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ABO-incompatible living-donor kidney transplantation

M. Arias[1], M. López-Hoyos[2]

Departments of [1] Nephrology and [2] Immunology. Marqués de Valdecilla University Hospital. Santander, Spain

Nefrologia 2010;30(1):10-4

The long-standing problem of the disproportional ratio of kidney transplant donors and recipients recently acquired a new dimension, which is related to the even scarcer percentage of organs from young deceased donors. As a result, the most ideal recipients according to age accumulate on the waiting lists and their time on dialysis is drawn out further.

This qualitative aspect is another reasons for moving toward living donation, even in countries such as Spain, which has high cadaveric donation rates. These recipients, despite having a live donor whose decision has been firmly made, often find that their blood type is incompatible with their donor's blood. They may also find that due to prior blood transfusions or failed transplants, they have high anti-HLA antibody titres and a positive pre-transplant cross-match. These immunological obstacles are being overcome and these transplants are becoming possible.[1,2]

The push toward living-donor kidney transplants also stems from the therapeutic possibilities that have been developed to provide hyper-sensitised patients with high anti-HLA antibody titres with an alternative.[3-5] These patients are the ones who stay the longest on the transplant waiting list, and less than 10% of patients in a given year receive transplants with the classic marker of PRA > 80%. The desensitisation protocols intended to eliminate alloantibody titres and alloreactive B-cells from the recipient's body have made spectacular progress in the last five years. They have developed to such an extent that these strategies have permitted the introduction of kidney transplant programs between ABO-incompatible donor/receptor pairs.[6]

The differences between human blood types and the appearance of natural anti-A and anti-B antibodies are two obstacles that seemed insurmountable when performing a transplant. Compliance with the blood transfusion norms that had been established ever since Karl Landsteiner's discovery of blood types at the beginning of the 20th century was considered to be a given in organ transplants. But this barrier seems to have been overturned a few years ago, and ABO-incompatible kidney transplants have become an undeniable clinical fact, as shown by this article describing Spain's pioneer cases performed in Barcelona Clinical Hospital since 2006.[7]

The pressing problem of lack of donors, the advances in our understanding of mechanisms involved in humoral rejection of allografts, and the development of new treatment options have all led up to the fact that many countries currently have ABO-incompatible kidney transplant programs - an anecdotal practice that was considered "heresy" in the first two decades during which kidney transplants were performed. ABO-incompatible transplants of other organs have not had the success of kidney transplants; in general, they have only been performed in emergency situations when all other possibilities had been ruled out.

Two principal mechanisms are fundamentally responsible for the success of an ABO-incompatible kidney transplant: accommodation and humoral tolerance. The term "accommodation" comes from the first experiences in the 1980s with a surviving renal graft in cases of ABO incompatibility. ABO incompatibility induces a hyperacute rejection of the kidney graft which can be prevented by eliminating the anti-ABO haemagglutinins in the recipient prior to the transplant. Once the hyperacute rejection is overcome, the kidney graft can "accommodate".[8] Despite widespread use of the term, the mechanisms responsible for accommodation are still largely unknown even today.

Blood-type antigens are carbohydrate epitopes linked to four different types of sugar chains; these form bonds with membrane glycolipids or glycoproteins.[9] More than 180 polymorphisms of the glucosyltransferase gene for groups A and B are found on the National Center for Biotechnology Information Web site, and each of these polymorphisms may refer to one of the ABO alleles. Most of these polymorphisms do not alter enzyme activity, but can be used to identify ethnic groups with respect to migrations. Minimal

Correspondence: Manuel Arias
Servicio de Nefrología.
Hospital Universitario Marqués de Valdecilla. Santander. Spain.
nefarm@humv.es

differences in DNA determine glucosyltransferase function, which results in different blood types. The specific enzyme for antigen A differs from antigen B in four out of 354 amino acids, and there are differences in the sequences of the alleles coding for the specific enzymes in the A and O antigen. The differences are substantial enough to change the characteristics of the terminal sugar that distinguishes between A, B and O blood types.[9] One related matter, which needs further progress to achieve clinical use, is xenotransplant. Xenoreactive natural antibodies, especially antiGal-alfa(1,3)Gal, have a clear relationship with human blood types. The Gal-alfa(1,3)Gal molecule shares close structural similarities with human blood types, and therefore, each individual's blood type can have an influence on the formation of anti-Gal antibodies. Therefore, xenoreactive antibody titres are higher in individuals with blood types O and A than in those with blood types B and AB.[10] The progress made with ABO-incompatible transplants will mark the path to be followed for transplants between different species, since both obstacles have appeared with similar molecular changes throughout evolution.

In addition to membrane antigens, there are soluble A and B epitopes bound to the circulating von Willebrand (vW) factor.[11] This fraction of circulating A and B antigens is largely released by endothelial cells. In particular, the presence of blood antigens bound to the vW factor has been demonstrated in renal artery samples, which could be important in the modulation of the immune response during the accommodation period by means of a still undetermined mechanism. The best ABO-incompatible transplant results were obtained from transplanting A2 kidneys in O recipients, and the A2 subtype is precisely the one that correlates to an absence of A antigen bound to the VW factor in blood.[12] As a result, from an antigen standpoint, it is possible that the activated endothelial cells in an ABO-incompatible transplant would be the source of blood antigens bound to the vW factor, and the modulation of this activation would be important in the accommodation process.

On the other hand, a transient or very low iso-agglutinin titre has been described during the accommodation period in ABO-incompatible transplants. Something similar occurs in the Barcelona Clinic Hospital series, and very low iso-agglutinin titres are observed in all cases but three (one with no detectable antibodies, one in which they were not measured and the last one with high titres). The physiopathological meaning of this phenomenon is unknown. The methodology employed for studying these antibodies is still basically the same as the original, and the exact nature of the iso-agglutinins that reappear have barely been investigated.[13] It is likely that clinical implementation of this practice will lead to a deeper understanding of the specific antigens recognised by antibodies, how they have to do with blood type (the epitope of the blood type, sugar chain regions to which they link, shared epitopes with vW factor, etc), and the possible effects on the accommodation of the ABO-incompatible kidney graft.

The formation of iso-agglutinins that react to antigens in the incompatible blood type induces the deposit and activation of complement factors. Along with the presence of low iso-agglutinin titres, we find C4d deposits in most ABO-incompatible kidney grafts (100% in Barcelona Clinical Hospital). C4d is a C4b degradation factor with no biological activity as yet identified which forms deposits in peritubular capillaries after activation of the classical complement pathway. As a result, its presence in renal biopsies of a normal ABO-compatible allograft is associated with alloantibody formation and humoral rejection with a very poor prognosis.[14] Surprisingly, the presence of these deposits in ABO-incompatible transplants is associated with accommodation, rather than with rejection of the graft. One possible explanation is that C4d reflects the activation of the complement that does not manage to generate the membrane attack complex C5-9. On the other hand, activation of the complement induced by the union of group A or B epitopes bound to the vWfactor and released by endothelial cells would generate complement factors (C1q, iC3b, C5L2) with anti-inflammatory capabilities and the ability to suppress antigen presentation and the activation of T cells.[15-17] Along with protective factors derived from the complement, other possible regulatory mechanisms in the graft itself have been described.[18] Therefore, in vitro incubation with xenoantibodies from endothelial cells induces the production of nitric oxide, which is capable of inducing the expression of molecules that inhibit endothelial apoptosis, such as Bcl-2 or Bcl-XL.

On the other hand, nitric oxide inhibits secretion of the vW factor and P-selectin by endothelial cells. In addition to nitric oxide, other cytoprotective molecules with similar mechanisms, such as haem oxygenase-1 or survivin[18] have been described.

We must not forget that the presence of C4d deposits in routine biopsies of ABO-incompatible grafts may be associated with the development of chronic kidney disease. The series at Barcelona Clinical Hospital has a very short follow-up time, and most of the biopsies were performed during the first year, so they do not show chronic damage indications. Likewise, series at the Mayo Clinic[19] and Johns Hopkins Hospital that analysed the presence of chronic lesions, such as transplant glomerular disease, found a very low incidence rate (below 20%), but they only studied it in routine biopsies during the first year. The long-term impact of acute antibody-mediated rejection on ABO-incompatible kidney transplants has not yet been well established, but in the study by Toki and Tanabe, the prevalence of post-transplant glomerular disease was higher and survival lower in the group that developed this complication.[21] The risk factors were a high titre of IgG class anti-erythrocyte

antibodies and the presence of donor-specific anti-HLA antibodies; the latter have a more significant correlation than the former.[21] In a small series at Basilea University Hospital, routine biopsies were performed up to 18 months after an ABO-incompatible kidney transplant, and only mild rejection was observed. However, this group stated that five out of the ten patients showed signs of mild chronic antibody-mediated rejection.[22] In short, as with ABO-compatible transplants, rejection, particularly humoral, during the first year spells out the long-term prognosis.

Lastly, accommodation of the ABO-incompatible kidney graft depends necessarily on the success of treatment to reduce iso-agglutinins prior to the transplant and during the first weeks after the transplant. The desensitisation protocols to overcome the ABO barrier were introduced in the 1980s, but their general use was delayed due to high infection and rejection rates.[23,24] However, in the modern era of immunosuppression, the use of protocols combining extracorporeal elimination of antibodies and immunosuppressant treatment has produced reassuring results, despite the protocols' progressive simplification.[21] The most commonly employed extracorporeal technique used for the first experiences was plasmapheresis, while the most common current method is immunoadsorption, as used in the Barcelona Clinical Hospital's series. Along with extracorporeal techniques, all pre-transplant conditioning protocols include intravenous infusions of immunoglobulins; depending on the series, immunoglobulins are administered immediately after plasmapheresis or else intensified just before the transplant. Furthermore, nearly all of the programmes tend to administer an infusion in the first days following the transplant.[19,20,25] The immunomodulator properties of intravenous immunoglobins are well-known, and they extend across multiple branches of the immune response. There is more debate over the use of splenectomy. This practice has nearly been discarded, and is no longer used in the Barcelona Clinical Hospital, although it is still widespread in some countries, such as Japan.[23] The rationale for splenectomy in ABO-incompatible kidney transplant rests upon its use for eliminating memory B cells and plasma cells. However, it is known that these cells are also present in areas other than the spleen. Furthermore, the critical period for ABO-incompatible kidney transplant spans the first 15 days following the transplant; antibody production must be reduced to less than a ratio of 1:8 during the first week and less than 1:16 in the second week.[19]

Splenectomy is not necessary to obtain this effect, as effective desensitising immunosuppressive treatments do exist. For example, rituximab, the anti-CD20 antibody, is capable of eliminating all B cells from the pre-B stage up to the memory cell stage.[26] This treatment must be launched before the transplant, unlike other immunosuppressant treatments designed to block the cellular response, and it must continue during the post-transplant period until accommodation has been safely reached. The importance of eliminating B cells with rituximab before the treatment is exemplified by the change in its management as described by the kidney transplant group at the Barcelona Clinical Hospital. The immunosuppressor treatment directed against the T-cells must be started from the time of the transplant, and is usually based on a triple treatment with tacrolimus, mycophenolate (the drug that demonstrated an ability to inhibit humoral response and which some studies are now using in pre-transplant conditioning) and prednisone, along with induction with an anti-CD25 antibody and thymoglobulin.[19-23]

ABO-incompatible transplant is possible today using the available treatment options, although the basic mechanisms that lead to graft conditioning are, generally speaking, not yet understood. There is no doubt that this treatment is less costly than a patient's remaining on dialysis for years and that it may be extremely useful for living-donor kidney transplants when blood group incompatibility is present with a high rate of anti-HLA antibodies, given that the treatment is able to eliminate the two antibody types. However, the treatment is very expensive (obviously more than an ABO-compatible transplant). This new technique is based on the use of special immunoadsorption filters that are more efficient than plasmapheresis, but which are also more costly, which forces us to address financial aspects if its use becomes more common. On the other hand, alternative treatments for overcoming ABO incompatibility are being researched. For example, the ONT (Spanish national transplant organisation) began sponsoring a cross-donor kidney transplant programme last year. Within this programme, patients unable to receive a kidney from a donor due to ABO incompatibility or a positive cross-match are able to exchange donors, so that each of the recipients receives a compatible kidney and each donor is able to make a donation. This is a complex programme from an organisational, ethical and legal standpoint, but it was successfully implemented in July 2009 and a cross-donor transplant was carried out between the first two pairs. The patients for whom an ABO-incompatible transplant is proposed must be informed of the possibility of cross-donor transplants and the advantages and risks for both techniques. To resume, we must recall that as many as 36% of the patients under study for a living-donor transplant have an ABO-incompatible donor and, on the other hand, for cross donation, only 31% of the patients were able to find an exchange pair under optimal conditions.[27]

There are still unknowns to be solved in ABO-incompatible kidney transplants, but we have taken yet another step forward in employing kidney transplants in complex individual cases and solving problems for specific patients, which is the end goal of transplantation and of any other medical innovation. We would like to congratulate the team and the hospital which introduced this technique in Spain and congratulate our entire community on having the possibility of using this technique in our patients.

KEY CONCEPTS

1. The blood type obstacle seems to have been overcome and ABO-incompatible kidney transplants have become an undeniable clinical fact.
2. Two principal mechanisms are fundamentally responsible for the success of an ABO-incompatible kidney transplant: adjustment and humoral tolerance.
3. The presence of C4d deposits in routine biopsies of the ABO-incompatible graft is very common, and does not seem to have a harmful effect on the graft in the short term; we have yet to see its effect over the long term.
4. The greatest advance in clinical implementation of ABO-incompatible transplants came about through desensitisation and isoagglutinin elimination techniques; here, immunoadsorption and anti-CD20 antibodies have become the norm, and splenectomy is fading out.
5. The different treatment protocols have been evolving, and the good results continue despite progressive protocol simplification.

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