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Long-term outcomes after ABO-incompatible kidney transplantation; a single-center French study

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ABSTRACT

Background: ABO-incompatible (ABOi) is as efficient as ABO-compatible (ABOc) kidney-transplantation in the setting of live-donation.

Objectives: To evaluate the long-term outcomes (i.e. >6 months) of 44 consecutive ABOi living-donor kidney-transplants (KTx). The results were compared to those from 44 ABOc KTx that were matched with ABOi-patients on age, gender, and date of transplantation.

Patients and Methods: With regards to immunosuppression (IS) only ABOi-patients received pre-transplant IS, that included rituximab. Induction therapy relied significantly more frequently on basiliximab in ABOc- than in ABOi-patients 77.2% vs. 38.6% ($P=0.0002$). Post-transplant IS relied only on tacrolimus/mycophenolic acid and steroids in ABOi-patients, whereas some ABOc-patients were alternatively on cyclosporine (13.6%)/everolimus (11.3%) and no steroids (7%), respectively ($P=0.05$).

Results: In ABOi-patients there was no isoagglutinin titer rebound posttransplant. At last follow-up patient and graft survival was similar in the two groups, as well as kidney-allograft function. Acute rejection rates (cellular, humoral, or mixed) were similar across both groups (ABOi: 22.7%; ABOc: 20.4%). With regards to bacterial and viral infections the only significant difference between the two groups was that at month three there were significantly more BKV viruria in ABOi (25%) vs. 6.8% in ABOc ($P=0.03$). De novo donor-specific alloantibody were detected in 13.6% ABOi and 4.5% ABOc patients (ns). Readmission rates in our department for less than two days were more frequent for ABOi conversely readmission rates for more than two days was similar across the groups.

Conclusions: ABOi-kidney transplantation after desensitization provides in the long-term same results as those observed in live-donor ABOc-kidney transplantation.

Original Article

Implication for health policy/practice/research/medical education:
We are facing more and more end-stage renal disease (ESRD) patients; of these a large proportion are waitlisted for a kidney transplant. However, due to the scarcity of deceased donors we have to develop live-kidney donor programs. In the setting of living-donation we can face with either ABO and/or HLA incompatible transplantation. ABO incompatible kidney transplantation is associated as we demonstrated in this study with very good long-term results, i.e. similar to those obtained with ABO compatible kidney transplantation provided desensitization is implemented at pre-transplant.

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1. Background

Kidney transplantation (KT) is the preferred option for patients with end-stage renal disease (ESRD) because of its association with longer and better quality of life compared to dialysis (1,2). However, the lack of deceased donors and the increasing numbers of patients with ESRD and on a KT waiting-list has caused long waiting times for a suitable allograft (3). For this reason a living-donor KT becomes an important option (4). ABO-incompatible (ABOi) living donor KT is an option for KT that has helped fill the need and has increased the living-donor population by about 10%–20% (5-10).

ABOi KTs are becoming a safe and accepted method of choice for KT (11), with excellent outcomes for patients and graft-survival rates with the recent advances in immunosuppression protocols (12). Nowadays, graft survival of ABOi KT recipients matches those of ABO-compatible (ABOc) KT recipients (13-15).

However, ABOi KT is complicated in the way that, because of isoagglutinins present in the circulation of the recipient at transplantation, in the absence of their removal, this can result in early acute antibody-mediated rejection (AAMR). However, a few weeks after ABOi KT, accommodation takes place, i.e., even in the presence of high isoagglutinin titers, provided the patient receives immunosuppression and no rejection occurs (16-19).

In 1901, the Nobel Laureate Karl Landsteiner, a scientist from Austria, discovered the human ABO blood groups (20). There are four blood groups (A, B, AB and O), with the correlative antibodies (anti-A and/or anti-B), which are known as isohemagglutinins (21).

These antigens are a glycosylated form of antigen H, which consists of blood groups A and B; in contrast, blood group O is related to the non-glycosylated form of Ag-H. These antigens are found on the surfaces of human erythrocytes, tissue cells, and vascular endothelial cells. Blood group O does not have A or B antigens but does have anti-A and anti-B antibodies in its sera (19,22-24). Both groups A and B are co-dominantly genetically inherited.

Blood group A, which is separated into the subtypes A1 (80%) and A2 (20%), represents the A antigen (Ag) on cells and patients with group A will develop anti-B isohemagglutinins in their serum. A1 is more immunogenic than A2 (25,26). Patients that are blood-group AB have no serum antibodies to blood-groups A or B (22).

Isohemagglutinins are mostly IgM subtypes and sometimes other isotypes, such as IgG1, IgG2, and IgA (5,28). These are natural antibodies produced in early childhood through a reaction against the polysaccharides membranes of commensal bacteria and persist into adulthood (27,28).

These isohemagglutinins, which are part of innate immunity, react against their corresponding antigens, which are present on different cells, e.g., endothelial cells, erythrocytes, (19) and may cause a severe AAMR if there is insufficient preconditioning and desensitization of the recipient (29,30).

The earliest report of ABOi KT was in 1955 by Hume et al (17) and later by Starzl et al (29): however, the early experiences resulted in rapid rejection of transplants (31).

Alexandre et al, in Belgium, reported the first successful ABOi KT in 1982 (32). They reported on 26 patients who received an ABOi living donor-KT after removing anti-A and -B isohemagglutinins from the patients' plasma by plasmapheresis, combined with a splenectomy to prevent acute AAMR. Their study reported a 1-year graft-survival rate of only 75% (33).

Japanese groups started ABOi living donor-KT in 1989 because of the impossibility of obtaining cadaveric organs in Japan until a law on brain death was implemented in 2011 (19). The overall patient-survival rate was 97% in the first year, and was 95%, 93%, and 90% at 3, 5, and 9 years after a KT, respectively (34). ABOi KT now accounts for ~30% of living-donor KTs in Japan (35).

Tydén et al, in 2003 (36), reported an effective method for ABOi KT that involved isoagglutinin anti-A and/or anti-B reduction using ABO blood-group A- or B-specific adsorption columns (Glycosorb®-ABO, Glycorex, Sweden) (37,38). Furthermore, splenectomy was substituted by the comparably simpler treatment of using anti-B-cell monoclonal antibody therapy targeting CD20 molecule. This treatment consisted of a single dose of rituximab (39-42), followed by intravenous immunoglobulin (IV-Ig); this method led to very good short-and longer term outcomes (43).

In order to achieve successful ABOi living-donor-KT, a prolonged prior period of recipient preconditioning is needed in the form of desensitization. This is comprised of rituximab, apheresis, and immunosuppressants that target T-cells (6,44) in order to remove/reduce high levels of anti-A and -B antibodies (isohemagglutinins) (45). In cases that have low isohemagglutinin titers, ABOi KT can be performed with a reduced risk of acute AAMR and without the need for rituximab and apheresis (16).

The general acceptable goals for pre-transplant ABOi titers range from 1:8 to 1:32 (46,47), according to different transplant centers (48).

Hemagglutination is regarded as the preferable method to quantify isohemagglutinins, and s still commonly used (49). It is based on semi-quantitative measurement of blood-group-specific IgM (direct agglutination) or IgG (indirect detection using anti-IgG reagents) (15,50).

Alternative techniques used to detect anti-A/B antibodies include flow cytometry and surface plasmon resonance, which is a cell-independent method that enables detection–reagent-independent analysis of antibody–antigen binding using immobilized blood group A or B trisaccharides (6,51,52).

Many different strategies to remove anti-blood-type antibodies for desensitization have been developed (53-55). The basic current principles for desensitization protocols in ABOi KT are the use of plasma exchange in association with B-cell immunomodulation using rituximab. This is followed by administration of intravenous immunoglobulin (IV-Ig), which is considered an immunomodulator by preventing antibodies binding to their particular receptors. It is believed that IV-Ig interacts with Fc receptors on phagocytes and B-cells, and inhibits T-cell differentiation and stimulation (15,56). This protocol is completed with maintenance immunosuppressive drugs that include calcineurin inhibitors (CNI), mycophenolic acid (MPA), and corticosteroids (57). There are many types of apheresis: conventional plasmapheresis eliminates the main plasma components, such as immunoglobulins and clotting factors. Another technique is double-filtration plasmapheresis (DFPP), which is more selective at removing plasma immunoglobulin. Another method is semi-specific immunoadsorption (IA), which removes immunoglobulins and allows more efficient removal of ABO antibodies without the loss of other major plasma components (37,58).

There are also more specific IA techniques, which include the selective capture of anti-A or anti-B antibodies in columns through the formation of antigen–antibody complexes (42).

In the past, splenectomy was often conducted whereas, nowadays, rituximab is usually given instead, which depletes B cells (42). Although a splenectomy is performed in some patients who have treatment-resistant antibody-mediated rejection (59,60), in ABOi KT recipients, it has been noted that specific isohemagglutinins against the donor may return to pretransplant levels within1 to 2 weeks after transplantation (61). However, no antigen–antibody reaction happens and hence no AAMR occurs (16,62,63). This phenomenon is known as accommodation (64,65).

2. Objectives

The aim of this study is to compare the long-term outcomes of ABOi KT versus ABO compatible (ABOc) KT in terms of graft and patient survival rates and renal function, and to assess the presence of infections, surgical issues, or other medical complications.

3. Patients and Methods

3.1. Patients

This single-center retrospective study was performed in the Department of Nephrology and Organ Transplantation at Toulouse University Hospital, France. We included all ABOi living-kidney-transplant recipients (n = 44, 27 males, overall mean age of 44.7 ± 13.5 years) who had attended our institution between April 2011 and June 2015. These 44 patients were matched regarding gender, age, and time of transplantation with 44 ABOc patients who were also recipients of a living kidney (i.e., 27 males, overall mean age of 45.2 ± 13.1 years).

We collected all pertinent data that could have contributed to early and longer term peri- or postoperative (i.e., maximum of 48 months) complications. Information collected included surgical complications, renal-function parameters, rejection episodes, infections, and metabolic disorders (lipids and glucose metabolism). The following data were also collected from both groups: donor's and recipient's demographic characteristics, histocompatibility antigen (HLA) and ABO types, the donor's renal function, HLA matching, the recipient's original kidney disease, HLA sensitization in the recipient, warm and cold ischemia times.

Data were collected on days (D) 0, D5, D15, at month 1, and then at regular 6-month intervals for the long-term follow-up. The mean follow-up time was 24 months range (1-48 months). These post-transplant data comprised hemoglobin levels (Hb), leucocyte and platelet counts, polymorphic neutrophils, total number of lymphocytes and their fractions (CD19%, CD3%), serum creatinine, estimated glomerular-filtration rate (eGFR), any infectious complications (bacterial, viral, fungal, or parasitic), cytomegalovirus (CMV) with the donor/recipient status and BKV DNAemias, BKV viruria, and the occurrence of an acute or chronic rejection and their subtypes according to Banff 2013 criteria.

We also monitored calcineurin inhibitors (CNI), MPA, and mTOR daily doses as well as tacrolimus trough levels. In addition, for the ABOi group, we assessed and collected data on isoagglutinin titers at pre-and post-transplantation, and of tacrolimus levels at pre-

transplant. We also collected data on the duration of initial hospitalization and the numbers of short- and long-term hospitalization periods throughout the follow-up period.

3.2. Immunosuppression

Immunosuppression differed across the two groups. In ABOc patients, the induction therapy was based on basiliximab (20 mg IV, on days 0 and 4) unless the patient was highly sensitized, i.e., panel-reactive alloantibodies >25%. In that event, basiliximab was replaced by Thymoglobulin® (1.25 mg/kg, on days 0, 2, and 4). In addition, the patients received the following; (*i*) tacrolimus at 0.2 mg/kg/d to achieve trough levels of between 7 and 10 ng/mL between days 0 and 30, and then between 5 and 7 ng/mL thereafter; (*ii*) mycophenolic acid (MPA) at 720 mg b.i.d. or mycophenolate mofetil (MMF) at 1 g/b.i.d. between days 0 and 15, with doses halved thereafter; and (*iii*) steroids (methylprednisolone IV 10 mg/kg, 2 mg/kg, and 1 mg/kg on days 0, 1, and 2, respectively, with doses rapidly tapered to 10 mg/d by day 30 and to 5 mg/d on D90.

For ABOi patients, immunosuppression was begun at pre-transplant; i.e., rituximab 375 mg/m^2 at 30 days pretransplant, and conventional immunosuppression was started at 12 days pre-transplant, i.e., tacrolimus (0.15 mg/kg/d aiming at trough levels of 7–10 ng/mL), MPA (360 mg b.i.d.) or MMF (500 mg b.i.d.), plus prednisone (0.5 mg/kg/d).

In addition to these treatments, according to the isoagglutinin titers at 30 days pre-transplant, we did or did not add apheresis sessions. If the specific isoagglutinin titer was <1/8, no apheresis was performed; if the isoagglutinin titer was between 1/8 and 1/16, the patients received plasmapheresis sessions to decrease titers to <1/8. For titers that were between 1/32 and <1/128, patients were given specific IA (Glycorex® column, Lund, Sweden) with or without DFPP. In cases where the isoagglutinin titer was ≥1/128, we always started desensitization with four DFPP sessions that were followed, if necessary, by specific immunoadsorption in order to achieve an isoagglutinin titer on the day of transplantation of ≤1/8. In a few cases where ABOi patients had a pretransplant donor-specific alloantibody(ies) with a mean fluorescence intensity of ≥3000, we replaced DFPP and/or specific immunoadsorption with semi-specific immunoadsorption (Adasorb® or Globaffin® reusable columns, Fresenius, Bad Homburg, Germany).

An induction therapy based on Thymoglobulin® (1.25 mg/kg on D0, D2, and D4) was given to cases where there were associated DSAs, ABO-incompatibility, and to the first 14 ABOi patients. Thereafter, ABOi patients received basiliximab (20 mg on D0 and D4). Post-transplant immunosuppression relied on tacrolimus (0.2 mg/kg/d aiming at trough levels of between 8 and 12 ng/mL until D15, which was then reduced to 5–8 ng/mL), MPA (720 mg b.i.d.) or MMF (1 g b.i.d.), which was given until D15 and then doses were halved; plus steroids (methylprednisolone 10 mg/kg on D0, 2 mg/kg on D1, 1 mg/kg on D2, and then prednisone at 0.5 mg/kg until D10, which was then progressively tapered to attain 5 mg/d by D90).

3.3. Prophylaxis

If the donor was sero-CMV positive and the recipient was sero-CMV negative, valganciclovir (900 mg/d, adapted to eGFR) was given for 6 months. In there was a seropositive CMV recipient, valganciclovir prophylaxis (900 mg/d, adapted to eGFR) was given for 3 months to ABOc patients and for 6 months to ABOi patients. With regards to *Pneumocystis jirovecii* prophylaxis, we gave sulfamethoxazole/trimethoprim (400 mg/80 mg) every other day for 6 months to ABOc patients and for 12 months to ABOi patients.

3.4. Ethical issues

The research followed the tenets of the Declaration of Helsinki; 2) informed consent was obtained, and 3) the research was approved by the ethical committee of Toulouse university hospital, France.

3.5. Statistical analysis

The results are expressed as their means (SD) or medians (ranges). Comparisons between continuous variables were made using the χ^2 test; comparisons between discontinuous variables were made using Student's *t* test. Statistical significance was set at $P = 0.05$.

4. Results

Table 1 shows the general demographic characteristics of ABOi and ABOc recipients, which are comparable in terms of gender, mean age, renal function, body mass indices (BMIs), mean time on dialysis before KT, and the leading causes for ESRD. The major leading causes were glomerulonephritis, polycystic kidney, nephroangiosclerosis, diabetic nephropathy, and urological causes.

There was a significant difference in the duration of cold ischemia (in minutes) between the two groups: (247.5 ±61.9 for the ABOc group vs. 290.3 ±85.0 minutes for the ABOi group; $P = 0.008$). In contrast, there was little difference in duration of warm

Table 1. Recipients' general characteristics

General characteristics of recipients	ABOc (n = 44)	ABOic (n = 44)	*P* value
Recipient gender, n (%)			NS
Male	26 (59%)	26 (59%)	
Female	18 (41%)	18 (41%)	
Recipient age (years: mean)	45.2 ±13	45.2 ±13.5	NS
Follow-up time (between 1 and 48 months) n (%)			
1 mon	3 (6.8%)	2 (4.5%)	NS
3 mon	3 (6.8%)	7 (15.9%)	
6 mon	9 (20.4%)	7 (15.9%)	
12 mon	8 (18.1%)	6 (13.6%)	
18 mon	5 (11.3%)	2 (4.5%)	
24 mon	5 (11.3%)	5 (11.3%)	
30 mon	4 (9%)	5 (11.3%)	
36 mon	2 (4.4%)	2 (4.5%)	
42 mon	2 (4.4%)	2 (4.5%)	
48 mon	3 (6.8%)	3(6.8%)	
Mean follow-up time (mo) ± SD	18 ± 13.8	18 ± 14.8	NS
Causes of ESRD, n (%)			NS
Glomerulonephritis	15 (34%)	11 (25%)	
Diabetic nephropathy	2 (4.4%)	4 (9%)	
Nephroangiosclerosis	6 (11.3%)	3(6.8%)	
Polycystic kidney disease	10 (22.7%)	6 (13.6%)	
Uropathy	3 (6.8%)	5(11.3%)	
Other or undetermined	8 (18.1%)	15 (34%)	
BMI: mean ± SD	24.2 ±4.56	25 ±3.5	NS
Time on dialysis (mon) ±SD	10.4 ± 17.8	14.9 ±5.6	NS
Duration of cold ischemia (min) mean ± SD	247.5 ±61.9	290.3 ±85	0.008
Duration of hot ischemia (min) mean± SD	60.6 ± 24.8	68.4 ±24.6	NS
Serum creatinine before KTx, µmol/L: mean ± SD	644 ± 238.7	555.3 ±164.3	0.04
eGFR (MDRD) mL/min/1.73 m² mean ± SD	8.6 ± 3.6	9.6 ±3.6	NS
Blood group, n (%)			
A	23 (52.2%)	2 (4.5%)	NS
B	3 (6.8%)	4 (9%)	NS
O	14 (31.8%)	38 (86.3%)	NS
AB	3 (6.8%)	0	NS
HLA mismatches /8, mean ± SD	2.6/8 ± 3.9	5.8/8 ±2	0.01
More than one KTx	4 (9%)	13 (29.5%)	
HLA-A mismatch, mean ± SD	1 ± 0.7	1.2/8 ±0.6	0.09
HLA A 1-2 mismatch, n (%)	32 (72.8%)	40 (91%)	0.02
HLA A 0 mismatch, n (%)	12 (27.2%)	4 (9%)	0.02
HLA-B mismatch, mean ± SD	1.2±0.8	1.5 ±0.6	NS
HLA-B 1-2 mismatch, n (%)	33 (75%)	41 (93.2)	0.04
HLA-B 0 mismatch, n (%)	11 (25%)	3 (6.8%)	0.01
HLA-DR mismatch, mean ± SD	1 ± 0.7	1.2 ±0.7	NS
HLA-DR 1-2 mismatch, n (%	31 (70.5%)	40(91%)	0.01
HLA-DR 0 mismatches, n (%)	13 (29.5%)	4 (9%)	0.01
HLA DQ mismatch, mean ± SD	0.8 ± 0.6	1.1 0.7	0.03
HLA-DQ 1-2 mismatch, n (%)	29 (66%)	37(85%)	0.04
HLA-DQ 1-2 mismatch, n (%)	15 (34%)	7(15.9%)	0.04
Patients with noHLA mismatches, 0/8, n (%)	8(18.1%)	2 (4.5%)	0.08
Patients with all HLA mismatches, 8/8, n (%)	1 (2.2%)	7(15.9%)	0.05
Patients with at least one HLA mismatch	36 (81.8%)	42 (94.4%)	NS

Abbreviations: ESRD, end-stage renal disease; BMI, body-mass index; HLA, histocompatibility antigen; NS, not significant; ABOi, ABO incompatible; ABOc, ABO compatible; SD, standard deviation; KTx, kidney transplantation; eGFR, estimated glomerular filtration rate.

ischemia.

There were notable differences in pre-KT mean serum creatinine levels (i.e., 644 ± 238.7 for ABOc vs. 555.3 ±164.3 µmol/L for ABOi; $P = 0.04$). Most recipients were blood group O (38: 86.3%) within the ABOi group whereas most ABOc recipients were blood group A (23: 52.2%).

4.1. HLA mismatches

Patients in the ABOi group had more HLA

mismatches in terms of the number of the type of HLA mismatches and the number of patients with a total HLA mismatch (*P*= 0.01, *P*=0.05, respectively). An HLA type-B mismatch was the most common type in both groups, and HLA type-DQ was the least common.

4.2. Donors' characteristics

Table 2 shows the donors' general characteristics. The mean age was 48.8 ±13 vs. 51.6 ± 10for the ABOc donors. There were 24 (54.5%) ABOi females and 26(59%) ABOc females. Their characteristics were comparable in terms of mean BMIs, medical history (hypertension and diabetes mellitus), and renal function (mean GFR was obtained according to inulin clearance and the MDRD formula). There were more CMV-positive donors in the ABOi group. Most donors in both groups were blood-group A.

4.3. Donor/recipient CMV status

More ABOi patients were D+/R+ (*P* = 0.01), whereas there were more D+/R- and D-/R- patients in the ABOc group. We noted one case of reactivated CMV in the ABOi group that had a D+/R+ status, whereas three cases of reactivated CMV in the ABOc group had a D+/R- status.

In the ABOi group, most KTs were between blood groups A and O (n = 32: 72.7%). Table 3 shows isoagglutinin levels throughout the 24-month follow-up period, starting from 30 days before KT. The median and ranges of anti-A and anti-B at 30 days before and on the day of KT were 1:20 (range: 1/128–1) and 1:2 (range: 1/32–1) respectively. These ranges remained relatively low throughout the 24-month follow-up. Seven ABOi patients needed a plasma exchange after KT because of high titers of isoagglutinins.

4.4. Immunological characteristics

Table 4 shows that all ABOi patients received an induction therapy, with most receiving anti-thymocyte globulin; in contrast, more ABOc patients received basiliximab (*P* = 0.002) and four did not receive an induction therapy.

Patients in the ABOi group had more class-II DSAs (6: [13.6%] vs. 0 in group ABOc, *P*= 0.02). DSAs were statistically more prevalent at 60 days before KT in the ABOi group (*P*=0.01), whereas data were comparable on the day of KT.

It should be noted that more patients in the ABOi group had their drug regimen changed from MPA to receive mTORi at 3 months post-KT (6 [13.6%] vs. 0 in the ABOc group, *P*=0.05). This was because of increased incidences of BKV infection by 3 months after KT, or episodes of leukopenia, or the development of cancer in some patients at 12

Table 3. Isoagglutinin titers throughout the 24-month follow-up

Time	Anti-A, median (ranges)	Anti-B, median (ranges)
D –30	1/20 (1/128-1)	1/20 (1/128-1)
D 0	1/2 (1/32-1)	1/3(1/16-1)
D 5	1/2 (1/5-1)	1(1/5-1)
D 15	1/2 (1/40-1)	1 (1/5-1)
M 3	1/2 (1/16-1)	1/2 (1/10-1/2)
M 6	1/4 (1/16-1)	1/2 (1/2-1)
M 12	1/5 (1/10-1)	1/4 (1/32-1)
M 18	1/5 (1/15-1)	1/3.5 (1/16-1)
M 24	1/5 (1/15-1)	1/3 (1/5-1)

Abbreviations: D: day, M: months.

Table 2. Donor's general characteristics

Variable	ABOc, n =44	ABOic, n=44	P value
Donors age (years: mean)	51.6 ± 10	48.8 ±13	NS
Gender female, n (%)	26 (59%)	24 (54.5%)	NS
BMI (mean)	26 ± 4	25 ± 3.6	NS
eGFR (MDRD) mL/min/1.73 m² (mean)	98 ± 18.6	97.4 ± 22.5	NS
Inulin clearance, mL/min/1.73 m²	94.4± 13.8	99 ±17	NS
Creatinine µmol/L (mean)	73.4±17.9	72.8 ±18	NS
HTN, n (%)	5 (11.3%)	4 (9%)	NS
CMV +ve, n (%)	22 (50%)	28 (%63.6)	NS
BK virus in blood, n (%)	0 (0%)	0 (0%)	NS
BKV in urine, n (%)	1 (2.27%)	0 (0%)	NS
Blood group, n (%)			
A	22 (50%)	35 (79.54%)	0.003
B	5 (9%)	6 (13.6%)	NS
O	17 (36.3%)	0 (0%)	NS
AB	1 (2.27%)	5 (11.3%)	NS

Abbreviations: BMI, body mass index; BKV, BK virus; CMV, cytomegalovirus; HTN, hypertension; eGFR, estimated glomerular filtration rate; NS, not significant; ABOi, ABO incompatible; ABOc, ABO compatible.

Table 4. Posttransplant immunosuppression, and the immunological characteristics

Variable	ABOc, n=44	ABOi, n=44	Total, n=88	*P* value
CNI, n (%)				
Tacrolimus	38 (86.3%)	44 (100%)	82 (4.5%)	0.01
CsA	5 (11.3%)	0 (0%)	5 (6.8%)	0.05
MPA, n (%)	38 (86.3%)	44 (100%)	80 (90.9%)	NS
mTORi, n (%)				
Everolimus	6 (13.6%)	0 (0%)	6 (5.68%)	0.05
Sirolimus	0 (0%)	0 (0%)	0 (0%)	NS
Steroids, n (%)	41 (93%)	44 (100%)	85 (96.5%)	NS
Induction, n (%)				
ATG	6 (13.6%)	27 (61.3%)	33 (37.5%)	NS
Basiliximab	34 (77.2%)	17 (38.6%)	51 (57.9%)	0.0002
Without induction, n (%)	4 (9%)	0 (0%)	4 (4.5%)	NS
Specific immunoadsorption, n (%)	0	7 (15.9%)	7 (10.2%)	0.01
Anti-HLA Ab, n (%)				
Anti-class I	3 (6.8%)	5 (11.3%)	8 (9%)	NS
Anti-class II	0	6 (13.6%)	6 (6.81%)	0.02
Both anti-class I & II	4 (9%)	8 (18.1%)	12 (13.68%)	NS
DSA(s) on D–60	4 (9%)	13 (29.5%)	17 (19.3%)	0.01
D –30	4 (9%)	7 (15.9%)	11 (12.5%)	NS
D 0	4 (9%)	6 (13.6%)	10 (11.3%)	NS
PRA >20%	1 (2.2%)	3 (6.8%)	4 (4.54%)	NS
PRA <20%	2 (4.5%)	2 (4.5%)	4 (4.54%)	NS
IgG level, mean ± SD	NA	12 ± 3.9	NA	NA

Abbreviations: CNI: calcineurininhibitors; CsA: cyclosporine; ATG: anti-thymocyte globulins; mTORI: mammalian target of rapamycininhibitor; MPA, mycophenolic acid; PRA: panel-reactive antibodies; DSA: donor-specific antibody, Ab: antibody; ABOi: ABO incompatible; ABOc: ABO compatible; SD: standard deviation; IgG, immunoglobulin G; D, day; NA, not available; NS, not significant.

months after KT. All patients continued to receive corticosteroids.

4.5. Hematological characteristics throughout the 24-month follow-up period

As shown in Table 5, ABOi patients had lower levels of Hb and platelets in the early post-KT period (*P* = 0.02, *P* = 0.0001, respectively), but there was no statistical difference by the end of the 24-month follow-up: i.e., 13.8 for ABOi ± 1.7 versus 13 ± 1.7 g/dL for the ABOc group for Hb, and 202.7 ± 46.4 for ABOi versus 204.6 ± 67.7×10^3/mm^3 for the ABOc group for platelets.

Amongst all peripheral lymphocytes, there were lower proportions of lymphocyte CD19 in the early post-KT period in ABOi recipients (1.5±2.1 in the ABOi group vs. 14.3±19.5% in the ABOc group, *P*=0.002); these results correspond to use of rituximab in ABOi recipients.

4.5.1. Times and causes of hospitalization throughout the 24-month follow-up period

More ABOi recipients needed a short period of hospitalization: this was mainly for IV-Ig infusions in the setting of post-transplant profound hypogammaglobulinemia; however, there were similar rates and durations of initial and longer post-KT hospitalizations for both groups (6±3.1 for ABOi vs. 4.2±2.2 days for the ABOc group; *P* = 0.01; Table 6).

4.6. Complications

As seen in Tables 6 and 7, infections were the main cause of long hospitalization in both groups, and occurred at similar rates. The most common type of infection was associated with the urinary system in both groups, and was most frequent in the early KT period in both groups. However, there were more incidences of BKV infection in ABOi recipients in the early post-KT period.

There were similar rates of surgical complications in both groups. Most were lymphocele and hemorrhagic shock. However, hemorrhagic shock occurred more frequently within the ABOi group, i.e., 6 (13.6%) in the ABOi versus 1 (2.2%) in the ABOc group (*P*=NS).

4.7. Patient- and graft-survival rates

Overall outcomes were similar in terms of the patients' survival, which was 100%in both groups. However, the number of graft losses were greater in the ABOi group (4 [9%] in the ABOi vs. 1 [2.2%] ABOc recipient; *P* = NS). Two graft losses occurred in the ABOi group after graft rejection (one acute and one chronic).In the

Table 5. Hematological characteristics throughout the 24-month follow-up period

Variable	Time	ABOi	ABOc	*P* value
Hb(g/dL) Mean ± SD	D0	9.8 ± 1.1	11 ± 1.5	NS
	D5	9.6 ± 1.4	10.3 ± 1.3	0.02
	D15	10.8 ± 2	10.9 ± 1.3	NS
	M1	11.9 ± 1.5	11.6 ± 1.2	NS
	M3	12.9 ± 1.5	12.6 ±1.4	NS
	M6	13.3 ± 2	13 ± 1.9	NS
	M12	13.7 ± 1.8	13.2 ± 1.8	NS
	M18	13.4 ± 1.9	13.8 ± 1.6	NS
	M24	13.8 ± 1.7	13 ± 1.7	NS
Platelets ($x10^3/mm^3$) Mean ± SD	D0	142.2 ± 36	201 ± 56.7	NS
	D5	133 ± 57.4	180.6 ± 54.3	0.0001
	D15	237.3 ± 98.7	241.8 ± 83.3	NS
	M1	190.6 ± 76.3	244 ± 87.7	0.006
	M3	229.2 ± 63.6	258.2 ± 93	NS
	M6	230.2 ± 79.8	230.9 ± 69.7	NS
	M12	212.1 ± 69.7	217,2 ± 69.6	NS
	M18	231.2 ± 67.6	209.5 ±64.5	NS
	M24	202.7 ± 46.4	204.6 ± 67.7	NS
PNN ($x10^3/mm^3$) Mean ±SD	D0	11.3 ± 5.7	8.7 ± 5.6	NS
	D5	7.3 ± 3.3	6.9 ± 2.6	NS
	D15	7.1 ± 3.5	8.1 ± 3.4	NS
	M1	6.2 ± 2.9	5.6 ± 2.2	NS
	M3	3.6 ± 2	4.6 ± 2.3	0.04
	M6	4.1 ± 2.5	4.5 ± 2	NS
	M12	4.4 ± 2.3	5.2 ± 2	NS
	M18	5.5 ± 2.9	5.2 ± 2.3	NS
	M24	4.7 ± 1.6	5.2 ±1.8	NS
$CD3^+$lymphocytes (%) mean ±SD	D0	85.3 ± 12.6	71.6 ± 22.5	0.04
	D5	77 ± 17.4	71.2 ± 20.9	NS
	D15	88.4 ± 5.5	80.5 ± 6.4	NS
	M1	78.4 ± 25.28	64 ± 7.1	NS
	M3	70.3 ± 27.7	75.8 ± 11	NS
	M6	77.4 ± 14	73.1 ± 21	NS
	M12	75.4 ± 13.5	74 ± 11	NS
	M18	73.4 ± 14.6	86.6 ± 11	NS
	M24	74.4 ± 13.3	79.2 ± 11.9	NS
$CD19^+$ lymphocytes (%) mean ±SD	D0	1.5 ± 2.1	14.3 ± 19.5	0.002
	D5	1.2 ± 2	24.5 ± 21.4	NS
	D15	0.3 ± 1	9.7 ± 7.8	NS
	M1	0.5 ± 0.7	7.2 ± 4.8	0.01
	M3	0.26 ± 0.65	7.1 ± 5.3	NS
	M6	2.8 ± 4.2	7.6 ± 3.3	NS
	M12	4 ± 5.7	8.9 ± 5	NS
	M18	6.2 ± 7.7	3 ± 5.1	NS
	M24	7.3 ± 7.2	5.5 ± 5.5	NS

Abbreviations: Hb; hemoglobin; PNN, polymorphic neutrophils; ABOi, ABO incompatible; ABOc, ABO compatible; D, days, M, months, SD, standard deviation, NS, not significant.

ABOi group, two other graft losses were caused by the recurrence of initial oxalate nephropathy and early renal-vein thrombosis. There was one graft loss in the ABOc group, caused by *de novo* focal segmental disease in the transplanted kidney (Table 8).

We found no differences in renal function throughout the 24-month follow-up period between the two groups: as shown in Figure 1 (eGFR (by MDRD) at month 24 was 52±19.1 for ABOi versus 62.3±23.7 in the ABOc group (P = NS).

The numbers of acute-rejection episodes were similar between the groups: 10 (22.7%) in the ABOi group versus 9 (20.4%) in the ABOc group. Most acute rejections occurred before the first month post-KT in

Table 6. Times and causes of hospitalization throughout the 24-month follow-up

Variable	ABOi, n = 44	ABOc, n = 44	*P* value
Initial duration of hospitalization, in days, mean ± SD	12.8 ±7.2	10.8 ±4.2	NS
No. of short hospitalizations, i.e., <2 days, mean ± SD	6 ± 3.1	4.2 ±2.2	0.01
No. of long hospitalizations, i.e., >2 days; mean ±SD	1.96 ±1.4	1.8 ± 1.6	NS
Duration of long hospitalizations (> 2 days), in days, mean ± SD	10 ± 11	6.5 ±4.5	NS
Causes of long hospitalizations, n (%)			
Infections, n (%)	14 (27.2%)	13 (29.5%)	NS
Surgical problems, n (%)	10 (22.7%)	6(13.6%)	NS
Others, n (%)	14(31.8%)	13(29.5%)	NS

Abbreviations: ABOi: ABO incompatible; ABOc: ABO compatible; D: days, M: months, SD: standard deviation, NS: not significant.

Table 7. Complications after transplantation and during the 24-month follow-up

Complications, n (%)	ABOi, n = 44	ABOc, n = 44	P value
Infection, at least one	25 (56.8%)	23 (52.2%)	NS
Urinary tract infection, at least one	15 (34%)	12 (27.2%)	NS
<M1	3 (6.8%)	1 (2.2%)	NS
From M1–M6	12 (27.2%)	5 (11.3%)	NS
M7–M12	2 (4.5%)	3 (6.8%)	NS
M12–M24	1 (2.2%)	2 (4.5%)	NS
Pneumonia	5 (11.3%)	3 (6.8%)	NS
Sepsis	3 (6.8%)	4 (9%)	NS
Other	4 (9%)	7 (15.9%)	NS
CMV infection	2 (4.5%)	5 (11.3%)	NS
BKV in urine: M1	5 (11.3%)	1 (2.2%)	NS
M3	11 (25%)	3 (6.8%)	0.03
M6	8 (18.1%)	4 (9%)	NS
M12	7 (15.9%)	4 (9%)	NS
M18	5 (11.3%)	2 (4.5%)	NS
M24	5 (11.36%)	1 (2.2%)	NS
BKV in blood: M1	0	0	
M3	5 (11.3%)	1 (2.2%)	NS
M6	4 (9%)	1 (2.2%)	NS
M12	1 (2.2%)	1 (2.2%)	NS
M18	1 (2.2%)	1 (2.2%)	NS
M24	1 (2.2%)	0	NS
Posttransplant surgical complication, at least once	16 (36.3%)	13 (29.5%)	NS
Lymphocele	5 (11.3%)	6 (13.6%)	NS
Hemorrhagic shock	6 (13.6%)	1 (2.2%)	NS
Others	10 (22.7%)	7 (15.9%)	NS
Other complications	11 (25%)	11 (25%)	NS
HTN (n; %)	28 (63.%)	22 (50%)	NS
NODAT (n; %)	9 (20.4%)	6 (13.6%)	NS

Abbreviations: CMV, cytomegalovirus; HTN: hypertension; NODAT, new onset of diabetes mellitus after transplantation; BKV, BK virus; ABOi, ABO incompatible; ABOc, ABO compatible; D, days; M, months; SD, standard deviation; NS, not significant.

both groups (total of eight [18.1%] in the ABOi group; i.e., three humeral, two mixed type, one borderline, and two cellular mediated; whereas there were five [11.3%]in the ABOc group, i.e., one humeral, two borderline, one cellular, and one mixed type).

In both ABOi and ABOc recipients, most acute rejections were treated successfully and had favorable outcomes. There was one chronic rejection, which was treated but did not have a favorable result. No chronic rejection occurred amongst the ABOc patients (Table 9).

Both ABOi and ABOc groups developed similar rates of delayed graft function (DGF). In our study, DGF was defined as serum creatinine >200 µmol/L after D7. As shown in Table 10, most causes of DGF in both groups were caused by an acute rejection: CNI toxicity and infections (such as acute pyelonephritis) were also involved.

5. Discussion

ABOi donor kidneys are being increasingly used and (28) have become an accepted type of KT. Their success rates and associated potential risks are equivalent to those for ABOc KT.

This study compared the long-term outcomes of ABOi living-donor KT and ABOc living-donor KT in our center in southern France. The overall early and long-term outcomes were similar between the groups in terms of patients' survival (100%) and graft survival (91% in the ABOi and 99% in the ABOc group), and renal function, within the mean follow-up period of 24 months.

Our results are similar to those from other studies. In a recent Korean study, Shin et al reported survival rates of patients at 1 and 3 years of 99.0% and 98.5% in the ABOc group, respectively, and of 97.3% and 95.9% in the ABOi group. In addition, death-censored graft survival was comparable between the ABOc and ABOi groups (99.7% vs. 98.6% at 1 year; 98.7% vs. 98.6% at 3 years; $P = 0.386$) (66).

Similarly, a German study by Wilpert et al reported

Table 8. Overall outcomes after renal transplantation in ABOi and ABOc patients

Events, n (%)	ABOi, n = 44	ABOc, n = 44	Total, n = 88	*P* value
Acute rejection: total (%)	10 (22.7 %)	9 (20.4%)	17 (19.3%)	NS
<1 month	8 (18.1 %)	5 (11.3%)	13 (14.7%)	NS
>1 month	2 (4.25%)	2 (2.4%)	4 (9%)	NS
Chronic rejection, total (%)	2 (4.5%)	0	2 (4.5%)	NS
Patients with 1> rejection	0	1 (2.2%)	1 (1.13%)	NS
Graft losses, total (%)	4 (9%)	1 (2.2%)	5 (5.6%)	NS
Graft loss (rejection-related)	2 (4.5%)	0	2 (2.2%)	NS
Graft loss (not rejection related)	2 (4.5%)	1 (2.2%)	3 (3.4%)	NS
Early graft loss <1 month	1	0	1	NS
Late graft loss,>1 month	3	1	3	NS
Death	0	0	0	NS

Abbreviations: ABOi, ABO incompatible; ABOc, ABO compatible; NS, not significant.

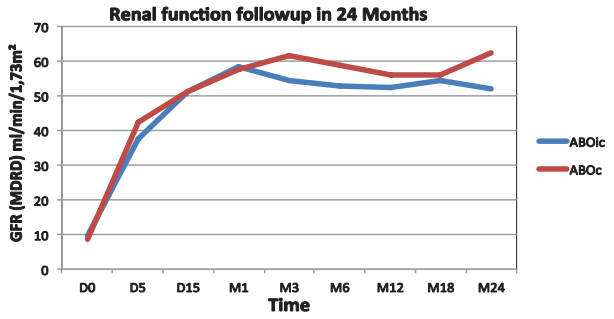

Figure 1. Mean estimated GFR (according to MDRD formula) during the 24-month follow up period.
Abbreviations: D: day, M: months, ABOi: ABO incompatible, ABOc: ABO compatible, GFR: glomerular-filtration rate.

on 40 ABOi living-donor KTs, and found similar patient- and graft-survival rates compared with 43 ABOc living-donor KTs. Patient survival was 98% in the ABOi group and 98% in the ABOc group (*P* = 1.00), and death-censored graft-survival rates were 100% and 93%, respectively (*P* = 0.24) (67).

A Japanese study by Tanabe et al reported excellent long-term outcomes for ABOi living-donor KTs (13). Survival rates of patients in ABOi and ABOc groups were 99% and 97.7%, respectively, at 5 years post-KT, and 99% and 95.2% at 10 years after KT, respectively (*P*=0.083). Graft-survival rates were 92.2% and 93.5% at 5 years, and 90.9% and 84.7% at 10 years, respectively (*P* = 0.355).

Another large registry analysis compared the 3-year outcomes of 1420 ABOi KTs performed at 101 centers in Europe, Australia, and New Zealand, which were compared with matched ABOc transplantations: the overall 3-year graft-survival rates did not differ between the two groups (~90%) (3).

In our study, there was no significant difference in early graft loss (before day 30 post-transplant), i.e., one (2.2%) ABOi patients versus no ABOc patients (*P* = NS), or in the late post-transplant period, i.e., three (6.8%) ABOi patients versus one (2.2%) ABOc patient (*P* = NS). In contrast, a US study by Montgomery et al reported significantly higher graft losses, particularly within the first 14 days post-transplant in ABOi patients (*P* = 0.001), but with little to no difference beyond day 14 post-transplantation (*P* = 0.058) (68).

Genberg et al, like us, found similar rates of infection in both groups during the early and longer term follow-up period (21) (i.e., overall infection complications between ABOi KT and ABOc KTs were 40% vs. 63.3%, respectively, in their study). In contrast, Habicht et al analyzed 21 ABOi KT recipients who had undergone desensitization with ABO-specific IA and rituximab compared to 47 ABOc patients. These authors found more infections amongst ABOi patients, such as CMV, herpes simplex, varicella zoster, and BKV (50% versus 21% in ABOc patients; *P* = 0.038) (41).

ABOi kidney recipients may be at more risk of developing BK viremia or nephropathy because of the increased intensity of induction protocols and the subsequent immunosuppressant needed for maintenance and to prevent graft rejection (41).

In our study we observed more incidences of BKV infection in ABOi recipients in the early post-KT period but there were less BKV infections during the later post-KT period. Some studies have observed a higher risk of BK viremia or nephropathy whereas others have not (8,13).

Because we used very efficient apheresis techniques for desensitization, such as semispecific immunoadsorption or DFPP, this led to greater loss of coagulation factors; thus, there were more incidences of early post-KT bleeds, and lower levels of hemoglobin and platelets in the ABOi group. Similar results were found by Hwang et al (69), and de Weerd et al (70). After de Weerd et al performed a median of four sessions (range: 0–10) of plasmapheresis before KT, depending on the initial isoagglutinin titer and

Table 9. Characteristics of rejection types in ABOi and ABOc groups

Types, n (%)	ABOi n=44	ABOc n=44	*P* value
Acute rejections, total (%)	10 (22.7%)	9 (20.4%)	NS
Cellular	2 (4.5%)	3(6.8%)	NS
Mixed (cellular+humoral)	2 (4.5%)	1 (2.2%)	NS
Humoral	4 (9%%)	2 (4.5%)	NS
Borderline	1 (2.2%)	3 (6.8%)	NS
Undetermined	1 (2.2%)	0	NS
Treated, *n* (%) Yes	8 (15.9%)	7 (15.9%)	NS
No	2 (4.5%)	2 (4.5%)	NS
Treatment type, *n* (%)			
Methylprednisone boluses	8	7	NS
+ ATG	1	0	NS
+ PE + IA	1	1	NS
PE+ rituximab	2	2	NS
PE+ATG + eculizumab + rituximab	0	1	NS
Chronic rejection	2 (4.5%)	0	NS
De novo DSAs, total	6 (13.6%)	2 (4.5%)	NS
<M3	1 (2.2%)	0	NS
<M6	2 (4.5%)	1 (4.5%)	NS
<M12	0	1 (2.2%)	NS
<M18	1 (2.2%)	0	NS
<M24	2 (4.5%)	1 (2.2%)	NS

Abbreviations: ABOi, ABO incompatible; ABOc, ABO compatible; D, days; M, months; NS, not significant; PE, plasma exchange; ATG, anti-thymocyteglobulins; IA, immunoadsorption; DSA, donor-specific alloantibody.

titer reduction during plasmapheresis. Postoperative hemorrhagic risk was higher in the ABOi KT group and was correlated with a greater number of sessions of plasmapheresis before transplantation (70).

Our main surgical complication was lymphocele, which occurred similarly between the two groups, and also hemorrhagic complications, which were more common in the ABOi group. These results contrast with those from a German study, where they found lymphocele complications in ABOi patients occurred statistically more frequently than in ABOc patients (41,67,71). There is no specific explanation for this finding, but some studies have shown that early introduction of MMF may be a participatory factor (72).

Despite the intensive immunosuppressive protocols used in our study, two cases of cancer complications were found in ABOi patients: both were skin-type cancers that developed after month 18 post-KT, whereas no incidence of cancer was found in ABOc patients.

No studies have comprehensively analyzed the risk of cancer among ABOi KT patients; however, Hall et al reported seven cases of cancers diagnosed at a median of 3.6 years post-KT, but there was no difference in the overall risk of cancer between recipients of ABOi or ABOc transplants (73).

Table 10. Patients with delayed graft function and patients who had a creatinine level >200 µmol/L at D7

Characteristics	ABOc, n=44	ABOi, n=44	*P* value
Delayed graft function (creatinine >200 µmol/L atD7 post-KT, n (%)	5	8	NS
Causes of delayed graft function			
CNI toxicity	1	2	NS
Acute rejection	2	4	NS
Infection	2	2	NS
Causes of creatinine >200 µmol/L within 24 months follow up			
Acute rejection	1(M12)	2(M1), 1(M3)	
Chronic rejection	0	2(M6), 1(M12)	
De novo glomerular disease	1(M18)	0	
Resolving acute renal failure due to infection	2 (M12),	1(M1), 1(M6), 1(M18)	

Abbreviations: D: day; M: months; CNI: calcineurin inhibitors; KT: kidney transplant; NS: not significant.

6. Conclusions

We found similar long-term graft and patient-survival rates between ABOi and ABOc groups, despite that ABOi patients received more intensive immunosuppression. Rates of infection were relatively similar, although more BKV infections were noted in the ABOi group early during the follow-up period.

Limitations of the study

This is a single-center study that included a limited proportion of patients with limited follow-up.

Authors' contribution

AZ, and BNH collected the data. AL performed pre-transplant apheresis sessions; SF performed the kidney transplants; DB performed isoagglutinin titration; GFC analyzed the kidney allograft biopsies; EL, KN and RL recruited the patients and managed them at pre- and post-transplant.

Conflicts of interest

There were no points of conflicts to declare.

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