Ther Adv Infectious Dis
2020, Vol. 7: 1–7
DOI: 10.1177/2049936120957931

Convalescent plasma appears efficacious and safe in COVID-19

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***Abstract*:** A cluster of pneumonia cases of unknown etiology associated with pyrexia and acute respiratory distress was identified in Southern China. Links between the previous severe acute respiratory syndrome (SARS) cases and the region's seafood market were noted with the possibility of a new zoonosis and SARS-CoV-2 was identified as the responsible agent. Currently, there are no effective prophylactic or therapeutic options to deal with coronavirus disease-19 (COVID-19) or any other human coronavirus (HCoV) infections. Convalescent plasma (CP) therapy is a classic adaptive immunotherapy which has been in use for more a century to prevent and treat infections including SARS, Middle East respiratory syndrome (MERS), and H1N1 pandemic. Moreover, the World Health Organization regarded CP transfusion as the most promising therapy to treat MERS-CoV. This review was undertaken to demonstrate the potential of CP in the treatment of the pandemic COVID-19 disease. A total of eight studies conducted on CP therapy in patients with COVID-19 were reviewed wherein 25,028 patients above 18 years of age were involved. The vast majority of patients reported favorable outcomes when treated with CP with <1% serious adverse events. Despite its promising beneficial effects in patients severely ill with COVID-19, CP therapy requires further evaluation in randomized clinical trials (RCTs) as a lack of satisfactory efficacy data from this area certainly enhances the hesitancy with regard to employing this treatment. In the present circumstances of unsatisfactory pharmacological therapy and the urgent need for a successful curative remedy, considering the use of CP therapy is reasonable provided RCTs confirm its safety, efficacy, and tolerability.

Keywords: convalescent plasma, coronavirus disease-19, plasma donation, SARS-CoV-2

Received: 3 May 2020; revised manuscript accepted: 19 August 2020.

Introduction

In December 2019, Chinese health authorities in the city of Wuhan in Hubei province identified a cluster of pneumonia cases of unknown etiology associated with pyrexia, acute respiratory distress, reduced or normal white blood cells, and failure to resolve over 3–5 days of antibiotic treatment. Links between the severe acute respiratory syndrome (SARS) cases and the city's South China Seafood Market were noted with the possibility of a new zoonosis or SARS outbreak considered.[1] Investigations were undertaken and a novel coronavirus, SARS-CoV-2 (formerly 2019-nCoV), was identified as the responsible agent[1] and the clinical illness caused by this agent is referred to as coronavirus disease-19 (COVID-19).[2]

CoVs are members of the family Coronaviridae and subfamily Coronavirinae. They were first identified by Tyrell and Bynoe in 1966, who cultivated these viruses from patients suffering from common colds.[3,4]

CoVs are categorized into four groups as α-, β-, γ-, and δ-CoVs based on genetic and antigenic criteria.[3,5] α- and β-CoVs generally infect mammals and cause respiratory ailments in humans.[6] Certain strains from α- and β-CoVs are endemic in the human population causing up to 30% of mild respiratory tract infections as well as occasional severe disease in children, the elderly, or immunocompromised people.[6,7]

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SARS-CoV-2 is reported to be the third known highly pathogenic human coronavirus (HCoV) infection in the last two decades after Middle East respiratory syndrome (MERS)-CoV and SARS-CoV, two highly infectious CoVs of zoonotic origin identified earlier that caused widespread epidemics and fatality in many countries.[2]

It is widely accepted that many viruses have existed in their natural reservoirs for a very long time, but CoVs are well known to undergo genetic recombination leading to new genotypes and outbreaks.[8] Therefore, SARS-CoV-2 is believed to have originated from bats but its exact source, animal reservoir, and enzootic patterns of transmission remain uncertain.[2]

Most HCoVs are transmitted from human to human by the respiratory route, fecal–oral route, or through infected secretions.[1,9–11] The lack of awareness in hospital infection control and international air travel facilitated the rapid global dissemination of this agent.[8] Studies reported that, on average, each infected person spreads the infection to an additional two individuals. Until this number falls below one, it will more likely continue to spread. Latest reports of high titers of virus in the oropharynx in the initial course of disease rouse concern about increased infectivity during the period of minimal symptoms.[12] The viral load peaked during the first week of illness followed by a gradual decline over the second week, and it was also shown to correlate with age. Recent reports indicate that patients 60 years of age and older are at higher risk compared with children who might be less prone to become infected or, if so, may exhibit milder symptoms or even remain asymptomatic.[3]

The dynamic speed of COVID-19 development reflects the ease of SARS-CoV-2 spread in the human population. Several healthcare workers have been infected and many clusters of cases are being detected with each passing day.[13] Worldwide, more than 14.5 million cases have been confirmed, and 600,000 deaths were witnessed by 21 July 2020.[14] Elderly people, cardiovascular disease, chronic respiratory disease, diabetes, cancer, smoking, hypertension, and obesity were reported to be associated with an increased risk of death.[15] The disease may also cause damage to other organs such as the heart, the liver, and the kidneys, as well as to the blood and the immune system thereby causing multiple organ failure (MOF), shock, acute respiratory distress syndrome (ARDS), heart failure, arrhythmias, and renal failure.[16]

Diagnosis

RT-PCR-based RNA detection of SARS-CoV-2 in respiratory samples provided the only precise diagnostic test in the early phase of the outbreak. More recently, enzyme-linked immunosorbent assay (ELISA) kits for immunoglobulin G (IgG) and IgM detecting antibodies against *N* and other SARS-CoV-2 proteins have also been available. This has made specific diagnosis of ongoing and past infection possible.[10] Currently, COVID-19 is managed by supportive care and respiratory failure resulting from ARDS is the leading cause of mortality.[17]

The US Food and Drug Administration (FDA) has defined criteria for categorizing COVID-19 into severe and life-threatening stages. While severe disease is characterized by dyspnea, blood oxygen saturation $\leqslant$93%, respiratory frequency $\geqslant$30 breaths per minute, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen 50% within 24–48 h, the life-threatening condition is defined as respiratory failure, septic shock, or MOF.[18]

Treatment

Currently, there are no effective prophylactic or therapeutic options to deal with COVID-19 or any other HCoV infections. Supportive care is the present approach to managing the disease.[2]

Pharmacological options

Remdesivir, a novel analog RNA polymerase inhibitor, seems promising but no antiviral agents have proven to be effective so far. Another antiviral, umifenovir known by its brand name Arbidol, is licensed in Russia and China for preventing or treating influenza and other respiratory infections.[19] Apart from antiviral agents, an antimalarial drug, hydroxychloroquine, has been shown to interfere with surface binding sites for the S protein of SARS-CoV (ACE2) resulting in its inhibition.[19] It has shown a higher potential against COVID-19 when given in combination with azithromycin.[20,21] However, another study has linked this combination with an increased risk

of 30-day cardiovascular mortality, angina, and heart failure.[21] Corticosteroids are not recommended as a routine therapy for COVID-19 by the World Health Organization (WHO) in view of the higher mortality risk associated with these.[22] Lately, dexamethasone was found to be a life-saving drug as it reduced one-third of deaths among patients critically ill with COVID-19 in a large trial.[23]

Around 20% of patients with COVID-19 have shown abnormal coagulation which is managed by anticoagulant therapy.[22] There are a few promising drugs under trial and solnatide (AP301) is one of these. Krenn *et al.* demonstrated the beneficial effects of solnatide in patients with ARDS on mechanical ventilation,[24] and consequently it has been approved for trials in Austria and Italy to test in patients with COVID-19.[25]

Nonpharmacological options

When it comes to nonpharmacological therapy, nasal catheters, masks, and high-flow nasal cannula oxygen therapy are advised for patients with mild to moderate infection with hypoxemia, whereas noninvasive or invasive mechanical ventilation and extracorporeal membrane oxygenation are being considered for severe and critically ill patients.[22]

Alternative treatment

Immunotherapy is considered an effective approach to treat infectious diseases. Monoclonal antibodies have been successful in providing an efficient therapeutic intervention against diseases with many agents against viruses developed in recent years and a few are in the clinical pipeline.[2] Another alternative from immune-related treatments is convalescent plasma (CP) therapy, which is usually considered when there are no proven therapeutics to prevent or treat infection-related diseases.[19]

CP therapy

CP therapy is a classic adaptive immunotherapy which has been in use for more a century to prevent and treat infections,[26,27] including the dreadful Ebola virus disease,[20] polio, measles, mumps, and the 1918 flu epidemic.[18] Recently, it was found to be successful in the treatment of SARS, MERS, and H1N1 pandemics.[21,26–29] Moreover, the WHO regarded CP transfusion as the most promising therapy to treat MERS-CoV.[22]

Potential of CP in COVID-19

Firstly, similarities in the virological and clinical features of SARS and MERS with COVID-19 signifies the immunotherapeutic potential of CP in COVID-19 based on its efficacy record from these outbreaks.[22] Secondly, findings from these past infections reported the presence of neutralizing antibodies in CP.[28] These cross-neutralizing antibodies may target a common epitome on the viruses, thereby providing prevention and treatment for COVID-19.[30] Thirdly, CP was employed in past influenza infections when no specific treatment was available[21] and COVID-19 therapy is in a similar situation. Fourthly, passive antibody administration in CP therapy offers the only short-term approach to confer instant immunity to susceptible individuals.[28] Lastly, the possibility of frequent blood donations with a large volume collection in each session without any impact on the donor's hemoglobin makes CP therapy an ideal way to treat COVID-19.[11]

Risks associated with CP

Plasma transfusion in modern hospitals is a routine event and human anti-SARS-CoV-2 plasma varies from standard plasma because of the presence of antibodies. The risks to recipients of CP are expected to be no different from those of standard plasma if the blood samples are collected in FDA-licensed blood centers and the donors fulfill the criteria stated by their respective federal and state authorities.[28]

Serum disease and antibody-dependent enhancement of infection are the probable risks associated with passive administration of CP. While serum disease is related to transmission of other blood infections, antibody-dependent enhancement is the increased risk of infection to a virus strain resulting from the presence of antibodies to another strain.[30]

Mechanism of CP therapy

Blood is collected from individuals who have recovered from viral infection and the serum is separated.[30] The serum, which contains antigen-raised antibodies,[30] is transfused into a newly infected patient as postexposure prophylaxis.[31]

Antibodies are proteins generated by B cells of the immune cells capable of binding to an antigen, a specific molecule found on the pathogen that helps in invasion into humans and the activation of immune responses.[30] In contrast to IgG-derived antibodies, such as monoclonal antibodies, CP is a passive antibody therapy that can neutralize a virus *via* various mechanisms.[31] The antibody-rich CP can mediate complement activation, antibody-dependent cellular cytotoxicity, and/or phagocytosis.[11,28,31] Non-neutralizing antibodies through pathogen binding may also contribute to prophylaxis and/or enhance recovery without interfering with its ability to replicate in *in vitro* systems.[28]

Outcomes of CP therapy in COVID-19 trials

A total of eight studies conducted on CP therapy in patients with COVID-19 were obtained from the National Center for Biotechnology Information database[32] and were examined for the current review.

The studies included a clinical trial comprising 5000 patients with COVID-19 to assess the safety of CP with mortality and serious adverse events (SAEs) as the experimental outcomes.[33] The trial was further expanded to over 20,000 patients and the latest update demonstrated a mortality rate of 8.6%, which was far less than the previous findings of 14.9%.[34] Although these trials successfully demonstrated the safety of CP therapy, its efficacy was not studied. These trials also lacked a control arm against which to compare the findings.

The efficacy of CP therapy in COVID-19 was assessed by a few small studies and case reports. While improvement in clinical symptoms post-CP therapy was the outcome in a few of the studies, other studies focused on changes in laboratory and radiological findings. Parameters such as length of hospitalization and reduction in respiratory support were also taken into consideration. Interestingly, few of the patients involved in these studies responded well to the CP therapy, despite showing no improvement on antivirals and hydroxychloroquine administration

Altogether, 25,028 patients above 18 years of age were enrolled in these studies from the USA, China, and Korea as represented in Table 1. While <1% of patients witnessed SAEs, the majority showed favorable outcomes. An AE can be defined as a detrimental, unintended effect of a therapy which occurs at doses commonly used for the prophylaxis, diagnosis, or treatment.[35] Although Ahn *et al.* noticed a reduction in viral load post-CP transfusion, they are still undetermined if the findings are a result of therapy or the pathology of COVID-19 itself.[36] Concluding remarks from other studies reflect their investigators' credence in CP for COVID-19 therapy.

Challenges of CP therapy in COVID-19

Although CP therapy showed satisfactory efficacy in treating patients with severe COVID-19,[41] this approach requires evaluation in randomized clinical trials (RCTs)[38] as lack of data from this area certainly enhances the hesitation with regard to employing this treatment.[42] The symptoms of SARS-CoV-2 mimic few of the common adverse reactions from CP therapy such as chills, fever, and transfusion-related acute lung injury,[43] thereby augmenting difficulty in identifying transfusion-related threats. The variable dosing of CP,[28,44] its co-administration with antiviral or other therapies can also affect the relationship between CP and antibody leading to result discrepancies.[36,44]

Studies have reported a differential response of viruses based on the stage. While infections like SARS peak in the first week of infection, patients usually develop an immune response which probably causes a lethal cytokine storm in the second week. This suggests that CP therapy can be more effective in the earlier stages of SARS. Hence, optimal timing of CP transfusion in COVID-19 needs to be carefully considered.[43,44] Finally, it must be determined whether plasma from donors with no clinical symptoms offers more protection than those with clinical symptoms.[44]

An RCT is the finest model to determine the efficacy, tolerability, and safety of a therapy.[45] Patients are being recruited to the CONCOVID trial in The Netherlands by the Erasmus Medical Center to test the CP from patients recovered from COVID-19 as therapy for hospitalized patients with COVID-19 with an estimated enrollment of more than 400 patients.[46] Recently, the FDA has approved use of CP to treat critically ill patients while a clinical trial of plasma therapy for COVID-19 has been approved in the UK.[47]

Table 1. Details of convalescent plasma therapy trials in patients with COVID-19.

Country	Recipients (age range)	Prior to CP therapy	Post-CP therapy	Adverse effects
USA[33]	Total: 5000 (18–97) Male: 3153 Female: 1824 Intersex/transgender: 17 Undisclosed: 6	81% of patients (4051) had severe or life-threatening COVID-19 and 19% (949) were at a higher risk of progressing to severe or life-threatening COVID-19. A total of 3316 patients (66%) were admitted to the ICU.	Efficacy of CP was not reported but early indicators from the study suggested CP as a safe therapy in patients hospitalized with COVID-19. Mortality rate of 14.9% did not appear excessive to investigators owing to the lethal nature of the disease and the large population of critically ill patients involved.	<1% reported serious adverse events.
USA[34]	Total: 20,000 (18+) Male: 12,152 Female: 7777 Intersex/transgender: 54 Undisclosed: 17	71% of patients were suffering from life-threatening COVID-19 disease and 58% were admitted to the ICU with 34% on mechanical ventilation.	The 7-day mortality rate was found to be 8.6% and was commonly seen in more critically ill patients.	<1% incidence of transfusion-related reactions.
China[26]	Total: 10 (34–78) Male: 6 (4–67) Female: 4 (34–78)	Three patients received high-flow nasal cannula oxygenation, and two received conventional low-flow nasal cannula oxygenation.	All symptoms in the 10 patients disappeared or largely improved within 1–3 days. While two patients were weaned from mechanical ventilation to high-flow nasal cannula, one patient discontinued high-flow nasal cannula.	None.
China[37]	Total: 6 (28–75) Male: 3 (56–69) Female: 3 (28–75)	Serum anti-SARS-CoV-2 antibodies titers for IgM and IgG were low. GGO were seen.	IgM and IgG levels increased up to 2-fold, GGOs were resolved, and respiratory distress was alleviated. Overall, CP was found to be clinically beneficial in all patients.	None.
China[38]	Total: 5 (36–73) Male: 3 (60–70s) Female: 2 (30–50s)	SARS-CoV-2 was still detectable in all five patients even after antiviral treatment was given for at least 10 days.	Virus was undetectable soon after therapy.	Not reported.
China[39]	Total: 4 (31–73) Male: 2 (55, 73) Female: 2 (31, 69)	GGOs and honeycombing change in lungs were seen. ARDS in one patient was severe even after methylprednisolone treatment. Another patient developed high viral load which led to MOF with bilateral white lung. A pregnant lady with GGOs developed severe ARDS, MOF, and septic shock. Invasive ventilation and cesarean section were performed, and her new born died of endo-uterine asphyxia.	A patient with severe ARDS improved and tested negative soon after therapy. Viral load decreased in the patient with MOF. The pregnant woman recovered from SARS-CoV-2 infection and was discharged. All patients showed negative RT-PCR test results at 3–22 days post-transfusion.	None.
Korea[36]	Total: 2 (67–71) Male: 1 (71) Female: 1 (67)	Both patients showed steady fever, rapidly aggravated hypoxemia, and progressive bilateral infiltrations despite taking lopinavir/ritonavir and hydroxychloroquine.	Patients showed favorable outcomes with improved oxygenation, decreased inflammatory markers in chest X-rays, and reduced viral loads.	None.
China[40]	Total: 1 (64) Male: 0 Female: 1 (64)	Although the patient was in the ICU on invasive mechanical ventilation, virus was undetectable at the time of intubation.	The patient did not require mechanical ventilation 11 days post-transfusion, and was transferred to a general ward.	None.

ARDS, acute respiratory distress syndrome; COVID-19, coronavirus-19; CP, convalescent plasma; GGO, ground glass opacities; ICU, intensive care unit; Ig, immunoglobulin; MOF, multiple organ failure; RT-PCR, real-time reverse transcription polymerase chain reaction.

Conclusion

CP appears to be a potential therapy for COVID-19 disease in view of the findings reported by the reviewed studies. Further, its safety has been well established by an RCT on a large population. In the present circumstances of unsatisfactory pharmacological therapy and urgent need for a successful curative remedy, considering CP therapy is justifiable provided RCTs confirm its efficacy. In addition, the challenges addressed in the current review need to be addressed at the earliest opportunity.

Author contributions

Conception and design: DK and MSA; Data production, analysis, and/or interpretation: DK, MSA, RS and NJ; writing the manuscript: DK, MSA, and RS. All authors reviewed the manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Fundig

The authors received no financial support for the research, authorship, and/or publication of this article.

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