Living-donor kidney transplantation across ABO barriers: the first case in Thailand

Yingyos Avihingsanon, Natavudh Townamchaia, Supanit Nivatvongs, Supoj Ratchanon, Kearkiat Praditpornsilpa, Khajohn Tiranathanagul, Paweena Susantitaphong, Boonchoo Sirichindakul, Bunthoon Nonthasoot, Onchuma Sooklim, Wipawee Kittikowit, Ruenreong Leelanukrom, Somchai Eiam-Ong, Kriang Tungsang

Department of Medicine, Department of Surgery, Department of Pathology, Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Background: Transplantation among ABO blood group incompatibility was considered an absolute contraindication until recent development of successful protocols. A living-donor across ABO barriers may provide another option for end-stage kidney disease patients.

Objective: To report the first case of ABO-incompatible living-donor kidney transplantation (ABOi-LKT) in Thailand.

Patients and method: The kidney transplantation across ABO barriers was performed following the Japanese recommended protocol. The kidney recipient was a thirty-four years old woman with blood group O, whereas the kidney donor was her brother with blood group A. To reduce anti-donor (anti-blood group-A antibody) blood levels, the patient underwent double filtration plasmapheresis and received an intravenous anti-CD20 monoclonal antibody. A maintenance immunosuppressive regimen was similar to the one of ABO-compatible setting.

Results: The kidney allograft had immediate good function. The transplantation was uneventful, and the patient went home within two weeks. Kidney allograft biopsies were performed on a protocol-driven basis at time-zero, the first and sixth month post-transplantation. Histologic studies showed unremarkable findings. The patient is now twelve months after transplantation and has achieved excellent kidney function.

Conclusion: ABOi-LKT provides an alternative treatment for end-stage kidney disease patients. A multi-center study of ABOi-LKT in Thailand is ongoing, and this may change the national policy of organ donation in the near future.

Keywords: ABO incompatible, Asia, double filtration plasmapheresis, kidney transplantation.

Since 1972, Thailand has recognized kidney transplantation as the best treatment option for end stage renal diseases [1]. However, less than 400 transplants have been performed each year, while over 2,000 end-stage renal disease patients are registered on the waiting list. The median waiting time is four years for a deceased donor. Many patients die waiting. The organ donor center of the Thai Red Cross Society and their allied societies, have strived to increase organ donors by many strategies, such as public relations campaign, and through special events. Recent anniversaries of the King and Her royal highness the king’s sister collected the most number of organ donations in the history of the country, but that was only for one year.

Kidney transplantation across ABO barriers, or ABO-incompatible living-donor kidney transplantation (ABOi-LKT), has been performed in Western countries [2-7] as well as in Japan where the greatest number of ABOi-LKT has occurred [8]. This was considered an absolute contraindication to transplantation until development of the protocol for lowering anti-ABO titer. In Japan, this strategy has considerably increased the donor pool by up to 20-30 percent. A large cohort in Japan demonstrated a
comparable graft survival between ABO-incompatible and ABO-compatible kidney transplantation. For Thai patients, we considered adopting the Japanese protocol for the following reasons: 1) Thai patients shared an Asian ethnic background, 2) the protocol was the most cost-effective approach, and 3) it avoided splenectomy. By the end of the year 2008, there are more than 1,700 Thai patients on waiting lists with blood group non-AB. ABOi-LKT may have benefited these patients since the waiting time would be shortened for improving their quality of life.

Case report

A thirty-four years old woman with blood group O, Rh-positive, has end-stage renal disease from chronic glomerulonephritis. Two potential living-related donors were evaluated. The first was her brother with similar blood group. However, he has a positive anti-HCV antibody, which precluded him from kidney donation. The other potential donor is a younger brother of the patient, but he has an ABO-incompatible blood group (A1). Otherwise, he was a good candidate for kidney donation.

Six months after waiting for a deceased-donor, the patient gave consent for the living-donor kidney transplant from her brother who had the incompatible ABO blood group. The pre-transplant evaluation was negative, including screening for hepatitis B/C and HIV. The tissue typing of human leukocyte antigen (HLA) found zero-mismatched HLA and direct cross-matching showed negative result. Panel reactive antibodies of patient sera were negative. After passing the medical review board of the King Chulalongkorn Memorial Hospital, the patients were admitted one week prior to the operation.

The titers of anti-blood group A IgG and IgM antibodies were 1:256 and 1:32. The recipient underwent double filtration plasmapheresis (DFPP) using the EC 30 dialyzer (Kawasumi Co, Tokyo, Japan) every other day for four times before transplantation. The result of anti-blood group A IgG and IgM titer decreased to 1:16 and 1:2 respectively. Immunosuppressive regimen included 500 mg of intravenous anti-CD20 monoclonal antibody (Mabthera®, Roche, Basel, Switzerland), oral tacrolimus (0.1 mg/kg/day) (Prograf®, Astellas, Osaka, Japan), oral mycophenolate mofetil (1.5 g/day) (CellCept®, Roche, Nutley, USA) and oral prednisolone (20 mg/day). The target trough level of tacrolimus and mycophenolic acid were over 10 and 2.1 ng/mL, respectively (see Fig. 1, 2). Two-doses of intravenous Daclizumab (Zenapax®, Roche, New Jersey, USA) were given on the operation day and two weeks post-transplant.

![Image](image_url)

**Fig. 1** Preconditioning and immunosuppression for ABO-incompatible kidney transplantation for this recipient. DFPP = double filtration plasmapheresis, FK = tacrolimus, \( C_0 \) = trough level, MMF = mycophenolate mofetil.
After achieving a target anti-ABO titer below 1:32, the operation was performed without difficulty. As a precaution, blood components were prepared. We had leukocyte-poor packed red cell of blood group O, fresh frozen plasma of blood group AB, and leukocyte-depleted platelet of blood group A. However, blood components were not used since the transplant operation was performed uneventfully. The donor kidney was removed laparoscopically. Immediate urine output was observed and was over four liters for the first 24-hour post operation. Serum creatinine decreased dramatically from 6.4 to 1.2 mg/dL within 72 hours.

The Anti-blood group A IgG and IgM titers were below 1:32 at all times post-transplant. Immunosuppressive drugs levels were kept within the target range. The protocol biopsies were performed at time-zero (post-reperfusion), on the first and sixth month post-transplant. There was mild mesangial IgA deposition at time-zero biopsy with normal light microscopic findings. The first and sixth month post-transplant of allograft biopsy showed mild interstitial mononuclear cell infiltration and mild interstitial fibrosis with tubular atrophy. C4d staining was negative at all times.

The recipient had catheter-related urinary tract infection on the first-day post-transplant, which was successfully treated with intravenous antibiotics. The surveillance for hepatitis B (HBV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and polyoma (BK) virus infection was negative. The anti-HBs antibody titer was reduced from baseline levels from 240.4 to 23.1 mIU/mL. At six months, the immunosuppressive drugs were successfully tapered and the patient had returned to her work (Fig. 3). Serum creatinine was 0.9 mg/dL. No complication was seen up to the time of this report (12 months post-transplant).

**Fig. 2** The immunosuppressive regimen of the Japanese protocol [8]. DFPP = double filtration plasmapheresis, FK = tacrolimus, C0 = trough level, MMF = mycophenolate mofetil.

**Fig. 3** The first recipient (left) and donor (right) of ABOi kidney transplantation in Thailand (with consent from the patient).
Discussion

The success of kidney transplantation across immunologic barriers essentially originates from advanced immunosuppressive therapy. Transplantation across ABO blood group is a good example of overcoming the major immunologic barrier. The most important factor for ensuring successful engraftment is lowering anti-ABO antibody titers before operation. The greatest advantages of ABOi-LKT are a large donor-pool from living-related donors. The Japanese registry data reports a 30% increase in its donor-pool, and has shown a wide-spread acceptance of ABOi-LKT among transplant centers in that country. Protocols to reduce anti-ABO titers have demonstrated efficacy and safety. The Japanese protocol can be advantageous in Thailand due to the lower cost of care (see Table 1).

A series of failure cases of ABOi-LKT due to hyperacute rejection were reported after 1955 [9]. Thereafter, presence of anti-ABO antibodies was viewed as an absolute contraindication to transplantation. In clinical practice, without ABO-compatible donor, the patient will have to undergo hemodialysis or peritoneal dialysis and will register for a deceased donor at the Thai Red Cross Society. Morbidity and mortality rates are associated with waiting time on dialysis. The average yearly death rate on the waiting list has been reported to be six percent [10]. Given the median waiting time of four years, we will lose approximately one-fourth of patients. Furthermore, patients on dialysis for a longer time also have an increased risk of morbidities from cardiovascular diseases, stroke, and dialysis-related infection.

Compared with deceased donor kidney transplantation, the advantages of ABOi-LKT comprise better patient and graft survival rates, lower rates of delayed graft function, and hospitalization. The additional cost of ABOi-LKT from conventional transplant is from the pre-transplant, pre-conditioning and monoclonal antibody therapy. However, the expense for this type of treatment will be less than a year of dialysis on the waiting list. The potent immunosuppressive therapy in the first month of ABOi-LKT may increase the risks of infection as compared with the conventional transplantation. However, the infection risk will decline after the first few months post-transplantation.

One important problem of ABOi-LKT is anti-ABO antibody, which could cause antibody-mediated rejection (AMR) during the first hour to week after transplantation. The successful reduction of anti-ABO antibody titers significantly decreases this risk of AMR. The preoperative method of antibody reduction has three techniques; plasmapheresis, double-filtration plasmapheresis, and antigen-specific immuno-adsorption [2-8]. Previously, splenectomy was performed at the time of transplantation to reduce antibody-producing B-lymphocytes [11-13]. Anti-CD20 monoclonal antibody (Mabthera, Roche, Basel, Switzerland) has now been successfully used for depleting B-lymphocytes. Splenectomy can be avoided by the pre-operative use of intravenous anti-CD20 mAb. The maintenance of an immunosuppressive protocol is similar to the conventional kidney transplantation one. It could be reimbursed by all health care programs in Thailand. The most critical period of ABOi-LKT is the first two-week post-transplant.

Table 1. Comparison of different protocols for ABO-incompatible kidney transplantation.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Anti-A/B removal</th>
<th>Induction</th>
<th>Preoperative anti-A/B titer</th>
<th>Postoperative anti-A/B removal</th>
<th>Expense (Baht/session)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European [3,4,6]</td>
<td>antigen-specific immunoadsorption</td>
<td>rituximab ±IVIg</td>
<td>&lt;1:8</td>
<td>prophylactic/preemptive</td>
<td>150,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>antigen-specific</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>immuno-adsorption</td>
<td></td>
</tr>
<tr>
<td>American [5,7]</td>
<td>plasmapheresis</td>
<td>CMV IgG or rituximab</td>
<td>≤1:16</td>
<td>prophylactic plasmapheresis</td>
<td>20,000</td>
</tr>
<tr>
<td>Japanese [8]</td>
<td>double filtration plasmapheresis</td>
<td>rituximab and basiliximab</td>
<td>≤1:32</td>
<td>none</td>
<td>45,000</td>
</tr>
</tbody>
</table>

IVIg = intravenous immunoglobulin, CMV IgG = cytomegalovirus immunoglobulin G.
By unknown mechanisms. Allograft acceptance will be established later. The re-emergence of anti-ABO antibody in the blood of the recipient without harm to the allograft will occur, and it is called “accommodation”.

In this reported case, the donor had blood group A (subtype A1) that express as A antigen stronger than the A2 subtype. The transplant from A2 donor to O or B recipient is considered less of an immunologic risk. The pre-transplant evaluation requires detection of blood group-A subtype. However, the percentage of A2 subtype in Asians is rare. Transplant physician should work closely with the laboratory on measuring the anti-ABO titer since it is the most critical factor before engraftment. In this reported case, we used the conventional method of measuring the anti-ABO antibody titer. The precision and reproducibility were acceptable [2-4, 8].

Conclusion

We reported the first successful case of transplant across the ABO blood group barrier in Thailand. The patient could avoid the prolonged waiting time for a deceased donor. ABOi-LKT should not be the first line treatment because it exposes the patients to an increased risk of potent immunosuppressive treatment and additional expenses. After an exhausting search of all potential donors, the patient should be informed of all the potential risks of ABOi-LKT. The medical review board or ethical review board of the hospital should be involved in the final decision-making process.

Acknowledgements

The authors would like to thank Professor Kazunari Tanabe and Dr. Hideki Ishida for their help. We thank Sunisa On-pun, MSc for technical assistance. We thank Salin Sittakom, RN, MD, Jade Supaphol, MD, Rattanaporn Burimsittichai, MD for taking care of the patients. This work was partly supported by a grant from Faculty of Medicine, Chulalongkorn University (Visiting professorship program).

References