Transplanting blood group incompatible kidneys: potential utilisation of A2 donors

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Introduction

We were asked by the Chair of KAG to consider whether utilisation of A2 deceased donor kidneys would be worthwhile in the UK, following recent reports from this approach in the US. In the UK, the Hammersmith group carried out 2 or 3 such transplants over a decade ago, with low titre recipients and no additional induction therapy or antibody removal (personal communication Prof Warrens). A recent report[1] suggested that a third of pediatric patients on the deceased donor waiting list had low anti-A or anti-B titres, and could therefore undergo a deceased donor blood group incompatible (ABOi) transplant, and although this approach was ratified by the Pediatric KAG, to our knowledge no such transplants have occurred. This paper summarises the current evidence for the use of A2 deceased donor kidneys for ABOi transplants, assesses the potential value of this approach and suggests a practical approach for implementation.

Background

The use of A2 deceased donor kidneys for transplantation without antibody removal is well described, and is based on the lower expression of the A2 antigen, in combination with low anti-A titres in the recipient.[2,3]

In the US, the OPTN changed its policy in 2002 to allow transplantation of A2 or A2B kidneys from deceased donors into group B recipients[4]. The aim was to increase transplantation rates in group B recipients, and recipients were required to have anti-A IgG titre levels of less than 1 in 8. Titres were repeated at 3 monthly intervals, and 2 consecutive low titre results were required to enter the scheme. Interestingly, 42% of candidates were excluded due to a high first titre, and of the remainder 84% had a consistently low titre. Thus one might estimate that around a half of group B recipients could benefit from this approach.

Recent studies with at least 50 patients are summarised in Table 1, although there is overlap in these datasets. The most recent report of 560 such transplants, showed no significant difference in graft survival, when compared with compatible deceased donor transplants. However, there was no attempt to match the groups and antibody-mediated rejection rates were not reported[5].

Subsequently, in 2014 the OPTN extended the approach to formally incorporate this approach into the national allocation scheme[6]. A report of the effect of this change shows increased allocation and transplantation of A2 or A2B kidneys to incompatible recipients, although as yet, the effects on improving equity of access to transplantation for minorities has not been demonstrated[7].

Table 1: Outcomes after A2 Transplantation

Author	Year	N	Recipients	Outcome	Follow-up
Forbes	2016	560	B, O	No sig difference in GS with ABOc	Median 116 months
Williams	2015	101	B	ABOi 85% v ABOc 83% NS	3 years
Redfield	2012	204	B,O	ABOi85% and 87% v ABOc 86%. NS	5 years
Futagawa	2005	56	B, O	ABOi 61% v ABOc 74%	5 years

Rationale

The longer waiting time for Group B candidates, and the high proportion of ethnic minorities amongst these patients, are well-known and will not be considered in further detail here. An increase in transplant rates for these patients would clearly be attractive, assuming this did not significantly disadvantage other groups. There are two further groups who could be considered: the Group O or B highly sensitised (CRF>85%) deceased donor candidates, who number 19% and 27% of those waiting respectively, and the NKSS, which already allows blood group incompatible transplantation for HLAi pairs.
Between 14 and 20% of A donors would be expected to be A2.[6] Assuming a cut-off of anti-A titres of 1 in 8, 3% of Group O but 68% of Group B waiting list recipients would be eligible for a deceased donor A2 transplant.[8]

Practical considerations

The first issue is the acceptable titre level. 4 centres in the UK use a level of 1 in 4 for the level on the day of transplant in their ABOi living donor transplant programmes, 2 decide on a case by case basis, and the remainder use 1 in 8[9]. However, many centres do not subtype for A2; at Guys, when this was done a titre level of 1 in 16 in the recipient is considered acceptable. It would therefore seem conservative, and therefore reasonable to consider eligibility for a deceased donor A2 kidney at 1 in 8 or less, with individual centres able to set local criteria as lower. Data from Australia demonstrate that anti-ABO titres of 1:16 or less have been successfully used across all combinations of ABO-incompatibility without any additional immunosuppression or antibody removal prior to transplantation, and supports UK findings[10-12].
The OPTN/UNOS requires 2 tests to confirm the A subgroup[5]. This may be difficult, but subgrouping should be possible in all hospitals. Out of hours testing may be challenging in some centres. It would also be important that donor subgroup be tested on pre-transfusion blood samples.

Titres may vary over time, so regular titre measurement would be important, as with HLA antibodies in the context of virtual cross-matching. It would seem reasonable to adopt a similar approach as the US, and require 2 titres of 1 in 8 or less, prior to inclusion. UK data shows that around 85% of wait-listed transplant candidates have titres which do not differ beyond 1 dilution over a 6 month period[13]. KAG may wish to consider whether all candidates for such a programme should have titres measured in a central laboratory, given the tremendous variation in titre measurement, as reported to the LDKT 2020 Strategy group[14].

Efficacy

The key questions are firstly whether this approach would significantly benefit Group B as well as O recipients (and in particular ethnic minorities), and secondly whether it would disadvantage other patients.
Lisa Mumford is currently modelling the effects both within the deceased donor allocation scheme, and the NKSS.

Suggested protocol

It is proposed that a two-year pilot scheme be undertaken for the use of A2 deceased donor organs for Group B recipients, with centres and patients deciding whether to enter into the scheme.

Preoperatively:

1) Centres would be required to subtype A donors prior to donation. Donors who are A2 should have a second, confirmatory subtype test. These tests should be done prior to blood transfusion. If no samples are available prior to blood transfusion the donor could not be considered for the scheme.
2) Recipients entered into the scheme would have Anti-A titres measured at 3 monthly intervals, and 2 consecutive samples of 1 in 8 or less would be required for the patient to remain active.
3) A Patient Information Sheet should be provided to all patients entered into the scheme. This could be developed centrally.

Perioperatively

1. Participating centres should have the facility to perform titres at short notice- **KAG should consider** whether a single testing method should be required, and whether a central titre facility be provided.
2. Titres should be confirmed to be 1 in 8 or less within 24 hours prior to transplantation
3. Recommended immunosuppressive therapy would consist of tacrolimus, mycophenolate and prednisolone. Induction therapy would be at the local centre's discretion, although basiliximab would be the preferred choice of most centres.

Postoperatively

1. Titre measurements would normally be measured on days 1, 3, 5,7 and 10 postoperatively. A significant (2 or more dilutions) rise in titres should prompt concern. If there is no change in renal function, either no action or a biopsy is taken (up to a third of recipients will exhibit a titre rise with no graft dysfunction). Clearly if the recipient is in DGF, a biopsy will be necessary.
   In patients with functioning grafts, a rise in creatinine accompanied by a rise in titres would indicate the need for an immediate biopsy followed by plasma exchange or immunoabsorption as necessary. Participating centres should have the ability to perform these interventions as an emergency.
   An explosive rise in titres, to many dilutions above baseline, is likely to indicate a memory response leading to aggressive early AMR. In functioning grafts, anuria or a dramatic rise in creatinine is normal. In these cases, alternatives include immediate administration of eculizumab, or splenectomy. Currently the former is not funded for this indication by NHSE. A biopsy in this scenario may not be indicated, as the clinical diagnosis is usually clear, and a delay in treatment may result in loss of the kidney.

2. The value of continued measurement of titres after discharge, if renal function is stable, is unproven. However, an acute deterioration in creatinine should prompt titre measurement.

3. **KAG should consider** whether there is value in providing a list of clinicians who may provide advice in cases of uncertainty.

4. Data capture for these patients will be important, as the existing ABOi registry data may not capture sufficient detail. For example, it would be useful to determine whether 3 monthly titre measurements are necessary, or indeed insufficient, and examination of results over two years should provide some evidence. To this end, **KAG should consider** whether a process for data capture on all recipients entered into the scheme should be implemented.

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