Should convalescent plasma be used for COVID-19?

This write-up summarises a rapid evidence review of convalescent plasma in patients with COVID-19. The information may be revised as new evidence emerges.

Background

Convalescent plasma (CP) 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 antibody 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 raised CP as a potential treatment option for COVID-19 citing its use and perceived efficacy in SARS, Ebola virus, H1N1, and MERS outbreaks.[1,3] International news coverage has reported that CP has been applied in China against COVID-19.[4-6]

The Food and Drug Administration (FDA) in the USA has listed COVID-19 CP as an emergency Investigational New Drug (eIND) for patients who are critically ill with COVID-19.[7] This allows the use of COVID-19 CP for the treatment of an individual patient by a licensed physician upon FDA authorisation. Eligible patients must have laboratory confirmed COVID-19 with severe or immediately life-threatening disease and informed consent is required. The FDA also provides guidance on the criteria for plasma collection and the eligibility of both donors and recipients.[7]

Clinical evidence

There is limited published evidence for CP, IVIG, or H-IVIG in the treatment of patients with COVID-19. A case series of five patients critically ill with COVID-19 treated with CP in Shenzhen saw clinical status improve in all patients including a reduction in viral load. At the time of publication three had been discharged from hospital and the remaining two were in a stable condition. Any inference for the efficacy of CP is indicative only as all patients received multiple other treatments including antivirals.[8]

Existing literature covers the use of these products in viral severe acute respiratory syndrome (SARS) and severe influenza and Ebola with conflicting results:

- A systematic review of CP in SARS and severe influenza showed a reduction in mortality especially when treatment was administered early (odds ratio [OR] 0.25, 95% confidence interval [CI]: 0.14 to 0.45; I^2 0%). There was limited evidence of a reduction in critical care resource use and hospitalisation. Studies were of low quality and mainly uncontrolled.[9]
- A randomised controlled trial (RCT) compared H-IVIG and placebo in 313 hospitalised participants with influenza. The primary endpoint was clinical status at day seven (described by six categories ranging from death to resumption of normal activities post discharge) and the adjusted OR was 1.25 (95% CI: 0.79 to 1.97; p=0.33). The investigators concluded that H-IVIG plus standard care (mostly oseltamivir) was not superior to placebo.[10]
- Anti-influenza plasma plus standard care was compared with standard care alone in an RCT of 98 patients hospitalised with severe influenza. No significant effect on time to normalisation of respiratory status was observed (OR 1.17 95% CI: 0.96 to 3.06; p=0.069) but treatment was well tolerated.[11] A follow up phase III RCT was terminated early and no benefit was observed.[12]
- CP was fractionated to H-IVIG and compared with IVIG in an RCT in patients with severe influenza A in the ICU requiring ventilation. Respiratory viral load was significantly lower at days

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5 (p=0.04) and 7 (p=0.02) in the H-IVIG group and subgroup analysis revealed that H-IVIG was the only factor to reduce mortality (OR 0.14; 95% CI: 0.02 to 0.92; p=0.04).[13]

- Seven out of eight patients seriously ill with Ebola virus who received convalescent blood via transfusion in a case series from the Democratic Republic of the Congo in 1995 survived.[14] However, a study in Guinea was unable to find a significant improvement in survival related to CP transfusion although it was later confirmed that antibody levels in donated CP were low.[15,16]

Seven trials have been listed on the US National Library of Medicine's register and are in planning or active recruitment phases with data anticipated to mature in the near future (Table 1). There are an additional eight interventional trials listed on the Chinese Clinical Trial Registry.

Table 1: Ongoing or planned studies for convalescent plasma in patients with COVID-19

Study identifier	Study Design	Intervention	Comparator(s)	Date of primary completion
NCT04292340 [17]	SC,† observational	Anti-SARS-CoV-2 inactivated convalescent plasma	-	July 2020
NCT04264858 [18]	SC,† OL, clinical trial	Immunoglobulin of cured patients	ɣ-globulin	April 2020
NCT04261426 [19]	SC,† OL, phII/III, RCT	IVIG	standard care	April 2020
NCT04321421 [20]	SC,‡ OL, longitudinal assessment	Hyperimmune plasma	-	May 2020
NCT04323800 [21]	DB, SC,* phII, RCT	Anti-SARS-CoV-2 plasma	Non-SARS-CoV-2 immune plasma	December 2022
NCT04327349 [22]	OL, SC,** single arm	Convalescent plasma	-	May 2020
NCT04325672 [23]	OL, SC,* phII, single arm	Anti-SARS-CoV-2 convalescent plasma	-	December 2022

Abbreviations: DB, double-blind; OL, open label, phII, phase II; phIII, phase III; RCT, randomised controlled trial; SARS, severe acute respiratory syndrome.
* USA ** Iran † China ‡ Italy

Recommendations from professional bodies

The World Health Organization (WHO) makes no official mention of CP or related products specifically in relation to COVID-19 and it does not appear in the interim clinical guidance.[24] However, Dr Mike Ryan (head of WHO health emergencies program) notes "hyperimmune globulin… has been proven "effective and life-saving" against other infectious diseases. It is a very important area to pursue [although] it has to be carefully timed and it's not always successful." [5]

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.[25]

COVID-19 operational recommendations from the Peking Union Medical College Hospital list early intravenous infusion of human immunoglobulin for critically ill patients based on their clinical condition.[26]

In addition to the eIND classification, the US FDA, National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) are developing master protocols to coordinate the collection and use of COVID-19 CP.[7]

Conclusion

There is currently limited published evidence on the use of CP for treating COVID-19 infection. Studies are underway with results expected later this year. Evidence to date for convalescent plasma (including H-IVIG) is for the treatment of other viral infections with mixed results. Positive survival benefit is based on small, low-quality studies and case reports, while two RCTs in severe influenza do not show any significant benefit.

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