Chinese Medical Journal®

Commentary on transplant outcomes of 100 cases of living-donor ABO-incompatible kidney transplantation

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By the end of 1980, Japanese groups had started programs with ABO-incompatible kidney transplantation as a consequence of the very limited supply of cadaveric organs for transplantation. Since then, they have done successful transplantations across the blood type barrier in combination with plasmapheresis and splenectomy. In Japan, the strategy for ABO-incompatible transplantation has changed with the development of the tacrolimus (FK) /mycophenolate mofetil (MMF) combination in 2000 and rituximab in 2005.[1] In addition, preoperative 1-week administration of FK/MMF produced much more excellent results. Current graft survival (2005–2013) was almost over 90% in both ABO-incompatible at 9-year follow-up, which was comparable to ABO-compatible kidney transplantations.[1] Many researchers from other countries such as Sweden, the USA, as well as the UK also reported uncountable articles relating to ABO-incompatible kidney/liver transplantations. Unfortunately, the common observations from their reports are a high risk of hyperacute antibody-mediated rejection leading to graft loss, and a high incidence rate of postoperative complications like an infectious disease, probably due to the thymoglobulin regimen.[2] So, the future direction of ABO-incompatible transplantation in some countries is likely to go straight forward to a donor exchange program rather than a heavy immunosuppressive program at the time of ABO and/or human leukocyte antigen incompatible transplantation.[3]

I have read Yin *et al*'s[4] article reporting their experiences of first trial ABO-incompatible kidney transplantations in Sichuan Province with lots of interest. The difference between Yin *et al* team and other researchers are tailored-made programs according to the baseline titers of anti-blood type antibodies, sometimes only plasmapheresis and immunosuppression, not B cell targeting therapy like rituximab administration. It is noteworthy and surprisingly that recipients with low titers like ×16 or less were successfully transplanted even after a rituximab-free regimen.

The immunological barrier in ABO-incompatible organ transplantation can be overcome by performing pre-transplant extracorporeal antibody removal therapy but there are several risks associated with ABO-incompatible kidney transplantations including early graft loss, postoperative bleeding, and infection. These complications may relate to the presence of donor-directed antigen specific-antibody, the treatments required for removal of antibodies and inhibition of its re-synthesis of antibodies or using excessively heavy immunosuppression because of presumed high risks of ABO-incompatible transplantations. In terms of considering such risks, Yin *et al*'s[4] report describing modulated regimen depending upon baseline titers is worthy of publication with novelty, although the number of reported cases is just reaching 100 cases.

Different forms of extracorporeal antibody removal therapy have been successfully adopted in combination with B cell-targeting therapies, all guided by hemagglutination assay (HA)-based antibody detection qualitatively and quantitatively. However, the HA assay is not well standardized over the world, exhibiting intra- and inter-laboratory center variables as well as intra- and inter-individual researcher's variables, leading to incomplete patient's management. Also, the precise understanding between HA titers and biological tissue injuries relevant to organ transplantation is ill-defined.[5] The return of anti-blood type antibodies after ABO-incompatible kidney transplantation may result in antibody-mediated rejection, but very often is not associated with graft injuries, which situation is called immunological accommodation. The detailed and precise mechanism underlying accommodation in ABO-incompatible organ transplantation is also still not elucidated.

A few months ago, xenotransplantation using swine kidney and heart was performed in the USA, although the heart recipient has already been dead, probably due to humoral vigorous rejection postoperatively. ABO-incompatible

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002332

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Chinese Medical Journal 2022;135(19)

Received: 30-03-2022; **Online:** 04-10-2022 **Edited by:** Yuanyuan Ji

transplantation is a model for hyperacute rejection and also raised an important question—why do only some ABO-incompatible allografts undergo hyperacute rejection whereas all discordant xenografts undergo this same process.[6]

That hyperacute rejection of ABO-incompatible allografts occurs less frequently than hyperacute xenograft rejection might be explained if the level of isohemagglutinins in serum is lower than the level of xenoreactive antibodies. However, the few studies which address this possibility suggest otherwise. Isohemagglutinin titers ranged from ×4 to ×256 whereas heteroagglutinin titers from ×1 to ×4. Despite these findings, hyperacute rejection of ABO-incompatible cardiac allografts is only 33%, whereas the hyperacute rejection of pig to baboon cardiac xenograft occurred in nearly all grafts. Thus, factors other than hemagglutinin must determine whether hyperacute rejection will occur.

A second possibility is that the binding of xenoreactive natural antibodies is more avid than the binding of isohemagglutinin and as a result complement activation is greater following the binding of xenoreactive antibodies. It is still possible that anti-blood type A antibodies bind less avidly to endothelial cells than to erythrocytes.

A third potential reason why hyperacute rejection occurs more frequently in xenografts than in ABO-incompatible allografts is that the density of xenoantigens might be significantly greater than the density of ABO antigens. Each human erythrocyte of blood type contains one million blood type A or B molecules. Each rabbit erythrocyte has approximately one million Gal xenoantigens (epitopes). These similar levels of expression of ABO antigens and xenoantigens suggest that quantitative difference in antigen levels does not explain the difference in the outcome of ABO-incompatible grafts *vs*. discordant xenografts. However, the core structures bearing Gal antigens and blood type A antigens on the endothelial cells differ from the core structures on erythrocytes.

A fourth possibility for the lower incidence of hyperacute rejection in ABO-incompatible grafts compared to xenografts is that ABO-incompatible allografts might be less susceptible to hyperacute rejection. One factor opposing the development of hyperacute rejection in ABO-incompatible grafts is the expression of cell-associated complement regulatory proteins such as decay-accelerating factors which inhibit activation of homologous complement cascade pathways. Because porcine complement regulatory proteins may function poorly against heterologous complement, a porcine xenograft may be especially susceptible to complement-mediated injuries. On the other hand, the functional capacity of complement regulatory proteins can be clearly overcome since some grafts undergo hyperacute rejection. Like these observations, we have to tackle and overcome higher and more difficult hurdles until achieving a 100% successful rate in ABO-incompatible transplantation, because the mechanism for the establishment of graft accommodation in ABO-incompatible transplantation is incompletely understood and apparently multi-faceted. At the same time, this concept of accommodation and the success of ABO-incompatible renal grafts using various kinds of an immunosuppressive regimen such as Yin *et al*'s tailored-made immunosuppression provides an important impetus toward the clinical application of xenotransplantation. This kind of research by Yin *et al* will shed light on the clinical transplantation using xenograft at the bedside in near future.

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How to cite this article: Ishida H. Commentary on transplant outcomes of 100 cases of living-donor ABO-incompatible kidney transplantation. Chin Med J 2022;135:2301–2302. doi: 10.1097/CM9.0000000000002332