CHAPTER 5.3 ABO-incompatible living donor kidney transplantation

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1 Introduction

Although kidney transplantation is still best performed in the absence of major ABO incompatibility, long waiting times for a deceased donor kidney transplant exceed eight years for adults in some countries, such as Germany, due to a large kidney failure population and an increasing organ shortage. One way to reduce waiting times is to perform transplants across ABO antibody barriers [1]. In theory, the number of kidney transplants from living donors could increase by up to 30% if patients were transplanted across the ABO antibody barrier. Using current protocols, up to 90% of patients with ABO incompatibility with their living donor can be effectively desensitised and transplanted. Desensitisation protocols aim to reduce and maintain anti-A/B antibodies (isoagglutinins) below a safe threshold (e.g., < 1:32 in the tube technique) during the first two weeks after transplantation. Thereafter, even when anti-A/B antibodies reappear at high levels, they will not harm the kidney transplant, a phenomenon known as accommodation. In recent years, graft survival rates after ABO-incompatible (ABOi) kidney transplantation have almost equalled those after ABO-compatible (ABOc) procedures. However, transplantation in the presence of major ABO incompatibility places the patient at a somewhat higher risk of early rejection,

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infection and infection-associated death. Therefore, ABOc procedures should be preferred wherever possible.

2 Blood group antigens and antibodies

The ABO antigen system consists of oligosaccharides that are predominantly found on red blood cells, as well as on endothelial cells, tubules and glomeruli. This makes the ABO antigen system important for kidney transplantation. Patients with different blood groups have different antigen densities on their erythrocytes. Compared to individuals with blood group A1 or B, individuals with blood group A2 (who make up 20% of all Caucasians with blood group A) have low expression (30–50%) of blood group antigen molecules on the surface of erythrocytes. This is believed to be responsible for the lower immunogenicity of organs from A2 donors [2, 3]. Due to the lower immunogenic risk posed by the A2 antigen, A2 donor kidneys can generally be successfully transplanted into non-A recipients with low pre-transplant anti-A titres without the need for desensitisation [4].

Anti-A/B antibodies are formed upon contact with gut bacteria in the early stages of infancy. Naturally occurring anti-A/B antibodies are predominantly of the IgM class, but in individuals with blood group O, they also consist of the IgG and IgA classes [5]. While the pathogenic importance of anti-A/B antibodies in solid organ transplantation is well known, the relative contribution of the different immunoglobulin isotypes and their subclasses to organ rejection remains to be elucidated. Individuals with blood group O tend to produce higher levels of anti-A and anti-B isoagglutinin antibodies than individuals with blood groups A or B, and recipients with blood group O have a higher incidence of antibody-mediated rejection (ABMR) following ABOi transplantation, although graft survival does not differ among blood groups.

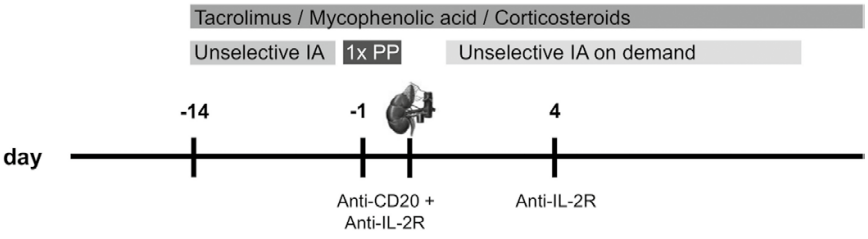
The way in which institutions measure and report isoagglutinin antibody titres varies [8, 9], which makes it difficult to compare ABOi protocols and outcomes in the literature. The classic tube dilution method is most commonly used to report IgM isoagglutinin titres (saline test) and total isoagglutinin titres (indirect antiglobulin [Coombs] test), although direct IgG measurements can be obtained by treating plasma with dithiothreitol prior to testing to inactivate IgM. As the test depends on visual interpretation of the degree of agglutination, it should be considered semi-quantitative and may be subject to interobserver variability. Therefore, the reported result should be considered an approximation, meaning

that a titre of 1:128 could represent values between 1:64 and 1:256. Although centre-specific protocols vary, the total isoagglutinin antibody titre is generally reduced to ≤ 1:8 before transplantation, as higher titres are associated with acute antibody-mediated rejection (ABMR) post-transplant [10].

3 Desensitisation for ABOi kidney transplantation

Despite the absence of a generally accepted desensitisation protocol for transplantation across the ABO antibody barrier, all currently proposed strategies share some common principles: (i) anti-A/B antibody depletion at the time of transplantation using plasmapheresis (PP), double-filtration PP/membrane filtration or selective/unselective immunoadsorption (IA); (ii) modulation of the recipient's immune system using intravenous immunoglobulins (IVIG); and (iii) reduction of the B lymphocyte pool using the anti-CD20 antibody rituximab. Figure 1 provides an overview of the Heidelberg desensitisation protocol for ABO-incompatible living donor kidney transplantation.

Figure 1 Desensitization protocol for ABOi living donor kidney transplantation at the University of Heidelberg. Anti-CD20 therapy is usually performed with rituximab 375 mg/m^2, anti-IL-2R therapy is performed with basiliximab. IA, immunoadsorption; PP, plasmapheresis (modified from ref. [1]).



3.1 Antibody depletion by extracorporeal treatment

The patient's initial ABO isoagglutinin titres must be ≤1:256 for both IgG and IgM, as determined by the tube dilution method. Reducing circulating anti-A/B antibody levels to predetermined target titres is a key component of the ABO desensitisation protocol. The two most commonly used methods of antibody

removal are plasmapheresis and immunoadsorption, with the aim of achieving titres of ≤ 1:8. In general, the titre can be expected to decrease by one dilution with each plasmapheresis session. This can be used to estimate the number of sessions necessary to achieve the target titre. For example, if the initial antibody level is 1:128, three plasmapheresis sessions are required to achieve a level of 1:16 (1:128 to 1:64, 1:64 to 1:32 and 1:32 to 1:16).

Antibody removal strategies can be categorised as methods that completely remove plasma proteins, such as plasmapheresis (PP); methods that remove a specific fraction of plasma proteins, including immunoglobulins, such as membrane separation; and more specific methods, such as unselective or selective immunoadsorption (IA). PP is the preferred antibody removal strategy in the United States, whereas membrane separation is popular in Japan and unselective and selective IAs are commonly used in Europe. Selective anti-A/B antibody removal is feasible using Glycosorb columns (Glykorex Transplantation AB, Lund, Sweden) containing a synthetic terminal tri-saccharide A or B blood group antigen linked to a sepharose matrix. These columns can also reduce total IgG, as well as IgG against polysaccharide antigens, such as anti-pneumococcus IgG [11]. Our centre in Heidelberg uses a desensitisation protocol for ABOi kidney transplant candidates that is very similar to the Swedish protocol [12, 13]. The main difference is the use of unselective instead of selective IA, which also allows desensitisation for HLA-incompatible living donor kidney transplantation. Other differences include the omission of IVIG application and the number of IA treatments varying depending on the strength of the anti-A/B antibodies. To more efficiently remove pathogenically relevant anti-A/B antibodies of the IgM class, at least one additional plasma purification (PP) treatment is performed in all patients the day before surgery [14].

3.2 Intravenous immunoglobulins

Many centres administer intravenous immunoglobulins before ABOi kidney transplantation to prevent anti-A/B antibody rebound in the early phase after transplantation. Additionally, IVIG infusion is believed to reduce infectious complications by replacing depleted immunoglobulins. However, it should be noted that IVIG preparations contain IgG antibodies directed against A/B antigens, which can increase anti-A/B antibody titres upon administration [12]. Some centres administer 0.5–2 g/kg of IVIG (maximum dose 140 g) immediately after the final plasmapheresis session. The optimal IVIG dose is uncertain.

3.3 B-cell depletion by splenectomy or rituximab

Prior to the introduction of pharmacological anti-B-cell therapies, splenectomy was an integral component of reducing the B-lymphocyte pool before ABOi kidney transplantation. However, due to the associated surgical risks and increased risk of sepsis, splenectomy has gradually been replaced by the anti-CD20 antibody rituximab. More recently, several groups have completely abandoned anti-B cell therapies in their protocols. However, the Collaborative Transplant Study (CTS) revealed a numerically higher rate of death-censored graft loss in ABOi kidney transplant recipients when rituximab was omitted (see below) [15].

3.4 Monitoring after transplantation

Following ABO desensitisation and transplantation, patients are monitored using an approach similar to that used for recipients of ABOc transplants. In addition, we monitor isoagglutinin titres daily while the patient is in hospital and twice weekly for the first month post-transplant. Pre-emptive plasmapheresis should be performed in patients with an isoagglutinin titre of ≥ 1:16 in the first week or ≥ 1:32 in the second week post-transplant, and a kidney biopsy should be performed if there is evidence of graft dysfunction (e.g., delayed/slow graft function or rising serum creatinine). We do not routinely perform protocol plasmapheresis post-transplant.

4 Outcome

The Heidelberg group reported CTS data on the three-year outcomes of 1,420 adult ABOi kidney transplant recipients who underwent transplantation at 101 different centres between 2005 and 2012 [15]. Patients were compared to a matched group of ABOc kidney transplant recipients, as well as to all ABOc kidney transplant recipients from centres that had performed at least five ABOi procedures. There were no statistically significant differences in overall graft survival, death-censored graft survival, or patient survival between the groups. However, early patient survival was reduced in ABOi kidney transplant recipients due to a higher rate of infection-associated death in the early stages. Specifically, an additional death per 100 patients occurred within the first year of

ABOi kidney transplantation due to an infectious complication. There was a trend towards a better 3-year death-censored graft survival in patients receiving anti-CD20 therapy, suggesting the need for anti-B cell therapies in cases of ABO incompatibility.

While studies initially focused on adult donors and recipients, evidence supporting this practice for paediatric recipients has increased in recent years. In 2018, an analysis of the Japanese Kidney Transplant Registry was published which described the results of 102 children who received ABOi kidney transplants from living donors. The outcomes of these recipients were compared with those of children on the registry who had undergone ABOc living donor transplantations. No difference was found in patient or allograft survival between the two groups [16]. The protocol involved the use of rituximab ± immunoadsorption and/or double filtration plasmapheresis if titres were ≥ 1:8. Several centres in the UK have reported on the outcomes of ABOi kidney transplantation in a cohort of 23 children, and have similarly found no statistically significant difference in patient or allograft survival, acute rejection, or graft function compared to ABO-compatible living donor transplants [17]. Other centres in Sweden [18] and Japan [19], which use a similar desensitisation approach, have also shared equally encouraging results. Some studies have even found that infants with low antibody titres prior to ABOi transplantation did not require pre-transplant desensitisation to achieve excellent results [18].

5 Complication and hurdles

5.1 Accommodation versus rejection

Unlike transplantation in HLA-sensitised patients, accommodation appears to be a frequent phenomenon after ABO incompatible (ABOi) kidney transplantation and is often associated with C4d deposition in the peritubular capillaries of allograft biopsies. The accommodation phenotype can be achieved through controlled exposure to anti-A/B antibodies in the early post-transplant phase. Approximately two weeks after successful transplantation, accommodation is established, rendering the kidney transplant resistant to even high anti-A/B antibody exposure. One possible mechanism is the local upregulation of complement regulatory proteins, such as CD45, CD55 and CD59, as a consequence of anti-A/B antibody-dependent inactivation of the ERK1/2 signalling pathway [20].

5.2 Infection and malignancy

The literature contains conflicting results regarding infectious complications after ABOi kidney transplantation. A higher frequency of viral infections, such as cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV) and BK virus, as well as Pneumocystis jiroveci pneumonia, wound infections and severe urinary tract infections, has been reported in adults [1]. In the CTS and Heidelberg cohorts, an increased risk of severe early infections was observed, resulting in approximately one additional death per 100 ABOi kidney transplant recipients during the first year post-transplant [15]. We and others have also observed a higher incidence of BK virus replication and BK virus-associated nephropathy [1]. An increased risk of malignancy was, however, not found in an analysis of 1,420 ABOi transplants from the CTS study [15].

5.3 Risk of bleeding and surgical complications

A study from the US Renal Data System registry found an increased risk of early haemorrhage in 119 ABOi kidney transplant recipients compared to ABOc controls [21]. A higher bleeding risk was also observed in our cohort of three paediatric kidney transplant recipients, with two experiencing major bleeding episodes. This was attributed to the non-specific binding of coagulation factors during repeated IA [22]. This is supported by the findings of de Weerd et al., who found a significant correlation between the number of pre-transplant apheresis treatments and peri- and post-transplant bleeding risk [23]. Some authors have observed an increased rate of surgical complications following ABOi kidney transplantation. These complications have been attributed to the intensified immunosuppression involving mycophenolic acid, as well as the removal of coagulation factors through apheresis. The Freiburg group reported a significantly higher number of lymphoceles in ABOi patients than in ABOc controls (33% versus 15%; P = 0.003), with surgical revision required in 20% and 8% of patients, respectively (P = 0.013) [24]. Furthermore, the overall need for surgical revision was significantly higher in ABOi patients than in ABOc controls (38% vs. 24%; P = 0.032).

6 An ABOi transplant from a living donor or an ABOc transplant from a deceased donor?

In light of mounting evidence of favourable outcomes following ABOi kidney transplantation in children as well as evidence of improved allograft survival in kidneys from living donors, some centres are considering ABOi living donor kidney transplantation for children prior to listing them for deceased donor organs. However, to date, there has been no prospective study comparing the outcomes of patients receiving ABOi living donor transplants with those receiving ABO-compatible transplants from deceased donors. Some experts argue that ABOi transplants should be considered as an option for paediatric patients prior to proceeding with a transplant from a deceased donor, as this approach has the potential to lead to improved patient and allograft outcomes.

Other authors have argued that ABOi kidney transplantation carries a higher risk of rejection compared to ABO-compatible transplantation, particularly antibody-mediated rejection [25]. To overcome this, extensive pre-transplant conditioning and additional pre-transplant immunosuppressive therapy are required, including desensitisation techniques and intensified immunosuppression protocols. However, such complex treatments may expose children to a higher risk of bacterial and viral infections, post-transplant lymphoproliferative disease and other neoplasms. Apheresis techniques require central venous lines in the absence of an arteriovenous fistula, particularly in children undergoing peritoneal dialysis or pre-emptive transplantation. These procedures can be complicated by infection, thrombosis or bleeding, which can jeopardise future access to dialysis. Furthermore, these techniques may be impractical or risky in young children due to the volume of extracorporeal fluid required during immunoadsorption sessions. Therefore, ABOi kidney transplantation is rarely performed in children with a body weight below 20 kg. Furthermore, from an economic standpoint, ABOi transplantation is more expensive and resource-intensive than ABOc transplantation. The additional procedures, prolonged hospital stays and specialised therapies required for desensitisation significantly increase the overall cost of the transplant procedure. Additionally, some parents may wish to retain the option of donating a kidney for a second transplant in adulthood, when organ shortages may be even greater. Therefore, the advantages and disadvantages outlined above must be considered in the context of each child's specific medical condition and individual circumstances. The decision to pursue ABOi kidney transplantation should be made in consultation with the child's medical team, weighing up the potential benefits and risks.

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