The Role of ABO-Incompatible Living Donors in Kidney Transplantation: State of the Art

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Summary: In the past, ABO incompatibility has been considered an absolute contraindication for living donor kidney transplantation. Over the past 25 years, advances in immunosuppressive therapy and progressively more refined desensitization protocols have allowed increasingly successful transplantations across the ABO barrier. Current results of kidney transplants from ABO-incompatible living donors are quite favorable and comparable in the long term with the outcome of ABO-compatible organs both in Japan and in the United States. The present article reviews the history, outcomes, and current issues in kidney transplantation with ABO-incompatible living donors in adult and pediatric recipients.
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In the past 15 years the number of kidney transplants performed in the United States has increased significantly. In 1990 there were 9,416 kidney transplants performed—7,322 (78%) from cadaver donors and 2,094 (22%) from living donors. In contrast, in 2005 there were 16,481 kidney transplants performed, including 9,913 (60%) from cadaver donors and 6,568 (40%) from living donors. Therefore, the increase in volume over the past decade and a half mainly is the result of a 250% increase in the number of living donor transplants.[1] Over the same time span the waiting time on the cadaver donor list has continued to increase because of the exponential increase in the number of candidates for kidney transplantation. Reviewing 2003 data, only 18.4% of blood group B patients on the list were transplanted in the first 2 years whereas 19.8% of group O were transplanted over the same time period. The median waiting times for patients listed in 2001 in both of these groups now exceeds 5 years. In comparison, the waiting time for group AB (the shortest of all) is 2 years.[1] Therefore, the effort in expanding the pool of living donors for kidney transplant is becoming increasingly more important and is the most effective current solution to the cadaver donor shortage.

The advantages of living donor transplantation compared with cadaver donor transplantation have been well documented and include, but are not limited to, increased patient and graft survival rates, avoidance of prolonged cold ischemia, lower rates of delayed graft function, and pre-emptive transplantation, allowing patients to avoid dialysis altogether.[2-5]

A significant number of patients are unable to undergo living donor transplant despite the availability of willing and otherwise suitable donors because of ABO incompatibility. Paired donation has been applied successfully in this setting, with excellent results in terms of patient and graft survival.[6] Application of this on a large scale of paired donation programs surely will contribute to increase the chances of transplantation in this subgroup of candidates. However, at present, paired donation has not been able to help the vast majority of these patients.

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The present review focuses on desensitization techniques to allow living donor kidney transplantation despite ABO incompatibility.

BRIEF HISTORY

The first attempt at crossing the ABO barrier was made in 1955 by Hume et al.[7] In that series, 8 of 10 ABO-incompatible renal allografts were lost within the first few postoperative days because of hyperacute rejection. Although in 1964 Starzl et al[8] reported 3 successful kidney transplants across the ABO barrier, over the next 2 decades several case reports of unsuccessful attempts at kidney transplant across ABO antigens were published.[9-15] The largest series published at the time, a review of 25 ABO-incompatible kidney transplants, revealed a graft survival rate of 4% at 1 year.[15] Therefore, ABO incompatibility generally was considered an absolute contraindication to kidney transplantation.

One promising area identified quite early was the potential use of A2 donors for O and B recipients. In 1967, Economidou et al[16] showed that the expression of A antigens on erythrocytes from A_2 individuals was much weaker than the expression in A_1 individuals. In whites, the A2 subtype constitutes approximately 20% of blood group A individuals.[17] Based on this premise and previous experiments using skin grafts from both A1 and A2 donors, a clinical trial was begun in 1974 to transplant blood group A2 donors into O recipients. In 1987, Rydberg et al[18] reported that in 20 transplants performed under this protocol, 8 were lost within a month, whereas 12 maintained long-term function. With improvements in immunosuppression medications and intensive immunologic monitoring, results of A2 donors into O or B recipients have now reached outcomes equal to that of compatible donors.[19-22] Unfortunately, these interesting findings have been able to help only a minority of kidney transplant candidates with available ABO-incompatible living donors.

The modern era of effective and reliable desensitization in ABO-incompatible living donor kidney transplant was introduced by Alexandre et al[23] between 1982 and 1987. The Belgian group was the first to introduce plasmapheresis as a strategy to reduce the titers of anti-A or -B antibodies. Furthermore, after 3 transplants failed secondary to hyperacute rejection, they introduced recipient splenectomy at the time of the kidney transplant to minimize the risk of humoral rejection. Immunosuppression included cyclosporine, steroids, and azathioprine, with induction based on antilymphocyte globulin. In the original series of 26 patients, the investigators reported a 75% 1-year graft survival rate. With remarkably few modifications, their strategy has been the mainstay of all modern protocols in this setting.

Further development in the field has come from centers in Japan. In 2004 the number of patients on dialysis in Japan exceeded 240,000 and increased by 13,000 annually.[24] Because very few cadaver kidney transplants are performed in Japan, living donor transplantation remains virtually the only chance at life without dialysis. Since the late 1980s the use of ABO-incompatible donors has become increasingly popular in Japan and recently reached 14% of all living kidney transplants performed in Japan. Because only 0.15% of the Japanese population is positive for A2 subgroup,[25] the majority of these cases are across strong expression of incompatible A and B antigens. The major contribution of their large experience to the field has been the clear demonstration that, with modern desensitization protocols, the long-term results of ABO-incompatible living donor transplantation compared well with cadaver graft data.

It has been only in the past decade that ABO-incompatible living donors have been used more consistently in Europe and in the United States, although not to the extent of the Japanese experience. The introduction of immunoabsorption (mostly in Europe) and the availability of rituximab recently have offered the potential to eliminate disincentives to ABO-incompatible living donor kidney transplantation (such as the need for splenectomy) and the potential to improve the outcomes of the procedure.

RESULTS

Because of the relatively small volume of ABO-incompatible living donor kidney transplants in

single-center experiences, the best data available come from registries. Takahashi and Saito[24] recently reviewed the long-term follow-up evaluation of ABO-incompatible living donor kidney transplants performed at 60 institutions reporting to the Japanese registry from 1989 through 2003. Seventy percent of patients received preoperative plasmapheresis and 98% underwent splenectomy. Immunosuppression consisted of a calcineurin inhibitor (59% cyclosporine, 41% tacrolimus), steroids, and an antimetabolite. Graft survival in this series was 86%, 82%, 74%, and 53% at 1, 3, 5, and 10 years posttransplant, respectively. Of note, transplants performed since 2001 (n = 124) had significantly higher 2-year graft survival rates (94%) compared with the previous experience. This group suggests that this improvement may be the result of the use of mycophenolate mofetil and the anti-CD25 monoclonal antibody basiliximab during this period. When compared with a control group of 1,055 patients who underwent a compatible living donor transplant, graft survival rates were statistically better in the compatible-donor group during the first 5 years, however, there was no difference beyond this point. Graft survival did not differ based on blood type incompatibility, human leukocyte antigen mismatch, or which calcineurin inhibitor was used. Of note, about 57% of patients received anticoagulation therapy. Graft survival in patients who did receive anticoagulation was significantly better than for those who did not.

Futagawa and Terasaki[26] reviewed the United Network for Organ Sharing registry data to evaluate the outcomes of ABO-incompatible transplants in the United States. From the database, reflecting the activity of 256 transplant centers, 201 recipients of ABO-incompatible deceased donors were identified and compared with the more than 59,000 compatible deceased donor kidney transplants performed over the same time period (1995-2003). In addition, 191 recipients of live-donor, ABO-incompatible transplants were compared with 37,612 compatible live-donor transplants. For deceased donors there was no difference in graft survival at any time frame between the compatible and incompatible groups. Although it was reported previously that better graft survival may be established with the use of A2 donors because of a lower expression of antigens, in this series it was found that non-A2 donors were significantly better than outcomes with A2 donors at both 1 year (91.3% versus 86.5%, respectively) and at 5 years (77.4% versus 60.5%, respectively). As mentioned previously, the A2 blood group is much more common in Caucasians than it is in Asian populations, and in this study 27.9% of donors were A2 and went to B- or O-group recipients. For living donor transplants, graft survival for ABO-incompatible transplants was significantly worse than for compatible transplants at 5 years (66.2% versus 79.5%, respectively). However, these authors point out that the majority of this graft loss occurs in the first year and for patients who retain their grafts for more than 1 year, the 5-year graft survival is no different between the 2 groups.[26]

Although the larger numbers of patients available for evaluation in this study obviously adds power to the analysis, it should be noted there are some significant limitations to this study. Not all characteristics of the recipients and donors were matched between groups and included such differences as cold ischemia time, human leukocyte antigen match, panel reactive antibody (PRA)%, and recipient age. In addition, there was no mention of pretransplant AB titers, what strategy was used to decrease the titer, and any posttransplant titers or rejection episodes. Furthermore, immunosuppression regimens were of a wide variety and differed from group to group.

The results in experienced centers appear to be superior to the registry data both in the United States and in Japan. Tanabe et al[27] reported a 91% patient survival and a 73% graft survival rate at 8 years after transplant in their large single-center series. Excellent results have been reported in the United States by the John Hopkins and Mayo Clinic groups.[5,28] These studies also identified the initial titer of anti-A or -B antibodies as one of the most important prognostic predictors of success. Regardless of the modality used to decrease the titers, patients naturally starting from a low titer of such antibodies had a better outcome compared with those who started with higher titers.

The use of ABO-incompatible donors for kidney transplants in the pediatric population has been addressed mostly by single-center Japanese reports. Shishido et al[29] reported an 87% and 85% graft survival rate at 1 and 5 years posttransplant, respectively, in a series of 16 pediatric recipients receiving ABO-incompatible living donor grafts. All the recipients underwent splenectomy and were treated with plasmapheresis perioperatively. The patient survival rate was 100% at 5 years and no life-threatening infectious complications related to the splenectomy or the preconditioning protocol were reported. Shishido et al[29] found no correlation between isoagglutinin titers and acute rejection after the third week posttransplant. This phenomenon, widely reported in adult literature, has been defined as accommodation and its basis remains uncertain. Another single-center report from Otha et al[30] confirmed the favorable outcome of ABO-incompatible kidney transplants in children. Interestingly, a recent follow-up evaluation of the original series of ABO-incompatible kidney transplants performed in the 1980s by Alexandre and Squifflet has documented a superior long-term graft survival in recipients younger than 15 years of age at the time of transplant (78% versus 58% at 15 years posttransplant) in comparison with older recipients.[31]

CURRENT ISSUES

An increasing number of transplant centers currently are using ABO-incompatible living donors for kidney transplantation. Although the results have improved over the years, this strategy still has significant drawbacks in comparison with standard ABO-compatible living donor transplantation. Inferior early graft survival and an increased rate of acute rejection (especially antibody-mediated) have been documented clearly in the literature previously cited. Furthermore, the need for splenectomy at the time of transplant and for complex preconditioning regimens surely contribute to increase the overall morbidity of the procedure.

The standard way to perform ABO-incompatible living donor kidney transplantation is based on 3 main points: (1) deconditioning protocols to decrease the titer of anti-A and -B antibodies, mostly based on plasmapheresis; (2) splenectomy at the time of transplant, with the intended purpose to decrease the risk of hyperacute rejection and antibody-mediated rejection; and (3) standard immunosuppression with liberal use of polyclonal antibodies for induction, especially in Western countries. In the past few years several important innovations have been introduced to the classic approach of ABO-incompatible kidney transplantation, concerning all the points listed previously.

Deconditioning Protocols

Plasmapheresis with or without intravenous immune globulin has been the mainstay of all protocols aimed at reducing the titers of isoagglutinins in preparation for an ABO-incompatible kidney transplant. This modality is still the standard in the United States and in most cases in Japan. Recently, several European centers have championed the use of immune absorption to selectively remove anti-A and -B antibodies, claiming it can be as efficient as plasmapheresis and present the advantage to avoid an indiscriminate depletion of serum proteins with excellent results.[32-34] In particular, plasmapheresis potentially can cause a significant alteration of the coagulation profile and deplete the body's reserve of immunoglobulins. Selective immune absorption seems to be a more logical way to remove preformed anti-A and -B antibodies and the interest for this strategy currently is growing. However, to date, no data are available to confirm or disprove this hypothesis. A randomized trial comparing the 2 modalities may be necessary.

Splenectomy

Adding a splenectomy to a standard kidney transplant causes 2 important sets of problems. The specific complications linked to the surgical procedure might complicate the recovery and surely will increase the overall surgical risk. Furthermore, the potentially increased risk of infectious complications and in particular the so-called *overwhelming postsplenectomy sepsis* from capsulated micro-organisms should be kept in consideration. Although in many centers the current approach to splenectomy at the time of transplant is based on minimally invasive techniques, the surgical risk cannot be eliminated. The widespread use of polyvalent pneumococcal, hemophilus, and meningococcal vaccines has re-

duced but not eliminated the risk for post-splenectomy overwhelming sepsis. Recently several European, Japanese, and American groups have developed protocols aimed to avoid the need for splenectomy in the setting of ABO-incompatible kidney transplantation.[32-38] The results to date have been extremely favorable, regardless of the use of plasmapheresis (US centers) versus immune absorption (European centers). Although initially treatment with anti-CD20 monoclonal antibodies was considered essential to perform ABO-incompatible kidney transplant without splenectomy, recent experience from John Hopkins suggests otherwise.[38] The role of anti-CD20 monoclonal antibodies is discussed further in the next section. Although to reach final conclusions it would be necessary to perform a randomized trial of ABO-incompatible kidney transplantation with or without splenectomy (not performed to date), this early experience has shown clearly that splenectomy avoidance is feasible in this setting.

Immunosuppressive Protocols

ABO-incompatible kidney transplantation is rightly considered an increased immunologic risk. Therefore, aggressive immunosuppressive protocols traditionally have been used since the 1980s to reduce the risk of immunologic graft loss. Most centers have been using polyclonal or monoclonal (anti-CD25) antibodies as induction and chronic immunosuppression based on tacrolimus, mycophenolate mofetil, and steroids. The introduction of a commercially available anti-CD20 antibody that specifically targets B cells has led to several trials in which this molecule was used as induction.[32-37] The timing of administration has been either 2 weeks before the transplant or at the time of transplant. The intended goal was to decrease the chance of humoral rejection and eliminate the need for splenectomy. As discussed previously, those trials have been extremely successful, although the combination of multiple innovations in the treatment make it difficult to dissect the real value of each single component of the protocol. As already mentioned, ABO-incompatible kidney transplants already have been performed successfully without anti-CD20 induction.[38] The role of anti-CD20 therapy in this setting deserves further investigation.

CONCLUSIONS

The early dogma suggesting that ABO incompatibility should be considered an absolute contraindication to living donor kidney transplantation has been challenged successfully in the past 2 decades. In experienced centers the procedure can be performed with satisfactory results even in the long term for both adult and pediatric recipients. However, this strategy exposes patients to an increased risk of early graft loss and a higher rate of acute rejection, as well as to the morbidity inherent to the necessary use of deconditioning protocols.

At this time, it is prudent to consider a deconditioning protocol for ABO-incompatible kidney transplants only after exhausting all other alternatives and with full disclosure to the potential candidate of all the potential risks and complications related to the procedure. In particular, especially for recipients in blood group A or B, in the presence of a single suitable but ABO-incompatible donor, full consideration should be given to paired donation, either limited to the institution or within a regional or national network.

Recent trials have suggested the possibility to decrease and in some cases eliminate the drawbacks of ABO-incompatible kidney transplantation. As the protocols become progressively safer and simpler, the indications for the procedure and the acceptance among living donor transplant candidates and transplant centers will increase.

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