EDITORIAL

A Randomized Trial of Convalescent Plasma for COVID-19—Potentially Hopeful Signals

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Convalescent plasma for the treatment of infectious diseases has been used since the early 20th century and was associated with reduced mortality during the 1918 influenza,[1] 2003 SARS,[2] and 2009 influenza H1N1[3] pandemics. However, most published studies of these diseases were case series and retrospective comparisons of treated and nontreated individuals. Consistent with this, several uncontrolled case series of convalescent plasma use in patients with coronavirus disease (2019) COVID-19 have suggested a possible benefit.[4-6] Given encouraging historical precedents and the absence of proven SARS-CoV-2 (severe acute respiratory disease coronavirus 2) antiviral therapies, convalescent plasma therapy has been proposed as a treatment option for COVID-19.[7] The availability of clinical information generated from randomized clinical trials is therefore of substantial importance given that the world remains in the grip of the COVID-19 epidemic and convalescent plasma is currently in use in many countries, including the US.

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In their article in *JAMA*, Li et al[8] present findings from the first randomized clinical trial of convalescent plasma therapy for patients with COVID-19 conducted in China. In contrast to most other reports of convalescent plasma use in past epidemics, this study is noteworthy in that it used a randomized trial design and well-characterized plasma units with a high titer of antibody to SARS-CoV-2. It was an important accomplishment to conduct a carefully controlled trial during a pandemic with an entirely new highly contagious disease that stressed health systems in an unprecedented way.

However, the authors report that because the COVID-19 outbreak in China was being contained while the trial was ongoing and new cases were unavailable for enrollment, the trial was terminated before it reached its targeted original sample size of 200 patients; only 103 were enrolled (for whom randomization was stratified by disease severity). Consequently, the study was underpowered and many comparisons between the convalescent plasma group and the control group were not statistically significant.

In the primary analysis, based on 52 patients who were randomized to receive convalescent plasma in addition to standard treatment and 51 patients who were randomized to receive standard treatment alone (control), the primary outcome of time to clinical improvement within 28 days (defined as being discharged alive or having a reduction of 2 points on a 6-point disease severity scale) was 2.15 days shorter (95% CI, −5.28 to 0.99 days) in the intervention group compared with the control group, and clinical improvement at 28 days occurred in 27 patients (51.9%) in the intervention group vs 22 patients (43.1%) in the control group (difference, 8.8%; 95% CI, −10.4% to 28%; hazard ratio, 1.40 [95% CI, 0.79-2.49]; $P = .26$).

In analyses stratified by disease severity, among patients with severe disease (23 in the convalescent plasma group and 22 in the control group), time to clinical improvement within 28 days was 4.94 days shorter (95% CI, −9.33 to −0.54 days) in the intervention group compared with the control group, and clinical improvement at 28 days occurred in 21 patients (91.3%) in the intervention group vs 15 patients (68.2%) in the control group (hazard ratio, 2.15 [95% CI, 1.07-4.32]; $P = .03$). Among the subgroup of patients with life-threatening disease (29 in the convalescent plasma group and 29 in the control group), there were no significant differences in the primary outcome or rates of clinical improvement at 28 days: 6 patients (20.7%) in the convalescent plasma group vs 7 patients (24.1%) in the control group (HR, 0.88 [95% CI, 0.30-2.63]; $P = .83$) (P for interaction = .17).

In the entire study population, the findings for several of the secondary end points appeared to signal a more favorable outcome for patients who received convalescent plasma, although there were no statistically significant differences between the convalescent plasma group vs the control group in any of the major secondary outcomes, including 28-day mortality (15.7% vs 24.0%, respectively; $P = .30$) or rate of discharge at 28 days (51% vs 36%; $P = .13$).

Convalescent plasma use in the study by Li et al[8] was associated with some clinical improvement in severely ill patients, but not in critically ill patients. Greater efficacy in less ill individuals is expected because antibody therapies generally work best when administered earlier in disease.[9] Historically, antibody therapy was effective in reducing the mortality of pneumococcal pneumonia when instituted in the first 3 days of symptom onset.[10] Consequently, it is not surprising that patients with COVID-19 who had tachypnea and hypoxia might benefit more from convalescent plasma than those who required mechanical ventilation. However, any indication of possible benefit in the severely ill group is noteworthy because these individuals had advanced disease, which is not considered optimal for antibody therapy. Lack of efficacy among patients who were receiving mechanical ventilation, some with multiorgan failure, highlights that the pathologic process in these individuals is likely irreversible.

The convalescent plasma used in the study by Li et al had high titers of IgG to SARS-CoV-2, which correlated with neutralizing activity. While neutralizing activity is considered to be the main determinant of convalescent plasma efficacy,

other antibody functions may also mediate protection. Correlates of antibody efficacy should be investigated in future studies. As reported in case series from Wuhan,[4,5] plasma-treated patients had large reductions in their serum viral loads and most were virus negative 3 days after infusion. This observation establishes that convalescent plasma has antiviral activity, which is important because it indicates that antibody administration mediates a clear biological effect. The precedent of antiviral drug use against HIV and hepatitis C shows that reductions in viral load translate into clinical improvement, and earlier therapy is more effective than later therapy when organ damage is already present. In this regard, antibody-mediated viral elimination removes damaging antigens, which may translate into reduced tissue damage and inflammation. Hence, the antiviral effect of COVID-19 convalescent plasma suggests that its use earlier in the course of disease could have potentially important therapeutic activity, especially in less severely ill individuals.

Significant concerns have been raised about the use of convalescent plasma in COVID-19.[11] These include transfusion-related lung injury and transfusion-related circulatory overload. In addition, there have been theoretical concerns that the administration of antibodies might aggravate disease through antibody-mediated enhancement of proinflammatory effects.[11] The study by Li et al[8] reported only 2 adverse events among the 52 individuals who received convalescent plasma, each of whom responded to corticosteroid administration. The occurrence of one episode within 2 hours of plasma administration characterized by chills and rash suggests a transfusion reaction. However, the second episode occurred within 6 hours and its association with plasma infusion is less certain. Overall, the paucity of adverse effects is reassuring and reduces concerns about adverse effects from antibody administration.

Although the observed differences in mortality rates and hospital discharge rates between the convalescent plasma group and the control group did not reach statistical significance, these data provide valuable information for the magnitude of effects that may be expected in convalescent plasma studies. For example, the observed overall mortality difference of 24% vs 15.7% provides actionable information for the design of future trials to help ensure they are adequately powered. This difference in mortality is smaller than mortality reductions associated with convalescent plasma reported in prior studies involving 1918 influenza,[1] SARS,[2] and 2009 influenza H1N1,[3] which ranged from 50% to 70%. Hence, assuming the results of the study by Li et al[8] are generalizable, the findings may be helpful in estimating effect sizes for future studies of convalescent plasma use in hospitalized patients with COVID-19.

In the study by Li et al, the median age of the patients with severe disease was 70 years, and the median time between symptom onset and randomization was 30 days. Promising results with convalescent plasma treatment in patients with SARS[2] and influenza H1N1[3] were obtained among younger patients, and in the case of SARS, earlier in the disease. The importance of a possible treatment benefit in older persons, in whom mortality from COVID-19 is markedly higher than in younger persons,[12] cannot be overstated. In addition, the apparent improvement in the clinical status of the subgroup of less severely ill patients a month after the onset of symptoms suggests that the beneficial effects of antibodies in COVID-19 may be measurable as an improvement in inflammatory markers and viral elimination before clinical improvement is observed. The prolonged course of COVID-19 in patients who recover also should be considered in the design of future studies.

However, the study by Li et al has several important limitations, which are acknowledged by the investigators. The early termination of the trial most likely resulted in an underpowered study, thereby precluding any definitive conclusions about the role and potential efficacy of convalescent plasma for patients with COVID-19. In addition, the open-label design, the possibility of an element of subjectivity for the primary outcome, lack of a protocolized approach to standard therapy, and variability among study centers also must be considered when interpreting the study findings. Despite these limitations, by virtue of its randomized design, this study takes prior case studies[5,6] one step further by helping to separate the effects of convalescent plasma from concurrently administered agents, such as corticosteroids and antiviral agents.[13]

The signal of potential benefit of convalescent plasma in the subgroup of patients with severe COVID-19 disease (ie, those without life-threatening COVID-19 disease) is similar to findings from a recent preliminary report of a clinical trial of remdesivir for COVID-19.[14] Like remdesivir, convalescent plasma administration was associated with clinical improvement without a statistically significant effect on mortality, with the important caveat that remdesivir was evaluated in a larger study (n = 1063 randomized patients), whereas the study by Li et al[8] was terminated prematurely and underpowered. For both studies, the importance of clinical improvement as a primary end point became apparent as the trials progressed.[14]

The availability of both convalescent plasma and remdesivir means that physicians now have at least 2 therapeutic options for COVID-19, which raises the question of combination therapy. Despite only a few studies of the efficacy of combination therapy with antiviral drugs and specific antibodies, there is evidence that these agents may work well in combination.[9] Given that the mechanisms of action of antiviral drugs and neutralizing antibodies are distinct, they could be synergistic. Future trials should consider the efficacy of combination antiviral and antibody therapies.

In summary, the first randomized clinical trial of convalescent plasma in COVID-19, reported by Li et al in *JAMA*, showed no statistically significant benefit in clinical improvement at 28 days or mortality among all randomized patients, but does provide an important signal of possible benefit in the subgroup of severely ill patients and suggests that high titer antibody against SARS-CoV-2 may have antiviral efficacy. These results, while preliminary and subject to important study limitations, should stimulate more clinical trials to establish the optimal conditions for antibody therapies against COVID-19 and suggest that future studies

should focus on determining efficacy in less severely ill patients. If the efficacy of convalescent plasma is established by future studies, the ratio of donor to patients is favorable because individuals who recover from COVID-19 can donate 2 or 3 units of plasma, which could be used to treat more than 1 person with COVID-19 disease. Therapeutic success against such a complex and challenging disease as COVID-19 is likely to require more than 1 modality, and the results from Li et al[8] provide optimism for the future of antibody therapy in this disease.

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