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Individualized Preconditioning for ABO-Incompatible Living-Donor Kidney Transplantation: An Initial Report of 48 Cases from China

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Background: ABO-incompatible (ABOi) living-donor kidney transplantation (KTx) is well established in developed countries, but not yet in China.

Material/Methods: We developed individualized preconditioning protocols for ABOi KTx based on initial ABO antibody titers. After propensity score matching of ABOi with ABO-compatible (ABOc) KTx, post-transplant outcomes were compared.

Results: Between September 2014 and June 2018, 48 ABOi living-donor KTx candidates received individualized preconditioning, and all underwent subsequent KTx (median initial ABO titers: 16 for IgM and 16 for IgG). Thirty-one recipients (64.6%) were preconditioned with rituximab (median dose: 200 mg, range: 100–500 mg). Among 37 patients (77.1%) who received pre-transplant antibody removal, the median number of sessions of antibody removal required to achieve ABOi KTx was 2 (range: 1–5), which was conducted between days –10 and –1. Eleven ABOi recipients (22.9%) were preconditioned with oral immunosuppressants alone. Hyperacute rejection led to the loss of 2 grafts in the ABOi group. After a median follow-up of 27.6 months (ABOi group) and 29.8 months (ABOc group), there were no significant differences in graft/recipient survival, rejection, and infection. There were marginally higher rates of severe thrombocytopenia (<50×10^9/L) (P=0.073) and delayed wound healing (P=0.096) in ABOi recipients.

Conclusions: Our individualized preconditioning protocol evolved as our experience grew, and the short-term clinical outcomes of ABOi KTx did not differ from those of matched ABOc patients. ABOi KTx may be a major step forward in expanding the kidney living-donor pool in China.

MeSH Keywords: **ABO Blood-Group System • China • Immunologic Desensitization • Kidney Transplantation • Living Donors**

Abbreviations: **ABOi** – ABO-incompatible; **ABOc** – ABO-compatible; **AMR** – antibody-mediated rejection; **ATG** – antithymocyte globulin; **CMR** – cell-mediated rejection; **DFPP** – double-filtration plasmapheresis; **EC-MPS** – enteric-coated mycophenolate sodium; **eGFR** – estimated glomerular filtration rate; **IVIG** – intravenous immunoglobulins; **KTR** – kidney transplant recipient; **KTx** – kidney transplantation; **MMF** – mycophenolate mofetil; **PE** – plasma exchange; **PRA** – panel reactive antibodies; **Pred** – prednisone; **SCr** – serum creatinine; **Tac** – tacrolimus

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3053 5 3 29

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Background

Kidney transplantation (KTx) from living donors has substantially increased the number of available kidneys for patients with end-stage renal disease [1–4]. However, one-third of potential living donors are ABO-incompatible (ABOi) with their intended recipients [5]. An alternative for candidates with no ABO-compatible (ABOc) donors is ABOi KTx [6,7]. To prevent hyperacute rejection [8], pre-existing anti-donor ABO antibodies must be removed before ABOi KTx, and antibody rebound must be prevented after transplantation [9]. Most transplant centers use highly uniform preconditioning protocols for all ABOi recipients [10]. Increasing experience with ABOi KTx has led to attempts to reduce the preconditioning intensity by administering lower doses of rituximab, fewer sessions of antibody removal, or both, which should decrease the risk of infectious and hemorrhagic complications [11–13]. After more than 2 decades of experience, graft and recipient survival are now comparable for ABOi and ABOc KTx [14–16].

With these encouraging results, KTx from ABOi living donors was introduced to China in 2006 [17]. Initial attempts at ABOi KTx in China were sporadic and experienced high rates of early graft loss and coagulation disorders. West China Hospital initiated an ABOi KTx program in September 2014, in which both preconditioning elements (rituximab and antibody removal) are based on initial ABO antibody titer. The hypothesis is that preconditioning can be individualized according to baseline titer and that patients with lower titers may require less intensive preconditioning. This protocol has led to a wider use of ABOi KTx in China, and the number of transplant centers using our protocol has grown rapidly. From September 2014 to June 2018, 48 consecutive ABOi living-donor KTx were performed at our institution.

This study describes the first case series of ABOi KTx recipients from China and presents our initial experience with individualized ABOi preconditioning regimens.

Material and Methods

Study population

This was a retrospective analysis of prospectively collected data of KTxs from living donors at our institution. All the ABOi candidates had no suitable ABOc living donor, and were informed regarding the potential complications and expected outcomes of ABOi KTx, then provided written informed consent for participation. Each KTx procedure from a living donor was approved by the Institutional Review Board of West China Hospital and the Health Commission of Sichuan Province. The first ABOi KTx was performed on September 12, 2014 and as of June 2018, 48 consecutive patients received our individualized preconditioning, and all ABOi underwent subsequent KTxs. During this time, our institution performed a total of 1074 ABOc KTxs from living donors. Propensity scores were used to match ABOc and ABOi recipients according to measured covariates (donor/recipient age, transplant surgical team, and maintenance immunosuppression) using a 1: 2 nearest neighbor matching algorithm.

This study protocol was reviewed and approved by the Biomedical Ethics Committee, West China Hospital (No. 2019SHEN418).

Measurement of ABO blood group antibody titers

Anti-donor IgG titers were measured using a gel card technique throughout the study period. IgM titers were initially measured using a tube test, but a gel card test was used after hyperacute rejection in Cases 10 and 19 [18].

Individualized preconditioning protocol

Table 1 shows the evolution of our individualized preconditioning protocols for ABOi KTx. Our first ABOi KTx followed the protocol of South China University, where the first ABOi KTx in China was performed [17]. The second ABOi kidney transplant recipient (KTR) received 400 mg of rituximab (200 mg on day –14, 200 mg day –7), oral tacrolimus (Tac)+mycophenolate mofetil (MMF)+prednisone (Pred) from day –7, and plasma exchange (PE) on days –3 and –1. The outcomes were successful and our preconditioning protocol was gradually modified to consider initial ABO antibody titers such that patients with lower initial titers received less preconditioning [19,20]. Splenectomy, immunoadsorption, and intravenous immunoglobulins (IVIG) were not used during preconditioning. If the target titer was not achieved on the anticipated transplant day, surgery was postponed and PE/double-filtration plasmapheresis (DFPP) was continued until the desired titer was achieved. Post-transplant PE/DFPP was performed only when the antibody titer was at least 1: 32 or when there was suspicion of antibody-mediated rejection (AMR).

Immunosuppression and induction

All ABOi KTRs received triple oral immunosuppression 2 to 4 weeks before transplantation. This treatment consisted of Tac (3 mg/day), MMF (1500 mg/day) or enteric-coated mycophenolate sodium (EC-MPS, 1080 mg/day), and Pred (5 mg/day). Basiliximab (20 mg on days 0 and 4) or antithymocyte globulin (ATG; 1 mg/kg on days 0 to 3 or 0 to 4) were used for induction, depending on the perceived immunologic risk determined by panel reactive antibodies (PRA). On the transplant day, oral Tac and Pred were stopped, and the dose of mycophenolic

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Table 1. Evolution of individualized preconditioning protocols used for ABO incompatible living donor kidney transplantation in West China Hospital.

		Imitation period, Case #1 (Sept 2014)	Exploration period, Cases #2–19 (Dec 2014 – Jun 2016)	Improvement Period, Cases #20–34 (Jun 2016 – Apr 2017)	Stable period, Cases #35–48 (May 2017 – Jun 2018)
ABO antibody titer measurement		IgM by tube, IgG by gel	IgM by tube, IgG by gel	IgM by gel instead of tube, IgG by gel	IgM and IgG both by gel
Preconditioning principles		South China University preconditioning protocol (highly uniform preconditioning applied to all ABOi candidates indiscriminately)	Based on initial ABO antibody titers: ≤1: 16 OIs±PE/DFPP, >1: 16 OIs+rituximab+PE/DFPP	Based on initial ABO antibody titers: ≤1: 4 OIs alone, 1: 8 OIs+PE/DFPP, ≥1: 16 OIs+rituximab+PE/DFPP	Based on initial ABO antibody titers: ≤1: 8 OIs alone, 1: 16 OIs±PE/DFPP, ≥1: 32 OIs+rituximab+PE/DFPP
Preconditioning details	Rituximab	200 mg on Day –14, 200 mg on Day –7, 100 mg on Day 0	1 dose, 200–300 mg depending on the recipient's body weight, 2 weeks before transplant	1 dose, 200–300 mg depending on the recipient's body weight, 2 weeks before transplant	1 dose, 200 mg, 2–4 weeks before transplant; an additional 100 mg given if CD19+CD5+ B cell count ≥10/ul at 1 week after the first dose
	Initiation of OIs	Day –7	2 weeks before transplant	2 weeks before transplant	2–4 weeks before transplant
	Antibody removal	1 session of DFPP (Day –5) and 2 of PE (Days –3 and –1)	PE was the first choice; DFPP used if there was a continuous shortage of type AB fresh frozen plasma	PE still the first choice	PE and DFPP both preferable
Acceptable titer at transplant		1: 8	≤1: 16	≤1: 4*	≤1: 8–16
Notes		ABO antibody titer: initial: 32 (IgM), 16 (IgG); transplant day: 8 (IgM), 4 (IgG)	Two cases of hyperacute rejection leading to graft loss**	Starting to observe effect of rituximab on elimination of peripheral CD19+CD5+ B cells	/

* Cut-off, established after the two cases of hyperacute rejection, is based on safety concerns and an understanding that the inter-measurement variability of antibody titer may vary. ** The first case of hyperacute rejection: 24-year-old male, blood group O, received a blood-group A kidney from his father. His pretransplant PRA was 0. Intitial anti-A IgM titer was 128 and IgG was 16, which was reduced to 8 (IgM) and 4 (IgG) on the transplant day, after a single dose of rituximab (300 mg, day –14) and one course of DFPP (day –3). Immunosuppression was tacrolimus, prednisolone, and mycophenolate without induction. The anti-A titers immediately after transplantation were 2 (IgM) and 0 (IgG). The second case: 36-year-old female, blood group O, received a blood-group B kidney from her mother. Her pretransplant PRA was 21% but no HLA DSA. Intitial anti-B IgM titer was 4 and IgG was 16, which was reduced to 4 (IgM) and 4 (IgG) on the transplant day, after oral immunosuppressants alone with ATG induction. The anti-B titers immediately after KTx were 2 (IgM) and 0 (IgG). The intraoperative biopsies of the two grafts showed hyperacute rejection. OIs – oral immunosuppressants; PE – plasma exchange; DFPP – double-filtration plasmapheresis.

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Table 2. Medical background of kidney donors and recipients in the two groups.

	ABO incompatible group (n=48)		ABO compatible group (n=96)		P value
Donor					
Median age, years (range)	49.5	(34–63)	49	(22–65)	0.349
Male (%)	12	(25)	30	(31.3)	0.437
Median BMI, kg/m^2 (range)	23.5	(18.6–31.1)	23.6	(17.6–31.6)	0.869
Spouse of the recipients (%)	9	(18.8)	5	(5.2)	**0.022**
Recipient					
Median age, years (range)	30	(9–53)	29	(15–53)	0.146
Male (%)	35	(72.9)	67	(69.8)	0.697
Median BMI, kg/m^2 (range)	20.4	(14.8–32.6)	20.2	(14.7–31.6)	0.918
Cause of end stage renal failure					
Glomerulonephritis (%)	18	(37.5)	35	(36.5)	0.527
Non-glomerulonephritis (%)	14	(29.2)	21	(21.9)	
IgA nephropathy (%)	4	(8.3)	7	(7.3)	/
Lupus (%)	2	(4.2)	2	(2.1)	/
Polycystic (%)	2	(4.2)	5	(5.2)	/
Hypertensive (%)	2	(4.2)	2	(2.1)	/
Diabetic (%)	2	(4.2)	3	(3.1)	/
Obstructive (%)	1	(2.1)	1	(1.0)	/
Medication nephrotoxicity (%)	1	(2.1)	1	(1.0)	/
Unknown (%)	16	(33.3)	40	(41.7)	
Pretransplant dialysis (%)	47	(97.9)	91	(94.8)	0.664
Median duration on dialysis, months (range)	12	(0–96)	12	(0–108)	0.386
HLA mismatch (%)	3	(1–5)	3	(0–5)	0.060
PRA >0 (%)	19	(39.6)	11	(11.5)	**<0.001**
Second transplant	0		0		/
ABO-incompatibilitiesa					
A→O (%)	19	(39.6)	0		/
B→O (%)	11	(22.9)	0		/
A→B (%)	4	(8.3)	0		/
B→A (%)	4	(8.3)	0		/
AB→A (%)	6	(12.5)	0		/
AB→B (%)	4	(8.3)	0		/
AB→O (%)	0		0		/
Median warm ischemia time, s (range)	178	(114–300)	178	(96–489)	0.928

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Table 2 continued. Medical background of kidney donors and recipients in the two groups.

	ABO incompatible group (n=48)		ABO compatible group (n=96)		P value
Induction					
IL-2 receptor antagonist (%)	34	(70.8)	68	(70.8)	**0.011**
Antithymocyte globulin (%)	5	(10.4)	23	(24.0)	
No induction (%)	9	(18.8)	5	(5.2)	
Initial immunosuppression					
Tac+MPA+Pred (%)	48	(100)	94	(97.9)	0.552
CsA+MPA+Pred (%)	0		2	(2.1)	

[a] We did not subtype blood group A into A1 and A2 because the frequency of A2 in East Asian populations is below 1%; thus, most of our type A donors would have subtype A1. BMI – body mass index; HLA – human leukocyte antigen; ND – not determined; PRA – panel reactive antibody; Tac – tacrolimus; MPA – mycophenolic acid; Pred – prednisone; CsA – cyclosporin A.

acid was increased to 2000 mg/day (MMF) or 1440 mg/day (EC-MPS). ABOc KTRs began treatment with MMF/EC-MPS 1 day before transplantation and with Tac 2 days after transplantation. Intravenous methylprednisolone was administered intraoperatively at a dose of 500 mg, and at 200 mg/day on days 1 to 3, followed by oral Pred (60 mg/day, tapering to 5 mg/day within 2 weeks). Tac was re-initiated on post-transplant day 2, and the target trough level was 5 to 8 ng/mL during the first year after transplantation, and 4 to 6 ng/mL thereafter.

Coagulation monitoring and anticoagulation

Coagulation function was monitored at admission, after every session of PE/DFPP, and on days 0, 1, 3, and 5 after transplantation. If there was no bleeding tendency, ABOi KTRs received subcutaneous enoxaparin sodium (2000 AxaIU/day) from days 1 to 3 after transplantation, followed by oral aspirin (100 mg/day) for 1 month. ABOc KTRs received no routine anticoagulation treatment.

Statistical analysis

Categorical variables are presented as numbers (percentages) and continuous data as medians (minima, maxima). The baseline characteristics of the ABOi and ABOc KTRs were compared using the chi-square or Mann-Whitney U test, as appropriate. The differences in post-transplantation clinical complications in the ABOi and ABOc groups were tested by proportion test based on a binomial distribution. Graft and recipient survival rates were estimated by the Kaplan-Meier method, and differences in survival rates within patient subgroups were compared using univariate analysis with the log-rank test. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA), and a *P* value below 0.05 was considered significant.

Results

Annual number of ABOi kidney transplantations

From the start of the ABOi program in September 2014 to June 2018, the ABOi cases and percentages among all living-donor KTxs in West China Hospital were 2/105 (1.9%) from September to December 2014, 9/306 (2.9%) in 2015, 19/284 (6.7%) in 2016, 11/280 (3.9%) in 2017, and 7/147 (4.8%) from January to June 2018.

Baseline characteristics of ABOi and ABOc groups

After propensity score matching, the ABOi and ABOc groups had comparable baseline clinical and immunological characteristics, except that higher percentages of ABOi KTRs had a spousal relationship with the donor, were sensitized (PRA >0%), and did not receive induction therapy (Table 2).

Effect of individualized preconditioning regimens

Table 3 summarizes the individualized preconditioning regimens used for the 48 ABOi patients. In brief, 31 ABOi patients (64.6%) received rituximab; 2 patients received high doses (400 mg and 500 mg) and the others received low doses (≤300 mg), with an overall median of 200 mg (range: 100–500 mg). Among the 37 patients (77.1%) who received pre-transplant antibody removal, a median of 2 sessions (range: 1–5) were needed to achieve ABOi KTx between days –10 and –1.

The efficacy of the individualized preconditioning regimens is indicated by the significant decreases in anti-donor ABO antibody titers and peripheral blood CD19+CD5+ B cell counts and percentages (Figure 1). Detection of CD20 is affected by rituximab because rituximab binds CD20 and interferes with the

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Table 3. Summary of Individualized preconditioning regimens for the 48 ABO-incompatible living donor kidney transplantation recipients.

Median Initial anti-donor ABO antibody titer (range)	Individualized preconditioning regimen	ABOi patients (n)
IgM: 8 (0–16), IgG: 4 (0–16)	Oral immunosuppressants alone	11
IgM: 16, IgG: 16	+DFPP (one session)	1
IgM: 16 (8–16), IgG: 5 (0–8)	+PE (one session)	4
IgM: 16, IgG: 0	+DFPP (one session)+PE (one session)	1
IgM: 128 (16–128), IgG: 0 (0–16)	+rituximab+DFPP (one session)	3
IgM: 64 (16–256), IgG: 32 (4–64)	+rituximab+DFPP (two sessions)	7
IgM: 16 (16–64), IgG: 48 (0–64)	+rituximab+PE (one session)	4
IgM: 16 (16–256), IgG: 32 (0–128)	+rituximab+PE (two sessions)	8
IgM: 32 (16–128), IgG: 48 (32–64)	+rituximab+PE (three sessions)	4
IgM: 256, IgG: 0	+rituximab+DFPP (one session)+PE (one session)	1
IgM: 32, IgG: 16	+rituximab+DFPP (one session)+PE (two sessions)	1
IgM: 64, IgG: 4	+rituximab+DFPP (two sessions)+PE (one session)	1
IgM: 128, IgG: 64	+rituximab+DFPP (two sessions)+PE (two sessions)	1
IgM: 128, IgG: 32	+rituximab+DFPP (four sessions)+PE (one session)	1

PE – plasma exchange; DFPP – double-filtration plasmapheresis.

reaction of the reagents used in flow cytometric analysis [21]. In the field of ABOi KTx, most primary studies used CD19 as a surface marker of B cells after rituximab treatment. After ABOi KTx, 3 patients (6.3%) experienced ABO antibody titer rebounds – 1 on day 3 (IgG=1: 16) and 2 on day 7 (IgM=1: 16). The 2 patients with IgM rebound also developed AMR at the time of rebound.

Patient and graft outcome

Two grafts (4.2%) in the ABOi group were lost due to hyperacute rejection, compared to 3 losses (3.1%) in the ABOc group (P=0.76, Figure 2) due to anti-HLA AMR at months 12 and 18 after transplantation, and nephropathy relapse at month 35. After a median follow-up of 27.6 months (range: 4–51.6) for the ABOi group and 29.8 months (range: 2–52) for the ABOc group, the death-censored graft survival rates were not significantly different at 1 year (97.9 *vs.* 97.9%, P=0.22), 2 years (97.9 *vs.* 95.8%, P=0.48), and 3 years (97.9 *vs.* 94.0%, P=0.75). We assessed graft function by measuring serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) (Figure 3). The median SCr and eGFR were slightly higher in the ABOi group during the early post-transplantation period.

An analysis of recipient deaths indicated no significant difference between the groups (P=0.76; Figure 2). There were 2 deaths in the ABOi group (1 from bacterial and fungal pneumonia at month 4, and 1 from bacterial pneumonia at month 5), and 3 deaths in the ABOc group (1 from fungal pneumonia at month 2, 1 from EBV-associated hemophagocytic syndrome at month 12, and 1 fungal pneumonia at month 15). The ABOi and ABOc groups had no significant differences in recipient survival rate at 1 year (97.9 *vs.* 95.8%, P=0.48), 2 years (97.9 *vs.* 93.8%, P=0.75), and 3 years (97.9 *vs.* 93.8%, P=0.75).

Acute rejection

There were 10 episodes of acute rejection (20.8%) in the ABOi group, 6 of which were biopsy-proven. Three cases had cell-mediated rejections (CMRs) and the remaining 7 were AMRs. All CMRs responded well to pulse steroids without ATG. The times of AMR onset were post-transplantation days 0, 0, 2, 7, and 7, and months 1 and 30; the anti-blood group antibody titer (IgM/IgG) for each of these patients at the time of AMR was 8/4, 4/4, 1/0, 16/4, 16/0, 2/0, and 4/0, respectively. Only 1 of these patients (month 30, pre-transplant PRA of 50%) developed donor-specific HLA antibodies. Excluding 2 cases of hyperacute rejection, the graft function recovered well after PE alone in 2 patients, IVIG alone in 1 patient, PE+steroids in 1 patient, and IVIG+ATG in 1 patient.

Fifteen ABOc patients (15.6%) developed acute rejections (7 CMRs and 8 HLA AMRs). The times of AMR onset were post-transplantation day 5, and months 2, 6, 10, 12, 18, 25, and 32. The onset of AMR was earlier in the ABOi group than in the ABOc group, but this difference was not statistically significant (P=0.10).

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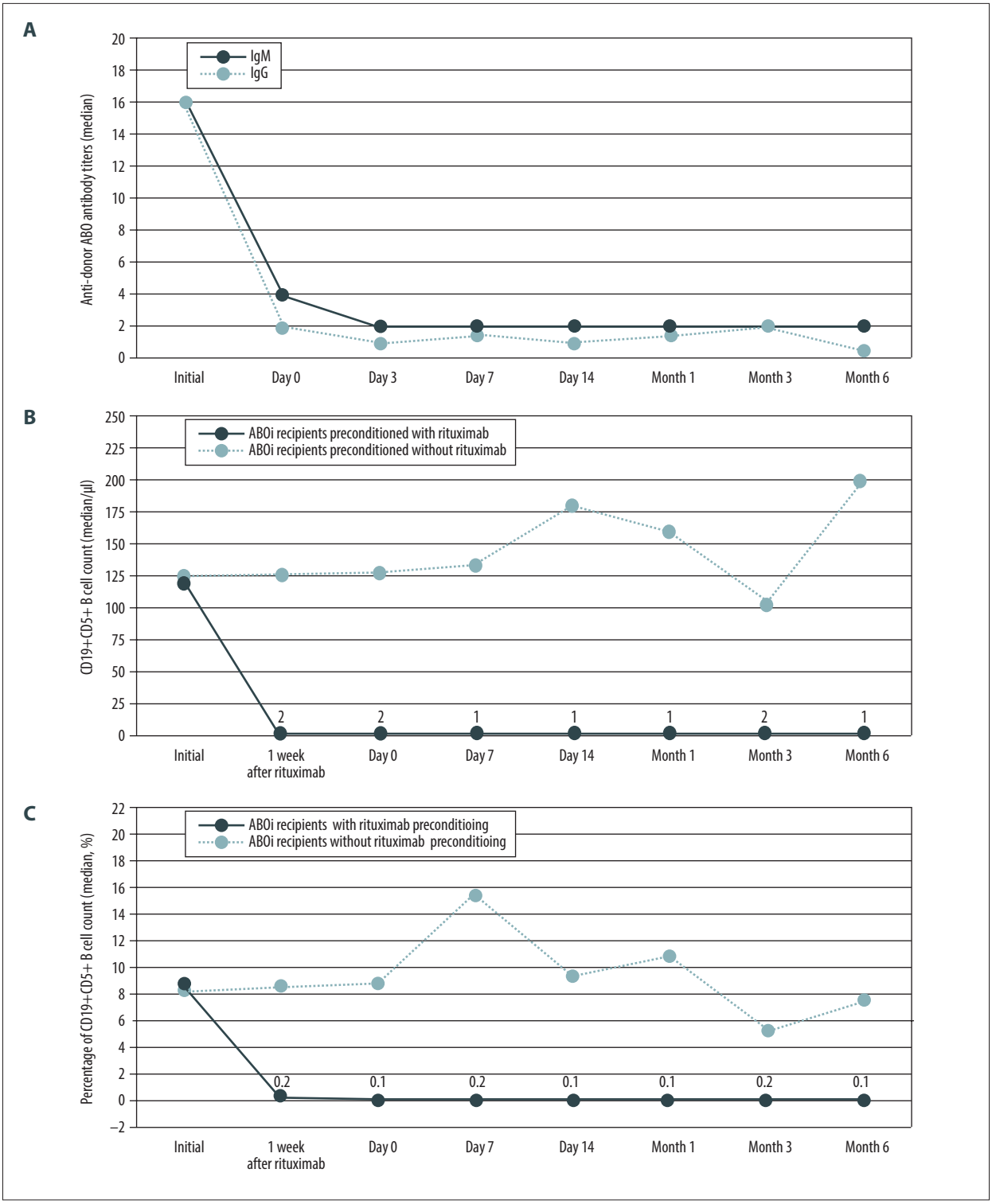

Figure 1. Anti-donor ABO IgM/IgG titers (**A**) in ABO-incompatible kidney transplant recipients; peripheral blood CD19+CD5+ B cell count (**B**), and percentage of CD19+CD5+ B cells (**C**) in ABO-incompatible kidney transplant recipients who did and did not receive rituximab.

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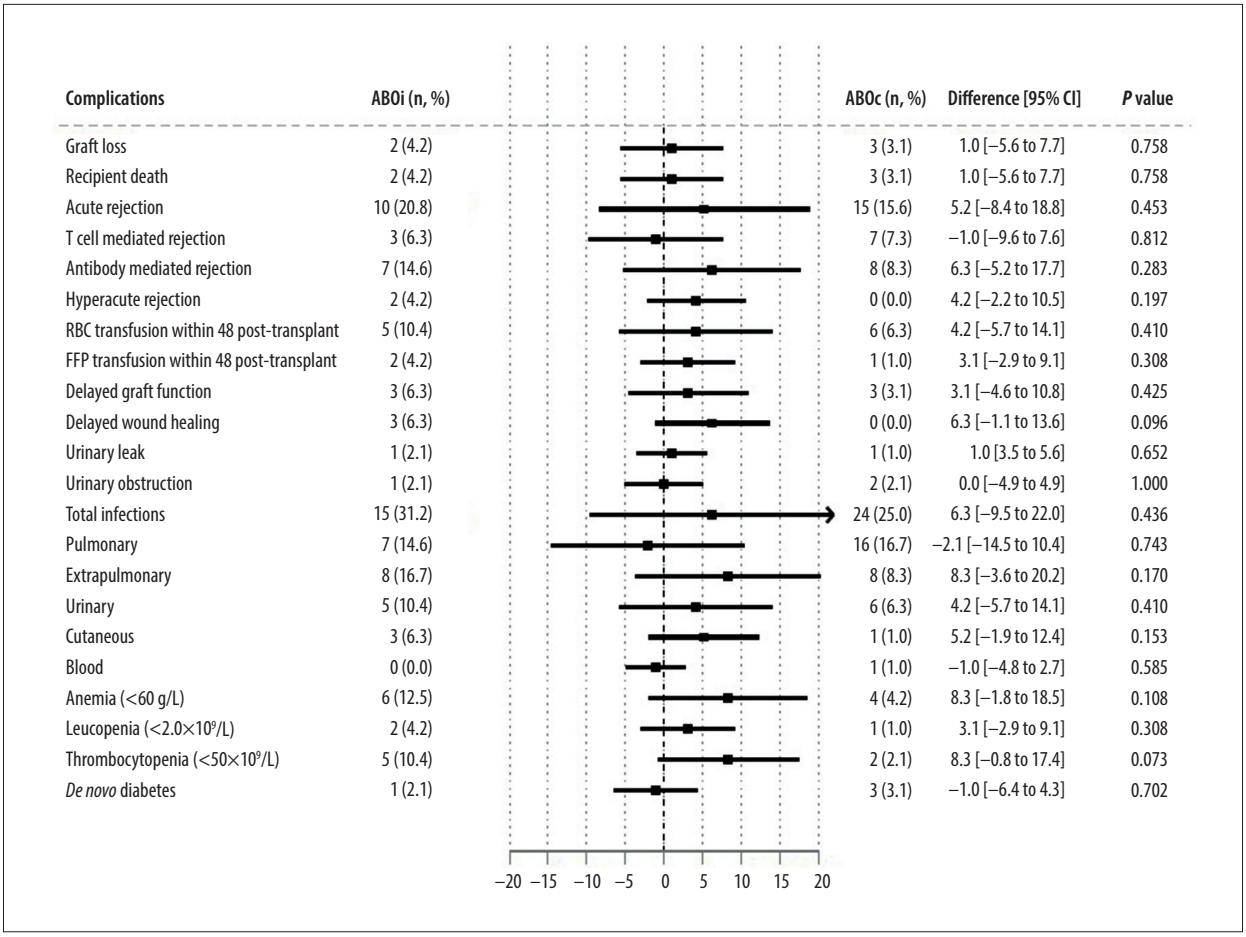

Figure 2. Post-transplantation clinical complications in the ABO-incompatible and ABO-compatible groups.

Adverse complications

Analysis of the post-transplantation clinical complications in the 2 groups indicated the ABOi group had a marginally higher incidence of delayed wound healing and severe thrombocytopenia (Figure 2). The 2 groups had similar percentages of infectious complications within the first 3 months after transplantation, with 10 of 15 (66.7%) in the ABOi group and 15 of 24 (62.5%) in the ABOc group (P=0.79).

Analysis of post-transplantation laboratory parameters (Table 4) indicated that the ABOi group had a higher prevalence of bone marrow suppression, as indicated by lower levels of hemoglobin, platelets, and white blood cells, at various times after transplantation.

Distribution of clinical complications based on evolution periods in the ABOi group

The distribution of clinical complications based on the 4 evolution periods in the ABOi group is listed in Table 5. Our individualized preconditioning protocols evolved as our experience grew, and hyperacute rejection, acute rejection, graft loss, and recipient death did not occur in the stable period, although this observation may be biased by the shorter follow-up duration in this period.

Discussion

Current preconditioning protocols for ABOi KTx

Transplant centers use heterogeneous desensitization protocols for ABOi KTx, and there is no generally accepted preconditioning protocol. To date, these strategies have been used in more than 7000 ABOi KTxs worldwide [14,16,22]. Most ABOi transplants in Japan use antibody removal with DFPP, while in Europe most ABOi use immunoadsorption. In the USA, desensitization protocols use PE and IVIG without rituximab. The lack of head-to-head comparisons makes it difficult to identify the most effective and safe protocol.

Notably, ABOi preconditioning is associated with a higher risk of severe infection and bleeding [23]. Therefore, moderation

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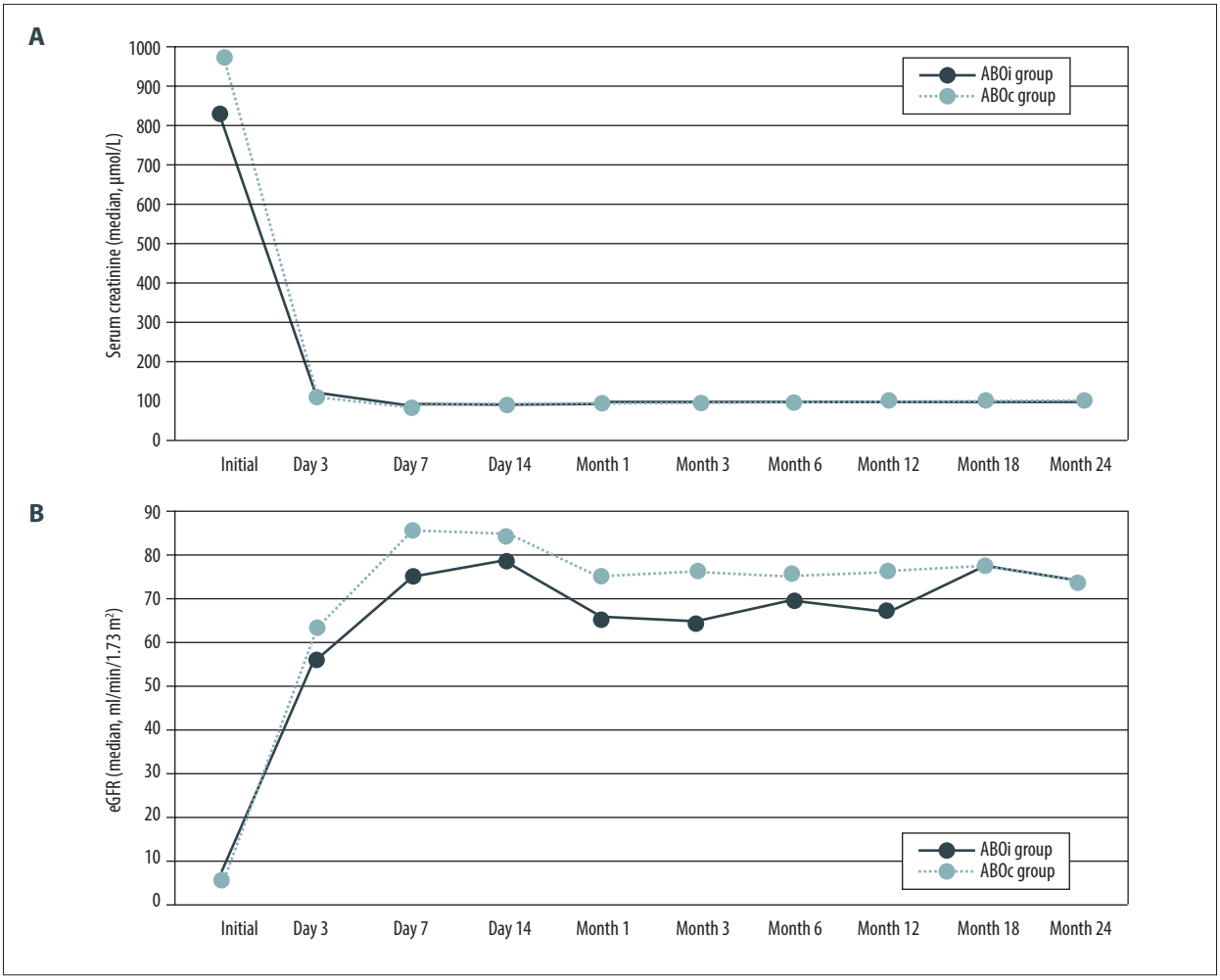

Figure 3. Post-transplant serum creatinine (**A**) and estimated glomerular filtration rate (**B**) in the ABO-incompatible and ABO-compatible groups.

has been tried, either by lowering the rituximab dose or using fewer sessions of antibody removal [11–13]. Barnett et al. proposed a tiered approach for ABOi desensitization according to initial antibody titers [19]. Furthermore, Masterson et al. reported that ABOi KTx could even be performed without rituximab or antibody removal in recipients with sufficiently low baseline ABO antibody titers [20]. These approaches may reduce the morbidity and costs associated with ABOi, and should also increase access to ABOi KTx.

Key findings

After the early loss of 2 grafts due to hyperacute rejection, we used a gel card instead of a tube test for measurement of the IgM titers and began to further develop individualized desensitization protocols. There were no subsequent hyperacute rejections. Thus, intense preconditioning using rituximab and antibody removal appears unnecessary for successful transplantation in some ABOi KTRs. Oral immunosuppressants alone were sufficient for ABOi candidates with very low titers, and no ABOi patients received splenectomy, routine post-transplant antibody removal, or IVIG. Notably, our ABOi and ABOc groups had similar short-term graft and recipient survival, and similar rates of rejection and infection.

Scurt et al. performed a meta-analysis of more than 65 000 patients, over 7000 of whom received ABOi KTx [24]. Compared with ABOc KTx, ABOi KTx was associated with significantly higher mortality after 1 year (OR=2.17, 95% CI=1.63–2.90), 3 years (OR=1.89, 95% CI=1.46–2.45), and 5 years (OR=1.47, 95% CI=1.08–2.00). They also reported that death-censored graft survival was lower in the ABOi KTx group after 1 year (OR=2.52, 95% CI=1.80–3.54) and 3 years (OR=1.59, 95% CI=1.15–2.18).

There were marginally higher rates of delayed wound healing and severe thrombocytopenia (<50×10^9/L) in our ABOi recipients, possibly because of the preconditioning procedure. Six out of 7 (86.7%) AMR cases in the ABOi group and 1 of 8 (12.5%)

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Table 4. Laboratory parameters of the two groups at different times after kidney transplantation.

	ABOi group (n=48)		ABOc group (n=96)		P value
1 week					
Hemoglobin (g/L)	84	(56–134)	103	(62–160)	**<0.001**
Platelet (×10^9/L)	163.5	(63–336)	170	(61–356)	0.403
White blood cell (×10^9/L)	7.39	(3.81–15.65)	7.3	(2.9–24.7)	0.244
Alanine aminotransferase (IU/L)	14	(2–162)	20	(4–208)	0.216
Glucose (mmol/L)	4.69	(3.15–11.49)	4.7	(3.4–10.5)	0.650
LDL cholesterol (mmol/L)	1.96	(0.84–3.11)	1.91	(1.0–2.8)	0.645
1 month					
Hemoglobin (g/L)	111.5	(69–153)	122	(68–159)	**0.009**
Platelet (×10^9/L)	194.5	(71–407)	195	(62–358)	0.435
White blood cell (×10^9/L)	7.16	(3.25–12.44)	6.8	(2.5–19.1)	0.347
Alanine aminotransferase (IU/L)	18.5	(6–92)	19	(7–110)	0.939
Glucose (mmol/L)	4.83	(3.29–6.76)	5.1	(3.29–9.21)	0.238
LDL cholesterol (mmol/L)	2.06	(0.93–5.48)	2.37	(0.28–3.99)	0.187
6 months					
Hemoglobin (g/L)	138	(107–186)	144	(97–190)	0.103
Platelet (×1^9/L)	158	(79–331)	188	(64–343)	0.125
White blood cell (×1^9/L)	5.89	(1.89–11.57)	6.73	(2.93–12.4)	**0.017**
Alanine aminotransferase (IU/L)	14	(7–106)	19	(1–174)	0.476
Glucose (mmol/L)	4.97	(4.04–6.45)	4.77	(3.92–11.1)	0.234
LDL cholesterol (mmol/L)	2.42	(1.24–6.06)	2.43	(0.97–5.26)	0.817
12 months					
Hemoglobin (g/L)	142	(96–208)	149	(68–202)	0.057
Platelet (×1^9/L)	154	(75–300)	186.5	(72–423)	**0.021**
White blood cell (×1^9/L)	6.27	(1.92–12.11)	6.91	(1.91–19.6)	0.196
Alanine aminotransferase (IU/L)	15	(5–228)	15	(5–180)	0.879
Glucose (mmol/L)	4.82	(4.07–9.28)	4.82	(3.34–6.51)	0.593
LDL cholesterol (mmol/L)	2.21	(0.85–5.2)	2.53	(1.01–4.71)	0.064
18 months					
Hemoglobin (g/L)	145	(105–223)	155	(106–193)	**0.029**
Platelet (×10^9/L)	147	(91–335)	193	(47–433)	0.057
White blood cell (×10^9/L)	6.6	(4.12–10.37)	7.09	(2.52–13.72)	0.306
Alanine aminotransferase (IU/L)	17	(6–216)	15	(6–70)	0.546
Glucose (mmol/L)	4.75	(3.72–6.07)	4.77	(2.85–6.64)	0.624
LDL cholesterol (mmol/L)	2.35	(1.32–3.81)	2.34	(1.49–4.12)	0.400

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Table 4 continued. Laboratory parameters of the two groups at different times after kidney transplantation.

	ABOi group (n=48)		ABOc group (n=96)		P value
24 months					
Hemoglobin (g/L)	141	(117–206)	153	(106–207)	**0.033**
Platelet (×10^9/L)	168	(71–301)	201	(82–362)	0.133
White blood cell (×10^9/L)	6.82	(4.85–11.47)	6.86	(4.19–13.88)	0.924
Alanine aminotransferase (IU/L)	15	(5–72)	15	(7–66)	0.434
Glucose (mmol/L)	4.73	(3.11–7.35)	4.90	(4.04–12.77)	0.663
LDL cholesterol (mmol/L)	2.58	(1.08–3.32)	2.89	(1.41–4.96)	0.116

Table 5. Distribution of clinical complications based on four evolution periods in the ABOi group.

	Imitation Period, Case #1 (Sept 2014)		Exploration period, Cases #2–19 (Dec 2014–Jun 2016)		Improvement Period, Cases #20–34 (Jun 2016–Apr 2017)		Stable period, Cases #35–48 (May 2017–Jun 2018)	
	n	Timepoints of onset	n	Timepoints of onset	n	Timepoints of onset	n	Timepoints of onset
Graft loss/hyperacute rejection	0	/	2	Day 0, 0	0	/	0	/
Recipient death	0	/	1	Month 5	1	Month 4	0	/
Acute rejection								
T cell mediated rejection	1	Day 6	2	Day 7, Month 5	0	/	0	/
Antibody mediated rejection	1	Month 30	3	Day 0, 0, 2	3	Day 7, 7, Month 1	0	/
Delayed graft function	0	/	3	/	0	/	0	/
Delayed wound healing	1	Day 8	2	Day 7, 8	0	/	0	/
Urinary leak	0	/	0	/	0	/	1	Month 3
Urinary obstruction	0	/	0	/	1	Month 10	0	/
Total infections								
Pulmonary	0	/	3	Week 2, Month 3, Year 1	2	Month 1, 4	2	Month 2, 3
Extrapulmonary	0	/	2	Month 1, 10	4	Week 1, 3, Month 2, Year 2	2	Month 3, 5
Anemia (<60 g/L)	0	/	4	Day 1, 3, 3, 3	0	/	2	Week 1, Month 3
Leucopenia (<2.0×10^9/L)	0	/	1	Month 1	1	Month 6	0	/
Thrombocytopenia (<50×10^9/L)	0	/	3	Day 1, 1, 1	1	Day 3	1	Day 3
De novo diabetes	0	/	0	/	1	Month 9	0	/

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AMR cases in the ABOc group developed within 1 month after transplantation. This may explain the slightly higher SCr and eGFR in the ABOi group during the early post-transplantation period. We treated these rejections effectively in most patients, and none of them had permanent negative effects on graft function. Excluding the 2 cases of hyperacute rejection, 2 of 5 ABOi individuals with AMR did not have ABO antibody rebound or donor-specific HLA antibodies at the time of rejection. It is possible that ABO antibodies were responsible; however, other studies have demonstrated that the clinical significance of an increased ABO antibody titer after transplantation is variable and had no significant correlation with AMR [25].

Strengths and limitations

To the best of our knowledge, this is the first study of Chinese ABOi living-donor KTxs to be published in the English medical literature. A strength of our study is that we reduced baseline differences between the ABOi and ABOc groups using propensity score matching (1: 2 ratio) for donor/recipient age, transplant surgical team, and maintenance immunosuppression regimen. In addition, our ABOi preconditioning regimen used an individualized desensitization strategy based on initial antibody titers, and 11 of 48 ABOi KTRs were preconditioned with oral immunosuppressants alone. We thoroughly investigated the clinical outcomes of the 2 groups, and reported the comprehensive clinical data after a median follow-up of 27.6 months (ABOi group) and 29.8 months (ABOc group).

There were some limitations to this study that may affect the validity of our findings. First, the follow-up duration was short and unequal between the groups, and the sample size was small. These factors could have obscured some differences between the 2 groups. Second, some rejections were not biopsy-proven, and we did not perform protocol biopsies, which could have led to a miscalculation of the incidence of rejection. Third, the highest ABO antibody titer in our study was 1: 256, meaning that extrapolating our results to very high-titer transplant candidates should be done with caution. However, we did not set an upper limit for ABO titer for participation in our ABOi program, possibly meaning that Chinese patients with end-stage renal failure might have relatively low initial antibody titers. Fourth, our individualized preconditioning protocols evolved as our experience grew, and hyperacute rejection and recipient death only occurred in the first few patients. Our current ABOi KTx outcome is better than the overall outcome of all 48 cases over more than 4 years.

Clinical implications

Due to the limited donor organ availability and the absence of kidney paired donation in some countries (e.g., China), ABOi KTx has become a viable option for patients without ABOc donors [26.27]. The first ABOi KTx in China was successfully performed at South China University in 2006 and was reported in a Chinese journal [17]. No additional successful ABOi KTx cases were reported in China until we reported our first 6 cases in 2015 [28]. Our individualized preconditioning protocol led to wide acceptance of ABOi KTx in China, and the number of transplant centers adopting our protocol is rapidly growing. To promote ABOi KTx, the Chinese Society of Organ Transplantation and Chinese Transplant Doctor Association published the *Clinical Guideline for ABO-Incompatible Living-Donor Kidney Transplantation* in 2017 [29]. Although more cases are required for further refinement of these protocols, the main findings of our research are that the use of personalized protocols allows a wider range of patients to benefit from ABOi transplantation, especially those with low initial titers [26].

Conclusions

In summary, this is the first case series to describe ABOi KTxs in China. Our individualized preconditioning protocol has developed over time, and includes tailoring of rituximab administration and antibody removal based on initial ABO antibody titers and the use of oral immunosuppressants alone for patients with low initial antibody titers. This approach led to similar short-term graft and recipient survival for patients receiving ABOi and ABOc KTxs, without significantly increasing the risk of complications. ABOi KTx is thus an important step forward in expanding the kidney donor pool in China.

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Data availability

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Conflict of interest

None.

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