

## ABO incompatible renal transplants: Good or bad?

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**Author contributions:** Muramatsu M, Cacciola R, Aikawa A, Yaqoob MM and Puliatti C contributed to conception and design, acquisition of data, or analysis and interpretation of data; Muramatsu M, Gonzalez HD, Cacciola R, Aikawa A, Yaqoob MM and Puliatti C contributed to drafting the article or revising it critically for important intellectual content; Muramatsu M, Yaqoob MM and Puliatti C contributed to final approval of the version to be published.

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Received: December 7, 2013 Revised: February 12, 2014

Accepted: February 18, 2014

Published online: March 24, 2014

### Abstract

ABO incompatible kidney transplantation (ABOi-KT) was previously considered to be an absolute contraindication for patients with end-stage kidney disease (ESKD) due to hyperacute rejection related to blood type barrier. Since the first successful series of ABOi-KT was reported, ABOi-KT is performed increasingly all over the world. ABOi-KT has led to an expanded donor pool and reduced the number of patients with ESKD awaiting deceased kidney transplantation (KT). Intensified immunosuppression and immunological understanding has helped to shape current desensitization protocols. Consequently, in recent years, ABOi-KT outcome is comparable to ABO compatible KT (ABOc-KT). However, many questions still remain unanswered. In ABOi-KT, there is an additional residual immunological risk that may

lead to allograft damage, despite using current diverse but usually intensified immunosuppressive protocols at the expense of increasing risk of infection and possibly malignancy. Notably, in ABOi-KT, desensitization and antibody reduction therapies have increased the cost of KT. Reassuringly, there has been an evolution in ABOi-KT leading to a simplification of protocols over the last decade. This review provides an overview of the history, outcome, protocol, advantages and disadvantages in ABOi-KT, and focuses on whether ABOi-KT should be recommended as a therapeutic option of KT in the future.

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**Key words:** Kidney transplantation; ABO incompatible; Antibody depletion; Immunosuppression; Desensitization protocols; Living donor transplantation

**Core tip:** This article demonstrates merits and demerits of ABO incompatible kidney transplantation (ABOi-KT). Although the excellent outcome of ABOi-KT has been achieved, unresolved matters still remain. We review the role of ABOi-KT for patients with end-stage kidney disease and considered validity whether ABOi-KT should be recommended as a therapeutic option of KT in the future.

Muramatsu M, Gonzalez HD, Cacciola R, Aikawa A, Yaqoob MM, Puliatti C. ABO incompatible renal transplants: Good or bad? *World J Transplant* 2014; 4(1): 18-29 Available from: URL: <http://www.wjgnet.com/2220-3230/full/v4/i1/18.htm> DOI: <http://dx.doi.org/10.5500/wjt.v4.i1.18>

### INTRODUCTION

Kidney transplantation (KT) is known as a standard therapy for patients with end-stage kidney disease (ESKD) and has been adopted widely in the world. However, the

living and deceased kidney donor pool does not resolve the shortage of transplantable organs. Different ways have been proposed to increase the donor pool and ABO incompatible KT (ABOi-KT) represents a valid source of organs to decrease the donor waiting list. ABOi-KT requires extra strategies and suffers extra risks across ABO blood type barrier compared to ABO compatible KT (ABOc-KT). ABOi-KT was previously considered to be contraindicated for many years. Presently, ABOi-KT has been accepted as a valid alternative therapy for ESKD and the outcome of ABOi-KT has become equivalent to ABOc-KT in adult and pediatric recipients<sup>[1-4]</sup>. When a patient with ESKD requires KT and an acceptable living donor is ABO incompatible with the recipient, the patient can currently chose one of three options: (1) stay on the waiting list for deceased donor KT; (2) have paired kidney donor exchange (PKDE); or (3) undergo ABOi-KT.

According to the Organ Procurement and Transplantation Network (OPTN) report 2011, 86500 patients on the deceased donor waiting list, and almost 28000 were added to the list annually in the United States. Ten thousand patients received deceased donor KT, and 4900 patients received living KT. Almost 5000 patients died while waiting for a kidney. The median waiting time depended on the blood type of patients, but it is reported to be around 4 years for all patients on the OPTN report<sup>[5]</sup>. Various reports analysing graft and patient survival related to the waiting time showed that 6 mo or more of dialysis negatively affect the outcome<sup>[6,7]</sup>. PKDE is an innovative method whereby 2 or more incompatible donor-recipient pairs exchange donors to create 2 or more compatible pairs. It is a very reasonable idea for human leukocyte antigen (HLA) sensitized and/or ABO incompatible patients. This primary idea was reported first by Rapaport in 1980s<sup>[8]</sup>. There are currently several variations of exchange such as three-way, four-way and domino paired donation<sup>[9]</sup>. PKDE provides a recipient with an incompatible donor the chance to receive a compatible kidney, which is available by expanding the donor source and reducing the waiting time for deceased donor KT. Advantages of PKDE are low immunological risk, avoidance of intensified immunosuppression due to desensitization, and cost effectiveness<sup>[10]</sup>.

Alexandre *et al*<sup>[11]</sup> demonstrated the ABOi-KT strategy using plasmapheresis and splenectomy to break the ABO barrier. This has been used as a desensitization strategy for ABOi-KT for 20 years. ABOi-KT has become common in Japan due to the lack of deceased donors, and ABOi-KT has accounted for approximately 30% of all living-donor KT in that country.<sup>[12]</sup> On the contrary, a tiny proportion, only 738 cases (0.94%) of ABOi-KT were performed between 1995 and 2010 in the United States<sup>[4]</sup>, but this number is increasing annually. The same trend continues in the United Kingdom: over the last decade, there has been an increase of ABOi-KT from less than 10 per year to 100 per year representing 1.0% of living donor transplants performed<sup>[13]</sup>. This increase is possibly due to the fact that protocols have been simplified

**Table 1** Combination of blood type and compatibility

		Donor			
		A	B	O	AB
Recipient	A	-	+	-	+
	B	+	-	-	+
	O	+	+	-	+
	AB	-	-	-	-

+: ABO incompatible transplantation; -: ABO compatible transplantation.

over the years from complex surgical and pharmacological processes that variably may have involved splenectomy, rituximab (RIT), plasmapheresis and antibodies titration.

Although the use of ABOi-KT has increased worldwide, there are arguments against ABOi-KT as a universal treatment. To consider whether ABOi-KT is viable a therapeutic option for patients with ESKD, this review will focus on the transitional outcomes alongside current and future prospects in ABOi-KT.

## ABO ANTIGENS AND ANTIBODIES

The concept of blood groups A, B and O (H) was established by Nobel laureate Karl Landsteiner in the early 1900s. These are polysaccharide antigens which are found in red cell, platelets, and other tissues such as endothelium<sup>[14]</sup>. The antibodies to blood group antigen are isohemagglutinins and can be of either immunoglobulin M (IgM) or immunoglobulin G (IgG) type antibodies. However, in the context of transplantation it is IgG that is functionally significant. Blood type A develops anti-B antibody, and blood type B has anti-A antibody. Blood type AB with A and B antigen has both antibodies, while blood type O with both antibodies does not have any antigen. Blood type incompatibility means the exposure of A or B antigen to a person who has antibodies against these antigens. Therefore, these antigen expressions of an organ have been obstacles for ABOi-KT (Table 1). All blood type recipients accept a blood type O donor as a universal donor, and a blood type AB accepts all blood type donors as a universal recipient. Blood group type A, however, carries A1 or A2. The expression of A2 antigen is weaker than that of A1 antigen<sup>[15]</sup>. The A2 subtype constitutes approximately 20% of blood type A in white races, while it is only 0.15% in Japanese population<sup>[16]</sup>. A2 kidney may be less likely to suffer antibody rejection in the presence of anti-A antibody. In fact, non-A recipients receiving kidneys from A2 donors<sup>[17]</sup>, can universally and safely accept the transplantation without preconditioning at times of KT.

## HISTORY

### *Splenectomy, rituximab and no B-cell depletion*

Previous clinical studies related to ABOi-KT are summarized in Table 2<sup>[1-4,11,18-42]</sup>. The first successful report of ABOi-KT is dated back to 1987 when authors achieved long-term allograft survival in a series of 23 patients<sup>[11]</sup>. Plasmapheresis and splenectomy were performed to re-

**Table 2** Historical clinical reports in ABO incompatible kidney transplantation

Ref.	Type of study	Study population	ABOi population	Desensitization	Outcome
Hume <i>et al</i> <sup>[18]</sup>	Observational	9	1	No treatment	Graft nephrectomy day 17
Starzl <i>et al</i> <sup>[19]</sup>	Observational	3	2	SPx (1 case)	Graft survival 74 d (1 case), patient death day 24 (1 case)
Sheil <i>et al</i> <sup>[20]</sup>	Observational	2	2	No treatment	Graft nephrectomy day 14
Alexandre <i>et al</i> <sup>[11]</sup>	Observational	23	23	PE/SPx	2-yr graft survival: 88% (related donor), 50% (unrelated donor)
Ota <i>et al</i> <sup>[21]</sup>	Observational, comparative	51	51	DFPP and/or IAs/SPx	2-yr graft survival: 87% vs 84.6% vs 50% (A- vs B- vs ABO-incompatible)
Tanabe <i>et al</i> <sup>[22]</sup>	Observational, comparative	433	67	DFPP and IAs/SPx	8-yr graft survival: 73% vs 80% (ABOi vs ABOc)
Ishida <i>et al</i> <sup>[23]</sup>	Observational	93	93	DFPP/SPx	5-yr graft survival: 73%
Ohta <i>et al</i> <sup>[24]</sup>	Observational, pediatric	10	10	DFPP or PE or IAs/SPx	5.4-yr graft survival: 100%
Shishido <i>et al</i> <sup>[25]</sup>	Observational, pediatric	16	16	PE and IAs/SPx	5-yr graft survival: 85%
Takahashi <i>et al</i> <sup>[2]</sup>	Observational, comparative	1496	441	DFPP or PE or IAs/SPx	9-yr graft survival: 59% vs 57% (ABOi vs ABOc)
Shimmura <i>et al</i> <sup>[26]</sup>	Observational, comparative	167	167	DFPP and/or IAs/SPx	5-yr graft survival: 74.3% vs 78.5% (CYA with AZ or MZ vs TAC or MMF)
Futagawa <i>et al</i> <sup>[27]</sup>	Observational, comparative	37803	191	NA	5-yr graft survival: 66.2% vs 79.5% (ABOi vs ABOc)
Ishida <i>et al</i> <sup>[28]</sup>	Observational, comparative	222	222	DFPP/SPx	5-yr graft survival: 73% vs 90% (CYA with AZ vs TAC with MMF)
Tyden <i>et al</i> <sup>[29]</sup>	Observational, comparative	334	60	IAs/RIT/IVIG	Graft survival: ABOi 97% (1.5-yr) vs ABOc 95% (1.8-yr)
Galliford <i>et al</i> <sup>[30]</sup>	Observational	10	10	PE/RIT/IVIG	1-yr graft survival: 100%
Genberg <i>et al</i> <sup>[31]</sup>	Observational, comparative	45	15	IAs/RIT/IVIG	Graft survival: ABOi 86.7% (3.4-yr) vs ABOc 86.7% (4.0-yr)
Oetli <i>et al</i> <sup>[32]</sup>	Observational	10	10	IAs/RIT/IVIG	1.3-yr graft survival: 100%
Toki <i>et al</i> <sup>[33]</sup>	Observational, comparative	57	57	DFPP/SPx	8-yr graft survival: 49% vs 95% (AAMR vs non-AAMR)
Wilpert <i>et al</i> <sup>[34]</sup>	Observational, comparative	83	40	IAs/RIT/IVIG	Graft survival: ABOi 100% (3.3-yr) vs ABOc 93% (1.5-yr)
Tyden <i>et al</i> <sup>[1]</sup>	Observational, comparative, pediatric	38	10	IAs/RIT/IVIG	Graft loss within 3 years: ABOi 1 case, ABOc 2 cases
Flint <i>et al</i> <sup>[35]</sup>	Observational, comparative	89	37	PE/IVIG	1-yr graft survival: 100% (ABOi vs ABOc)
Fichinoue <i>et al</i> <sup>[36]</sup>	Observational, comparative	393	113	DFPP or PE/SPx or RIT	5-yr graft survival: 88.4% vs 90.3% vs 100% (ABOc vs ABOi-SPx vs ABOi-RIT)
Habicht <i>et al</i> <sup>[37]</sup>	Observational, comparative	68	21	IAs/RIT/IVIG	1-yr graft survival: 100% (ABOi vs ABOc)
Lipshutz <i>et al</i> <sup>[38]</sup>	Observational	18	18	PE/RIT/IVIG	1-yr graft survival: 94.4%
Shirakawa <i>et al</i> <sup>[39]</sup>	Observational, comparative	74	74	DFPP/RIT	1-yr graft survival: 95.7% vs 98% (RIT 500mg vs RIT 200mg)
Shishido <i>et al</i> <sup>[3]</sup>	Observational, comparative, pediatric	323	52	PE/SPx or RIT	15-yr graft survival: 86% vs 78% (ABOi vs ABOc)
Montgomery <i>et al</i> <sup>[4]</sup>	Observational, comparative	78193	738	NA	10-yr cumulative incidence of graft loss: 27.1% vs 23.9% (ABOi vs ABOc)
Morath <i>et al</i> <sup>[40]</sup>	Observational, comparative	19	19	IAs or IAns/RIT/IVIG	1-yr graft survival: 100% (IAs vs IAns)
Uchida <i>et al</i> <sup>[41]</sup>	Observational	25	25	DFPP or PE/SPx or RIT	4.5-yr graft survival: 100%
Ashimine <i>et al</i> <sup>[42]</sup>	Observational, comparative	320	92	DFPP/SPx or RIT or none	5-yr graft survival: 87% vs 97.7% (ABOi vs ABOc)

ABOi: ABO incompatible; SPx: Splenectomy; PE: Plasma exchange; DFPP: Double-filtration plasmapheresis; IAs: Antigen-specific immunoadsorption; ABOc: ABO compatible; CYA: Cyclosporine; AZ: Azathioprine; MZ: Mizoribine; TAC: Tacrolimus; MMF: Mycophenolate mofetil; NA: Not available; RIT: Rituximab; IVIG: Intravenous immunoglobulin; AAMR: Acute antibody-mediated rejection; IAns: Non-antigen-specific immunoadsorption.

duce anti-blood type A or B (anti-A/B) antibody and to minimize the risk of hyperacute humoral rejection. Most of the modern desensitization protocols of ABOi-KT have been derived from their procedure and have since evolved. Their work was further greatly expanded in Japan due to the shortage of deceased donors with successful outcomes in ABOi-KT<sup>[2]</sup>.

Nowadays, splenectomy has been totally abandoned and the various desensitization protocols in use are combinations of antibody removal by plasmapheresis or immunoadsorption (IA), intravenous immunoglobulin (IVIG) to neutralize preformed antibodies, B lymphocyte depletion by anti-CD20 monoclonal antibody (RIT) and standard triple immunosuppression (calcineurin inhibitor, CNI; mycophenolate mofetil, MMF; and steroid). Recently, some authors reported successful outcomes of

ABOi-KT without RIT and splenectomy<sup>[35,42,43]</sup>.

## ABOi-KT PREOPERATIVE MANAGEMENT

Current strategies of ABOi-KT compose three common principles: (1) antibody measurement; (2) B-Cell depletion; and (3) antibody depletion.

### Antibody measurement

Assessment of anti-A/B antibody titer is crucial in ABOi-KT. It guides the effectiveness of operative preconditioning and determines the period to permit transplantation. In addition, posttransplant monitoring helps early detection of antibody-mediated rejection (AMR) by antibody rebound.

There are various measurement methods of anti-A/

B titer, the most common used are tube technique, gel technique and flow cytometry<sup>[44-48]</sup>. Although each center uses their familiar technique, there is a discrepancy of measured titer level. Kobayashi *et al*<sup>[46]</sup> surveyed the differences of anti-A/B titers from the same blood samples which were measured by tube test in 29 Japanese centers. It was revealed that inter-institutional differences were 1:8 to 1:32 in IgM and 1:16 to 1:256 in IgG, because of low reproducibility by visual observation. Therefore, they concluded standardized measurement should be necessary. Kumlien *et al*<sup>[47]</sup> analyzed the same blood samples in three centers. They also pointed out an inter-center variation of titer level using tube technique and suggested that gel technique is more reproducible than tube technique. Flow cytometry showed excellent reproducible compared with other techniques and would be suitable for the accurate measurement<sup>[48]</sup>. However, this technique is not available in all centers due to the expensive equipment required.

High preoperative anti-A/B IgG titers are associated with poor long-term allograft survival in ABOi-KT<sup>[49]</sup>. Gloor *et al*<sup>[50]</sup> showed preoperative high anti-A/B IgG titers is a predictor for AMR, and the rapid increasing of titers is also associated with AMR and graft loss. In addition, Tobian *et al*<sup>[51]</sup> also demonstrated that AMR was also associated with high titer at 1-2 wk posttransplant. Chung *et al*<sup>[52]</sup> described there was no statistically significant difference between high- (> 1:256) and low-titer (< 1:128) at the baseline in allograft function at 6 mo after transplantation. Therefore, appropriate monitoring of anti-A/B titer is essential before and after ABOi-KT. Although anti-A/B antibody titer has to be measured during the early period after ABOi-KT due to the risk of AMR, but how long the monitoring should be continued remains unclear. Preoperative titer should be low in ABOi-KT, but the acceptable titer of anti-A/B antibody at the time of transplant has varied between 1:4 and 1:32 in line with the protocol of individual centers<sup>[1,30-43,53-55]</sup>. After the ABO incompatible transplant necessitating initiation of antibody-depletion procedures, the level of anti-ABO antibody titer must be monitored to detect rebound in the serum antibody production.

### **B-cell depletion**

**Splenectomy:** Splenectomy was considered a prerequisite for desensitization protocol in ABOi-KT after Alexandre *et al*<sup>[11]</sup> reported that it reduced the risk of AMR. The principle of splenectomy was based on the concept that spleen is reservoir of antibody producing B-cells and antibody-producing plasma cells in the body. However, the efficacy of splenectomy in ABOi-KT is debatable, because severe AMR sometimes still occurs after splenectomy. The effect of splenectomy on the immune system is permanent. Following splenectomy the patients are at risk for the development of life-threatening sepsis, especially from encapsulated bacteria and they require life-long antibiotic prophylaxis. Splenectomy can lead to surgical complications such as hemorrhage, pancreatic

injury, pancreatic leakage, and portal vein thrombosis<sup>[56]</sup>.

A comparative analysis of splenectomized recipients compared with RIT treated but without splenectomy, showed no statistically significant difference in the anti-A/B titer of KT and liver transplantation<sup>[57,58]</sup>. It was concluded that splenectomy was not an essential prerequisite treatment in ABOi-KT. Although splenectomy has been replaced with RIT, Locke *et al*<sup>[59]</sup> reported that splenectomy could be useful as salvage treatment for severe AMR secondary to anti-HLA antibody. Current consensus states that splenectomy is not necessary for the induction of ABOi-KT.

**Rituximab:** Splenectomy has been largely replaced by RIT in ABOi-KT protocols to remove B-cell. RIT is an anti-CD20 monoclonal antibody, which binds to CD20 on immature and mature B-cell resulting in depletion of B-cell. RIT was originally developed for the treatment of non-Hodgkin's lymphoma<sup>[60]</sup>. RIT has been used extensively in the treatment of patients with autoimmune diseases and KT besides hematological malignancies<sup>[61]</sup>. Adverse events related to B-cell depletion by RIT include fever, chill, headache, and nausea<sup>[60]</sup>, whilst serious cardiovascular and pulmonary events are rare<sup>[61]</sup>.

In the field of KT, RIT has been used as part of desensitization protocols in ABO- and HLA-incompatible KT, treatment of AMR, post-transplant lymphoproliferative disorder, and recurrent nephrotic syndrome<sup>[62]</sup>. In the first experience of RIT use in ABOi-KT recipients, Sawada *et al*<sup>[63]</sup> tried RIT, splenectomy, and double-filtration plasmapheresis (DFPP) for A1 to O ABOi-KT with persistent high anti-A antibody titer. The dosage of RIT was 375 mg/m<sup>2</sup> per week for 4 wk pretransplant and there was no rebound of the titer after transplantation. Tydén *et al*<sup>[64]</sup> succeeded with 4 ABO incompatible recipients using RIT and antigen-specific IA (IAs) with standard immunosuppression, without splenectomy. In their protocol, RIT (375 mg/m<sup>2</sup>) was administered once 10 d prior to transplant which was enough to deplete peripheral B-cell. Moreover, its effect was long-active for at least 12 mo without any serious side effects. After these successful reports were published, RIT has replaced splenectomy in desensitization protocol. Recently, some have tried low dose of RIT or even omitting it in ABOi-KT protocol to avoid over-immunosuppression without compromising excellent outcomes<sup>[35,42,43,55]</sup>.

Twenty-seven recipients who were diagnosed with steroid-resistant cell-mediated rejection or AMR received a single dose of RIT (375 mg/m<sup>2</sup>) as a salvage treatment<sup>[65]</sup>: twenty-four (88.9%) among these demonstrated improved renal function. Serum creatinine decreased from a mean of 5.6 mg/dL before the treatment to a mean of 0.95 mg/dL after the treatment. RIT is useful not only in AMR, but also in chronic antibody-mediated rejection (CAMR) prevention. Kohei *et al*<sup>[66]</sup> observed that ABOi-KT with RIT had a statistically significant lower rate of CAMR at 2 years posttransplant than living ABOc-KT (3.5% *vs* 28.9%). However, this beneficial effect of RIT



needs independent verification.

### Antibody depletion

The antibody depletion treatments are the basis of ABOi-KT. In order to eliminate existing anti-A/B antibody, plasma exchange (PE), DFPP and IA<sup>[67]</sup> are available. They differ in their mechanisms of action, specificity, efficiency and cost.

In PE, plasma is removed and replaced by human albumin, colloid solutions, and/or fresh frozen plasma (FFP). It has been widely used around the world for antibody removal in ABOi-KT. This method is simple, but it has several disadvantages compared with more specific techniques. Because of non-selective apheresis, PE removes not only anti-A/B antibody, but also coagulation factors and anti-viral/-bacterial immunoglobulin. Consequently, the risk of bleeding and infection is increased. FFP is generally needed for the last session before KT to prevent these complications. Other complications were reported by Tobian *et al*<sup>[68]</sup>. In all PE sessions ( $n = 512$ ), the total rate of complications was 15.4%. The most common complication was hypocalcemia (6.8%), followed by urticaria or pruritus (4.3%), hypotension (2.9%) and nausea or vomiting (1.2%).

DFPP is designed to remove selectively the immunoglobulin from plasma and requires less substitution fluid compared to PE. When plasma separated by a first filter is passed through a second filter, IgG and IgM are filtered out and discarded. By single DFPP, 70% of IgM and 60% of IgG were removed and a one-fold titer reduction of anti-A/B antibody was observed<sup>[69]</sup>. This technique also avoids the loss of coagulation factors and albumin unlike PE. However, significant amounts of albumin are lost by DFPP, and almost always albumin is needed as the replacement fluid. DFPP is also removes variable amount of fibrinogen<sup>[70]</sup>, and its measurement is necessary to avoid bleeding complication.

IA can be A/B antigen IAs or A/B non-antigen IAs (non-specific/semi-selective immunoadsorption) respectively if it removes only a specific antibody such as anti-A/B antibody or removes non-antigen-specific immunoglobulin. Between the two techniques IAs is most utilized method in ABO incompatible setting. On the other hand, IAs is suitable for the elimination of HLA antigens and it is most used in HLA incompatible/ABOi KT recipients. In IAs, the plasma is processed through an ABO immunoadsorbent column, which is coated with either blood type A or B antigens and allow selective removal of anti-A or B antibody, and the processed plasma is re-infused into the patient. Volume replacement is not necessary. IAs is selective and free from side effects of PE and DFPP. Single IAs reduces 2- to 4-fold titer between pre- and post-IAs, and at least four preoperative IAs are usually needed to obtain an acceptable titer at the expense of increased cost compared to PE and DFPP<sup>[67]</sup>. IAs is generally safer and more effective, and therefore normally preferred. However, ultimate choice depends on each center's decision, based on the availability of infrastructure and skill mix of staff.

## USE OF IVIG

IVIG's recognized immunomodulatory properties have been employed for the treatment of autoimmune diseases<sup>[71]</sup>. IVIG is believed to act through various mechanisms: (1) complement down-regulation; (2) interactions with the Fc receptors; (3) inhibit of B/T-cell proliferation; (4) inhibit of CD8 T-cell cytotoxicity; and (5) increased apoptosis of B-cell<sup>[71-73]</sup>. Mild and early adverse effects of IVIG include headache, chill, nausea, fatigue, myalgia, arthralgia, chest pain, back pain, and elevated blood pressure<sup>[74,75]</sup>. However, rare but serious delayed adverse effects include renal toxicity, thromboembolic events (cerebrovascular accident and deep venous thrombosis), neurological toxicity (aseptic meningitis), hematological toxicity (neutropenia), and dermatological toxicity<sup>[76]</sup>. The administration of high dose IVIG can cause hemolysis by anti-A/B antibody within the IVIG<sup>[77]</sup>. In ABOi-KT, it is preferable if possible to use IVIG with low anti-A/B titer in order to avoid not only hemolysis but also AMR after transplantation due to anti-A/B titer elevation.

There is no uniformity in the dose IVIG used in the desensitization protocols of ABOi-KT<sup>[1, 30-32,34,35,37,38,40,43,54,78]</sup>. IVIG is usually administered after plasmapheresis, to reconstitute the natural levels of IgG. In the absence of control data, the use of IVIG in ABOi-KT can best be described as empirical.

## ACCOMMODATION

Without adequate anti-A/B antibody reduction and desensitization before KT, an incidence of AMR and irreversible damage cannot be avoided. Successful ABOi-KT requires the reduction of anti-A/B antibody titers against ABO antigens on the graft at the time of KT. However, anti-A/B antibody titer returns to the baseline level within almost 1 wk after KT<sup>[11,79,80]</sup>, even if optimal desensitization is performed. Therefore, intense monitoring is necessary during critical first two weeks after ABOi-KT<sup>[12]</sup>. Paradoxically, a phenomenon of accommodation is acquired in this term.

Accommodation is defined as a phenomenon whereby graft rejection is avoided despite reemergence of incompatible antibody. The mechanism was originally discovered in the field of xenotransplantation<sup>[81]</sup>, whereby endothelial cell posttransplant humoral injury was avoided, possibly due to changes of antibody specificity, avidity, affinity and alteration of the antigen structure. This phenomenon is allegedly responsible for normal graft function and structure despite reemergence of anti-A/B antibody against incompatible A or B antigen in the graft<sup>[82]</sup>. However, it is fair to accept that mechanism as well as the very existence of accommodation remains speculative.

## CURRENT PROTOCOL OF ABOi-KT

In ABOi-KT, intensified immunosuppressive protocol usually starts before KT in order to deplete anti-A/B

antibody. Many centers have modified original successful protocol of ABOi-KT<sup>[11]</sup>. The splenectomy-free protocols published in the last decade are summarized in Table 3<sup>[1,30-32,34-43,53-55,78]</sup>. RIT has been adopted in the place of splenectomy by majorities of centers. However, the timing and dose of RIT administered remains variable. RIT or splenectomy-free protocols have successfully, used low dose IVIG after plasmapheresis. The basis of the North Europe protocol is IAs followed by high dose IVIG. However, postoperative IAs is not performed routinely and its use is determined by antibody titers<sup>[83]</sup>. Maintenance immunosuppressive agents are mostly triple agents which are CNI, MMF and steroid. Tacrolimus is the CNI of choice in these ABOi-KT protocols. MMF was taken 7-14 d pretransplant in order to inhibit antibody production. Some centers use a protocol without daclizumab, basiliximab or antithymocyte globulin, and report excellent outcomes. Thus it is controversial whether these clonal antibodies should be introduced in ABOi-KT or not. All protocols of ABOi-KT have resulted in satisfactory outcome in the absence of randomized control trials. It is impossible to select an ideal protocol fit for all purpose.

## MINIMIZE IMMUNOSUPPRESSION

Efforts have been made to minimize immunosuppression in order to reduce the long-term risk of over-immunosuppression<sup>[84,85]</sup>. The long-term effect of steroid use remains unclear in ABOi-KT. Oetl *et al*<sup>[86]</sup> described 11 ABOi-KT recipients with late steroid withdrawal. Six recipients showed biopsy-proven acute rejection during or soon after steroid cessation. However, Galliford *et al*<sup>[30]</sup> tried early steroid sparing protocol in 10 recipients. Prednisolone was maintained at 1 mg/kg until 3 d posttransplant. It was reduced to 0.5 mg/kg at 4 d posttransplant, and discontinued after 1 wk posttransplant. In this study, patient and graft survival were 100% at 1 year posttransplant but 3 patients experienced acute rejection within 1 mo after transplantation.

## HISTOLOGICAL FINDINGS IN ABOI-KT

In ABOi-KT, acute AMR by anti-A/B antibody is a well-recognized cause of early graft loss. Diagnosis of acute AMR needs C4d staining in the peritubular capillary (PTC) and the presence of anti-donor antibodies<sup>[87,88]</sup>. Morphologic changes include acute tubular necrosis, capillary and/or glomerular inflammation, and transmural arteritis and/or arterial fibrinoid change. C4d staining is the hallmark of humoral induced complement activation and like ABOc-KT was thought to be a useful indicator of AMR even in the setting of ABOi-KT<sup>[89]</sup>. However, C4d deposition without AMR was seen in 85.7% of ABOi-KT at 3 mo posttransplant<sup>[90]</sup>. Setoguchi *et al*<sup>[91]</sup> analyzed protocol biopsies of ABOc-KT and ABOi-KT. C4d expression of PTC was detected in 94% of ABOi-KT, whereas in only 11% of ABOc-KT. In protocol biopsies during stable allograft function, 80% of ABO incompatible grafts

showed as C4d positive, while 74% of HLA incompatible grafts were C4d negative<sup>[92]</sup>. These histological studies indicate that the detection of C4d alone in ABO incompatible graft does not indicate AMR and support a concept of accommodation in ABOi-KT. Therefore, AMR after ABOi-KT can only be diagnosed on the basis of morphological evidence, serological evidence and the clinical course.

Morphologically transplant glomerulopathy (TG) at 1 year after transplantation was reported as an indicator of poor outcome<sup>[93]</sup>. ABOi-KT had more severe TG than ABOc-KT without HLA antibody at 1 year posttransplant<sup>[94]</sup>. However, there were no differences in interstitial fibrosis, tubular atrophy, chronic vasculopathy and allograft function between both groups. In the absence of prior AMR, histological change at 1 year posttransplant was mild irrespective of ABO compatibility. Moreover, prior AMR in ABOi-KT was associated with TG and interstitial fibrosis and not to arteriolar hyalinosis and chronic vasculopathy<sup>[91]</sup>. Consequently, ABO incompatible grafts with TG and/or interstitial fibrosis had lower GFR at 1 year after transplantation than those with normal histology.

## THE INCIDENCE OF ACUTE CELLULAR AND ANTIBODY MEDIATED REJECTION IN ABOI-KT

As previously described, the outcome of graft survival in ABOi-KT has been similar to ABOc-KT. However, there is an increased risk of AMR in ABOi-KT due to anti-A/B antibody. Protocol biopsies at 3 mo posttransplant in ABOi-KT had a significantly higher incidence of AMR compared to ABOc-KT (17.9% *vs* 1.1%). However, there was no significant difference in the rate of acute cellular rejection between ABOi-KT and ABOc-KT (48.4% *vs* 35.7%)<sup>[90]</sup>. In the acute lesion score based on Banff classification<sup>[95]</sup>, *t*2-3 and *g*2-3 following ABOi-KT was higher than that of ABOc-KT (*t*2-3: 42.9% *vs* 19.4%, *g*2-3: 28.6% *vs* 6.5%). Gloor *et al*<sup>[94]</sup> described in the study of protocol biopsies at 1 year posttransplant that there was a significant difference in the incidence of acute rejection between ABOi-KT and ABOc-KT without HLA antibody (50% *vs* 13.6%). Acute rejection in ABOi-KT was mainly AMR (73.3%) as compared to ABOc-KT without HLA antibody (12.5%). Setoguchi *et al*<sup>[91]</sup> also compared the histologic findings of protocol biopsies in 48 ABO incompatible and 133 compatible grafts. There was no difference in clinical and subclinical rejection between ABO incompatible and compatible grafts (clinical: 37.5% *vs* 25.6%, subclinical: 10.4% *vs* 15%). However, ABO incompatible grafts had a high incidence of AMR compared to ABO compatible grafts (27% *vs* 5.3%). Interestingly, rejection was detected in only 15.0% at 1 mo in ABOi-KT compared to 34.7% in ABOc-KT, but in 30.0% at 6-12 mo compared to 10.5%. Wilpert *et al*<sup>[34]</sup> demonstrated that the rejection rates in ABOi-KT were similar to that in ABOc-KT. Acute cellular rejection was

**Table 3 Current protocols for ABO incompatible kidney transplantation**

Author	Country, year	Rituximab dose	Pretransplant IS	Antibody depletion	IVIG	Target titer at the time of transplantation	Induction IS	Maintenance IS	Posttransplant antibody depletion
Adult recipients									
Rituximab protocol									
Saito <i>et al</i> <sup>[53]</sup>	Japan, 2006	375 mg/m <sup>2</sup> (twice) at -14 and -1 d	MMF/MP at -1 Mo	DFPP or PE	-	< 1:16	BAS (20 mg at 0 and 4 d)	CYA/MMF/MP	-
Tyden <i>et al</i> <sup>[54]</sup>	Sweden, 2006	375 mg/m <sup>2</sup> (once) at -1 mo	TAC/MMF/Pred at -13 d	IAs	0.5 g/kg after last IAs	< 1:8	-	TAC/MMF/Pred	IAs, 3 times
Chikaraishi <i>et al</i> <sup>[55]</sup>	Japan, 2008	100 mg/m <sup>2</sup> (twice) at -8 and -1 d	MMF/MP at -14 d, TAC at -3 d	DFPP and PE	-	< 1:8	BAS (20 mg at 0 and 4 d)	TAC/MMF/MP	-
Galliford <i>et al</i> <sup>[50]</sup>	United Kingdom, 2008	1000 mg (twice) at first day of PE and at the operative day	TAC/MMF at -14 d	PE	0.1 g/kg after each PE	< 1:4	DAC (2 mg/kg at 0 and 14 d)	TAC/MMF/Pred	PE at 1 and 3 d
Genberg <i>et al</i> <sup>[31]</sup>	Sweden, 2008	375 mg/m <sup>2</sup> (once) at -1 mo	TAC/MMF/Pred at -10 d	IAs	0.5 g/kg at -1 d	< 1:8	-	TAC/MMF/Pred	IAs, 3 times
Oettl <i>et al</i> <sup>[32]</sup>	Switzerland, 2009	375 mg/m <sup>2</sup> (once) at -1 mo	TAC/MMF/Pred at -14 d	IAs	0.5 g/kg after last IAs	< 1:8	BAS (20 mg at 0 and 4 d)	TAC/MMF/Pred	IAs or PE (not routinely)
Sivakumaran <i>et al</i> <sup>[78]</sup>	United States, 2009	375 mg/m <sup>2</sup> (once) at -3 wk	MMF at -1 mo	PE	2 g/kg after last PE	NA	ALE (1 mg/kg at 0 and 14 d)	TAC/MMF/Pred	-
Wilpert <i>et al</i> <sup>[34]</sup>	Germany, 2010	375 mg/m <sup>2</sup> (once) at -1 mo	TAC/MMF or MPS/Pred at -7 d	IAs	0.5 g/kg at -1 to -5 d	< 1:4	BAS (20 mg at 0 and 4 d)	TAC/MMF/Pred	IAs (not routinely)
Fuchinoue <i>et al</i> <sup>[36]</sup>	Japan, 2011	100-1000 mg, 1-3 times	CYA or TAC/MMF at -2 d	DFPP or PE	-	< 1:16	BAS (20 mg at 0 and 4 d)	CYA or TAC/MMF/steroid	-
Habicht <i>et al</i> <sup>[37]</sup>	Germany, 2011	375 mg/m <sup>2</sup> (once) at -1 mo	TAC/MMF/Pred at -1 mo	IAs	30 g at -1 to -2 d	< 1:8	-	TAC/MMF/MP	IAs (not routinely)
Lipshutz <i>et al</i> <sup>[38]</sup>	United States, 2011	375 mg/m <sup>2</sup> (once) at -1 mo	TAC/MMF at the first day of PE	PE	10 g after each PE	< 1:8	ATG (1.5 mg/kg for 4 d)	TAC/MMF/Pred	PE (not routinely)
Shirakawa <i>et al</i> <sup>[39]</sup>	Japan, 2011	500 or 200 mg/m <sup>2</sup> (once), at -5 to -7 d	TAC/MMF/MP at -7 d	DFPP	-	< 1:32	BAS (20 mg at 0 and 4 d)	TAC/MMF/MP	-
Morath <i>et al</i> <sup>[40]</sup>	Germany, 2012	375 mg/m <sup>2</sup> (once) at -1 mo	TAC/MMF/MP at the first day of IAs	IAs	0.5 g/kg after last IAs	< 1:16	BAS (20 mg at 0 and 4 d)	TAC/MMF/MP	IAs or PE (not routinely)
Uchida <i>et al</i> <sup>[41]</sup>	Japan, 2012	150 mg/m <sup>2</sup> (twice) at -14 and 0 d	MMF/MP at -1 Mo, CYA or TAC at -3 d	DFPP or PE	-	< 1:16	BAS (20 mg at 0 and 4 d)	CYA or TAC/MMF/MP	-
Rituximab-free protocol									
Montgomery <i>et al</i> <sup>[43]</sup>	United States, 2009	-	TAC/MMF at the first day of PE	PE	0.1 g/kg after each PE	< 1:16	DAC (2 mg/kg initial dose, 1 mg/kg every 2 wk for total 5 doses)	TAC/MMF/Pred	PE, at least twice (with IVIG 0.1 g/kg)
Flint <i>et al</i> <sup>[35]</sup>	Australia, 2011	-	MMF at -10 to -14 d	PE	0.1 g/kg after each PE	< 1:8	BAS (20 mg at 0 and 4 d)	TAC/MMF/Pred	PE (not routinely)
Ashimine <i>et al</i> <sup>[42]</sup>	Japan, 2013	-	MMF at -14 d	DFPP	-	< 1:8	BAS (20 mg at 0 and 4 d)	CYA or TAC/MMF/Pred	-
Pediatric recipients									
Genberg <i>et al</i> <sup>[31]</sup>	Sweden, 2008	375 mg/m <sup>2</sup> (once) at -1 mo	TAC/MMF/Pred at -10 d	IAs	0.5 g/kg at -1 d	< 1:8	-	TAC/MMF/Pred	IAs, 3 times
Tyden <i>et al</i> <sup>[1]</sup>	Sweden, 2011 <sup>[1]</sup>	375 mg/m <sup>2</sup> (once) at -1 mo	TAC/MMF/Pred at -13 d	IAs	0.5 g/kg after last IAs	< 1:8	-	TAC/MMF/Pred	IAs, 3 times

IS: Immunosuppression; IVIG: Intravenous immunoglobulin; MMF: Mycophenolate mofetil; MP: Methylprednisolone; DFPP: Double-filtration plasmapheresis; PE: Plasma exchange; BAS: Basiliximab; CYA: Cyclosporine; TAC: Tacrolimus; Pred: Prednisolone; IAs: Antigen-specific immunoadsorption; DAC: Daclizumab; NA: Not available; ALE: Alemtuzamab; MPS: Mycophenolate sodium; ATG: Antithymocyte globulin.

**Table 4 Pro and cons for ABO incompatible kidney transplantation**

Pro ABOi-KT
Reducing waiting list and time
Expanding living donor pool
Improvement of patient's prognosis
Excellent graft survival (comparable with ABOc-KT)
Contra ABOi-KT
Comparative high immunological risk
Higher incidence of acute AMR
Intensified immunosuppression
Antibody depletion therapy
Increasing expenditure
Higher incidence of viral infection

ABOi-KT: ABO incompatible kidney transplantation; ABOc-KT: ABO compatible kidney transplantation; AMR: antibody-mediated rejection.

detected in 23.2% of ABOi-KT and in 22.5% of ABOc-KT. Acute AMR was shown in 4.7% of ABOi-KT, which was similar to ABOc-KT (5.0%).

## ADVERSE EFFECT OF ABOI-KT

### Infection

The improvement in ABOi-KT graft survival rate has come at the expense of increased posttransplant infection. The infection rate in ABOi-KT is significantly higher than in ABOc-KT (60% *vs* 29.8%)<sup>[37]</sup>. The rates of infection including cytomegalovirus (CMV), herpes simplex virus, varicella zoster virus and BK virus (BKV) in ABOi-KT were also significantly higher than in ABOc-KT. The most common viral infection was BKV in 25% of ABOi-KT compared to only 8.5% of ABOc-KT. However, the incidences of rejection, graft survival rate and function of ABOi-KT patients were compatible with those of ABOc-KT patients. On the contrary, Genberg *et al*<sup>[31]</sup> showed that there was no statistical difference in overall infection complications between ABOi-KT with RIT and living ABOc-KT (40% *vs* 63.3%). However, ABOi-KT patients who were treated with RIT, may have had different infection profiles. Grim *et al*<sup>[96]</sup> retrospectively analyzed the incidence of posttransplant infection in HLA sensitized KT or ABOi-KT treated with RIT and compared to HLA sensitized KT without RIT. The acute rejection rate in RIT treated KT was similar to KT without RIT (40% *vs* 33%). However, posttransplant infection rate was 48.0% RIT with KT, but only 11.1% without RIT. Kamar *et al*<sup>[97]</sup> reported that infection rate was 45.5% in KT with RIT which was similar to KT without RIT (53.9%). Bacterial, viral and fungal infection were observed in 36.3%, 18.2% and 16.9% in KT with RIT, against 31.6%, 34.3% and 5.32% in KT without RIT. Polyoma virus infection rate (64.3%) was relatively high in RIT. Moreover, infection related-death was significantly higher in RIT treated patients. This data ascertained that RIT was associated with severe infection which causes death rather than an increased risk of infection. Other report confirmed earlier observation showing that the incidence of posttransplant infection in RIT-treated recipients was similar to RIT-

untreated recipients (52.2% *vs* 40.2%)<sup>[98]</sup>. However, as in earlier studies the incidences of CMV and BKV infection in RIT-treated recipients were higher than in non RIT-treated recipients (CMV: 16.4% *vs* 5.7%, BKV: 13.4% *vs* 8.0%).

### Malignancy

It is generally accepted that immunosuppression is associated with an increased incidence of malignancy in KT recipients compared to the general population<sup>[99]</sup>. However, several studies have demonstrated that ABOi-KT did not increase the risk of posttransplant malignancy compared with ABOc-KT. Yamamoto *et al*<sup>[100]</sup> analyzed the risk of ABOi-KT compared to ABOc-KT retrospectively. ABOi-KT recipients were older than ABOc-KT recipients and all ABOi-KT recipients received splenectomy, in this study despite increased age and splenectomy<sup>[101,102]</sup>, there was no significant difference in the incidence of malignancy between ABOi-KT and ABOc-KT (4.8% and 4.2%). Similarly, Hall *et al*<sup>[103]</sup> showed that 7 of 318 ABOi-KT recipients experienced posttransplant cancer. The incidence rate ratio (IRR) of cancer in ABOi-KT was identical to that in matched control ABOc-KT (IRR: 0.99). This limited data reassuringly indicates that ABOi-KT is not associated with an increasing incidence of malignancy after KT. Thus, a further analysis of long-term observations in ABOi-KT after RIT is needed.

## COST OF ABOI-KT

It is recognized that KT is a cost-effective option over dialysis<sup>[104-106]</sup>. The estimated cost for ABOi-KT over 20 years was \$315600, which was approximately 15% lower than dialysis<sup>[107]</sup>. ABOi-KT is more expensive than ABOc-KT because of requirement for desensitization and removal of anti-A/B antibody. The cost of ABOi-KT in the first 90 d posttransplant is \$90300 compared to \$52500 for ABOc-KT<sup>[108]</sup>. The additional cost of ABOi-KT amounts to €31948 for IAs, RIT, IVIG, and prolonged hospital stay<sup>[31]</sup>. The cost of single IA is approximately €4340-1433<sup>[40]</sup>. However, despite more expensive, ABOi-KT is still more cost-effective than dialysis in the long-term and delivers a better quality of life.

## CONCLUSION

Since first performed over 50 years ago, ABOi-KT has become an accepted source of KT. Reassuringly, despite lack of control trials in ABOi-KT, more than satisfactory outcomes have been observed in adult and pediatric recipients, in many studies equivalent to living ABOc-KT. ABOi-KT also has disadvantages in spite of excellent outcomes (Table 4). Preconditioning treatment of ABOi-KT, such as antibody reduction and desensitization, is more intensified and complicated than that of ABOc-KT. With current protocols, the occurrence of early graft loss and AMR are not completely abolished. Preconditioning strategy in ABOi-KT has evolved over time. RIT has replaced splenectomy which was once thought a cru-



cial procedure for ABOi-KT, although this is increasingly abandoned in favor of IAs and IVIG. Overall, ABOi-KT is more expensive than ABOc-KT which may restrict its adoption in resource poor countries. We believe that a live donor ABOi-KT is a viable alternative to waiting on deceased donor list.

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