Abstract

The ABO-incompatible living-donor kidney transplantation was developed in Japan in 1989. Currently, most transplant physicians and surgeons have noted that outcomes are unexpectedly excellent, and no hyperacute rejections have been reported since 2001. In the registry of the Japanese ABO-Incompatible Kidney Transplantation Committee, the data of 2434 ABO-incompatible living-donor kidney transplants were collected from 120 Japanese kidney transplant centers. Overall patient and graft survival rates were 97% and 94% at 1 year, 93% and 86% at 5 years, 90% and 71% at 10 years, and 73% and 52% at 20 years. The patient survival and graft rates in 2001 to 2012 were 93% and 81%, which were significantly better than 83% and 55% reported in 1989 to 2000. The addition of novel immunosuppressive treatments has improved results. Azathioprine has been replaced by mycophenolate mofetil since 2000 to 2001, and basiliximab and rituximab were introduced in 2002 and 2004. The titer of antidonor blood group antibody before transplantation was not correlated with graft survival in 2001 to 2012. De novo antibodies against vascular endothelium of peritubular and glomerular capillaries seemed to be more important than natural antibodies against red blood cells. Therefore, recipients with antidonor blood group antibody titers < 1:128 did not require antibody-removal procedures such as plasmapheresis or immunoabsorption. In particular, children (regardless of their peritoneal dialysis status) do not need to be catheterized for plasmapheresis or immunoabsorption. It is better to avoid the risks of catheterization and antibody removal procedures in children with end-stage renal failure.

Key words: ABO-Incompatible kidney transplantation, Antidonor blood group antibody, Outcome

Introduction

ABO-incompatible living-donor kidney transplantation (ABOi) has been popular in Japan since 1989. This procedure was not accepted for a long time because the associated hyperacute rejection was believed to occur because of an incompatible blood group between the donor and recipient. However, no institution has reported intraoperative hyperacute rejection since 2001. Antibody-mediated rejection (AMR) usually occurs within 2 weeks of ABOi.1 The outcomes of ABOi have improved markedly since 2001 compared with 1989 to 2000. We started using mycophenolate mofetil (MMF) instead of azathioprine in 2000 to 2001 and introduced basiliximab in 2002 and rituximab in 2004, thereby avoiding splenectomy after 2004. These recent developments in immunosuppression may result in less acute rejection, including AMR, with ABOi.

Natural antibodies against red blood cells were measured and considered to be an index for AMR. However, ABO blood group antigens against renal tissue were different from those against red blood cells. Therefore, a de novo antibody against renal tissue appeared to be the risk factor for AMR rather than the titer of natural antibodies against red blood cells. The Japanese ABO-Incompatible Transplantation
Committee suggested that antibody removal, such as plasmapheresis and/or plasma exchange before ABOI may be avoided if the antidonor blood group antibody (ADBGAb) titer is \( \leq 1:64 \). It is beneficial not to place a catheter for antibody removal in children who have no vascular access.

**Number and outcomes of ABO-incompatible living-donor kidney transplantations in Japan**

There were 14 cases of ABOI performed in 1989, and since then, the annual number of ABOI has increased until 2011. In 2011, there were 293 ABOI performed but the number decreased to 196 in 2012 (Figure 1). A total of 2434 cases of ABOI were registered with the Japan ABO-Incompatible Transplantation Committee. The rate of ABOI (n = 196) in living-donor kidney transplantations in Japan (n = 1431) is 13.7%. An immunosuppression desensitization protocol using MMF was initiated in 2001. Basiliximab was introduced for ABOI in 2002. Rituximab replaced splenectomy in 2004.

Overall patient and graft survival rates were 97% and 94% at 1 year, 93% and 86% at 5 years, 90% and 71% at 10 years, and 73% and 52% at 20 years (Figure 2). The patient and graft survival rates in 2001 to 2012 (n = 1985) were 98% and 96% at 1 year, 95% and 90% at 5 years, and 93% and 81% at 10 years. These rates were significantly better than 92% and 82% at 1 year, 86% and 70% at 5 years, and 83% and 55% at 10 years in 1989 to 2000 (n = 449) (Figures 3 and 4). The graft survival rate in 1989 to 2000 remarkably decreased within 1 year of transplantation (Figure 4). In contrast, the graft survival rate in 2001 to 2012 did not decrease as much as that in 1989 to 2000 (Figure 4). The higher incidence of AMR in 1989 to 2000 appeared to be a cause of poor graft survival within 1 year of ABOI. The use of MMF and rituximab may have contributed to better graft survival in 2001 to 2012.

The graft survival rates of the recipients with a preoperative ADBGAb immunoglobulin G (IgG) titer \( \geq 1:64 \) were significantly worse than those with titer \( < 1:64 \) in 1989 to 2000 (Figure 5). In contrast, patients with a preoperative ADBGAb IgG titer \( \geq 1:64 \) were not significantly different from those with titer \( < 1:64 \) in 2001 to 2012 (Figure 6). New immunosuppression protocols, including treatment with MMF and rituximab, may have resulted in better outcomes in 2001 to 2012.

Tanabe and associates reported that the graft survival of ABOI exceeded that of ABO-compatible
living-donor kidney transplantation (ABOc). This may explain why the incidence of de novo donor-specific antibody was significantly higher in ABOc than ABOi. Desensitization using rituximab may suppress donor-specific antibody in ABOi.

**Advances in immunosuppression for ABO-incompatible living-donor kidney transplantation**

In 1989, immunosuppression for ABOi consisted of azathioprine and/or cyclophosphamide, steroids, cyclosporine, and splenectomy. Azathioprine was replaced by MMF in 2001, and basiliximab was introduced in 2002. Rituximab was introduced in 2004 to avoid the need for splenectomy. Preoperative desensitization using MMF and rituximab to suppress ADBGAb for ABOi appeared to be more effective than antibody-removal procedures. Ramos and associates reported that plasmapheresis and intravenous immunoglobulin (IVIG) could not suppress splenic B-cell subsets, but using rituximab with these procedures could almost deplete them. In our desensitization protocol, MMF (20-30 mg/kg/d), a calcineurin inhibitor (cyclosporine, 6 mg/kg/d or tacrolimus, 0.2 mg/kg/d), methylprednisolone (8 mg were given for 10 d), and rituximab (100 mg) was given twice 10 days and 1 day before ABOi. After such desensitization, de novo ADBGAb IgG was suppressed to a lower titer until 1 year after transplantation.

The drug mycophenolate mofetil (MMF) is a stronger agent to suppress antibody formation than azathioprine; therefore, the incidence of acute rejection, including AMR, was much lower after using MMF instead of azathioprine. Basiliximab is an interleukin 2 receptor monoclonal antibody that suppresses T-cell-mediated rejection. The incidence of acute cellular rejection used to be higher with ABOi than ABOc. However, the incidence of acute cellular rejection decreased after the introduction of MMF and basiliximab. Tacrolimus is used more frequently than cyclosporine for ABOi; however, graft survival was not different between patients using cyclosporine or tacrolimus. Recent postoperative immunosuppression for ABOi consists of MMF, tacrolimus or cyclosporine, and a steroid, with induction using basiliximab.

**Necessity of antibody removal procedures and intravenous immunoglobulin before and after transplantation**

The natural antibodies against red blood cells appear to be different from the de novo antibodies against the vascular endothelium of peritubular and glomerular capillaries. This is likely because the blood group antigens (band 3 and bands 4 and 5) against red blood cells are different from those against the vascular endothelium of peritubular and glomerular capillaries (such as platelet endothelial cell adhesion molecule-1, plasmalemma vesicle-associated protein, and von Willebrand factor). Takahashi and coworkers reported that all 4 patients who experienced acute AMR showed C4d deposition in their peritubular capillaries in the biopsy on the episode but no deposition at the biopsy 1 hour after recirculation in the graft during the operation. None of the 5 patients with C4d deposition at the 1-hour biopsy had an episode of acute AMR. Therefore, acute AMR in these patients was not induced by natural antibodies remaining after pretransplant antibody removal, but was associated with antibodies produced de novo after transplantation. The Japan ABO-Incompatible Transplantation Committee suggested that preoperative antibody removal procedures, such as plasmapheresis, plasma exchange, and immunoabsorption, may not be
required in ABOi recipients with a low ADBGAb titer (< 1:128).

We studied 10 ABOi recipients, including 2 children (aged 4 and 7 y), without pre- and posttransplant antibody removal. The titers of ADBGAb IgG in all recipients were < 1:128. The patients were given MMF (20-30 mg/kg body weight for 10 d) and rituximab (100 mg at 10 days and 1 day before ABOi twice). Postoperative immunosuppression was based on triple therapy with cyclosporine or tacrolimus, MMF, and methylprednisolone. The maximum titers of ADBGAb IgG before transplantation were 1:8 in 2 recipients, 1:1 in 1 recipient, and 0 in 7 recipients. No recipients had clinical acute rejection, including AMR, but 1 recipient had subclinical borderline rejection determined by the biopsy performed according to protocol at 3 months and 1 year after transplantation. Mean follow-up was 21.2 ± 12.3 months (range, 11-48 mo). This may suggest that it is not necessary to perform pretransplant antibody removal in ABOi recipients who have a titer < 1:128. As previously mentioned, the graft survival in the recipients with a preoperative ADBGAb IgG titer ≥ 1:64 was not different from graft survival in recipients with a titer < 1:64 in 2001-2012.

Posttransplant antibody removal procedures for ABOi were routinely performed in most transplant centers globally except Japan.8,9 We have not performed posttransplant plasmapheresis following ABOi since 1990 at Toho University.3 This procedure should be avoided except in severe AMR following ABOi. In pediatric ABOi, it is beneficial not to insert a catheter for antibody removal in children without arteriovenous fistula. Most younger children scheduled for preemptive kidney transplantation or on peritoneal dialysis do not have an arteriovenous fistula. There were 2 children (aged 4 and 7 y) on peritoneal dialysis who had ABOi without pre- and posttransplant antibody removal procedures at our center. Their titers of ADBGAb were ≤ 1:2 both before and after transplantation. They had no clinical or subclinical rejection, including AMR, and have maintained good renal function 0.26 and 0.50 μmol/L (0.30 and 0.57 mg/dL) for 1 year since ABOi.

The IVIG was used routinely worldwide for desensitization with ABOi except in Japan.8,9 It does not appear necessary to use IVIG for ABOi, but it is necessary to use IVIG for human leukocyte antigen-incompatible kidney transplantation.

**Pediatric ABO-incompatible living-donor kidney transplantation**

In the Japanese ABO-Incompatible Transplantation Committee registry, 89 children aged < 16 years were registered before 2012. Overall, patient and graft survival rates in the 89 pediatric cases of ABOi were 99% and 94% at 1 year, 99% and 93% at 3 years, 97% and 90% at 5 years, 97% and 80% at 10 years, and 81% and 68% at 20 years after transplantation (Figure 7).10 In contrast, graft survival rates in 2129 adult cases of ABOi (age > 16 y) were 93% at 1 year, 89% at 3 years, 85% at 5 years, 70% at 10 years, and 50% at 20 years after transplantation (Figure 8). Graft survival rates were significantly better in the pediatric than adult cases of ABOi (P ≤ .05) (Figure 8).10

Based on these good results, ABOi is indicated in children with end-stage renal failure. Although deceased-donor kidney transplantation is beneficial for children in any country, ABOi should be considered when the patients want preemptive kidney transplantation or the waiting time for deceased-donor kidney transplantation is very long.

Figure 7. Overall Patient and Graft Survival Rates in Children (Age < 16 Y)

Figure 8. Graft Survival of ABOi Compared Between Pediatric and Adult Recipients
Conclusions

The ABOi has been popular in Japan since 1989. Most transplant physicians and surgeons had concerns about hyperacute rejection and did not expect good long-term outcomes with ABOi. However, long-term graft survival with ABOi is excellent and not inferior to that with ABOc. Pretransplant desensitization with rituximab and MMF appeared to be important in the avoidance of AMR. Pretransplant antibody removal procedures usually are not required because de novo ADBGAb against the endothelium of peritubular and glomerular capillaries appears to be different from natural ADBGAb against red blood cells. Post-transplant antibody removal should not be performed except for the treatment of severe AMR. Pediatric ABOi should be considered because the outcomes are better in children than adults are. Antibody removal should be avoided in children who are on peritoneal dialysis, are waiting for preemptive kidney transplantation, and have very low ADBGAb titer.

References