

Convalescent plasma therapy for B-cell depleted patients with protracted COVID-19 disease

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Abstract:

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Title: COVID-19, plasma, and hypogammaglobulinemia

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1054 words; 8 references; 1 Figure

Hueso et al¹ report a study of COVID-19 convalescent plasma (CCP) in patients with COVID-19 and negative IgG-IgM SARS-CoV-2 serology with severe immunodeficiency due to prior treatment with anti-CD20 monoclonal antibodies. The study reports on the safety and efficacy of COVID-19 convalescent plasma (CPT) in 17 patients with profound B-cell lymphopenia and protracted COVID-19 disease.

The risk factors for COVID-19 are well reported and include cancer, especially hematologic malignancies. Given the devastation wrought on the immune system by both the underlying malignancy and the therapy, this is hardly surprising. This combination of factors is particularly worrisome in B cell malignancies where treatment with anti-CD20 monoclonal antibodies such as rituximab is standard for many tumors. Rituximab is also used to treat autoimmune disorders. Repeated doses of rituximab results in prolonged B-cells depletion, which impairs the adaptive immune response and the ability to produce neutralizing antibodies.

Hueso et al report outcomes of an uncontrolled experience of 17 patients, mostly with hematological malignancies, with prolonged COVID-19 disease and negative SARS-CoV-2 serology, B-cell lymphopenia and hypogammaglobulinemia.¹ Patients were treated with 4 units of CCP, and within 48 hours all patients but one, who eventually died of bacterial pneumonia, had marked clinical improvement. SARS-CoV-2 RNAemia decreased in 9/9 patients tested. While the data in Hueso et al's study appear to be promising in terms of clinical response and improvement in some laboratory markers, limitations of their study include that the 17 patients had diverse underlying conditions accounting for their immunodeficiency, and received variable other treatments for COVID-19 disease. In addition, some of the patients appeared to be recovering before the administration of plasma, as evidenced by decreasing temperature and falling levels of C-reactive protein (CRP).

Today, we are challenged with a new infectious threat and there is an urgent need to identify safe and effective treatments. Although there are numerous studies in progress exploring the use of CCP

to treat patients with COVID-19 disease, there is currently only one published peer-reviewed RCT.⁴ Two additional RCTs were released prior to peer review.^{5,6} All three studies failed to show clinical improvement and they were closed due to futility. One of the studies found neutralizing antibodies in 44 of the 56 (79%) hospitalized COVID-19 infected patients tested with median titers comparable to the 115 donors (1:160 vs 1:160, $p=0.40$).⁵ This finding raised concerns about the potential benefit of convalescent plasma and the study was discontinued. It is worth pointing out that the study population in Hueso et al's study is very different with negative SARS-CoV-2 serology, B-cell lymphopenia and hypogammaglobulinemia.¹

Clinical studies of CCP without randomization and without placebo controls continue to be published. For patients with unusual disorders, such as certain forms of immune deficiencies, adequately powered RCTs may not be possible due to length of time (years) required to accrue patients to the trial and the expense and time needed to build the infrastructure required to run such a trial with broadly dispersed participating centers that may or may not be able to contribute a single patient. RCT in such patient populations also require substantial differences between the arms to be practical, hence incremental improvements which are clinically meaningful may be impossible to evaluate.

The report by Hueso et al also serves to remind us of how little we understand about which parts of the host immune response to SARS-CoV-2 are most important for clinical recovery. While passive transfer of antibody to patients unable to make antibody is a logical strategy, the value of antibody infusion to patients with normal immune systems may be placing undue emphasis on humoral immunity. This is especially true in light of the fact that for many viruses which cause infection in humans (e.g., EBV, HCV, HIV, Adenovirus, Enterovirus, Zika virus) antibodies serve as a useful diagnostic marker of disease but antibody formation does not drive recovery. In patients infected with SARS-CoV-2, it is likely that a coordinated host immune response is key to recovery (see Figure). This is an important concept because, should CCP infusions prove to be of no substantial benefit for immunocompetent patients, such a finding would not preclude efficacy from vaccination as a prevention strategy given that vaccination is expected to trigger both cellular and humoral responses.

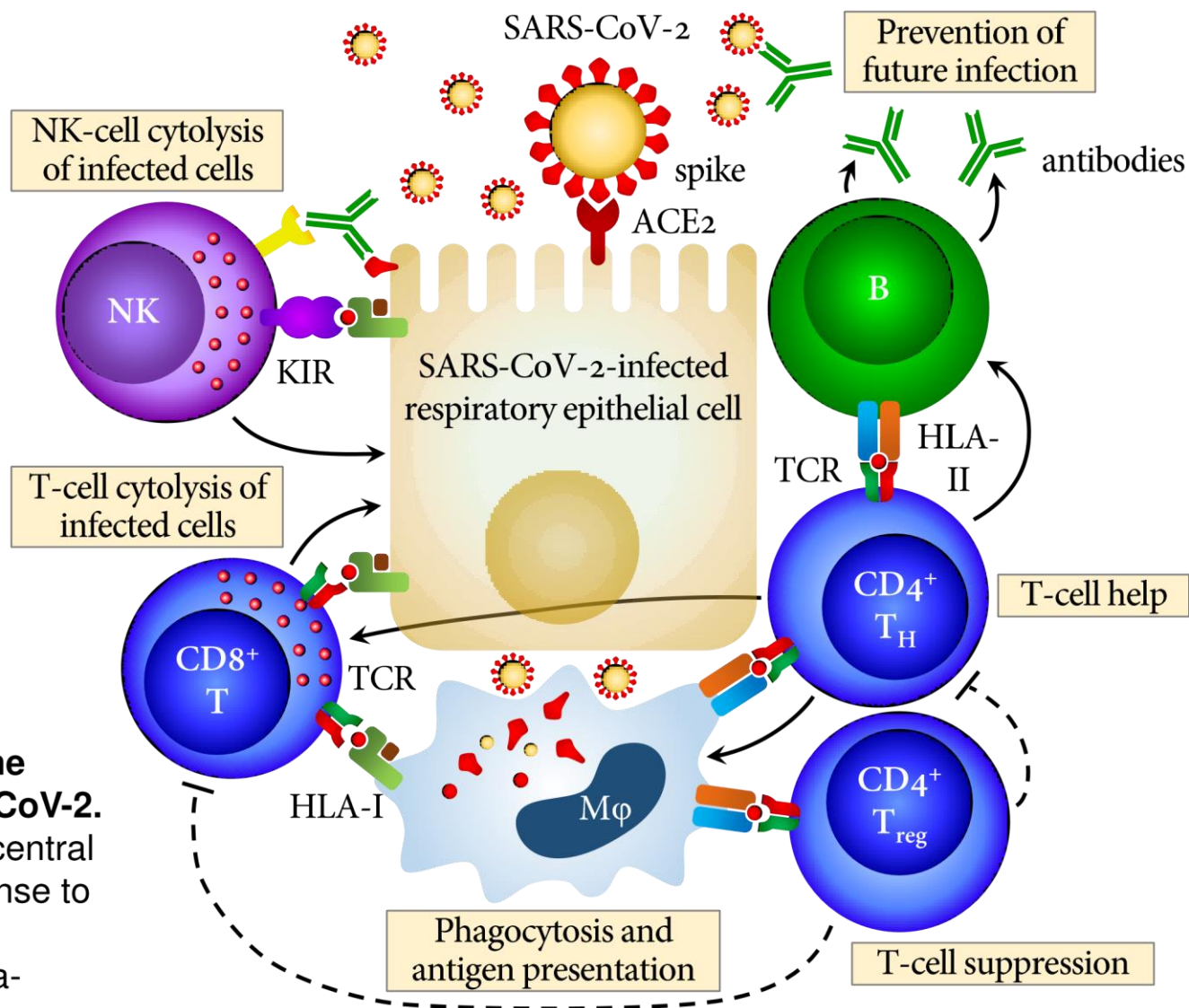
All trials must be interpreted with an understanding of the limitations of the trial design. Non-randomized studies in any patient population may misinterpret the findings of the study. With no group generated by randomization available for '*between group*' comparisons, these studies may resort to '*within group*' comparisons with the potential for misleading conclusions. A striking example is the recent report which claimed that COVID-19 patients treated earlier with CCP had improved outcomes compared with those treated later in the course of their disease.⁷ When studying infectious

diseases, any intervention (even one with no effect) will appear to have better results when applied early compared with later because the cohort of early patients has, by definition, a higher proportion of individuals who are destined to quickly recover (even with no treatment) compared with the cohort of patients with more refractory late-stage disease. A second obvious problem with studies that lack randomized control groups is that the study cohort receives other treatments in addition to the treatment of interest. It becomes very difficult, if not impossible, to attribute any outcome (good or bad) to the treatment of interest. Finally, as has been known for more than a century, clinical outcomes depend on multiple risk factors. Randomization balances the two study groups for other factors (both known and unknown) which may influence the outcome. Observational studies lacking randomization risk allowing confounding factors to be misattributed to the intervention of interest resulting in an over-estimate of its effect. This is why RCTs are the gold standard and are important to advance knowledge of therapies to combat COVID-19 and other diseases. A recent statement from the National Institutes of Health underscored that CCP is not the standard of care for patients with COVID-19 and that well powered RCTs are needed to determine whether CCP is an effective treatment.⁸ But when RCTs are not feasible, phase II trials such as the one presented here do suggest, but not prove, that administration of convalescent plasma may be a useful approach for the treatment of patients whose immune systems have been compromised by both an underlying disease and anti-CD20 monoclonal antibody therapy.

References

1. Hueso T, Pouderoux C, Pere H, Beaumont A-L, Raillon L-A, Chatenoud L, et al. Convalescent plasma for B-cell depleted patients with protracted COVID-19 disease. *Blood* 2020; xx, xxx-xxx.
2. Streptomycin in Tuberculosis Trials Committee (1948). [Streptomycin treatment of pulmonary tuberculosis. A Medical Research Council investigation. Br Med J 2 \(4582\): 769– 82. doi:10.1136/bmj.2.4582.769. PMC 2091872. PMID 18890300.](https://doi.org/10.1136/bmj.2.4582.769)
3. Brown D. Landmark study made research resistant to bias. [Washington Post](https://www.washingtonpost.com/archive/politics/1998/11/02/landmark-study-made-research-resistant-to-bias/2f9685fd-5369-44d1-9aa7-b13fb7018833/). November 2, 1998. <https://www.washingtonpost.com/archive/politics/1998/11/02/landmark-study-made-research-resistant-to-bias/2f9685fd-5369-44d1-9aa7-b13fb7018833/>
4. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. (2020). Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. *JAMA*, 324(5), 1–11. <https://doi.org/10.1001/jama.2020.10044>
5. Gharbharan A, Jordans CCE, Geurtsvankessel C, den Hollander JG, Karim F, Mollema FPM, et al. Convalescent Plasma for COVID-19. A randomized clinical trial. *medRxiv* 2020.07.01.20139857. <https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1> doi: <https://doi.org/10.1101/2020.07.01.20139857>
6. Avendano-Sola C, Ramos-Martinez A, Munoz-Rubio E, Ruiz-Antoran B, Malo de Molina R, Torres F, et al. Convalescent Plasma for COVID-19: A multicenter, randomized clinical trial. *medRxiv* 2020.08.26.20182444 doi: <https://doi.org/10.1101/2020.08.26.20182444>
7. Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel PS, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. *medRxiv*. 2020;2020.08.12.20169359. Published 2020 Aug 12. doi:10.1101/2020.08.12.20169359

8. National Institutes of Health. The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Convalescent Plasma for the Treatment of COVID-19.
<https://www.covid19treatmentguidelines.nih.gov/statement-on-convalescent-plasma-eua/>
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Coordinated immune response to SARS-CoV-2. Cellular immunity is central to the immune response to SARS-CoV-2. Figure courtesy of W. Garcia-Beltran, MD, PhD