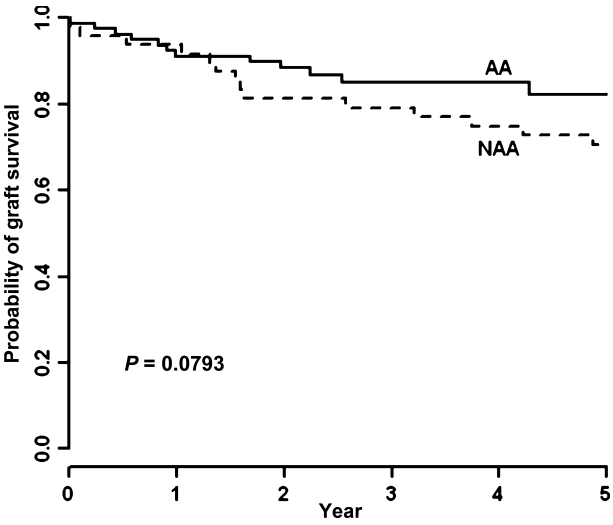

Figure 2 Kaplan–Meier analysis of graft survival between African American (AA) group and non-African American (NAA) group.

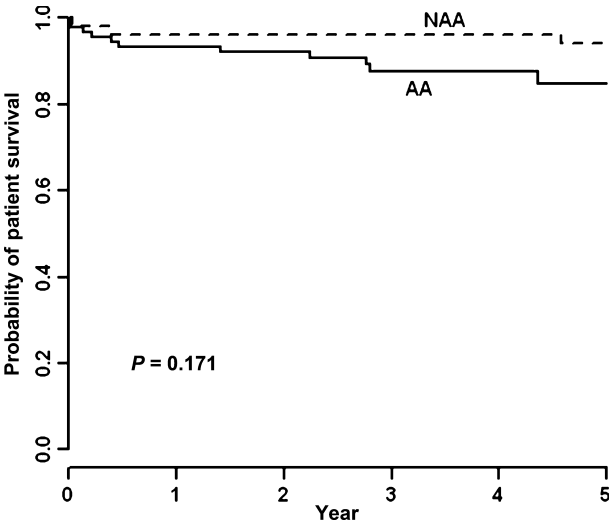

Figure 3 Kaplan–Meier analysis of patient survival between African American (AA) group and non-African American (NAA) group.

group (7.5%), which was mainly from cardiovascular disease (CVD) and infection/sepsis.

The risk factors for graft loss and for acute rejection were examined by Cox's proportional hazard regression analysis and significant risk factors were further analysed by a stepwise variable selection model. The risk factors included CMV infection, DGF as well as all donor and recipient factors listed on Table 1. Acute rejection was found to be the only significant risk factor for graft loss (OR 7.45, 95% CI 1.62–35.5, P = 0.01). Interestingly, HLA mismatch, but not the previous transplant,

pregnancy or transfusion was an independent risk for acute rejection (OR 1.70, 95% CI 1.3–2.5, $P = 0.03$).

Discussion

During the past 15 years from 1994 to 2009, the percentage of highly sensitized patients with PRA >80% who were added to UNOS waitlist each year or who were on the waitlist at the end of each year increased by 10% [2]. The higher the PRA level, the lower likelihood of receiving a compatible kidney and longer waiting time on the waitlist. For patients with a HLA and/or ABO incompatible living donor, they may be transplanted through kidney-paired donation and/or with a desensitization protocol [3–5]. Among the various desensitization protocols, only one protocol using large dose-IVIG with or without rituximab can practically improve the transplant rate of patients with a DD kidney [6,7]. Similar 1- and 2-year graft survival as the control group, but much higher incidences of acute rejection, especially the AMR were reported [6,7]. The long-term outcome remains to be studied [5,16,17].

In 1985, ET started a pioneer acceptable mismatch program for highly sensitized patients with PRA >85% [8,9]. Acceptable mismatches are defined as the HLA mismatches against which the patient has never formed antibodies and are considered to be acceptable as mismatch for the future donor organ [8–10]. About 60% of sensitized patients successfully received DD kidney transplant in the first 2 years after entering this program, and graft survival was reported to be identical to nonsensitized patients (87% at 2 years) [9]. Similar to this ET program, virtual crossmatch by identifying anti-HLA antibodies and listing unacceptable HLA antigens has been used in the US transplant centers [11,12,18–20]. Bray *et al.* reported this strategy in the Emory program [11]. A total of 492 adults received DD kidneys from 1999 to 2003, 58 of them (11.8%) had PRA >80%. The 5-year graft survival of patients with PRA >80 was 70%, which was identical to the nonsensitized patients and similar to the patients with PRA 1 to 29% (69%) as well as patients with PRA >30% (66%). They estimated that patients with PRA >30% were transplanted at a rate that was twice the national average (25% vs. 12%). Recently, Bingaman *et al.* also demonstrated a significant increase in their transplant rate using a virtual crossmatch protocol [12]. From October 2006 to June 2008, 15 of the 122 DD kidney recipients (12.3%) were sensitized with PRA >80%, which was higher than the national rate of 5.5% (590/10 659) by Scientific Registry of Transplant Recipients (SRTR) in 2006 ($P = 0.004$).

In 1998, our transplant center implemented a unique protocol that combined virtual crossmatch with donor lymph node crossmatch. In our experience, donor lymph nodes can provide more T and B cells for final crossmatch and HLA antigens are better expressed on lymph node cells, which avoid a false negative crossmatch and decrease the risk of rejection. With this protocol, a significantly higher percentage of highly sensitized patients were transplanted with DD kidneys than the national average by SRTR data in 2006 (17% vs. 5.5%, $P < 0.0001$). Our study indicates that the highly sensitized AA patients can be transplanted at a similar rate as the NAA patients (16.6% vs. 17.7%, $P = 0.72$).

African American patients are usually associated with a higher incidence of rejection and graft loss when compared with other patients [13–15]. Many transplant centers would use T -cell depleting antibody thymoglobulin as induction in AA patients [21,22]. Compared with IL-2 receptor antibody basiliximab, thymoglobulin reduces the risk of rejection, but it may also increase the risk of infection and possibly malignancy [21–23]. Its advantage on graft or patient survival has not been well established. A recent analysis based on United States Renal Data System from 2000 to 2005 indicated that both patient and graft survival were similar in AA and Caucasian patients using either thymoglobulin or IL-2 receptor antibody induction [24]. As reported previously, our center's experience suggested that T-cell depleting antibody induction might no longer be necessary in the era of potent maintenance of tacrolimus, mycophenolate acid and steroids [25,26]. Non-T-cell depleting antibody basiliximab induction was used for our high-risk patients, including in this study. The AA patients had a similar cumulative incidence of rejection as the NAA patients (21.4% vs. 26.4% in 5 years, $P = 0.25$). The rejection rates, especially the AMR (5.6% in AA group and 7.5% in NAA group), were considerably lower than the reported rejection rates (36–62%) by desensitization protocols [3–7]. Acute rejection was not a leading cause of graft loss, and AMR only contributed to one graft loss in AA group and two in NAA group. When the risk factors for acute rejection and graft loss were further analysed, we found that HLA mismatch was the only independent risk factor for acute rejection and acute rejection was the significant risk for graft loss. This suggests that highly sensitized patients could benefit from a well matched kidney. The incidence of CMV disease was very low in both groups despite the fact that a limited and short-term CMV chemoprophylaxis regimen was used in our center. Interestingly, no induction therapy was used in any highly sensitized patient from an ET program reported by van den Berg-Loonen *et al.* [10]. Of note, in the ET area, the patient and donor population are more homogenous than ours. Our study extends their experience and demonstrates that even highly sensitized AA patients may not necessitate thymoglobulin induction.

African American patients had a similar incidence of post-transplant complications and a comparable quality of graft function as the NAA patients. AA patients did not have an inferior graft survival at 1, 3 or 5 years (91%, 85% and 82%) when compared with NAA patients (94%, 79% and 71%, $P = 0.08$). Our graft survivals were comparable to the SRTR data for DD kidneys in the same time period (90.4%, 79.3% and 68.2% in 1, 3 and 5 years) [1]. The death-censored graft survival was also similar between AA (93%, 86% and 84%) and NAA (96%, 83% and 78%) groups ($P = 0.11$). The 1-, 3- and 5-year patient survival were not significantly different between the AA (93%, 88% and 85%) and the NAA group (96%, 96% and 94%, $P = 0.17$). Our patient survival rates were also similar to the SRTR data for DD kidney recipients (95%, 88.5% and 81% in 1, 3 and 5 years) [1]. There were numerically more patient deaths (15.7%) in the AA group than in the NAA group (7.5%). This likely represents the patient selection bias in our center, as the average age of the AA group was 5 years older than the NAA group (46.4 vs. 41.5 years, $P = 0.04$) at the time of transplantation, and there were several more deaths from CVD and infection in the AA group.

To our knowledge, this is the first study comparing the various outcomes of highly sensitized AA patients and NAA patients who were transplanted with DD kidneys. Our comparison is fair, as both groups received the same immunosuppressive regimen and were cared for by the same transplant team. However, this study is limited by its single center data, relative small sample size, retrospective nature, and the lack of routine DSA monitoring after transplant. Development of DSA after transplant may contribute to both acute and chronic AMR and decrease graft survival [16,17]. It is possible that both acute and chronic AMR were not truly recognized in this study, and some cases of chronic allograft nephropathy (CAN) were actually caused by subclinical rejection. The pretransplant DSA detected by the sensitive Luminex assay and not by the less-sensitive crossmatch was reported to be related to rejection episodes, but might not be detrimental to long-term graft survival [10].

As the acceptable mismatch program in ET, virtual crossmatch avoids the problem of DSA, while desensitization protocols address this issue directly. Our data shows that a low incidence of rejection and rejection-associated graft loss, excellent long-term graft function and graft survival can be achieved not only in NAA patients, but also in AA patients. Our study supports a universal adoption of this approach. Virtual crossmatch should be considered as the preferred method for all sensitized patients. Because of the nature of HLA polymorphisms, virtual crossmatch may not get all patients transplanted, especially those with rare HLA antigens [8,9]. Desensitization can be used as a rescue therapy for these difficult cases.

In conclusion, highly sensitized AA patients could be transplanted with DD kidneys at a similar rate as the NAA patients by virtual crossmatch. With the triple maintenance of tacrolimus, mycophenolate acid and steroid, basiliximab induction is adequate and thymoglobulin may not be necessary. Highly sensitized AA patients did not have a higher incidence of acute rejection, CMV disease or other complications, and they may have a comparable quality of graft function and a similar long-term graft survival as NAA patients.

Authorship

QR: participated in data collection; CLY: participated in data analysis; MK, SF, LLH and DS: participated in research design; BA, ES and JB: participated in editing; AP and RZ: participated in data collection, research design and writing.

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