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Review Article

BENEFIT AND CLINICAL TRIAL OF CONVALESCENT PLASMA FOR THE TREATMENT OF COVID-19: AN OVERVIEW

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A B S T R A C T

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease (COVID-19), has spurred a global health crisis. To date, there are no proven options for prophylaxis for those who have been exposed to SARS-CoV-2, nor therapy for those who develop COVID-19. We provide an overview of convalescent plasma, from evidence of benefit, and proposed clinical trials, as scale up is brought underway to mobilize this critical resource.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus, SARS-CoV-2, that was first recognized in Wuhan City, China, in December 2019. Genetic sequencing of the virus suggests that SARS-CoV-2 is a beta-coronavirus closely linked to the SARS virus (Team NCPERE, 2020). Other coronavirus infections include the common cold (HCoV 229E, NL63, OC43 and HKU1), Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). The 2019 novel coronavirus has been named "SARS-CoV-2" and the disease it causes has been named coronavirus disease 2019 (abbreviated COVID-19). The situation is changing rapidly as the outbreak spreads to the whole World.

Most cases of COVID-19 globally have evidence of human to human transmission. This virus can be readily isolated from respiratory secretions, faeces and fomites.

On 30 January, the World Health Organization declared the 2019 coronavirus disease (COVID-19) outbreak a public health emergency of international concern (PHEIC) (WHO, 7th March, 2020). Since 31 December 2019 and as of 16 April 2020, 2029930 cases of COVID – 19 have been reported globally including 136320 deaths as per the report of ECDC.To date, no specific treatment has been proven to be effective for SARS-CoV-2 infection.

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Apart from supportive care, (Chen, *et al*. 2020) such as oxygen supply in mild cases and extracorporeal membrane oxygenation for the critically ill patients, specific drugs for this disease are still being researched.

Numerous therapeutics have been explored or developed during the outbreak including recent trial of antiviral drugs lopinavir ritonavir. This has no treatment benefit for severe illness caused by SARS-CoV-2 (Cao, *et al*. 2020). Immunotherapy with virus specific antibodies in convalescent plasma or immunoglobulin had been used as a last resort to improve the survival rate of patients with serious infectious diseases, such as severe acute respiratory syndrome, middle east respiratory syndrome coronavirus, Ebola virus disease, pandemic influenza A, and avian-origin influenza A (Chen, *et al*. 2020). Previous reports have shown treatment with convalescent plasma collated from recovered patients could reduce the hospital stay and mortality of patients. (Soo, *et al*. 2004). In 2014, WHO recommended the use of convalescent plasma collected from patients who had recovered from Ebola virus disease as an empirical treatment during outbreaks (WHO, 2014). Again in 2015, a protocol for the use of convalescent plasma in the treatment of Middle East respiratory syndrome coronavirus was established (Arabi, Balkhy and Hajeer, 2015).

Aims and Objectives

The main objective of this paper is to review the available data from various recent relevant published papers on convalescent plasma for the treatment of COVID-19 patients in different

countries and to establish the use of convalescent plasma as an empirical treatment of COVID – 19.

METHODS AND MATERIALS

Being an unparalleled global health crisis in modern history, currently, there are neither proven prophylactic options for those who have been exposed to SARS-CoV-2 nor therapy for those who go on to develop COVID-19. Emerging viruses like SARS-CoV-2, rarely provide time to develop vaccines, and prophylactic vaccines are rarely effective in therapeutic setting and their manufacturing is hard to scale up in short times when the outbreak is of international emergency concern. Passive immunotherapy with plasma derived from patients that have recovered from SARS-CoV-2 infections can be a promising approach in the treatment of COVID-19 patients (Shen, *et al*. 2020). Immune (or "convalescent") plasma refers to plasma that is collected from individuals, following resolution of infection and development of antibodies. Passive antibody therapy, through transfusion of convalescent plasma, may prevent clinical infection or blunt clinical severity in individuals with recent pathogen exposure. Antibody therapy can also be used to treat patients who are already manifesting symptoms of varying severity. However, passive antibody therapy is most effective when administered prophylactically or used early after the onset of symptoms (Casadevall and Pirofski, 2003). For over a century, passive antibody therapy (PAT) has been in use (Luke, Kilbane, Jackson and Hoffman, 2006). The active agents in PAT are antibodies against the target pathogen of interest. Presently, PAT relies primarily on pooled immunoglobulin preparations that contain high concentrations of antibodies. In contrast, plasma has been used emergently in epidemics where there is insufficient time or resources to generate immunoglobulin preparations. The antibodies present in Convalescent plasma mediate their therapeutic effect through a variety of mechanisms. Antibody can bind to a given pathogen (e.g. virus), thereby neutralizing its infectivity directly, while other antibody- mediated pathways such as complement activation, antibody-dependent cellular cytotoxicity and/or phagocytosis may also contribute to its therapeutic effect. Non-neutralizing antibodies that bind to the pathogen may also contribute to prophylaxis and/or enhance recovery (van Erp, 2019). Importantly, passive antibody administration offers the only short-term strategy to confer immediate immunity to susceptible individuals.

This is particularly the case in the setting of a novel, emerging infectious disease such as SARS-CoV-2/COVID-19. While fractionated plasma products (e.g. hyperimmune globulin, monoclonal antibodies) and/or vaccination may offer durable therapeutic options, human anti-SARS-CoV-2 plasma is the only therapeutic strategy that is immediately available for use to prevent and treat COVID-19. So, collection of convalescent plasma for the treatment of COVID-19 patients has started in different countries (among which China, Mauritius, the USA, Italy and the Netherlands) and others will follow in the very next days. Due to this, many clinical trials are ongoing, as regularly updated by the WHO (http://apps.who.int/trialsearch/default.aspx) and also by the NIH (https://clinicaltrials.gov/ct2/home). Fractionated plasma products (e.g. hyperimmune globulin, monoclonal antibodies) and/or vaccination may offer durable therapeutic options but, human anti-SARS-CoV-2 plasma is the only therapeutic strategy that is immediately available for use to prevent and treat COVID-19.

Plasma will be collected by apheresis from patients recently recovered from laboratory confirmed infection by SARS-CoV-2 (either hospitalized or self-isolated at home) with the following characteristics:

- at least 14 days from clinical recovery of the patient (no symptoms) and from a negative result of two NAT test on nasopharyngeal swab and on serum/plasma, performed 24 hours apart, following recovery or prior to discharge if hospitalized;

- not mandatory (and not required by the majority of protocols in place) is a further negative result of a NAT testing on nasopharyngeal swab and on serum/plasma, performed 14 days after the first one;

- an adequate serum titer of neutralizing specific antibodies (> 160 by EIA method or equivalent with other methods) (AABB, 2015) (Cheng, *et al*. 2005). It should be pointed out that these persons are selected to donate immune plasma because they are COVID-19 convalescent patients: the scope of plasma collection is only related to the use for COVID-19 patients and not as plasma for clinical use. However, from now on, we can expect a huge number of people who have recovered from an asymptomatic infection (or from a disease with minor clinical signs). Appearance of serum IgM and IgA antibody in COVID-19 occurs since day 5 after symptom onset, while IgG is detected since day 14 (Guo, *et al*. 2020) (Zhao, *et al*. 2020). IgG are universally detected since day 20. Severe female patients generate IgG earlier and higher titers (Zeng, *et al*. 2020). Duration of anti-SARS-CoV2 antibodies in plasma remains unknown, though for other betacoronaviruses immunity typically lasts 6-12 months (Chan, *et al*. 2005). So a suitable donor could donate 600 ml plasma (equivalent to 3 therapeutic doses) every 14 days for a minimum of 6 months. When dealing with convalescent patients, collected units should be initially tested as required for plasma intended for clinical transfusion (HIV, HCV, HBV NAT and serology testing, syphilis); moreover, it is advisable to further test by NAT for HAV e PVB19 and to treat the units by pathogen reduction technologies. A negative result of NAT testing for SARS-CoV-2 is also clearly expected in both cases. There is also required testing of female donors with a history of pregnancy for HLA antibodies to mitigate the risk of transfusion related acute lung injury (TRALI). On each plasma unit it is advisable to determine the total content of immunoglobulins (IgG, IgA e IgM) and neutralizing specific antibody titer (> 160 by ELISA method or equivalent with other methods); this is intended to have a rough evaluation of the amount of immunoglobulins administered to the patients, which will allow subsequent comparison between dose and effectiveness. Due to the schedule of administration, it is suggested to freeze and store the units in aliquots of around 300ml. There are reports that convalescent plasma has been used in China to treat patients with COVID-19 (Shen, *et al*. 2020). In a pilot study of 10 patients with severe COVID-19, the investigators collected convalescent plasma with neutralizing antibody titers at or exceeding a 1:640 dilution (Duan, *et al*. 2020).

The pre-donation screening is left to the clinical provider who performs an assessment of the donor, collects a nasopharyngeal swab for nucleic acid testing to confirm that the individual is virus free (i.e. in the event that a negative test has not yet been obtained), and collects a blood sample for

antibody testing before referring the donor to a collection facility. Anti-SARS-CoV-2 provides evidence of resolved infection. Nonetheless, current FDA guidance mandates evidence of a negative molecular test to ensure a reasonable measure of caution. This recommendation reflects the overriding mandate to protect safety given the current state of knowledge, which associates the presence of SARS-CoV-2 RNA in nasopharyngeal specimens with potential infectivity.

Antibody testing

Antibody testing comes with its own challenges as is reflected in the FDA guidance. In general, one cannot qualify donors or manufacture a therapeutic agent using tests that have not been vetted appropriately. However, there is uncertainty as to which antibodies are optimally effective in the context of COVID-19. Neutralizing antibodies are likely to correlate better with function. However, neutralizing antibody assays are not amenable to high throughput screening in clinical laboratories and are not widely available. By contrast, quantitative assays (e.g. ELISA) are available but commercially available assays have not been rigorously validated. Further, the relationship between total anti-SARS-CoV-2 antibodies and neutralizing anti-SARS-CoV-2 antibodies remains unclear. There is also uncertainty as to whether total antibodies or subclasses (e.g. IgM, IgG or IgA) are the optimal measure and which antigen is most informative; in this regard, various forms of the spike or S protein have been tested and used (Amanat, *et al*. 2020) (Okba, *et al*. 2020).

Limited data are currently available on the ELISAs. One group reported findings, demonstrating both "strong reactivity against IgG3, IgM and IgA" using assays targeting spike antigens as well as low cross-reactivity when testing other human coronaviruses (Amanat, *et al*. 2020). Another group reported on performance of a point of care antibody test for combined detection of IgM and IgG, demonstrating a sensitivity and specificity of 88.7% and 90.6% respectively (Li, *et al*. 2020).

The antibody titer will be impacted by the timing of collection relative to onset of infection. While data are limited, seroconversion has been observed to occur between 8 and 21 days after the onset of symptoms (Okba, *et al*. 2020) (Guo, *et al*. 2020). Coupled with reports from China of high titers of anti-SARS-CoV-2 antibodies in the overwhelming majority of convalescent patients, the findings suggest that units of plasma that are collected ≥14 days after resolution of symptoms should contain high titers of antibodies (Duan, *et al*. 2020). In the setting of a temporizing therapy, one needs to balance acuity of need with a desire for a highly validated assay and a refined treatment modality. Indeed, the FDA guidance manages this uncertainty by suggesting, rather than requiring testing i.e. *"Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320)"* (CBER, 2020). This will certainly change as antibody testing becomes more widely available. One could even foresee routine sero-surveillance of blood donors, which would bypass the need for pre-donation screening, particularly if the convalescent plasma is produced from whole blood collections.

Pertinent to the current pandemic, a study in China, employed a single (200 mL) unit of plasma (Duan, *et al*. 2020). In the planned clinical trials, one unit has been proposed for use for post-exposure prophylaxis and one to two units have been proposed for treatment. The antibodies' duration of efficacy is unknown but is postulated to last weeks to a few months (Casadevall, 2002). The selected dosing was based on experience with previous use of convalescent plasma therapy in SARS, where 5 mL/kg of plasma at a titer of ≥ 1:160 was utilized (Cheng, *et al*. 2005). Historically, prophylactic doses (in some cases only a quarter of that of the proposed treatment dose) have been used successfully. This was considered when designing the clinical trials. Considering first-order linear proportionality, 3.125mL/kg of plasma with a titer of >1:64 would provide an equivalent immunoglobulin level to one-quarter of 5ml/kg plasma with a titer of ≥ 1:160.

Convalescent Plasma banking

Convalescent Plasma is typically used as a fresh product. Banking at temperature below -25˚C (according to EDQM guidelines for ordinary plasma for clinical use) (Healthcare EDQM. 2017) is encouraged in order to translate Convalescent Plasma in an off-the-shelf, ready-to-use product. Most regulatory system requires that Convalescent Plasma is tracked informatically as a blood component different from ordinary plasma for clinical use. The final validation label should report that the donor has tested negative at PCR for the convalescent disorder and additional microbiological tests, and describe the inactivation method. There is no evidence that a single cycle of freezing and thawing significantly affects quantity or function of immunoglobulins.

RESULTS

This therapy is in trial process and various works are going on round the globe. From the available data, it can be concluded that the model highlights overwhelming benefit from prophylaxis or treatment with convalescent plasma even when conservative (e.g. 25%) estimates of efficacy are modelled. The proposed clinical trial was designed with a projected attack rate of 20% (10.5-35%) (Liu, Eggo and Kucharski, 2020). All patients had improvement in symptoms (e.g. fever, cough, shortness of breath and chest pain) within 1-3 days of transfusion; they also demonstrated radiological improvement in pulmonary lesions. Further, screening of more than 97.5% of recovered COVID-19 patients treated with convalescent plasma therapy displayed neutralizing antibody titers ≥160. A case series of critically ill patients in China also reported improvement in clinical status following transfusion with convalescent plasma (SARS-CoV-2 IgG titers >1000) as evidenced by weaning off mechanical ventilation, reduction in viral loads, improved oxygenation and clinical stabilization (Shen, *et al*. 2020)

DISCUSSION AND CONCLUSION

The risks to transfusion recipients are likely to be no different from those of standard plasma. Risk of transfusion-transmissible infection is very low. Human plasma from recovered COVID-19 patients is projected to be a safe and potentially effective therapy for treatment and post-exposure prophylaxis alike. Whole blood and plasma may be the first and only options to consider during a pandemic in the meanwhile antivirals and vaccines are tested. They should be prepared under ethical and controlled conditions to ensure optimal safety to both donors and recipients. Substantial evidence of benefit with prior use for viral infections offers strong precedent for such an approach.

Conflict of Interest

None declared.

Reference

AABB. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. Springerplus. 2015 Nov 19;4:709.

Amanat F, Nguyen T, Chromikova V, Strohmeier S, Stadlbauer D, Javier A, *et al*. A serological assay to detect SARS-CoV-2 seroconversion in humans. *medRxiv*. 2020:2020.03.17.20037713.

Arabi Y, Balkhy H, Hajeer AH. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. *Springerplus* 2015; **4:** 709.

Cao B, Wang Y, Wen D, *et al*. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19 [published online ahead of print March 18, 2020]. *N Engl J Med*. https://doi.org/10.1056/NEJMe2005477.

Casadevall A, and Pirofski LA. Antibody-mediated regulation of cellular immunity and the inflammatory response. *Trends Immunol.* 2003;24(9):474-8.

Casadevall A. Passive antibody administration (immediate immunity) as a specific defense against biological weapons. *Emerg Infect Dis.* 2002;8(8):833-41.

CBER. Investigational COVID-19 Convalescent Plasma - Emergency INDs. https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ideprocess-cber/investigational-covid-19-convalescent-plasma-emergency-inds (Accessed on April 17, 2020.)

Chan KH, Cheng VC, Woo PC, Lau SK, Poon LL, Guan Y, Seto WH, Yuen KY, Peiris JS. 2005. Serological responses in patients with severe acute respiratory syndrome coronavirus infection and crossreactivity with human coronaviruses 229E, OC43, and NL63. *Clin Diagn Lab Immunol* 12:1317-21.

Chen L, Xiong J, Bao L, *et al*. Convalescent plasma as a potential therapy for COVID-19 [published online ahead of print February 27, 2020]. *Lancet Infect Dis*. https://doi.org/10.1016/S1473-3099(20) 30141 9.

Chen N, Zhou M, Dong X, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513

Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, *et al*. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis.* 2005;24(1):44-6.

Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, *et al*. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. *medRxiv*. 2020:2020.03.16.20036145.

Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, Dela Cruz CS, Wang Y, Wu C, Xiao Y, Zhang L, Han L, Dang S, Xu Y, Yang Q, Xu S, Zhu H, Xu Y, Jin Q, Sharma L, Wang L, Wang J. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). *Clinical Infectious Diseases* 2020:10.1093/cid/ciaa310.

Healthcare EDQM. 2017. 19th Edition of the Guide to the Preparation, Use and Quality Assurance of Blood Components.

Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, *et al*. Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis. *J Med Virol.* 2020.

Liu Y, Eggo RM, and Kucharski AJ. Secondary attack rate and superspreading events for SARS-CoV-2. *Lancet.* 2020;395(10227):e47.

Luke TC, Kilbane EM, Jackson JL, and Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Ann Intern Med.* 2006;145(8):599-609.

Okba NMA, Muller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, *et al*. SARS-CoV-2 specific antibody responses in COVID-19 patients. *medRxiv*. 2020:2020.03.18.20038059.

Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, *et al*. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA*. 2020

Soo YO, Cheng Y, Wong R, *et al*. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin Microbiol Infect.* 2004;10:676-678.

Team NCPERE. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) – China. China CDC Weekly. 2020;2(8):113-22

van Erp EA, Luytjes W, Ferwerda G, and van Kasteren PB. Fc-Mediated Antibody Effector Functions During Respiratory Syncytial Virus Infection and Disease. *Front Immunol.* 2019;10:548

WHO Responding to community spread of COVID-19: Interim guidance, 7th March, 2020; Geneva

WHO. Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks. 2014

Zeng F, Dai C, Cai P, Wang J, Xu L, Li J, Hu G, Wang L. A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: a possible reason underlying different outcome between gender.*medRxiv:2020* 10.1101/2020.03.26.20040709:2020.03.26.20040709.

Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, Wang X, Yuan J, Li T, Li J, Qian S, Hong C, Wang F, Liu Y, Wang Z, He Q, Li Z, He B, Zhang T, Ge S, Liu L, Zhang J, Xia N, Zhang Z. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019.*medRxiv*: 2020:10.1101/2020.03.02.20030189:2020.03.02.20030189.

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