ABO-Incompatible Heart Transplantation

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Clinical evolution of ABO-incompatible heart transplantation (ABOi HTx)

In the 1990s infants needing heart transplantation were facing greater than 50% waitlist mortality. Driven by this desperate situation and based on knowledge of the immature immune system during early childhood, especially in response to polysaccharide antigens such as those defining the ABO-blood groups, clinician-researchers in Toronto, Canada performed the first series of intentional ABOi HTx in 10 infants published in 2001(1). Antibodies against the non-self blood group antigens, ubiquitous in adults and older children, were known to be absent or low in this age group, slowly evolving during age 6-12 months. Thus infants awaiting transplant could have expanded access to organs independent of the donor blood group, resulting in greater numbers of children surviving to transplant and fewer donor organs wasted. Exceeding these goals, the first ten patients showed a unique change in development of ABO antibodies in the years after transplant (1, 2): antibodies towards the donor blood group as measured by erythrocyte agglutination remained minimal. Encouraged by these findings the approach was included as a general option in Canadian listing guidelines and embraced throughout Canada, followed by first cases in Germany and the United Kingdom (3). Eventually UNOS policies allowed allocation of infant hearts to ABOi recipients, however, only secondarily if the organ was not claimed first for an ABO-identical then an ABOc recipient, and with very restrictive criteria (recipient isoagglutinin titers <1:4 and age <1 year). Despite the cautious approach with ABOi initially offered to children with significantly worse risk profiles than ABOc (4), Everitt et al. reported shorter wait times for ABOi recipients in the United States (5) with comparable survival and frequency of acute rejection in the first year. Long-term data from the original cohort (6) and a large international study on 55 patients from 7 centers in Canada, Europe and the United States (7) reported similar rates of acute rejection and graft vasculopathy when comparing infants recipients of ABOi and ABOc transplants. This study also confirmed persistent immune tolerance specific to the donor blood group with isoagglutinin titers absent or multiple log-steps below normal values and no reported cases of late antibody-mediated rejection (AMR). Limits and boundaries remain unclear: In 2015 Irving et al. reported outcomes of patients whose ages and isoagglutinin titers would previously have been considered prohibitive, with reasonable success rates in patients up to 8 years of age and with titers as high as 1:256 (8). Similarly, older patients receiving B-cell depletion for HLA-sensitization may become candidates for ABOi transplant after experiencing reduction in isoagglutinins, reflecting depletion of their ABO-directed B-cell immunity. Tyden et al. reported successful intentional ABOi HTx in 2 carefully selected and pre-treated adults, and an analysis of the ISHLT registry found that adult patients unintentionally transplanted with hearts from ABOi donors had a high mortality of 35% in the first year, however, similar conditional survival after the first year as for ABOc recipients.

Immunology of ABO-incompatible transplantation

The key immunological difference of the ABO histo-blood group structures (ABH-antigens) in comparison to other relevant antigens such as HLA is their carbohydrate nature, with strong parallels to polysaccharide structures forming the capsule of certain bacteria such as Hemophilus influenzae type B (HiB), Streptococcus pneumoniae and meningococcus. These bacteria result in dramatically higher incidence and severity of infections during the first two years of life than later childhood, the same period revealing reduced levels of ABO antibodies and long-term tolerance to donor ABH-antigens. Our research team previously showed that key deficits in T-independent (TI) alternative pathways of B-cell activation, using the interplay between the complement system and the B-cell co-receptor, facilitate ABO-directed B-cell tolerance and graft accommodation (9). We further found that CD27+ memory B-cells are the main population responding to TI stimulation, and that the IgM-expressing subgroup of these cells is the sole B-cell population specifically activated by non-self blood group erythrocytes (10). These cells are nearly absent at birth in peripheral blood and spleen of healthy and transplanted children, reaching near adult values only by about five years of age, and their maturation is altered after ABOi transplantation. Interestingly, we observed that children after ABOi HTx showed significantly lower prevalence of de novo class II HLA antibodies than ABOc HTx recipients of similar age (11), a finding that has been confirmed by other studies. This suggests that tolerance to donor ABH antigens may

result in an overall more accepting immune response to other (graft) antigens, but also raises a concern about potentially reduced immune response to infections, especially with polysaccharide encapsulated bacteria. So far, neither a benefit of a potentially less aggressive overall anti-graft response including HLA-directed immunity, nor a higher frequency of infections with encapsulated bacteria in ABOi HTX has been documented.

PHTS-ABOi transplant studies

These immunological observations and associated concerns drove analyses arising from a PHTS proposal on ABOi HTx. Another primary question was how widely ABOi HTx listing and transplantation have become in recent years and whether a tendency to reserve this approach for sicker patients is still observed in the most recent era as it was described in a previous PHTS study (4). Conclusions of these studies are summarized below and a more detailed description can be found in the PHTS graphic and lay summaries:

A current era analysis of ABOi listing practice and impact on outcomes in young children requiring heart transplantation

We have studied 2039 children <2 years of age reported to the PHTS from 2010 to 2018. While listing for ABOi transplant increased from 49% to 72%, patients listed for ABOi had more risk factors, suggesting that centers were still concerned to use this newer approach in more stable patients. 239 children received an ABOi heart, with the yearly proportion going from 15% in 2010 to 40% of transplanted children in the last reported year. Those listed for ABOi transplant received an organ sooner, especially when they were blood group O, the chance to survive until transplant was similar. After transplantation survival was not different between ABO compatible and incompatible transplants. This study shows that ABOi transplantation has become standard practice for children under 2 age years in the past 10 years and this has reduced waiting times, especially for blood group O children. Although there is still a tendency to reserve ABOi donors for sicker patients, survival after transplant is not different from ABOc transplant recipients.

Clinical outcomes of children receiving ABO-incompatible versus ABO-compatible heart transplantation: a multicentre cohort study

Analyzing children after heart transplantation younger than 2 years of age between 1999 and 2018, 364 had received an ABOi transplantation and 1842 a compatible (ABOc) heart providing information on over 11 000 patient-years of follow-up. We compared the ABOi children with all ABOc recipients but also with 728 ABOc children that were matched for age, diagnosis, clinical situation and year of transplantation since we noticed clinical differences. Children receiving ABOi heart transplants in the first 2 years of life have equal survival to those after ABOc transplant and have no higher risk of rejection, graft vasculopathy or tumors. ABOi recipients encounter less severe infections overall and particularly with encapsulated bacteria; therefore, the observed changes in the immune system do not result in a higher risk of post-transplant complications, but rather a lower risk. For this age group, receiving an ABOi heart is safe and may even provide some benefits.

Conclusions and ongoing challenges:

ABOi HTx has evolved to a widely accepted standard option for infants in many areas, however, inclusion criteria, limitations, management and monitoring approaches remain variable. Recent studies using PHTS data have provided invaluable clinical insight on ABOi HTx outcomes, safety and increasing acceptance of this approach. This will encourage more centers worldwide to adopt this strategy to allow earlier transplantation of young children and reduce numbers of non-allocated organs.

A challenge to efficient application of ABOi organ transplantation, as well as comparison of protocols and post-transplant clinical courses, arises from lack of standardization in techniques to quantify ABO antibodies and to characterize their fine specificities and isotypes. Some ABH-antigen carbohydrate subtype-chains present on erythrocytes are not identical to subtype-chains expressed on vascular endothelium (ie, of cardiac tissue).

Consequently, antibodies detected by erythrocyte agglutination assays may not reflect antibodies actually posing a threat to the transplanted organ. Current efforts focus on development and validation of assays to quantify and characterize serum ABO antibodies towards the graft ABH-antigens using microarray (12) or standardized multiplexed cytometry (Luminex™) 'solid-phase' technology. These technologic developments and their analysis in research studies, together with increasing clinical experience, will allow improved risk assessment and more precise delineation of boundaries of safe ABOi HTx as well as the potential for immune manipulation to expand the pool of eligible recipients in regards to age and transplanted organs. The immunological studies in this unique patient population open a window to explore the impact of immaturity on the immune response to polysaccharide and combined antigens that may have major impact on treatment and prophylaxis of infectious diseases and also autoimmune mechanisms.

Financial support:

Research in the West and Urschel laboratories discussed here was supported through grants from The Transplantation Society and the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), the Women and Children's Health Research Institute (Univ. of Alberta), the Canadian Institutes of Health Research, the National Institutes of Health (USA), the Enduring Hearts Foundation, and the Gordon English Family.

Drs. West and Urschel are investigators in the Canadian Donation and Transplant Research Program (CDTRP).

Conflicts of Interest:

Neither author has financial relationships influencing the content of the manuscript or leading to a conflict of interest.

References:

1. *West LJ, Pollock-Barziv SM, Dipchand AI, et al.: ABO-incompatible heart transplantation in infants. New England Journal of Medicine 2001;344:793-800.*
2. *Fan XH, Ang A, BarZiv SMP, et al.: Donor-specific B-cell tolerance after ABO-incompatible infant heart transplantation. Nature Medicine 2004;10:1227-33.*
3. *Roche SB, M; O´Sullivan, J; Wallis, J; Parry, G; Kirk, R; Elliot, M; Shaw, N; Flett, J; Hamilton, JRL; Hasan, A.: Multicenter Experience of ABO-Incompatible Pediatric Cardiac Transplantation. American Journal of Transplantation 2008;8:208-15.*
4. *Henderson HT, Canter CE, Mahle WT, et al.: ABO-incompatible heart transplantation: analysis of the Pediatric Heart Transplant Study (PHTS) database. J Heart Lung Transplant 2012;31:173-9.*
5. *Everitt MD, Donaldson AE, Casper TC, et al.: Effect of ABO-incompatible listing on infant heart transplant waitlist outcomes: analysis of the United Network for Organ Sharing (UNOS) database. J Heart Lung Transplant 2009;28:1254-60.*
6. *Dipchand AI, Pollock BarZiv SM, Manlhiot C, West LJ, VanderVliet M, McCrindle BW: Equivalent outcomes for pediatric heart transplantation recipients: ABO-blood group incompatible versus ABO-compatible. Am J Transplant 2011;10:389-97.*
7. *Urschel S, Larsen IM, Kirk R, et al.: ABO-incompatible heart transplantation in early childhood: an international multicenter study of clinical experiences and limits. J Heart Lung Transplant 2013;32:285-92.*
8. *Irving CA, Gennery AR, Carter V, et al.: ABO-incompatible cardiac transplantation in pediatric patients with high isohemagglutinin titers. J Heart Lung Transplant 2015;34:1095-102.*
9. *Urschel S, Ryan LA, Larsen IM, et al.: C3d plasma levels and CD21 expressing B-cells in children after ABO-incompatible heart transplantation: Alterations associated with blood group tolerance. J Heart Lung Transplant 2014;33:1149-56.*
10. *Urschel S, Ryan LA, I ML, Biffis K, Dijke IE, West LJ: Development of B-cell memory in early childhood and the impact on antigen-specific tolerance after heart transplantation. J Heart Lung Transplant 2016;35:491-9.*
11. *Urschel S, Campbell PM, Meyer SR, et al.: Absence of donor-specific anti-HLA antibodies after ABO-incompatible heart transplantation in infancy: altered immunity or age? Am J Transplant 2010;10:149-56.*
12. *Jeyakanthan M, Meloncelli PJ, Zou L, et al.: ABH-Glycan Microarray Characterizes ABO Subtype Antibodies: Fine Specificity of Immune Tolerance After ABO-Incompatible Transplantation. Am J Transplant 2016;16:1548-58.*