High-Dose Convalescent Plasma for Treatment of Severe COVID-19

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To the Editor: We commend our colleagues in Brazil for completing a multicenter, open-label, randomized controlled trial (RCT) of coronavirus disease (COVID-19) convalescent plasma (CCP) against wild-type severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (*1*). This RCT had some strengths, including use of high-dose CCP (600 mL CCP for 3 days at a median neutralizing antibody titer of 1:128). The overall results were negative, but the authors caution that this finding probably reflects inclusion of patients late in disease, as evident by enrollment criteria (oxygen saturation <93%, partial pressure of oxygen/fraction of inspired oxygen <300, or need for mechanical ventilation), median transfusion at day 9 after symptom onset, 100% seropositivity, and 35% requiring hemodialysis at enrollment. The severity of disease in those patients means that disease was driven by inflammation as opposed to ongoing virus replication. To date, 2 CCP RCTs have shown benefit, 1 that provided outpatient treatment (D. Sullivan, et al., unpub. data, https://www.medrxiv.org/content/10.1101/2021.12.10.2126748v1) and 1 that provided inpatient treatment within 3 days of symptom onset (*2*). Hence, we caution against negative conclusions about the efficacy of CCP based on these data.

We find it remarkable that despite late CCP use, the authors observed a lower mortality rate among CCP-treated patients (31%) than controls (35%), given that the prevailing view is that this therapy functions as an antiviral and should not be effective in late disease. A similar finding is apparent in most other RCTs of hospitalized patients (*3*). This reduced mortality rate did not reach statistical significance because of the low sample size, which was estimated by assuming a 50% reduction in mortality rate from the intervention, much higher than that assumed in the RCTs of anti-spike monoclonal antibodies (typically in the range of 20%); further, recruitment was halted at 110 out of 120 patients. A recent article suggests that there is a population with high World Health Organization severity scores that benefits from CCP (*4*). We wonder if the authors can reanalyze their data by using the treatment benefit calculator (https://covid-convalescentplasma-tbi-calc.org) (*4*) to gain more insight into whether a small subset of patients benefited from CCP.

A.C. was a co-investigator in the CSSC-004 RCT. D.F. was a co-investigator in the TSUNAMI RCT.

D.F. conceived the manuscript and wrote the first draft. A.C. revised the manuscript.

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In Response: We thank Focosi and Casadevall for their comments (*1*). One strong contribution of our study was the high dose (i.e., 1,800 mL in 3 days) of coronavirus disease (COVID-19) convalescent plasma (CCP), which, in our opinion, would be more likely to benefit patients than a lower dose (e.g., 200–600 mL in 1 or 2 doses), as is the protocol in most CCP studies (including but not limited to COVID-19 treatment) (*2*).

The weak point of our study was the relatively large therapeutic window (up to 10 days of signs/symptoms) for CCP transfusion, which may have included the later inflammatory process of illness. One early trial suggested benefit for COVID-19 patients who received CCP within the first 14 days (*3*). Nevertheless, subsequent trials showed that CCP (or serum) administration could be most beneficial for COVID-19 patients when administered as prophylaxis or within the first days of infection (*4*,*5*), ideally, within the first 3 days (*6*) but perhaps not later (*7*,*8*).

We emphasize that CCP transfusion was considered experimental at the beginning of the pandemic, and inclusion criteria comprised only patients with severe illness, for whom ≥7 days of infection are needed for illness to become evident.

We think that applying the suggested formula to identify which COVID-19 patients are likely to benefit from CCP (higher risk for progression to severe disease) would not be applicable to our study because it was envisaged for patients not receiving mechanical ventilation (*9*), whereas the patients in our study had severe disease (90% receiving mechanical ventilation).

In summary, our study emphasizes that CCP should not be transfused late in the course of disease, when the clinical course is driven by inflammation. This conclusion does not exclude the possibility of transfusing CCP as soon as patients are identified for potential benefit, as suggested by other studies (*6*,*7*).

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