Study shows no significant benefit of convalescent plasma for COVID-19 outpatients with early symptoms

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The final results of the Clinical Trial of COVID-19 Convalescent Plasma in Outpatients (C3PO) demonstrate that COVID-19 convalescent plasma did not prevent disease progression in a high-risk group of outpatients with COVID-19, when administered within the first week of their symptoms. The trial was stopped in February 2021 due to lack of efficacy based on a planned interim analysis. The formal conclusions from the trial, which was funded primarily by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, and by the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services, appear in the current online issue of The New England Journal of Medicine.

"We were hoping that the use of COVID-19 convalescent plasma would achieve at least a 10% reduction in disease progression in this group, but instead the reduction we observed was less than 2%," said Clifton Callaway, M.D., Ph.D., the contact principal investigator for the C3PO trial and professor of emergency medicine at the University of Pittsburgh. "That was surprising to us. As physicians, we wanted this to make a big difference in reducing severe illness and it did not."

COVID-19 convalescent plasma, also known as "survivor's plasma," is blood plasma derived from patients who have recovered from COVID-19. Last year, the U.S. Food and Drug Administration issued an Emergency Use Authorization to allow use of convalescent plasma in hospitalized patients with COVID-19. Researchers wanted to know whether administering COVID-19 convalescent plasma might also be beneficial in persons who were recently infected with SARS-CoV-2, the virus that causes the disease, but who were not severely ill and could be treated as outpatients. The objective was to prevent progression to severe COVID-19 illness.

The C3PO trial, launched in August 2020, was designed to answer that question. The randomized, controlled clinical trial involved adult outpatients who presented to emergency departments with mild COVID-19 symptoms during their first week post-infection. The trial was conducted by the SIREN clinical trials network, and enrolled more than 500 participants from 48 emergency departments across the United States. The participants were racially and ethnically diverse with a median age of 54 years, and slightly more than half were women. Participants also had at least one risk factor for progression to severe COVID-19, such as obesity, hypertension, diabetes, heart disease, or chronic lung disease. The researchers randomly assigned the participants to receive treatment with either high-titer COVID-19 convalescent plasma (containing anti-COVID-19 antibodies) or placebo (salt solution infused with multivitamins and lacking antibodies).
Researchers compared outcomes in both groups within 15 days of treatment, looking specifically at whether the patients needed to seek further emergency or urgent care, were admitted to the hospital, or died. The researchers found no significant difference in disease progression between the two groups. Of the 511 participants, disease progression occurred in 77 (30%) in the COVID-19 plasma group compared with 81 patients (31.9%) in the placebo group. The plasma intervention did not cause harm, the researchers found.

"The results show that convalescent plasma does not appear to benefit this particular group," said Nahed El Kassar, M.D., Ph.D., one of the study’s co-authors and medical officer in the Blood Epidemiology and Clinical Therapeutics branch of the NHLBI’s Division of Blood Diseases and Resources. "But the findings answer an important clinical question and may help bring researchers a step closer to finding more effective treatments against this devastating disease."

The reason the intervention did not produce the expected results is unclear, Callaway said. Researchers are continuing to look at possible explanations, including insufficient plasma dose, timing of plasma administration, host-related factors, or other aspects of the host tissue responses to the infection, he added.

Additional studies of COVID-19 convalescent plasma are ongoing or planned in different populations. These included the Pass It On trial, a nationwide, NIH-funded randomized clinical trial using convalescent plasma to treat hospitalized adult patients with COVID-19 infection to see if the treatment can help them recover faster. Other trials include one in outpatients who are recovering at home and one in individuals with high risk of exposure to COVID-19 to see if COVID-19 convalescent plasma can prevent infection.

"We need the results of these other convalescent plasma studies to get a clearer, more conclusive picture of its value for future treatments of COVID-19," said Simone Glynn, M.D., M.P.H., chief of the NHLBI’s Blood Epidemiology and Clinical Therapeutics branch, who is coordinating the trial.


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