Should convalescent plasma be used for COVID-19?

This clinical evidence summary outlines existing evidence on the use of convalescent plasma in patients with COVID-19. The information may be revised as new evidence emerges. The summary is not exhaustive of the subject matter and does not replace clinical judgement. The responsibility for making decisions appropriate to the circumstances of the individual patient remains at all times with the healthcare professional.

Background

Convalescent plasma is blood plasma from a person who has recovered from an infection. It contains antibodies against the infection such as SARS-CoV-2. Recovered patients with high titres of neutralising antibodies can donate plasma for administration to those at-risk to prevent infection (prophylaxis) or to those with confirmed disease to reduce symptoms and mortality.[1] This is known as passive antibody therapy or passive immunotherapy.

Convalescent plasma can be fractionated to immunoglobulin for intravenous use (IVIG), which contains concentrated globulin from pooled human plasma with the benefit that it can be given in a smaller volume and is a more uniform product compared with plasma. Hyperimmune immunoglobulin (H-IVIG) is IVIG chosen for its high titre of specific antibodies.[2]

Published articles have suggested convalescent plasma could be a potential treatment option for COVID-19 citing its use and perceived efficacy in SARS, Ebola virus, H1N1, and MERS outbreaks[1,3] and international news coverage has reported on its use in China.[4-6]

The Food and Drug Administration (FDA) in the USA has issued Emergency Use Authorisation (EUA) for COVID-19 convalescent plasma in patients who are hospitalised with COVID-19.[7] The FDA concluded that the known and potential benefits outweigh the known and potential risks of COVID-19 convalescent plasma, while noting that well-conducted randomised controlled trials (RCTs) remain necessary for a definitive demonstration of efficacy. In addition, the FDA, National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) have developed guidance to coordinate collection and use of COVID-19 plasma.[8]

Clinical evidence

High quality published evidence for convalescent plasma in the treatment of patients with COVID-19 is sparse; therefore, and as noted in a rapid Cochrane review,[9] decisive conclusions on relative efficacy and safety cannot yet be drawn:

- An open-label, RCT evaluated high-titre convalescent plasma versus standard therapy in 103 patients with severe or life-threatening COVID-19 in Wuhan, China (ChiCTR2000029757). The primary endpoint was time to clinical improvement within 28 days, which was either an improvement of two points on a six-point disease severity scale (from discharge to death) or patient discharge alive. No significant difference in the primary endpoint was observed between groups with 51.9% of the convalescent plasma group compared with 43.1% of the control group experiencing clinical improvement (absolute difference 8.8%; 95% confidence interval [CI]: -10.4% to 28%, and hazard ratio [HR] 1.40; 95% CI: 0.79 to 2.49, p=0.26). No difference in secondary outcomes of 28-day mortality or time to discharge was seen although 87.2% of the convalescent plasma group had a negative conversion rate of viral polymerase chain reaction compared with 37.5% of controls (odds ratio [OR] 11.39; 95% CI: 3.91 to 33.18, p<0.001). Most patients tolerated plasma transfusion well with two experiencing adverse events (AEs) that were managed with supportive care. A major limitation of the study was its early termination before full recruitment (intended n=200) due to the containment of SARS-CoV-2 in China reducing its power to detect a benefit of convalescent plasma.[10]
- A preprint article described a multicentre, open label RCT of convalescent plasma versus standard of care conducted in the Netherlands (NCT04342182). The trial was stopped early when 53 of 66 patients tested were found to have anti-SARS-CoV-2 antibodies at baseline. At

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the time of termination, no difference between arms was observed in the primary outcome of day 60 mortality or the secondary outcomes of hospital stay or day 15 disease severity.[11]

- The outcomes of 42 patients who received convalescent plasma for severe or critical COVID-19 (40 in China and two in Korea) are documented in eight articles, three of which are pre-print.[12-19] The majority saw positive clinical improvement and were considered successful and without serious adverse events (AEs) although most received a variety of therapies in addition to plasma. Better outcomes were seen in patients receiving plasma earlier. One patient experienced serious anaphylactic shock and the transfusion was considered a failure.[15] A subset of patients from China was compared with an historic matched control group which revealed a significant improvement in outcomes in favour of convalescent plasma ($p<0.001$). However, this result was derived from low-quality evidence at high risk of bias.[20]
- Six patients with respiratory failure due to COVID-19 were administered convalescent plasma in China at a median of 21.5 days after detection of viral shedding. Three days post infusion all patients tested negative for SARS-CoV-2; however, five of the six patients died. The authors concluded that convalescent plasma therapy may inhibit viral shedding but not reduce mortality in patients with end-stage COVID-19 and that treatment should be initiated earlier.[21]
- A single arm safety study of 25 patients with COVID-19 conducted in the US stated that no AEs were observed as a result of plasma transfusion.[22]
- A single arm study of ten patients in Mexico reported improvement in the sequential organ failure assessment score over eight days ($p=0.014$) in all patients and also improvement across other outcomes measured in some patients.[23]
- A preprint publication reviewing the safety of convalescent plasma in 5,000 hospitalised patients with COVID-19 reported an incidence of serious AEs of less than 1% leading the authors to conclude in favour of its safety.[24]
- An article in preprint describes 39 patients who received convalescent plasma for severe or life-threatening COVID-19 in the USA. This group was matched with retrospective controls and a comparison showed that plasma recipients were more likely to remain the same or have improvement in supplemental oxygen requirement at day 14 (OR 0.86; 95% CI: 0.75 to 0.98, $p=0.028$) and improved survival ($p=0.039$) compared with the control group.[25]

Table 1: Registered international RCTs for convalescent plasma in patients with COVID-19

Study identifier	Study Design	Intervention	Comparator(s)	Date of primary completion
NCT04264858[26]	SC, OL, clinical trial	Immunoglobulin of cured patients	ɣ-globulin	April 2020
NCT04323800[27]	DB, SC, phII, RCT	Anti-SARS-CoV-2 plasma	Non-SARS-CoV-2 immune plasma	December 2022
NCT04345289[28] EudraCT 2020 001367-88	MC, DB, phIII, RCT (6 arms)	Convalescent plasma, sarilumab, hydroxychloroquine, baricitinib,	Injective placebo, oral placebo	June 2021
NCT04332835[29]	OL, SC, phII/III, RCT	Convalescent plasma, hydroxychloroquine, azithromycin	Hydroxychloroquine, Azithromycin	August 2020
NCT04345991[30]	OL, SC, phII, RCT	Convalescent plasma	Standard of care	May 2020
NCT04345523[31]	MC, OL, phII, RCT	Convalescent plasma	Standard of care	July 2020
NCT04342182[32] [Terminated]	single blind, MC, phII/III, RCT	Convalescent plasma	Standard of care	July 2020
NCT04344535[33]	OL, SC, phI/II, RCT	Convalescent plasma	Standard plasma	April 2021
NCT04346446[34]	OL, SC, phII, RCT	Convalescent plasma	Supportive care	June 2020
NCT04333251[35]	OL, phI, RCT	High-titre anti SARS-CoV-2 plasma	Best supportive care (oxygen therapy)	December 2022
NCT04372979[36]	DB, MC, phIII, RCT	Convalescent plasma	Standard plasma	October 2020
NCT04356534[37]	OL, SC, RCT	Convalescent plasma	Standard of care	May 2020
NCT04385043[38]	OL, MC, phII/III, RCT	Hyperimmune plasma	Standard therapy	October 2020
NCT04374487[39]	OL, SC, phII, RCT	Convalescent plasma	Standard of care	May 2021
NCT04388410[40]	DB, MC, phII/III, RCT	Convalescent plasma	Placebo	October 2020
NCT04390503[41]	DB, phII, RCT	Convalescent plasma	Albumin	April 2021
NCT04348656[42]	OL, MC, phIII, RCT	Convalescent plasma	Standard of care	October 2020
NCT04384588[43]	OL, MC, phII/III,	Convalescent plasma	Convalescent plasma	April 2021
NCT04354831[44]	OL, SC, phII,	Convalescent plasma	Convalescent plasma	May 2022
NCT04380935[45]	OL, MC, phII/III, RCT	Convalescent plasma	Standard of care	August 2020

Study identifier	Study Design	Intervention	Comparator(s)	Date of primary completion
NCT04373460[46]	DB, MC, phII, RCT	Convalescent plasma	Standard plasma	December 2022
NCT04355767[47]	DB, phII, RCT	Convalescent plasma	Standard plasma	December 2022
NCT04385199[48]	OL, SC, phII, RCT	Convalescent plasma	Standard therapy	August 2020
NCT04375098[49]	OL, SC, phII, RCT	Convalescent plasma	Convalescent plasma	December 2020
NCT04377568[50]	OL, MC, phII, RCT	Convalescent plasma	Standard of care	December 2021
NCT04383535[51]	DB, MC, RCT	Convalescent plasma	Placebo	July 2020
NCT04374526[52]	OL, phII/III, RCT	Convalescent plasma	Standard therapy	September 2020
NCT04376788[53]	OL, SC, phII, RCT	Standard blood transfusion, Convalescent plasma,	Standard blood transfusion + convalescent plasma,	June 2020
NCT04381858[54]	DB, phIII, RCT	Convalescent plasma	Human immunoglobulin	August 2020
NCT04362176[55]	DB, phIII, RCT	Convalescent plasma	Ringer's solution with multivitamins	April 2021
NCT04361253[56]	DB, phIII, RCT	Convalescent plasma	Standard plasma	June 2021
NCT04366245[57]	OL, MC, phI/II, RCT	Hyperimmune plasma	Hydroxychloroquine + azithromycin or lopinavir/ritonavir + interferon β + hydroxychloroquine	December 2021
NCT04364737[58]	DB, MC, phII, RCT	Convalescent plasma	Ringer's solution or saline	January 2023
NCT04359810[59]	DB, phII, RCT	Convalescent plasma	Standard plasma	December 2020
NCT04385186[60]	SB, MC, phII, RCT	Convalescent plasma	Support treatment	September 2020
NCT04376034[61]	OL, phIII, non-randomised	Convalescent plasma	Standard of care ± convalescent plasma	March 2021
NCT04358783[62]	DB, phII, RCT	Convalescent plasma	Best available therapy	February 2021
NCT04415086[63]	OL, MC, phII, RCT	Convalescent plasma 200ml, 400ml	Standard of care	April 2022
NCT04421404[64]	DB, SC, phII, RCT	Convalescent plasma	Fresh frozen plasma	April 2021
NCT04393727[65]	OL, MC, phII, RCT	Convalescent plasma	Standard therapy	September 2020
NCT04405310[66]	DB, MC, phII, RCT	Convalescent plasma	Placebo	June 2020
NCT04395170[67]	OL, phII/III, RCT	Convalescent plasma, human immunoglobulin	Standard therapy	December 2020
NCT04391101[68]	OL, MC, phIII, RCT	Convalescent plasma	Standard therapy	June 2021
NCT04403477[69]	OL, SC, phII, RCT	Convalescent plasma 200ml, 400ml	Standard of care	July 2020
NCT04392414[70]	OL, SC, phII, RCT	Convalescent plasma	Fresh frozen plasma	August 2020
NCT04381936[71]	OL, phII/III, RCT	Corticosteroids, hydroxychloroquine, lopinavir + ritonavir, azithromycin, convalescent plasma, tocilizumab	Standard of care	December 2020
NCT04347681[72]	OL, MC, phII, RCT	Convalescent plasma	Standard therapy	December 2020
NCT04442958[73]	DB, RCT	Convalescent plasma	Standard of care	June 2020
NCT04521309[74]	SB, phI/II, RCT	SARS-CoV-2 IVIG	Standard of care	January 2021
NCT04483960[75]	OL, MC, phIII, RCT	Hydroxychloroquine, lopinavir + ritonavir, lopinavir + ritonavir + hydroxychloroquine, convalescent plasma	Standard of care	June 2021
NCT04441424[76]	OL, RCT	Convalescent plasma	Hydroxychloroquine + azithromycin	June 2020
NCT04429854[77]	OL, MC, phII, RCT	Convalescent plasma	Standard of care	November 2021
NCT04516811[78]	DB, MC, phIII, RCT	Convalescent plasma	Standard of care	December 2021
NCT04479163[79]	DB, MC, RCT	Convalescent plasma	Placebo	July 2020
NCT04468009[80]	OL, SC, phII, RCT	Convalescent plasma	Standard of care	June 2021
NCT04425915[81]	OL, MC, phIII, RCT	Convalescent plasma	Standard of care	May 2021
NCT04428021[82]	DB, phII, RCT	Convalescent plasma, standard plasma	Standard therapy	June 2021
NCT04467151[83]	DB, phII, RCT	Convalescent plasma	Placebo	October 2021
NCT04425837[84]	SB, phII/III, RCT	Convalescent plasma	Standard of care	February 2021
NCT04433910[85]	OL, MC, phII, RCT	Convalescent plasma	Best supportive care	December 2020
NCT04442191[86]	DB, SC, phII, RCT	Convalescent plasma	Placebo	May 2021
NCT04521036[87]	OL, phI/II, RCT	Convalescent plasma	Standard of care	June 2021
NCT04438057[88]	OL, SC, phII, RCT	Convalescent plasma	Standard of care	August 2020
NCT04397757[89]	OL, SC, phI, RCT	Convalescent plasma	Standard of care	September 2020
NCT04456413[90]	OL, phII, RCT	Convalescent plasma	Best supportive care	July 2021
NCT04418518[91]	OL, MC, phIII, RCT	Convalescent plasma	Standard of care	June 2021
NCT04497324[92]	OL, phII, RCT	Convalescent plasma	Standard of care	November 2020

Study identifier	Study Design	Intervention	Comparator(s)	Date of primary completion
ChiCTR2000031501[93]	OL, SC, non-RCT	Convalescent plasma	Routine treatment	July 2020
ChiCTR2000030929[94]	DB, SC, RCT	Convalescent plasma	Ordinary plasma	June 2020
ChiCTR2000030702[95]	OL, MC, RCT	Convalescent plasma	Conventional treatment	August 2020
ChiCTR2000030627[96]	SC, RCT	Convalescent plasma	Conventional treatment	May 2020
ChiCTR2000030179[97]	SC, RCT	Routine treatment plus plasma	Routine treatment	April 2020
ChiCTR2000030039[98]	MC, non-RCT	Convalescent plasma	Conventional therapy	Not stated
ChiCTR2000030010[99]	DB, SC, RCT	Anti-SARS-CoV-2 inactivated convalescent plasma	Ordinary plasma	May 2020
ChiCTR2000029850[100]	SC, non-RCT	Convalescent plasma	Standardised comprehensive treatment	Not stated
ChiCTR2000029757 [Terminated][101]	OL, MC, RCT	Convalescent plasma	Conventional treatment	Not stated
EudraCT 2020 001310-38[102]	OL, phII, RCT	Convalescent plasma	Best supportive care	Not stated
EudraCT 2020 001632-10[103]	OL, phII, RCT	Convalescent plasma	Best supportive care	Not stated

Abbreviations: DB, double-blind or better; OL, open-label, phI-III, phase I-III; RCT, randomised controlled trial; SB, single blind

Recommendations from professional bodies

The World Health Organization (WHO) recommends that plasma therapy (among other therapeutics) not be administered as treatment or prophylaxis for COVID-19 outside of a clinical trial setting.[104]

In Singapore, the National Centre for Infectious Diseases (NCID) has issued interim treatment guidelines for COVID-19, which recommend that, if remdesivir is not available or is contraindicated, convalescent plasma therapy may be considered for patients requiring oxygen or who have oxygen saturation of less than 93% on room air, in particular for patients less than 14 days from onset of illness, as part of a monitored expanded access programme.[105]

The National Institutes of Health COVID-19 Treatment Guidelines (US) state there are insufficient data to recommend for or against the use of convalescent plasma or SARS-CoV-2 immune globulins for the treatment of COVID-19.[106]

The Johns Hopkins Coronavirus COVID-19 guide proposes convalescent plasma as a useful treatment noting that RCTs are in progress. The guide also identifies risks including pathogen transmission, allergic reactions, transfusion-associated circulatory overload and transfusion-related lung injury.[107]

The China National Health Commission (NHC) has issued a seventh edition of guidance for COVID-19 diagnosis and treatment in which it refers to the use of recovered patients' plasma therapy as suitable for severe and critically severe patients with rapid disease progression.[108]

The Peking Union Medical College Hospital recommends early intravenous infusion of human immunoglobulin for critically ill patients based on their clinical condition.[109]

Conclusion

There is currently limited good quality published evidence on convalescent plasma for treating COVID-19 infection. A range of studies are underway with data expected later this year. The best evidence to date for convalescent plasma to treat COVID-19 is from an open label RCT in 103 patients in China which did not show a significant difference in clinical improvement between groups; however, the trial was terminated early before full recruitment and may not have had the necessary power to detect a benefit of convalescent plasma. The safety profile of convalescent plasma in patients with COVID-19 based on the published evidence is acceptable.

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