

## Further Comments on the RECOVERY trial of Convalescent Plasma

### Introduction

On January 15, 2021, The RECOVERY randomized clinical trial (RCT) of COVID-19 convalescent plasma (CCP) was first made public via a news release. Data in this news release were viewed as sufficiently important for their use in a meta-analysis summarizing RCT findings on CCP published in JAMA on March 23, 2021 (1). Inasmuch as RECOVERY was several-fold larger than the next largest CCP trial, these unpublished, not peer-reviewed data, known to the authors of the JAMA review only from a news release and a trial protocol, dominated the meta-analysis.

On March 10, 2021, the RECOVERY trial report appeared on the medRxiv pre-print server (2) and contained several details that differed from the news release. Most notably, 11% more participants and 50% more trial deaths were reported, along with a supplement showing several early treatment sub-groups with favorable CCP outcomes that approached, and in one case, exceeded, the threshold of statistical significance.

On March 10, 2021, members of the CCPP-19 leadership team wrote to Drs. Horby and Landray, leaders of the RECOVERY trial, asking for clarification of the above points. That letter is posted on this website (ccpp19.org). We received no answer. On May 21, 2021, the RECOVERY paper was published in Lancet (3).

The RECOVERY RCT was carried out in the United Kingdom from May 28, 2020, to January 15, 2021 (3). 5,795 participants were allocated to receive CCP and 5,763 to usual care, and the trial found no overall effect of CCP on mortality. The large size of the RECOVERY trial, the media coverage of the news release and the use of the news release data in a JAMA meta-analysis (1) made RECOVERY highly influential in leading guideline committees and clinicians to conclude that CCP treatment was ineffective for COVID-19. It is reasonable to assume that the RECOVERY findings contributed to the 75% decline in CCP use in the US (from 40% of all hospitalized patients to 10%) from September-October 2020 to March 2021, a decline that we found to be strongly associated with rise in COVID-19 hospital fatality rates (4).

### Trial Issues of Concern

Quality control. The RECOVERY trial design was open label, meaning that the treatment was not blinded to either participant or treating physician. Taking place in 177 National Health Service Hospitals, the average hospital treated just 33 participants with CCP. With so many centers, and so few patients per center, there has to be a concern, especially in an open-label trial, that the same standards of care, level of quality control, protocol oversight, and procedural consistency may not have been possible across all study sites amid the catastrophic conditions of the pandemic.

Administrative difficulties in the trial are seen in the following:

1. Nine percent of participants assigned to the CCP arm received no plasma, while a few control participants received plasma (see below)
2. Some 2% of participant forms were not returned to the study center. (Webtable 3, page 53 of supplementary materials).

3. The fraction of participants whose antibodies were not tested at baseline, as noted in the paper, was twice as high in the control group as in the CCP group (22.4% vs 12.1%). That a key test differed so greatly between the CCP group and the control group *at baseline* suggests differential treatment of the two groups, and failure of study equipoise.

Late usage. CCP is a time-dependent therapy that is most effective when infused in the early viral replication phase of COVID-19. In RECOVERY, the median time from symptom onset to *randomization* was 9 days, which is late enough, but further delay resulted from the time required to ascertain blood type, obtain and transfuse type-matched CCP (2). This likely added a day more on average to the delay from symptom onset to treatment. We are only told that 96% of patients had CCP *issued* (not necessarily received and infused) within 36 h of randomization. Promptness of treatment, in relation to symptom onset, had a clear effect on CCP efficacy. In patients randomized within 4 days of symptom onset, mortality was 9% less in the CCP arm; 5-7 days – 7% less; 8-11 days, 5% more; and those treated 12 days or more from symptoms, there were 7% more deaths in the CCP arm (2). RECOVERY tested CCP at a time in the disease course in which a benefit was unlikely based on biological plausibility and ample historical data showing that convalescent sera/plasma efficacy is dependent upon use early in disease (2).

Severity of disease. The active ingredient in CCP is specific antibody to SARS-CoV-2 which, based on *in vitro* data and animal models, presumably reflects its antiviral mechanism of action. Most individuals enrolled in RECOVERY were very ill (overall mortality was over 24%) and were likely, after 10 days of symptoms on average, to have progressed from the viral to the inflammatory phase of disease. Supplemental oxygen, including noninvasive oxygen supplementation, was provided to 87% of participants and 5% required mechanical ventilation. The fact that so many patients were receiving supplemental oxygen is consistent with the presence of pulmonary inflammation sufficient to compromise gas exchange. Antiviral antibodies are unlikely to reverse such inflammation.

Nearly all (92%) of RECOVERY participants were treated with steroids, another indication of most patients being in the inflammatory phase of their illness. Notably, amongst those who did not receive steroids, allocation to the plasma group was associated with fewer deaths at 28 days: 74/391 (19%) vs. 100/413 (24%). While this difference did not reach statistical significance (RR 0.78; 0.58–1.05) it is a strong suggestion of efficacy. CCP recipients without antibody at baseline, another indicator of being in the viral phase of illness, were 10% less likely to die or become ventilated, and this result was statistically significant.

All four subgroup analyses that address early or milder disease (treated within 4 days of symptom onset, no oxygen requirement, not receiving corticosteroids, and lacking endogenous SARS-CoV-2 antibodies) are consistent with the hypothesis that patients in an earlier and less severe phase of disease benefited from the intervention. No analysis has been provided of *combinations* of patients in these four categories. Such an analysis might define a group of patients with early COVID-19 who can clearly benefit from CCP.

Data analysis. It is unclear why individuals in the CCP group who did not receive plasma and individuals in the usual care group who received plasma were included in the final analysis. Importantly, a substantial number of 5,795 participants (494 or 9%), allocated to the plasma group and analyzed as having received plasma, received no units of CCP. An additional 17 (<1%) of the 5763 patients in the control group did receive convalescent plasma. Although we recognize that this analysis represents adherence to the intention to treat protocol, it would have

been useful to see the findings with the untreated participants excluded, especially in the several subgroups noted above that showed trends towards CCP efficacy but that were short of statistical significance at the 0.05 level. Re-analysis of the data in these subgroups would help to appropriately contextualize the results of RECOVERY among all CCP trials and shed additional light on the ideal timing for initiation of high titer CCP.

### **CCPP19 Leadership Comments.**

Passive immunotherapy such as high titer CCP (or monoclonal antibodies) is effective when treatment occurs early in an infectious disease. When used in patients with early phases of COVID-19, high titer CCP has been shown to be beneficial. Multiple randomized, controlled studies have now demonstrated that high titer CCP can substantially reduce the risk of COVID-19 progression if initiated before patients are ill enough to require corticosteroids for and/or develop inflammatory complications (5-7). Other studies have shown that CCP initiation early in hospitalization can be protective (8, 9). An analysis of 3082 COVID-19 hospitalized patients who received CCP through an emergency access protocol found that, among those not receiving mechanical ventilation, transfusion of plasma with higher anti-SARS-CoV-2 IgG antibody levels was associated with lower mortality (10). The RECOVERY trial, on the other hand, which was a randomized, controlled, open-label study comparing high titer CCP with usual care found that CCP did not reduce 28-day mortality, probability of discharge within 28 days, or probability of progressing to the composite outcome of invasive mechanical ventilation or death in patients not receiving invasive mechanical ventilation at randomization. Although we agree that the overall result of RECOVERY revealed no effect of CCP, and the primary cause of the negative result was likely to have been late administration of CCP, concerns about the trial design and data analysis make us question the definitiveness of their conclusions. Instead, we note the trends for CCP efficacy among patients who received CCP early in their disease course that suggest CCP effectiveness in early disease. That these trends are consistent with both more recent studies of CCP use and the biological principles of antibody action (11) in an otherwise negative study underscores their plausibility.

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