






Current Perspectives in ABO-Incompatible Kidney Transplant

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Abstract: For a long time, ABO incompatible living donor kidney transplantation has been considered contraindicated, due to the presence of isohe magglutinins, natural antibodies reacting with non-self ABO antigens. However, as the demand for kidney transplantation is constantly growing, methods to expand the donor pool have become increasingly important. Thus, in the last decades, specific desensitization strategies for ABOi transplantation have been developed. Nowadays, these regimens consist of transient removal of preformed anti-A or anti-B antibodies by using plasmapheresis or immunoadsorption and B-cell immunity modulation by CD20+ cells depletion with rituximab, in association with maintenance immunosuppression including corticosteroids, tacrolimus and mycophenolate mofetil. The outcome in ABOi kidney transplantation have markedly improved over the years. In fact, although randomized trials are still lacking, recent meta analysis has revealed that there is no difference in terms of graft and patient's survival between ABOi and ABO compatible kidney transplant, even in the long term. However, many concerns still exist, because ABOi kidney transplantation is associated with an increased risk of bleeding and infectious complications, partly related to the effects of extracorporeal treatments and the strong immunosuppression. Thus, a continuous improvement in desensitization strategies, with the aim of minimize the immunosuppressive burden, on the basis of immune pathogenesis, antibodies titers and/or ABO blood group, is warranted. In this review, we discuss the main immune mechanisms involved in ABOi kidney transplantation, the pathogenesis of tolerance and the desensitization regimens, including immunoadsorption and plasmapheresis and the immunosuppressive protocol. Finally, we provide an overview on outcome and future perspectives in ABOi kidney transplant.

Keywords: ABO incompatible kidney transplant, blood group, plasma exchange, rituximab

Introduction

Kidney transplantation provides a considerable survival advantage compared to hemodialysis in patients with end-stage kidney disease. Thus, the organ demand is continuously growing while a considerable gap exists between organ availability and waiting listed patients, although the pool of deceased donors has been successfully expanded with donation after circulatory death or kidneys from extended criteria donors.^{1,2} In fact, in 2020 in Italy, of the 8310 patients listed in the deceased-donor waiting list, only 1623 underwent kidney transplant, with a mean waiting time of 40 months.³

Kidney transplant from living donor offers a superior survival of both patient and graft than transplant from deceased donation and is the most effective way to expand the donor pool.⁴ However, immunologic barriers frequently pose limitations to this transplant. These barriers are mainly represented by preformed anti-human leukocyte antigen (HLA) antibodies and ABO system antibodies, which can cause hyperacute rejection.^{5,6}

For a long time, ABO incompatible (ABOi) living donor kidney transplantation was contraindicated, due to its immunological impediment based on the presence of isohe magglutinins, natural antibodies reacting with non-self ABO antigens.⁷ Nevertheless, in 1987, Alexandre et al reported the first results of their pioneering program of ABOi living donor kidney transplantation. They laid the basis for the recipient preconditioning, commonly termed desensitization, a combination of treatments and procedures aiming at reducing isohe magglutinins levels.⁸

Nowadays, preconditioning consists in the combination of immunosuppressive agents, administered before transplantation (ie, rituximab) to prevent the production of new antibodies, apheresis techniques and maintenance immunosuppressants.⁹ No consistent data regarding the non-inferiority or superiority of individual regimens are currently available, due to the paucity of randomized controlled trials.

Outcomes in ABOi kidney transplantation have markedly improved over the years. Recently, a meta-analysis including 21 studies reporting the outcome of ABOi kidney transplant by comparing ABO compatible (ABOc) has revealed that there is no difference in terms of graft failure, biopsy-proven acute rejection and patient survival.⁹ In their consistent series including 62 ABOi kidney transplant, Barnett et al reported a three-year graft survival of 98.4%, a T-cell mediated rejection rate of 27.4% and an antibody mediated rejection rate of 4.8% at one-year post transplant. No statistically significant differences were found between the ABOi group and the group of ABOc kidney transplant performed in the same time period and in the same Transplant Center.¹⁰

The aim of this review is to summarize the principal aspects of ABOi kidney transplantation and the techniques and strategies used to treat recipients to overcome the isohemagglutinin barrier.

The ABO System

The ABO system is based on the expression of genetically determined A, B and H blood group antigens on the surface of different cell types, including red blood cells (RBCs), endothelial cells and kidney parenchymal cells.¹¹ Blood group O is determined by the antigen H, an oligosaccharide produced by the enzyme α -1,2-fucosyltransferase which is able to add a fucose molecule on a core-chain.¹² The antigen H serves as a matrix for the A and B antigens by a terminal α -d-galactose residue, which consists of a carbohydrate backbone bound to glycolipids or proteins. In individuals with A blood group, the terminal α -d-galactose residue is modified by the enzyme α -1,3-n-acetylgalactosaminyltransferase (A transferase), which attaches β -n-acetylgalactosamine, leading to the expression of A antigen. In individuals with B blood group the α -1,3-galactosyltransferase (B transferase), modifies the α -d-galactose residue of antigen H, by attaching α -d-galactose, leading to the expression of B antigen. Subjects who co-dominantly express the genes of the human ABO system have AB blood group because are able to produce both A and B transferases. Conversely, O group individuals do not have detectable A or B transferase activity and their H antigen remains unmodified. Blood group A consists of two subtypes, A1 and A2 (or, more appropriately, not-A1 subtype).¹³ The A1 subtype is more frequent, including about the 80% of individuals with A blood group. The quantitative or qualitative expression of ABO antigens may vary substantially between individuals. Individuals with A1 and A2 subtypes differ considerably with respect to the A antigen expression. Subjects with A2 subtypes express a small amount of A antigen and/or have a low A transferase activity.¹⁴ For these reasons, their immunological risk associated to ABO incompatibility in kidney transplant is significantly low.^{15–17}

The Isohaemagglutinins Barrier in ABO Incompatible Transplantation

The immunological barrier of ABOi kidney transplant is related to the presence of preformed isohaemagglutinins, that are natural antibodies with the intrinsic ability to agglutinate erythrocytes reacting against non-self ABO antigens.¹⁷ Isohaemagglutinins emerge in early childhood, increase their strength in the first decade of life and persist in adults.¹⁸ They are probably induced upon contact with the cell membrane polysaccharides of the gut commensal bacteria.¹⁹ In addition, the repertoire of antibodies towards ABO antigens may include autoantibodies against the terminal monosaccharide, disaccharide or trisaccharide residues of the “self” blood group or autoantibodies against the core chain. However, most of these autoantibodies have low-affinity and their clinical relevance is still unknown.²⁰ Isohaemagglutinins consist of IgM, IgG and IgA, with levels and distribution pattern which have consistent variability between individuals. The pathogenic potential of anti-A/B reactivity patterns might markedly differ with regard to the distribution of IgG subclasses and antibody avidity.¹⁸ It depends on the quality of the B-cell response, particularly the relative contribution of B-1 cell versus B-2 cell driven immunity.²¹ CD5+ B-1 are a small population of long-lived, self-renewing B cells, which produce low avidity, polyreactive natural IgM. By contrast, the larger CD5– B-2 cell pool produces high-affinity antibodies, including complement-activating IgG isotypes, which typically arise after stimulation with non-self antigens.^{22,23} In a cytofluorimetric study evaluating B cell subsets in 10 ABOi kidney transplant patients, Ishida et al found an initial increase in CD5+ B-1 cell, which was accompanied by an increase in levels of IgG2 and IgM. Interestingly, those patients who experienced rejection showed a change in the B cell subset distribution towards an increase of CD5– B-2 cells and high levels of complement-fixing IgG1.²⁴ The exact mechanism by which ABO antigens are able to induce B-1 and B-2 cell activation to

produce and sustain high-affinity immunoglobulin responses remains unclear. Some evidences suggest that thymus-independent antigens with highly repetitive epitopes induce the production of IgM via B-cell-receptor crosslinking and can cause an isotype switch (Figure 1).²⁵ Further mechanisms of antibodies production may include cytokine secretion by the B cells or T helper cells in response to the antigens,²⁶ or by invariant natural killer T cells, activated by the recognition of the glycolipid compounds of the CD1d MHC-like molecule expressed on B-cells or dendritic cells surface.^{27,28}

Mechanisms of Tolerance in ABOi Transplantation

In ABOi transplantation, preformed anti-A/B antibodies are responsible for a severe antibody-mediated rejection (ABMR) and in the worst cases, for a hyperacute rejection which lead to immediate renal allograft loss. Recipient desensitization allows the acceptance of ABOi graft both immediately after transplantation and in the long-term follow up even after the recurrence of detectable levels of isohemagglutinins.^{10,17} In ABOi transplantation, the presence of circulating antibodies against the graft (isohemagglutinins) activate the complement system resulting in C4d deposition along peritubular capillaries at kidney biopsy. However, differently from HLA-incompatible transplantation, in which persistent or recurrent donor-specific antibodies frequently leads to rejection and chronic tissue injury, in ABOi transplant this process does not cause graft damage. This phenomenon is called “accommodation”.^{29–31}

The mechanisms of accommodation are still unclear. An analysis in vitro evaluating the effects of anti-A/B antibody binding on complement-mediated cytotoxicity and signal transduction, have revealed that anti-A/B antibodies increase the expression of complement regulatory proteins such as CD55 and CD59 and inactivate ERK1/2 pathway, contributing to this phenomenon.³⁰ The upregulation of the complement regulatory proteins CD59 and CD46 and of the anti-apoptotic proteins Bcl-2 and clusterin has also been demonstrated in a pre-sensitized non-human primate study. Interestingly, in this study, the inhibition of complement activation with the Yunnan-cobra venom factor (Y-CVF) successfully prevented accelerated ABMR and facilitated accommodation.³² Other proposed mechanisms that potentially contribute to the acceptance of ABOi transplants include blood group chimerism or shift. In 2004, Koestner et al described the case of an O blood group patient who accidentally received a B blood group heart transplant. The patient survived for five years. The monitoring of the antigenic profile of the graft endothelial cells by immunohistology demonstrated that it changed progressively from B to O.³³ In kidney transplantation has been suggested that endothelial chimerism related to immunological or non-immunological injury may also facilitate accommodation.³⁴ The possible formation of a soluble A or B transferase inhibitor, able to reduce transferases activity, is another mechanism postulated to prevent isohemagglutinin injury in ABOi transplants.³⁵ Based on the finding that isohemagglutinins titer remains low during the first months of life, West et al performed a trial including ABOi infant heart transplant recipients treated with standard immunosuppression without splenectomy. No cases of hyperacute or acute humoral rejection were demonstrated in this study.³⁶ The same group reported in a subsequent study a persistent and selective deficiency of circulating antibodies to donor A and B antigens in the children followed up to eight years after heart transplantation. Authors speculated that these children have

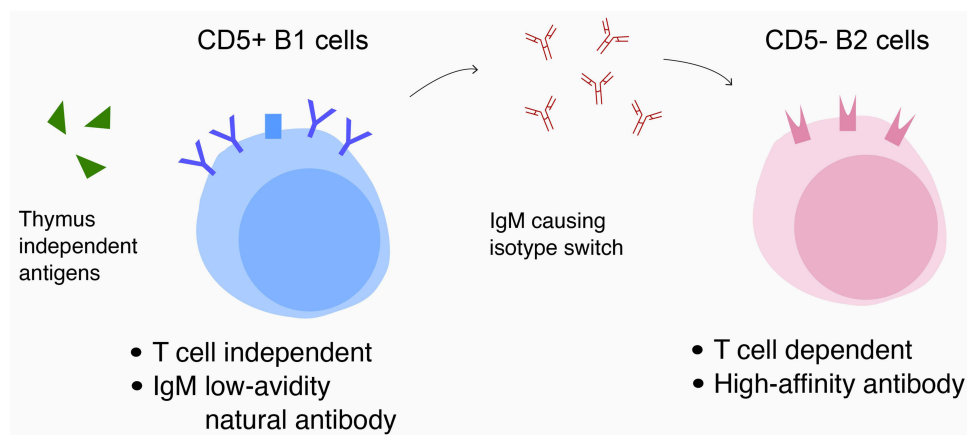


Figure 1 The possible pathogenetic mechanism of different B cell response in patients receiving ABOi kidney transplant. Thymus-independent antigens may cause the switch from B1 cells producing low avidity IgM to B2 cells able to produce high levels of complement-fixing IgG1, which can predispose to rejection.

acquired a tolerance through the elimination of ABO-specific B cells. Interestingly, in children with ABOi heart transplantation has been shown a less frequency of donor-specific antibodies and class II antibodies, suggesting that the specific B-cell tolerance may be associated also with an altered response to HLA antigens.³⁷

Antibodies Depletion Strategies and Results

The desensitization protocols for ABOi kidney transplantation are based on pre-existing anti-A/B isohemagglutinins removal by combining extracorporeal techniques with immunosuppressive therapy.

The key point for desensitization is currently based on apheresis techniques. Serial antibodies titers monitoring is used to tailor the need of adjunctive apheresis treatments after transplantation, in order to prevent the rebound in isohemagglutinins levels until tolerance or accommodation occur.^{17,38}

The apheresis techniques can be either non-selective or selective. Plasma exchange (PEX) is a non-selective apheresis technique, in which the plasma is separated from the whole blood by centrifugation or filtration and then eliminated; the discharged plasma is replaced with albumin, colloid solutions or fresh frozen plasma. PEX has the important disadvantage of losses in coagulation factors, hormones, albumin, anti-bacterial and anti-viral immunoglobulins. For this reason, the total plasma volume that can be treated in each session is limited. Conversely, the advantage respect to more selective strategies, is that it can remove also other antibodies, such as anti-HLA antibodies, and complement components that may be implicated in the pathogenesis of allograft injury mediated by isohemagglutinins. Moreover, PEX is the less expensive and more widely and rapidly available apheresis technique.^{38,39}

An alternative apheresis technique, the double-filtration plasmapheresis (DFPP), has been designed to selectively remove the immunoglobulin fraction from the serum and, as a result, to minimize the volume of substitution fluid required. In this method, plasma is firstly separated by a plasma separator and later it passes through a second filter (the plasma fractionator) which remove the gamma globulin fraction. Thus, the amount of immunoglobulin eliminated in one DFPP session is equivalent to that concentrated in 5 L of plasma, but only 1 L of substitution fluid is necessary to replace the plasma removed.⁴⁰

The most selective apheresis technique is ABO-specific immunoabsorption (IA), in which the separated plasma pass through an antigen-specific absorber, consisting of blood group A or B antigens immobilized on a sepharose matrix, and then it is returned to the patient. This technique provides a highly efficient elimination of ABO antibodies without the loss of essential plasma components.¹⁷ It can also reduce complement components levels, which can contribute to prevent the antibody-mediated rejection related to isohemagglutinins, resulting in a high treatment efficiency. Biglarnia et al demonstrated a decline in complement components (C3a and C3a/C3 ratio) with the start of IA in 19 ABOi living donor kidney transplant and that these proteins were detected in the eluate. The binding of C3a could be explained by its high isoelectric point which may result in the affinity with the negative charged resin of the immunoabsorbent.⁴¹ The main disadvantage of this approach is represented by the high costs of the ABO-columns. However, in their prospective trial, Schiesser et al have demonstrated that the reuse after restoration of these columns does not reduce the antibody-depletion capability and has the same safety and tolerability profile, resulting in a consistent cost saving.⁴²

There are no randomized controlled trials comparing PEX and IA techniques and the decision on which antibody depletion protocol to choose depends on physicians' experience. PEX is the favorite preconditioning treatment in Transplant Centers from the USA and Japan. The John Hopkins Hospital and the Mayo Clinic use similar preconditioning methods. In the first group, as reported by Montgomery et al, the PEX treatment plan is based on anti-A and anti-B titers with the goal of achieving isohemagglutinins titer of 1:16 or less before surgery. The number of PEX sessions before transplantation is estimated by the titers. Each PEX treatment consists of 1-plasma-volume exchange replaced at 100% volume with 5% serum albumin. PEX sessions are usually performed every other day. After each procedure, low-dose cytomegalovirus immunoglobulins intravenous are administered because of their immunomodulatory effect. After transplantation, all patients receive at least two PEX sessions; patients who have high starting titers, antibody rebound, or antibody mediated rejection undergo to further session.^{43,44} There is no general agreement about the sufficient lowering of antibody titer before kidney transplant. Some centers require anti-A/B IgG titers of less than or equal to 1:8, others require titer less than or equal to 1:32 at the time of transplantation. Actually, no randomized control studies are available in order to compare the outcome of higher versus lower titers in ABOi kidney transplant.

In the experience reported by Tyden et al, 60 consecutive ABOi kidney transplant were performed in Stockholm, Uppsala and Freiburg, using antigen-specific IA, rituximab, intravenous immunoglobulin and conventional tacrolimus, mycophenolate mofetil, and prednisolone immunosuppression as desensitization. The target preoperative isohemagglutinins titer was <1:8. Graft survival was 97% for the ABOi compared with 95% in the control group of 267 ABO-compatible living donor kidney transplant performed in the same period. No late rebound of antibodies or humoral rejections were observed.⁴⁵

Montgomery et al reported of 60 ABOi kidney transplant which received the John Hopkins desensitization protocol with cytomegalovirus immunoglobulin, immunosuppression, splenectomy at the time of transplant (later replaced by a single-dose anti-CD20 administered the night before transplantation and, recently, both interventions have been stopped). Graft survival was comparable with the United Network for Organ Sharing data for compatible live donor transplants. There were no cases of hyperacute rejection or graft losses from acute mediated rejection (AMR). Ten patients experienced AMR (four were mixed, ABMR and cellular mediated rejection); no significant difference in starting (pre-treatment) isohemagglutinin titers were detected, but a rise in the post-operative titers, compared with no rejection patients.⁴⁶

Outcomes in ABOi kidney transplantation have markedly improved over the years. Graft survival and patients' safety is comparable to those in ABO-compatible kidney transplant.^{10,47–50} The main studies which compare the outcome of patients who underwent ABOi kidney transplant with patients who received ABOc kidney transplant have been reported in [Table 1](#).

Indeed, some reports show even a better renal function and a less incidence of chronic ABMR in patients with ABOi kidney transplant than patients receiving an ABO-compatible living transplant.^{51,52}

Immunomodulation and Immunosuppressive Therapy

In the initial era of ABOi kidney transplantation the desensitization protocol included also splenectomy, because the spleen contains a large pool of antibody-secreting B cells. In the last decades, splenectomy has been replaced with a single dose of rituximab, an antibody anti-CD20.^{53,54} The effect of rituximab on blood-group-specific immunity is still incompletely understood. It is able to effectively deplete peripheral B cells, but it might not reduce B-cell counts in secondary lymphoid organs. However, rituximab may result also in a modulation of B cell and T cell immunity by the changes in the pattern of B-cell subpopulations, including a disappearance of transitional B cells and an increase in memory B cells in lymph nodes.⁵⁵

Importantly, in ABOi kidney transplantation, excellent outcomes have been shown also for desensitization protocols that employ reduced rituximab dosages or even do not use rituximab.

Based on the recognition that accommodation occur rapidly after ABOi transplantation and AMR is relatively uncommon and usually experienced in the first two weeks after transplant, Montgomery et al eliminated both splenectomy and anti-CD20 therapy, in favor of a tight control of isohemagglutinin titers with PEX treatment during the window of graft major vulnerability.⁴⁶ In their series including 60 ABOi transplant, they report that the recipient who did not receive rituximab or splenectomy had the same outcome in renal function than those who were treated with the conventional antibody depletion therapy.

In order to improve immunological outcome, desensitization protocols include induction with an IL-2 receptor antibody and maintenance immunosuppression with tacrolimus and mycophenolate mofetil (MMF) which is commonly initiated before transplantation. Retrospective studies have suggested a greater outcome with the use of these two immunosuppressive agents compared to ciclosporin-based regimens. Alternative immunosuppressive strategies have been proposed in few case series including a low number of patients. The conversion from MMF and standard-dose calcineurin inhibitors (CNIs) to everolimus and low-dose CNIs in a cohort of 16 stable ABOi kidney transplant recipients has been reported effective and safe.⁵⁶

In [Figure 2](#), we reported the desensitization strategy commonly performed in patients who undergo ABOi kidney transplant.

Future Perspectives and Conclusions

Many innovative strategies have been recently proposed in order to overcome immunological barriers in ABOi kidney transplant. Kobayashi et al have proposed the goal to reduce the blood group antigen expression in the kidney, by applying

Table 1 Main Papers Comparing the Outcome of Patients Who Underwent ABOi Kidney Transplant with Patients Who Received ABOc Kidney Transplant

Study	Population	Anti-A/B Antibodies Median Initial Titer	Desensitization Strategy	Target Anti-A/B Pre-Operative Titer	Post-Operative Target	Outcomes	Adverse Events
Genberg et al (2008) ⁴⁹	15 adult ABOi vs 30 adult ABOc vs 5 pediatric ABOi vs 18 pediatric ABOc (September 2001-December 2005)	1:32 (adults) 1:16 (pediatrics)	-Repeated antigen-specific IA + -RTX 375mg/m ² on day -30 and immunosuppressive therapy on day -10 -IVIG 0.5 g/kg on day -1 and for five days after transplant	NR	-3 IA sessions after transplant	-No differences in graft and patient's survival -No differences in rejection episodes	-No differences in infective complications
Barnett et al (2014) ¹⁰	62 ABOi vs 167 ABOc KT (July 2005-November 2011)	NR	-Repeated antigen-specific IA (if titer > 1:64) or DFPP (if titer 1:16-1:64) + -RTX 375mg/m ² on day -30 and immunosuppressive therapy -IVIG 0.5 g/kg pre and post-transplant (until 2009)	NR	- On demand post-transplant antibody removal	-No differences in graft survival -No differences in rejection episodes	- 3 deaths in ABOi group due to Pneumocystis pneumonia - 1 death in ABOi group due to sepsis
Okumi et al (2015) ⁵⁰	247 ABOi vs 785 ABOc KT (January 1989 – December 2013)	NR	-Three or four sessions of DFPP before transplantation + -Splenectomy (from 1989 to 2004) or RTX 200 mg on day -7 (after 2004)	< 1:32	-No prophylactic postoperative DFPP or IGIV to maintain low titers	-Significant difference in graft survival until 2004 (68.9% for ABOi and 78.1% for ABOc KT, p=0.026) -No differences in graft survival after 2005 -No differences in patient survival	- Higher rates of CMV and adenovirus infections were observed in ABOi KT recipients before 2004 -No differences in infective complications after 2005
Becker et al (2015) ⁴⁸	34 ABOi vs 68 ABOc KT (August 2005-December 2013)	1:64	-Nonantigen-specific IA (number of sessions depending on initial titer, median = 7) -PE (until 2012 only additional PE to reach the target titer; from 2012 at least one pre-transplant treatment, median = 2) + -RTX 375mg/m ² 2-4 weeks before surgery and immunosuppressive therapy started with IA -IVIG 0.5 g/kg in 7 patients	≤ 1:8	-21 pts had PE to maintain ≤ 1:16 in the first week and ≤ 1:32 in the second week after surgery.	-No differences in graft survival or rejection episodes. -Statistically significant difference in patient survival (2 deaths in ABOi group vs 0 deaths in ABOc group, p=0.05)	-No differences in surgical complications. -Higher risk of BKV nephropathy (p=0.01) and of colonization of multidrug-resistant bacteria (p=0.02) in ABOi group.
Speer et al (2019) ⁴⁷	48 ABOi vs 96 ABOc KT (August 2005-August 2018)	1:32	-Semiselective IA (number of sessions depending on initial titer, median = 6) -PE (at least one treatment to reach target preoperative titer, median = 2) + RTX 375mg/m ² 2-4 weeks before surgery and immunosuppressive therapy started with IA	≤ 1:8	-50% pts had IA or PE to maintain titers ≤ 1:16 in the first week and ≤ 1:32 in the second week after surgery.	-No differences in graft and patient survival or rejection episodes.	-ABOi more postoperative bleeding and more complicated UTI, severe pneumonia, CVC-related infections by MDR bacteria. -No differences in BKV or CMV infections.

Abbreviations: ABOi KT, ABO incompatible kidney transplant; ABOc KT, ABO compatible kidney transplant; IA, immunoadsorption; PE, plasma exchange; DFPP, double-filtration plasmapheresis; RTX, rituximab; IVIG, intravenous immunoglobulins; UTI, urinary tract infections; CMV, cytomegalovirus.

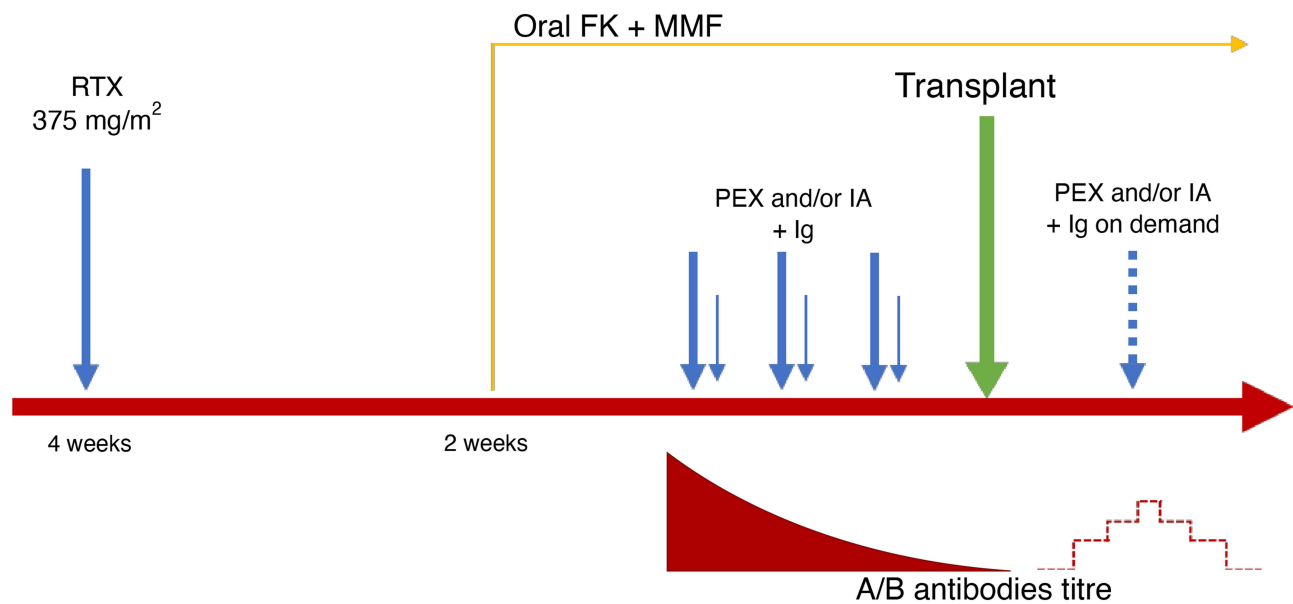


Figure 2 The desensitization strategy performed in ABOi kidney transplant patients. A single infusion of rituximab 375 mg/mq is administered four weeks before kidney transplant. Two weeks before kidney transplant, patient starts oral immunosuppressive therapy (tacrolimus and mycophenolate mofetil). A variable number of immunoadsorption and/or plasma exchange (PEX) sessions is performed before kidney transplant, until a titer $<$ or $=$ at 1:8 is achieved. The isohemagglutinin titer is measured every day after ABOi kidney transplant and further PEX sessions are performed on demand.

a recombinant endo- β -galactosidase (ABase) produced in *E. coli* BL-21. In vivo experiments performed in blood type A, baboons revealed a marked reduction of A antigen expression in the glomeruli.⁵⁷ Another target could be the interference with the binding of anti-A/B antibodies to blood group antigens by using a monoclonal anti-A or B antibody Fab fragment or by neutralizing preformed antibody with an ABO blood group trisaccharide carbohydrate epitope.^{58,59} The terminal complement inhibitor eculizumab in the induction of ABOi transplantation has also been proposed, with the aim of interfering with the antibody-triggered complement activation induced by anti-A/B antibodies.⁶⁰

However, it is crucial, in the management of ABOi kidney transplant, to be aware of the risks related to the high degree of immunosuppression. This is the topic which needs for further improvements. More data regarding the tailored approach based on pre-transplant isohemagglutinins titers and/or donor/recipient blood group are warrants. A better understanding of the underlying immunologic mechanisms of anti-A/B immune responses and ABOi graft tolerance will provide the basis for the development of new and safer desensitization strategies.

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Disclosure

The authors have no conflict of interest to declare.

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