

## Convalescent Plasma for Covid-19 — Making Sense of the Inconsistencies

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Before the Covid-19 pandemic, the use of passive immunotherapy in patients with severe respiratory viral infections was thought to be beneficial, but the evidence was limited. We now know that the use of passive immunotherapy (monoclonal antibodies or convalescent plasma) in an unselected hospitalized population with Covid-19 is not beneficial.<sup>1,2</sup> However, monoclonal-antibody therapy (casirivimab and imdevimab, administered together) has been shown to be beneficial in patients who have not yet had an antibody response.<sup>1,3</sup> A similar, albeit nonsignificant, signal was observed with the use of convalescent plasma in a subgroup of patients with immunocompromise in the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP).<sup>4</sup> A trial conducted by Libster et al.<sup>5</sup> involving 160 patients raised the possibility that early high-titer plasma therapy might be beneficial, but the trial was not sufficiently powered to detect a between-group difference in the incidence of death from any cause.

In this issue of the *Journal*, Sullivan et al.<sup>6</sup> report on a large trial involving 1181 outpatients who received either convalescent plasma or control plasma. In this well-conducted double-blind, randomized, controlled trial, adults with SARS-CoV-2 infection were assigned to receive convalescent plasma or control plasma within 9 days after the onset of symptoms, regardless of their vaccination status or their risk factors for progression of Covid-19. The primary outcome was Covid-19–related hospitalization within 28 days after transfusion; this outcome occurred in 17 of 592 participants (2.9%) who received convalescent plasma and in 37 of 589 participants (6.3%) who received control plasma (absolute risk reduction, 3.4 percentage points). The effectiveness of this treatment in vaccinated persons (149 participants) could not be assessed because none of the fully vaccinated participants were hospitalized. The participants were much younger than those in the trial by Libster et al.<sup>5</sup> Only

6.8% of the participants were 65 years of age or older, and only three deaths occurred during the trial, so the effectiveness of convalescent plasma at reducing the incidence of death from any cause could not be assessed.

How do we make sense of the continued lack of certainty regarding the effectiveness of convalescent plasma, despite numerous randomized trials with a low risk of bias that have involved more than 21,000 patients? First, what do we know about the role of passive immunity? Monoclonal-antibody therapy, which has an antibody content that is markedly higher than that in convalescent plasma, improves patient outcomes when administered to outpatients early in the course of Covid-19 or to those without an antibody response,<sup>1,3</sup> although there is concern regarding loss of efficacy because of viral evolution and transmission of resistant variants.<sup>7</sup> High-titer convalescent plasma that is obtained from donors after natural infection does not have benefit in unselected patients who present to the emergency department or in those who are admitted to the hospital.<sup>2</sup> Sullivan et al. also found that fully vaccinated patients appeared to have a minimal benefit from convalescent plasma. Our collective hard work in evaluating passive immunity in patients with Covid-19 is providing dividends.

The trials by Libster et al.<sup>5</sup> and Sullivan et al. raise the possibility that there may be a role for the use of convalescent plasma in outpatients before they present to the emergency department. However, caution is warranted regarding the adoption of convalescent plasma as standard of care for outpatients, because two other large trials — CoV-Early (Early Convalescent Plasma Therapy for High-Risk Patients with COVID-19 in Primary Care) and CONV-ERT (Plasma for Early Treatment in Non-hospitalised Mild or Moderate COVID-19 Patients)<sup>8,9</sup> — did not detect the same efficacy signal. The population in the trial conducted by Sullivan et al. was younger and healthier than that in other trials of conva-

lescent plasma, and this population may warrant further study. This was also a plasma-controlled trial — not a placebo-controlled trial — and the control plasma may have had its own unique biologic effects. In persons with Covid-19, the immunologic effect of control plasma that contains antibodies to non-SARS-CoV-2 coronavirus (common cold) strains is not clear; severe disease is more likely to develop in health care workers with higher levels of such antibodies than in those with lower levels.<sup>10</sup>

Two ongoing trials may provide additional clarity regarding the use of convalescent plasma in patients with Covid-19. The COVIC-19 trial (Early High-Titre Convalescent Plasma in Clinically Vulnerable Individuals with Mild COVID-19; ClinicalTrials.gov number, NCT05271929) plans to enroll 680 outpatients in two target groups (participants who are  $\geq 70$  years of age or who are  $< 70$  years of age with coexisting conditions, and participants with immunocompromise). In the immunoglobulin domain of the REMAP-CAP trial (NCT02735707), the investigators plan to enroll hospitalized patients with immunocompromise.

It is unclear whether narrowing the dose gap between convalescent plasma and monoclonal-antibody therapy will lead to a consistent efficacy signal, particularly if these agents are used in outpatients or persons with immunocompromise. This narrowing of the dose gap can be achieved by recruiting vaccinated donors and increasing the qualifying antibody titer; both the COVIC-19 and REMAP-CAP trials plan to evaluate such “higher-titer” plasma (approximately 500 ml of plasma with a titer  $\geq 1:640$ ). Theoretically, contemporaneous convalescent plasma (either with antibodies against current circulating variants or with the use of vaccines) may also be less prone to viral evolutionary immune escape than monoclonal-antibody therapy.

We owe it to blood donors, blood centers, taxpayers, and our patients not to deploy unproven therapies until a consistent efficacy signal is observed. In the future, a prepandemic plan will be needed to ensure that we work col-

laboratively across countries to test the efficacy of convalescent plasma quickly and in a coordinated fashion during pandemics. It would be unfortunate if we came to the end of this pandemic and still lacked clarity on the efficacy of convalescent plasma and appropriate donor selection.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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