Anti A/B Antibody Titer Rebound: Are we Making it Worse? Be Aware of Your Intravenous Immunoglobulin

Sir,

ABO-incompatible (ABO-I) transplants are increasing across the world[1] and in India.[2,3] One of the common problems encountered in these transplants is the rebound of anti-blood group antibodies (Anti-A or Anti-B) during their desensitization protocols. It has been predominantly thought to be either due to production of new antibodies (by plasma cells and B–cells, hence the need to start immunosuppression prior to plasmapheresis) or equilibration from extra- to intra-vascular compartment (as only 45% of IgG is intravascular, hence repeated plasmapheresis are required). Intravenous immunoglobulin (IVIG) is made from pooled plasma of donors that include donors from various blood groups. Hence, IVIG will contain anti-blood group antibodies. Most desensitization protocols use IVIG, either low dose or high dose, especially postplasmapheresis. The impact of these anti-blood group antibodies in IVIG on rebound

of anti-blood group titers is not well described. The variability of anti-blood group antibodies in different IVIG products and lots is also unknown.

A 26-year-old female presented with mother as ABO-I donor 0/6 HLA mismatch (donor blood group B, recipient blood group O). Her initial titer was 1:256. The titers were measured by column agglutination technology by ORTHO BioVue™ System, Ortho Clinical Diagnostics, Pencoed, UK. She received rituximab 200 mg 2 weeks prior to planned transplant. She was started on tacrolimus (0.05 mg/kg/day) and mycophenolate sodium (720 mg BD) 1 week later. Tacrolimus was increased to 0.1 mg/kg/day on the night before transplant (the initial lower dose is to limit the side effects of tacrolimus such as posterior reversible encephalopathy syndrome). She received double-filtration plasmapheresis (DFPP) on day-9, day-7, day-5, day-3, and day-1. To assess the impact of IVIG on anti-B titer, a titer was done post-DFPP and then post-IVIG infusion, the other issues of IgG production and equilibration were minimized as this was within 3–4 h of the previous sample. On day-7, it was noted that, when IVIG with a titer of 1:8 was used, the post-IVIG titer did not increase; however on day-5, when IVIG with a titer of 1:32 was used, the titer increased from 1:16 to 1:32 immediately post-IVIG and had increased to 1:64 prior to the next DFPP on day-3 (negating any effect of the previous DFPP) [Table 1]. In light of this information, the last DFPP prior to transplant was done on day-1 without any IVIG and transplant performed the next day. The transplant was successful and 6-month posttransplant creatinine is 1 mg/dl.

Following these results, IVIG was tested by our blood bank from three products (Reliance-ImmunoRel, Intas-Gammaren, and PlasmaGen-(PlasmaGlob) and different batches within the same product. Another vial from the same product and batch (9703005) was also retested to ensure the reliability of testing. The results are shown in Figure 1. The results show that there is large variability in anti-A/B titers (1:4–1:512, a 7-fold difference) in the different IVIG products and that there is also large variability in the different batches of the same product (1:4–1:64, a 4 -fold difference). Our study also demonstrates that, when IVIG with a low titer is used, the post-IVIG titer does not increase, while if IVIG with a high titer is used, the post-IVIG titer increases.

These results replicate and add to the results shown by Staley *et al*.[4] Staley *et al*. had tested three lots of Privigen® and one lot of CytoGam® and shown the large difference in titers between the two products. However, they only noted a 1-fold difference in the anti-A/B titer within the 3 lots of Privigen® that they tested. Our results show a much larger variation between the IVIG products from different companies and within the different batches from the same product. Our study is the first one to test products currently available in India.

Staley *et al*. tested the post-IVIG titer only once to show the increase that had occurred from the IVIG. They did not show that using an IVIG with low titer does not increase the titer. Our study documents that, if IVIG with low anti-A/B titer is used, then the post-IVIG titer does not increase and hence low-titer IVIG can be used without concern for an increase in anti-A/B titer.

The impact of this rebound in titer on the likelihood of antibody-mediated rejection is not known as the antibody detected by testing may be different from the one that attacks the renal endothelium. However, this rebound may lead to increased need for plasmapheresis, occasionally a delay in transplant, and may even lead to cancellation of the ABO-I transplant if the titer does not reduce. Hence, we recommend that all centers doing ABO-I transplant should

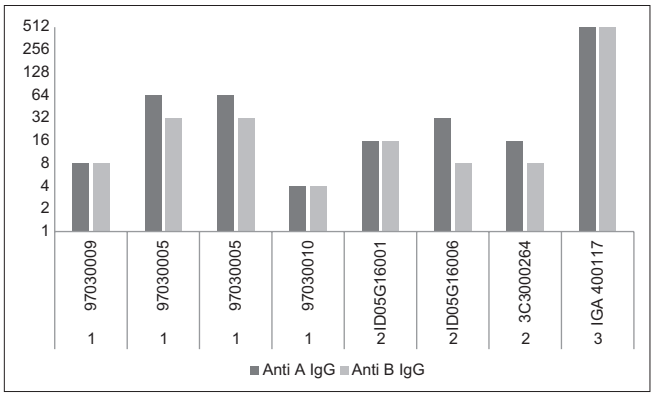

Figure 1: Variability in anti-A and anti-B titer in intravenous immunoglobulin of different products and batches

Table 1: Anti-B titer in patient pre- and post-plasmapheresis and postintravenous immunoglobulin administration and anti-B titer of intravenous immunoglobulin administered

Date	Anti-B IgG pre-PP	Anti-B IgG post-PP	Anti-B IgG post-IVIG	IVIG Anti-B IgG
POD-9	256	128		
POD-7	128	32	32	8
POD-5	64	16	32	32
POD-3	64	16	32	32
POD-1	32	8		
POD	16			
POD+1	8			

IVIG: Intravenous immunoglobulin, PP: Plasmapheresis, POD: Postoperative day

use IVIG products and lots that have low anti-A/B titers. As currently, anti-A/B titers in IVIG products and lots are not routinely measured at this threshold, transplant centers may have to do this on their own. Another option may be to perform ABO-I transplant without IVIG, especially when using specific (Anti-A/B) immunoadsorption columns.

There is a large variability in the anti-A/B titer in IVIG from different products and different batches of the same product. IVIG with high anti-A/B titer can increase titers during desensitization, and using IVIG with low titers does not increase titers post-IVIG administration. Transplant programs performing ABO-I transplants should be aware of the anti-A/B titer of their IVIG products.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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