Initial Experience with ABO-incompatible Live Donor Renal Transplantation

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The serious shortage of cadaveric organs has prompted the development of ABO-incompatible live donor renal transplantation. We report our experience of the initial two live donor ABO incompatible renal transplants at our hospital. The first patient was a 55-year-old type A female who received a kidney from her AB type husband. The second patient was a 27-year-old type O male who received renal transplantation from his type A father. Preconditioning immunosuppressive therapy in the two patients with tacrolimus, mycophenolate mofetil and methylprednisolone was started 7 days before transplantation. During the period of preconditioning, double filtration plasmapheresis (DFPP) was employed to remove anti-A and -B antibodies. Laparoscopic splenectomy and renal transplantation were performed after the anti-donor ABO antibodies were reduced to a titer of 1:4. Rituximab, a humanized monoclonal anti-CD20 antibody, was administered to the second patient due to a rebound in the anti-A antibody titer during the preconditioning period. Under a tacrolimus-based immunosuppressive regimen, both patients recovered very well without any evidence of rejection. Serum creatinine levels were 1.0 and 1.4 mg/dL at 6 and 3 months after transplantation, respectively. These cases illustrate that with new immunosuppressive agents, DFPP and splenectomy, ABO-incompatible renal transplantation can be successfully conducted in end-stage renal disease patients whose only available live donors are blood group incompatible. [J Formos Med Assoc 2006;105(9):775–779]

Key Words: ABO blood type, renal transplantation

Organ shortage is one of the most serious problems for patients with end-stage renal disease (ESRD) waiting for renal transplantation. In 2004, there were 42,550 chronic dialyzed ESRD patients in Taiwan, but only 161 were lucky enough to receive renal transplantation from deceased donors.1,2 Another 46 patients underwent living-related renal transplantation.2 Renal transplants either from genetically related or from unrelated live donors have yielded excellent survival rates. Evidence indicates that there is little long-term medical risk to a healthy donor after unilateral nephrectomy.3 The annual number of live kidney donors in the United States has surpassed that of deceased donors since 2001.4

Blood type compatibility between donor and recipient has been a determining factor in conducting organ transplantation. ABO-incompatible renal transplantation has long been considered to run a high risk of rejection and graft loss. With advances in immunosuppressive agents and therapeutic plasmapheresis, excellent long-term outcome has...
been achieved in ABO-incompatible live donor renal transplantation in Japan.\(^5\)\(^6\) We accordingly attempted to establish this transplant modality for ESRD patients with potential ABO-incompatible live donors in Taiwan. Here, we report our initial experience with two patients who received ABO-incompatible live donor renal transplantation.

### Case Reports

**Case 1**

A 55-year-old woman with blood type A was admitted because of intermittent lower leg edema for 20 years. Despite records indicating elevated blood pressure and fasting blood sugar several years ago, no regular medical treatment had been given. Physical examination showed palpe conjunctivae and mild pitting edema in the lower extremities. Laboratory data showed a leukocyte count of 7450/mm\(^3\), hemoglobin of 8.9 g/dL and platelet count of 231,000/mm\(^3\). Biochemistry studies showed serum creatinine of 8.4 mg/dL and blood urea nitrogen of 97.2 mg/dL. Chronic renal failure was diagnosed. Her family was willing to donate a kidney to her, but all family members were of AB blood type. Her husband, a 57-year-old man with type AB blood type, decided to donate his kidney for ABO-incompatible live donor renal transplantation. Typing of human lymphocyte antigens (HLA) showed that the donor was 1, 0, 1 (HLA-A, B, DR) mismatched with the recipient. Details of pretransplant immunologic evaluations, including blood type, HLA, recipient panel reactive antibody and donor-specific complement-dependent cytotoxicity, are shown in the Table.

After admission, the patient received four sessions of double filtration plasmapheresis (DFPP) to reduce the anti-B antibody titer from 1:16 to 1:2. Anti-A and -B antibody titer was determined using the saline method. Twofold serial dilutions of sera were made in saline and tested for agglutinating activity toward A or B red blood cells respectively and were subjected to centrifugation with a blood bank serocentrifuge. Titers were read macroscopically. DFPP was performed using KM-8800 in a Kuraray plasmapheresis system (Kuraray, Okayama, Japan) incorporating a Plasmacure PS-06 as the plasma separator and an Evaflex 5A as the plasma fractionator (Kuraray). The exchange volume was set at 50 mL/kg with normal saline 300–500 mL as the replacement fluid.

In addition to plasmapheresis, the patient received a 7-day tacrolimus-based immunosuppressive therapy including tacrolimus (Prograf, Fujisawa, London, UK), mycophenolate mofetil (MMF; Cellcept, Roche, Humacao, Puerto Rico) and methylprednisolone before transplantation. The initial dose of tacrolimus was 0.2 mg/kg/day, and the trough blood levels of tacrolimus were maintained around 10 ng/mL by dose adjustment. The daily dose of MMF was 2 g/day and that of methylprednisolone was 80 mg/day. Liver function tests, complete blood counts, blood sugar and coagulation profiles were checked every other day to facilitate early identification of

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**Table.** Results of pretransplant immunologic examinations in cases 1 and 2, including blood type, human lymphocyte antigen, recipient panel reactive antibody and donor-specific complement-dependent cytotoxicity

<table>
<thead>
<tr>
<th>Case</th>
<th>Blood type/HLA</th>
<th>PRA (%)</th>
<th>CDC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donor</td>
<td>Recipient</td>
<td>Class I</td>
</tr>
<tr>
<td>1</td>
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<td>A A26/B60, Bw6/Cw7/DR11, DR15, DR51, DR52</td>
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<tr>
<td>2</td>
<td>A A2/B75, B46, Bw6/Cw1, Cw8/DR9, DR12, DR52, DR53</td>
<td>O A2/B46/Cw1/DR9, DR53</td>
<td>0 0</td>
</tr>
</tbody>
</table>

*HLA = human lymphocyte antigen; PRA = panel reactive antibody; CDC = complement-dependent cytotoxicity.*
side effects of DFPP and the immunosuppressive drugs. Intravenous immunoglobulin was not given but fresh frozen plasma was administered for correction of coagulopathy.

Our first ABO-incompatible live donor renal transplantation was conducted on November 22, 2004. Laparoscopic nephrectomy was performed to retrieve the left kidney of the donor, and the recipient received laparoscopic splenectomy.7,8 After splenectomy, the spleen was left behind in the peritoneal cavity until accomplishment of vascular and urinary reconstruction of the graft kidney. The spleen was then pulled out of the abdominal cavity through the incision for the renal implantation. During the transplant operation, bolus intravenous methylprednisolone (10 mg/kg) was given before vascular reperfusion. The dose of methylprednisolone was then tapered to 20 mg/day by day 8 and changed to oral prednisolone thereafter. Continuous intravenous infusion of tacrolimus was administered until the patient could tolerate oral tacrolimus. The doses of tacrolimus were adjusted to achieve a target blood level of 10 ng/mL for the first 3 months, and those of prednisolone were tapered to 0.1 mg/kg/day in month 3. MMF was given at a dose of 2 g/day initially, with the dosage adjusted to keep the white blood cell counts in the range of 4000–6000/mm³. The postoperative course was uneventful and the renal function of the graft was good. Neither signs of rejection nor anti-B antibody rebound was detected. The patient was discharged 3 weeks after the operation. The serum creatinine level was 1.0 mg/dL with an anti-B antibody titer of 1:2 6 months after the transplant. Details of the serum creatinine levels and anti-B antibody titers of case 1 are summarized in Figure A.

Case 2

A 27-year-old man with blood type O was admitted for live donor renal transplantation. His father, a 45-year-old man of blood type A, expressed his desire to donate a kidney to him. The patient had developed gouty arthritis without regular medical treatment several years ago. His renal function had progressively deteriorated, and he had received chronic peritoneal dialysis for 3 years. Physically, he was anemic with pale conjunctivae. Hemoglobin level was 8.5 g/dL and platelet count was 216,000/mm³. Serum creatinine was 16.3 mg/dL and blood urea nitrogen was 87.3 mg/dL. Anti-A and -B antibody titers were 1:64 and 1:16, respectively. Results of the pretransplant immunologic evaluations are shown in the Table.

After admission, the patient received the same preconditioning immunosuppressive regimen as in case 1. However, six sessions of DFPP were required to reduce the anti-A antibody titer to 1:4. The anti-A antibody titer rebounded once during the course of DFPP (Figure B). Rituximab (MabThera, Roche, Hertfordshire, UK), a monoclonal anti-CD20 antibody, was additionally given at a dose of 375 mg/m² before graft reperfusion to deplete the patient’s B-lymphocytes. The
transplant operation was conducted and post-transplant immunosuppressive therapy was as described in case 1. Although the graft renal function was good, the patient suffered from severe epigastralgia and vomiting after the operation. MMF was discontinued and changed to sirolimus (Rapaume, Wyeth-Ayerst, PA, USA) 10 days post-transplantation. The serum creatinine level was 1.4 mg/dl and the anti-A antibody titer was 1:4 3 months after transplantation. The pre- and post-transplant serum creatinine levels and anti-A antibody titers of case 2 are summarized in Figure B.

**Discussion**

ABO-incompatible renal transplantation is an alternative therapeutic modality for ESRD patients whose only live donors have incompatible blood groups. Takahashi et al. reported that the outcome of ABO-incompatible renal transplantation was similar to ABO-compatible transplantation. The excellent long-term outcome in Japan fully justified ABO-incompatible live donor renal transplantation in countries extremely short of cadaveric kidneys with strict requirement for living donation. The success in overcoming ABO-incompatibility in these two cases may serve as a model for increasing the pool of live donors and the number of renal transplantsations in Taiwan.

Immunosuppressive therapy plays a central role in ABO-incompatible renal transplantation. Tacrolimus has been demonstrated to have a potent immunosuppressive effect resulting in good renal function in randomized studies worldwide. MMF has been shown to suppress the production of anti-blood type antibodies in ABO-incompatible transplantation. These properties have led to the use of tacrolimus and MMF therapy in nearly all the reports on ABO-incompatible renal transplantation. The success of ABO-incompatible renal transplantation also depends on effective removal of anti-A and -B antibodies and splenectomy. While DFPP is associated with hypoalbuminemia and coagulopathy, antigen-specific immunoadsorption of anti-A or -B antibody is a preferable alternative to DFPP in ABO-incompatible transplantation. However, we chose to employ DFPP because the immunoadsorption columns for anti-A and -B antibodies are not available in Taiwan. Besides, DFPP can remove not only anti-A and -B but also anti-HLA antibodies in patients who are positive for panel reactive antibodies. Successful application of DFPP in transplant recipients could be an initial step toward transplantation with donor-specific preformed antibodies.

The requirement for splenectomy in ABO-incompatible transplantation is debatable, especially with the advent of rituximab. Rituximab is a humanized monoclonal anti-CD20 antibody that was primarily approved for therapy of CD20-positive B-cell lymphoma. Rituximab has been successfully adopted as a B-cell ablative agent in immunosuppressive preconditioning for ABO-incompatible renal transplantation without splenectomy. In case 2, we encountered difficulty in reducing the anti-A antibody titer to the target level, and successful reduction of anti-A titer was actually achieved by intensive DFPP. The risk of humoral rejection might have been very high if further immune intervention had not been instituted. We therefore classified case 2 as resistant to DFPP and gave rituximab in order to prevent antibody rebound and humoral rejection. Large-scale randomized trials are needed to investigate the effect of rituximab on the outcome of allograft transplantation.

In summary, this report describes two successful cases of ABO-incompatible live donor renal transplantation. With the use of new immunosuppressive agents, DFPP and splenectomy, ABO-incompatible renal transplantation is an established alternative for the treatment of ESRD patients whose only live donors are blood group incompatible.

**References**