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Abstract

Previously, ABO-incompatible kidney transplantation (KTx) was believed to be a “taboo” for immunological reasons. In Japan, the Tokyo Women’s Medical University reported the first successful case of such transplantation, performed on January 19, 1989. Since then, we have been striving to improve the outcome of ABO-incompatible transplantation for a quarter of a century.

At Niigata University, ABO-incompatible KTx was performed in April 1996, with 80 patients being operated by 2013. The graft survival rates for those patients were 92.5%, 92.5%, 68.6%, and 61.0% for the 1st, 5th, 10th, and 15th years after transplantation, respectively. In September 2004, we were the first medical institution in Japan to introduce desensitization therapy into our clinical practice, which involved the use of rituximab and did not include splenectomy. The graft survival rate dramatically improved after 2004: 96.7% at 1 year, 96.7% at 5 years, and 87.9% at 10 years after transplantation, respectively. Our department initiated translational research on structural analysis and immune response of ABO histo-blood group carbohydrate antigens. Based on our experimental and clinical results, desensitization therapy before transplantation was more effective to inhibit B-cell immunity than multiple antibody removal.

Keywords: ABO blood group antigen, ABO-incompatible kidney transplantation, accommodation, antibody-mediated rejection, ABO kidney transplantation

1. Introduction

Since Karl Landsteiner discovered the human ABO blood groups in 1901 [1], ABO-incompatible transplantation has been considered as an immunological contraindication because of the risk of forming antibodies against ABO blood group antigens in the grafts, leading to hyper-
acute rejection followed by the loss of the kidney graft function. In Japan, kidney transplantation (KTx) using deceased donors is uncommon because the number of organ donations is very low. However, the number of end-stage renal disease (ESRD) patients who require a transplant is high. This situation required us to broaden the indications for living-donor KTx.

To expand the use of living-donor transplantation, ABO-incompatible KTx has been performed in Japan since 1989. In recent years, the outcome of ABO-incompatible KTx has improved to the point that it is now in no way inferior to ABO-compatible KTx. The number of cases using incompatible transplants per year now exceeds that using deceased-donor transplants, and incompatible KTx accounts for approximately 30% of all living-donor KTx. As of 2014, more than 3500 patients have been saved by this treatment in Japan.

In this chapter, we review ABO-incompatible transplantation and describe a strategy to overcome antibody-mediated rejection (AMR) after ABO-incompatible KTx.

2. History of ABO-incompatible KTx

The first ABO-incompatible KTx was performed by Yu Yu Voronoy in Ukraine in 1933 on a 26-year-old acute renal failure patient. The recipient with type O blood group received a blood type B kidney graft from a 64-year-old male donor. One of the donor’s kidneys was harvested within 6 h of his death and grafted into the recipient’s femoral region, but the patient died 2 days after transplantation. In this case, the failure of the graft to function was probably due to prolonged ischemic time rather than incompatibility [2]. Thereafter, some cases of ABO-incompatible KTx achieved long graft survival [3,4]. However, in 1967, Gleason and Murray [5] compiled the statistics on KTx, applied statistical analysis to ABO-incompatible cases, and reported very discouraging results.

Some years later, in 1981, Slapak et al. [6] of the University of Portsmouth, UK, published the remarkable finding that plasma exchange effectively reduced acute AMR in a transplant from a deceased donor when, because of a procedural error, the donor and recipient were of incompatible blood types. This was the first report that clearly showed the effectiveness of plasma exchange to remove antibody for ABO-incompatible KTx.

Alexandre et al. [7–10] from Belgium were the first to design a transplantation procedure using plasma exchange for pretransplantation removal of anti-A and -B antibodies. They also strongly emphasized the importance of splenectomy in achieving long-term graft survival. However, at that time, deceased-donor KTx was the mainstream procedure in Europe, and the techniques outlined in Alexandre et al.’s study were not widespread.

In Japan, the number of deceased-donor kidney donations has always been extremely low. KTx is an absolute indication for children with chronic renal insufficiency because of their need for healthy growth and development. Thus, to broaden the indications for living-donor KTx, ABO-incompatible KTx has mainly been developed in Japan since 1989 [11–21].
3. AMR

Anti-A and/or -B antibodies are present in the recipients, and ABO histo-blood group antigens are expressed on endothelial cells of kidney grafts [22]. In ABO-incompatible transplantation, these antibodies react to ABO histo-blood group antigens followed by complement activation. Bleeding and thrombosis develop, which eventually lead to graft loss [23,24] (Figure 1). As observed in 441 cases of ABO-incompatible KTx from Japan [15], no incidence of hyperacute rejection occurred within 48 h of transplantation [24] (Figure 2). Many cases of acute AMR occurred during the first 2–7 days after transplantation. After this period, the incidence of AMR decreased, and rejection ceased to occur 1 month after transplantation. Based on the results of this study, we divided the posttransplantation clinical course into three periods: a 48-h “silent period” with no sign of hyperacute rejection, an 18-day “critical period” from days 2 to 19 (average, day 7) when acute AMR is most likely to develop, and a subsequent “stable period” during which acute AMR no longer occurs because transplant accommodation has been established [24]. Accommodation is defined as a phenomenon in which no clinical grafted organ injury occurs despite the presence of antibodies in the recipient’s body against the ABO histo-blood group antigens of the graft [15].

Figure 1. Acute AMR in ABO-incompatible KTx and its mechanism [23].
AMR in ABO-incompatible KTx is classified into two types based on antigen stimulation and the immunological response to such stimulation [25] (Table 1). Type I acute AMR is caused by resensitization due to ABO histo-blood group antigens on the endothelial cells of the kidney graft. In patients at high immunological risk with high antibody titer, ABO histo-blood group antigens of the grafts can directly stimulate immunological responses, resulting in the explosive production of antibodies and leading to acute AMR. Typically, IgG antibody titers increase, accompanied by a parallel increase in IgM antibody titers. Once rejection develops, its course is dramatic, with no response to currently available therapy and ultimately leading to graft loss. Because serum IgG antibody titers are generally high before transplantation and a “rebound” in antibody production often occurs after pretransplantation antibody removal, desensitization therapy, including the suppression of memory cells, should be administered before transplantation (detailed in a later section).

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence of critical period</td>
<td>Early phase</td>
<td>Late phase</td>
</tr>
<tr>
<td>Recipient</td>
<td>Immunologically high-risk host</td>
<td>Immunocompromised host</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Inadequate</td>
<td>Possible immunosuppression</td>
</tr>
<tr>
<td>Antigens</td>
<td>ABO histo-blood group antigens</td>
<td>ABO blood group-associated antigens</td>
</tr>
<tr>
<td>Sensitization</td>
<td>Resensitization</td>
<td>Primary sensitization</td>
</tr>
<tr>
<td>Response</td>
<td>Secondary and severe</td>
<td>Primary and less than type I</td>
</tr>
<tr>
<td>Antibody production</td>
<td>Explosive</td>
<td>Slow</td>
</tr>
<tr>
<td>Antibody titer</td>
<td>IgG↑&gt; IgM↑</td>
<td>IgG→ IgM↑</td>
</tr>
</tbody>
</table>

Figure 2. Onset of acute AMR [15,24].
Table 1. Classification of acute AMR due to ABO blood group antigens in ABO-incompatible KTx [23].

<table>
<thead>
<tr>
<th>Type</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Unresponsive</td>
<td>Responsive in early period</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Desensitization</td>
<td>Prevention of infection</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Graft loss</td>
<td>Possible graft survival</td>
</tr>
</tbody>
</table>

Type II AMR is caused by a primary sensitization by ABO blood group-associated antigens. In response to bacterial infections, such as sepsis, ABO antigen-like substances on the surface of bacterial cells act as cross-reacting antigens, causing sensitization and antibody production. Type II AMR usually progresses more slowly and is less severe than type I AMR [25]. A major difference from type I rejection is the elevation of IgM antibody titers. Type II AMR also has a greater chance of responding to currently available treatment. Antibody removal and anticoagulation therapy should therefore be promptly administered.

4. Development of desensitization therapy for ABO-incompatible KTx

In this section, we summarize the history of ABO-incompatible KTx performed at our institute, Niigata University, focusing on the transition of immunosuppressive therapy as well as on the development and implementation of desensitization therapy [21].

Figure 3. Immunosuppression protocol, early phase, period 1, extending from April 1996 to January 1997. Antibody removal with DFPP started from 5 to 7 days before transplantation, without any immunosuppression. FK506 and AZ were started 2 days before transplantation and splenectomy was “routinely” performed at the time of transplantation. MP, methylprednisolone.
In 1996, tacrolimus (FK506), azathioprine (AZ), steroids, and antilymphocyte globulin (ALG) were used for ABO-incompatible KTx (Figure 3). FK506 and AZ were initiated 2 days before surgery, splenectomy was performed at the time of transplantation, and ALG was administered for 14 days after KTx. For antibody removal therapy, double-filtration plasmapheresis (DFPP) or plasma exchange was performed. The target anti-A and -B titer immediately before KTx was set at eightfold or less, and the antibody removal protocol was repeated until the target titer was reached because high pretransplantation antibody titer against donor blood type has been reported to correlate with acute AMR [26–30].

In patients whose antibody titer rebounded after antibody removal therapies, acute AMR occurred in some cases with the increase in posttransplantation antibody titer. To avoid this, cyclophosphamide (CPA) treatment, which inhibits B cells, has been initiated along with low-dose steroids 10–14 days before transplantation since 1997 (Figure 4). Antibody removal, FK506, and splenectomy were performed in a conventional manner.

However, the new protocol seemed to be less than fully adequate because two patients lost their grafts due to AMR during this period. Mycophenolate mofetil (MMF) and basiliximab have been included since 2001. To avoid AMR, MMF and steroids were started 14–28 days before the transplantation surgery (Figure 5). Antibody removal, FK506, and splenectomy were performed in a conventional manner.

Figure 4. Immunosuppression protocol, early phase, period 2, extending from February 1997 to September 2001. CPA, a low steroid dose, and AZ were administered starting 10 days before transplantation, at the beginning of antibody removal.
Figure 5. Immunosuppression protocol, early phase, period 3, extending from October 2001 to August 2004, using MMF and basiliximab. MMF and a low-dose steroid were started 2–4 weeks before transplantation. The concept of B-cell desensitization was adopted. AUC, area under the curve; CYA, cyclosporine.

Figure 6. Late phase (September 2004–). Desensitization protocol with two doses of rituximab, MMF, a steroid, and antibody removal without splenectomy. The concept of “desensitization therapy” for ABO-incompatible KTxs was introduced. MMF and a low-dose steroid were started 4 weeks before transplantation, and two doses of rituximab and a minimum antibody removal session followed. Splenectomy was completely abandoned in this phase.
Splenectomy has been considered a prerequisite for a successful outcome of ABO-incompatible KTx [31] because the spleen has a specific structure for entrapping extrinsic antigens and contains the largest pools of memory B cells and antibody-producing plasma cells in the body. However, splenectomy can lead to complications, including postoperative hemorrhage, pancreatic injury, and leakage of pancreatic juices [32]. Furthermore, the assumed immunological benefits of splenectomy are doubtful because severe AMR can still occur sometimes [26]. In such patients, extrasplenic memory B cells and plasma cells are activated to produce anti-A and -B antibodies in response to antigen loading after KTx. Strategies for preoperative immunosuppression must therefore be reconsidered. Instead of splenectomy, 375 mg/m² rituximab (a chimeric mouse-human monoclonal antibody formulation directed to CD20 antigens expressed on premature and mature B cells) has been administered twice since 2004: once 2 weeks before and once on the day before ABO-incompatible KTx [33] (Figure 6). The major goal of treatment with rituximab and MMF is to suppress the induction of differentiation from memory B cells into antibody-secreting plasma cells. Antibody removal was mainly intended for the physical removal of anti-A and -B antibodies already present in the circulating blood and also to aid in assessing the suppressive effects on the B cell line by determining the extent of antibody rebound after removal. Thus, antibody removal was considered to be a form of auxiliary therapy. As a general rule, antibody removal was limited to two times because of the serious concerns regarding the side effects of antibody removal, such as allergic reactions.

![Figure 6](image-url)

**Figure 6.** Late phase, modified desensitization protocol (2007–). Starting in 2007, a CNI was added 4 weeks before transplantation and one dose of rituximab was reduced to 100 mg/body. Antibody removal was limited to a minimum, and splenectomy was completely avoided.

**Phase 5 (2007 ~)**
- Low dose Cyclosporine/Tacrolimus, low dose MP, MMF, Basiliximab, Low dose Rituximab+ without splenectomy

![Diagram](image-url)
hemorrhagic tendency due to decreased anticoagulant factors, and decreased colloid osmotic pressure and intravascular volume depletion due to hypoalbuminemia. Calcineurin inhibitors (CNI) suppressed the differentiation of B-0 cells to B-1a cells, which would otherwise progress to be anti-A and -B antibody-producing B cells [34]. Taking this point into account, CNI was started 28 days before KTx with MMF and steroids. To avoid over-immunosuppression, the dose of rituximab was eventually reduced to 100 mg/body (Figure 7). The number of peripheral B cells was well suppressed with this strategy for approximately 6 months after ABO-incompatible KTx (data not shown).

5. Outcomes of ABO-incompatible KTx in Niigata University

We show our clinical results divided into two periods, before and after 2004. As mentioned above, MMF and rituximab were used as a desensitization therapy without splenectomy since 2004. Table 2 shows the characteristics of the patients who underwent ABO-incompatible KTx in Niigata University [21].

<table>
<thead>
<tr>
<th></th>
<th>1996–2004.5 (n=20)</th>
<th>2004.9–2013 (n=60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age</td>
<td>33.5±11.3</td>
<td>44.9±13.3</td>
<td>0.069</td>
</tr>
<tr>
<td>Donor age</td>
<td>57.5±6.3</td>
<td>55.2±9.1</td>
<td>0.224</td>
</tr>
<tr>
<td>Male recipient (%)</td>
<td>75</td>
<td>72</td>
<td>0.555</td>
</tr>
<tr>
<td>Male donor (%)</td>
<td>50</td>
<td>28</td>
<td>0.037</td>
</tr>
<tr>
<td>Graft weight (g)</td>
<td>165.1±27.1</td>
<td>173.4±31.3</td>
<td>0.581</td>
</tr>
<tr>
<td>HLA MM</td>
<td>2.6±1.6</td>
<td>3.2±1.3</td>
<td>0.391</td>
</tr>
<tr>
<td>HD duration (months)</td>
<td>46.9±39.7</td>
<td>36.4±48.7</td>
<td>0.774</td>
</tr>
<tr>
<td>TIT (min)</td>
<td>63.3±27.6</td>
<td>82.8±28.0</td>
<td>0.644</td>
</tr>
<tr>
<td>WIT (min)</td>
<td>6.0±1.6</td>
<td>4.1±2.1</td>
<td>0.092</td>
</tr>
<tr>
<td>TAC for CNI (%)</td>
<td>85</td>
<td>50</td>
<td>0.000</td>
</tr>
<tr>
<td>Preemptive KTx (%)</td>
<td>0</td>
<td>20.3</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of the patients who received ABO-incompatible KTx in Niigata University.

5.1. Patient survival rate

Patient survival rates are shown in Figure 8 [21]. Before 2004, the patient survival rate was 95% for the first year, 90% for the first 5, 7, and 10 years, and 80% for the first 15 years after transplantation. After 2004, the patient survival rate was 100% for all available study periods (1, 5, 7, and 10 years) after transplantation. A statistically significant difference in patient survival rate was observed between the late and early phases (Kaplan-Meier analysis, P<0.03).
Patient survival before and after 2004 in ABO-incompatible KTx (Kaplan-Meier analysis). Patient survival rate of cases after 2004 was significantly improved compared to that of cases before 2004 (log-rank, $P=0.03$). N.A., not yet available.

### 5.2. Cause of death

Four patients died after transplantation, with their causes of death (time of death) being sepsis due to pleuritis (at 4 months after transplantation), sepsis (46 months), sepsis due to gastrointestinal perforation (123 months), and brain tumor (123 months). Three of these deaths (two due to sepsis and one due to brain tumor) were deaths with functioning graft (DWFG).

### 5.3. Graft survival rate

Graft survival rates are shown in Figure 9 [21]. Before 2004, the death-censored graft survival rate was 80% at 1 year, 80% at 5 years, 68.6% at 7 years, 51.4% at 10 years, and 45.7% at 15 years after transplantation. After 2004, the death-censored graft survival rate was 96.7% at 1 year, 96.7% at 5 years, 96.7% at 7 years, and 87.9% at 10 years after transplantation. A statistically significant difference in graft survival rate was observed between the late and early phases (Kaplan-Meier analysis, $P=0.006$).
5.4. Cause of graft loss

Table 3 shows the cause of graft loss [21]. The graft was lost in 17 patients. The causes of graft loss were chronic allograft nephropathy in five cases (70, 98, 194, 133, and 102 months after transplantation), acute AMR in three cases (10, 10, and 9 days after transplantation), thrombotic microangiopathy (TMA) in one case (1 day after transplantation), acute rejection in one case (4 months after transplantation), recurrent membranoproliferative glomerulonephritis (MPGN) in one case (114 months after transplantation), recurrent IgA glomerulonephritis (IgAGN) in one case (114 months after transplantation), drug-induced nephropathy in one case (2 months after transplantation), graftectomy/total nephroureterectomy/cystectomy due to urothelial tumor in one case (76 months after transplantation), and patient death in three cases.
Table 3. Cause of graft loss in ABO-incompatible KTx.

<table>
<thead>
<tr>
<th>Cause of graft loss</th>
<th>n</th>
<th>Posttransplantation duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic allograft nephropathy</td>
<td>5</td>
<td>194, 133, 102, 98, and 70 months</td>
</tr>
<tr>
<td>Death with function</td>
<td>3</td>
<td>123, 46, and 4 months</td>
</tr>
<tr>
<td>AMR</td>
<td>3</td>
<td>10, 10, and 9 days</td>
</tr>
<tr>
<td>TMA</td>
<td>1</td>
<td>1 day</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>1</td>
<td>4 months</td>
</tr>
<tr>
<td>Recurrent MPGN</td>
<td>1</td>
<td>114 months</td>
</tr>
<tr>
<td>Recurrent IgAGN</td>
<td>1</td>
<td>114 months</td>
</tr>
</tbody>
</table>

AMR: antibody mediated rejection, TMA: thrombotic microangiopathy, MPGN: membranoproliferative glomerulonephritis, IgAGN: IgA glomerulonephritis.

6. Acute AMR by de novo antibody

In our studies, the indicator for acute AMR, C4d in peritubular capillaries (PTCs), was observed by graft biopsy over time, at 0-h, 1-h, or 1-month protocol biopsy or by episode biopsy. The positive rate for C4d in PTCs at 1-h biopsy was only 16.1% [24,35]. The positive rate increased to 70.9% for the 1-month protocol or episode biopsy. Biopsy was negative at 1 h in all four cases in which acute AMR developed due to anti-A and -B antibodies after ABO-incompatible KTx in our institute but was positive 1 month later. Among the cases that turned positive after negative results, no acute AMR developed except in these four cases. Considering this fact, we made the following hypotheses: (1) preexisting anti-A and -B natural antibodies do not always bind to histo-blood group antigens on the graft vascular endothelial cells and subsequently activate complement, (2) it is likely that antibodies with high affinity to the kidney allograft are newly formed postoperatively and deposited, and (3) not all antibodies produced postoperatively elicit acute AMR, and accommodation is induced and established in cases where the graft survives [22,24,35]. The important matter is that titration of anti-A and -B antibodies is most widely performed by isohemagglutinin using red blood cells (RBCs) in ABO-incompatible KTx. Our observations also suggested the diversity of anti-A and -B antibodies and antibody-producing clones and indicated that it is more important to control postoperatively produced anti-A and -B antibodies that injure target graft vascular endothelial cells (not RBCs) than to mechanically remove preformed antibodies. Finally, we previously reported that there were differences regarding the presentation of ABO blood group antigens between RBCs and endothelial cells of the kidney [22]. According to our results, we have recently excluded, on a trial basis, antibody removal before ABO-incompatible KTx in patients with antibody titers below 64-fold [36]. In 14 patients who did not receive antibody removal, the patient and graft survival after 1 year were each 100% [36].
7. Strategies for ABO-incompatible KTx

1. In ABO-incompatible KTx, tissue-destroying acute AMR is elicited by an extensive antibody production. This drastic antibody elevation occurs because memory B cells and plasma cells having immunological memory are inadequately suppressed and thus can react to histo-blood group carbohydrate antigens introduced by the graft, producing a second set phenomenon (type I AMR).

2. Acute AMR can be elicited by anti-A and -B antibody production that has been made possible because of a prior exposure to blood group-associated carbohydrate antigens due to certain bacterial infections (type II AMR).

3. Effective desensitization therapy should be performed by suppressing B-cell immunity rather than by several sessions of mechanical antibody removal. The effective method to protect from AMR is a pretransplantation procedure with a combination of rituximab and MMF/CNI, which blocks the induction of B-cell differentiation. The most important consideration is to inhibit B-cell immunity to a sufficient extent before ABO-incompatible KTx and potential new antibody production in the critical period. Accommodation has been established after ABO-incompatible KTx, and the recipient’s posttransplantation antibody titer becomes less relevant.

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