Comment on: Nature and Dimensions of the Systemic Hyper-Inflammation and its Attenuation by Convalescent Plasma in Severe COVID-19

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TO THE EDITOR,

We read with great interest the manuscript of Bandopadhyay *et al*., [1] in which the effects of convalescent plasma (CP) on the inflammatory response in COVID-19 were evaluated. The authors reported that transfusion of CP was associated with a reduction of IL-6, IP-10, and M-CSF. In addition, authors showed that CP was associated with a rapid but transient improvement of PaO_2/FiO_2 when compared with standard therapy. Although these results are of interest, we would like to stress out some points.

We recently conducted an immunological study in which the effects of CP on cytokines and lymphocyte populations in 28 days follow-up was evaluated [2]. We found that CP induces an early but transient effect on the antibody (i.e., 4 days) and cytokine (i.e., 4 to 7 days) profile of patients with severe disease, attenuates the exhausted phenotype and increases memory T and B-lymphocytes at day 28 post-transfusion together with a reduction of IL-6/IFN-γ and IL-6/IL-10 ratios (i.e., 14 to 28 days). These results differ from those of Bandopadhyay *et al*., [1] since they observed an early decrease of inflammatory cytokines (IL-6, IP-10, and M-CSF) 3 to 4 days post-transfusion. Between days 4 to 7 post-transfusion we observed an increase of IFN-γ, GM-CSF, IL-8, TNF-α and IL-17A, but a late reduction of IL-6/IFN-γ and IL-6/IL-10 ratios, indicating that CP effects may take longer, but induce a modification on parameters that have been previously associated with COVID-19 mortality and severity [3].

The authors describe that the anti-inflammatory role of CP is independent of the content of neutralizing antibodies (NAbs), and that other components of CP could induce relevant biological effects. In our study, we did not observe differences between donors (i.e., low IgG and IgA antibody titers) and super-donors (i.e., high

IgG and IgA antibody titers) in terms of cytokines, autoantibodies, and metabolomic profile [2]. In fact, total IgG and IgA antibodies against S1-SARS-CoV-2 are key factors for the selection of CP. We found that these antibodies highly correlated with NAbs. The use of CP with high titers modified the immune response of patients with COVID-19.

Results from Bandopadhyay et al., [1] may differ from ours since they conducted paired test for each group and did not evaluate intergroup differences. It would be of interest to know whether the reduction of cytokines in the plasma receptor group significantly differed from those on standard therapy, and whether the effect persists longer than 4 days. Authors randomized mild and severe patients to both therapy groups. However, randomization of patients with similar clinical characteristics (i.e., confirmed viral pneumonia or severity according to validated classification criteria) may have allowed a better evaluation of the immune response. In addition, it is unknown if patients were transfused in early stages of the disease or in the first days of hospitalization. This has critical implications in the evaluation of cytokine kinetics.

The evaluation of lymphocyte populations may had offer better information about the real therapeutic implications of CP. As our study showed, CP ameliorates activated T and B cell phenotypes, with an increase in memory cell subsets. All these data suggest that early administration of CP influences the immune response, even after the resolution of the acute phase of the disease. However, it is unknown whether these phenomena persist after 28 days of transfusion.

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Competing interests

The authors declare that they have no competing interests.

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