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Outcomes of ABO Incompatible Kidney Transplantation: A Single Center Experience

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ABSTRACT

Background: Kidney transplantation (KT) is the treatment of choice for patients with end-stage renal disease (ESRD). General organ donor shortage remains an important limitation on KT, given the increasing number of patients waiting for transplantation. This has led to the adoption of different strategies to increase the pool of donors, such as ABO incompatible (ABOi) living KT. In this single center study, we retrospectively evaluated all donor/recipient pairs proposed for ABOi KT since the beginning of this transplantation program in our hospital in 2014. **Methods**: Between November 2014 and March 2022, 609 deceased donor and 223 living donor KT were performed in our center. Seventy-one donor/recipient pairs were proposed for ABOi KT and were evaluated for ABO/Rh group, Coombs tests, human leukocyte antigen (HLA) type I (A, B, C) and II (DR) high resolution genotyping and receptor to donor isoagglutinin titers and HLA antibodies. Recipients with immunoglobulins G (IgG) and/or M (IgM) isoagglutinin titers > 1:512 and/or with HLA donor specific alloantibodies (DSAs) were excluded from the ABOi transplantation program. Isoagglutinins removal was performed recurring to therapeutic plasma exchange (TPE) and/or immunoadsorption techniques. Transplanted patients were evaluated for demographic data, diagnosis, relationship with donor, sessions of antibodies removal, pre- and post-KT isoagglutinin titers, graft function, transfusion support, significant complications and overall patient survival. **Results**: Eighteen patients (14 males and 4 females) were transplanted with an ABOi graft out of 71 ABOi studied pairs. Median baseline IgG and IgM isoagglutinin titers were 1:32 (min 1:2, max 1:256) and 1:8 (min 1:2, max 1:32), respectively. Fifteen patients (83.3%) had pre-KT TPE and/or immunoadsorption sessions for isoagglutinin removal (mean 2.4 ± 1.8 session per patient). Seven patients (36.8%) were submitted to post-KT TPE (mean 1.9 ± 3.2 session per patient). No acute antibody mediated rejection was observed and overall graft survival was 100% on a follow-up period between 3 and 92 months (47.6 ± 25.2 months). All patients were dialysis-free with serum creatinine steady levels (median 1.4 mg/dL) at 47.6 ± 25.2 months of follow up. **Conclusion**: These results confirm that ABOi KT is a viable treatment for patients with ESRD, thus expanding living donor pool and reducing access time to transplantation.

Descriptors: ABO Blood Group System Incompatibility. Kidney Transplantation. Living Donors. Plasma Exchange. Therapeutic Immunoadsorption. Immunosuppression Therapy.

Resultados do Transplante Renal ABO Incompatível: A Experiência de um Centro

RESUMO

Introdução: O transplante renal (TR) é o tratamento de eleição dos doentes com doença renal terminal. A escassez de órgãos continua a ser uma limitação importante, dado o número crescente de doentes a aguardar transplante, levando à adoção de diferentes estratégias para aumentar o número de doadores, tal como o TR ABO incompatível (ABOi) de doador vivo. Neste estudo unicêntrico, avaliamos retrospectivamente todos os pares doador/receptor propostos para TR ABOi desde a implementação do programa de transplante no nosso hospital em 2014. **Métodos**: Entre novembro de 2014 e março de 2022, foram realizados 609 TR de doador cadáver e 223 TR de doador vivo. Setenta e um pares doador/receptor foram propostos para

TR ABOi e avaliados para grupo ABO/Rh, teste de Coombs, genotipagem de alta resolução de antígeno leucocitário humano (HLA) tipo I (A, B, C) e II (DR), titulação de isoaglutininas receptor/doador e anticorpos HLA. Receptores com títulos de isoaglutininas da classe G (IgG) e/ou M (IgM) > 1:512 e/ou aloanticorpos HLA doador específicos (DSAs) foram excluídos do programa de transplante ABOi. A remoção das isoaglutininas foi realizada através de técnicas de troca plasmática terapêutica (TPT) e/ou imunoadsorção. Os doentes transplantados foram avaliados quanto a dados demográficos, diagnóstico, relação com o doador, sessões de remoção de anticorpos, títulos de isoaglutininas pré- e pós-TR, viabilidade do enxerto, suporte transfusional, complicações significativas e sobrevida global do doente. **Resultados**: Dezoito doentes (14 homens e 4 mulheres) foram transplantados com enxerto ABOi dos 71 pares ABOi estudados. A mediana dos títulos de isoaglutininas IgG e IgM foram 1:32 (min. 1:2, máx. 1:256) e 1:8 (min. 1:2, máx. 1:32), respetivamente. Quinze pacientes (83.3%) foram submetidos a sessões de TPT e/ou imunoadsorção pré-TR para remoção de isoaglutininas (média 2.4 ± 1.8 sessões por doente). Sete doentes (36.8%) foram submetidos a TPT pós-TR (média 1.9 ± 3.2 sessões por doente). Não foi observada rejeição aguda mediada por anticorpos e a sobrevida global do enxerto foi de 100% num período de seguimento entre 3 e 92 meses (47.6 ± 25.2 meses). Todos os doentes estavam livres de diálise com níveis estáveis de creatinina sérica (mediana 1.4 mg/dL) em 47.6 ± 25.2 meses de seguimento. **Conclusão**: Estes resultados confirmam que o TR ABOi é um tratamento viável para doentes com doença renal terminal, expandindo assim o número de doadores vivos e reduzindo o tempo de espera para transplante.

Descritores: Incompatibilidade no Sistema de Grupos Sanguíneos ABO. Transplante de Rim. Doadores Vivos. Troca Plasmática. Imunoadsorção Terapêutica. Terapia de Imunossupressão

INTRODUCTION

Kidney transplantation (KT) is the treatment of choice for patients with end-stage renal disease (ESRD).[1] A successful KT improves the quality of life and reduces the mortality risk for most patients when compared with maintenance dialysis.[2,3] Patient survival is higher in preemptive renal transplantation or when the transplant is performed up to 2 years after starting dialysis, followed by a progressive decrease.[4] Survival is further increased if kidney comes from a living donor, and graft survival is also better when compared to deceased donor.[5-8]

General organ donor shortage is an important limitation, given the increasing number of patients in need of a transplant. Traditionally, blood group O patients waited significantly longer for a KT than patients with other blood groups due to ABO antibody barrier. This has led to the adoption of different strategies to increase the donor pool, and, in the last 40 years, ABO incompatible (ABOi) living donor KT has become a viable alternative, increasing the donor pool up to 30%.[9-11]

The first intentional ABOi KT was performed in 1951, but the transplant recipient died within a month. At that time there was no knowledge that ABO antigens are expressed not only on erythrocytes but also on cells from various tissues, including the vascular endothelium. Therefore, the standard procedure at the time, which consisted in rinsing the graft intensely with saline solution to remove blood, was not sufficient to overcome the immunological issues related to ABO incompatibility.[12]

Since ABO blood group antigens are considered the most antigenic in transplantation, it was originally thought that ABOi KT would lead to hyperacute rejection with graft loss mediated by preformed ABO groups antibodies. Nowadays, we additionally know that carbohydrate antigens in human kidney vary depending on the blood group A subtype (A_1/A_2) and Lewis status.[12-15]

For a long time, ABOi KT was considered unfeasible because of major ABO incompatibility.[11,16] In 1982, the first large study on ABOi KT was an important hallmark.[8] Successful desensitization was achieved by repeated plasmapheresis, splenectomy, donor platelet transfusion, and infusion of A or B substance, together with intensified immunosuppression with a one-year graft survival of 75%.[4,8,11,16] This led to a wider implementation of ABOi KT, first in Japan in late 1980s, then in United States in mid 1990s and Europe in early 2000s.[17-19]

Considering the increased risk of graft loss as a result of hyperacute humoral rejection, patients undergoing ABOi KT were classically splenectomized, as the spleen is a reservoir for immunoglobulins M (IgM) and G (IgG) producing B-cells and plays an important role in producing anti-blood group A and B antibodies (isoagglutinins).[4,20] Nowadays, splenectomy is no longer necessary to inhibit antibody production. Adequate desensitization therapy prior to transplantation yields equally satisfactory results, inhibiting antibody production until the induction of accommodation, an acquired resistance of an organ to immune-mediated damage.

The availability of monoclonal antibodies such as anti-CD20 (rituximab) allowed to overcome splenectomy with good results.[21] Nowadays the improvement of immunosuppressive protocols and antibody removal techniques and the additional knowledge of

the biochemistry of the ABO antigens, subtypes A1/A2 and Lewis status allow transplantation to be performed despite the ABO blood group barrier, minimizing the risk of humoral rejection.[12-15,22]

Standard approach for ABOi KT is based on two premises: removal of circulating ABO antibodies (isoagglutinins) and pharmacological immunosuppression, that included depletion of antibody-producing B-cells.[11,12,23]

The main goal is to maintain the isoagglutinin titer below a threshold considered safe for KT.[11,12,23] Firstly, antibody removal is essential, and the two most used methods are therapeutic plasma exchange (TPE) and immunoadsorption. The baseline anti-A/B antibody titer will determine the number of treatment sessions.[24] Immunoadsorption techniques can be antigen-specific (single use) or non-antigen-specific. The non-antigen-specific technique employs reusable adsorption columns that also have the advantage of depleting potential HLA donor specific alloantibodies (DSAs),[25-27] when compared to antigen-specific immunoadsorption techniques.

The initial goal of antibodies removal is to decrease isoagglutinin titer to < 1:16 before transplantation, a limit which has been based on empirical evidence.[13] Ideally, isoagglutinin titer should remain ≤ 1:8 during the first week and ≤ 1:16 during the second week after surgery. Thereafter, even if there is a rebound increase of anti-A/B antibodies, the graft will not be harmed. This phenomenon is called accommodation and refers to the lack of reaction between the patient's antibodies in blood and antigens on endothelial cells within the graft.[11,13] It ensures graft survival without antibody-mediated rejection, reflecting changes in antibodies, control of complement or acquired resistance to injury by antibodies, complement or other factors.[20,28] According to Park *et al.*,[29] accommodation can be determined by detectable anti-A and/or anti-B isoagglutinins with graft function similar to that of ABO-compatible (ABOc) patients and normal histological findings on graft biopsy.

Depletion of antibody-producing B-cells is also important and is obtained with rituximab and basiliximab (T-cell IL-2 receptor antagonist). Pharmacological immunosuppression also includes triple therapy with corticosteroids, mycophenolate mofetil and calcineurin inhibitors, such as tacrolimus, or cyclosporine-based immunosuppression. An individualized immunosuppression protocol allows a balance between prevention of rejection and the increased risk of infection.[30]

KT ABOi shows results comparable to ABOc KT.[17,20,31] A KT candidate with an ABOi living donor may wait for a deceased ABOc donor while remaining on dialysis, participating in a Kidney Exchange Program (KEP), or proceeding with desensitization for ABOi KT. In order to ensure the ability to make an informed decision about which option to choose, the incremental risk of desensitization for ABOi KT donor-recipient pairs should be known.[32]

Strategies to increase the donor pool and access to KT are needed. Recent resolutions from the Council of Europe urges member countries to implement a KEP and to adopt ABOi KT programs due to the good results, organ shortages and long waiting list for cadaver KT expanded criteria.[33] A national KEP is a possibility of overcoming the ABO mismatch, but there is in these programs excess of group O recipients and donors from other ABO groups, making it difficult to find a matching pair. Organizing a KEP requires transparent protocols and efficient trust-based cooperation between the multidisciplinary teams of professionals. In Europe, the further development of a KEP must follow the Council of Europe resolutions on living donation and the European Union legal framework.[34-36]

In Portugal, many potential living donors have been turned down due to ABO incompatibility. About 20–25% of the pairs studied in various national KT programs were rejected for this reason.[37]

Our center is the only one performing ABOi KT in the country and started in 2014. This work pretends to present our experience with a retrospective evaluation on donor/recipient pairs referred between 2014 and 2022.

METHODS

Between November 2014 and March 2022, 609 deceased donor and 223 living donor KT were performed in our center. Seventy-one donor/recipient pairs were proposed for ABOi KT.

In each pair ABO/Rh group, Coombs tests, HLA type I (A,B,C) and II (DR, DQ) high resolution genotyping was performed.

Receptor isoagglutinin titers were performed for IgG and IgM isotype recurring to microcolumn gel technology (Diamed-Biorad).

Titer was performed by using commercial cells and donor red blood cells, with the highest titer being the result. Isoagglutinins titer should be < 1:16 on surgery day (D0), ≤ 1:8 during the first week (D1–D7), and ≤ 1:16 during the second week (D8–D14) post-KT. Titer monitoring was performed daily during hospitalization. After hospital discharge, it was performed twice a week in the 1st month, once a week during the 2nd month and once a month up to the 6th month.

Receptor HLA antibodies (class I and II) were screened by complement dependent cytotoxicity and bead-array methodology (Luminex Multiplex Assays, Thermo Fisher Scientific). The result was expressed as mean fluorescence intensity and the cut-off for

a positive result was 1,000. The crossmatch between lymphocytes of donor and serum of recipient was performed by flow cytometry. Recipients with IgG and/or IgM isoagglutinin titers > 1:512 and/or with HLA donor specific alloantibodies were excluded from the ABOi transplantation program. The reason was the exponential relationship between pretreatment isoagglutinins titers and the minimum number of TPE required to achieve a goal pre-surgery titer. Titers ≥ 1:512 should have required more than 10 TPE sessions before KT and a higher incidence of antibody rebound.[24]

Isoagglutinins removal was performed recurring to plasmapheresis or immunoadsorption techniques.

TPE was performed by single-membrane filtration (Omni, Braun) with the exchange of 1.5 plasma volumes per session. The replacement fluid was 5% albumin and, for the last liter of replacement, fresh frozen plasma (FFP) was used, except on D0 when the fluid consisted of half volume 5% albumin and half volume FFP. After each TPE, 100 mg/kg of human polyvalent immunoglobulin was administered intravenously.

The immunoadsorption technique was performed with non-specific and reusable adsorption columns (Adasorb, Medicap). They consisted of two parallel, regenerable columns with protein A and peptide GAM covalently bound to Sepharose (Cytiva). The main advantage of immunoadsorption technique compared to TPE is the avoidance of substitution fluids, such as albumin and FFP. Immunosuppression protocol is described in Table 1. CMV prophylaxis was performed with valganciclovir in all patients.

Table 1. Pharmacological immunosuppression.

Drug	Dose and time of administration
Rituximab	375 mg/m^2 single intravenous dose, 2 weeks before KT
Tacrolimus	0.15 mg/kg/day, starting 7 days before KT; Dose was adjusted to levels of 10 to 12 ng/mL until 3rd month after KT
Mycophenolate mofetil	1 g 12/12 h, starting 2 days before KT
Basiliximab	20 mg intravenous on surgery day and 4 days after
Methylprednisolone	500 mg intravenous on surgery day; 125 mg daily on days 1 and 2; 62.5 mg daily on days 3 and 4
Prednisolone	20 mg orally daily starting 5 days after KT

KT: kidney transplantation.

Transplanted patients were evaluated for demographic data, ESRD diagnosis, relationship with donor, Pre- and post-KT isoagglutinins titer on D0, D14, D30, 6th month and last measured titer, number of TPE and immunoadsorption before and after KT, serum creatinine on D0, D1, D14, D30, 6th month and last measured value, functional graft (considered a serum creatinine level below 2 mg/dL at D30); blood component transfusion support perioperatively and after the transplant; significant KT associated complications; overall patient survival; outcome of patients accepted for ABOi KT and patients who were evaluated for ABOi KT but did not go through with it.

Statistical analysis was performed using the IMB SPSS Statistics 28 software. The data distribution were tested for normality using the Kolmogorov–Smirnov test. Normally distributed data were presented as mean ± standard deviation and non-normally distributed data were presented as median and interquartile range (IQR); age comparisons were performed using independent variables t-test and Levene's F test. Correlation between antibody titer and TPE sessions number was conducted using the Spearman correlation. A very strong correlation is defined as Spearman's rank correlation coefficient (r_s) ≥ 0.80.

RESULTS

Over a period of 7 years, 71 donor-receptor pairs were studied for ABOi KT. Of the patients, 38% (27/71) were excluded due to isoagglutinin titer ≥ 1:512 and 7.0% (5/71) patients were identified as having HLA DSAs, hence being excluded from the program.

From the 39 patients initially considered suitable for ABOi KT, 18 (46.1%) underwent ABOi KT and 7 (17.9%) underwent another type of transplant (3 deceased-donor, 2 KEP transplants and 2 unrelated isogroupal living donors). One (2.6%) patient was excluded for not meeting the surgical criteria for transplantation, 8 (20.5%) are on the waiting list for deceased or KEP transplant, 4 (10.3%) died and 1 (2.6%) patient was lost during follow-up.

A group of 18 pairs underwent ABOi KT, 38.9% (n = 7) were siblings, 33.3% (n = 6) were couples, 16.7% (n = 3) were parent-child, 5.6% (n = 1) were uncle/nephew and 5.6% (n = 1) were mother-in-law/son-in-law.

In regard to the donors, 77.8% (n = 14) were women with a mean age at the time of transplant of 46.7 ± 5.5 years, while 77.8%(n = 14) of the recipients were men with a mean age of 42.8 ± 9.3 years. Independent samples t-test analysis showed no significant differences between the ages of donors and patients (p > 0.05, CI: 95%).

Two patients underwent preemptive KT without performing dialysis while the remaining patients were on dialysis before KT on a mean time of 17 ± 16 months. Transplanted demographics data are presented in Table 2.

Table 2. Demographic data of donors and recipients. Blood group and clinical conditions.

Pair	Donor			Recipient				
	Relationship	Age Mean 46.7 ± 5.5	Blood group	Relationship	Age Mean 42.8 ± 9.3	Blood group	Diagnosis	Time on dialysis (months) Mean 16.6 ± 16.3
1	Sister	52	B+	Sister	50	O-	PKD	10
2	Mother	58	AB+	Daughter	29	A+	Alport syndrome	49
3	Brother	50	B+	Brother	59	A+	Diabetic nephropathy	5
4	Brother	46	A-	Brother	51	O+	Unknown etiology	16
5	Sister	38	A+	Brother	39	O+	MPGN	1
6	Aunt	49	B+	Nephew	30	A+	Alport syndrome	21
7	Sister	39	B+	Brother	43	O+	Unknown etiology	1
8	Mother	49	A+	Son	31	O+	ICN	29
9	Wife	47	B+	Husband	55	O+	IgA nephropathy	0
10	Wife	41	B+	Husband	43	A-	Unknown etiology	32
11	Sister	41	AB+	Sister	42	A-	Iatrogenic nephrotoxicity	2
12	Father	49	A2+	Son	28	O+	FSGS	15
13	Wife	39	B+	Husband	41	A+	MPGN	5
14	Wife	47	A+	Husband	50	B+	Unknown etiology	39
15	Wife	47	A+	Husband	45	O-	FSGS	8
16	Wife	44	A+	Husband	51	B+	Unknown etiology	19
17	Brother	51	B+	Sister	48	A+	PKD	0
18	Mother-in-law	53	B+	Son-in-law	36	O+	Alport syndrome	47

D: Donor; R: Recipient; FCGS: Focal segmental glomerulosclerosis; ICN: Interstitial chronic nephritis; MPGN: Mesangial proliferative glomerulonephritis; PKD: Polycystic kidney disease.

Of the 18 patients who underwent transplantation, 9 were blood group O, 7 blood group A and 2 blood group B. Eleven patients presented ABO major incompatibility and 7 patients presented major and minor ABO incompatibility with their donors. Four patients had HLA antibodies, but none had DSA. Results are summarized in Tables 3 and 4.

Table 3. HLA antibodies and mismatches, Isoagglutinin titer, TPE and immunoadsorption sessions.

Pair	Anti-HLA*	HLA mismatches** (Median 3.8;2.3)	Titer of isoagglutinins							TPE sessions		IA sessions
			pré-KT IgM*** Median 1:8	pré-KT IgG*** Median 1:32	D0 Median 1:4	D14 Median 1:4	D30 Median 1:4	D180 Median 1:4	Last titer Median 1:3	Pre-KT Median 2	Post-KT Mean 1.91± 3.2	Pre-KT Median 0
1	No	3	1:16	1:128	1:8	1:8	1:8	1:32	1:4	7	6	0
2	Yes	1	1:4	1:16	1:2	1:4	1:4	1:2	1:16	1	0	0
3	No	1	1:8	1:32	1:2	1:4	1:2	1:2	1:8	3	3	0
4	No	3	1:2	1:8	1:8	1:8	1:4	1:8	1:8	0	0	0
5	No	5	1:16	1:128	1:4	1:16	1:64	1:32	1:32	4	10	0
6	No	4	1:2	1:8	1:2	1:2	1:2	ND	1:2	0	0	0
7	No	3	1:16	1:256	1:4	1:8	1:8	1:4	1:2	4	2	0
8	Yes	2	1:16	1:256	1:4	1:16	1:32	1:8	1:8	7	8	0
9	No	5	1:8	1:128	1:4	1:8	1:8	1:4	1:4	4	6	0
10	Yes	6	1:32	1:128	1:8	1:8	1:8	1:16	1:2	3	3	0
11	No	6	1:4	1:16	1:2	1:2	1:8	1:4	1:2	1	0	0
12	No	3	1:8	1:32	1:4	1:4	1:8	ND	1:2	2	0	0
13	No	5	1:8	1:16	1:16	1:8	1:4	ND	1:8	2	0	0
14	Yes	2	1:4	1:32	1:4	1:2	1:4	1:8	1:8	0	0	2
15	No	5	1:32	1:64	1:4	1:2	1:2	1:2	1:2	1	0	2
16	No	5	1:4	1:8	1:4	1:2	1:4	1:2	1:2	0	0	1
17	No	3	1:2	1:2	1:2	1:2	1:2	ND	1:2	0	0	0
18	No	6	1:16	1:64	1:2	1:2	1:2	1:2	1:2	2	0	1

IA: immunoadsorption; ND: no data; TPE: therapeutic plasma exchange. * Antibodies anti-HLA class I (A, B, C) and class II (DR, DQ) presence; ** HLA mismatches in loci A, B and DR; *** Titer of isoagglutinins IgM or IgG before TPE and/or IA.

In the initial assessment, the median titer of isoagglutinins was 1:8 (min 1:2, max 1:32) and 1:32 (min 1:2, max 1:256) for IgM and IgG, respectively. Target isoagglutinin titer immediately before KT was accomplished in all patients (1 patient required an additional TPE session on surgery day because he presented a 1:16 isoagglutinin titer). On D8 and D14 all patients were within target levels. Fifteen patients (83.3%) had pre-KT TPE and/or immunoadsorption for isoagglutinin removal (mean 2.4 ± 1.8 session per patient). Seven patients (36.8%) were submitted to post-KT TPE (mean 1.9 ± 3.2 session per patient). No patient underwent post-transplant immunoadsorption. A higher pre-KT titer was significantly related to a higher number of TPE (r_s 0.879, $p < 0.001$).

Regardless infections, 2 (11.1%) patients had urinary infection during the first week post-KT. A J-J stent was applied during surgery in all patients submitted to KT. Up to D30 post-KT, all patients had a serum creatinine decrease to acceptable values with a median serum creatinine of 1.4 mg/Dl (IQR 0.5).

There was no transfusion during KT. Before KT, one patient was transfused after a gastric ulcer bleeding and one because anemia. One patient was submitted to reintervention for renal vein thrombosis in D1 and was transfused. Another had bleeding from epigastric artery and had surgery and transfusion in D1. Three patients were transfused postoperative because anemia (D2, D8 and D13). One case had important bleeding after kidney biopsy and required transfusion.

Table 4. Patients follow-up data (serum creatinine, time and blood transfusions).

Pair	Serum creatinine (mg/dL)						Follow-up (months)	RBC pack transfusion (units)
	Pre-KT	D1	D14	D30	D180	Last level		
	Median 7.5	Median 4.8	Median 1.5	Median 1.4	Median 1.6	Median 1.4	Mean 47.6 ± 25.2	Median 0 (IQR 1)
1	6.9	4.2	1.0	1.1	1.2	1.1	92	4
2	6.4	2.1	1.5	1.3	1.2	1.2	83	0
3	7.7	5.2	4.9	1.3	3.4	1.7	81	1
4	14.7	1.2	1.0	1.1	0.7	1.2	69	0
5	7.7	5.1	1.5	1.3	1.7	1.4	64	5
6	16.3	9.5	1.5	1.4	1.5	1.8	62	0
7	3.7	2.4	1.8	2.1	2.3	1.9	58	1
8	6.0	2.3	1.1	1.5	1.6	1.2	53	0
9	4.8	2.7	1.8	1.7	1.7	1.5	49	1
10	10.9	5.8	1.24	1.4	2.1	4.0	49	1
11	4.6	1.2	0.8	0.8	0.7	0.8	36	0
12	8.8	5.6	1.5	1.9	1.8	2.1	35	0
13	8.6	4.9	1.6	1.5	1.5	1.3	33	0
14	13.1	6.1	1.8	1.7	1.4	1.4	33	0
15	7.4	4.9	1.6	1.4	1.6	1.8	29	0
16	5.8	4.7	0.9	0.9	0.9	0.9	14	0
17	5.0	2.0	1.1	0.9	ND	1.2	3	2
18	10.1	9.0	3.5	1.8	1.8	1.8	13	6

During follow-up, all patients maintained immunosuppression with tacrolimus (see monitoring in Fig. 1), MMF and prednisolone with no need to change the scheme.

A graft survival of 100% on a follow-up period between 3 and 92 months (47.6 ± 25.2 months) was observed. All patients are dialysis-free and maintained steady serum creatinine (median 1.4 mg/dL; IQR 0.6) on their last medical records.

Renal biopsy was performed in four patients: one patient had biopsy on D7 that showed autoimmune interstitial nephritis, methylprednisolone was then prescribed and on D23 the biopsy was repeated with normal histologic findings; a second patient had histologic findings of acute vascular rejection (Banff Classification of Kidney Allograft Pathology grade IIB) in biopsy performed on D19, methylprednisolone and antithymocyte immunoglobulin were used with a good clinical response; a third patient performed a biopsy on D18 without signs of rejection; a fourth patient had a renal biopsy performed 16 months post-KT and an incipient glomerulopathy was documented, even though the isoagglutinins titer was persistently low and no evidence of HLA alloantibodies found out—on his last observation graft function was preserved and renal biopsy showed no signs of rejection.

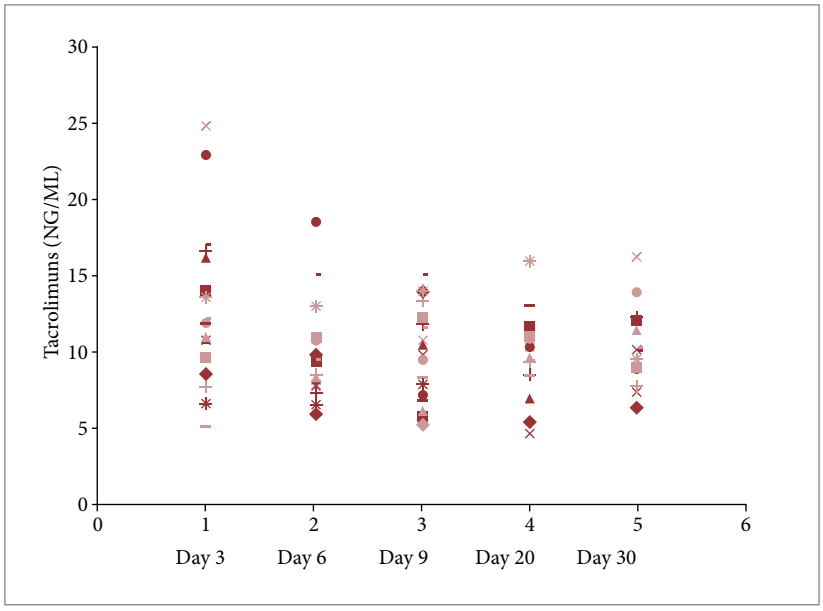

Figure 1. Pharmacological monitoring of tacrolimus in 18 patients. Each patient is represented by a different symbol.

DISCUSSION

About 20% of eligible living kidney donors are ABOi with their potential recipients. The lack of options and sources regarding KT led to the development of alternative strategies, namely ABOi KT. This procedure is becoming a common procedure in several European countries, Australia, Japan and the United States. The literature has shown that ABOi KT has results comparable to ABOc KT.[17,20,31] Survival of ABOi living donor KT recipients is similar to that of compatible transplants at 1, 3, 5 and 10-year, and the cumulative loss of kidneys at three months and on 1, 3 and 5-year are also similar, except for ABOi recipients with preformed HLA DSA.[41-45] Zschiedrich *et al.*[31] reported a median estimated 10-year patient and graft survival in ABOi KT of 99 and 94%, respectively. Flint *et al.*[37] reported 26-month graft survival rate and overall survival rate of 100%. Tanabe *et al.*[38] reported 3-year graft overall survival rate of 100%.

In our study, the long-term outcome (mean of 47.6 months) follow-up of ABOi living donor KT was excellent with a 100% overall patient and graft survival rate in agreement with other published studies.[37,38] However, our patient sample is still small (n = 18) when compared to the experience of other centers.

Some studies suggest that the incidence of rejection, significant infectious complications and malignancies are not increased, despite the more vigorous immunosuppression in ABOi KT.[37,38] In our cohort, 1 (5.6%) patient had rejection and 2 (11.1%) had significant infection episodes in the first month.

According to published data, the ABOi KT is an acceptable treatment for patients with ESRD in terms of patient survival and graft survival.[37,39-41] Our data and experience support the published results.[20,26,37,38,40,42-45]

CONCLUSION

We were able to expand living donor kidney pool and reduce time of access to transplantation. Because of the good results we look forward to increase the numbers of ABOi KT in the next future.

A multidisciplinary team is required for ABOi KT, with a strict synergy between Hematology, Nephrology and Urology Departments. The ABOi KT should be encouraged in more transplant centers as a tool to overcome organ shortage.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Oliveira R, Sampaio M, Falavigna M, Cardoso DH, Sousa JL, Malheiro J, Almeida M and Martins MLS; **Conception and design**: Oliveira R and Antunes MB; **Data analysis and interpretation**: Oliveira R; **Article writing**: Oliveira R, Falavigna M, Sampaio M, Antunes MB; **Critical revision**: Antunes MB; **Final approval**: Antunes MB.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data were generated or analyzed in ongoing study.

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