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INVITED COMMENTARY

Titer rebound after ABO-incompatible kidney transplantation – is all accommodated for?

Carsten A. Böger and Bernhard Banas

Department of Nephrology, University Hospital Regensburg, Regensburg, Germany

Correspondence
Carsten A. Böger
Department of Nephrology, University Hospital Regensburg, 93042 Regensburg, Germany.
Tel.: +49-941-944-7301;
fax: +49-941-944-7302;
e-mail: carsten.boeger@ukr.de

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The blood group antigens A and B of the ABO system are expressed not only on erythrocytes but also on the kidney's vascular endothelium, the convoluted distal tubules, and the collecting tubules [1]. This explains why hyperacute graft rejection almost always ensues after ABO-incompatible kidney transplantation and why kidney transplantation across the ABO blood group barrier without a prior preconditioning protocol is considered an absolute contraindication. Such protocols typically aim at reducing the IgG and IgM antibody titers against the incompatible donor blood group (anti-A1, anti-A2, or anti-B) by (i) depleting B lymphocytes, either by splenectomy or by infusion of rituximab, a monoclonal antibody against the B-cell marker CD20 and (ii) removing the incompatible antibody prior to transplantation [2,3]. The performance of ABO-incompatible kidney transplantation is deemed safe when antiblood group antibody titers are 'low' just before transplantation, with center-to-center differences in the definition of 'low' [2,4]. Indeed, long-term follow-up studies consistently show that ABO-incompatible kidney transplantation is a safe procedure with long-term outcomes similar to ABO-compatible transplantation [5].

These good results are somewhat surprising, given the many uncertainties around the key 'villain', the antibodies against the ABO-incompatible donor.

First, the minimum 'safe' antibody titer has not been defined, either by randomized controlled studies or by consensus guidelines [2,4]. Second, there is a wide range of assay techniques available for measuring antibody titers, and new methods are in development [6–9]. Third, there is no international standardization of laboratories measuring anti-A or anti-B antibodies with wide, up to 256-fold inter-laboratory differences in titers, making comparability between the centers' transplantation programs impossible [6,10,11]. Fourth, there is debate on which immunoglobulin subclass is the potential culprit leading to hyperacute rejection – is it only IgG or only IgM, or both [12]? Fifth, the A1 and B antigens show more intense expression in kidney than A2, with implications for a potentially higher risk of acute rejection in certain donor–recipient constellations [1]. Finally, the clinical relevance of rebounding titers in the first weeks or even months or years after transplantation is unknown.

A cohort study in the current issue of *Transplant International* tries to shed some light on the latter issue [13]. In

one of the largest single-center cohort studies of ABO-incompatible kidney transplantation with long-term follow-up (n = 191, mean duration of follow-up >5 years), Ishida *et al.* examine the clinical relevance of rebound of anti-A and anti-B antibody titers after transplantation by dividing their cohort into a low-rebound group (n = 170, defined as a rebound to a maximum of 1:32) and a high-rebound group (n = 21, defined as a rebound to an antibody titer of at least 1:64). Their key findings are (i) recipients with high titers prior to preconditioning showed significantly higher rebound of titers postoperatively, with similar results obtained for those treated with splenectomy or rituximab, (ii) graft function in terms of serum creatinine in the high-rebound group was slightly, but significantly lower than in the low-rebound group in the first month after transplantation (serum creatinine 1.51 mg/dL vs. 1.76 mg/dL in the low vs. high rebound group respectively, p=0.02), but there were no differences after long term follow-up, (iii) overall graft survival at 5 and 10 years post-transplantation tended to be lower in the high-rebound group compared with the low-rebound group (94% vs. 93% at 5 years, 93% vs. 86% at 10 years), although this difference was statistically not significant in Kaplan–Meier analysis (P = 0.5), (iv) there were no statistically significant differences in type or severity of rejection between the low- and high-rebound groups.

Overall, the authors conclude that antibody titer rebound does not correlate with poor outcome and that treatment of antibody rebound is not necessary as there is 'accommodation' for elevated titers. While statistically speaking, the authors reach the correct conclusion, the reader should be aware that there is a trend to more graft loss in those with rebound (14.0% vs. 6.5%, P = 0.1, similar to results in Kaplan–Meier analysis). Also, the study is most likely underpowered to detect a statistically significant difference, although a formal power calculation is missing. A smaller study from Korea showed significantly worse outcomes for patients with high rebound [14]. Most importantly, the main caveat in interpreting the study by Ishida *et al.* is the continuing uncertainty regarding antibody titer measurement as discussed above. Unfortunately, the authors provide little detail on methods of anti-A and anti-B measurement. Also, the authors do not differentiate between anti-A1 and anti-A2, even although there is the potential for higher reactivity of anti-A1 [1].

Given the uncertainties around the methodology of antibody titers, the findings of Ishida *et al.* and previous, similar studies [12,15–17] thus should be interpreted with caution. A larger study encompassing all ABO-incompatible transplantations worldwide with uniform and validated antibody titer measurement could adequately evaluate outcome upon titer rebound with sufficient statistical power.

On the basis of current literature, there appears to be some degree of 'accommodation' to high-rebounding antibody titers, but it is unclear why the antidonor blood group antibodies should differ in detrimental effect from HLA antibodies. Indeed, the mechanism of accommodation, which is observed also in the setting of HLA antibodies, is unclear [18]. Chimerism of vascular endothelium whereby the recipient's endothelial cells replace the donor's in the transplanted kidney is an enticing theory. However, endothelial chimerism developed in only 25% of ABO-incompatible transplants in one study and was associated with antibody-mediated rejection and not with 'accommodation' to incompatible blood group antibodies [19]. These findings negate an effect of chimerism in accommodation and are supported by ultrastructural studies performed in kidney biopsies where endothelial damage was only detected in rejection in an ABO-compatible setting and not after ABO-incompatible transplantation [20].

In summary, the work by Ishida *et al.* and other studies [12,15–17] points the community to two major unresolved issues in ABO-incompatible transplantation: the uncertainties around measurement of and accommodation to the incompatible blood group antibody. The transplant community should urgently address these issues, particularly, however, the issue of titer measurement to allow well-powered international outcome studies.

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