

Comment on Hueso et al, page 2290

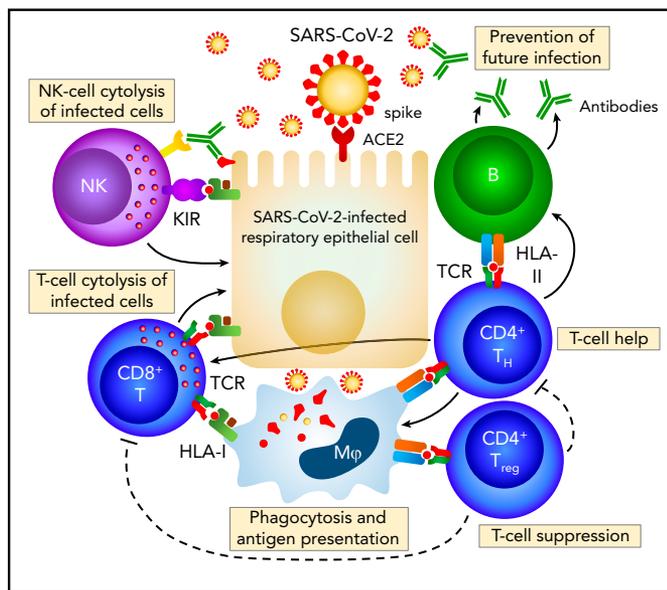
COVID-19, plasma, and hypogammaglobulinemia

Michael F. Murphy^{1,2} and Sunny Dzik³ | ¹NHS Blood & Transplant; ²National Institute for Health Research Oxford Biomedical Research Centre; ³Massachusetts General Hospital

In this issue of *Blood*, Hueso et al¹ report a study of COVID-19 convalescent plasma (CCP) in patients with COVID-19 and negative severe acute respiratory syndrome coronavirus 2 (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 CCP 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-cell 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. 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 of 9 patients tested. Although the data in the Hueso et al study appear to be promising in terms of clinical response and improvement in some laboratory markers, limitations of their study include that the



Coordinated immune response to SARS-CoV-2. Cellular immunity is central to the immune response to SARS-CoV-2. ACE2, angiotensin converting enzyme 2; KIR, killer cell immunoglobulin-like receptor; NK, natural killer; TCR, T-cell receptor; Treg, regulatory T cell. Figure courtesy of W. Garcia-Beltran.

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.

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 1 published peer-reviewed randomized controlled trial (RCT).² Two additional RCTs were released prior to peer review.^{3,4} All 3 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; $P = .40$).³ This finding raised concerns about the potential benefit of CCP, and the study was discontinued. It is worth pointing out that the study population in the Hueso et al study is very different with negative SARS-CoV-2 serology, B-cell lymphopenia, and hypogammaglobulinemia.

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 because of 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. RCTs in such patient populations also require substantial differences between the arms to be practical; hence, incremental improvements that 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. Although passive transfer of antibody to patients unable to make 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 that cause infection in humans (eg, Epstein-Barr virus, hepatitis C virus, 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. Nonrandomized 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 that claimed that COVID-19 patients treated earlier with CCP had improved outcomes compared with those treated later in the course of their disease.⁵ 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,^{6,7} clinical outcomes depend on multiple risk factors. Randomization balances the 2 study groups for other factors (both known and unknown) that may influence the outcome. Observational studies lacking randomization risk allow confounding factors to be misattributed to the intervention of interest, resulting in an overestimate of its effect. Therefore, 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 However, when RCTs are not feasible, phase 2 trials, such as the one presented here, do suggest, but not prove, that administration of CCP 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.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

REFERENCES

- Hueso T, Poudroux C, Péré H, et al. Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19 disease. *Blood*. 2020;136(20):2290-2295.
- Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial [published correction appears in *JAMA*. 2020; 324(5):519]. *JAMA*. 2020;324(5):460-470.
- Gharbharan A, Jordans CCE, Geurtsvankessel C, et al Convalescent plasma for COVID-19. A randomized clinical trial [published online

ahead of print 3 July 2020]. *medRxiv*. doi: 10.1101/2020.07.01.20139857.

- Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E, et al Convalescent plasma for COVID-19: a multicenter, randomized clinical trial [published online ahead of print 1 September 2020]. *medRxiv*. doi:10.1101/2020.08.26.20182444.
- Joyner MJ, Senefeld JW, Klassen SA, et al Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience [published online ahead of print 12 August 2020]. *medRxiv*. doi:10.1101/2020.08.12.20169359.
- Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment of pulmonary tuberculosis. *BMJ*. 1948;2(4582):769-782.
- Brown D. Landmark study made research resistant to bias. *Washington Post*. November 2, 1998. <https://www.washingtonpost.com/archive/politics/1998/11/02/landmark-study-made-research-resistant-to-bias/2f9685fd-5369-44d1-9aa7-b13fb7018833/>. Accessed 28 September 2020.
- 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/>. Accessed 28 September 2020.

DOI 10.1182/blood.2020008963

© 2020 by The American Society of Hematology

LYMPHOID NEOPLASIA

Comment on Ogiya et al, page 2334

We need CD38 STAT-JAK

Benjamin G. Barwick and Sagar Lonial | Emory University

In this issue of *Blood*, Ogiya et al show that multiple myeloma CD38 expression is inhibited by the bone marrow microenvironment, in particular interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) signaling, resulting in less effective targeting by monoclonal antibodies.¹

Monoclonal antibodies have changed the treatment landscape in multiple myeloma by adding a third “backbone” to the standard treatment approaches, resulting in deeper and more durable responses than those achieved with steroids, alkylators, proteasome inhibitors, or immunomodulatory agents. Daratumumab and isatuximab target CD38, an adenosine 5'-diphosphateribose hydrolase that regulates calcium signaling. CD38 is expressed at high levels on myeloma cells but is also expressed on T cells, B cells, and natural killer cells. While targeting CD38 clearly improves patient outcomes, monotherapy in refractory

disease has limited efficacy.² It has also been demonstrated that CD38 expression is linked to the degree of antibody-dependent cellular cytotoxicity (ADCC).³ Here, Ogiya et al show how the microenvironment can regulate CD38 expression which potentially impacts the therapeutic efficacy of this target.¹ Using a focused panel of cytokines, they identify the culprit as IL-6, a cytokine that promotes plasma cell differentiation, myeloma cell growth, and drug resistance.⁴ They also found that interferon-β (IFN-β) and IFN-γ increase CD38 expression, consistent with previous reports.⁵