8. Shaldon S, Deschodt G, Branger B *et al*. Haemodialysis hypotension: the interleukin hypothesis restated. *Proc Eur Dial Transpl Assoc* 1985; 22: 229–243
9. Cotter DJ, Stefanik K, Zhang Y, Thamer M, Scharfstein D, Kaufman J. Hematocrit was not validated as a surrogate end point for survival among epoetin-treated hemodialysis patients. *J Clin Epidemiology* 2004; 57: 1086–1095
10. Cotter DJ, Tharner M, Narasimhan K, Zhang W, Bullock K. Translating epoetin research into practice: the role of government and the use of scientific evidence. *Health Affairs* 2006; 25: 1249–1259

Received for publication: 20.9.06
Accepted in revised form: 5.10.06

Nephrol Dial Transplant (2007) 22: 25–27
doi:10.1093/ndt/gfl557
Advance Access publication 27 September 2006

ABO-incompatible transplantation—a safe way to perform renal transplantation?

Jörg Beimler and Martin Zeier

Department of Nephrology, University of Heidelberg, Heidelberg, Germany

Keywords: ABO-incompatible renal transplantation; desensitization; immunoadsorption; living kidney donation; plasmapheresis; rituximab

The shortage of donor organs, especially in renal transplantation, leads to an increasing discrepancy between the number of end-stage renal disease patients on waiting lists and the number of available deceased donor kidneys. Expansion of the donor pool can be achieved by increasing the numbers of living kidney transplantation and by overcoming the immunological barriers of ABO-incompatibility and HLA-sensitization. Despite a substantial increase in the number of patients, receiving living kidney transplant, otherwise suitable donors have to be rejected due to pre-existing human leuocyte antigen antibodies or ABO-incompatibility. Isoagglutinins (ABO-antibodies) represent a major barrier in optimizing living kidney donation and organ distribution. As blood group antigens are expressed by the endothelium of solid organs including the kidney, transplantation across the blood group barrier can result in hyperacute antibody-mediated allograft rejection. Depending on blood group distributions in different populations, as much as 30–35% of potential living donors have to be excluded from living donation due to ABO-incompatibility. ABO-incompatible transplantation was already performed as early as in the 1970s, but due to hyperacute rejection, results were discouraging. In 1987, Alexandre *et al*. [1] published a first series of 26 ABO-incompatible kidney transplantations using splenectomy and an immunosuppressive regimen with steroids, cyclosporine, azathioprine, antithymocyte globulin and donor-specific platelet transfusions. Due to a severe shortage of available deceased donor organs, most ABO-incompatible kidney transplantations have taken place in Japan. Recently published data demonstrated an excellent long-term outcome of ABO-incompatible living donor kidney patients in Japan [2]. Similar successful short-term results have been shown for protocols developed in Europe and the United States. Results from Japan, the United States and Europe are promising, but a lot of questions remain unanswered and there is a lack of standardization among the different protocols. Different approaches to performing successful ABO-incompatible kidney transplantation have been used in different countries over the last decade.

The European way

The recent availability of specific anti-A or anti-B immunoadsorption columns (Glycosorb®) and the use of anti-CD2O monoclonal antibody (rituximab) in different immunosuppressive regimens resulted in the introduction of ABO-incompatible renal transplantation as a routine procedure in different European countries, mainly in Sweden and Germany, including our centre. The first series of ABO-incompatible renal transplantation without splenectomy, using antigen-specific immunoadsorption and rituximab, was published by the Stockholm group of Tyden *et al*. [3,4]. In 21 patients successfully treated with this protocol, the immunosuppressive regimen consisted of one dose of rituximab (375 mg/m^2) given 2–4 weeks

Correspondence and offprint requests to: Jörg Beimler, Nierenzentrum Heidelberg, Department of Nephrology, University of Heidelberg, Im Neuenheimer Feld 162, 69120 Heidelberg, Germany. Email: beimler@gmx.de

before immunoadsorption, followed by a conventional triple-drug immunosuppression consisting of tacrolimus, mycophenolate mofetil and prednisolone, starting 1 week before immunoadsorption. Pre-operatively, anti-A or anti-B antibodies were removed using the Glycosorb® ABO column, a low-molecular carbohydrate column with A or B blood group antigen linked to a sepharose matrix. Immunoadsorption with Glycosorb® columns is very effective, and IgG and IgM isoagglutinin titres can be reduced by two to three titre steps with every immunoadsorption session. Typically, four pre-operative immunoadsorption sessions were performed, aiming for a pre-operative ABO antibody titre of <1:8. After the last pre-operative session, 0.5 g/kg of intravenous immunoglobulin (IVIG) was administered. To avoid early post-operative rebound of ABO antibodies, three more immunoadsorption sessions were done over a period of 9 days. Based on their data with a maximum follow-up of 4 years, it can be said that there were no major side effects of the treatment regimen, patients showed normal serum creatinine levels and no late reappearance of isoagglutinins was observed during follow-up. In recent publications, similar results using this regimen have been shown by other groups in Germany and Sweden [5,6]. In summary, about 60 ABO-incompatible renal transplants have been performed successfully in Sweden and Germany over the last 5 years with this protocol.

The Japanese way

Recently, Takahashi *et al.* [1] published the surveillance data of 494 ABO-incompatible kidney transplantations performed in Japan between 1989 and 2001. Over this time period, a variety of immunosuppressive regimens, including extracorporal strategies to remove antibodies (pre-operative titre <1:8–16), pharmacological immunosuppression, anticoagulation and splenectomy (98%), were used. Splenectomy of the recipient was performed due to the role of the spleen in anti-A/B antibody production. Immunosuppressive triple therapy was based on calcineurin inhibitors, steroids and antimetabolites, differing among centres, on the basis of which additional immunosuppressive agents, such as antilymphocyte globulin, deoxyspergualin or cyclophosphamide, were administered. Antibody removal was usually not performed after transplantation. Compared with historical cases of living kidney transplantation ($n = 1055$), the short-term results were not as good as those of ABO-compatible cases, but the long-term outcome showed no statistically significant difference. Patient survival rates were 93, 89, 87 and 84% at 1, 3, 5, 7 and 9 years, while graft survival rates were 84, 80, 71, 65 and 59%, respectively. The graft survival rate did not show any significant differences between A-incompatible and B-incompatible transplants or among different ABO blood type incompatible combinations. Looking at the outcome of the most recent cases since 2001, results have substantially improved, with a 1- and 2-year graft survival of 96 and 94%, showing that, based on newer immunosuppressive regimens, short-term graft survival in ABO-incompatible renal transplantation has improved. This improvement might be at least partially due to the introduction of mycophenolate mofetil and the anti-CD25 monoclonal antibody basiliximab into therapy. Based on registry data, splenectomy has been considered to be an essential part of successful ABO-incompatible renal transplantation. But even with splenectomy, severe antibody-mediated rejection can be observed [7]. Antibody-mediated rejection typically occurred within the first month after transplantation, particularly in the first week. Since 2004, a desensitization protocol without splenectomy starting 4 weeks prior to transplantation, including double filtration plasmapheresis, anti-CD20 treatment, mycophenolate mofetil and steroids, was introduced, showing a successful short-term outcome. No additional post-operative antibody removal or administration of IVIG was performed [8].

The American way

The Johns Hopkins group established a preconditioning protocol of plasmapheresis, CMV hyperimmune globulin (CMVIg) and anti-CD20 to allow ABO-incompatible renal transplantation without splenectomy [9]. The treatment protocol demands four to five pre-operative plasmapheresis sessions to remove anti-A/B antibodies, each session followed by the administration of cytomegalovirus hyperimmune globulin at 100 mg/kg. After achieving a pretransplant A/B-antibody titre of <1: 16, 1 or 2 days prior to transplantation, a single dose of rituximab was given at 375 mg/kg. Thereafter, immunosuppression with tacrolimus and mycophenolate mofetil was initiated, followed by steroids and daclizumab after transplantation. Post-operative treatment included another three plasmapheresis/CMVIg sessions on days 1, 3 and 5. At follow-up, mean serum creatinine was 1.3 ± 0.1 mg/dl in the first six patients. The absence of humoral rejection and stable kidney graft function in their initial experience shows the potentials of preconditioning regimens with the use of rituximab, avoiding the risks of splenectomy.

ABO-incompatible renal transplantation—questions to be answered

ABO blood group incompatibility has long been considered to be an absolute contraindication to renal transplantation. The recent development of desensitization protocols has been shown to reduce and maintain anti-A/B titres against the donor blood group sufficiently, preventing antibody-mediated rejection and allowing successful ABO-incompatible living-donor kidney transplantation. The key factor to successful graft outcome is the prevention of hyperacute rejection, to establish accommodation as early

as possible. Accommodation is defined as the absence of an antigen–antibody reaction, despite the presence of 'foreign' antigen on the vascular endothelial cells within the graft and the presence of antibody in the recipient's blood [10]. Protocols in the United States and Japan differ from those used in most centres in Europe, where antigen-specific immunoadsorption, rather than plasma exchange, is the preferred mode of removing antibodies. Humoral rejection seems to correlate more closely with pre-transplant antibody titre than with the antibody-lowering regimen used. Immunoadsorption with the anti-A/B-specific Glycosorb® column offers a very effective way of removing anti-ABO antibodies without the known side effects of plasmapheresis, such as coagulation disorders, the possibility of viral infection or allergic reactions to fresh frozen plasma. Despite higher overall costs and additional resource utilization, ABO-incompatible kidney transplantation offers a safe option to perform renal transplantation successfully in patients whose only living donor is blood-group-incompatible. Depending on different patient populations and worldwide waiting list systems, kidney paired donation or list paired donation may be an alternative for patients with ABO-incompatible donors, reducing the need for desensitization strategies. Despite all efforts recently made, important questions about ABO-incompatible transplantation are yet to be answered. We do not know the acceptable upper limits of ABO antibody titres at the time of transplantation to prevent antibody-mediated rejection. With recent immunosuppressive regimens, antibody titres as high as 1:32 might be sufficient to perform transplantation safely [11]. Due to technical reasons, methods for isoagglutinin monitoring and therefore reproducibility of results differ between centres. Whether patients with anti-CD20 therapy and without a substantial rebound of antibody titre after transplantation need additional plasmapheresis treatments remains to be elucidated, though preliminary data from Japan suggest successful outcomes without post-operative plasmapheresis. Whether such a regimen is feasible for all ABO-incompatible kidney transplantations is yet to be determined. Anti-CD20 treatment as a B-cell ablative therapy has been shown to replace splenectomy successfully. Interestingly, recent protocols based on rituximab therapy showed little or no cellular rejection episodes, but whether this is due to the addition of anti-CD20 to the immunosuppressive regimen remains unclear. As one dose of rituximab (375 mg/kg) often effectively removes CD20-positive cells, most centres administer one single dose of rituximab in their pre-treatment protocol. Concerning its off-label use and the fact that some insurance companies do not pay for it, the question of whether all patients for ABO-incompatible renal transplantation need anti-CD20 pre-conditioning has been raised [12]. Recently at Johns Hopkins, 13 successful ABO-incompatible transplants, A1 and AB donors into O recipients with titres as high as 1: 512, were performed without splenectomy or anti-CD20 therapy [13]. Although many questions have yet to be answered, ABO-incompatible renal transplantation has become a viable option for patients who lack blood-group-compatible kidney donors. Furthermore, collaboration between centres performing ABO-incompatible kidney transplantation, for example, by collecting data in registries, might answer open questions.

Conflict of interest statement. None declared.

References

1. Alexandre GPJ, Squifflet JP, De Bryere M *et al*. Present experience in a series of 26 ABO-incompatible living donor allografts. *Transplant Proc* 1987; 19: 4538–4542
2. Takahashi K, Saito K, Takahara S *et al*. Excellent long-term outcome of ABO-incompatible living donor kidney transplantation in Japan. *Am J Transplant* 2004; 4: 1089–1096
3. Tyden G, Kumlien G, Genberg H *et al*. ABO-incompatible kidney transplantations without splenectomy, using antigen-specific immunoadsorption and rituximab. *Am J Transplant* 2005; 5: 145–148
4. Tyden G, Kumlien G, Genberg H *et al*. The Stockholm experience with ABO-incompatible kidney transplantations without splenectomy. *Xenotransplantation* 2006; 13: 105–107
5. Donauer J, Wilpert J, Geyer M *et al*. ABO-incompatible kidney transplantations using antigen-specific immunoadsorption and rituximab: a single center experience. *Xenotransplantation* 2006; 13: 108–110
6. Norden G, Briggs D, Cockwell P *et al*. ABO-incompatible live donor renal transplantation using blood group A/B carbohydrate antigen immunoadsorption and anti-CD20 antibody treatment. *Xenotransplantation* 2006; 13: 148–153
7. Ishida H, Koyama I, Sawada T *et al*. Anti-AB titer changes in patients with ABO-incompatibility after living related kidney transplantations: survey of 101 cases to determine whether splenectomies are necessary for successful transplantation. *Transplantation* 2000; 70: 681–685
8. Saito K, Nakagawa Y, Suwa M *et al*. Pinpoint targeted immunosuppression: anti-CD20/MMF desensitization with anti-CD25 in successful ABO-incompatible kidney transplantation without splenectomy. *Xenotransplantation* 2006; 13: 111–117
9. Sonnenday C, Warren DS, Cooper M *et al*. Plasmapheresis, CMV hyperimmune globulin and anti-CD20 allow ABO-incompatible renal transplantation without splenectomy. *Am J Transplant* 2004; 4: 1315–1322
10. Takahashi K.A. New concept of accomodation in ABO-incompatible kidney transplantation. *Clin Transplant* 2005; 19 [Suppl 14]: 76–85
11. Shimmura H, Tanabe K, Ishikawa N *et al*. Role of anti-A/B antibody titers in results of ABO-incompatible kidney transplantation. *Transplantation* 2000; 70: 1331–1335
12. Montgomery RA, Simpkins CE, Segev DL. New options for patients with donor incompatibilities. *Transplantation* 2006; 82: 164–165
13. Segev DL, Simpkins CE, Warren DS *et al*. ABO incompatible high-titer renal transplantation without splenectomy or anti-CD20 treatment. *Am J Transplant* 2005; 5: 2570–2575

Received for publication: 14.8.06
Accepted in revised form: 21.8.06