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The Progress and Challenges of Convalescent Plasma Therapy for Coronavirus Disease 2019

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Abstract

Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and SARS-CoV-2 infection (causing coronavirus disease 2019 [COVID-19]) are serious diseases. To date, no effective post-exposure prophylaxis, prevention, or therapeutic agents are recommended as effective for these diseases. Convalescent plasma (CP), donated by individuals with established humoral immunity to the virus after recovering from coronavirus infection, has been successfully applied to treat several infectious diseases, including SARS, MERS, and COVID-19. Nonetheless, there are obstacles and challenges to using CP that should be taken into account. In this review, we summarize the evidence derived from clinical attempts to treat COVID-19 with CP, which represents a promising therapy for severe coronavirus infection. Furthermore, we outline the remaining challenges and general issues that should be considered when using CP treatment for therapeutic or prophylactic purposes.

Keywords: Clinical trial; Convalescent plasma; COVID-19

Introduction

The coronavirus family causes a variety of diseases, such as the common cold, and more serious diseases, such as severe acute respiratory syndrome (SARS) (causing an outbreak in 2003) and Middle East respiratory syndrome (MERS) (causing an outbreak in 2012), which represent dangerous respiratory disease. The recent outbreak of novel SARS-CoV-2, which causes coronavirus disease 2019 (COVID-19), has resulted in a worldwide pandemic. Up to November 30, 2020, over 62.629 million COVID-19 cases have been reported in 191 countries or regions, resulting in over 1.458 million deaths.[1] The spread of COVID-19 is more severe than that of SARS and MERS, resulting in a global health crisis. Consequently, scientists and physicians are urged to develop effective and safe therapeutic strategies to cure this disease.

To date, no effective post-exposure prophylaxis and prevention for COVID-19, and no specific anti-SARS-CoV-2 agents, are recommended as effective for COVID-19. Some drugs are being investigated, such as lopinavir/ritonavir, chloroquine, and remdesivir; however, their efficacy is in dispute.[2,3] Lopinavir/ritonavir has been recommended to treat COVID-19 in Chinese guidelines; however, lopinavir-ritonavir was shown to have no treatment benefit for severe COVID-19 in a recent trial;[4] therefore, a definite effect remains to be confirmed. Remdesivir

has been reported to possess a potential anti-viral effect, and is considered as one of the best hopes to treat COVID-19.[5] Remdesivir has been shown to improve clinical status, and shorten the hospital stay of patients with COVID-19,[6–8] however, treatment with remdesivir provided no significant effect to reduce mortality in seriously ill patients with COVID-19 in another randomized, double-blind, placebo-controlled, multi-center trial.[9] The anti-malarial drug hydroxychloroquine has been shown to reduce the SARS-CoV-2 viral load or reduce the risk of progression to severe illness in patients with COVID-19. However, several studies showed that hydroxychloroquine administration to patients with mild-to-moderate COVID-19 did not produce a significantly higher probability of negative conversion compared with that of standard care alone.[10–13] Hydroxychloroquine recipients experienced higher rates of adverse events compared with those in non-recipients.[14] Furthermore, in the absence of an effective vaccine, alternative strategies to treat COVID-19 are urgently required.

The therapeutic potential of convalescent plasma

Convalescent plasma (CP) therapy has been used to prevent and treat infectious diseases for over a century. Suppression of viremia by the antibodies present in CP is one possible reason for its therapeutic use.[15] CP obtained from patients with an established humoral immunity against the virus and who recovered, comprises abundant neutralizing antibodies (NAb) that could neutralize virus and lead directly to its eradication.[16–19] The antibody-mediated therapeutic effect of CP might act via other mechanisms, such as phagocytosis, antibody-dependent cellular cytotoxicity, and complement activation.[20] In addition to NAb, other proteins in CP such as anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, pentraxins, and other undefined proteins may provide further benefits such as immunomodulation via amelioration of systemic hyper-inflammation, which was supposed to be an important

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mechanism of disease deterioration in COVID-19 patients.[17] Since 2000, SARS, MERS, H5N1, and H1N1 pandemics have been treated successfully using CP.[21–24] Early CP treatment for SARS was reported to be associated with a decreased viral load, a reduction in hospital stay, and lower mortality.[21,25,26] The CP therapeutic approach was recommended as an empirical treatment during outbreaks of Ebola in 2014, and a protocol for using CP to treat MERS coronavirus has been established.[27] Considering the similar virological and clinical characteristics among COVID-19, MERS, and SARS, CP obtained from an infected person who has recovered from SARS-CoV-2 infection was considered as a promising option to treat COVID-19.[28,29] A patient who has recovered from COVID-19 and has a high titer of SARS-CoV-2 specific NAb might be a valuable CP donor.[30] CP treatment for COVID-19 is also suggested to alleviate the inflammation and overactivation of the immune system, which also suggested that CP could be a promising approach to treat COVID-19; such that a study provided evidence that all enrolled patients showed increased oxygen saturation levels and lymphocyte counts, together with improved liver function and decreased C-reactive protein.[30]

CP clinical trials for coronavirus infection disease

There are no specific anti-viral treatments that are effective to manage COVID-19; therefore, clinicians have turned to CP as a last resort to improve the survival of patients with severe coronavirus infection. Studies have shown that CP could be successfully employed to treat several coronavirus infection diseases, including SARS-CoV[21,26,31–34] and MERS-CoV [Table 1].[22,35]

Several studies applied CP to treat SARS and indicated that CP exhibited a neutralizing antibody response toward the S protein of SARS-CoV-2. These antibodies block the entry of SARS-CoV into cells via angiotensin I converting enzyme 2 and could be detected up to 2 years after SARS-CoV infection.[36] Thus, it was hypothesized that patients infected with SARS-CoV-2 would benefit from CP transfusion.

During the early phase of the COVID-19 pandemic, some clinical trials, especially in China, were conducted to employ CP to treat COVID-19, and safety and efficacy were evaluated. Subsequently, several clinical trials on the safety and efficacy of CP administration to treat COVID-19 patients all over the world have been published [Table 1]. Duan et al.[30] assessed 10 patients with severe COVID-19 administered with one dose (200 mL) of CP infusion, who showed good tolerance and achieved SARS-CoV-2 ribonucleic acid negativity, improved clinical symptoms within 3 days, and lung lesion absorption within 7 days, which were accompanied by a high neutralizing antibody level. Shen et al. reported that five critically ill patients with acute respiratory distress syndrome were transfused with CP containing NAb. These patients also received antiviral agents, methylprednisolone, and mechanical ventilator support. After the above treatment, their clinical status improved significantly, and three patients were discharged from the hospital after 51–55 days of hospitalization, and two patients under an incubation period of 37 days.[37] Ye et al. reported that six patients with COVID-19 were transfused with blood types (ABO)-compatible CP with no obvious adverse effect. Five patients showed absorption of lung lesions, two patients achieved SARS-CoV-2 ribonucleic acid negativity, and two patients had increased serum titers of anti-SARS-CoV-2 antibodies immediately.[38] Zhang et al. tested six donors who had recovered from COVID-19 for anti-SARS-CoV-

2 antibodies using ELISA. Five of the samples tested weakly positive for suspicious IgM positivity and high titers of IgG. One patient who needed invasive mechanical ventilation received 200 mL CP from one of the above donors and did not require mechanical ventilation at 11 days post-CP transfusion.[39] Zhang et al. reported that four critically ill patients with COVID-19, including a pregnant woman, received CP transfusions within 200–2400 mL, among whom the pregnant woman was given a 300 mL CP transfusion. No serious adverse events were observed. The clinical status of all patients improved, and for all patients, repeated RT-PCR tests of respiratory samples were negative for SARS-CoV-2.[40] The aforementioned trials were mainly case series without a group control, Abolghasemi et al. reported a non-randomized multi-center case control clinical study that 115 patients with COVID-19 received 500 mL CP transfusion initially, and another 500 mL of CP were infused into patients at 24 hours after the initial transfusion according to the physician's decision. The results indicated that patient survival improved, the hospitalization period decreased significantly, and the need for intubation declined after CP administration.[41] Olivares-Gazca et al.[42] reported that 10 critically ill patients with COVID-19 received 200 mL of ABO-compatible CP transfusion, after which their overall respiratory function and clinical condition improved, and no adverse events were observed. Salazar et al. reported that 25 patients with severe or life-threatening COVID-19 were administered with 300 mL CP, after which most patients showed an improved clinical status, and no serious adverse events occurred; moreover, no correlation was found between strain genotype and disease severity.[43] In another report, 26 patients with severe COVID-19 were administered with 200 mL of CP transfusion, and those with early-stage COVID-19 who did not require mechanical ventilation improved after CP treatment, and no severe adverse effects were found.[44] An open-label, multi-center, randomized clinical trial was published recently by Li et al., which enrolled 103 patients with severe or life-threatening COVID-19. Fifty-two patients received standard treatment and 4–13 mL/kg body weight of ABO-compatible CP (400 mL total) transfusions, the other 51 patients received standard treatment only. Overall, between the patients treated with CP plus standard care and those treated with standard care alone, there was no statistically significant improvement in time to clinical improvement within 28 days.[45] Xia et al.[46] reported that 138 patients received 200–400 mL of ABO-compatible CP at a median time of 45 days after symptom onset, no severe adverse effects were observed, and the symptoms and mortality in patients with severe or critical COVID-19 improved. Liu et al. studied 39 patients with severe or life-threatening COVID-19 to assess CP therapy effectiveness using a retrospective, propensity score-matched case-control study. Approximately 500 mL of ABO type-compatible CP was transfused into each patient, and they found that the rate of oxygen requirement in the CP group was less than that in the control group and survival improved in the CP group; moreover, no significant transfusion-related morbidity or mortality was observed in the CP group; however, anaphylaxis, while rare, could occur.[47] Zeng et al. reported that eight patients with COVID-19 who were critically or severely ill received 200–400 mL of CP treatment. They found that all patients tolerated CP well without any adverse effects, six of eight patients showed an improved clinical status (oxygen support and pulmonary lesions), the viral load was decreased to a negative in five patients, and laboratory parameters tended to improve in most patients; additionally, the results implied that the clinical efficacy might be

Table 1: The clinical trials of convalescent plasma treatment for coronavirus infection diseases

Source	Disease	Study design	Patients (n)* / Male/female† / Age‡	Intervention	Summary findings	Primary sponsor	Reference	Admission date
Cheng et al. (2005)	SARS	Retrospective Cohort Study	* 80 † 37/43 ‡ Range: 21–82	Patients were given CP (range, 160–640 mL) around day 14 (range, 7–30 days) following the onset of symptoms.	(1) No adverse effects. (2) Patients receiving CP had a lower mortality rate. (3) No correlation between clinical outcome and either the volume of infused CP or the titers of coronavirus antibody.	Prince of Wales Hospital, Hong Kong, China.	[21]	Between March 10, 2003, and May 20, 2003.
Soo et al. (2004)	SARS	Retrospective comparison study	CP group: * 19 † NA ‡ Mean: 38.7 ±12.39 Steroid group: * 21 † NA ‡ Mean: 47.9±19.60	200–400 mL of CP was transfused into each patient.	(1) No immediate adverse effects. (2) CP should be more effective when given early in the course of the disease.	Prince of Wales Hospital, Hong Kong, China.	[26]	Between March 10, 2003, and April 10, 2003.
Yeh et al. (2005)	SARS	Uncontrolled case series	* 3 † 1/2 ‡ 44, 26, 25	500 mL of CP was transfused into each patient.	(1) No adverse effects. (2) All three patients survived. (3) The anti-SARS- CoV antibody can transfer from the mother to the infant.	Taipei Municipal Hoping Hospital, Taiwan, China.	[31]	April 22, 2003.
Wong et al. (2003)	SARS	Case report	* 1 † 0/1 ‡ 57	200 mL of CP was transfused into the patient.	(1) No adverse effects. (2) The fever subsided, chest X-ray showed further resolution of basal lung infiltrates.	Prince of Wales Hospital, Hong Kong, China.	[32]	From mid-February to mid-March, 2003.
Kong et al. (2003)	SARS	Case report	* 1 † 0/1 (pregnant) ‡ 28	500 mL of plasma was transfused into the patient by two batches at 12 hours interval.	(1) No adverse effects. (2) Oxygen saturation and pulse improved. (3) Came off the respirator and the lung shadows had distinctly faded.	Apheresis Department, Shenzhen Blood Center, China.	[33]	March 28, 2003.
Zhou et al. (2003)	SARS	Case report	* 1 † 1/0 ‡ 74	50 mL of CP was transfused into the patient.	(1) No adverse effects. (2) Shorter hospital stay.	Beijing 302 Hospital, China	[34]	March 5, 2003, to April 14, 2003.
Ko et al. (2018)	MERS	Case series	* 3 † 3/0 ‡ 55, 32, 32	Four donors provided CP to three recipients.	(1) All patients survived. (2) The antibody titers should be tested and the neutralization activity of a PRNT titer ≥1:80 might be required.	Samsung Medical Center, Seoul, Republic of Korea.	[22]	During the 2015 Korean MERS outbreak.
Chun et al. (2016)	MERS	Case report (letter to editor)	* 1 † 1/0 ‡ 32	250 mL of CP from a female donor was transfused into the patient.	(1) CP infusion led to possible TRALI. (2) CP therapy should be cautiously approached. (3) It is recommended that CP be processed from male donors only.	Samsung Medical Center, Seoul, Korea.	[35]	June 16, 2015.
Duan et al. (2020)	COVID-19	Uncontrolled case series of 10 patients	* 10 † 6/4 ‡ Range: 34–78	200 mL of CP with neutralization activity >1: 640 was transfused into each patient.	(1) No severe adverse effects. (2) One dose of CP with a high antibody titer (>1: 640) can rapidly reduce the viral load and tends to improve clinical outcomes. (3) The recovered patients with COVID-19 with neutralizing antibody titer above 1:640 were considered as suitable donors.	(1) Wuhan Jinyintan Hospital, (2) the Jiangxia District Hospital of Integrative Traditional Chinese and Western Medicine, (3) the First People's Hospital of Jiangxia District, Wuhan, China.	[30]	From January 23, 2020, to February 19, 2020.
Shen et al. (2020)	COVID-19	Uncontrolled case series of 5 critically ill patients	* 5 † 3/2 ‡ Range: 36 –73	2 consecutive transfusions of 200 to 250 mL of ABO- compatible CP (400 mL total) to the patients.	All patients showed an improved clinical status.	Shenzhen Third People's Hospital, Shenzhen, China.	[37]	From January 20, 2020, to March 25, 2020.

(continued)

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Table 1 (continued).

Source	Disease	Study design	* Patients (n) † Male/female ‡ Age	Intervention	Summary findings	Primary sponsor	Reference	Admission date
Ye et al. (2020)	COVID-19	Uncontrolled case series of 6 critically ill patients	*6 †3/3 ‡Range: 28–75	1–3 batches of ABO-compatible CP were transfused into the patients (200 mL for each batch)	(1) No adverse events. (2) Lung lesions disappearances were recorded in five patients; elimination of SARS-CoV-2 was seen in two patients; anti-virus antibodies titers were increased in two patients.	Wuhan Huoshenshan Hospital. Hubei, China.	[38]	From March 5, 2020, to March 18, 2020.
Zhang et al. (2020)	COVID-19	Case report	*1 †0/1 ‡64	200 mL of CP was transfused into the patient.	(1) No adverse events. (2) The critically ill patient achieved a favorable outcome.	The Second Hospital of Nanjing University of Chinese Medicine, Nanjing, China.	[39]	During the COVID-19 outbreak, 2020.
Zhang et al. (2020)	COVID-19	Uncontrolled case series of 4 critically ill patients	*4 †2/2 (including a pregnant woman) ‡Range: 31 –73	The CP were administrated to four patients, respectively as follow: A: 900 mL (3 batches transfusion) B: 200 mL C: 2,400 mL (8 batches transfusions) D: 300 mL	(1) No serious adverse event. (2) Improvement in clinical status of all patients. (3) SARS-CoV-2 by repeat RT-PCR tests were negative for all patients.	The First Affiliated Hospital of Jinan University, Guangzhou, China.	[40]	From January 30, 2020, to March 17, 2020.
Abolghasemi et al. (2020)	COVID-19	Nonrandomized multi-center clinical trial.	CP group: *115 †67/48 ‡Mean: 54.41±13.71 Control: *74 †37/37 ‡Mean: 56.83±14.98	The first 500 mL (one unit) of CP was infused within four hours and if the patient did not show any improvement after 24h, based on the decision of responsible physician, another unit of plasma was administrated.	(1) No adverse effects. (2) CP treatment improved patients' survival, significantly reduced the hospitalization period and the need for intubation.	Baqiyatallah Hospital, MasihDaneshvari Hospital, Labbafinejad and RasoolAkram (Tehran), Beheshti Hospital (Qom), Qarazi Hospital (Isfahan) and Sadouqi Hospital (Yazd), Iran.	[41]	Between March to April, 2020.
Olivares-Gazca et al. (2020)	COVID-19	Uncontrolled case series of 10 critically ill patients	*10 †10/0 ‡Range:27–72	200 mL of ABO-compatible CP transfused to each patient.	(1) No adverse effect. (2) Improved overall respiratory function and clinical condition.	Centro de Hematología y Medicina Interna, Clínica Ruiz, Puebla, Pue, Mexico.	[42]	Between April 17, 2020, and May 8, 2020.
Salazar et al. (2020)	COVID-19	Uncontrolled case series of 25 critically ill patients.	*25 †11/14 ‡Range:22–77	All patients received one 300 mL of CP, and one patient received a second transfusion 6 days after the initial transfusion.	(1) No adverse effect. (2) Improved clinical status. (3) Did not identify a strain genotype-disease severity correlation.	Houston Methodist hospitals, Texas.	[43]	From March 28, 2020, through April 28, 2020.
Erkurt et al. (2020)	COVID-19	Uncontrolled case series of 26 severely ill patients.	*26 †18/8 ‡Mean: 67.4±15.5	200 mL of CP was transfused into each patient.	(1) No severe adverse effects. (2) Patients with early-stage COVID -19 who did not need mechanical ventilation, improved with CP treatment.	Inonu University, Turgut Ozal Medical Center, Adult Hematology Department, Malatya, Turkey.	[44]	NA
Li et al. (2020)	COVID-19	Open-label, multicenter, randomized clinical trial for 103 severe and life-threatened patients.	CP group: *52 †27/25 ‡Range:62–80 Control group: *51 †33/18 ‡Range:63–76	4–13mL/kg body weight of ABO-compatible CP (400 mL total) was transfused into the patients. All enrolled patients received standard treatment.	(1) Two patients in the CP group experienced adverse events within hours after transfusion. (2) CP did not result in a statistically significant improvement in time to clinical improvement within 28 days.	Institute of Blood Transfusion of the Chinese Academy of Medical Sciences; Union Hospital of Tongji Medical College of Huazhong University of Science and Technology; the Guanggu District Maternal and Child Health Hospital of Hubei Province; Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology; General Hospital of the Central Theater Command of the People's Liberation Army; Wuhan Red Cross Hospital; Wuhan Asia Heart Hospital; Wuhan Pulmonary Hospital, Hubei, China.	[45]	From February 14, 2020, to April 28, 2020.

(continued)

Table 1 (continued).

Source	Disease	Study design	Patients (n)* Male/female† Age‡	Intervention	Summary findings	Primary sponsor	Reference	Admission date
Xia et al. (2020)	COVID-19	Open-label, nonrandomized, controlled single-center clinical trial.	CP group: * 138 † 77/61 ‡ Range: 57–73 Control group: * 1430 † 720/710 ‡ Range: 53–71	200–400 mL of ABO-compatible CP was transfused into each patient.	(1) No severe adverse effects. (2) CP treatment could improve the symptoms and mortality in patients with severe or critical cases of COVID-19.	Wuhan Huoshenshan Hospital, China.	[46]	From February 4, 2020, to March 30, 2020.
Liu et al (2020)	COVID-19	Retrospective, propensity score-matched case-control study	CP group: * 39 † 25/14 ‡ Mean: 55 ±13 Control group: * 156 4:1 matched to CP	Two units (250 mL/Unit) of ABO type- compatible CP was transfused into each patient.	(1) The rate of oxygen requirement was less in the CP group than in the control group. (2) Survival improved in the CP group. (3) No significant transfusion-related morbidity or mortality was observed in CP; however, anaphylaxis, while rare, can occur.	The Mount Sinai Hospital, New York	[47]	Between March 24, 2020, and April 8, 2020.
Zeng et al (2020)	COVID-19	Multi-center case series study	* 8 † 4/4 ‡ Range: 46–84	200–400 mL of CP was transfused into each patient.	(1) No adverse events were observed. (2) Most patients showed improved clinical status. (3) Laboratory parameters tended to improve in most patients. (4) Viral load was decreased to a negative value. (5) Clinical efficacy might be associated with CP transfusion time, transfused dose, and the NAb levels of CP.	Chongqing Public Health Medical Center; Chongqing Three Gorges Central Hospital; Yongchuan Hospital of Chongqing Medical University, Affiliated Hospital of North Sichuan Medical College, China	[48]	From February 17, 2020, to April 10, 2020.
Rogers et al (2020)	COVID-19	A matched cohort study	CP group: * 64 † 27/37 ‡ Range: 47–70 Control group: * 177 † 82/95 ‡ Range: 50–75	1–2 units of CP were transfused into each patient.	(1) The risk of in-hospital mortality between the two groups showed no significant difference. (2) The overall rate of hospital discharge between the two groups was not significantly different. (3) The frequency of transfusion reactions in the CP group was greater than expected.	Rhode Island Hospital; The Miriam Hospital; Newport Hospital, USA	[49]	Prior to May 31, 2020.

* Indicates number of patients enrolled.
† Indicates gender information of patients enrolled.
‡ Indicates age information of patients enrolled.
COVID-19: Coronavirus disease 2019; CP: Convalescent plasma; MERS: Middle East respiratory syndrome; NA: Not available; SARS: Severe acute respiratory syndrome; TRALI: Transfusion-related acute lung injury.

associated with CP transfusion time, transfused dose, and the NAb levels of CP.[48] Rogers et al. explored a matched cohort study, in which 64 patients with COVID-19 received CP and another 177 matched patients were enrolled as controls. One to two units of CP were transfused into each patient in the CP group. The results showed that between the two groups, the overall hospital discharge rate and the risk of in-hospital mortality were not significantly different, but there was a signal for improved outcomes among the elderly, necessitating further studies within this subgroup.[49] Despite growing evidences supporting the use of CP for treatment of COVID-19, further studies are necessary to fully characterize its safety and efficacy.

Safety issues and obstacles to CP application

Although clinical trials using CP to treat coronavirus infection have comprised small case series including no controls, and few have been performed in a randomized manner, they have shown favorable results, such as no severe adverse event and some degree of benefit.[2,17] However, the safety issues and some important aspects should be taken into account, including the following: (1) case inclusion criteria suitable for CP treatment for therapeutic or prophylactic purposes, including sex, age, clinical indications or clinical classification of COVID-19, and eligibility criteria to collect the donors of convalescent COVID-19 patients, which might be based on national regulations; (2) a standard procedure for the screening and collection of COVID-19 plasma, including obtaining plasma during convalescence in a licensed blood center; (3) quality control and follow-up monitoring focusing on the risks of serum transmissible infectious diseases (such as hepatitis B, hepatitis C viruses, and HIV) and antibody-dependent enhancement of infection, which can lead to worsened symptoms in secondary viral infections, transfusion-associated circulatory overload, and transfusion-related acute lung injury (TRALI);[50–52] (4) the interference effects of other therapies, such as anti-viral drugs, steroids, and immunoglobulin; (5) the optimal NAb titer of the donated CP, the optimal dosage, the time line, and the batch of administration of CP for therapy or prophylaxis; (6) NAb assays are not widely available, and there is a lack of clarity regarding the relationship between neutralizing anti-SARS-CoV-2 and total anti-SARS-CoV-2 antibodies; (7) the definite efficacy should be confirmed by multi-center, larger scale, randomized controlled trials;[53] and (8) how to reduce the high cost, should also be considered.

Prospects

The world urgently requires the development of a specific treatment for COVID-19 that ameliorates disease symptoms and reduces mortality. Until such treatments are available, CP treatment might represent a feasible response to the ever increasing number of cases and deaths from COVID-19.[29] As more patients with COVID-19 recover, the number of potential CP donors will increase. Nevertheless, CP's therapeutic effectiveness cannot be inferred without a controlled clinical trial. Even if the existing data support the safety and potential efficacy of CP, high-quality, large-scale, randomized controlled trials are needed before using CP as standard care for COVID-19.

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Author Contributions

Ming Shi and Chao Zhang drafted the manuscript. Fu-Sheng Wang critically revised the manuscript. All the authors reviewed and approved the final manuscript.

Conflicts of Interest

None.

References

[1] COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Available from: https://coronavirus.jhu.edu/map.html. Accessed November 30, 2020.

[2] Syal K. COVID-19 herd immunity and convalescent plasma transfer therapy. J Med Virol 2020;92(9):1380–1382. doi: 10.1002/jmv.25870.

[3] Zhang JC, Xie B, Hashimoto K. Current status of potential therapeutic candidates for the COVID-19 crisis. Brain Behav Immun 2020;87:59–73. doi: 10.1016/j.bbi.2020.04.046.

[4] Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N Engl J Med 2020;382(19):1787–1799. doi: 10.1056/NEJMoa2001282.

[5] Ledford H. Hopes rise for coronavirus drug remdesivir. Nature 2020;doi: 10.1038/d41586-020-01295-8. Online ahead of print.

[6] Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382(10):929–936. doi: 10.1056/NEJMoa2001191.

[7] Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe covid-19. N Engl J Med 2020;382(24):2327–2336. doi: 10.1056/NEJMoa2007016.

[8] Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of covid-19 - Final Report. N Engl J Med 2020;383(19):1813–1826. doi: 10.1056/NEJMoa2007764.

[9] Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicenter trial. Lancet 2020;395(10236):1569–1578. doi: 10.1016/S0140-6736(20)31022-9.

[10] Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;56(1):105949. doi: 10.1016/j.ijantimicag.2020.105949.

[11] Mahévas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ 2020;369:m1844. doi: 10.1136/bmj.m1844.

[12] Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. JAMA 2020;323(24):2493–2502. doi: 10.1001/jama.2020.8630.

[13] Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med 2020;382(25):2411–2418. doi: 10.1056/NEJMoa2012410.

[14] Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020;369:m1849. doi: 10.1136/bmj.m1849.

[15] Chen L, Xiong J, Bao L, et al. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis 2020;20(4):398–400. doi: 10.1016/S1473-3099(20)30141-9.

[16] Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus 2016;14(2):152–157. doi: 10.2450/2015.0131-15.

[17] Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest 2020;130(6):2757–2765. doi: 10.1172/JCI138745.

[18] Kumar GV, Jeyanthi V, Ramakrishnan S. A short review on antibody therapy for COVID-19. New Microbes New Infect 2020;35:100682. doi: 10.1016/j.nmni. 2020.100682.

[19] Arabi YM, Hajeer AH, Luke T, et al. Feasibility of using convalescent plasma immunotherapy for MERS-CoV infection, Saudi Arabia. Emerg Infect Dis 2016;22(9):1554–1561. doi: 10.3201/eid2209.151164.

[20] Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19. J Clin Invest 2020;130(4):1545–1548. doi: 10.1172/JCI138003.

[21] Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24(1):44–46. doi: 10.1007/s10096-004-1271-9.

[22] Ko JH, Seok H, Cho SY, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther 2018;23(7):617–622. doi: 10.3851/IMP3243.

[23] Zhou B, Zhong N, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) infection. N Engl J Med 2007;357(14):1450–1451. doi: 10.1056/NEJMc070359.

[24] Hung IF, To KK, Lee CK, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis 2011;52(4):447–456. doi: 10.1093/cid/ciq106.

[25] Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211(1):80–90. doi: 10.1093/infdis/jiu396.

[26] 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(7):676–678. doi: 10.1111/j.1469-0691.2004.00956.x.

[27] Arabi Y, Balkhy H, Hajeer AH, et al. 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. doi: 10.1186/s40064-015-1490-9.

[28] Epstein J, Burnouf T. Points to consider in the preparation and transfusion of COVID-19 convalescent plasma. Vox Sang 2020;115(6):485–487. doi: 10.1111/vox.12939.

[29] Zhou M, Zhang X, Qu J. Coronavirus disease 2019 (COVID-19) a clinical update. Front Med 2020;14(2):126–135. doi: 10.1007/s11684-020-0767-8.

[30] Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci USA 2020;117(17):9490–9496. doi: 10.1073/pnas.2004168117.

[31] Yeh KM, Chiueh TS, Siu LK, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J Antimicrob Chemother 2005;56(5):919–922. doi: 10.1093/jac/dki346.

[32] Wong VW, Dai D, Wu AK, et al. Treatment of severe acute respiratory syndrome with convalescent plasma. Hong Kong Med J 2003;9(3):199–201.

[33] Kong L. Severe acute respiratory syndrome (SARS). Transfus Apher Sci 2003;29(1):101. doi: 10.1016/j.transci.2020.102790.

[34] Zhou XZ, Zhao M, Wang FS, et al. Epidemiologic features, clinical diagnosis and therapy of first cluster of patients with severe acute respiratory syndrome in Beijing area. Zhonghua Yi Xue Za Zhi 2003;83(12):1018–1022.

[35] Chun S, Chung CR, Ha YE, et al. Related acute lung injury following convalescent plasma transfusion in a patient with Middle East respiratory syndrome. Ann Lab Med 2016;36(4):393–395. doi: 10.3343/alm.2016.36.4.393.

[36] Liu W, Fontanet A, Zhang PH, et al. Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. J Infect Dis 2006;193(6):792–795. doi: 10.1086/500469.

[37] Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020;323(16):1582–1589. doi: 10.1001/jama.2020.4783.

[38] Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol 2020;92(10):1890–1901. doi: 10.1002/jmv.25882.

[39] Zhang L, Pang R, Xue X, et al. Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of six donors who have recovered from COVID-19. Aging (Albany NY) 2020;12(8):6536–6542. doi: 10.18632/aging.103102.

[40] Zhang B, Liu S, Tan T, et al. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. Chest 2020;158(1):e9–e13. doi: 10.1016/j.chest.2020.03.039.

[41] Abolghasemi H, Eshghi P, Cheraghali AM, et al. Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: results of a multicenter clinical study. Transfus Apher Sci 2020;59(5):102875. doi: 10.1016/j.transci.2020.102875.

[42] Olivares-Gazca JC, Priesca-Marín JM, Ojeda-Laguna M, et al. Infusion of convalescent plasma is associated with clinical improvement in critically ill patients withCOVID-19: a pilot study. Rev Invest Clin 2020;72(3):159–164. doi: 10.24875/RIC.20000237.

[43] Salazar E, Perez KK, Ashraf M, et al. Treatment of coronavirus disease 2019 (COVID-19) patients with convalescent plasma. Am J Pathol 2020;190(8):1680–1690. doi: 10.1016/j.ajpath.2020.05.014.

[44] Erkurt MA, Sarici A, Berber İ, et al. Life-saving effect of convalescent plasma treatment in covid-19 disease: clinical trial from eastern Anatolia. Transfus Apher Sci 2020;59(5):102867. doi: 10.1016/j.transci.2020.102867.

[45] Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020;324(5):1–11. doi: 10.1001/jama.2020.10044.

[46] Xia X, Li K, Wu L, et al. Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. Blood 2020;136(6):755–759. doi: 10.1182/blood.2020007079.

[47] Liu STH, Lin HM, Baine I, et al. Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study. Nat Med 2020;26(11):1708–1713. doi: 10.1038/s41591-020-1088-9.

[48] Zeng H, Wang DF, Nie JM, et al. The efficacy assessment of convalescent plasma therapy for COVID-19 patients: a multi-center case series. Signal Transduct Target Ther 2020;5(1):219. doi: 10.1038/s41392-020-00329-x.

[49] Rogers R, Shehadeh F, Mylona EK, et al. Convalescent plasma for patients with severe COVID-19: a matched cohort study. Clin Infect Dis 2020;ciaa1548. doi: 10.1093/cid/ciaa1548. Online ahead of print.

[50] Wan Y, Shang J, Sun S, et al. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. J Virol 2020;94(5):e02015–e2019. doi: 10.1128/JVI.02015-19.

[51] Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest 2020;130(4):1545–1548. doi: 10.1172/JCI138003.

[52] MacLennan S, Williamson LM. Risks of fresh frozen plasma and platelets. J Trauma 2006;60(6 Suppl):S46–50. doi: 10.1097/01.ta.0000199546.22925.31.

[53] Shankar-Hari M, Estcourt L, Harvala H, et al. Critical Care-Convalescent plasma to treat critically ill patients with COVID-19: framing the need for randomised clinical trials. Critical Care 2020;24(1):449. doi: 10.1186/s13054-020-03163-3.

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