

Received: 2017.06.05
Accepted: 2017.07.21
Published: 2017.10.06

ISSN 1941-5923
© Am J Case Rep, 2017; 18: 1073-1076
DOI: 10.12659/AJCR.905633

ABO-Incompatible Renal Transplantation with High Antibody Titer: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 33
Final Diagnosis: ABO-incompatible kidney transplantation with high antibody titer
Symptoms: Symptoms of end stage renal disease
Medication: —
Clinical Procedure: —
Specialty: Transplantology

Objective: Management of emergency care





Background: Even though renal transplantation across blood groups is not uncommonly practiced nowadays, there is still hesitation regarding ABO-incompatible transplantation with very high baseline antibody titer. In this case report, the outcome of an ABO-incompatible kidney transplant recipient with a high baseline isoagglutinin titer is reported.

Case Report: The patient was a non-diabetic, 33-year-old man with end-stage renal disease secondary to chronic glomerulonephritis. The only kidney donor available was his mother, who was blood-group incompatible. The patient's blood group was O positive, whereas his mother was B positive. We evaluated him for an ABO-incompatible renal transplant. The baseline anti-B isoagglutinin titer was >1: 8196. With a desensitization protocol of low-dose Rituximab, plasmapheresis, and IVIG, this titer was brought down to 1: 32 before transplantation. He successfully underwent renal transplantation across the ABO barrier, and maintains good graft function after 1 year of follow-up.

Conclusions: In the present era, a high baseline isoagglutinin titer is no longer a contraindication for successful kidney transplantation in ABO-incompatible recipient-donor pairs.

MeSH Keywords: Antibody Formation • Kidney Transplantation • Preconditioning Protocol

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/905633>

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Background

ABO-incompatible kidney transplantation (ABOiKT) is gradually becoming widely accepted worldwide. Over the past 2 decades, the results of ABO-incompatible kidney transplants have become equal with those of ABO-compatible transplants because of progress in immunosuppression and desensitization strategies, and has been established as a feasible option to expand the donor pool. Despite advances in preconditioning protocols, recipients with high isoagglutinin titer are generally excluded from ABO-incompatible transplant programs.

Here, we report the case of an ABOiKTR man whose antibody titer on initial evaluation was very high (> 1: 8196). He underwent a successful ABOiKT transplant after undergoing the preconditioning protocol followed at our institution.

Case Report

A 33-year-old man from West Bengal with ESRD secondary to chronic glomerulonephritis was on maintenance hemodialysis. His only donor was his mother, whose blood group was incompatible. The patient's blood group was O positive and the mother B positive. The HLA showed a 3/6 mismatch. The donor-recipient pair was evaluated for an ABOiKT. The CDC cross-match was negative.

The IgG anti-B antibody titer was measured by column agglutination method. The LISS/Coomb's ID card with 6 microtubes containing polyspecific AHG was used for antibody titration. We added 50 µL of 0.8% donor red cell suspension to the microtubes, and 25 µL of serially diluted serum from the patient was added to each microtube. The ID card was incubated for 15 min at 37°C and then centrifuged for 10 min. The reaction was graded macroscopically with the highest dilution showing +1 agglutination. The IgG antibody titer was more than 1: 8196 after macroscopic examination by 2 medical technicians and 2 laboratory physicians.

We started him on a preconditioning protocol of B cell depletion with Rituximab, antibody removal by conventional plasmapheresis, immunomodulation by IVIG, and triple immunosuppression comprising CNI (Tacrolimus), mycophenolate sodium, and Prednisolone. The patient was given induction with antithymocyte globulin (ATG).

He was given Rituximab in the dose of 200 mg 2 weeks prior to transplant. Triple immunosuppression was given starting 2 weeks before transplantation. Tacrolimus was given in the dose of 0.1 mg/kg twice a day, mycophenolate sodium in the dose of 360 mg 3 times daily, and Prednisolone 20 mg once daily. He was admitted 7 days later for transplantation.

After admission, antibody depletion was done with plasmapheresis. Plasmapheresis was done every alternate day. The volume of plasma exchanged was 30 ml/kg body weight. Replacement fluid used was Ringer's lactate and 0.9% normal saline. Fresh frozen plasma with blood group of the donor (B positive) was given after plasmapheresis. Each session of plasmapheresis was followed by IVIG in the dose of 5 gm, with a total of 8 sessions.

The total dose of IVIG given was 40 gm (Figure 1 shows the preconditioning protocol). The initial anti-B antibody titer was >1: 8196 by column agglutination method. The anti-B antibody titers were measured every day and before each session of plasmapheresis. Maintenance hemodialysis was done 3 times weekly. On reaching an anti-B antibody titer of <1: 32 for 2 consecutive days, the transplant was planned (Figure 2 shows the course of anti-B antibody titer). Induction therapy was given with IV Methylprednisolone, 2 doses of 500 mg, 1 day prior to transplant and on the day of transplant. ATG was given in the dose of 3 mg/kg divided in 2 doses on the day of transplant and on the first postoperative day.

The immediate graft function was good. On the day of transplantation, anti-B antibody titer was <1: 32 and it was <1: 16 postoperatively. The Tacrolimus (Tac) trough level was maintained at 8–10 ng/ml for the first few weeks after transplantation. Prednisolone was given in the dose of 20 mg/day and gradually tapered to 10 mg by the end of the third post-transplant month. After 1-year follow-up, the patient is maintained on Prednisolone 10 mg/day and mycophenolate sodium 360 mg twice a day, and the Tacrolimus dose was adjusted to maintain a trough level of 3–5 ng/mL.

At 1, 3, 6, and 12 months of follow-up, the serum creatinine levels were 1.3 mg%, 1.28 mg%, 1.34 mg%, and 1.34 mg%, respectively, and the corresponding anti-B antibody body titers were 1: 16, 1: 32, 1: 64, and 1: 32, respectively. The anti-B antibody titers were measured every day for the first 2 weeks after transplantation. The frequency was reduced to 3 times a week in the next 2 weeks, weekly for next 2 months, and fortnightly for 3 months, then monthly for 6 months.

After 1 year, the graft is functioning well, with a serum creatinine of 1.34 mg%. At present, the Tacrolimus trough level is adjusted at 5 ng/ml, mycophenolate sodium is being given in the dose of 720 mg/day, and Prednisolone in the dose of 10 mg/day.

Discussion

Although most popular in Japan, ABOiKT has gradually become accepted all over the world as a good modality for use during the current organ shortage crisis. There have been significant

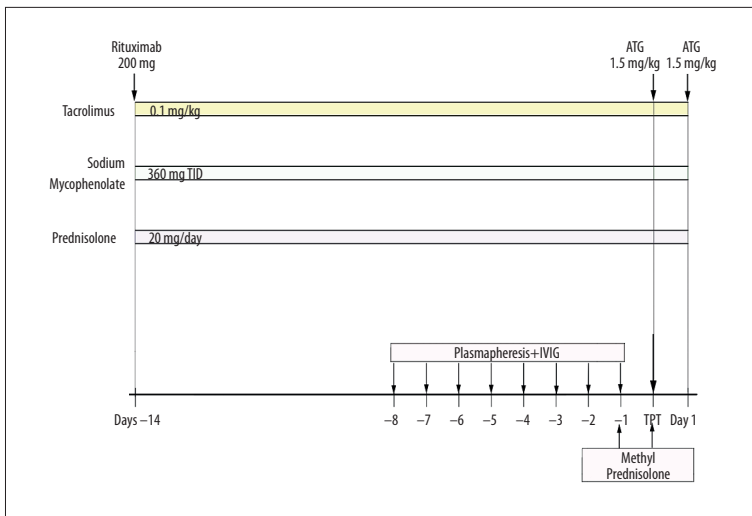


Figure 1. Preconditioning protocol for ABOiKTRs.

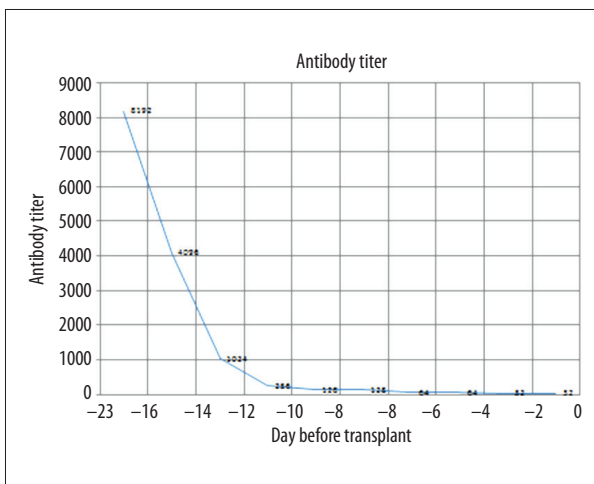


Figure 2. Anti-B antibody titer before and after transplant.

advances in the preconditioning protocols and immunosuppressive therapies over the last 2 decades. However, most ABOiKT programs exclude recipients with high isoagglutinin titers and consider other options like paired organ donation for such recipients [1]. Whether baseline isoagglutinin titer affects the graft outcome is a matter of debate.

Some centers, especially in the past, reported high rates of antibody-mediated rejection (AMR) and early graft loss in recipients with high baseline antibody titers. It was considered to be due to a rebound of anti-ABO antibodies in the post-transplant period. Pre-transplant apheresis removes the anti-ABO antibodies but it rebounds post-transplant. The strongest predictor of graft outcome was considered to be baseline antibody titer [2].

High baseline antibody titers were associated with greater incidence of antibody-mediated rejection and graft loss in the cyclosporine and azathioprine era [3,4].

However, a study from Japan in 2005 reported that high baseline antibody titer does not affect graft outcome and there was no correlation between baseline anti-ABO antibody titer and AMR. This was attributed to the use of MMF- and Tacrolimus-based immunosuppressive regimens [5].

A recent study by Lee et al. from Samsung Medical Center, Korea, concluded that high isoagglutinin titer was associated with increased incidence of AMR ($\geq 1: 64$ on DTT -37°C phase or $\geq 1: 256$ on AHG phase). The use of low-dose Rituximab increased the risk of AMR in patients with high baseline isoagglutinin titer. It was concluded that patients with high baseline isoagglutinin titers should be given intensified preconditioning with Rituximab at a dose of 375 mg/m^2 along with IVIG [6].

In a comparative study by Chung et al., the outcomes of high and low baseline antibody titer groups (anti-ABO antibody titer $\geq 1: 256$ and anti-ABO antibody titer $\leq 1: 126$) were compared. The target pre-transplant isoagglutinin titer was kept at below $1: 32$. It was concluded that if the isoagglutinin titer was maintained below $1: 32$ in the early post-transplant period, the graft survival was good. The outcomes in both the groups were similar in terms of graft and patient survival. There was no episode of AMR in any group [7].

In addition, the preconditioning protocols were more intense in patients with high baseline isoagglutinin titer. At some centers, splenectomy or a combination of Rituximab with splenectomy was used for patients with high baseline isoagglutinin titers.

In the study done by Chung et al., splenectomy was not done, but recipients with baseline antibody titers $\geq 1: 1024$ were administered Rituximab in the dose of 375 mg/m^2 twice or Rituximab was administered once and Bortezomib twice before transplant [7].

We used a relatively lower dose of Rituximab (200 mg/body) and splenectomy was not done in our recipient with extremely high isoagglutinin titer because, in our previous experience with ABOiKT with antibody titer as high as 1: 2048, the outcomes were excellent in terms of patient survival and graft function with Rituximab in the dose of 200 mg/body. The immunosuppression used at our center was also less intense than that used in other transplant centers due to the increased risk of infection in tropical countries. The isoagglutinin titers were monitored closely during the post-transplant period and no rebound of antibodies was observed. No post-transplant isoagglutinin removal was required in our case.

It is important to monitor the isoagglutinin titers meticulously after transplant. In a study done by Chung et al., 5 out of 8 patients with high baseline isoagglutinin titer required post-transplant plasmapheresis and IVIG due to a rebound of antibodies [7].

Due to the prolonged effect Rituximab, B cells remain suppressed for many months, preventing AMR and facilitating transplantation across the blood group barrier in recipients with high isoagglutinin titer [8].

Won et al. studied the significance of isoagglutinin titer in ABO-incompatible kidney transplantation by comparing the outcomes of high- (anti-ABO antibody titer ≥ 1 : 256) and low-titer (anti-ABO antibody titer ≤ 1 : 256) groups. The number of preoperative plasmaphereses, anti-ABO titer on day of transplantation, peak postoperative isoagglutinin titer within 2 weeks, and isoagglutinin titer at 1 year were higher in the high-titer

group than in the low-titer group. But the graft function for a follow-up period over 1 year was not statistically different between the groups. There was 1 episode of AMR in the high-titer group (anti-ABO titer more than 1: 512), which was successfully treated with pulse steroid [9].

There are few reports of successful ABOiKTs with high anti-ABO antibody titer. The highest titer reported to be done without splenectomy is ≥ 1 : 2048, done using 2 doses of Rituximab, 200 mg/body on days -14 and -7 and 2 doses of anti-CD 25 at 20 mg were given on day 0 and day 4. Isoagglutinin removal was done by plasmapheresis and triple immunosuppression with Tacrolimus (0.2 mg/kg) and MMF (1000 mg) and steroids were used. The outcome was excellent in terms of graft and patient survival [10].

In another report from Japan, 3 patients with isoagglutinin titers >1 : 512 underwent successful ABOiKT after preconditioning with 2 doses of Rituximab at 150 mg/m², 6–8 sessions of plasmapheresis, Basiliximab induction, and Tacrolimus-based triple immunosuppression. Splenectomy was performed on the day of transplant [11].

Conclusions

ABOiKT can be performed safely, without any increase in the risk of AMR, in renal transplant recipients with high baseline isoagglutinin titers, using a simple preconditioning protocol including plasmapheresis, IVIG, Rituximab, and ATG induction and a triple Tacrolimus-based immunosuppressive regimen.

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