Horizon Scanning Technology
Prioritising Summary

Kidney transplantation using incompatible blood group donors

February 2008
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This Horizon scanning prioritising summary was prepared by Ms Caryn Perera and Ms Deanne Leopardi from the Australian Safety and Efficacy Register of New Intervventional Procedures – Surgical (ASERNIP-S).
PRIORITISING SUMMARY

REGISTER ID  S000071

NAME OF TECHNOLOGY  KIDNEY TRANSPLANTATION USING INCOMPATIBLE BLOOD GROUP DONORS

PURPOSE AND TARGET GROUP  PATIENTS WITH CHRONIC KIDNEY DISEASE

STAGE OF DEVELOPMENT (IN AUSTRALIA)
- Yet to emerge
- Experimental
- Investigational
- Nearly established

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL
- Yes
- No
- Not applicable

INTERNATIONAL UTILISATION

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IMPACT SUMMARY
Kidney transplantation using incompatible blood group donors is an alternative to kidney transplant from a compatible blood group donor and/or dialysis for patients with chronic kidney disease.
kidney disease. The technology is currently in the investigational stage in Australia, with the first kidney transplant across incompatible blood groups performed in Melbourne in 2006.

BACKGROUND
Living donor kidneys present an advantage over cadaveric donor kidneys due to their effect on recipient waiting periods, demands on dialysis resources, initial and long term organ functionality and patient survival rates (Gloor et al. 2003). Although using living donor kidneys in addition to cadaver organs increases the capacity of kidney transplants, there is still a significant strain on hopeful kidney recipients who are forced to wait until a suitable blood group donor is available. Kidney transplantation across incompatible blood groups was introduced as a novel methodology to address this pressure.

When performing kidney transplantation across incompatible blood groups, there is a high risk of immediate, rapid graft loss due to antibody-mediated rejection. This risk was reported as early as the 1950’s, when transplantation across the ABO (blood group) barrier resulted in the rapid loss of most transplanted kidneys due to hyperacute rejection (Cooney et al. 2007). Early attempts to address this risk associated with incompatible blood group transplantation employed plasmapheresis (PEX) for antibody removal. This was followed by the use of splenectomy in the mid 1980’s which reported improved results, leading to the conclusion that removal of the spleen in patients with very high levels of antibodies wards off graft rejection (Cooney et al. 2007).

Between 1989 and 2001 over 400 Japanese blood group incompatible kidney transplants were performed using splenectomy and PEX to remove antibodies in combination with intense immunosuppression (Cooney et al. 2007). The nine-year transplant survival rate using this technique was approximately 60%. The survival rate was comparable to that observed for concurrent blood group kidney transplantations in Japan and Australia during the same period (Cooney et al. 2007). This research prompted interest in ABO-incompatible transplantation using immunospression.

Immunosuppressant protocols vary slightly; however each protocol recognises the importance of immunosuppression, prior to both ABO-compatible and incompatible kidney transplantation, for optimal graft survival. Takahashi (2005) noted five components of immunosuppressive therapy for ABO-incompatible kidney transplantation:

1. Removal of anti-A and anti-B antibodies (e.g. using anti-CD20 therapy such as rituximab or immunoabsorption treatments such as Glycosorb and PEX).
2. Pharmacotherapy for T and B cell inhibition, using several immunosuppressant agents simultaneously, (e.g. corticosteroids, azathioprine, mycophenolate mofetil [MMF], cyclosporine, tacrolimus [TAC], sirolimus, polyclonal immune globulins, and monoclonal antibodies ) (Brenner 2004 and Schrier 2007).
3. Splenectomy or suppression of antibody production with anti-CD20 monoclonal antibodies (rituximab). Cooney et al. (2007) however states that most of the ABO-
incompatible transplants performed globally over the past four years have been performed without splenectomy.

4 Anticoagulation therapy.
5 Inducing accommodation (the survival of a graft without antibody-mediated rejection). For ABO-incompatible kidney transplantation, accommodation is encouraged by employing antibody removal and immunosuppression, both pre- and post-operatively, as well as immediately prior to surgery.

The introduction of ABO-incompatible kidney transplantation in addition to the existing end stage kidney disease (ESKD) treatment protocol could potentially decrease pressure on both patients with ESKD and the Australian health care system.

**CLINICAL NEED AND BURDEN OF DISEASE**

It is estimated that 1% of deaths per year are suitable for organ donation, unfortunately only a small proportion actually donate (ABS 2002). The number of Australians on waiting lists for kidney transplantation in February 2000 and January 2001 totalled 1,531 and 1,487, respectively (ABS 2002). The number of kidney transplants using cadaveric donation in 2000 was only 350 (ABS 2002).

Live kidney donor transplants have recently become a necessity and an improvement to the existing kidney donation protocol. In 2000, 180 (34% of all kidney transplants) were live-donors, the majority of which (69%) were biological relatives (ABS 2002). By 2003 the number of live-donor kidney transplants increased to 218 (40%) of the 543 procedures carried out (AIHW 2005a). This number continued to grow resulting in a 29% rise in live kidney donations over a five-year period (AIHW 2005a).

In 2003 chronic kidney disease was reported as the underlying cause for 1,986 deaths and the associated cause for another 11,940 deaths (AIHW 2005b). Between 2001 and 2003 a total of 3,407 patients underwent dialysis with a survival rate of 86% (AIHW 2005a). During this same period 1,497 patients underwent kidney transplantation with a survival rate of 97% (AIHW 2005a).

At the end of 2006, 16,027 patients were receiving renal replacement in Australia, 6,845 of which had functioning kidney transplants (5% increase from the previous year) and 9,182 continued to receive dialysis (ANZDATA). Fifteen per cent (1378) of the dialysis recipients were on a waiting list to receive kidney transplantation. The death rate per 100 patient years due to ESKD was 14.8% in patients receiving dialysis and much lower (2.0%) in those with functioning kidney transplants (ANZDATA). The number of kidney transplant operations in 2006 was 641, 274 grafts (43%) were from lives donors, which is a 4% increase in live-donor grafts from the previous year (ANZDATA).

**DIFFUSION**

Kidney transplantation using incompatible blood group donors is currently in the investigational stage in Australia. Cohney et al. (2007) reported a successful kidney
transplant (A1 donor to an O recipient) in a 24 year old man at the Royal Melbourne Hospital. The transplant, which was performed in 2006 and without splenectomy, was the first such transplant in Australia.

In Japan ABO-incompatible kidney transplants are widely performed. By 2001, 400 kidney transplants across blood group barriers had been performed in Japan (Morozumi et al. 2001). The number of ABO-incompatible transplants in Japan has since increased, recently accounting for 14% of all kidney transplantations (Takahashi et al. 2006).

In Europe a protocol for ABO-incompatible kidney transplantation was introduced in 2001, when the first transplantation using this protocol was performed in Sweden (Tyden et al. 2007). The protocol has been implemented as a routine procedure in Sweden since 2002 and was implemented in Germany in 2004 (Tyden et al. 2007).

Trials are also underway in a number of other countries, including; the Netherlands, Switzerland, Greece, France and Spain.

**COMPARATORS**

Kidney transplantation using compatible blood group donors is the conventional manner of performing kidney transplantation and is the primary comparator for ABO incompatible kidney transplantation. Dialysis on the other hand is a management option for patients with severely compromised kidney function where kidney transplantation is not able to be performed and is another comparator for kidney transplantation using incompatible blood group donors.

**SAFETY AND EFFECTIVENESS ISSUES**

Three comparative studies were retrieved for inclusion in this summary. These studies compared ABO-incompatible and ABO-compatible kidney transplant outcomes.

Gloor et al. (2003) conducted a non-randomised comparative study investigating the use of ABO-incompatible live-donor kidney transplants to treat patients with ESKD. The aim of the study was to determine the outcome differences between donor blood groups (A2 versus non-A2), and the effect of baseline antibody titers, PEX, intravenous immunoglobulin and splenectomy on graft rejection rates. Eighteen patients underwent ABO-incompatible kidney transplant; ten from A2 donors and eight from non-A2 donors. Specifically, O blood type recipients received eight A2 kidneys, five A1 kidneys and two B kidneys. The B group recipients received two A2 kidneys, while the A blood group recipient received one B kidney. The control group in this study consisted of 81 comparable ABO-compatible kidney transplant recipients. Patients were followed up for one year during which time they underwent serum creatinine concentration and iothalamate clearance (measurement of glomerular filtration rate) tests (Gloor et al. 2003).
The ABO-incompatible transplant recipients had antibody induction with rabbit anti-human T-cell polyclonal antibody (Thymoglobulin) for ten days. Immunosuppression maintenance treatment included TAC, MMF and corticosteroids. All ABO-compatible transplant recipients received similar maintenance treatment with the exception of patients receiving their second graft or with prior allosensitisation (these patients were treated with anti-interleukin-2 receptor antibody induction at day 0 and 14). A2 recipients did not receive pre-transplant conditioning (n = 8) however two graft rejections triggered a requirement for conditioning in the remaining two A2 patients (one also underwent splenectomy). Non-A2 patients underwent PEX and splenectomy (Gloor et al. 2003).

In another non-randomised comparative multicentre study, Takahashi et al. (2006) investigated 564 patients (65% male, 35% female) who received ABO-incompatible kidney transplants. The majority (82%) of patients were under 50 years of age, with the mean age being 34.5 years (range: 4 to 71 years). Eighty per cent of donor-recipient relationships were biological, with parent-child donation being the most common (70%). The blood type of the recipients included type O (56%), type A (24%) and type B (20%). A-incompatible transplants occurred in 53% of patients, B-incompatibility in 46% and AB incompatibility in 1%.

The historical control group consisted of 1055 comparable patients. Immunosuppressant therapy included a calcinurine inhibitor (CNI) base, a steroid and an antimetabolite. In the early 1990’s antilymphocyte globulin (ALG) or deoxyspurgualin (DSG) were also used. For induction and maintenance, cyclosporine A (CYA) and TAC were used. Seventy per cent of patients received pre-transplant PEX and 20% received post-transplant PEX. Up until the end of 2003 splenectomy was performed in 98% of recipients, while anticoagulation therapy was carried out in 57% of recipients. Preoperative antibody titers were also conducted. Any incidence of organ rejection observed during the follow up period (mean: three years and nine months) was proven by biopsy (Takahashi et al. 2006).

In a 10-year multicentre experience, conducted by Nelson et al. (1998), 50 patients underwent ABO-incompatible kidney transplants. Kidney donors were of blood type A2 (n = 47) or A2B (n = 3) and recipients were O (n = 31) and B (n = 19) type. Forty-six (92%) kidneys were cadaveric and four (8%) were from living donors. The characteristics of the ABO-incompatible transplants were as follows; A2 to O transplants made up 62% (n = 31), A2 to B transplants made up 32% (n = 16) and A2B to B transplants made up 6% (n = 3). The control group consisted of 640 consecutive ABO-compatible cadaveric kidney transplants over the same period. Immunosuppressant therapy was the same for the experimental and control groups. All recipients received methylprednisolone (MP), CYA and azathioprine. No patients receiving a live A2 kidney were given induction therapy.

a) Safety
In the study by Gloor et al. (2003), 10 out of 18 (56%) ABO-incompatible transplant recipients experienced uncomplicated postoperative recovery. In the remaining patients,
Intraoperative complications included pneumothorax after central line placement (n = 1), a urine leak requiring revision (n = 1), and delayed graft functionality resulting in cytomegalovirus (CMV) infection (n = 1), in the A2 group. In the non-A2 group one patient required transfusion after splenectomy. There were a total of three postoperative complications (two for A2 and one for non-A2), all were associated with antibody-mediated graft rejection. These included a subphrenic abscess, erosive gastroesophagitis and urosepsis in one patient, neutropenia, a urinary tract infection and atrial fibrillation in a second patient, and graft loss, wound infection, atrial fibrillation and recurrent pneumonia in a third patient. This third patient died of a cerebrovascular accident 132 days after receiving the transplant (Gloor et al. 2003).

In the study by Takahashi et al. (2006), 210 major complications were reported among the 564 patients. Infection accounted for the majority (56%) of these, with 118 cases of infection reported. The rate of infection decreased during the postoperative period. During the first year, the infection rate was 27%, between the first and third postoperative years the infection rate was 10% and between the third and fifth years the infection rate was 9%. Graft losses totalled 136 and 71 patient deaths occurred (study group not specified). Two recipients experienced post-transplant lymphoproliferating disease, acute pancreatitis, pulmonary congestion and meningitis (Takahashi et al. 2006).

In the study by Nelson et al. (1998) two fatalities were reported in patients, with functional allografts shortly before death (study group not specified). These occurred at one and 12 months, with the first death due to bacterial endocarditis (Nelson et al. 1998). No other safety issues were reported.

b) Effectiveness
In the study by Gloor et al. (2003), the patient survival rates for ABO-incompatible and ABO-compatible transplant recipients were 94% (17 patients) and 99% (80 patients), respectively. The one-year graft survival rates for ABO-incompatible and ABO-compatible transplant recipients were 89% (16 grafts) and 96% (78 grafts), respectively. For the A2 versus non-A2 groups, patient survival rates were 90% (9 patients) and 100% (8 patients) respectively and their one-year allograft survival rates were 8 (80%) and 8 (100%) grafts, respectively. Two ABO-incompatible transplants failed; one at 14 days due to uncontrolled antibody-mediated rejection and one at 12 months due to chronic allograft nephropathy. One (A2 patient) died. Graft function was similar in ABO-incompatible and compatible transplant groups. Antibody-mediated rejection occurred in 5 (28%) patients, all within 12 days of transplantation. One (non-A2) patient experienced asymptomatic rejection detected by surveillance biopsy. Antibody-mediated rejection rate was higher in A2 (40%) than in non-A2 donor groups (13%). Baseline immunoglobulin G (IgG) antibody titer appeared to be the best indicator of antibody mediated rejection. No patients with a baseline $\leq 1:32$ experienced rejection and four of eight (50%) patients with a baseline $\geq 1:128$ had rejection. After one year IgG and immunoglobulin M (IgM) antibody titers decreased below baseline for 15 of 16 (94%) patients with functioning allografts. All rejections were confirmed by biopsy.
Postoperative surveillance biopsies were also taken in both groups 30 mins after reperfusion. For the non-A2 donor group surveillance occurred on days three, seven, 14, 28, 90 and 12 months and for the A2 donor group at three and 12 months (Gloor et al. 2003).

In the study by Takahashi et al. (2006), 237/564 patients (42%) experienced graft rejections within three months of transplantation. After three months chronic allograft nephropathy occurred in 404 recipients (19%). Follow up data was calculated at one, three, five and 10 years post-transplant. Patient survival rates in ABO-incompatible transplant recipients were 94%, 91%, 88% and 81%, respectively, during this time. The patient survival rates in ABO-compatible transplant recipients were 98%, 97%, 94% and 87%. Graft survival rates during the follow up period were 86%, 82%, 74% and 53% for ABO-incompatible transplants and 96%, 89%, 81% and 56% for ABO-compatible transplants. While short term results appeared to favour the control group, long term results found no significant statistical difference between the two groups. The study also found success rates decreased with age (best results seen in patients under 15 years) and the most recent transplants (2001 onwards) were significantly more successful than initial procedures (p<0.05). Patients who received concomitant anticoagulation therapy also experienced significantly higher graft survival rates than those who did not (p<0.05). The prominent cause of graft loss (in 136 transplants) was chronic allograft nephropathy (35%), death (26%), acute rejection (23%) and accelerated acute rejection (7%). Causes of death (71 patients) included; heart failure (16%), pneumonia (8%), apoplexy (7%), sepsis (6%), hepatic failure/cancer (4%) and multiple organ dysfunction/disseminated intravascular coagulation syndrome (4%) (Takahashi et al. 2006).

In the study by Nelson et al. (1998) the two-year post-transplant graft survival rate was 94% in A2-incompatible transplants and 88% for ABO-compatible transplant. Four (22%) cadaveric grafts were lost due to rejection at 0.5 months (number of days not specified), 21 months, 27 months and 41 months. Before the introduction of titer history patient selection criteria (pre 1991) 19/28 (68%) had a functional graft one month postoperatively, all of the kidneys had failed or suffered dysfunction by 10 days post-transplant. During this time patients with early graft loss were noted to have elevated anti-A IgG titers. All of the live-donor kidney transplants were still functioning 71 months after the graft took place. A major predictor of graft success was antibody levels at baseline, that is those patients with ‘low’ anti-A titers were less likely to reject their donor kidney.

**Cost Impact**

Cohney et al. (2007) estimates the direct economic benefit of transplantation compared with maintenance dialysis to be between $40,000 and $60,000 per patient per year. Significant indirect benefits also arise from greater participation in the workforce and reduced reliance on welfare or social services (Cohney et al. 2007).
ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS
No issues were identified from the retrieved material.

OTHER ISSUES
It is important to note that there is a significant quantity of studies available regarding the effectiveness of different immunosuppressant protocols in ABO-incompatible kidney transplant. However, the purpose of this summary was to compare the safety and effectiveness of ABO-incompatible kidney transplantation with ABO-compatible.

SUMMARY OF FINDINGS
Evidence from three comparative studies suggests that ABO-incompatible kidney transplant is feasible, safe and effective to use in addition to ABO-compatible kidney transplant in order to improve the current management and treatment of patients with ESKD. Antibody titers appear to be a useful way of predicting a patients likelihood of graft survival.

Further studies of higher level evidence and with longer follow up would be useful in assessing the efficacy of kidney transplant across the blood groups, as well as assisting in the production of guidelines regarding an immunosuppressant regime to ensure successful operative efforts.

HEALTHPACT ACTION
Based on the level of evidence available and potential uptake of the technology, kidney transplantation using incompatible blood group donors will proceed to a Horizon Scanning Report.

NUMBER OF STUDIES INCLUDED
Total number of studies 3
Level III evidence 3

REFERENCES


**Sources of Further Information**


Sonoda T, Takahara S, Takahashi K, Uchida K, Ohshima S, Toma H, Tanabe K and Yoshimura N. Japanese Tacrolimus Study Group. Outcome of 3 years of
immunosuppression with tacrolimus in more than 1,000 renal transplant recipients in Japan. *Transplantation* 2003; 75(2): 199-204.


**SEARCH CRITERIA TO BE USED**
kidney transplantation
kidney transplant
blood
blood group
blood group incompatibility
compatibility
incompatibility