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LETTER TO THE EDITOR

Convalescent plasma in oncohematological patients

Dear Editor,

We read with interest the recent article by Lanza et al., reporting no benefit in 30- and 90-days mortality from COVID-19 convalescent plasma (CCP) in a retrospective propensity score-matched study in patients with hematological malignancies.[1] While we agree with the need for national retrospective studies to learn from our experiences during this pandemic, we caution against accepting negative results from studies with serious limitations, especially when they contradict other compelling studies that provide a cohesive body of data consistent with efficacy.

We have concerns about CCP quality in this study. The authors wrote that *"Serum titer of specific neutralizing antibodies was >160 in all cases […] using the [enzyme-linked immunosorbent assay] method"*, which is not specified and has no correlation with viral neutralization titers. Because the SARS-CoV-2 Delta variant became predominant in Italy midway through this study, CCP units from prior non-Delta infections should have been evaluated by variant-specific viral neutralization assays or the authors should have at least noted the collection and administration times of CCP units. Next, the authors note that *"pathogen (viral) inactivation treatment of the plasma was performed in all CP preparations, in view of presence of viral DNA in donor population"*: SARS-CoV-2 RNA has never been found in CCP units, while pathogen inactivation, no longer mandated by the Italian guidelines, has not been used in CCP for most published studies and may be associated with a failure of Fc-dependent functions such as antibody-dependent cell cytotoxicity and complement-dependent cytotoxicity.[2] A lack of Fc-dependent immune functions would be expected to notably diminish CCP efficacy.

We also note the absence of clinical information likely to speak to the efficacy of antibody therapies in this study. Previous or concomitant antiviral therapies that could mask efficacy signals from CCP yet were not reported. While treatment timing is a strong determinant of efficacy in the literature and is noted by the authors in this study, the number of days from COVID-19 diagnosis or onset of symptoms prior to CCP transfusion were not reported. Moreover, pre-transfusion serostatus (a major determinant of CCP efficacy) was known for only eight out of 59 recipients. Given that the vaccine campaign started in Italy midway through this study in January 2021 and cancer patients were prioritized for this, we don't know how many of the patients were previously infected or vaccinated. Additional determinants of antibody efficacy such as vaccination status, corticosteroid use, B-cell depleting agents or previous chemotherapy are not reported or included in the propensity score-matching. After propensity score-matching, 52% of patients in both arms had progressive hematological disease or partial responses, making it unlikely that death at day 90 was due to hematological malignancies in only 10% of cases. Related to this concern, the methods section does not describe how COVID-19 was distinguished from hematological malignancy as the leading cause of death. Given these concerns, the only viable conclusion in the paper by Lanza et al. is about CCP safety, and we agree with the conclusion that CCP is fully safe. In contrast to the findings of Lanza et al., a recent metanalysis of nine controlled studies (including four randomized controlled trials (RCT)) totaling 535 CCP-treated patients and 1365 controls investigating immunosuppressed patients (most of them oncohematological patients), revealed a risk ratio for mortality of 0.65 in treatment with CCP versus standard of care.[3] We note that Food and Drug Administration,[4] Center for Disease Contro/Infectious Disease Society of America,[5] American Association of Blood Banks[6] and European Conference for Infections in Leukemia 9[7] guidelines currently recommend CCP in selected populations, including those who are immunocompromised.

In contrast to the authors' conclusions, when CCP is given to immunocompetent patients with COVID-19 using units with high-nAb titers, and early in disease, it has comparable efficacy to other currently authorized antiviral therapies.[8] The meta-analyses cited in the introduction are dated and do not include evidence from RCTs evaluating early usage. CCP from vaccinated donors (dubbed VaxCCP or hybrid plasma) is currently available from regular plasma donors, and contains more than 10-fold higher nAb titers than 2020 CCP[9]: of note, those units are able to neutralize any Omicron sublineage thanks to robust and uniform heterologous immunity.[9] Hence, we note that the VaxCCP currently used in immunocompromized patients is a very different preparation than that used in this study.

We are concerned that the current absence of RCT data focused on immunocompromized patients for small-molecule antivirals, combined with misconceptions about the inefficacy of VaxCCP, could favor the unacceptable practice of prescribing anti-Spike monoclonal antibodies against resistant SARS-CoV-2 variants.[10] As such, we encourage the oncohematology community to initiate novel RCT investigating VaxCCP in their vaccinated COVID-19 patients with a focus on serostatus at recruitment.

KEYWORDS

convalescent plasma, COVID-19, oncohematology, SARS-CoV-2

AUTHOR CONTRIBUTIONS

Daniele Focosi wrote the first draft; Michael J. Joyner, MD, Jeffrey P Henderson and Arturo Casadevall revised the final version.

CONFLICT OF INTEREST

We have no relevant conflict of interest related to this manuscript.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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PEER REVIEW

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