Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Perspective

Controlled trials needed to prove efficacy and safety of convalescent plasma therapy in coronavirus disease 2019

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The novel coronavirus disease 2019 (COVID-19) emerged from Wuhan, People's Republic of China, in December 2019, and by March 2020, it was recognized as a global pandemic by the World Health Organization. The speed with which the disease has spread and its sizable case fatality have led to the clinical application of various therapies with at most minimal evidence of efficacy or safety. This is of renewed and persistent importance as the number of polymerase chain reaction–positive cases of COVID-19 continues to increase in much of the United States of America.

Use of convalescent plasma therapy for COVID-19 was initially reported in 5 patients in the People's Republic of China. Its use has grown rapidly to become a mainstay of COVID-19 therapy owing to the United States Food and Drug Administration (FDA) expanded access and single-arm expanded access coordinated through the Mayo Clinic with greater than 105,000 patients being treated before the program closure owing to the FDA approving emergency use authorization (EUA). As the pandemic continues, the efficacy of convalescent plasma therapy remains to be established and has been unconvincing at best in its previous use in Ebola, influenza, severe acute respiratory syndrome–associated coronavirus 1, or Middle East respiratory syndrome coronaviral infections.[1] Thus far, no placebo-controlled randomized controlled trial has revealed the efficacy of convalescent plasma in COVID-19. Despite this lack of evidence from a clinical trial, the FDA recently issued an EUA for convalescent plasma in COVID-19.

In the past 2 decades, the use of blood products in critically ill patients has been discouraged by multiple societies and guidelines owing to inferior outcomes. The risks of convalescent plasma therapy include but are not limited to transfusion-associated circulatory overload, transfusion-related acute lung injury, complement-mediated tissue damage, allergic reactions, and antibody-dependent enhancement of disease.[2] The very nature of transfusion-mediated injuries dictates that an "inflammatory first hit" be present, thus laying the foundation for virus-related pulmonary manifestations to serve that role. Therefore, the adverse effects could not only be amplified in COVID-19 infections but also go clinically unrecognized and be attributed to the natural course of the disease without the close monitoring afforded by randomized, placebo-controlled trials.[2] The safety data for the first 5000 patients infected with COVID-19 and treated with convalescent plasma have revealed 36 serious adverse events, including 7 cases of transfusion-associated circulatory overload, 11 cases of transfusion-related acute lung injury, 3 cases of severe allergic reactions, 15 total deaths, and 4 deaths judged to be secondary to plasma therapy.[3] In that article, the authors provide a somewhat lukewarm support, stating convalescent plasma provides no signal of toxicity beyond what is expected in plasma use in severely ill patients and the mortality rate does not seem excessive.[3] However, this statement is made without a control group to compare. Potential for unexpected harm from convalescent plasma was recently highlighted by the presence of neutralizing immunoglobulin G autoantibodies against interferon found in 10.2% of patients with life-threatening COVID-19 and were absent in patients with mild or asymptomatic COVID-19.[4] This adds to mounting evidence of a defective type I interferon response

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Table 1
Suggested Convalescent Plasma Trial Design

Possible trial arms • Placebo • Convalescent plasma infusion from donor with low titer • Convalescent plasma infusion from donor with high titer • Fresh frozen plasma infusion
Potential laboratory monitoring of patient, suggested before infusion and at multiple time points (before and after therapy) • COVID-19–specific IgG and IgM • Lymphocyte flow cytometry • Cytokine panel • Single-cell RNA sequencing • Radiographic improvement
Evaluate effectiveness of convalescent therapy based on pretherapy respiratory status/oxygen requirement • No supplemental oxygen • Nasal cannula oxygen supplementation • Noninvasive ventilation • Invasive ventilation
Evaluate effectiveness of convalescent therapy based on time since symptom onset and current active viral replication as evaluated by viral culture or PCR.

Abbreviations: COVID-19, coronavirus disease 2019; Ig, immunoglobulin; PCR, polymerase chain reaction.

contributing to severity of disease, and transfer of these autoantibodies from donor to critically ill patient by convalescent plasma presents distinct potential for worsening disease with this specific therapy. The presumption that the risk of convalescent plasma is low may not be true and remains to be proven in prospective trials.

To determine the efficacy of plasma therapy, we must understand the characteristics that predict a favorable response; this includes the optimal donor COVID-19 antibody titer level so that the dose, recipient outcome, and timing of infusion can be ascertained. Special consideration and attention should be given to patients with primary and secondary immunodeficiencies and potential benefit of convalescent plasma in these patients. A properly designed study should address the deficiency of data for convalescent plasma therapy. One such potential approach to further studying convalescent plasma therapy that could be considered is a 4-armed study that would include immunologic monitoring to collect data on effectiveness, mechanism of action, immunologic modulation, and risks (Table 1). In addition to lack of data on effectiveness, there is a paucity of data on dose-dependent response. Stratifying treatment groups by COVID-19–specific antibody level present in the plasma will allow us to tease out potential differences based on dose-dependent response. If effective, the ideal timing of administration of convalescent plasma is unknown, whether early in disease when viral replication is the highest or later in the disease during cytokine storm when we often found clinical decline but decreasing viral load. Answering the question of ideal timing of administration would require randomization of patients at various time points in disease progression. Furthermore, analyzing serial RNA sequencing will allow researchers to understand transcriptomic changes mediated by convalescent plasma treatment and tease out the patients who deteriorate owing to the transfusion from ones experiencing the impact of a severe COVID-19 infection. RNA sequencing has the advantage to ascertain unique and complex interplay between the host and virus, moving toward precision medicine.[5] Further advantage of RNA sequencing is the ability to get robust data with a smaller number of patients, allowing for quicker turnaround of actionable data in the midst of a pandemic. Moreover, comparing transcriptomic data with serial cytokine profiles and flow cytometry in the setting of a placebo-controlled randomized trial will allow detailed immunologic description of changes likely attributable to convalescent plasma therapy on a cellular level. Disadvantages of this approach could include cost, accessibility, and varying reference ranges across centers, but they could be overcome with centralized processing and analysis of samples.

We must not forget the scientific method, even when faced by a deadly pandemic. Offering therapies at such a broad level with minimal evidence has the distinct potential to mislead patients and cause harm. We strongly encourage well-designed studies to evaluate risk and benefit of therapies before large-scale, single-arm expanded access and EUA, especially now that there is evidence of harm with plasma therapy, without proven benefit.

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