ABO-Incompatible Kidney Transplantation: Overview and New Strategies

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Abstract

The increasing shortage of human organs for transplantation has regained interest in blood group ABO-incompatible kidney transplantation, especially living donor kidney transplantation. After being performed at a few centers during the 1980s, ABO-incompatible renal transplantation has continued to expand over the years. More than 1000 ABO-incompatible living donor transplantations have been performed during the last decade in Europe, Japan, and the USA. Today, most centers use anti-ABO antibody removal combined with slightly different immunosuppressive drug protocols based on anti-CD20 (rituximab), tacrolimus, mycophenolate mofetil, and steroids. Splenectomy, once considered a prerequisite for ABO-incompatible transplantation, is now being replaced by anti-CD20 monoclonal antibody and this has, together with carbohydrate antigen-based immunoadsorption of anti-A/B antibodies, contributed to the expanded ABO-incompatible living donor programs. The short-term results of these new protocols are, so far, excellent with very few graft losses. In the years to come, the expanding clinical experience will tell which pretransplant regime will be optimal and the long-term graft survival outcome. Controlled trials are so far lacking and will, most likely, not be performed.

Despite being successful in the short term, there are still a number of clinical as well as scientific issues to be addressed. The pretransplant anti-ABO antibody titer target level to allow a safe transplantation is still not determined and more efficient immunoadsorbent material to remove anti-A/B antibodies are expected to be developed. Our knowledge of the molecular mechanisms behind the accommodation phenomenon where anti-ABO antibodies return without graft damage is not known. Knowledge gained within ABO incompatibility has been applied to allow transplantation of HLA-sensitized patients and may be of value in the development of xenotransplantation.

Paired kidney donation is another way of overcoming recipient/donor blood group ABO incompatibility and will probably expand. However, this concept has mainly ethical and logistic aspects, since the individual recipient immune system is not challenged with incompatible blood groups antigens. **(Trends in Transplant 2007;1:61-8)**

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Introduction

In the early days of transplantation, blood group ABO-incompatible renal transplantations performed due to mistyping of the donors had a very poor outcome[1] and Landsteiner´s principle was compulsory for organ transplantation, as it has been for decades in blood transfusion. In 1974, the first deliberate trial to cross the classical ABO barriers was initiated by Gelin and Sandberg[2], grafting cadaveric kidneys of the serologic blood group subtype A_2 into O recipients. The rationale was the knowledge that A_2 erythrocytes had less A antigens compared to A_1 cells, and that skin grafts from human A_2 donors were not rejected by O recipients in contrast to A_1 grafts[3]. In total, 21 cases were performed and no hyperacute rejection occurred and graft outcome was comparable to that of ABO-compatible cases at the time[4,5]. In the 1980s, clinical trials using A_1 and B donors were performed[6,7]. Alexandre performed a series of ABO-incompatible living donor renal transplantations using an immunosuppressive protocol including preoperative anti-A/B antibody removal, infusion of soluble A/B saccharides to neutralize remaining antibodies, and splenectomy[7].

Thereafter, ABO-incompatible living donor transplantations were performed mainly in Japan, but also to some extent in the USA and Europe[5,8-10], and about 500 cases have been reported with a one-year graft survival of about 85%[5]. However, the protocol did not receive general acceptance since it encompassed splenectomy and single cases with graft loss due to humoral rejection. The introduction of specific anti-A/B antibody immunoadsorption (see below) and new immunosuppressive drugs including anti-CD20 MAb (rituximab), initially developed for the treatment of B-cell lymphoma and used in transplantation as a “pharmacologic” splenectomy, has regained the interest in crossing the ABO barriers.

Blood group AB(O)H antigens have a great structural variation where the terminal trisaccharide antigen determinants are linked to various core chain structures, resulting in a large number of structurally different A and B antigens[11,12], and these structures have an organ- and cell-specific distribution[12]. Biochemical[13,14] and immunohistochemical[15] studies on blood group antigen expression in human kidneys have shown that renal grafts can, from an antigen perspective, be divided into “major” (A_1 and B donors) and “minor” (A_2 donors) incompatible challenge to the recipient immune system.

Anti-A and anti-B antibody levels are reported as a titer, which is the maximum dilution of recipient serum causing agglutination. The NaCl (sodium chloride) and IAT (indirect antiglobulin test) titers reflects hemagglutinin (mainly IgM) and immune (mainly IgG) antibodies, respectively. Blood group O individuals have, in general, slightly higher levels of anti-A/B antibodies compared to A and B individuals, and anti-A/B antibody levels vary considerably between different individuals, but the IAT titer is usually in the range of 16 to 256[16]. In clinical studies, anti-A/B titers are mainly tested using panel A_1 and B erythrocytes, but in some reports donor erythrocytes have been used as test cells. This has to be borne in mind when comparing results from different transplant centers.

The first applied anti-A/B antibody removal technique in ABO-incompatible renal transplantation was plasmapheresis. Despite being an effective antibody removal technique, plasmapheresis has known side effects such as coagulation disorders, possibility of viral infections, etc. In the 1980s, specific blood group A and B immunoadsorption columns were produced (Biosynsorb®, Chembiomed Ltd, Edmonton, Canada) for clinical use[17], having A and B trisaccharides linked to silica stationary phase. These columns were successfully used in renal transplantation[8,18]. However, this pioneering biotech company closed down and again plasmapheresis had to be used for antibody removal. Recently, a new A and B immunoadsorption column (Glycosorb®, Glycorex Ltd, Lund, Sweden), with the A/B saccharides

linked to sepharose, has been produced and tested clinically[19]. These columns are now used in several ABO-incompatible living donor programs in Europe[20-22]. The specific immunoadsorption columns remove the major part of anti-A/B antibodies, but antibodies needing a larger carbohydrate antigen-binding epitope structure[23] are not removed since the column antigen are the A and B trisaccharides. Grafting of an ABO-incompatible organ results in a further decrease in antibody titers in the following days due to adsorption to the graft[8,21] that contain a great diversity in A/B antigen structures exposed in a normal physiologic manner compared to saccharides linked to an inert solid phase.

ABO-incompatible renal transplantation protocol

Development of immunosuppressive regimes, including carbohydrate antigen-based immunoadsorption of anti-A/B antibodies, has led to the establishment of several ABO-incompatible living donor renal transplantation programs worldwide during the last five years, with slightly different protocols[20-22,24-26]. The results have been excellent, with very few graft losses. Our centre has enrolled 25 patients in our ABO-incompatible program, of which 23 were transplanted. Below is our current clinical protocol, together with results since the start in 2002.

Patients

Median recipient age was 48 (range 28-69) and male/female numbers were 13/11. Fifteen recipients received their first graft, seven their second, and in two cases their third graft. Recipient blood groups were O (n = 18), A (n = 3), and B (n= 2). Donor blood groups were A_1 (n = 7), A_2 (n = 5), B (n = 9), A_1B (n = 1), and A_2B (n = 1). Genetically nonrelated donors were most common (n = 14), followed by siblings (n = 5, of which two were HLA identical), parents (n = 3), and in one case a daughter.

Clinical protocol

Clinical evaluation of recipients and donors follow standard national guidelines. Donor (both open and laparoscopic techniques) and recipient operations as well as general treatment are performed similar to ABO-compatible living donor cases. Cytomegalovirus (CMV) and *Pneumocystis carinii* prophylaxis are given.

Recipients are pretreated with immunoadsorption, using A/B carbohydrate antigen columns (Glycosorb®, Glycorex AB, Lund, Sweden), aiming for an anti-A_1 panel erythrocyte IAT (indirect agglutination test) titer of ≤ 8 (A_1 and B donors) and ≤ 16 (A_2 donors) at the day of transplantation. Seven liters (10 l in selected cases) of plasma are processed at each immunoadsorption procedure. After the last preoperative immunoadsorption, one dose of intravenous immunoglobulins (0.5 g/kg) is administered. After grafting, three protocol immunoadsorptions are performed (days 2, 5, and 9). Additional immunoadsorptions are performed if anti-A/B titers increase or there is either suspicion of or biopsy confirmed rejection. Titers are monitored daily and, after discharge from the hospital, at outpatient clinic appointments.

Mycophenolate mofetil (MMF 1g twice daily) treatment is started 10 days prior to transplantation. Anti-CD20 (rituximab 375 mg/m^2) is given as a single dose (except for A_2 grafts if not indicated by other reasons) one week before scheduled transplantation. Tacrolimus (initial trough level 12-15 ng/l) and steroids are started at transplantation. After four to eight weeks, immunosuppressive drug dosages are tapered, similar as for ABO-compatible recipients.

Graft outcome

In total, 24 ABO-incompatible transplantations were performed in 23 patients. Patient survival was 23/23 and graft survival was 21/24 at a 1-58 months follow-up. The median measured

glomerular filtration rate (GFR) at 12 months follow-up (n = 15) was 53 (range 24-89) ml/min/1.73 m^2 and current median serum creatinine level (n = 20) was 129 (range 78-222) µmol/l.

Three grafts were lost. One graft was lost due to surgical complication with a recipient renal artery intimal dissection that completely obliterated the graft renal artery. This recipient was retransplanted after three weeks with another ABO-incompatible graft with excellent function at 12 months (GFR 89 ml/min/1.73 m^2). The other two grafts were lost due to rejection and infection and are described in more detail below.

Anti-A/B antibody titers

In 23 of 25 cases, anti-A and anti-B antibody target levels allowing transplantation were reached using A and B trisaccharide carbohydrate antigen immunoadsorption columns. Pre-immunoadsorption anti-A/B titers, measured by the NaCl and IAT techniques, were eight (range 1-64) and 32 (range 1-512) respectively. After a median of four (range 3-6) immunoadsorption procedures, the NaCl and IAT titers were reduced to one (range 0-2) and four (range 0-16). Three patients had a starting IAT titer of 512 and needed five to six immunoadsorption procedures to reach a target level, while four patients with starting IAT titer of 256 needed three to four immunoadsorptions.

Two blood group O patients (A_1 donors) with starting anti-A IAT titers of 128 and 256 antibodies could not reach the target level of titer 8 (6 and 9 immunoadsorption procedures, respectively), showing a rapid rebound of antibodies between each immunoadsorption. Both patients had received anti-CD20 (rituximab) and MMF prior to immunoadsorption start.

Altogether, more than 160 immunoadsorption procedures were performed and all procedures could be accomplished as planned and patients tolerated the procedures well. Anticoagulation treatment was standard heparin for the plasmapheresis circuit and citrate for the immunoadsorption column circuit. Standard heparin (not low-molecular heparin) was used for anticoagulation, since it is rapidly eliminated without accumulation in uremic patients. This is important in patients who undergo major surgery directly after being subjected to repeated extracorporeal procedures (immunoadsorption and hemodialysis).

The posttransplant antibody titers compared to the pre-immunoadsorption titers were lower in all recipients with functioning grafts except in one case (follow-up 5 weeks to 44 months). Follow-up data more than six months posttransplantation were available in 13 patients. The NaCl and IAT titers, comparing pre-immunoadsorption and six months posttransplantation, were reduced from eight (range 1-32) to two (range 0-8), and from 32 (range 2-512) to four (range 0-256), respectively.

Rejections

One patient (B to O) lost the graft due to irreversible humoral rejection caused by anti-B antibodies and the case has been described in detail[21]. This patient was successfully retransplanted with an ABO-compatible CD graft after three years.

In addition, three patients had rejections. These were of Banff IIA/B types in recipients that had received anti-CD20 MAb pretreatment. The rejections were not associated with anti-ABO titer increase and were reversed by anti-rejection treatment. Even if the rejection frequency is low, anti-CD20 seems not to completely eliminate cellular/vascular rejections as has been discussed.

Infections

In general, infectious complications were few. Patients treated with anti-CD20 MAb experienced very low lymphocyte count in peripheral blood as expected. Leucopenia ($< 3 \times 10^9$ l) was

noted in one patient and was reversed by decreasing the MMF dose.

One recipient with urethral obstruction experienced a severe urinary tract bacterial infection, resulting in complete necrosis of the graft renal pelvis and ureter. This could not be surgically reconstructed and urine was drained by a percutaneous catheter. Renal function was excellent (serum creatinine of 80 µmol/l). The patient had experienced both Banff IIA and IIB rejections. The anti-A titers were not increased and the rejections were regarded as not related to the ABO incompatibility. After the infection had subsided, the patient was retransplanted with an ABO-compatible CD graft. The removed ABO-incompatible graft showed no rejection upon histopathologic examination.

One case of primary CMV infection in a CMV-negative recipient and one case of graft polyoma virus infection were diagnosed. In both cases, MMF dosage was reduced and in the CMV case antiviral treatment was given and infections were successfully treated.

Future perspectives on ABO-incompatible renal transplantation

Today, blood group ABO-incompatible renal transplantation is an established treatment for end-stage renal failure. However, several clinical as well as scientific issues still remain to be addressed. Some of these are briefly discussed below.

Splenectomy versus Anti-CD20 versus "nothing"

Based on the original observation by Alexandre, et al.[27], splenectomy is regarded as necessary, in addition to antibody removal, for a successful outcome of ABO-incompatible renal grafts[5,8], but seems not to be required using A_2 grafts[10,28]. In single cases[6,21], A_1 and B grafts have been successfully grafted without splenectomy and the rational for splenectomy is debated (as reviewed[29]).

In recent years, anti-CD20 monoclonal antibody (rituximab), successfully used in treatment of B-cell lymphoma, SLE (Systemic lupus erythematosus) and vasculitis, has been introduced in clinical organ transplantation, both to treat rejections[30,31] and as induction therapy[20,21,24,26] in ABO-incompatible renal transplantation. One single dose of anti-CD20 eliminates peripheral B-cells for several months and has been suggested as a "pharmacologic" splenectomy. Anti-CD20 is administered as a single injection in a peripheral vein. This treatment is well tolerated and, so far, no significant side effects have been reported, in concordance with the experience from rheumatology and other clinical disciplines where usually significant higher doses of the antibody are used.

It has been postulated that ABO-incompatible renal transplantation can be performed without splenectomy or anti-CD20 antibody treatment. Successful short-term graft outcome was reported in four patients preconditioned with plasmapheresis, low-dose CMV hyperimmunoglobulin and no splenectomy or anti-CD20[32]. These results are supported by several single cases reported[6,21].

The issue of splenectomy versus anti-CD20 versus "nothing" will, most likely, be scientifically unresolved, since prospective clinical trials with sufficient numbers of patients will be difficult to perform. However, a clinical praxis may be settled in the future as our experience expands with the increasing number of cases transplanted.

Anti-A/B antibody estimation and removal

Estimation of anti-ABO titers is, in practical use, a quick and reliable method for clinical

care of the recipients. However, different techniques to estimate the antibody titers exist and the results also depend on target cells (donor or panel erythrocytes) used, which makes it difficult to compare data from individual transplant clinics. As a consequence, antibody target titer levels to allow a safe transplantation vary between transplant centers. A titer of eight or below (against panel red cells) is used by many centers, based on the report by Welsh et al.[33]. For A_2 grafts, a higher titer seems to be safe.

In some patients, the removal of anti-A/B antibodies is not sufficient enough to reach the target level to allow grafting. This may be due to a rapid re-synthesis, but as discussed above, another contributing fact may be that immunoadsorption using A and B trisaccharide-based columns cannot remove antibody clones requiring a larger saccharide-binding epitope. This may be overcome by producing immunoadsorbents with several different core chain-based A and B structures having an extended number of carbohydrate residues analogous to that shown for anti-Gal xenoantibodies[34]. Another possibility is to use a biologically generated compound with a great structural A and B antigen variation and multivalent exposure to the antibodies[35]. A recombinant P-selectin glycoprotein ligand-1 linked to the Fc portion of mouse IgG has been expressed in various host cells. This recombinant mucin/Ig expressing terminal Galα1,3 saccharides has been shown to be superior to solid phase linked Galα1,3Gal disaccharides in removing human plasma anti-Gal xenoantibodies[36]. By generating corresponding recombinant mucin/Ig product with multivalent A and B antigen determinants, a more efficient removal of anti-A/B antibodies may be achieved[35].

Accommodation

A state characterized by survival and continued function of ABO-incompatible renal allografts in the presence of reappearing (following their initial removal) anti-ABO antibodies and an intact complement system is referred to as accommodation[37]. The molecular mechanism(s) explaining the occurrence of accommodation is not known, but several theories have been suggested[38,39]. Thus, to achieve long-term graft survival in adult recipients of ABO-incompatible grafts, and eventually xenografts[40], preformed anti-carbohydrate antibodies have to be eliminated prior to grafting and for a defined period of time posttransplantation until accommodation has occurred. This is the rationale whereby several centers perform protocol immunoadsorption after ABO-incompatible grafting[20,21]. However, there are centers that find postoperative antibody removal unnecessary[8].

An interesting question is when accommodation occurs and when anti-A/B antibody titers can be allowed to increase without risk of initiating humoral rejection. Clinical experience indicates that this may be as early as two weeks posttransplantation. In our practice, as long as no signs of renal dysfunction are present, anti-A/B titers are allowed to increase after 3-4 weeks. When accommodation has occurred, it seems logical to treat the recipients similarly as for the ABO-compatible cases, and adjust the immunosuppressive baseline level to that used for corresponding ABO-compatible cases.

Long-term outcome

Recipients with higher antibody titers against blood group antigens have been reported to have an increased incidence of early graft failure similar as for recipients with HLA antibodies (reviewed[41]), but recent data indicates that new immunosuppressive regimes have eliminated this difference[42]. Long-term graft survival in ABO-incompatible renal graft recipients that had undergone splenectomy is reported to be similar for ABO-compatible cases[43]. Good long-term survival was recently reported in a limited number of recipients receiving living donor A_2 grafts without splenectomy[44], but long-term follow up of patients treated with anti-CD20 instead of splenectomy is still lacking. Recipients receiving

grafts from HLA-identical but ABO-incompatible siblings will be suitable to answer the question regarding long-term outcome related specifically to the ABO incompatibility. With growing numbers of ABO-incompatible transplantations and observation time this could be addressed in a multicentre evaluation. Other long-term side effects, such as the risk of malignancy due to a higher immunosuppressive load, have to be evaluated and also need a multicentre approach.

HLA-sensitized patients

The knowledge gained from ABO-incompatible transplantation and treatment of allo-sensitized recipients has developed in parallel during the years, exemplified by the use of protein-A columns to remove both anti-A[33] and anti-HLA[45] antibodies to enable renal transplantation. At present, several centers have successfully applied the use of plasmapheresis, anti-CD20 and intravenous immunoglobulin treatment to allow grafting in cross-match-positive living donor renal transplantation[46,47] as well as in combination with crossing the ABO barrier[48].

Paired donation

Another way to overcome ABO incompatibility is paired exchange donation, first introduced in Korea[49] and recently introduced in Europe[50] and the USA[51]. This concept is useful not only for ABO-incompatible pairs, but also for couples with positive cross-match test and could include pairs with a blood group O recipient.

Xenotransplantation

Although optimizing all alternatives, like increased donation willingness among the public and use of split organs, paired-exchange donation and ABO-incompatible donation will by no means overcome the lack of human organs for transplantation. At present, the stem cell technology and xenotransplantation are far from being a realistic clinical alternative for treatment of end-stage organ/cell failure. Nevertheless, they are the only options for the future as seen today.

Blood group ABO-incompatible allotransplantation and xenotransplantation have a natural affinity through their common determinant, the carbohydrate antigen/preformed anti-carbohydrate antibody barrier. Furthermore, information gained from studies of ABO-incompatible transplantation has been applied in xenotransplantation research. This is exemplified by Alexandre's demonstration of 21 days life-supporting survival of a porcine-to-monkey renal xenograft[40] in the 1980s that was achieved through the adaptation of his ABO-incompatible immunosuppressive protocol. Because of similarities in the immunologic hurdles that need to be overcome, knowledge obtained from ABO-incompatible allotransplantation might further promote advances in the field of xenotransplantation as recently reviewed[52,53].

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