Port J Nephrol Hypert 2015; 29(4): 332-337
Advance Access publication 28 December 2015

The first ABO-incompatible kidney transplantation performed in Portugal

Primeiro transplante renal ABO-incompatível realizado em Portugal

Patrícia Barreto[1,2], Pedro Vieira[1,3], Leonídio Dias[1], Manuela Almeida[1], Sofia Pedroso[1], La Salete Martins[1], António Castro Henriques[1], Marika Bini[4], António Cabrita[1]

[1] Department of Nephrology, Centro Hospitalar do Porto. Porto, Portugal
[2] Department of Nephrology, Centro Hospitalar de Vila Nova de Gaia. Vila Nova de Gaia, Portugal
[3] Department of Nephrology, Centro Hospitalar do Funchal, Funchal, Portugal.
[4] Department of Clinical Hematology, Centro Hospitalar do Porto, Porto, Portugal.

Received for publication: 05/09/2015
Accepted in revised form: 20/10/2015

ABSTRACT

Kidney transplantation is the optimal treatment of end-stage renal disease (ESRD) improving survival and quality of life for most recipients. In our country, potential living donors have been refused due to the ABO incompatibility barrier. However, ABO-incompatible living donor kidney transplant is presently common practice in several countries with good outcomes.

The authors describe a case of a 49-year-old female patient, with chronic kidney disease due to autosomal dominant polycystic kidney disease, who had started haemodialysis 10 months before and with blood group O. The living donor was a 53-year-old sister with blood group B. The desensitization protocol was based on rituximab and plasmapheresis. The induction protocol used was basiliximab, tacrolimus, mofetil mycophenolate and metilprednisolone. Five days post-transplant she presented a normal graft function that remained during the eight months follow-up. This case reveals the first ABO incompatible living donor kidney transplant performed in Portugal with excellent outcome.

Key-Words: ABO-incompatibility; kidney transplantation; living donor.

RESUMO

O transplante renal é a modalidade de tratamento da doença renal crónica estadio 5 associada a melhores sobrevivência e qualidade de vida. No nosso país muitos potenciais dadores vivos têm sido recusados devido à incompatibilidade ABO. Contudo, o transplante renal de dador vivo ABO incompatível é hoje prática comum em diversos países com resultados positivos. Os autores descrevem o caso de doente do sexo feminino, de 49 anos, com doença renal crónica secundária a doença renal poliquística autossómica dominante, que havia iniciado hemodiálise 10 meses antes e com grupo sanguíneo O. O dador vivo foi uma irmã de 53 anos, grupo sanguíneo B. O protocolo de dessensibilização baseou-se em rituximab e

plasmaferese. O protocolo de indução foi com basiliximab, tacrolimus, micofenolato de mofetil e metilprednisolona. Evoluiu com função normal do enxerto 5 dias pós-transplante que se manteve durante o follow-up de 8 meses. Este caso clinico ilustra o primeiro transplante renal de dador vivo ABO incompatível efectuado em Portugal com excelente resultado.

Palavras-Chave: Dador vivo; incompatibilidade ABO; transplantação renal.

INTRODUCTION

Kidney transplantation is the optimal treatment of end-stage renal disease (ESRD) improving survival and quality of life for most recipients[1]. However, nowadays, the waiting list for deceased donor transplantation continues to grow[2] due to increasing prevalence of ESRD worldwide whereat demand for kidneys far exceeds the available supply[3]. Patients with ESRD who receive a kidney transplant are associated with a reduced risk of mortality compared with patients who remain on the waiting list[4]. A longer time on dialysis is responsible for inferior health status and greater exposure risk to sensitizing events resulting in higher sensitization to human leukocyte antigens at the time of transplantation[5,6]. This leads to inferior long-term outcomes after transplantation[7,8]. Longer waiting times are not only associated with higher waiting list mortality and morbidity, but may also lead to inferior outcomes after transplantation[9,10]. Waiting time has been shown as the strongest modifiable risk factor for the outcome after kidney transplantation[7,8]. Blood group O recipients have significantly longer time on dialysis than patients from other blood groups[8]. A previous study[11] reported for deceased donor kidney transplant (DDKT) median times on dialysis of 77 months for blood group O recipients versus 21-42,5 months for other blood group recipients in the north of Portugal, in 2011.

Living donor kidney transplant (LDKT) allows not only superior outcomes in terms of both graft and patient survival[12] but also an earlier transplantation, which is associated with better outcomes. Nevertheless, this practice has been precluded in Portugal by ABO-incompatibility barrier and represents the reason for refusal of 20-25% of the potential living donors.

Patients with blood group O have disadvantages in the allocation of deceased donor organs in the Eurotransplant Kidney Allocation System and fewer ABO-compatible living donors[8].

ABO-incompatible (ABOi) LDKT is currently common practice in several European countries, Australia, Japan and United States with promising outcomes and is the alternative for kidney paired donation programmes[13] which have their efficacy compromised due to blood group O recipients saturation.

CASE REPORT

We report a case of a 49-year-old Caucasian autonomous woman that started haemodialysis, in January 2014, due to chronic kidney disease secondary to autosomal dominant polycystic kidney disease. The patient´s personal history included two term pregnancies, and right nephrectomy, in March 2014, complicated with upper gastrointestinal bleeding that required four blood transfusions.

On the 10th November 2014, she was admitted to ABOi LDKT preparation. Four potential living donors were evaluated and the choice fell on the one who caused the lowest ABO-antibody titre in the recipient. The living donor was a 53-year-old sister with blood group B, haploidentical.

The recipient had blood group O, a panel reactive antibody (PRA) of 0%, negative CDC crossmatch for B and T lymphocytes. Flow cytometry crossmatch was positive for B lymphocytes and negative for T lymphocytes. Anti-HLA alloantibody class I and class II research with luminex was negative.

Pre-treatment anti-B IgG titre was 1/128.

A desensitization protocol was begun on 11th November 2014 with rituximab (in a single dose of 375mg/m²). Seven plasmapheresis (PF) sessions were performed until reaching the target titre of anti-B IgG of 1/8. The induction protocol used was basiliximab, tacrolimus, mofetil mycophenolate and metilprednisolone.

Kidney transplantation was performed on 20th November 2014. The surgical procedure elapsed without problems and immediate diuresis presented.

Post-transplant PF sessions were performed according with anti-B IgG titres taking into account the target that in the first week post-transplant was ≤ 1/8 and in the second week post-transplant was ≤ 1/16. From the second week on there were no more anti-B IgG titres target. This patient in the first week performed daily PF sessions (6 sessions) and in the second week reduced PF sessions frequency (performed only 2 sessions). After each PF session anti-cytomegalovirus specific immunoglobulin (100mg/Kg) was administered, except on the session of 28th November when a single administration of non-specific human intravenous immunoglobulin (IVIG) (0.3mg/Kg) was made.

Serum creatinine (SCr) decreased progressively and on the 5th day post-transplant presented a normal graft function.

Eight months post-transplant the patients remained with normal graft function (SCr 1.2 mg/dL) and with anti-B IgG titer of 1/8.

DISCUSSION

The ABO-incompatibility was absolute contraindication for kidney transplantation until the 1980s. Owing to the shortage of deceased donors in Japan due to lack of brain death legislation, since 1989, ABOi LDKT has been performed to expand the indication for LDKT and during the past two decades about 2,000 ABOi LDKTs were performed[14]. There was an impressive improvement in the success rate for those kidney transplants and, since 2001, the outcomes are similar to those obtained in ABO-compatible LDKT.

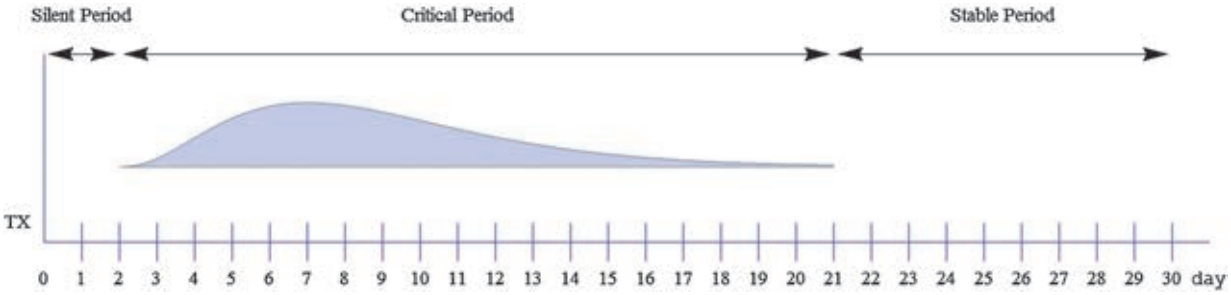
Anti-A/anti-B antibodies that elicit antibody-mediated rejection (AMR) are not only natural/preformed antibodies that generally may cause hyperacute rejection, but also *de novo* antibodies that are produced after transplantation, as a result of stimulation and sensitization by the ABO-histo group antigens present on the surface of the vascular endothelial cells in the graft and that cause acute AMR. It has been observed that the *de novo* antibodies are the most pathogenic. This fact has extremely important implications for therapeutic strategy in ABOi organ transplantation. Thus, the most important treatment step for ensuring a successful graft outcome is desensitization therapy mainly based on pre- and post-transplant antibody removal (plasmapheresis and immunoabsorption). Actually, the pre-transplant suppression of host B cell immunity with rituximab is considered an adjunctive therapy that performs a partial pharmacologic splenectomy and obviates surgical risks of splenectomy[15]. The newly described ABOi desensitization protocols advogate avoidance of a surgical splenectomy[15]. The utility of routine rituximab administration remains uncertain. Despite an absence of detectable B cells after rituximab administration, plasma cells lack CD 20 receptors and are able to produce isoagglutinin antibodies. The depletion of plasma cell precursors only decrease the risk of AMR if used in conjunction with other antibody-depleting measures. There are some reports that suggest that attention to the isoagglutinin titre at the time of transplantation and routine post-transplant antibody reduction with either plasmapheresis or immunoadsorption may significantly reduce the risk of AMR and allow for the elimination of splenectomy and rituximab from the ABOi desensitization protocol[16,17].

Acute AMR tends to occur especially within 2 to 7 days post-transplant[14]. The incidence decreases after this period, and instances of acute AMR occurring more than 1 month post-transplant were not found. This dangerous period is called “critical period” (Figure 1). It is preceded by the “silent period” that consists in the first 2 days post-transplantation once AMR due to ABO histo-blood group antigens does not arise. Accommodation was established 1 to 2 weeks post-transplant in many cases. Once accommodation has been established, there are no further instances of acute AMR throughout the graft´s life. This period is called “stable period”.

The accommodation phenomenon is defined as the situation in which, although the vascular endothelial cells in the graft carry ABO histo-blood

Figure 1

Onset of acute antibody-mediated rejection.



antigens on their surface and the blood of the recipients contains antibodies to those antigens, no antigen-antibody reaction occurs, and there is no occurrence of acute AMR. *In vitro* studies demonstrated that the binding of anti-A/B antibodies to human endothelial cells led to up-regulation of complement inhibitors, such as CD55 and CD59 and other graft-protecting genes, thereby leading to resistance to complement-dependent cytotoxicity[18].

The study by Montgomery *et al.*[13] showed that long-term patient survival was not significantly different between the cohorts of ABOi recipients and ABO compatible recipients. However, graft loss was significantly higher, particularly in the first 14 days post-transplant, with little-to-no difference beyond day 14. Graft loss in the first 14 days post-transplant was greater in patients with also pre-transplant donor specific antibodies.

Nevertheless, Fehr and Stussi´s review article[18] reported that short-term results of ABOi kidney transplantation, in terms of patient and graft survival, are excellent in all reported series worldwide and, altogether, it seems that ABOi kidney transplantation is well tolerated and has comparable outcomes to ABO-compatible transplantation. These results have been achieved with desensitization strategies based on antibody removal techniques (standard PF, double filtration PF, immunoadsorption) and on intensified immunosuppression protocols (inclusively using rituximab as an element of B-cell depletion). For maintenance immunosuppression there are no randomized trials available. Most groups performing ABOi kidney transplantation nowadays use the regimen based on tacrolimus, mycophenolate, and corticosteroids.

Desensitization regimens pretransplant and post-transplant used in the several studies were different, but all of them obtained good outcomes[13,19-22].

Recently, in 2015, Opelz *et al.*[23] reported outcomes of 1420 ABOi LDKT performed after ABO-antibody reduction in European patients. Once again was concluded that death-censored graft and patient survival rates in ABOi LDKT were similar to those achieved in ABO-compatible control groups.

In 2008, Tobian et *al.*[24] have already reported that higher anti-A/-B IgG baseline titres would require more PF sessions and established guidelines about the number of pre-transplant and post-transplant PF sessions according to ABO antibody baseline titre. Later, in 2011, Lawrence *et al.*[25] suggested that there is an exponential relationship between IgG titre and the number of PF sessions required to reach the target titre. This allows not only to predict with a reasonable degree of accuracy, from the baseline titre, how many PF sessions are likely to be required, but also to predict which patients should not enter the ABOi programme. As transplantation is only achieved in 33.3% of patients with anti-ABO titres ≥1:512, but 95.6% of patients with titres ≤1:256, shall only be accepted patients for ABOi kidney transplantation with IgG titre ≤1:256. Nowadays, it is not known at what titre it is prudent to proceed to transplantation and the cut-off titre for transplantation is between 1:4 and 1:32, depending on centre practice.

Our first ABOi LDKT in Portugal was performed based in the previous experience worldwide reported in the mentioned trials.

Table I

Anti-B IgG titres post-transplant (ABOi LDKT were performed on 20/11/2014)

Date	20/11	21/11	22/11	23/11	24/11	25/11	26/11	27/11	28/11	29/11	30/11	01/12	02/12	03/12	04/12
Anti-B IgG titre before PF	1/64		1/8	1/16	1/16	1/32	1/16	1/16	1/32	1/32	1/16	1/16	1/32	1/16	1/8
PF sessions	PF	PF	PF	PF	PF	PF	PF	–	PF	PF	–	–	–	–	–
Anti-B IgG titre after PF	1/8		1/8	1/4		1/4									

The positive flow cytometry crossmatch for B lymphocytes was interpreted in the context of ABO incompatibility. Furthermore, there were no present donor specific antibodies.

We used a desensitization protocol based on PF and rituximab. However, recent reports[23,26] showed that a rituximab free ABOi protocol yields similar excellent short- and long-term results after kidney transplantation. Maybe in the future we will perform ABOi LDKT with a lower dose of rituximab or without it. This is of considerable interest in order to reduce the high risk of infection and other complications associated with desensitization and intensified immunosuppression required for ABOi LDKT.

The outcomes were favourable and similar to those described in the literature (Table I).

CONCLUSION

This case reveals the first ABOi LDKT performed in Portugal with excellent outcome, representing a stimulus to the disclosure of this technique.

The encouraging results obtained worldwide and the advantages of ABOi LDKT, especially for blood group O ESRD patients, must be considered in order to expand this kind of kidney transplantation.

The ABOi LDKT programme shall not be faced as a substitute but as complementary to paired donation programmes that give answer to the patients with ABO antibody titres › 1:256. On the other hand, the ABOi LDKT programme consists in an alternative option for blood group O recipients with long time on dialysis due to blood group O saturation in those paired donation programmes.

Conflict of interest statement: None to declare.

References

1. Flint SM, Walker RG, Hogan C, *et al.* Successful ABO-incompatible kidney transplantation with antibody removal and standard immunosuppression. Am J Transplant 2011;11(5):1016-1024.

2. Lawrence C, Galliford JW, Willicombe MK, *et al.* Antibody removal before ABO--incompatible renal transplantation: how much plasma exchange is therapeutic? Transplantation 2011;92(10):1129-1133.

3. Wolfe RA, Roys EC, Merion RM. Trends in organ donation and transplantation in the United States, 1999-2008. Am J Transplant 2010;10(4 Pt 2): 961-972.

4. Tonelli M, Wiebe N, Knoll G, *et al.* Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. Am J Transplant 2011;11(10):2093-2109.

5. Wu HH, Tien YC, Huang CI, Chiang YJ, Chu SH, Lai PC.. HLA class I antibodies in patients awaiting kidney transplantation and the association with renal graft survival. Transplant Proc 2008;40(7):2191-2194.

6. Figueiredo A, Moreira P, Parada B, *et al.* Risk factors for delayed renal graft function and their impact on renal transplantation outcome. Transplant Proc 2007;39(8):2473--2475.

7. Meier-Kriesche HU, Kaplan B. Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis. Transplantation 2002;74(10):1377-1381.

8. Glander P, Budde K, Schmidt D, *et al.* The "blood group O problem" in kidney transplantation – time to change? Nephrol Dial Transplant 2010;25(6):1998-2004.

9. Noseworthy PA, Huang M, Zaltzman JS, Ramesh Prasad GV. Death with graft function in elderly patients after cadaveric renal transplantation: effect of waiting time. Transplant Proc 2004;36(10):2985-2987.

10. Aalten J, Hoogeveen EK, Roodnat JI, *et al.* Associations between pre-kidney-transplant risk factors and post-transplant cardiovascular events and death. Transpl Int 2008;21(10):985-991.

11. Lima BA, Mendes M, Alves H. Kidney transplantation in the north of Portugal: donor type and recipient time on dialysis. Port J Nephrol Hypert 2013;27(1):23-30.

12. Nishikawa K, Terasaki PI. Outcome of preemptive renal transplantation versus waiting time on dialysis. Clin Transplant 2002;367-377.

13. Montgomery JR, Berger JC, Warren DS, James NT, Montgomery RA, Segev DL. Outcomes of ABO-incompatible kidney transplantation in the United States. Transplantation 2012;93(6):603-609.

14. Takahashi K, Saito K. ABO-incompatible kidney transplantation. Transplant Rev (Orlando) 2013;27(1):1-8.

15. Tydén G, Kumlien G, Genberg H, Sandberg J, Lundgren T, Fehrman I. ABO incompatible kidney transplantations without splenectomy, using antigen-specific immunoadsorption and rituximab. Am J Transplant 2005; 5(1):145-148.

16. Montgomery RA, Locke JE, King KE, *et al.* ABO incompatible renal transplantation: a paradigm ready for broad implementation. Transplantation 2009;87(8):1246-1255.

17. Segev DL, Simpkins CE, Warren DS, *et al.* ABO incompatible high-titer renal transplantation without splenectomy or anti-CD20 treatment. Am J Transplant 2005;5(10):2570--2575.

18. Fehr T, Stussi G. ABO-incompatible kidney transplantation. Curr Opin Organ Transplant 2012;17(4):376-3785.

19. Tanabe K, Ishida H, Shimizu T, Omoto K, Shirakawa H, Tokumoto T. Evaluation of two different preconditioning regimens for ABO-incompatible living kidney donor transplantation. A comparison of splenectomy vs. rituximab-treated non-splenectomy preconditioning regimens. Contrib Nephrol 2009;162:61-74.

20. Gloor JM, Lager DJ, Fidler ME, *et al.* A Comparison of splenectomy versus intensive posttransplant antidonor blood group antibody monitoring without splenectomy in ABO-incompatible kidney transplantation. Transplantation 2005;80(11):1572-1577.

21. Flint SM, Walker RG, Hogan C, *et al.* Successful ABO-incompatible kidney transplantation with antibody removal and standard immunosuppression. Am J Transplant 2011;11(5):1016-1024.

22. Tobian AA, Shirey RS, Montgomery RA, *et al.* ABO antibody titer and risk of antibody-mediated rejection in ABO-incompatible renal transplantation. Am J Transplant 2010;10(5):1247-1253.

23. Opelz G, Morath C, Süsal C, Tran TH, Zeier M, Döhler B. Three-year outcomes following 1,420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction: results from 101 centers. Transplantation 2015;99(2):400-404.

24. Tobian AAR, Shirey RS, Montgomery RA, Ness PM, King KE. The critical role of plasmapheresis in ABO-incompativel renal transplantation. Transfusion 2008;48(11):2453--2460.

25. Lawrence C, Galliford JW, Willicombe MK, *et al.* Antibody removal before ABO--incompatible renal transplantation: how much plasma exchange is therapeutic? Transplantation 2011;92(10):1129-1133.

26. Agteren M, Weimar W, Weerd AE, *et al.* The first fifty ABO blood group incompatible kidney transplantations: The Rotterdam experience. J Transplant 2014; 2014, 913902.

Correspondence to:
Dra. Patrícia Barreto
Department of Nephrology
Centro Hospitalar de Vila Nova de Gaia/Espinho,
Rua Conceição Fernandes, 4434-502 Vila Nova de Gaia, Portugal.
E-mail: patricia820709barreto@gmail.com