Reply to Focosi et al

Hana Golding, and Surender Khurana

Division of Viral Products, Center for Biologics Evaluation and Research (CBER), FDA, Silver Spring, Maryland, 20993, USA.

Corresponding author:
Surender Khurana, Ph.D.
E. mail- Surender.Khurana@fda.hhs.gov
Dear Editor,

The letter in response to our recent publication[1] by Focosi et al., argues that COVID-19 Convalescent Plasma (2022-CCP) from breakthrough infected individuals (Omicron BA.1), based on our data, was superior to hyperimmune globulin (hCoV-2IG) manufactured from CP donors in 2020. However, the difference in neutralization titers were not significantly different between the 2022-CCP vs. hCoV-2IG across SARS-CoV-2 strains in Figure 1 panel A[1], possibly due to the limited number of samples. We acknowledge their arguments, which favor CCP over hCov-2IG. However, in our view a more balanced approach should consider the advantages and disadvantages of both products.

We disagree with several arguments made in the Focosi et al. letter. Although the randomized controlled trial (RCT) for hCoV-2IG in hospitalized patients did not show benefit, it is also true that the largest RCT for CCP did not show benefit in a similar patient group[2]. While IgM and IgA do add potency to CCP from acute infections, their role is diminished by their short half-lives, and much lower concentration in plasma than IgG. Furthermore, they are of lower affinity than IgG because of lack of somatic hypermutations. Importantly, several studies demonstrated increased affinity of IgG post-infection or vaccination[3] [4] with superior antibody affinity in individuals with hybrid immunity that correlated with increased cross-reactivity against SARS-CoV-2 variants of concern[5].
The issue of dilution is raised in the letter. However, hCoV-2IG can be administered in larger volumes than plasma because volume overload is less likely to occur. This is because plasma has a stronger osmotic effect due to the presence of albumin. Therefore, the dilution factor cited in actually favors use of hCoV-2IG over CCP.

Scarcity of hCoV-2IG is mentioned in the letter. This is not necessarily relevant to manufacture of hCoV-2IG, because the donor pool may be different.

We acknowledge that major advantage of CCP is that the lead time for availability is shorter. If new strains are appearing very rapidly, CCP may be more efficient approach, but once the time between new variants lengthens, this advantage is less of a factor.

The most striking advantage of hCoV-2IG vis-à-vis CCP is that the former can be manufactured to have consistent potency and specificity, whereas CCP varies from donor to donor in these parameters. The potential side effects from plasma and IgG overlap, but are much more common with plasma (e.g. volume overload, TRALI, hemolysis, hypersensitivity)[6]. Additionally, hCoV-2IG manufacture involves viral and bacterial inactivation/removal, unlike CCP. As a result, plasma infusion can result in serious viral infections, which are extremely rare following IVIG.

In summary, all therapeutic approaches should be explored for use in COVID-19 treatment, including CCP and hCoV-2IG. The choice should be based on the evidence for efficacy and safety in a particular patient group, taking into consideration the potency
of the product against the predominant circulating strain of SARS-CoV-2. While hCoV-2IG produced in 2020 demonstrated cross-reactivity against several Omicron subvariants, new hCoV-2IG manufactured from donors with hybrid immunity may provide valuable post-exposure therapy against circulating and emerging variants.

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Conflict of Interest: The authors declare that they have no competing interests.
## References:


