

# Conquering Immunological Barrier in Kidney Transplantation: ABO Incompatible Transplantation

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## Introduction

Chronic kidney disease is an ever growing global burden affecting nearly 10% of world population(1). Once a patient reaches end stage renal disease, kidney transplantation offers the best survival advantage and health related quality of life compared to other renal replacement modalities (2). Hence, the demand for organs continuously rises creating a gap between the organ availability and patients awaiting transplant.

Living donor kidney transplantation has demonstrated a significant patient and graft survival compared to deceased donation and is the most effective way to expand donor pool(3). However, immunological barriers such as ABO system antibodies and anti-Human Leukocyte Antigen antibodies pose restrictions to expansion. It's postulated that 30% of live donor kidney transplants are not feasible due these barriers(4). Hence, the ways to overcome this problem is to either transplant across the incompatibility upon immunomodulation or exchange the organs in one or more pairs with better compatibility.

ABO incompatible (ABOi) living donor kidney transplantation was long considered unfeasible, due the presence of isohemagglutinins, natural antibodies reacting with non-self ABO antigens(5). Nonetheless, utilization of pre conditional treatments to decrease isohaemagglutinins in recipient, commonly known as desensitization made ABOi kidney transplantation possible. Thenceforth, outcomes of ABOi kidney transplantation have markedly improved over the years(6).


The aim of this review is to summarize the principal aspects of ABOi kidney transplantation and its challenges ahead.

## ABO system and antibodies

The ABO antigen system consists of genetically determined expression of A,B or H oligosaccharide antigens predominantly found on red blood cells(7). Further, they are

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expressed on endothelial cells , glomeruli and tubuli making ABO antigen system in organ transplantation. Depending by the solitary expression of A or B antigen, A and B blood groups are determined respectively. AB Blood group is generated by co dominant expression of both A and B. In contrary blood group O has unmodified H antigen devoid of either A or B antigens. A blood group consists of two sub types, A 1 and A2(8). A1 subtype is more common comprising 80% of A blood group. Compared to blood group A1 and B individuals, blood group A2 individuals depicts a low expression of blood group antigen molecules on surface of red blood cells, hence low immunogenicity(9,10)

The immunological barrier in ABOi transplant is due to preformed of anti- ABO antibodies (isohaemagglutinins ) against non-self ABO antigens which emerge in early childhood(11). It's postulated that exposure of cell membrane antigens to gut commensal bacteria induces antibody production(12). Isohaemagglutinins show individual variations in class( IgM, IgG and IgA), titer, distribution hence pathogenic potential(6). Individuals with blood group O express higher antibody titers to both the A and B antigens. Hence, higher incidence of antibody-mediated rejection (ABMR) after transplantation is seen among blood type O recipients. (13)

## Immunomodulation and immunosuppression

Recipient desensitization is an integral part of ABOi transplantation to achieve a desirable isohaemagglutinin titer prior to transplant, yet here is no universally accepted desensitization protocol. The following strategies are routinely employed.

### 1.Apheresis

The key method for desensitization is currently based on apheresis techniques.

There are number of extracorporeal antibody removal techniques available. Plasma exchange removes all plasma proteins, while membrane separation can be used to remove certain plasma proteins like immunoglobulins. Immonoadsorption is another mechanisim which could be selective or unselective.

### Plasma Exchange

Plasma exchange introduced by Alexandre et al is a non-selective apheresis method widely used for desensitization globally(14). It is less expensive and readily available(15). PEX has the important disadvantage of removal of coagulation factors, hormones, albumin, anti-bacterial and anti-viral immunoglobulins. Further, rebound of antibody is frequently observed. An alternative apheresis technique, the double-filtration plasmapheresis (DFPP), removes only the immunoglobulin fraction from the serum, therefore needing minimal fluid substitution. The utility of single or DFPP and the number of treatments vary between centres but mainly depends on the antibody titres.

### Immunoadsorption

Bannett et al. introduced this more selective apheresis technique, in which separated plasma pass through A and B antigen immobilized solid phase columns to remove anti ABO antibodies known as immunoadsorption(16). It is more efficient than conventional plasma exchange with fewer side effects although it's more expensive(17,18). Hence, as an cost saving strategy, Schiesser et al demonstrated that reuse after restoration of these columns does not reduce the antibody-depletion capability with similar safety and tolerability profile(6,19).

There are no randomized controlled trials comparing plasma exchange or immunoadsorption, hence the utilization of apheresis technique depends on centers experience(6).

### 2.Reduction of the B lymphocyte pool

Splenectomy was an integral part desensitization protocol prior to the introduction of anti B cell therapies. Rituximab, anti CD 20 antibody has substituted the protocols due to the surgical and infection risk associated with splenectomy. Rituximab has shown to reduce the risk of isoagglutinin rebound and the risk of ABMR as well as chronic rejection(20). Yet, Flint et al. reported 100% median graft and patient survival at 26 months after transplantation without Rituximab(21). In contrary, a higher of death-censored graft loss was observed in ABOi kidney transplants done after omitting Rituximab (22). Currently, most protocols do employ Rituximab usually using a dose of 375 mg/m<sup>2</sup> administering from 1 month before the transplantation(23).

### 3.Immunomodulation with intravenous immunoglobulins (IVIgs)

It is postulated that IVIG given pre-transplant prevents antiA/B antibody rebound seen immediate post-transplant. Further, it is believed that IVIG reduces post infectious complications by substituting depleted

immunoglobulins(24). In contrary, IVIG contains IgG antibodies against A/B antigens hence can increase antiA/B antibody titres upon administration(25).

### Maintenance immunosuppression

The maintenance immunosuppression in ABOi transplantation is same as in ABOc kidney transplantation apart from desensitization. The basal immunosuppression is initiated together with the desensitization. The suppression of B-cells by Tacrolimus, Mycophenolate mofetil, and steroids seems to be vital for antibody suppression and eventual suppression of acute ABMR in ABO-ILKT recipients(26).The augmented risk of acute rejection upon early or late steroid withdrawal is well documented(27,28). Overall, patients receiving transplant involving ABOi are not allowed to reduce immunosuppression.

### History of ABOi Transplantation and current outcomes

ABOi kidney transplantation has been considered a contraindication based on the adverse experiences from early transplant era(29–31). In 1974, transplantation of A2 renal allografts to O recipients with standard immunosuppression showed a partial success(9). Upon identification of this low antigenicity of A2 blood group, this strategy was soon adopted by multiple groups. Nelson et al. reported a 10-year experience with 50 A2 incompatible transplantations in 1998 with 1-month and 2-year graft survival rates of 94% and 94%, respectively(32).

Slapak et al. reported the first A1 incompatible kidney transplantation with selective immunoadsorption or plasmapheresis pretreatment in 1984 with overall 1-year graft survival rate of 87% (13/16)(33). Alexandre et al. from Belgium reported successful A1 incompatible kidney transplantation after using splenectomy and plasmapheresis for desensitization(14). Since then many countries adopted ABOi transplantation with advancements in immunomodulation and immunosuppression.

Successful substitution of splenectomy using rituximab, a chimeric anti-CD20 antibody, to suppress anti-blood group antibody production was first reported by Tyden and group from Sweden depicting excellent short-term outcomes for ABOi kidney transplantation(34). Later Studies at Johns Hopkins, Mayo Clinic and Japanese teams also reported that excellent short-term outcomes for ABOi transplantation were achieved with rituximab, hence agreeing on a consensus that splenectomy is no longer required for desensitization in ABOi kidney transplantation(35–37).

With increased number of successful ABOi transplants, the attempts were made to reduce costs and desensitization

associated complications (25,36). Barnett et al. adopted a individually tailored desensitization strategy for ABOi. The desensitization was escalated with rising antibody titers, which showed similar allograft and patient survival rates at 1 and 3 years or in the ABMR rates highlighting the place for personalized therapy (38).

ABOi kidney transplantation outcomes have significantly improved over the years. Graft survival and patients' survival is comparable with ABO-compatible kidney transplant(39–42). Additionally, several studies show even a less incidence of chronic ABMR and better renal function in patients with ABOi kidney transplant compared to ABO-compatible living transplant(20,43).

### **Controversies and Challenges in ABOi transplantation**

#### **Accommodation**

Following ABOi transplant upon exposure to a low ABO antibody titre, the allograft develops ability to resist complement-mediated damage. This phenomenon is known as accommodation where no evidence of clinical rejection occurs in the presence of circulating ABO antibodies (44,45). There will be C4d deposition in kidney biopsy suggesting ongoing complement activity yet it's not considered as a marker of ABMR in ABOi transplantation in contrary to HLAi transplantation. The pathogenesis of the accommodation is believed to be due to low titer of low affinity antibodies, with blockage of complement activation, leading endothelial cells to develop an acquired resistance to antibody damage(46,47). Accommodation is also responsible for kidney protection over a long period of time.

#### **Antibody mediated rejection**

ABMR is the leading cause of graft loss in ABOi transplantations which usually occurs early post transplant(48). The risk for ABMR is related to the isoagglutinin level at transplantation and to the presence of anti-HLA antibodies(49). The incidence of ABMR ranges between 10% and 30%(50). Lo et al, in his meta-analysis demonstrated an acute rejection rate of 32.9%, most of which were ABMR(51).

#### **Isoagglutinin quantification**

The isoagglutinin titer is vital to decide on the immunosuppression and more importantly the apheresis technique to be used. The best available method is flow cytometry. However, the less expensive methods such as tube and gel techniques for ABO antibody titration are also frequently used (52,53). Most centers aim an antibody titer of 1:8 before transplantation(54). Nonetheless, it has been depicted that both the antibody basal titer before

desensitization and the post-transplantation titer have a low predictive value for ABMR(28).

#### **Post-operative antibody monitoring**

There is contradictory evidence for post operative antibody monitoring and therapeutic plasma exchange avoiding ABMR. Tobian et al. from Johns Hopkins reported that the incidence of ABMR was markedly higher in recipients with high post-transplant titers for the anti-blood group antibody of more than 1:64(55). In contrary, Ishida et al. from Japan described that (56) postoperative anti-blood group antibody rebound was not associated with the incidence of acute rejection therefore not recommending plasma exchange (57).

#### **Infection**

There is conflicting evidence regarding infectious risk post kidney transplantation. It's probably due to varying immunosuppression in different centers. Habicht et al. reported higher frequency of viral infection such as cytomegalo virus, Herpes simplex virus, varicella zoster and polyoma virus to be higher in ABOi transplants(58). Shariff et al. reported higher incidence of BK virus nephropathy among ABOi compared to HLAi recipients(59). Lentine et al. reported that ABOi is associated with higher risk of pneumonia, urinary tract infection and wound infections(60).

#### **Malignancy**

Hall et al. reported that ABOi recipients carry no higher cancer risk matched ABO compatible controls(61). The same was seen in a similar large scale study involving 1,420 ABOi recipients(22).

#### **Bleeding risk**

An increased risk of early post-operative bleeding was observed in several studies(60,62). This was postulated to be due to clotting factor removal during apheresis. Confirming this assumption, Weerd et al. showed a significant correlation between the number of pre-transplant apheresis treatments and the peri- and post-transplant bleeding risk(63).

#### **Future perspectives**

Multiple novel strategies have been proposed to overcome immunological barriers of ABOi transplantation. A novel ex-vivo therapy, endo-beta-galactosidase is proposed to reduce blood group antigens in the allograft kidney(64). Another method is to utilize a monoclonal anti-A or B antibody Fab fragment or neutralizing antibody with an ABO blood group trisaccharide carbohydrate epitope to interference with the binding of anti-A/B antibodies to blood group antigens (65,66). There is novel evidence emerging for usage

anticomplement antibody, Eculizumab in ABOi transplant. It is a monoclonal antibody against C5, which prevents complement mediated injury upon binding of antibodies to allograft endothelium(67,68).

Nonetheless, it is crucial to be attentive regarding the risks related to the augmented cumulative immunosuppression used in ABOi kidney transplant. Better comprehension of immunologic mechanisms of anti-A/B immune responses and ABOi graft tolerance will provide the basis for evolving new and safer desensitization strategies.

Paired kidney exchange transplantation is a great alternative to ABOi transplantation. It needs less immunosuppression hence lower infective complications. Paired exchange effectively increases donor pool as well as reduces the waiting times on maintenance haemodialysis(69).

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