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ABO-Incompatible Living Donor Kidney Transplantation without Post-Transplant Therapeutic Plasma Exchange

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Abstract

Blood group incompatibility remains a significant barrier to kidney transplantation. Approximately one-third of donors are blood group incompatible with their intended recipient. Options for these donor-recipient pairs include blood group incompatible transplantation or kidney paired donation. However, the optimal protocol for blood group incompatible transplantation is unknown. Protocols differ in techniques to remove ABO antibodies, titer targets and immunosuppression regimens. In addition, the mechanisms of graft accommodation to blood group antigens remain poorly understood. We describe a blood group incompatible protocol using pre-transplant therapeutic plasma exchange (TPE), high-dose intravenous immunoglobulin and rituximab in addition to prednisone, mycophenolate mofetil and tacrolimus. In this protocol, we do not exclude patients based on a high initial titer and do not implement post-transplant TPE. All 16 patients who underwent this protocol received a living donor transplant with 100 percent patient and graft survival, and no reported episodes of antibody-mediated rejection to date with a median follow-up of 2.6 years (range 0.75 to 4.7 years). We conclude that blood group incompatible transplantation can be achieved without post-transplant TPE.

Keywords

ABO-incompatible; kidney transplantation; ABO antibodies; ABO antibody titers; therapeutic plasma exchange

Introduction

Kidney transplantation is the treatment of choice for patients with end-stage renal disease (ESRD) [1]. Blood group incompatibility remains a significant barrier to kidney transplantation. Approximately one-third of donors are blood group incompatible with their intended recipient. Current options for blood group incompatible donor-recipient pairs are kidney paired donation (KPD) or blood group incompatible transplantation. KPD is a creative option that matches a blood type compatible donor with a recipient through a registry. However, difficult-to-match donor-recipient blood types, such as a blood type A

donor and a blood type O recipient, continue to pose a challenge. Moreover, highly sensitized patients often have few options for a compatible transplant except for a well-matched, blood group incompatible living donor transplant.

ABO blood type incompatible (ABOI) transplantation is often considered high risk due to antibody-mediated rejection, virus infections and possibly decreased graft survival; however, recent studies demonstrate improved long-term outcomes [2–6]. Protocols for ABOI transplantation have evolved over the past 30 years with modern immunosuppression including B-cell targeted therapy replacing the need for splenectomy [3,7,8]. At the same time, blood group incompatible transplantation requires more resources including the ability to perform ABO antibody titers and antibody removing procedures. However, ABOI transplantation is more cost effective compared to remaining on dialysis [9]. The optimal protocol for ABOI transplantation that minimizes cost and potential complications including infections and rejection episodes is unknown.

Therefore, we sought to design a simpler protocol that is less expensive. By carefully analyzing ABO antibody titers, our objective is to create an ABOI protocol to enable successful transplantation without post-transplant therapeutic plasma exchange (TPE).

Patients and Methods

Subjects

Between April 2010 to March 2013, 16 donor-recipient pairs underwent ABOI kidney transplantation at Stanford University Medical Center (Tables 1 and 2). During the same time period, 26 donor-recipient pairs were entered into the KPD program with 12 patients successfully receiving a transplant through the exchange. Patients with a blood group incompatible living donor had an ABO antibody titer drawn and underwent the standard donor and recipient evaluations. Patients and potential living donors were informed of all options including participation in KPD and ABOI programs as well as waiting for a deceased donor transplant. If patients decided to undergo the ABOI protocol with the respective blood group incompatible living donor, the risks, benefits and outcomes of the ABOI protocol were explained in detail to the patients and their donors. At the start of the protocol, patients with an initial titer greater than or equal to 512 were encouraged to pursue KPD instead of the ABOI protocol because of the potential difficulty in lowering the titer. However, after successfully lowering an initial titer of 2048 to the goal level of 16 prior to transplantation, the protocol was revised October 2012 to not exclude patients based on initial titer level. The Institutional Review Board at Stanford University approved this protocol.

ABOI Protocol

ABOI protocol is depicted in Figure 1. Therapy consisted of 5–11 TPE treatments pre-transplant depending on titer strength (Table 3) followed by one infusion of high-dose intravenous immunoglobulin (IVIG, 2 gm/kg, max dose 140 gm) at the completion of all TPE treatments and a repeat dose of IVIG (2 gm/kg, max dose 140 gm) 10–14 days post-transplant. One dose of rituximab (375 mg/m²) was administered 2–4 weeks prior to

transplantation and at least one week prior to the first TPE treatment. Immunosuppression was started 2 weeks prior to transplant with mycophenolate mofetil (MMF) 500 mg twice daily and prednisone 10 mg daily. The titer goal was less than or equal to 16 prior to transplantation. Maintenance immunosuppression post-transplant included antithymocyte globulin (ATG) induction (1.5 mg/kg/day, 6 mg/kg total dose), MMF 500–1000 mg twice daily, methylprednisolone/prednisone 250 mg/day tapered to 5 mg/day, and tacrolimus with target level of 10 ng/mL for the first 4 weeks post-transplant and adjusted per clinical course.

Blood Type Antibody Titers

ABO antibody titers were performed using the conventional tube method as previously described [10,11]. Serial dilutions of patient plasma were prepared and tested at either room temperature (RT) or anti-human globulin (AHG) phase against a commercially prepared A or B cell suspension. The titer corresponded to the quantity of antibody present in the sample. In brief, both titers at either RT or AHG phase for anti-A and anti-B were performed using serial, two-fold dilutions of patient plasma with 0.9 percent saline and known group A or B RBC reagents. These suspensions were then analyzed for agglutination after incubation for 15 minutes (RT phase) and for 60 minutes at 37°C before addition of the anti-human globulin reagent (AHG phase). The antibody titer was determined based on the highest two-fold dilution that demonstrated 1+ macroscopic agglutination.

ABO antibody titers were measured before and after each TPE session, daily for the first 5 days post-transplant and weekly for the first month post-transplant. Thereafter, titers were measured at 2 months, 3 months, 6 months and 1 year post-transplant or when there was a decline in kidney function.

Therapeutic Plasma Exchange

TPE was performed with the COBE® Spectra centrifugal blood separator with 1 plasma volume exchange using citrate as anticoagulant. In patients with titers of 256 or above, we started with 1.5 plasma volume exchange. Plasma was replaced with 5% human albumin. TPE was performed in patients through an arteriovenous fistula/graft or peripheral intravenous lines. Only a few patients with inadequate venous access required placement of tunneled dialysis catheters. Fibrinogen levels were monitored with each treatment and Group AB fresh frozen plasma (FFP) was made available and administered if fibrinogen levels were below 100 mg/dL. FFP was not used as replacement fluid in any of the patients. Patients received one infusion of IVIG (2 gm/kg, 140 gm max dose) after all TPE treatments were completed.

The number of TPE treatments was estimated based on the initial ABO antibody titer strength with a minimum of 5 treatments (Table 3). Titers were measured before and after each TPE session and adjustments to plasma volume from 1.5 to 1 plasma volume and number of treatments were made according to patient response based on pre- and post-TPE titers. The goal titer was 16 or less prior to transplantation. If this titer goal was not achieved, transplantation was postponed and more TPE sessions were added. The final TPE session was performed at least two days prior to transplant surgery to enable repletion of

clotting factors. IVIG formulations contain anti-A and anti-B and can increase titer levels leading to difficulty in interpretation of post-transplant titers [12]. Therefore, the titer value alone was not used to determine the need for TPE. Clinical assessment of kidney function including decrease in urine output and increase in creatinine levels in combination with elevated titers was used to determine the need for post-transplant TPE.

Diagnosis of Rejection

Patients were followed in clinic post-transplant per standard protocol. Participants in the ABOI protocol were screened for BK virus at 1 month, 2 months, 3 months, 6 months, 9 months and 1 year. Biopsies were performed as clinically indicated when there was a decline in kidney function as assessed by creatinine levels. Biopsy specimens were formalin-fixed, paraffin-embedded and stained with hematoxylin-eosin and periodic acid-Schiff. C4d staining was performed using immunoperoxidase technique. Biopsies were scored according to the revised Banff'97 classification [13,14].

Results

Patient Characteristics

Demographics of the patients are shown in Table 1. While diverse in age and sex, the proportion of Blacks is lower in our center compared to the US population. Two patients had a T-cell flow positive crossmatch with preformed donor specific antibodies. Five patients had prior transplants (liver [1], lung [1], pancreas and kidney [1], and kidney [2]). All donors, except one, were living related, and the majority was donor blood group A to recipient blood group O (Table 2). One donor was blood type A2 with a starting titer of 32, and the recipient was blood group O. Patients were informed of both the ABOI protocol and the KPD program and voluntarily selected to participate in the ABOI protocol. One donor-recipient pair (donor blood type A and recipient blood type O) underwent the ABOI protocol after a match was not successfully found in the KPD program.

ABO Antibody Titers and Therapeutic Plasma Exchange

The number of TPE treatments was determined based on initial titer strength with 5–6 treatments for titers 16 to 256 and 7–8 treatments for titers 256 and above (Table 3). The minimum number of TPE treatments was 5. One patient with an initial titer of 2048 required additional TPE sessions after the titer remained above 16 after 8 treatments. For this patient, the transplant was postponed for one week to reach the goal titer of 16, which required 11 treatments. The median initial titer for all patients was 64 at both AHG and RT phases, and the median titer after completing plasma exchange was 4 and 2 at AHG and RT phases, respectively (Figure 2). The median titers post-transplant were 4 to 8 at both AHG and RT phases. The highest titers detected during the first post-transplant week were 32 and 16 at AHG and RT phases, respectively (Figure 2).

Fibrinogen levels were drawn prior to each TPE session with the last TPE session performed at least two days prior to transplant to allow for repletion of clotting factors. Mean fibrinogen levels before the first TPE session was 401 ± 116 mg/dL (range 224–636 mg/dL) with normal levels 228–419 mg/dL. Mean fibrinogen levels prior to the final plasma

exchange was 171 ± 51 mg/dL (range 121–338 mg/dL). Fibrinogen levels were not routinely measured post-transplant unless clinically indicated. The criteria for instituting TPE post-transplant were based on kidney function assessed by decrease in urine output and increase in creatinine levels in combination with rising titer strength. No patients required post-transplant TPE.

Patient Outcomes

All patients successfully underwent living donor kidney transplantation. Both patient and graft survival was 100% with a mean creatinine value of 1.3 ± 0.3 mg/dl at last median follow-up of 2.6 years (range 0.75 to 4.7 years) (Table 4). Four patients underwent biopsies for increased creatinine levels and all biopsies had C4d deposition. There was one episode of acute cellular rejection (Banff IB) at 10 months post-transplant in a patient that underwent a T-cell flow positive crossmatch transplant with preformed donor specific antibodies. At the time of rejection, there were no donor specific antibodies detected, and the ABO antibody titer was 8 at both AHG and RT phases. The patient was successfully treated with methylprednisolone and ATG. There were no reported episodes of antibody-mediated rejection and no detected infectious complications including BK virus. There were no bleeding or wound complications (Table 4).

Discussion

This report demonstrates that patients can successfully undergo blood group incompatible kidney transplantation without post-transplant TPE regardless of a high initial titer. Our goals in designing this ABOI protocol were to minimize complications, rejection episodes and cost. In our protocol, we did not utilize post-transplant TPE and rather assessed patients' kidney function clinically by following urine output and creatinine levels in concert with titer levels. Some ABOI protocols institute routine post-transplant TPE in an effort to keep titers at 8 or below during the first week post-transplant [15,16]. Our protocol did not implement routine TPE. In addition to avoiding post-transplant TPE, we also utilized patients' arteriovenous fistulas/grafts or temporary intravenous lines in the majority of patients to decrease the risk of line-related infections.

It is still unclear what minimum titer is acceptable before and after ABOI kidney transplantation. Moreover, measurement of ABO antibodies is an important component of the ABOI protocol including the method and timeliness of the results. We utilized the conventional tube method testing at 22°C referred as RT phase at which IgM antibodies commonly react and testing at 37°C with anti-IgG reagent for IgG; we adhered to a titer threshold of 16 or less at both RT and AHG phases before transplantation. The cost associated with performing ABO antibody titers was considered necessary and minimum compared to the overall cost associated with the ABOI transplant and treatment of antibody-mediated rejection [9]. Titer results may vary depending on the technical operator or the technique used [17]. Indeed, while Kumlien *et al.* compared the tube and gel techniques for ABO antibody titration and showed less variation with the gel method, our center only supported the manual tube method [17]. Nevertheless, after transplantation, we followed both the kidney function and the titer strength. We measured titers frequently in the early

post-transplant period when the risk of antibody-mediated rejection was the highest and decreased frequency of titer measurements thereafter. Several patients had titers of 16 or 32 at both RT and AHG phases during the first post-transplant week without evidence of rejection or graft dysfunction. In addition, A2 donors are thought to be less immunogenic and have been transplanted successfully without preconditioning regimens in the setting of low titers [18]. However, in the setting of high titers, there have been reports of antibody-mediated rejection with A2 donors [19]. With a titer level of 32 that is higher than our goal of equal or less than 16, we chose to utilize the ABOI protocol in our A2 donor to O recipient living donor pair.

Expression of ABO antigens on the donor kidney has been shown to progressively decrease with time after ABOI kidney transplantation, contributing to graft accommodation [20,21]. Interestingly, ABO antibodies are known to bind complement. Although C4d complement binding to endothelial cells is increased on histologic ABOI graft biopsies, there is no correlation with increased antibody-mediated rejection [22]. Similarly, we did not diagnose any episodes of antibody-mediated rejection although we did not perform protocol biopsies. There are few studies on the role of protocol biopsies in patients undergoing ABOI transplantation. One retrospective study comparing protocol biopsies in 48 ABOI transplant recipients to control biopsies in ABO-compatible recipients showed increased subclinical cellular rejection in the ABOI biopsies within the first year post-transplant but no increase in transplant glomerulopathy [23]. Another study showed that the incidence of chronic transplant glomerulopathy might be lower in patients undergoing ABOI transplantation [24]. Furthermore, Tyden *et al.* reported that recipients treated with rituximab as an induction agent had fewer rejection episodes [25]. Perhaps B-cell depleting therapies could reduce post-transplant donor specific antibodies and prevent acute and chronic rejection episodes.

Although transplant centers in Japan commonly use a lower dose of rituximab with success, the optimal dose for rituximab in ABOI protocols is unknown in different demographic populations [26]. Therefore, we chose the standard rituximab dose of 375 mg/m². We also utilized high-dose IVIG after all TPE sessions rather than low-dose IVIG after each session with a second dose 10–14 days post-transplant. Although administration of IVIG may cause difficulty in interpretation of post-transplant titers because IVIG contains anti-A and anti-B, our rationale was that the long-lasting effect of IVIG on decreasing ABO antibodies by anti-idiotypic regulation or other mechanisms may be beneficial during the critical early post-transplant period to enable graft accommodation [12,27].

ABO incompatibility previously was a significant barrier to living donor transplantation. Recent studies report excellent graft and patient survivals in recipients undergoing ABOI kidney transplantation likely in part secondary to improved immunosuppression [3,28]. However, with the advent of KPD programs, it is controversial which patients should undergo the ABOI protocol. We successfully transplanted 16 patients that underwent ABOI protocol prior to transplantation. We enrolled one patient after failing to find a suitable match in the KPD program. Two patients were very highly sensitized with preformed donor specific antibodies and underwent crossmatch positive transplants with blood group incompatible related donors. After undergoing the ABOI protocol, the crossmatches became negative with decrease in the strength of donor specific antibodies. The majority of our

patients, notably, were well-matched by human leukocyte antigen (HLA), and therefore, we were able to minimize immunosuppression post-transplant. In fact, five of the kidney transplants were HLA-identical sibling pairs, which were reported to have excellent long-term outcomes in the setting of ABO incompatibility [29]. Furthermore, two patients were approaching dialysis but preferred to undergo preemptive ABOI living donor transplants rather than initiate dialysis and wait for either a match in the KPD program or a deceased donor on the waiting list.

Our initial outcomes ranging from 9 months to almost 5 years indicate no significant differences in kidney function, rejection episodes, infections including BK virus, wound or bleeding complications, and graft and patient survival compared to blood group compatible transplants. Although we did not implement protocol kidney biopsies, four patients underwent biopsies for graft dysfunction. One patient had an episode of late acute cellular rejection without evidence of antibody-mediated rejection based on light microscopy findings of margination of polymorphonuclear leukocytes in peritubular capillaries, fibrin thrombi and transmural necrotizing arteritis. All four patients had strong C4d staining, low ABO antibody titers and no evidence of kidney dysfunction, suggesting graft accommodation and confirming the absence of the histologic correlation between C4d deposition and injury associated with ABOI kidney grafts [20–22].

Conclusions

This report demonstrates that patients can successfully undergo ABOI kidney transplantation without post-transplant TPE in the setting of high initial titers. This strategy could minimize potential complications while allowing graft accommodation. We believe that ABOI transplantation is a valuable option for patients in this era of declining numbers of kidney donors, especially since living donors are favored over deceased donors. Careful selection of donor-recipient pairs, tailoring of the ABOI protocol based on titers and response to TPE, and further research in understanding the mechanisms of graft accommodation in the setting of ABO antibodies are warranted for continued successful outcomes.

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Abbreviations

ABOI	ABO-incompatible
AHG	anti-human globulin

ATG	antithymocyte globulin
ESRD	end-stage renal disease
HLA	human leukocyte antigen
IVIG	intravenous immunoglobulin
KPD	kidney paired donation
MMF	mycophenolate mofetil
RT	room temperature
TPE	therapeutic plasma exchange

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Figure 1. ABO-Incompatible Protocol and Timeline before and after Kidney Transplantation

Timeline begins at 21 days prior to transplantation with (x) designating additional TPE sessions performed on patients with initial titers greater than or equal to 256. Treatments received by all patients are designated with x. Rituximab dose was 375 mg/m² and was administered one week prior to first TPE session. IVIG dose was 2 gm/kg, 140 gm max dose. Immunosuppression dosages: ATG 1.5 mg/kg/day with 6 mg/kg total dose, prednisone 10 mg/day pre-transplant and methylprednisolone and prednisone post-transplant at 250 mg/day tapered to 5 mg/day, MMF 500–1000 mg twice daily, tacrolimus with target level of 10 ng/mL for the first 4 weeks post-transplant and adjusted per clinical course. TPE = therapeutic plasma exchange; IVIG = intravenous immunoglobulin; ATG = antithymocyte globulin; MMF = mycophenolate mofetil

Figure 2. ABO Antibody Titers before and after Kidney Transplantation

Timeline indicates AHG (figure a) and RT (figure b) titers pre-transplant, before and after TPE, and post-transplant from day 1 to 12 months. Each point represents a single titer value for each patient. Bars depict median values with interquartile range. n=16 per time point. AHG = anti-human globulin; RT = room temperature; TPE = therapeutic plasma exchange.

Table 1**Patient Demographics**

Age (yr)	
Mean $\pm$ SD	45 $\pm$ 14
Range	25–65
Male sex	7 (44%)
Race	
White	8 (50%)
Black	0
Hispanic	4 (25%)
Asian	4 (25%)
Cause of ESRD	
Diabetes	2 (12.5%)
GN	5 (31%)
PKD	2 (12.5%)
Unknown	7 (44%)
Dialysis	14 (87.5%)
Dialysis vintage (yr, mean $\pm$ SD)	2 $\pm$ 1.8
cPRA (median)	0% (range 0–100%)
cPRA 10%	10 (63%)
HLA mismatch (A, B, DR)	1.8 $\pm$ 1.4
Previous transplant	5 (31%)
Living related	15 (94%)
0-haplotype matched sibling	2 (12.5%)
1-haplotype matched sibling	6 (37.5%)
2-haplotype matched sibling	5 (31.25%)
Other relative	2 (12.5%)
Living unrelated	1 (6%)
Initial ABO antibody titer	
AHG (median)	64
AHG range	8–2048
RT (median)	64
RT range	8–256

AHG – anti-human globulin

ESRD – end-stage renal disease

GN – glomerulonephritis

HLA – human leukocyte antigen

PKD – polycystic kidney disease

cPRA – calculated panel reactive antibody

RT – room temperature

Table 2

Donor and Recipient Blood Type Combinations

Blood type		
Donor	Recipient	Number of patients
A1	O	11 (69%)
A2	O	1 (6%)
B	O	2 (12.5%)
AB	A	1 (6%)
B	A	1 (6%)

Table 3

ABO Antibody Titers and Therapeutic Plasma Exchange (TPE) Treatments

Starting AHG Titer	Patients (No.)	TPE Treatments (No.)
16	1	5
32	5	5–6
64	4	5–6
128	3	5–6
256	1	7
512	1	7
2048	1	11

Table 4

Clinical Outcomes

Parameters	
Acute rejection	
Borderline	0
Cell-mediated	1
Antibody-mediated	0
Creatinine (mg/dl)	
1 mos	1.3 ± 0.2
3 mos	1.3 ± 0.3
6 mos	1.3 ± 0.3
1 yr	1.4 ± 0.3
Last creatinine	1.3 ± 0.3
Post-transplant (median, yrs)	2.6 (range 0.75 – 4.7)
Graft loss (%)	0
BK virus (%)	0
Bleeding complications (%)	0
Wound complications (%)	0