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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Passive immunotherapy with convalescent plasma against COVID-19? What about the evidence base and clinical trials?

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Every severe viral infection since the Spanish Flu has stimulated interest in passive immunotherapy, in the absence of antiviral treatment and a vaccine program [1]. The rationale for convalescent plasmatherapy is very simple: it aims at providing neutralizing antibodies raised in donors having recovered from infection, to a mate recipient developing infection, in general, with a severe presentation [2,3]. The emergence of COVID-19 has swiftly elicited interest towards convalescent plasma as complications are not exceptional and even lethal [4–6]. Several position papers and reviews advocated for the rationale of developing fast access to convalescent plasma collection and treatment of SARS-CoV-2-infected patients (see, for example, references: [7–11]; more than 50 occurrences were found as of early May20 in PubMed searching for COVID-19 and convalescent plasma, that were published in the April, issues of medical and scientific journals, quickly expanding in the month of May 2020. Nearly all transfusion systems have launched programs to collect, process, inactivate and apply convalescent plasma to patients in need [12–14].

This, nevertheless, raises a number of questions: are neutralizing antibodies raised against the clinically invading forms of the virus i.e. in blood? How to make sure that no facilitating antibodies may develop [15]? What would be the most appropriate timing to collect plasma—enriched with neutralizing antibodies—after clinical recovery of the donor? And for how long (in other words, is the serological neutralizing response long-lasting)? Are titers of neutralizing antibodies in a recovering person high enough to enable protection in a recipient (or is there a need for preparing so-called hyperimmune immunoglobulins)? Next, questions arise relative to donors: can convalescent persons safely give plasma (in relatively high volume, representing an extracorporeal circulation and exposure, to non-negligible levels of calcium citrate)? Do those persons come forwardvoluntarily and freely, in the absence of pressure, or were there external motivations such as incentives or remuneration [16]? Last, questions arise regarding testing and qualification of donated plasma:will they be derogation of the normal rules or will restrictive qualification be applied to all donations at the expense of a potential wastage of plasma presenting an ad hoc level of antibodies but without the standard safety guarantee? Derogations could concern e.g. doubtful seropositivity of other viral markers; high-titer anti-HLA antibodies; irregular anti-red blood cell antibodies; history of transfusion, a contraindication e.g. in France and some other countries; Etc.

Next come the scientific questions relative to the timeframe for transfusing convalescent plasma to recipients. At which phase of the disease to transfuse the immune plasma to best neutralize the viral replication in order to prevent tissue/organ complications? Indeed, it would make sense that “the earlier the best”; this would indeed require smaller volumes of plasma. However, how to decipher between infected persons at-risk of manifesting complications in whom plasma therapy is sound, versus the many others who will not present with complications, in whom the exposure to plasma could cause an unnecessary risk and no or little benefit? Convalescent plasma is by all means a rare resource and only its judicious application for treatment will be acceptable, not to waste the resource. Then, which protocol to apply to ensure that there is enough contact between neutralizing antibodies and the virus (and at which site)? In all, what would be the best protocols, first to collect, secondly to qualify, and thirdly to apply specific plasma?

Dozens of hopes and disappointments characterize COVID-19

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therapeutic options, in particular because there have to quickly been communications about uncontrolled or methodologically unsound trials. This is explained first by the race against time in this devastating pandemic; then because even renowned journals fast-track publications prior to peer-review, often against publication ethics; and, last,because of the media hunt for spectacular discoveries, and also the identification of moguls as novel show-persons who surrogate the usual TV-stars.

It is obvious that ethically sound, quality reviewed, well conducted clinical trials are essential to situate convalescent plasma therapy among the therapeutic arsenal to treat SARS-Cov-2 infection. Controls would also be essential, ie against non-convalescent plasma or non-specific immunoglobulins; the situation will be complexified at a time when even standard Intravenous Immunoglobulins (IVIG) have been proposed in certain severe situations, especially with the aim to dampen the inflammatory phase in severe presentations (further, current IVIG forms seem to have certain antiviral properties [17]). Indeed, since the discovery of numerous thrombotic complications among the severe presentations of COVID-19 [18–20], it cannot be excluded that normal plasma factors resolve the DIC-like symptomatology or counteract the effects of lupus-like antibodies, or sooth the blood vessel endothelium if the disease associates to endotheliopathy (as was seen relative to Ebola-virus infection and convalescent plasma therapy [21]). Further, what about the ethics of transfusing supposedly large volumes of non-specific plasma as a control to a person in danger of developing severe complications of SARS-Cov-2? Last, the case of hemovigilance of plasma therapy must be addressed, to not harm recipients, especially having in mind that one of the most frequent hazards of transfusion is lung injury; it would be inappropriate to superimpose this hazard on the pulmonary complication of COVID-19. Of major interest is one of the first trials published so far—concerning about 5000 recipients—that has identified only limited and non-unexpected transfusion complications [22].

In aggregate, convalescent plasma therapy as a rescue treatment is sound considering a hundred years of experience [1], when no obvious form of treatment has yet been made available and in the absence of soon-coming vaccine. However, this raises a flurry of ethical questions that each need to be properly addressed. The question of alleviating ethical clearance for clinical trials has been raised by many investigation centers relative to COVID-19, considering the urgency in obtaining encouraging data; this is vigorously debated, however, to not raise false hopes nor to complicate the proper clinical management of patients [23,24]. In our opinion, it is unfortunate that the situation has not been anticipated, as recent SARS-CoV-1 and SARS-MERS—and also Ebola-virus—infections raised similar questions; the controlled use of plasma therapy on a large scale has not been possible in the preceding situations as the option was made available too late, at a time where the spreading epidemic reversed to sporadic cases. It would be urged that there is a general preparedness plan to evaluate the assets and liabilities of convalescent plasma to treat emergent infections; as a matter of fact, plasma therapy of convalescent plasma has not been thought of in a recent position paper on preparedness plans [25]. Models should be prepared (perhaps in animal hosts) and ethical questions should be prepared ahead of an exception context, such as the present one when elementary liberties have been notched despite the existence of democratic regimens in most industrialized countries. Clinical trials to evaluate the quality, the efficacy and the safety of convalescent plasma therapy as soon as possible after the onset of an epidemic threat would be mostly valuable. Conditions to validate treatment options under pressure are obviously non-optimal and may even be occasionally unethical.

Disclosures

The author has occasional consulting activity with Cerus Europe, Amersfoot, the Netherlands, a provider of solutions for plasma safety.

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