COVID-19 convalescent plasma donor recruitment: beware the Faustian bargains

As novel coronavirus infections (COVID-19) spread across the United States in March 2020, the Food and Drug Administration (FDA) announced a patient-specific emergency Investigational New Drug (eIND) pathway for convalescent plasma (CP) as well as an expanded access program.[1,2] With no clearly effective alternative therapy and high mortality rates for patients requiring mechanical ventilation, there is obvious interest in the immediate use of CP.[3] This presents a number of ethical issues, since randomized trials have not proven that CP is effective or safe.[4]

Given an exponential growth of cases and deferral period after illness (currently 14 days) there certainly will be less CP available than potential recipients over the coming weeks to months. As a result, less CP will be available for the randomized, placebo-controlled trials and for making commercial hyperimmune globulin, both of which are needed to determine if, how much, and when during the illness passive antibody therapy is beneficial. As we prepare a centuries-old therapy, let us not forget the battlefield advice to "hold your fire until the enemy is within range" or the lesson of Faust: avoid trading the appearance of short-term power for inevitable suffering.

Second, it is unclear how serology (antibody) tests relate to in vivo potency. Likely, the in vitro assay that best mirrors in vivo conditions—viral neutralization titer—is not readily available. Furthermore, it has not been proven that neutralization titer relates to in vivo potency. These issues of uncertain and variable potency may cripple our ability to learn from initial experiences.

Third, most blood is collected in the US by blood centers that are not affiliated with hospitals or patient testing laboratories, however physicians and hospitals are more readily able to identify and recruit potential CP donors. One proposed "work around" system would involve hospitals sending donors to blood centers for collection, with units returned to the hospital which sent the donor. If this mechanism is used for COVID-19 CP, large hospitals in areas with prevalent disease and wide-spread testing will be in the best position to identify and recruit potential CP donors, and have the best access to CP. This may produce a geographic inequality in the availability of CP.

Alternatively, using a traditional directed donor pathway, donors may designate their CP donation to a friend or family member. Suddenly, the question is not one of ethical medical triage, but whether a patient has someone to donate CP for them. This may create an incentive for donors to misrepresent during donor screening, in order to avoid being deferred. It raises another question: can donors donate for someone who is not yet eligible to receive CP? Should transfusion services "hold" the unit(s) in case or until the intended recipient becomes eligible, even while others in need die? If blood banks refuse to hold units for future directed use, then donors may be incentivized to not donate for the general good, due to the fear that they will be unable to donate when a loved one is in need. Would an ethical option for hospitals be to hold donor-directed units during the deferral period, then release them to general inventory if the donor does not present to donate again? But what if the donation fails due to vein infiltration or phlebotomist error?

Interestingly, hospital-based blood centers may have an early advantage in donor recruitment and collections, disrupting the recent advantage national blood centers have enjoyed over smaller, local collection centers. Hospitals that begin collecting CP effectively may provide alternative supply routes to other hospitals (especially without crossing state lines for unlicensed collection centers). These hospitals may face a different ethical problem: if the supply of CP is locally robust, should it be the patient, the attending physician, or the healthcare organization policymakers who decide whether to use the plasma on a compassionate use basis, despite the safety and efficacy unknowns? Similarly, who decides whether a patient could or should get a second dose of CP?

Although the rapid development of multicenter randomized control trials for CP is promising, these trials will only be enrolling at select sites and available to a small percentage of patients nationally.[3] Should we push forward with these trials and also collect as much CP as possible for compassionate use, in other words "not allowing perfect to become the enemy of a potential good"? However, how do we ethically offer both compassionate use (guaranteed CP) and randomized trial enrollment (potential placebo) to the same patients? Do we restrict compassionate use at some institutions but not others?

An alternative would be true nationalization of recruitment, collection, and treatment employing the nation's contract research organizations for nation-wide, prospective placebo-controlled trials combined with allocation to the rapid development of hyperimmune globulin.[4,5]

CONFLICT OF INTEREST

TJG is the principal investigator of the COVID-19 Convalescent Plasma Collection Study at NorthShore University HealthSystem.

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Convalescent plasma – this is no time for competition

As of May 30, 2020, a randomized trial for the use of remdesivir in patients with severe coronavirus disease 2019 (COVID-19) has provided the only first-level evidence of efficacy in this infection, albeit with modest results.[1] The other therapeutic modality reported to affect mortality in patients suffering from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the transfusion of plasma collected from donors who have recovered from the infection (convalescent plasma [CP]). Small observational studies in China[2-4]; larger studies in the United States,[5,6] including a study employing matched controls;[7] and a proof-of-concept study in Italy[8] have delivered promising results, while randomized trials have been proposed[9] or are under way.[10,11]

In tandem with the collection of CP for therapeutic use,[12] efforts are under way to collect plasma for manufacture into an immunoglobulin preparation rich in antibodies to SARS-CoV-2 (hyperimmune immunoglobulin [IG]), similar to other IGs used for prophylaxis against infections such as tetanus, hepatitis B, and other pathogens.[13] These efforts by the companies of the plasma therapeutics industry, most of whom have formed an umbrella "Plasma Alliance" to maximize plasma collection and the development of an IG.[14]

While several hyperimmune IGs are effective in prophylaxis against infectious agents, the use of these products for the treatment of infections is less well established. In recent years, only plasma-derived polyclonal IG against respiratory syncytial virus has been used therapeutically,[15] until replaced by a monoclonal antibody product.[16] Reservations exist regarding the evidence base for the efficacy of both of these therapies.[17] The efficacy of manufactured IG may be influenced by changes induced in the immunoglobulin G (IgG) subclass composition of these products by the plasma fractionation process. Changes of this kind have been reported for other IGs, and IgG3 has been shown to be particularly susceptible to depletion during fractionation.[18,19] IgG3 shows selectively enhanced potency against certain pathogens in polyclonal IGs,[20] as well as forming a substantial proportion of the neutralizing antibodies to SARS-CoV-2 generated during the infection.[21] Hence, extensive preclinical and clinical development of any anti–SARS-CoV-2 IG will be required to ensure therapeutic efficacy and equivalence to the antibody profile and clinical properties of CP.

We are therefore concerned by media reports of evolving competition for plasma donors between the two sectors collecting CP as outlined above.[22] We apprehend that potential CP donors who may approach the community blood sector for altruistic reasons may be deflected to the commercial sector through the high remuneration offered.[22] This may be accentuated during this period as the traditionally low-resource population of paid plasma donors[23] may be further augmented through the difficult economic situation, as occurred in previous economic crises.[24,25]

We propose that during the current phase of the epidemic, when 1000 of patients may benefit from CP transfusion, such a development may be detrimental to the public health. Given the previous history of hyperimmune IG, anti–SARS-CoV-2 IG may be limited to prophylaxis of groups at high risk of infection, rather than effective for treatment of patients with COVID-19 at different stages of clinical disease progression. Such a product should also be stocked in preparation for subsequent waves of the infection, particularly in the event that an efficacious prophylactic vaccine may not be widely available.

The best way forward, it seems, would be that national healthcare systems implement a structured and transparent policy that ensures continued collection and availability of therapeutic CP, coupled with a measured and regulated pace in the collection of plasma hyperimmune IG manufacturers require to validate their processes and fully characterize their products.

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