ABO Incompatible Transplantation: To B or not to B

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ABO antibodies (isoagglutinins) represent a formidable barrier to optimizing live donation and organ distribution. Blood group antigens are expressed on the endothelium of solid organs, and transplantation across a blood group barrier can result in hyperacute or acute antibody-mediated rejection (AMR). Based on blood group distributions in the United States, there is a 36% probability that any two individuals in the population will be ABO incompatible (ABOi), resulting in the exclusion of up to one third of willing live donors. The use of ABOi kidneys dates back to the earliest days of renal transplantation. Dismal results, enhanced availability of kidneys from deceased donors, and a better organ sharing infrastructure pre-empted further development of ABOi transplantation in the West. However, in Japan where cultural beliefs have limited utilization of deceased donors, ABOi renal transplantation flourished during the 1990s. The article by Takahashi et al. (1) reports the outcomes of 441 ABOi kidney transplants performed at 55 centers across Japan and shows no significant difference in graft survival when compared with historic recipients of ABO-compatible living donor organs. This is a landmark study representing the largest series of ABOi kidney transplants with the longest follow up to date. The results are the endorsement that the field of transplantation has been waiting for and a further expansion of the practice of ABOi transplantation now seems inevitable. While these results are very promising, many questions remain unanswered and there is a bewildering lack of standardization of protocol and reporting (titers, rescue treatments, biopsies) among the Japanese centers.

Splenectomy: Something’s Rotten in Denmark

The requirement for splenectomy in ABOi transplantation originated from an article by Alexandre and colleagues in which all patients in whom splenectomy was avoided as part of the preconditioning regimen lost their grafts to AMR (2). The unsavory nature of splenectomy among the immunosuppressed continues to be a major limiting factor to the wider acceptance of ABOi transplantation. In the Takahashi et al. series 98% of the patients underwent splenectomy and thus the question of the utility of splenectomy has not been addressed. Splenectomy reduces early graft loss from AMR but does not appear to affect graft survival after the first 3 months. We (3) and others (4) have begun using the B-cell ablative monoclonal antibody, anti-CD20, in place of splenectomy with excellent results in recipients of A3, B, and A1 kidneys. The theoretical advantage of this strategy is that the B-cell compartment is allowed to reconstitute with intact splenic function after the period when the risk of AMR is greatest, minimizing the life-long risk of infection.

A2 Advantage?: A2 Brute

Blood group A has two subtypes, A1 and A2. In Japan the A2 subtype is very rare, whereas in the United States about 20% of blood group A has the A2 phenotype. The expression of A antigen is both qualitatively and quantitatively reduced in A2 individuals (B is intermediate). For this reason the A2 donor has been considered preferable. However, there are recent data that bring into question the prima facie superiority of the A2 donor and suggest that initial isoagglutinin titers might be more predictive of outcome than donor subtype (5). Shimmura et al. reported an AMR rate of 71% and poor results when the starting A isoagglutinin titer was ≥128 (6). The protocol used in Japan does not include post-transplant plasmapheresis treatments and this may be responsible for their early graft losses from AMR. We have performed five ABOi transplants using A1 kidneys with initial recipient titers ≥128 (range 128–1024) without AMR by continuing plasmapheresis after the transplant and maintaining isoagglutinin titers <16 during the first 2 weeks post-transplant.

Accommodation: A Rose Is A Rose

We have observed that preconditioning for a positive cross-match durably suppresses donor-specific antibody while third-party antibodies persist (tolerance) (7). Conversely, isoagglutinins remain detectable in the circulation after an ABOi transplant without evidence of injury to the graft (accommodation). The mechanism of accommodation in the ABOi setting is unknown. One-year protocol biopsies of ABOi grafts show diffuse C4d staining, raising the possibility of a down-stream inhibitor of complement in the
accommodated kidney. We have stained biopsy samples for blood group antigen and have not observed a reduction in A or B antigen expression, however, these antigens can be released into the plasma bound to glycoproteins and platelets and could serve as decoys for isoagglutinins.

**Paired Kidney Exchange: Double, Double Toil and Trouble**

While logistically and ethically challenging, paired kidney exchange schemes may offer the best, lower cost alternative to preconditioning protocols for ABOi patients. One option is to assign elevated recipient status on the deceased donor list for contributing a live donor kidney to an organ bank. However, this has the effect of disadvantaging O patients on the waiting list. We favor live donor paired kidney exchanges as they provide the highest quality organs and do not impact on the deceased donor list. Implementation of a national database of incompatible donor/recipient pairs would allow highly sensitized and ABOi patients to receive live donor, crossmatch-negative, ABO-compatible organs in conventional and unconventional (Figure 1) exchanges.

**All’s well that ends well**

ABOi renal transplantation and the paired kidney exchange are two innovative approaches for ameliorating the current crisis in organ availability. It is time for the transplant community to come together and remove the remaining administrative, logistical, and financial barriers to wider application of these techniques.

**References**