Mini Review

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Plasma-derived therapy: can the survivors of COVID-19 help the defenseless?

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Abstract: Following the unprecedented global Coronavirus Disease 2019 (COVID-19) outbreak, multiple medical countermeasures ramped up to combat the virus and contain the spread of the pandemic. Despite continued uncertainty and a lack of clarity about the COVID-19, researchers have made tremendous strides in the development of prevention and treatment strategies. In this article, we focus on the use of convalescent plasma as therapeutic approach against COVID-19 infection.

Keywords: convalescent plasma; COVID-19; pandemic; plasma-derived therapy; treatment.

Introduction

Coronavirus is one of the many pathogens that primarily attacks the human respiratory system, causing severe acute respiratory syndrome. Among Coronaviruses, coronavirus 2 (SARS-CoV-2) has caused a major global outbreak originating in Wuhan, China, in late December 2019. A group of patients admitted to a hospital in Wuhan were diagnosed with pneumonia of unknown etiology, which is now named coronavirus disease 2019 (COVID-19). The most common symptoms at onset of COVID-19 are fever, dry cough, fatigue, and shortness of breath [1]. The symptoms may appear 2–14 days postexposure to the virus [1], but symptom severity ranges from mild to severe based on the age and immune system status of the patient [2]. The person-to-person transmission of COVID-19 infection led to a drastic increase in the number of confirmed cases affecting a growing number of countries. This urged the World Health Organization (WHO) to label the COVID-19 outbreak a pandemic on 12th March 2020 [3], leading to sweeping global measures in an attempt to curb sustained COVID-19 infection rates, such as imposing travel bans and placing citizens under lockdown. By March 2020, the number of confirmed cases worldwide surpassed 1,000,000; although almost 20% of those cases made it to full recovery, around 45% of the patients died. At present, there are no specific drugs to treat or prevent the infection; therefore, several potential therapeutic approaches are being investigated.

About convalescent plasma therapy

The Merriam-Webster Online Dictionary defines convalescence as “the time between the subsidence of a disease and complete restoration to health” [4]. Convalescent plasma refers to the plasma of patients whose immune system has responded to a certain infection generating antibodies that prompted the patients’ recovery. Convalescent plasma therapy is the transfusion of plasma from those who have overcome the infection to those who are still experiencing an active pathological infection. Such plasma is rich in antibodies that are able to neutralize the virus and thus co-support the patient’s immune response against the disease.

Prior to the development of antibiotics and vaccines, convalescent plasma was the traditional therapeutic approach for preventing and treating bacterial and viral infections [5]. With evolving antibiotics, the era of convalescent plasma therapy almost came to an end. However, outbreaks of pandemics such as Spanish influenza in the early 1990s and more recently Ebola [6] and Middle East respiratory syndrome coronavirus [7], restored convalescent plasma therapy to prominence [8]. Many research groups have explored the efficacy of convalescent plasma therapy in different viral infections [9–11] and, while the studies reported different results, there was consensus that convalescent plasma transfusion improved survival rates among recipients compared to control group. Interestingly,

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a study in nonhuman primates showed that multiple transfusions of high-dose purified polyclonal IgG antibodies from convalescent plasma to macaque monkeys 48 h postinfection provided complete protection against Ebola virus [12]. The use of convalescent plasma against another virus of the corona family, MERS-CoV, the virus linked to Middle East respiratory syndrome, showed that patients receiving the treatment significantly improved, with amelioration of symptoms and increased rates of hospital discharge [7]. Collectively, these studies indicate the potential use of convalescent plasma as a therapeutic and preventive approach against currently incurable viral infections.

To determine whether convalescent plasma therapy is a cure or prophylaxis, we first need to understand the definition of a cure. A cure is defined as a permanent solution or remedy that provides a full recovery from disease. However, a treatment is defined as the improvement in a patients' condition, enabling them to fight the disease. A cure is viewed from a perspective of prevention, treatment, and eradication while a treatment can be experimental or approved, and approved treatment is only part of the cure. In the history of infectious diseases, only smallpox and rinderpest have been successfully eradicated [13, 14]. In this context, convalescent plasma therapy is a treatment rather than a cure that could also be applied as a preventive measure.

In viral infections such as COVID-19, where specific anti-SARS-CoV-2 treatment is lacking, and a vaccine projected to be 1 year away from routine use, convalescent plasma therapy could help change the course of this pandemic. However, one needs to address the challenges to this approach; first, convalescent plasma remains an empirical treatment, meaning that it is based on clinicians' cumulative experience in handling the cases. Additionally, as an empirical treatment, it also means that large-scale, randomized, and well-designed clinical trials are lacking.

Challenges

There is a legitimate concern as to how the increasing needs of convalescent plasma could be met during pandemics. A potential solution to increased demand for convalescent plasma in the context of a pandemic is the creation of infection-specific banks of convalescent plasma, where donors' eligibility criteria is well-defined and standardized protocols for plasma collection and storage are applied. Raising public awareness about plasma donation is important to support the creation of such banks in terms of recruiting donors, and attracting funds necessary to sustain this endeavor. Most protocols advocate that donation should be made within 28 days of symptom onset, and 14 days postrecovery. This time window ensures the absence of the virus and the presence of high titers of antiviral antibodies. In countries where the number of positive cases outweighs the recovered ones, securing a sufficient pool of convalescent plasma could be a difficult endeavor but one that could be overcome by isolation and purification of the antibodies from convalescent plasma, for manufacture, and mass production. A benefit of this approach is that patients could be treated with a controlled dosage regimen.

The most critical step toward more widespread use of convalescent plasma therapy is to conduct well-designed randomized clinical trials where (1) the study groups are well selected, (2) disease stage is defined, (3) intervention protocols are well standardized, and (4) evaluation criteria of convalescent plasma administration between treatment group(s) compared to control group(s) is established prior starting the study.

Discussion

The first uncontrolled case series study conducted in Shenzhen Hospital, China, showed that five critically ill COVID-19 patients (age range, 36–73; two women) received convalescent plasma from five asymptomatic, SARS-CoV-2 negative donors (age ranged, 18–60) made it to full recovery [15]. Despite the limitations in the study design, this study provided some evidence to support the potential utility of convalescent plasma in treating COVID-19. On March 24th, Food and Drug Association (FDA) of the United States of America approved the use of convalescent plasma as an emergency treatment for severely ill COVID-19 patients. FDA permission is granted under certain conditions, (1) only severely ill or immediately life-threatening COVID-19 patients are eligible to receive the treatment, (2) convalescent plasma to be applied only as a treatment not a prevention, (3) a licensed physician must request an official approval prior to the procedure, (4) approvals are on single-patient basis, and (5) donors' eligibility should match the criteria set by FDA. Since then, many other studies [16, 17] and clinical trials investigating the potential of convalescent plasma therapy emerged. Table 1 summarizes active and recruiting interventional clinical trials of convalescent plasma therapy for COVID-19.

While the approval of convalescent plasma therapy by the FDA brings hope to many patients battling COVID-19, many questions are left unanswered. For example, what about the people at higher risk of severe COVID-19, like

Table 1: Active and recruiting interventional clinical trials of convalescent plasma therapy for COVID-19.

Title	Interventions	Sponsor/collaborators	Enrollment
COPLA Study: Treatment of Severe Forms of COronavirus Infection With Convalescent PLAsma	Biological: CP	Centro de HematologÃa y Medicina Interna|Laboratorios ClÃnicos de Puebla (Laboratorios Ruiz)	10
CP to Limit COVID-19 Complications in Hospitalized Patients	Biological: CP|Biological: Lactated ringer's solution or sterile saline	NYU Langone Health|Albert Einstein College of Medicine	300
Amotosalen-Ultraviolet A Pathogen-Inactivated CP in Addition to Best Supportive Care and Antiviral Therapy on Clinical Deterioration in Adults Presenting With Moderate to Severe COVID-19	Other: CP application to SARS-CoV-2 infected patients	University Hospital, Basel, Switzerland	15
COVID-19 CP	Biological: anti-SARS-CoV-2 CP	University of Chicago	10
Efficacy and Safety of Early COVID-19 CP in Patients Admitted for COVID-19 Infection	Biological: COVID-19 CP	Pontificia Universidad Catolica de Chile|Fundacion Arturo Lopez Perez	30
Plasma Therapy of COVID-19 in Critically Ill Patients	Biological: CP (anti-SARS-CoV-2 plasma)| Biological: Non-CP (control plasma)	Max R. O'Donnell|New York Blood Center| Columbia University	105
CP as Treatment for Acute Coronavirus Disease (COVID-19)	Biological: SARS-CoV-2 CP	Joakim Dillner|Danderyd Hospital|Karolinska Institutet|Karolinska University Hospital	10
CP for Patients With COVID-19	Biological: CP	Henry Ford Health System	30
CP Compared to the Best Available Therapy for the Treatment of SARS-CoV-2 Pneumonia	Biological: Plasma|Other: Best Available Therapy	Hospital Universitario Dr. Jose E. Gonzalez	30
A Study of COVID 19 CP in High Risk Patients With COVID 19 Infection	Drug: CP	TriHealth Inc.	100
Passive Immunity Trial of Nashville II for COVID-19	Biological: pathogen reduced SARS-CoV-2 CP|Biological: Placebo	Vanderbilt University Medical Center|Dolly Parton	500
CP for Treatment of COVID-19 Patients With Pneumonia	Drug: High-Titer Anti-SARS-CoV-2 (COVID 19) CP	University of Virginia	29
CP Collection and Treatment in Pediatrics and Adults	Biological: CP 1 Unit| Biological: CP two Units| Other: SOC	West Virginia University	240
Convalescent Antibodies Infusion in Critically Ill COVID 19 Patients	Biological: Anti-Coronavirus antibodies (immunoglobulins)obtained with DFPP from convalescent patients	A.O. Ospedale Papa Giovanni XXIII|Aferetica - Italy (BO)	10
CP as Treatment for Hospitalized Subjects With COVID-19 Infection	Biological: CP	Hackensack Meridian Health	55
CP for COVID-19 Close Contacts	Biological: CP (anti-SARS-CoV-2 plasma) |Biological: Control (albumin 5%)	Columbia University	200
Hyperimmune Plasma in Patients With COVID-19 Severe Infection	Other: plasma hyperimmune|Drug: SOC	University of Catanzaro|Azienda Ospedaliera Policlinico "Mater Domini"|Azienda Sanitaria Provinciale Di Catanzaro|Annunziata Hospital, Cosenza, Italy|Azienda Ospedaliera Bianchi-Melacrino-Morelli	400
CP Therapy vs. SOC for the Treatment of COVID19 in Hospitalized Patients	Other: Blood and derivatives.| Drug: SOC	Cristina AvendaÃ±o SolÃ¡|Puerta de Hierro University Hospital	278

Source: ClinicalTrials.gov. CP, convalescent plasma; N/A, not available; SOC, standard of care.

elderly at nursing homes or healthcare workers? Some argue that convalescent plasma transfusion is crucial to protect the high-risk groups. Others questioned the choice of the disease stage as, theoretically, receiving convalescent plasma therapy at the earliest stage is optimal as the viral load is still low. For example, an individual who has overcome COVID-19 may desire their convalescent plasma to be given to another family member who has an active infection but this may place the individual in a quandary as to whether they should follow FDA guidelines and wait for the patient to deteriorate into a more severe stage of the disease, or to act in what they perceive to be the patients' best interests? While we await specific treatments against COVID-19 to emerge, the coming few months will answer many questions about the use of convalescent plasma against COVID-19.

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