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ABO-Incompatible Kidney Transplantation in Children

Seiichirou Shishido

This article reviews the current status of ABO-incompatible kidney transplantation in the pediatric population. ABO blood type incompatibility between a donor and recipient was generally considered a contraindication to kidney transplantation because of the associated high risk for hyperacute rejection. However, due to a severe shortage of suitable cadaveric allografts, much effort has been made over the past decade to investigate whether successful and effective kidney transplantation is possible across the ABO blood group barrier. At present, ABO-incompatible kidney transplantation has been shown to be a valid alternative even for small children with end-stage renal disease. In this review, the author will discuss protocols available for successfully performing ABO-incompatible kidney transplantation in children: pretransplant extracorporeal immunomodulation with removal of preexisting anti-A and/or anti-B antibodies, immunosuppressive therapy and antirejection therapy, and splenectomy and the associated infectious complication in asplenic children. Also, the author will speculate with regard to the mechanisms underlying accommodation following transplantation.

ABBREVIATIONS:

PP	Plasmapheresis
IA	Immunoadsorption
CSA	Cyclosporine
CPM	Cyclophosphamide
MMF	Mycophenolate mofetil
DSG	Deoxyspergualine

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Introduction

Kidney transplantation is considered to be the optimal therapy for all children with end-stage renal disease because it is the only long-term therapy that offers children with chronic renal failure the potential of a near-normal life. Renal transplantation in Europe and to a lesser extent in North America is largely dependent upon the use of cadaveric kidneys. However, despite the use of numerous strategies aimed at increasing cadaveric organ donation, the disparity between organ demand and supply continues to widen. The recent data of the North American Pediatric Renal Transplant Cooperative Study[1] clearly indicate a decrease in the number of pediatric patients receiving a primary transplant since 1996. Some of the reduced activity could be consistent with the decreasing availability of cadaveric donor organs throughout the United States. In addition, patients with blood group type B and O are at a disadvantage when faced with the need for an organ transplant due to scarcity of donors with their blood group in the population. According to the United Network of Organ Sharing scientific registry,[2] the numbers of patients with blood group type A, B, and O waiting for kidney transplantation are 14,818 (27.9%), 8980 (16.9%), and 27,878 (52.6%), respectively. More important, the median waiting times for patients with blood group type B and O are about twice as long as those with blood group type A (544, 1329, and 1007 days for patients with blood group type A, B, and O, respectively).

Due to a severe shortage of suitable cadaveric allografts in Japan, more than 80% of pediatric patients receive a kidney from their living relatives.[3] If an appropriate living related donor is not available, a child may have to wait a considerable period of time for a cadaveric donor. In such circumstances, blood group ABO incompatibility was regarded as a major obstacle in screening potential living donors.

ABO blood type incompatibility between a donor and recipient was generally considered to be a contraindication to kidney transplantation because of the risk of preformed antibody-mediated hyperacute rejection. With significant advances in technology and improved understanding of the biochemical nature of the ABO antigens and their

TABLE 1 | IMMUNOSUPPRESSIVE THERAPY IN ABO-INCOMPATIBLE KIDNEY TRANSPLANTATION

Extracorporeal immunomodulation with removal of anti-A/anti-B antibodies
Pharmacotherapy for immunosuppression
Splenectomy
Anticoagulation therapy

IMMUNOADSORPTION:

Plasma is separated by a conventional plasmapheresis procedure and passed over a column containing an adequate adsorption agent to remove pathogenic substances.

HYPERACUTE REJECTION:

Hyperacute rejection is characterized by rapid thrombotic occlusion of the graft vasculature that begins within minutes after host blood vessels are anastomosed to graft vessels. It is mediated by preexisting antibodies that bind to endothelium and activate complement.

tissue distribution, however, several series of successful ABO-incompatible transplants were reported during the late 1980s.[4-7] In Japan, the severe shortage of cadaveric organs resulted in several investigators attempting to perform ABO-incompatible live related renal transplantation.[8-10] According to a recent report by Takahashi et al.,[11] a total of 312 ABO-incompatible living donor kidney transplants have been performed between January 1989 and November 1998 at 41 transplant centers in Japan. This is approximately 10% of the number of ABO-compatible renal allografts performed during the same period. However, less information is available with regard to the outcome in pediatric patients transplanted with ABO-incompatible renal allografts. Ohta et al.[3] reported a series of pediatric cases of ABO-incompatible living kidney transplantation. These data clearly demonstrated that the combination of preoperative reduction of isoagglutinins, splenectomy, and strict immunosuppression can lead to successful long-term results even in children. This article briefly reviews the features of ABO-incompatible kidney transplantation in the pediatric population.

ABO Blood Group Antigens and Kidney Transplantation

The first alloantigen system to be defined in mammals was a family of red blood cell surface antigens called ABO. All normal individuals synthesize a common core glycan, called the O antigen, that is attached to a sphingolipid. Individuals who possess an A allele form the A antigen by adding terminal N-acetylgalactosamine to some of their O antigens. Similarly, the B antigen is formed by adding terminal galactose to some of the O antigens. AB heterozygotes form both A and B antigens. These antigens are expressed not only on the surface of red blood cells but also in various organs including the kidneys. Immunofluorescence studies with monoclonal antibodies have shown that the ABO antigens are located on vascular endothelium and in the convoluted distal tubules and collecting tubules.[11,12] It is believed that anti-A and/or anti-B antibodies arise in response to carbohydrate antigens expressed by bacteria that normally colonize the bowel. It is highly possible, therefore, that binding of preexisting anti-A and/or anti-B antibodies to the vascular endothelium can cause hyperacute rejection and subsequent graft loss in the majority of ABO-incompatible renal transplants.

Blood group A can be further divided into A1 and A2 subgroups, and it is well known that there are some ethnic differences in the prevalence of the A2 subgroup. The A2 subtype is present in 20% of Caucasians with blood group A, whereas 98% of the Japanese population with blood type A are A1 positive.[11] A2 is a weaker antigen compared to A1 and does not induce an agglutinin reaction when exposed to anti-A1 reagents. In addition, patients with blood group A2 exhibit a lower total amount of A antigen and do not express the A3 and A4 subtypes in the kidney.[13] Since the early 1980s, transplantation using A2 kidneys has been performed with variable success.[13-16] Recently, Nicolas et al.[17] reported the long-term results of 40 cases of A2 or A2B into O or B recipients in 7 centers, which were performed from 1994 through 2000. The majority of these patients had a documented history of low anti-A titers (< 1:8) prior to transplantation. In this report, the 1-year and 5-year graft survival of A2 and A2B cadaveric kidneys transplanted into B recipients was equivalent to that of B patients who were transplanted with B or O kidneys (91%, 84% vs. 91%, 78% at 1 and 5 years, respectively).

Immunosuppressive Therapy in ABO-Incompatible Kidney Transplantation

Extracorporeal Immunomodulation Prior to ABO-Incompatible Kidney Transplantation

To prevent hyperacute rejection due to preexisting anti-A and/or anti-B antibodies reacting with vas-

cular endothelium, it is necessary to remove these antibodies from the recipient's serum prior to kidney transplantation. There are 2 different procedures for removing these antibodies: plasmapheresis (PP) and immunoadsorption (IA).

A single PP with a filtration technique is most commonly used for antibody reduction in children.[3,18] In our protocol, we used single PP with a continuous flow blood cell separator and exchanged 50 mL plasma/kg body weight on days 4, 2, and 1 before surgery. In all but the last session, the removed plasma was replaced by 3% to 5% albumin-containing solution and gamma globulin. During the last PP performed before transplantation, AB blood type fresh-frozen plasma was used as replacement fluid in order to supply complement and clotting factors. Such plasma is also useful to neutralize the remaining isoagglutinin in vivo to reduce anti-A or anti-B IgG and IgM antibody titers.

Double-filtration plasmapheresis (DFPP), which was developed to minimize the volume of substitution fluid, is the most popular plasma filtration method for the treatment of adults prior to ABO-incompatible kidney transplantation.[9,10] In DFPP, the plasma separator is the first filter and the plasma fractionator is the second filter. This combination makes it possible to selectively separate and discard only the plasma fraction consisting of high molecular weight proteins, including pathogenic substances such as antibodies. This procedure is also effective for pediatric patients, although care should be taken with small children to ensure that they do not develop hypervolemia and hypoalbuminemia.

Biosynsorb A and/or Biosynsorb B immunoadsorption column containing chemically synthesized human blood group ABO antigens covalently linked to crystalline silica is used to remove anti-A and/or anti-B antibodies.[19,20] We used plasma separation and perfusion of plasma through the IA column before reinfusion. In our experience, both PP and IA were similarly effective at removing anti-A and/or anti-B antibodies even in younger recipients. In IA, plasma and albumin replacement fluids are not required, since the patient's own plasma is reinfused following depletion of the isoagglutinins. Therefore, a major advantage of IA is the avoidance of nonautologous human blood products, which

DOUBLE-FILTRATION PLASMAPHERESIS:

This procedure uses a combination of 2 filtration units, a plasma separator, and a plasma fractionator, which makes it possible to selectively separate and discard only the plasma fraction consisting of high molecular weight proteins.

eliminates the risk of transmissible disease. However, this procedure is not used at present in Japan, since the use of Biosynsorb column mentioned above was not approved by the National Health Insurance of Japan due to its significant expense. Therefore, in our present protocol we use single PP in the protocol previously outlined.

Splenectomy

There is still some controversy with regard to the necessity of splenectomy in ABO-incompatible living kidney transplantation. The spleen plays a major role in the production of anti-A/anti-B antibodies and is likely to be involved in the initiation of the early stages of humoral rejection.[12]

Several investigators have emphasized the need for splenectomy to avoid acute vascular rejection.[5,7] Toma et al.[20] reviewed 155 ABO-incompatible renal transplants and indicated that the 1-year graft survival rates of the patients with and without splenectomy were 80.5% and 32.7%, respectively. Based on these results, splenectomy is currently considered to play an important role in the survival of ABO-incompatible kidney allografts.[11]

However, it should be noted that young recipients who undergo splenectomy are at a greater risk of serious infections posttransplant compared to adult patients.[21-23] These infections are most often due to encapsulated organisms, especially pneumococcus, *Haemophilus influenzae* type b, and meningococcus, but any bacterial agent may cause the rapid onset of septicemia, meningitis, pneumonia, and shock characteristic of the asplenic condition.[24] In a recent review of more than 12,000 patients who had undergone splenectomy, the incidence of serious postsplenectomy infections was found to be 15.7% in infants, 10.7% in children under the age of 5 years, 4% in children under the age of 16 years, and 0.9% in adults.[25] The efficacy of pneumococcal vaccination has been demonstrated in children with splenectomy.[26,27] To optimize antibody responses against T-cell-independent immunogens, it is recommended that the pneumococcal vaccine be administered at least 2 weeks before an elective splenectomy.[24] In addition, the use of long-term penicillin prophylaxis is recommended in asplenic children in order to prevent pneumococcal infection during the first 5 years of life.[27,28] Because most

children with end-stage renal disease have considerable growth retardation, penicillin prophylaxis as well as pneumococcal vaccination should be given to renal transplant recipients under 10 years of age.

Immunosuppression

Statistics with regard to ABO-incompatible kidney transplantation in Japan indicate approximately 20% graft loss during the first year, primarily due to acute humoral rejection within the first 2 months posttransplant.[10] Therefore, it has been generally thought that the initial immunosuppression for ABO-incompatible kidney transplant recipients should be more rigorous than that for ABO-compatible transplants in order to avoid antibody-mediated humoral rejection. In general, multiple drug regimens combining cyclosporine (CSA)/tacrolimus (TAC), steroids, azathioprine (AZA), cyclophosphamide (CPM), mycophenolate mofetil (MMF), antilymphocyte globulin (ALG), and deoxyspergualine (DSG) are used.[8,9,18] Tanabe et al.[9] and Ohta et al.[3] used a quintuple drug regimen consisting of CSA/TAC, AZA, steroids, ALG, and DSG with splenectomy for their ABO-incompatible kidney transplant recipients, including pediatric cases. Local irradiation (3 times at 150 rad) of the donor graft was added to this regimen. Our protocol is a quadruple drug regimen with CSA, methylprednisolone, CPM, and ALG. CPM 2 mg/kg was given to suppress the production of anti-A and/or anti-B antibodies for 10 days prior to transplantation and was switched to AZA at 2 months posttransplant. With regard to the origin of antibodies, it could be an advantage to inhibit antibody-producing B lymphocytes.[29] The effectiveness of CPM to suppress isoagglutinin production in ABO-incompatible kidney transplantation was supported by the recent work by Uchida et al.[30] MMF, a newly developed immunosuppressive agent, is rapidly becoming accepted within the pediatric renal community. Because this drug suppresses both T and B cell activity with fewer adverse effects compared to AZA, we recently changed our protocol and used MMF as a substitute for AZA at 2 months posttransplant. Several new immunosuppressive agents, including rapamycin and brequinar,[31] inhibit antibody synthesis and are therefore potentially useful in preventing acute humoral rejection.

ACUTE HUMORAL REJECTION:

Acute humoral rejection is characterized by necrosis of individual cells of the graft blood vessels. It is often mediated by IgG antibodies against endothelial cell alloantigens and involves activation of complement. However, the histological pattern is one of the vasculitis rather than of the bland thrombotic occlusion seen in hyperacute rejection.

Anticoagulation therapy is recommended to prevent microthrombosis and to maintain normal circulation of the renal allograft.[32] In our institution, dipyridamole and ticlopidine hydrochloride are administered, with treatment commencing at day 4 posttransplant.

Rejection and Accommodation

Early rejection in ABO-incompatible kidney transplantation may be clinicopathologically divided into 3 types: hyperacute rejection including the delayed-type hyperacute rejection, acute humoral rejection, and acute cellular rejection.

Despite the removal of anti-ABO natural antibodies before transplantation, hyperacute rejection crises may occur in some cases.[20] Hyperacute rejection in immunomodulated ABO-incompatible recipients seems to be somewhat different from that usually observed in unmodified ABO-incompatible patients. Several cases were reported to lose the graft due to delayed-type hyperacute rejection.[18,20,33] Patients who show a significant rebound increase of anti-A/anti-B isoagglutinn titers despite 3 to 4 consecutive PP/IA sessions before surgery are considered immunologic high responders.[11,18] Such patients could be poor candidates for ABO-incompatible kidney transplant.

Humoral rejection is most frequently observed in ABO-incompatible kidney allografts.[20,32] Moreover, acute rejection development during the first few weeks after ABO-incompatible kidney transplantation is frequently associated with the antibody-mediated humoral response.[32,33] The histological pattern of acute humoral rejection is one of transmural necrosis of the walls of the graft vessel with associated acute inflammation, which is distinct from the thrombotic occlusion without vessel wall necrosis that is evident in hyperacute rejection. DSG or muromonab-CD3 is used to treat this type of rejection, in addition to conventional antirejection therapy. In view of the fact that newly formed isoagglutinins may be associated with ongoing humoral rejection, the removal of such antibodies from the circulation using PP and/or IA may be also effective.

Several investigators have demonstrated that lowering the titer of the offending anti-ABO antibodies pretransplantation, and maintaining such lowered levels for several weeks postengraftment,

ACCOMMODATION:

The apparent resistance of a vascularized graft to humoral rejection despite the presence of antibodies directed against the donor endothelium.

SIMPLE PLASMAPHERESIS:

Blood is separated into hematocytic and plasma fraction, and the separated plasma fraction that includes pathogenic substances is replaced with a form of fluid supplement.

allows allograft survival even when antibodies are later permitted to return to predepletion levels and despite the presence of normal levels of complement.[33-36] The apparent resistance of a vascularized graft to humoral rejection despite the presence of antibodies directed against the donor endothelium is called accommodation.[37,38] The precise mechanisms responsible for accommodation are still not clear, but the prevailing view is that it involves an active change in endothelial cell physiology,[39] rendering the cells resistant to the effects of complement and refractory to activating stimuli.[40,41] Recent studies, using a hamster-to-rat cardiac xenotransplant model, have led to the hypothesis that changes in endothelial cell phenotype, particularly the expression of "protective gene" products such as hemoxygenase, A20, bcl-2, and bcl-x and antioxidant proteins such as HO-1, crucially determine whether grafts are rejected or survive by protecting these cells from apoptosis and preventing upregulation of proinflammatory genes.[38,42,43] Th2 responses are also shown to be associated with resistance to IgM- and IgG-mediated, complement-dependent, and complement-independent forms of rejection.[38] These findings suggest possible molecular mechanisms involved in the immunological phenomenon of accommodation.[44-47]

Infectious Complication

Infection remains the leading cause of morbidity and mortality throughout the posttransplant course. In the first month posttransplant, more than 95% of infectious disease syndromes are bacterial in nature.[48] Bacterial infections account for significant mortality after renal transplantation in children.[49] ABO-incompatible kidney transplant recipients usually have a relatively heavy immunosuppression compared to ABO-compatible patients. Moreover, as described previously, young recipients with splenectomy are at greater risk of serious bacterial infections posttransplant.[23,24] Therefore, it is assumed that they may have many more infectious complications than ABO-compatible patients. Contrary to these expectations, however, reported infectious complications in the pediatric population are few and, if any, not severe.[3,18] Pneumococcal vaccine and the use of long-term penicillin prophylaxis could be effective to prevent pneumococcal infection for young recipients with ABO-incompatible kidney allografts.

After the second month posttransplant, viral infection, most commonly CMV and opportunistic infection with *Pneumocystis carinii*, *Listeria monocytogenes*, and *Aspergillus fumigatus*, is common.[48] Human CMV generally is considered to be the most frequently occurring opportunistic pathogen and the most important infectious agent in pediatric renal transplantation. Because a higher percentage of young pediatric recipients are CMV negative at the time of transplantation, transplantation of a kidney from a CMV-positive donor into a CMV-negative recipient is associated with a significant incidence of posttransplant primary CMV infection. Appropriate prophylaxis, by anti-CMV IgG or antiviral chemotherapy, is warranted in the child at risk for primary infection.[50,51]

Long-Term Results in ABO-Incompatible Kidney Transplantation

According to the pooled analysis of ABO-incompatible kidney transplantation in Japan, the overall 1-, 5-, and 9-year patient survival rate is 91%, 89%, and 75%, respectively. The overall 1-, 5-, and 9-year graft survival rate is 82%, 68%, and 57%, respectively.[11] Long-term patient and graft survival in ABO-incompatible kidney transplantation is influenced primarily by acute rejection episodes occurring within 1 year.[20] There was no significant difference in graft survival between A-incompatible and B-incompatible kidney transplantation.[10] However, recent work by Shimmura et al.[52] has suggested that the maximum IgG, but not IgM, titers of anti-A/B antibody before transplantation may have a harmful effect on graft acceptance in ABO-incompatible kidney transplantation. Results are extremely favorable in children up to 15 years of age, with a graft survival rate of 100% at 1 year and 95% at 2 to 9 years.[11] Results are also good for patients 16 to 29 years of age, with a graft survival rate of 90% at 1 year, 87% at 3 years, and 76% at 5 to 8 years (Fig. 1). These long-term graft and patient survival rates are comparable to the rates for patients undergoing ABO-compatible kidney allografts. These data clearly show that young recipients might be better candidates for ABO-incompatible living donor kidney transplantation.
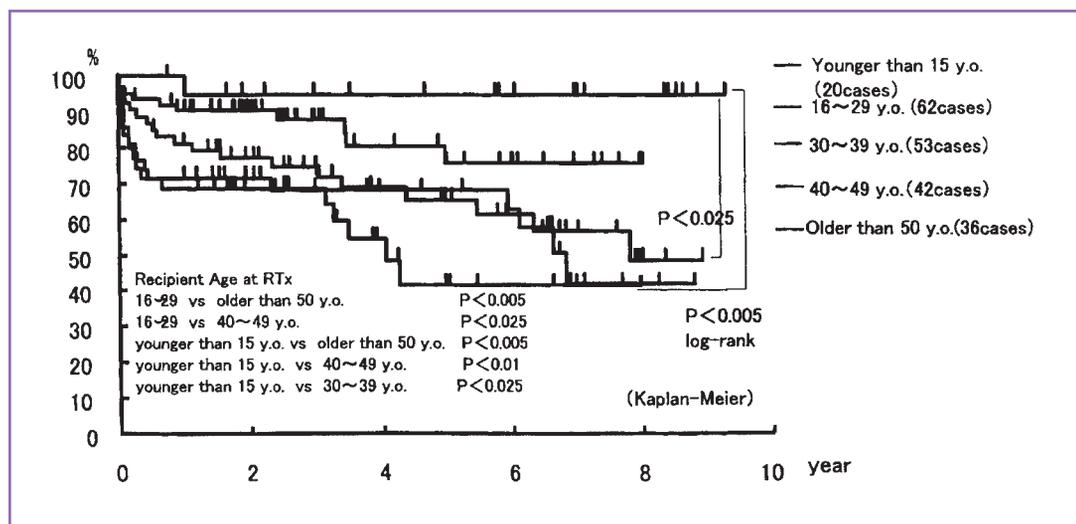
Figure 1. Graft survival rate by recipient age in ABO-incompatible kidney transplantation.

Summary

From recent works, with adequate pretransplant depletion of preexisting anti-A and/or anti-B antibodies by PP/IA, splenectomy, and posttransplant management, kidney transplantations across the ABO barrier are a valid alternative even for small children with end-stage renal disease. Patient and graft survival rates are compatible to those of ABO-compatible kidney transplantation. Despite successful removal of ABO blood group antibodies, however, hyperacute rejection may occur in some cases. In addition, acute humoral rejection is the most frequent type of early rejection in ABO-incompatible recipients. Further immunologic studies are needed to clarify the rejection/accommodation mechanism in ABO-incompatible renal transplants.

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