

## ABO incompatible kidney transplantation – A single center experience

Rajan Ravichandran<sup>a,\*</sup>, Arumugam Kanakaraj<sup>b</sup>, Ashok Shakthivel<sup>c</sup>, Chakravarthy N. Srinivas<sup>d</sup>

### ABSTRACT

**Aim/Objective:** ABO incompatible kidney transplantations are getting popular all over the world. It is essential that such transplantations are carried out in our country also.

**Material and methods:** Thirteen patients who had undergone ABO incompatible transplantations in a single center since 2009 were studied. The transplantations have been across different blood group combinations. The pre-conditioning of the patient was done as per the Japanese protocol.

**Results:** The patients were followed up between 4 weeks to 28 months. Two patients had immediate antibody-mediated rejection with loss of graft. The rest 11 patients have normal graft function without any complication.

**Conclusion:** Successful ABO incompatible transplantation is feasible in our country without endangering the life of recipient with reasonable cost control. Further studies are required to modify the protocol to prevent immediate antibody-mediated rejections (ABMR).

Copyright © 2012, Indian Society of Organ Transplantation. All rights reserved.

**Keywords:** ABO incompatible, Kidney transplantation, Pre-conditioning, Antibody-mediated rejections

### INTRODUCTION

The demand for kidney transplantation is steadily growing and it is important to expand the donor pool to satisfy the demands. Many centers are not able to accept related donors due to blood group incompatibility.<sup>1</sup>

ABO incompatible kidney transplantations are getting popular all over the world with excellent long-term results.<sup>2–4</sup> Japan has been on the foremost with the largest experience.<sup>4</sup> The success of ABO incompatible kidney transplantation depends on preconditioning of the patient with lowering of the antibody titers and adequate immunosuppression. Once the transplantation is successful, the long-term outcome is equivalent to regular kidney transplantation due to immune accommodation.<sup>5</sup> We report our experience in 13 patients who have undergone such kidney transplantations.

### MATERIAL AND METHODS

We started the ABO incompatible kidney transplantation in our center in 2009. So far 13 patients have undergone such transplantations. All transplants were worked up in a similar fashion to regular kidney transplantation assessing the fitness of both recipient and donor. Tissue typing by DNA for class I antigens, donor-specific antibody (DSA) for class I and class II by luminex assay, complement-dependent cytotoxicity (CDC) cross match with no sensitizing agent, with dithiothreitol (DTT) and with coombs reagent were done. Suitable approvals from the hospital committee and authorization committee of Tamil Nadu were taken as per the legal requirements. The recipients were admitted 1 week prior to kidney transplantation. Anti A and Anti B IgG titers were estimated on a daily basis using the tube method.<sup>6</sup>

<sup>a</sup>Director, MIOT Institute of Nephrology, <sup>b</sup>Consultant Nephrologist, <sup>c</sup>Transplant Surgeon and Urologist, <sup>d</sup>Transplant Immunologist, MIOT Hospitals, 4/112, Mount Poonamalle High Road, Manapakkam, Chennai 600089, Tamilnadu, India.

\*Corresponding author. Tel.: +91 22493440, email: ravidoc55@yahoo.co.in

Received: 4.7.2012; Accepted: 10.10.2012; Available online: xxx

Copyright © 2012, Indian Society of Organ Transplantation. All rights reserved.

<http://dx.doi.org/10.1016/j.ijt.2012.10.002>

The following preconditioning protocol was used:

- Minus 7 days.
- Rituximab 200 µg infusion.
- Oral immunosuppressive drugs – prednisolone 10 mg, mycophenolate mofetil 360/540 mg twice a day, tacrolimus 0.1 mg per kilogram body weight.
- Plasma exchange on alternate day after dialysis so as to lower the anti A/anti B titer to 1 in 4 with a maximum of 4 exchanges. Two liters of plasma exchange was carried out in adults and in children 40 ml per kilogram body weight. The replacement was done with 5% albumin. The last exchange was carried out on the day of kidney transplantation. After the 8th transplant, the protocol was changed to mandatory 4 plasma exchanges and IvIg low dose 5 g after the 3rd exchange.
- DSA and cross match were repeated on the day of kidney transplantation. The surgery was performed only if both of them were negative.
- Basiliximab 20 mg Iv infusion on Day 1 and Day 4 of transplantation.

Post transplantation protocol:

- Methyl prednisolone 500 mg – Day 1, 250 mg – Day 2 & Day 3.
- Prednisolone 20 mg from Day 4, tapered to 10 mg by 2 weeks.
- Mycophenolate mofetil 360 mg twice a day if patient weight less than 60 kg. 540 mg twice a day if weight more or equal to 60 kg.
- Tacrolimus to maintain level between 8 and 10 ng/mL.
- Prophylaxis with valganciclovir and cotrimoxazole.

## RESULTS

Thirteen patients underwent ABO incompatible kidney transplantation since 2009 (Table 1). One was done in 2009, 1 in 2010, 3 in 2011 and rest in 2012. Out of the 13 recipients 9 were male and 4 female. Age was between 13 and 57 years. Ten patients had haplo match and 3 patients had mismatch on HLA typing. Three were children. Two of the children had reflux nephropathy as their native disease. Prior nephrectomy was not done in them. Out of the other recipients 2 had diabetic nephropathy, 1 failed graft with re-transplantation, 1 focal segmental glomerulosclerosis (FSGS), 2 IgA nephropathy and rest the cause unknown. A to O was done in 5 patients, B to O in 3 patients, B to A in 2 patients and A to B in 3 patients. The immediate pre-operative titers were 1 in 2 in 4 patients, 1 in 4 in 8 patients, 1 in 8 in 1 patient. One patient underwent 2 plasma exchanges, 5 underwent 3 exchanges and 7 underwent 4 exchanges. Two patients (Sr. no. 1 and 7) had hyperacute rejection. In both of them the titers were 1 in 2 pre-operative. Hence after the 8th transplantation, the protocol was changed to mandatory 4 plasma exchanges with IvIg to ensure adequate immunosuppression. In the 11 patients with functioning graft, the follow-up period has been between 4 weeks and 28 months. All of them have normal renal function without any proteinuria. One patient (Sr. no. 6) had urinary tract infection (UTI) and cytomegalovirus (CMV) infection for which she received successful treatment and her immunosuppressants has been reduced to 2 drugs (steroids + tacrolimus). One patient (Sr. no. 8) had acute tubular necrosis (ATN)

**Table 1** Showing the results of ABO incompatible kidney transplantations.

Sr. no.	Sex	Age	Blood group		Tissue typing	Titer on the day of Tx	Plasma exchange	Outcome	Follow-up	Remarks
			Recipient	Donor						
1	M	54	O +ve	A	Haplo	1 in 2	3	Hyperacute rejection	–	On hemodialysis
2	M	26	O +ve	B –ve	Haplo	1 in 4	2	Serum creatinine – 1.5 mg/dL	28 months	No proteinuria DM/UTI
3	M	48	A +ve	B +ve	Mis-match	1 in 4	3	Serum creatinine – 1.1 mg/dL	15 months	Scorpion bite
4	M	47	B +ve	A +ve	Mis-match	1 in 2	3	Serum creatinine – 1.2 mg/dL	10 months	
5	M	13	O –ve	B +ve	Haplo	1 in 2	3	Serum creatinine – 0.8 mg/dL	10 months	
6	F	21	O +ve	A +ve	Haplo	1 in 8	4	Serum creatinine – 0.8 mg/dL	5 months	CMV infection, UTI
7	M	13	O +ve	A +ve	Haplo	1 in 2	3	Hyperacute rejection	–	On hemodialysis
8	F	45	O +ve	B +ve	Haplo	1 in 4	4 + Ivlg	Serum creatinine – 1.3 mg/dL	2.5 months	ATN, bleed
9	F	30	B +ve	A +ve	Haplo	1 in 4	4 + Ivlg	Serum creatinine – 1.4 mg/dL	2 months	Tacro toxicity
10	F	33	O +ve	A +ve	Haplo	1 in 4	4 + Ivlg	Serum creatinine – 1.2 mg/dL	1.5 months	
11	M	57	O +ve	A +ve	Mis-match	1 in 4	4 + Ivlg	Serum creatinine – 1 mg/dL	1.5 months	
12	M	27	A +ve	B +ve	Haplo	1 in 4	4 + Ivlg	Serum creatinine – 1 mg/dL	1 month	
13	M	14	B +ve	A +ve	Haplo	1 in 4	4 + Ivlg	Serum creatinine – 0.6 mg/dL	1 month	

following hypotension due to post-operative bleed on the second day which settled conservatively with blood transfusion. The coagulation parameters were normal. The ATN was confirmed by renal biopsy and the dose of tacrolimus was reduced. The renal function returned to normal after 3 days. One patient (Sr. no. 9) had Tacrolimus toxicity which was proved on biopsy and elevated level of tacrolimus. The drug was withdrawn and serum creatinine came down to 1.4 mg/dL from 2.7 mg/dL. She continues to be on 2 drugs (steroids + mycophenolate) with stable renal function. Patient Sr. no. 3 has the longest follow-up of 28 months with serum creatinine of 1.5 mg/dL without proteinuria. His donor was 64 year at the time of transplantation. None of these patients had any episode of rejection. In both patients who had biopsy, C4d was found positive. The renal function returned to normal without any anti rejection treatment. Post-operative anti A, anti B titers were measured for 1 week. The values continued to be the same as the pre-operative state in all recipients. The hospital stay was between 7 days and 14 days. The cost involved was a package of Rs 6.5 lakhs including all the treatment for donor and recipient.

## DISCUSSION

ABO incompatible kidney transplantation is gaining popularity all over the world.<sup>7</sup> More than a thousand transplantations have been done in Japan.<sup>4</sup> Other centers from USA,<sup>8</sup> Europe,<sup>9–11</sup> Australia<sup>12</sup> and UK<sup>13</sup> have also reported several such transplantations. The increasing demand for kidney transplantation and the shortage of cadaveric kidneys makes it important that we start such a program in India. The problem of ABO incompatible transplantation could be 2-fold – (a) aggressive pre-operative immunosuppressive protocols which can increase patient mortality and (b) cost of such therapy, which would deter this treatment in our country. For a successful ABO incompatible transplantation it is essential to lower the anti A and anti B titers and adequately immunosuppress the patient prior to transplantation. This is called pre-conditioning of the patient. Several protocols have been used all over the world.<sup>7</sup> Splenectomy, which was performed in the early days is not necessary with the present protocols.<sup>14</sup> Since splenectomy carried a high mortality in dialysis patients, it was a deterrent for us to start our incompatible transplant program until 2009. The various protocols involved a standard or low dose IvIg, rituximab, triple immunosuppressive drugs, interleukin receptor blockers and antibody depletion by plasmapheresis or immunoadsorption. The Japanese protocol of Tanabe<sup>4</sup> suited us most with the use of 1 dose rituximab 1 week prior to

the transplantation and the combination of tacrolimus, MMF, prednisolone, plasmapheresis and basiliximab. This has the advantage of less cost and less immunosuppression compared to the American and European protocols. The antibody titers were measured using the conventional tube test (CTT) with the addition of DTT which helps to separate the IgG antibodies.<sup>15</sup> CTT is commonly used in Japan.<sup>4,16</sup> The cutoff for the anti A and anti B antibody titers also varies from center to center. It could be as low as  $\leq 1$  in 4 or as high as 1 in 32.<sup>7</sup> There is of course, some difference in the values by the 2 methods – the microcolumn gel card (MG) test and CTT. According to Cheng and Hao who compared the 2 methods in 288 serum samples, the MG card test was more sensitive than CTT in detection of both anti A and anti B. IgG with the MG results being approximately 2-fold higher than those for CTT. When we started the program we took 1 in 4 as the cutoff point for our first 8 transplants. Therefore, the number of plasma exchanges varied from 2 to 3 to achieve this target. However, in 2 patients we had ABMR confirming the inadequacy of pre-conditioning. Hence, after the eighth transplant we decided to make 4 plasmapheresis mandatory for all patients and included a low dose of IvIg after the third plasmapheresis. We changed our protocol since a low antibody titer alone did not ensure the prevention of ABMR. Recent studies have reported ABMR occurring in 17.9–30% of ABO incompatible kidney transplants.<sup>17,18</sup> The greatest incidence of acute ABMR occurs 2–7 days after the transplant. The first 2 weeks is a critical period during which accommodation is usually induced and established.<sup>5</sup> The other eleven patients who had a functioning graft have been followed up from 4 weeks to 28 months. They have been on conventional triple immunosuppressive drugs like the other regular transplant recipients and have not had any serious complications. In 2 patients biopsy had to be done for deterioration of renal function – one had ATN due to hypotension which improved well with correction of the volume status and the other due to tacrolimus toxicity which also improved on withdrawing the drug. Both the biopsies showed the presence of C4D in the peritubular capillaries. It has been shown in ABO incompatible transplants that the mere presence of C4D does not necessarily indicate an ABMR.<sup>1,19</sup> Two of our patients had diabetes, 2 had reflux nephropathy with bladder dysfunction and one was a re-transplant after a failed graft. In spite of the additional morbid conditions they have done well till today. The 2 patients who lost their grafts are back on dialysis. In other 11 patients, the renal function has been excellent with no significant proteinuria. The cost for the ABO renal transplantation is of concern since the protocols could use immunoadsorption columns which are expensive and standard dose IvIg which is

equally expensive. With our protocol we have been able to do these transplants for a package of Rs 6.5 lakhs which includes the pre-conditioning and post-op treatment for 10 days. ABO incompatible kidney transplantation is feasible in our country without undue risk to the life of recipient and at reasonable cost. It is essential that we achieve an immunosuppressive protocol which would prevent graft loss also.

## CONFLICTS OF INTEREST

All authors have none to declare.

## REFERENCES

1. Magee CC. Transplantation across previously incompatible immunological barriers. *Transpl Int*. 2006;19(2):87–97.
2. Fuchinoue S, Ishii Y, Sawada T, et al. The 5-year outcome of ABO-incompatible kidney transplantation with rituximab induction. *Transplantation*. 2011;91(8):853–857.
3. Tyden G, Donauer J, Wadstrom J, et al. Implementation of a protocol for ABO-incompatible kidney transplantation – a three-center experience with 60 consecutive transplantations. *Transplantation*. 2007;83(9):1153–1155.
4. Tanabe K. Japanese experience of ABO-incompatible living kidney transplantation. *Transplantation*. 2007;84(12):S4–S7.
5. Ishida H, Tanabe K, Ishizuka T, et al. The mechanism responsible for accommodation after living-related kidney transplantations across the blood barrier. *Transpl Int*. 2005;18(6):716–720.
6. Lewis SM, Bain BJ and Bates I. *Practical Hematology*, 9th ed. 2001:478–480.
7. Shin M, Kim SJ. ABO incompatible kidney transplantation – current status and uncertainties. *J Transplant*. 2011;2011: 970421 [Epub 2011 Dec 10].
8. Montgomery RA. Renal transplantation across HLA and ABO antibody barriers: integrating paired donation into desensitization protocols. *Am J Transplant*. 2010;10(3):449–457.
9. Tyden G, Kumlien G, Genberg H, Sandberg J, Lundgren T, Fehrman L. ABO incompatible kidney transplantations without splenectomy, using antigen-specific immunoadsorption and rituximab. *Am J Transplant*. 2005;5(1):145–148.
10. Genberg H, Kumlien G, Wennberg L, Berg U, Tyden G. ABO-incompatible kidney transplantation using antigen-specific immunoadsorption and rituximab: a 3-year follow-up. *Transplantation*. 2008;85(12):1745–1754.
11. Wilpert J, Fischer KG, Pisarski P, et al. Long-term outcome of ABO-incompatible living donor kidney transplantation based on antigen-specific desensitization. An observational comparative analysis. *Nephrol Dial Transplant*. 2010;25(11):3778–3786.
12. Flint SM, Walker RG, Hogen C, et al. Successful ABO-incompatible kidney transplantation with antibody removal and standard immunosuppression. *Am J Transplant*. 2011; 11(5):1016–1024.
13. Galliford J, Charif R, Chan KK, et al. ABO incompatible living renal transplantation with a steroid sparing protocol. *Transplantation*. 2008;86(7):901–906.
14. Segev DL, Simpkins CE, Warren DS, et al. ABO incompatible high-titer renal transplantation without splenectomy or anti-CD20 treatment. *Am J Transplant*. 2005;5(10):2570–2575.
15. Lewis SM, Bain BJ, Bates I. *Practical Hematology*, 9th ed. 2001:215–216.
16. Tanabe K, Tokumoto T, Ishida H, et al. Excellent outcome of ABO-incompatible living kidney transplantation under pre-transplantation immunosuppression with tacrolimus, mycophenolate mofetil, and steroid. *Transplant Proc*. 2004;36: 2175–2177.
17. Fidler ME, Gloor JM, Lager DJ, et al. Histologic findings of antibody-mediated rejection in ABO blood-group-incompatible living-donor kidney transplantation. *Am J Transplant*. 2004;4:101–107.
18. Racusen LC, Haas M. Antibody-mediated rejection in renal allografts: lesson from pathology. *Clin J Am Soc Nephrol*. 2006;1(3):415–420.
19. Gloor JM, Stegall MD. ABO incompatible kidney transplantation. *Curr Opin Nephrol Hypertens*. 2007;16(6):529–534.