Desperate times can facilitate important innovation – the evolution of ABO incompatible heart transplantation in children.

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In the early 1990s many infants born with severe congenital heart disease, especially variants of single ventricle physiology were facing desperate perspectives: the surgeries for staged palliation creating a long-term stable circulation and oxygen distribution were just evolving and fraught with a high probability of non-survival. The first mid-term results for infant heart transplantation were very encouraging, however, there were far more children in need of a transplant organ than children considered for organ donation, especially with strict application of brain death criteria. The probability not to survive to a transplantation in Toronto in the early 90s was around 50%, while at the same time organs that were not of a suitable blood group for a potential recipient were discarded and lost as an opportunity to save another child's life. Facing these grim perspectives for their patients, the team around Dr Lori West started considering important features of the infant immune system: overall weaker targeted immune response in a period when learning to separate self from foreign reflected especially in absence of antibodies against blood group antigens that rise as 'natural' antibodies typically only between 12 and 24 months of age. They wondered if this gap in immune response could represent a window of opportunity to break with a dogma existing since the "infancy" of organ transplantation: transplanting across ABO-incompatibility is an unsurmountable obstacle. This dogma was based on previous experiences with hyperacute and acute rejection in blood group incompatible organ transplantation in adults and a small series in heart transplanted children with overall dismal outcomes.

The outcomes of the first 10 patients transplanted with an ABO-incompatible (ABOi) heart published in 2001 (1) showed that, similar to ABO compatible (ABOc) recipients, 8 of the 10 children survived the first year post-transplant and up to 4.6 years post-transplant at the time of publication. The study also found similar freedom from rejection compared to 10 ABOc recipients and reduction of the local wait list mortality from 58% to 15% in children listed up to 6 months of age. The most stunning discovery, however, was that in contrast to healthy children and recipients of ABOc hearts the children after ABOi transplantation did not develop antibodies against blood group of their donor in the expected age frame, suggesting persistent adaption of the immune response to tolerate this additional foreign surface. Convinced by these findings, other pioneer centers in Canada, Germany, and the United Kingdom followed the successful protocol with equally good results, leading up to the first published multicenter study including the experience of these and two progressive US centers (2). It showed that up to nearly 10 years post ABOi transplant the recipients still showed selective deficiency of antibodies against the donor blood group, and survival, freedom from cellular and antibody mediated rejection and coronary allograft vasculopathy not higher than expected for ABOc transplanted children of this age group on similar immune suppressive regimens.

In parallel to increasing documentation of excellent clinical outcomes, particularly the Edmonton group focused on elucidation of the immunological backgrounds facilitating this unique phenomenon of antigen-specific tolerance after solid organ transplantation. The biochemical nature of the antigens underlying the ABO blood group system is of crucial importance: these are polysaccharides in contrast to the human leucocyte antigens (HLA) which are proteins. Since the 1980s it was recognized in infectious diseases and vaccine studies, that children up to 5 years of age experience much more frequent and severe infections with polysaccharide encapsuled bacteria. Attempts to overcome these vulnerabilities by applying the surface antigens in pure polysaccharide vaccines did not result in the required antibody response observed in adults when given to children younger than 24 months of age. The underlying immunological difference is, that in contrast to peptides such as HLA-fragments, polysaccharides are not presented in the MHC II complex and thus cannot trigger the predominant pathway of T-mediated B cell activation. Instead, we found that similar to other polysaccharides, the response to the A and B blood group antigens relies heavily on T-independent pathways of B cell activation. These use cross-linkage between the innate immune system (complement cascade fragment C3d) and it's receptor on the B cell, CD21 as part of the B-cell co-receptor (3). The latter is mostly expressed on B cells of the marginal zone of the spleen, an area that is highly underdeveloped in the first 1-2 years of life. The immaturity in this complex immune interaction results in low presence of IgM expressing memory B cells, the cell type quickly and specifically responding to foreign blood group antigens (4). Interestingly, these memory B cells remain fewer after ABOi than ABOc transplantation and also the blood concentration of C3d remains lower, suggesting a permanent modulation

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modulation of the global immune response after ABOi transplantation. These alterations affect not only the response to the blood group antigen itself but also towards HLA and we found that donor specific and overall class II HLA antibodies were less common in children <2 years after ABOi than ABOc transplantation, leaving them at with a potential long-term benefit rather than added risk, a finding later confirmed by others. In keeping with this potential benefit, several studies suggested lower acute rejection rates for ABOi recipients, however, there may be confounding effects such as young age. In the most recent PHTS analysis a difference in incidence of rejection was no longer visible when comparing cohorts closely matched for age and clinical parameters (5). Fortunately, this study also showed that the immunological changes did not result in a vulnerability to other polysaccharides such as those of encapsulated bacteria. To our surprise infections with these and other bacteria were actually less common in the ABOi than the ABOc patients even in the matched comparison, dispelling a major concern and suggesting another potential benefit.

From an immunological perspective all these findings are very exciting, since they challenge many classic models and show that the immune response is much less black and white and more intertwined than suggested in textbooks. The non-responsiveness to polysaccharides in early childhood has been overcome by conjugating the polysaccharides to peptides or proteins in conjugate vaccines, that lead to the near extinction of some vital threats such as Haemophilus influenzae type B epiglottitis and are now successfully used for prevention of pneumococcal and meningococcal diseases in young children. Similarly, it is now evident, that the immune response to blood group antigens is using multiple modalities including T cell support, and that the tolerance towards the donor blood group also affects the immune response to other antigens on the transplant organ.

The key question is: how long does this immaturity persist and can it be re-induced at a later time in life with immune-manipulation. Plasma isohemagglutinin titers provide some guidance, however, the clinically used quantification methods are somewhat crude and determined thresholds also need to take other factors into account such as age, passively acquired antibodies, non-specific stimulation, the blood group and group A subtype against which they are directed (e.g. Anti A naturally reaches higher maximal titers than Anti B and Anti A1 antibodies are not directed against A2 donor hearts). Antibodies that bind red blood cells in the tests may also not be harmful to the transplanted organ since the A and B antigens expressed vary in different tissues. The quantification of memory B cells still requires clinical validation and determination of predictive thresholds, as do other, more sophisticated quantification techniques for isoagglutinin concentrations.

In regards to age, the real-life limits have well exceeded 2 years. A recent study from the UK reported successful ABOi transplant in children as old as 8 years (6), our own center has transplanted up to 6 years of age after desensitization with B cell depletion with persistent absence of donor directed isohemagglutinins and in the PHTS analysis 27 children older than 2 years at transplantation were found to have similar survival to the overall cohort (5). In fact, successful ABOi heart transplantation has been performed intentionally after desensitization in selected adult patients and in those adults reported to the ISHLT registry, who accidentally received an ABOi heart the long-term survival after an initially moderately elevated mortality was similar to ABOc recipients (7).

In summary, the immune response to polysaccharides such as blood group antigens still needs much better understanding and as such a cautious approach to novel strategies in transplantation is justified. However, extrapolation from adult findings, outdated dogmas and arbitrary limits prevent important progress and overly rigid regulations may have resulted in disadvantages to these patients that are most desperate in need for a donor heart in the past (8). The clinical evidence for the safety of ABOi heart transplant younger children with low isohemagglutinin titers is now vastly undisputed, but regulations need to keep possibilities open, at least on a case-by-case basis, to allow ABOi transplant in older children and adults. This includes

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patients with deficient or medically modulated immune systems, those needing retransplantation after initial ABOi transplant and other clinically unique situations. It has to be clear, that operating outside the well-established safe limits requires careful consideration and discussion with the affected families and possibly ethics boards, however, establishing arbitrary limits bares the risk of preventing progress and jeopardizing life-saving opportunities for individual patients.

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