

Blood Group Incompatible Kidney Transplantation: A Method to Increase the Rate of Transplantation and Free Patients from Dialysis

Gerald S. Lipshutz MD MS
Director, ABO Blood Type Kidney Transplant Program
Ronald Reagan UCLA Medical Center
Los Angeles, California
glipshutz@mednet.ucla.edu
310-267-9592

As of August 1, 2010, there were over 85,000 people in the United States with chronic kidney disease who are waiting to receive a kidney transplant.¹ About 15% of patients a year will receive a kidney transplant with a median waiting time for a deceased donor renal transplant of 4 years. Waitlist times have continued to increase in the United States for those desiring a deceased donor kidney transplant; this has been particularly notable for blood group O and B recipients where in some regions this routinely extends beyond 5 years.

One solution to the growing number of waitlist candidates is to increase the number of living donor kidney transplants performed. Many patients present to their kidney transplant center with a family member or friend who is willing to donate a kidney to them whereby they could undergo transplantation in a relatively short period of time. However, blood group incompatibility (about 30% of the time) prevents this and patients must wait for a blood group compatible kidney from the deceased donor waiting list. While solid organ transplantation has traditionally been governed by the rules of blood group compatibility, one potential solution to the growing kidney transplant waitlist is renal transplantation across the ABO blood group barrier.

Today, blood group incompatible kidney transplantation is possible and after the first 2 weeks post-transplant, patient's treatment regimens and medications in general are no different than those who have received a blood group compatible transplant. Patients do require a regimen of immunomodulation and desensitization pre-transplant to prepare the body and immune system to accept a kidney of an 'incompatible' blood type.

Blood group incompatibility without pre-transplant desensitization and immunomodulation presents with a high risk of immediate, rapid graft loss secondary to hyperacute antibody-mediated rejection.² Early attempts to cross the ABO blood type barrier in kidney transplantation in this country resulted in rapid loss of most kidneys.³ Blood group antigens are expressed throughout the body including on the RBC membrane, platelets, lymphocytes, and endothelium. After revascularization of the transplanted kidney, the ABO blood group antigens expressed on the kidney vascular endothelium are bound by anti-AB preformed natural antibodies (isoagglutinins) resulting in activation of complement, formation of thrombi, inflammatory changes, neutrophil aggregation, and graft loss.

More recent attempts in this area employed pre-transplant antibody removal with limited success. Small numbers of transplants performed in the 1980s demonstrated improved results;⁴⁻⁵ these patients routinely underwent splenectomy pre-transplant to have a successful transplant outcome. Further advancements were made by centers in Japan that did not perform deceased donor kidney transplantation.⁶ Between the late 1980's and 2001, more than 400 ABO incompatible kidney transplants were performed with all patients undergoing plasma exchange and splenectomy. The 9-year graft survival of these patients was similar to that of blood group compatible transplants that occurred during the same time period. These results led to a renewed

interest in considering ABO incompatible kidney transplantation as a viable option for some patients in other parts of the world.

The general tenets of a successful protocol are two-fold: 1) remove pre-existing anti-AB antibodies from the blood and 2) reduce the future production of these antibodies until the immunologic process of accommodation occurs resulting in graft acceptance. While this is not immunologic tolerance, it does result in the ABO blood type incompatible kidney to function; low-levels of isoagglutinins continue to circulate without evidence of injury to the graft either clinically or on biopsy. The principals of the protocol at our center are include (1) reduced immunoglobulin synthesis with anti-CD20 treatment (rituximab), (2) pre-transplant removal of isoagglutinins by repeated pre-transplant plasmapheresis, (3) immunomodulation with hyperimmune intravenous immunoglobulin (IVIg) and (4) post-transplant triple immunosuppression with tacrolimus, mycophenolate mofetil and prednisone.

Screening of patients who are interested in this type of program begins with measuring the isohemagglutinin titers. In our institution this is by using the standard tube method.⁷ In brief, the red blood cell group is determined with commercially available antisera with both positive and negative controls. Blood group A donors are designated as the A2 subgroup on the basis of the lack of reactivity of their red blood cells with the anti-A1 lectin *Dolichos biflorus*⁸. Titers are determined with assays for both direct and indirect isoagglutination. Standardized red blood cells are suspended in serial dilutions of recipient serum followed by centrifugation. Results immediately after centrifugation are defined as representing the IgM titer. This is then followed by incubation at 37 C for 30 minutes, washing, and addition of Coombs antiserum followed by centrifugation. Analysis for agglutination defines the IgG titer. The titer is determined by the endpoint where agglutination is macroscopically visible. While pre-transplant

immunomodulation is progressing, titers are determined before each plasmapheresis treatment. In addition, titer determination is performed daily in the post-transplant period while patients were in the hospital, and at each outpatient follow-up visit for the first posttransplant month. Patients are typically seen three times a week for the first 2 weeks post-transplant, two times a week for weeks 3 and 4, once a week for the second month, and monthly to 6 months.

The program at our center has now has been performing transplants for just over 2 years. At present we transplant approximately 1 patient per month with 23 patients transplanted to date as of summer 2010. All grafts functioned properly at the time of transplant and urine was either made in the operating room after reperfusion or shortly afterwards in the recovery room. Serum creatinine at discharge was 1.2 ± 0.5 mg/dl, 1 month 1.4 ± 0.5 mg/dl, 6 months 1.1 ± 0.3 mg/dl, and at 1 year 1.2 ± 0.2 mg/dl. There was one graft loss due to acute antibody-mediated rejection in a negative crossmatch patient with a moderately high pre-transplant IgG titer of 1:256.

While as a group successful ABOi renal transplantation is possible, the failure of an individual case does bring forth questions: there is some uncertainty about the meaning of small fluctuations in antibody titer and creatinine in the early postoperative period. This reminds us of the intensity of the anamnestic immune response to exposure to antigens under these conditions. The management of these cases during the early post-transplant period may require additional diagnostic maneuvers including Doppler ultrasound, early allograft biopsy if necessary, and the use of post-transplant plasmapheresis. With diligence, experience, and close examination of post-transplant clinical parameters, however, ABOi kidney transplantation can be performed successfully in many if not most patients, increasing both access to organs and removing the burden or dialysis for those with a living kidney donor.

1. www.unos.org. accessed August 1, 2010.
2. Higgins R, Hathaway M, Lowe D, Zehnder D, Krishnan N, Hamer R *et al*. New choices for patients needing kidney transplantation across antibody barriers. *J Ren Care* 2008; **34**(2): 85-93.
3. Hume DM, Merrill JP, Miller BF, Thorn GW. Experiences with renal homotransplantation in the human: report of nine cases. *J Clin Invest* 1955; **34**(2): 327-82.
4. Alexandre GP, Squifflet JP, De Bruyere M, Latinne D, Reding R, Gianello P *et al*. Present experiences in a series of 26 ABO-incompatible living donor renal allografts. *Transplant Proc* 1987; **19**(6): 4538-42.
5. Bryan CF, Nelson PW, Aeder MI, Beck ML, Helling TS, Hughes TM *et al*. Current experience with renal transplantation across the ABO blood group barrier. *Transplant Proc* 1992; **24**(6): 2527-9.
6. Tanabe K, Takahashi K, Sonda K, Tokumoto T, Ishikawa N, Kawai T *et al*. Long-term results of ABO-incompatible living kidney transplantation: a single-center experience. *Transplantation* 1998; **65**(2): 224-8.
7. Winters JL, Gloor JM, Pineda AA, Stegall MD, Moore SB. Plasma exchange conditioning for ABO-incompatible renal transplantation. *J Clin Apher* 2004; **19**(2): 79-85.
8. Gloor J, Stegall M. ABO-incompatible kidney transplantation with and without splenectomy. *Transplantation* 2006; **82**(5): 720.