Blood group incompatibility in kidney transplantation: definitely time to re-examine!

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We report a successful kidney transplant (A1 donor to an O recipient), with antibody removal pre- and post-transplant, and pre-transplant administration of anti-CD20 monoclonal antibody (rituximab), intravenous immunoglobulin, and conventional transplant immunosuppression. The transplant, which was performed without splenectomy, is the first such transplant in Australia. At 20 months, the patient's creatinine level was 110–130 μmol/L, with no evidence of rejection and no complications. ABO-incompatible transplantation should increase "live donor" kidney transplantation, reduce waiting times, and improve patient outcomes.

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Clinical record

A 24-year-old white man with an antineutrophil cytoplasmic autoantibody (ANCA)-positive crescentic glomerulonephritis remained dialysis-dependent despite several months of immunosuppression. He was placed on the deceased-donor transplant waiting list, and potential live donors were evaluated. His mother (ABO blood group-compatible) was medically unsuitable. His father was blood group A1, while the patient was blood group O. The patient's anti-A antibody titre, although moderately high at 1 : 256 (measured by conventional tube agglutination testing), was considered potentially amenable to lowering by systematic antibody removal to a preoperative target of between 1 : 8 and 1 : 16. A protocol for an ABO-incompatible transplant was established, reviewed and approved by the institutional ethics committee, and carefully discussed with the patient and his family.

A month before surgery, the patient received the anti-B-cell (anti-CD20) monoclonal antibody, rituximab (375 mg/m^2). Before infusion, his anti-A antibody titre was 1 : 1024 (the rise in titre was attributed to cessation of cyclophosphamide 6 months earlier). Two weeks before surgery, the antiproliferative immunosuppressant mycophenolate mofetil (MMF; 1000 mg orally, twice a day) was commenced, as was antibody removal using immunoadsorption treatments with Glycosorb ABO Columns (Glycorex Transplantation, Lund, Sweden). The antibody titre reduced to 1 : 64, but rebounded, and antibody removal was continued using plasma exchange.

The patient eventually underwent transplantation at a stable antibody titre of 1 : 32 (5 weeks after commencing rituximab, and after 14 antibody removal treatments [five immunoadsorption; nine plasma exchange]). Intravenous immunoglobulin, 0.5 g/kg (12 hours before surgery), and daclizumab, an interleukin-2 receptor blocker (immediately before surgery) were administered. After surgery, tacrolimus, an oral calcineurin inhibitor (target trough blood levels, 8–12 ng/mL), and oral prednisolone (25 mg/24 h) were commenced. Splenectomy was not performed.

The transplanted kidney functioned immediately, and the serum creatinine level fell from > 700 μmol/L to 110 μmol/L (reference range [RR], < 110 μmol/L) within 72 hours. Three postoperative antibody removal treatments were performed (one immunoadsorption, two plasma exchange) on postoperative Day 2, 4 and 6. By 1 month, immunosuppression consisted of 15 mg prednisolone, MMF, 750 mg twice daily, and tacrolimus (dosed to trough whole blood levels, 5–8 ng/mL) The serum creatinine level was 110 μmol/L (estimated glomerular filtration rate [eGFR], 75 mL/min [RR > 60 mL/min]). The anti-A antibody titre remained between 1 : 16 and 1 : 32.

At Week 6, the creatinine level rose to 140 μmol/L. A transplant biopsy showed no rejection, no recurrent disease and no drug toxicity. At 3 months, the patient resumed work (not having worked for the previous year). At 20 months, the creatinine level ranged between 110 and 130 μmol/L; there was no evidence of rejection (on protocol biopsy), no opportunistic infections, and the patient had had no unscheduled admissions to hospital. Maintenance immunosuppression at this time was MMF 500 mg twice daily, tacrolimus (trough levels, 3–6 ng/mL), and prednisolone 5 mg/24 h.

Discussion

Renal transplant recipients have an 80% lower mortality rate compared with those remaining on the transplant waiting list, largely due to the increased cardiovascular mortality rate in dialysis patients.[1] In the 20–39-year age group, kidney transplant recipients are estimated to gain, on average, more than 17 years of life.[2] The increase in deceased-donor transplant waiting times (which adversely affect the patient and transplant survival) has encouraged more transplantation from living donors (Australian average in 2004, > 37%[3]).

However, around 30% of potential live donors are thwarted by blood group incompatibility, where there is a high risk of immediate, rapid graft loss due to (hyperacute) antibody-mediated rejection. As early as the 1950s, transplantation across the ABO barrier resulted in rapid loss of most kidneys due to hyperacute rejection.[4]

Sporadic attempts at blood group incompatible transplantation have occurred with limited success, employing plasma exchange for antibody removal. A small uncontrolled series in the mid 1980s reported improved results, and concluded that splenectomy was essential for transplant success.[5] Japanese centres (without deceased-donor transplant programs) performed over 400 blood group incompatible kidney transplants between 1989 and 2001, all patients undergoing splenectomy, plasma exchange and intense immunosuppression.[6] While the Japanese cohort had inferior early graft survival, the 9-year transplant survival (around 60%) was comparable with that of the concurrent blood group compatible transplant population in Japan (and in Australia) over that period. These results, as well as greater attention to measuring and monitoring of anti-blood group antibody titres, and the concurrent development of diagnostic tools and therapies for antibody-

mediated rejection, revived interest in ABO-incompatible transplantation.

Small series with excellent results have been reported from the United States and Sweden using MMF-based immunosuppression, pre-transplant antibody removal and, in some cases, anti-T-cell antibody (thymoglobulin) therapy, and splenectomy and/or administration of rituximab.[7-10] The vast majority of the 300 ABO-incompatible transplants performed globally over the past 4 years have been performed without splenectomy; the collective 1-year graft survival is over 95% (First International Workshop on ABO-incompatible Kidney Transplantation, Stockholm, March 2007).

Ten years ago, under the heading "ABO incompatible renal transplantation: a chance to re-examine?", Mackie and Tiller reported an inadvertent ABO-incompatible transplant performed in Australia,[11] with a fortuitously good outcome attributable to a very low antibody titre (1 : 8), and an A2 donor kidney (A2 is associated with lower antigen expression than A1, but is found in only 20% of the Australian population).

The importance of antibody titres as a predictor of risk in ABO-incompatible transplantation has caused some centres to avoid transplanting patients with pre-treatment titres exceeding 1 : 128.[8] Gloor and colleagues reported a cohort of 18 patients where the risk of antibody-mediated rejection and graft loss correlated strongly with pre-treatment antibody titres regardless of whether the kidneys were from A1 or A2 donors.[9]

In this, the first intentional ABO-incompatible kidney transplant undertaken in Australia (performed without splenectomy or anti-T cell antibody), the pretreatment titre was 1 : 1024, and yet no antibody-mediated rejection occurred. An important factor in the avoidance of rejection may have been the "incorporation" of post-transplant antibody removal into the protocol, a practice adopted by most centres currently undertaking ABO-incompatible transplantation.[10-13]

Our patient received rituximab, but its significance in ABO-incompatible regimens remains unclear.[12] Although rituximab effectively eliminates B cells, it does not target the antibody-producing plasma cells (these express negligible amounts of CD20, the target antigen of rituximab). Segev et al have reported successful ABO-incompatible transplantation without splenectomy or rituximab,[12] even in the presence of relatively high-titre anti-ABO blood group antibody, and again identified post-transplant plasma exchanges as a key factor.

Both plasma exchange and immunoadsorbent columns are effective in removing antibodies. The latter are a safer alternative, as they specifically remove only the relevant anti-blood-group antibodies. Plasma exchange removes all antibodies, and other proteins; this includes clotting factors, which creates difficulties in the perioperative period and if diagnostic renal biopsies are required. Additional problems associated with plasma exchange are reactions to the replacement fluid and exposure to blood products. No complications have been reported to date with the use of the immunoadsorbent columns (but they are expensive).

The essential components of protocols for ABO-incompatible transplantation are yet to be determined, and significant questions remain. The use of tacrolimus and MMF is common to almost all centres, while significant numbers of patients have been transplanted without splenectomy or rituximab. What is the highest anti-ABO titre that can be successfully overcome, and the highest titre that is acceptable at the time of transplantation? Regardless of these unknowns, blood group-incompatible transplantation has become an acceptable procedure in selected individuals, and selected centres, and provides a transplant option where sometimes none existed previously. While the 9-year data from Japan is reassuring, longer-term outcomes in patients receiving transplants under present protocols are awaited.

An increase in transplantation from live donors by using ABO-incompatible donors should significantly reduce transplant waiting times, increase survival of patients with end-stage kidney disease, and improve the quality of the lives of patients and their families. The direct economic benefit of transplantation compared with maintenance dialysis is estimated to be between $40 000 and $60 000 per patient per year.[14] Significant indirect benefits also arise from greater participation in the workforce and reduced reliance on welfare or social services.

Safe, successful ABO-incompatible transplantation represents an important advance in the management of end-stage kidney disease in Australia.

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Competing interests

Shlomo Cohney has given talks on transplantation at CME meetings for Wyeth, Roche and Janssen-Cilag. He has received travel assistance to the International and American Transplant Congress from Novartis, Janssen-Cilag and Roche.

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