How should we use convalescent plasma therapies for the management of COVID-19?

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Convalescent plasma (CP) from blood donors with antibodies to severe acute respiratory syndrome coronavirus 2 may benefit patients with COVID-19 by providing immediate passive immunity via transfusion or by being used to manufacture hyper-immune immunoglobulin preparations. Optimal product characteristics (including neutralizing antibody titers), transfusion volume, and administration timing remain to be determined. Preliminary COVID-19 CP safety data are encouraging, but establishing the clinical efficacy of CP requires an ongoing international collaborative effort. Preliminary results from large, high-quality randomized trials have recently started to be reported. (*Blood*. 2021;137(12):1573-1581)

Introduction

Convalescent plasma (CP) is collected from donors who have recovered from an infection and whose plasma contains antibodies against the agent of interest.[1-3] In the absence of other specific therapy, CP may be used as either prophylaxis or treatment to provide immediate passive immunity, transfused as clinical plasma, or further manufactured into polyclonal hyperimmune immunoglobulin preparations. CP has been used with variable success in a range of infectious diseases, including in recent decades for Middle East respiratory syndrome, severe acute respiratory syndrome (SARS) caused by SARS–coronavirus 1 (SARS-CoV-1), H1N1 influenza, and Ebola, although evidence supporting its efficacy remains limited, as reviewed elsewhere.[4-10] Where CP is of benefit, a major part of its effect is likely through the action of donor neutralizing antibodies (NAbs) against virus in the recipient.[3,11] In this Spotlight, we provide an overview of current knowledge regarding the efficacy and safety of CP for SARS–coronavirus 2 (SARS-CoV-2) infection, and considerations for future studies.

What information is already available on COVID-19 CP?

As the COVID-19 pandemic unfolded,[12] use of CP was described in early case reports and case series from China, Italy, and elsewhere, and in larger nonrandomized studies, including through "compassionate access" schemes and "emergency use authorizations."[13-21] Results of randomized controlled trials (RCTs) are now appearing[22-34] and 104 ongoing clinical trials are registered globally.

The studies reported to date have generally specified that CP is collected from donors recovered from, and transfused to patients with, confirmed laboratory diagnoses of SARS-CoV-2 infection. However, other key characteristics vary greatly between studies, including donor and product characteristics, dose (volume, and

NAb titer), timing of administration and recipient characteristics (eg, severity of illness). Some of these differences are outlined in Table 1, and discussed later in text.

Eligibility criteria for donating CP, along with collection methods, product characteristics, and clinical application, also vary internationally.[11] All usual blood-donor eligibility and product-testing requirements apply, unless specific exemptions are permitted by regulatory authorities. CP may be collected by whole-blood donation or apheresis. Whole-blood donation is more widely available. Apheresis requires specialized equipment and longer duration of donation procedure, but permits larger volumes of plasma to be donated by a single donor at one time and, more frequently, with return of red cells to the donor.

What do reports from the first RCTs in COVID-19 tell us?

Twelve RCTs have already been reported, although only 6 are published in the peer-reviewed literature; 4 were terminated early, mostly due to falling local case numbers[22-34] (Table 2). Only 1 small trial[23] showed benefit from CP for a range of outcomes (including time to clinical recovery, progression to severe disease, and mortality), although others reported benefits in secondary outcomes (eg, viral clearance).

Li et al from Wuhan, China reported outcomes for 103 adults with severe or life-threatening COVID-19, of whom 52 received CP in addition to standard care in an open-labeled RCT.[22] The trial was terminated early, and was underpowered for its primary outcome of time to clinical improvement within 28 days. Patients receiving CP had no improvement in the primary outcome, 28-day mortality, or time to discharge, but did have higher rates of viral clearance (87.2% vs 37.5%; odds ratio, 11.39 [95% confidence interval, 3.91-33.18]; $P < .001$). One nonsevere allergic reaction and 1 episode of transfusion-associated dyspnea were reported.

Table 1. Examples of differences in clinical studies of convalescent plasma for COVID-19, and their potential impact

Element variable	Types of differences and potential impact
Study design and infrastructure	

Type of study	• Access/emergency use program without randomization or control group:
	   • May be faster to establish initially; cannot determine efficacy but useful for safety data
	   • May "compete" with concurrent RCTs for participant recruitment and/or product availability
	 • Adaptive design may permit faster testing of new therapies, with fewer patients, and more rapid allocation to promising therapies as results become available
	 • Platform study: may be faster and more efficient to add new therapeutic domains (eg, CP) to established trial platform or clinical registry

Study logistics	• Informed consent: practical issues of obtaining written consent from patients in physical isolation; deferred consent may reduce barriers to study entry
	 • Ethical issues: eg, equity of access to product/study vs "right to try"
	 • Issues of blinding vs open label, for example:
	   • If using a placebo control, product appearances and difficulty ensuring adequate concealment
	   • If using a plasma control: challenges in product labeling, checking, and storage and documentation requirements to preserve blinding
	 • If CP compared with non-CP plasma, ensuring that control plasma does not contain antibody to SARS-CoV-2
	 • Wider national/international collaboration and use of standardized protocols may enable continuation and prevent studies closing prematurely

Outcomes, monitoring, and follow-up	Can be difficult to compare results between studies due to many different outcomes and duration of follow-up: eg, • Mortality • Clinical improvement (variably defined, eg, use of COVID-19/other scales) • Requirement for intensive care unit/mechanical ventilation • Length of hospital/intensive care unit stay • Viral clearance • Data for health economics analyses generally lacking so far
Adverse event reporting	• Different SAEs recorded, both transfusion-related and other, at different times, eg, within 4 h, 24 h, 7 d, longer • Variation in use of local or international definitions for categorization, severity, imputability, etc
Blood donor eligibility and characteristics	
Blood donor sex	• Many countries do not routinely collect plasma for clinical use from female (especially multiparous) blood donors to minimize the risk of TRALI • If plasma from females not used as clinical plasma for CP, may be used for fractionation for hyperimmune-immunoglobulin product
Infection type, severity, recovery	Wide range internationally of clinical severity of prior COVID-19 illness and minimum recovery period prior to donation, eg, minimum 14 vs 28 d recovery; viral mutation/strain may influence immune profile and duration of antibody response ? clinical impact
Donor adverse events	Variably defined/captured/reported by blood establishments internationally Potential impact on donor health and well-being
Intervention	

Convalescent plasma product (see also "Study logistics" above)	• Inherent biological variability: nonstandardized product
	 • Collection method (whole blood vs apheresis) and interval: influence volume of CP available and whether multiple doses are from same or different donors
	 • Dose (volume, NAb content, other specification) administered
	 • Antibody and other characteristics (minimum NAb and other content)
	 • Testing performed
	   • What is measured: eg, IgM, IgG, total, neutralizing activity, other
	   • How measured: type of test (known variation between tests, both commercial and in-house), test sensitivity, specificity (mostly lacking so far)
	 • Use of pathogen reduction technologies
	 • Timing of doses (how soon after symptoms develop, interval between doses if >1)

Standard of care, any other interventions	• Standard/usual care may vary between sites • Other interventions, if any

Table 1. (continued)

Element variable	Types of differences and potential impact
Participants Demographics, baseline characteristics, and study eligibility criteria	• Clinical status, eg, exposed but asymptomatic, mild illness, hospitalized, critically ill, ventilated (note that all trials reported to date have been in hospitalized patients) • Infection type, eg, viral mutation/strain • Immune profile, eg, endogenous NAb detectable at baseline, presence of circulating viral nucleic acid, HLA type, impairment of immune function, either underlying condition, therapy, etc, effects currently unknown • Comorbidities: patients with impaired cardiorespiratory and/or renal function may be more at risk of TACO • Few data currently available for children • ABO blood group: preliminary data suggest certain ABO blood types may be associated with susceptibility to and/or severity of infection with SARS-CoV-2

In a study from Iran by Rasheed et al, 21 critically ill patients received 400 mL of CP in addition to standard care.[23] Patients receiving CP had shorter time to clinical improvement, shorter duration of illness, and lower mortality (4.8% vs 28% in controls; $P = .03$). One mild allergic reaction was reported.

Agarwal et al from India reported on the PLACID RCT, in which 464 hospitalized adults were randomized to receive either 2 doses of 200 mL of CP (with a median NAb titer of 1:40, given 24 hours apart) or control, in addition to standard care.[24] Participants who received CP did not show any improvement in the study's primary outcome (composite of progression to severe COVID-19 disease or mortality at 28 days) compared with standard care. Detectable NAbs at study entry were later detected in 80% of participants. Three possible transfusion-related severe adverse events (SAEs) were noted.

Two open-label RCTs have been reported (in preprint). Gharbharan et al in The Netherlands enrolled 86 of a planned 426 participants, but the study closed early, in part due to the observation that 79% of patients had NAb titers comparable with those of the CP donors.[25] There were no differences in mortality, length of hospital stay, or disease severity at day 15, but the study was underpowered. No plasma-related SAEs were reported. Avendano-Sola et al from Spain reported on an RCT that terminated after enrolling 81 of a planned 278 participants with no significant difference in their primary or secondary outcomes.[26] Nearly one-half of the patients enrolled were later identified as having detectable antibodies at baseline. No confirmed plasma-related SAEs were described.

These differences in requirements for a minimum CP NAb titer, NAb-measuring assays, heterogenous patient populations, and baseline NAb prevalence in recipients are likely important.[34,35] In PLACID, NAb assays were not available at study commencement and, therefore, were not used to prospectively select CP.[24] The median NAb in CP administered across the trial was 1:40 (interquartile range, 1:30-1:80); however, only 68% of patients allocated to CP received plasma with detectable NAbs, and only 29% received CP with NAbs >1:80. If future trials fail to show benefit, an important question will be whether this relates to insufficient antibody titer of the CP (due to low NAb titer and/or volume administered). Future analyses, including individual patient data meta-analyses, may be able to examine efficacy by antibody titer, but only if reported in a standard manner, so availability of standardized testing (performed by laboratories

meeting regulatory requirements for testing of blood products) is an important practical issue and a high priority.

Many patients already have anti–SARS-CoV-2 antibodies at study entry, even in studies with a relatively short time from symptom onset to randomization; the consequence of this for whether patients are likely to benefit from CP is unknown. There may be qualitative differences in humoral response between individuals that could support the rationale for testing CP in patients with measurable NAbs. Atyeo et al reported early functional differences in humoral responses between hospitalized patients who survived and those who died of COVID-19.[36] Although they had similar levels of SARS-CoV-2–specific immunoglobulin G (IgG) and NAbs, there were other differences between the 2 groups, with a shift toward spike-specific humoral response in the patients who recovered and elevated nucleocapsid response in patients who died. There may also be qualitative and quantitative differences between the endogenous anti–SARS-2 antibodies circulating in a recently infected patient and those collected from donors who may be many weeks out from infection, for example, IgG-affinity maturation. Finally, there may be other considerations, for example, a recent report described neutralizing autoantibodies against type I interferons in patients contributing to severity of COVID-19, which may have implications for CP donors and transfusion recipients.[37]

These results highlight a number of issues with designing and interpreting clinical trials of CP, and as a consequence of several of these trials stopping early, we still have limited evidence about the efficacy of CP. However, these reports generate important information and questions for ongoing studies, including whether we should be aiming to give CP with higher titers earlier in the course of the illness, and whether this approach will lead to better outcomes for patients. Addressing the logistical and other challenges required to identify patients with no or low titers of NAbs at study entry should be a high priority. The potential benefits of CP for patients who are unable to make their own NAbs is further discussed later in text.

In the past month, three large RCTs of CP have issued public statements announcing cessation of recruitment to CP interventions based on reaching prespecified end points of futility following analysis of available data. Interim analysis of the international REMAP-CAP trial (NCT02735707) indicated that the probability that convalescent plasma was beneficial in all critically ill patients was only 2.2%.[38] Preliminary analysis of data from 10 406 hospitalized patients in the RECOVERY trial (ISRCTN50189673) from the United Kingdom showed no significant difference in the

Table 2. Summary of reported RCTs to date

Study	Country	No./Planned	Study design	Participants*	Median time from symptom onset to randomization	Intervention†	Control	NAb assay	NAb titer in donor plasma	Primary outcome
Li et al[22]	China	103/200	Open label	Laboratory confirmed SARS-CoV-2, severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, requiring MV); excluded patients with high titer S-RBD–specific IgG (≥1:640)	27 d in CP and 30 in control	4-13 mL/kg of CP	Standard care	S-RBD–specific IgG antibody titer	Minimum of S-RBD–specific IgG of 1:640 (approximately equivalent to NAb of 1:40)	Time to clinical improvement (patient discharge or reduction 2 points on 6-point disease severity scale)
Rasheed et al[23]	Iraq	49/not stated	Open label	Laboratory confirmed SARS-CoV-2, critically ill with SpO2 <90%, receiving O2 or MV	21 d in CP and 28 in control	400 mL of CP on day 1	Standard care	SARS-CoV-2 IgG (semi-quantitative) and IgM (qualitative)	52% "moderately" positive and 48% "strongly" positive	Time to recovery from critical illness (clinical improvement permitting discharge from respiratory care unit to ward)
Agarwal et al[24]	India	464/464	Open label	Laboratory confirmed SARS-CoV-2, moderately ill with either SpO2 ≤93% and RR > 24/min or PaO2/FiO2 200-300; excluded critically ill (PaO2/FiO2 <200 or shock requiring vasopressors)	8 d in CP and 8 in control	Two doses 200 mL of CP, 24 h apart, preferably different donors	Standard care	Micro-neutralization test	NAb not used to select plasma, tested at end of study: 63% of donors had NAb titer >1:20 with median titer 1:40	Composite all-cause mortality or progression to severe disease (PaO2/FiO2 <100) within day 28
Gharbharan et al[25]	The Netherlands	86/426	Open label	Laboratory confirmed SARS-CoV-2 within 96 h; excluded patients on MV >96 h	9 d in CP and 11 in control	300 mL of CP on day 1	Standard care	SARS-CoV-2 PRNT	Minimum of PRNT50 titer of ≥1:80	Mortality until discharge or maximum of 60 d
Avendano-Sola[26]	Spain	81/278	Open label	Laboratory confirmed SARS-CoV-2, radiological changes or clinical features plus SpO2 <94%, <12 d onset Excluded: MV, high flow O2	8 d in CP and control	250-300 mL of CP on day 1	Standard care	VMNT pseudovirus neutralizing ID50 assay	NAb not available to select plasma, all donation on subsequent testing had VMNT-ID50 >1:80	Proportion of patients in category 5, 6, 7 of 7-category COVID-19 ordinal scale at day 15
Libster et al, NEJM[27]	Argentina	160/210	Double-blind	Laboratory confirmed SARS-CoV-2, mild illness, not requiring hospitalization, age >74 or 65 to 74 and comorbidity, ≤48 h from symptom onset	<3 d	250 mL CP on day 1	Saline	anti-S IgG SARS-CoV-2 (COVIDAR IgG)	Minimum titer 1:1000	Development of severe disease—defined as RR ≥ 30 breaths/min or oxygen saturations <93% on air
Simonovich et al, NEJM[28]	Simonovich et al, NEJM	333/333	Double-blind	Laboratory confirmed SARS-CoV-2, requiring hospitalization, age ≥18, pneumonia, plus SpO2 <93% or or PaO2/FiO2 <300 Excluded: MV or NIV	8 d in CP and control	10 to 15 mL/kg mini-pools (5 to 10 donors)	Saline	anti-S IgG SARS-CoV-2 (COVIDAR IgG)	IgG median titer of 1: 3200 (IQR 1:800 to 1:3200)	Clinical status at day 30 ordinal categories 1- death 2- invasive ventilatory support 3- hospitalized with supplemental oxygen requirements 4- hospitalized without supplemental oxygen requirements 5- discharged without full return of baseline physical function 6- discharged with full return of baseline physical function

IDS0, 50% inhibitory dose; MOF, multiorgan failure; MV, mechanical ventilation; NIV, noninvasive ventilation; PRNT, plaque reduction neutralization test; RR, respiratory rate; S-RBD–specific IgG, S protein–receptor-binding domain-specific IgG; VMNT, virus microneutralization test.

*Only hospitalized patients have been included in studies reported to date.

†Comparator was standard of care for all studies.

Table 2. (continued)

Study	Country	No./Planned	Study design	Participants*	Median time from symptom onset to randomization	Intervention†	Control	NAb assay	NAb titer in donor plasma	Primary outcome
Al Qhatani et al, preprint[29]	Bahrain	40/40	Open-label	Laboratory confirmed SARS-CoV-2, requiring hospitalization, age ≥21, pneumonia, plus SpO_2 <92% or PaO_2/FiO_2 <300 Excluded: MV or MOF	Not reported	Two doses 200 mL CP, 24 h apart	Standard care	Lansionbio COVID-19 IgM/IgG	Not reported	Requirement for ventilation
Bajpai et al, preprint[30]	India	29/20	Open-label	Laboratory confirmed SARS-CoV-2, requiring hospitalization, age 18 to 65, pneumonia, plus SpO_2 <93% or PaO_2/FiO_2 <300 Excluded: comorbidities (kidney, heart or liver disease, COPD)	Not reported	Two doses 250 mL CP, 24 h apart	Nonimmune plasma	SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) Kit (Genscript, USA)	Variable	Proportion of patients remaining free of mechanical ventilation day 7
Balcells et al, preprint[31]	Chile	58/58	Open-label	Suspected or confirmed SARS-CoV-2, requiring hospitalization, age ≥18, ≤7 d from symptom onset, CALL score ≥9 points at enrollment Excluded: PaO_2/FiO_2 <200, pregnant	5 d in CP and 6 days in control	Two doses 200 mL CP, 24 h apart	Delayed CP if clinical deterioration (PaO_2/FiO_2 <200 OR hospitalized on day 7)	anti-SARS-CoV-2 (S1) IgG titers	IgG ≥ 1:400	Composite of mechanical ventilation, hospitalization for >14 d or death during hospitalization
Hamdy Salman et al, EJA[32]	Egypt	30/30	Double-blind	Laboratory confirmed SARS-CoV-2, requiring hospitalization, age ≥18, 2 or more of RR ≥ 24, SpO_2 ≤93%, PaO_2/FiO_2 <300, pulmonary infiltrates Excluded: MOF, septic shock	30 d in CP and control	250 mL CP on day 1	Saline	Neutralizing antibody, Cusabio, ELISA Kit catalog number CSBEL23253HU	NAb not used to select plasma	At least 50% improvement of the severity of illness at any time during 5 d study period
Ray et al, preprint[33]	India	80/80	Open label	Laboratory confirmed SARS-CoV-2, requiring hospitalization, age ≥18, RR > 30, SpO_2 <90%, PaO_2/FiO_2 <300 Excluded: pregnant, MV	Not reported	Two doses 200 mL CP, 24 h apart	Standard care	anti-SARS-CoV2 spike IgG (Euroimmun)	Euroimmun ≥1.5	All-cause mortality at 30 d

ID50, 50% inhibitory dose; MOF, multiorgan failure; MV, mechanical ventilation; NIV, noninvasive ventilation; PRNT, plaque reduction neutralization test; RR, respiratory rate; S-RBD-specific IgG, S protein–receptor-binding domain-specific IgG; VMNT, virus microneutralization test.

*Only hospitalized patients have been included in studies reported to date.

†Comparator was standard of care for all studies.

primary end point of 28-day mortality (18% convalescent plasma vs 18% usual care alone; risk ratio 1.04 [95% confidence interval 0.95-1.14]; $P = .34$).[39] The international CONCOR-1 trial (NCT04348656) notified closing to recruitment after interim analysis of data from the first 614 patients of 973 patients randomized to CP indicated meeting the prespecific threshold for futility.[40] No safety concerns were reported. More information is anticipated soon from each of these trials, and we await full peer-reviewed publication of the results. Importantly, analysis of follow-up data from additional patients already recruited prior to closure of the entire trial or the CP intervention arm, and subgroup analyses will be important to understanding the full picture of the experience with CP in these trials. Another smaller trial (160 participants) of very early treatment (within 72 hours of symptom onset) with high-titer plasma showed potential benefit, with reduction in progression to severe disease by approximately 50%.[27] This, and other trial evidence has prompted the FDA to update its Emergency Use Authorization for convalescent plasma, so that only high titer plasma should be issued.[35]

Safety of CP for COVID-19
Plasma transfusions are associated with known hazards, including allergic reactions ranging from trivial to life-threatening anaphylaxis, along with transfusion-related acute lung injury (TRALI) and transfusion-associated volume overload (TACO).[10,11,41] CP-specific concerns include antibody-dependent enhancement of infection,[10,41] and potential transmissibility by transfusion. SARS-CoV-2 RNA has been detected in blood donations, but there is no evidence it is transmitted by transfusion.[42,43] Treatment of CP with pathogen reduction technologies may further minimize this risk.[1,41]

Joyner et al in the United States have reported 7-day mortality and other safety data on 20 000 adults receiving 200 to 500 mL of CP through a multicenter expanded-access program (EAP).[21] They described 141 transfusion-related SAEs and 63 deaths occurring within 4 hours of CP infusion. These events, representing <1% of all transfusions, included 36 reported TACO, 21 TRALI, and 21 severe allergic reactions, of which 10 were considered possibly transfusion-related and none were probably or definitely related. Furthermore, 1247 other SAEs were reported within 7 days of receiving CP, including 113 thromboembolic or thrombotic events, 457 sustained hypotensive events requiring IV pressor support, and 677 cardiac events. Of these, 75 thromboembolic/thrombotic SAEs and 597 cardiac events were considered unrelated to receiving CP. The authors report an overall mortality rate of 13.1% for patients in the EAP. It is not possible to determine efficacy from these studies, and it is noted that characteristics of patients in the study have changed over time (for example, to earlier use in less unwell patients). Salazar et al[16] from the United States and Abolghasemi et al[17] from Iran reported no plasma-related adverse events in 25 patients receiving 300 mL of CP and 115 patients receiving 500 mL of CP, respectively.

Published preliminary safety data have not identified any new early plasma-related SAEs or worsening of COVID-19 illness following receipt of CP, although comparative data are lacking. This is reassuring, but more information is certainly required. Other unforeseen hazards may exist. The most important way to prevent complications of plasma transfusions is to avoid unnecessary exposure: unless the benefits clearly outweigh the risks, the transfusion should not be given at all. All usual requirements for blood administration, including informed consent and product traceability, should be followed for CP transfusions.[18,44]

Which groups might benefit from COVID-19 CP?
Reported studies to date have mostly focused on hospitalized adults, including the critically ill. If the main mechanism of CP action is through viral neutralization, earlier administration, including prehospital or as prophylaxis, may be of benefit, and several trials are under way (eg, NCT04323800, NCT04438057).

There may also be specific patient groups who are more likely to benefit, including patients with inherited or acquired immunodeficiencies. Higher SARS-CoV-2 viral load in patients with hematological malignancies compared with noncancer patients, and delayed clearance of SARS-CoV-2 in immunosuppressed patients, has been reported.[45,46] In a French case series, 17 patients who had received anti-CD20 therapies and were profoundly lymphopenic with persistent COVID-19 symptoms and SARS-CoV-2 viremia without detectable antibody received 800 to 880 mL of CP at a median of 56 days (range, 7-83 days) from the onset of symptoms.[47] Sixteen recovered with rapid abatement of symptoms. SARS-CoV-2 virus became undetectable in all 9 patients who were retested using sensitive methods. No transfusion-related SAEs were observed. Finally, results from trials in adult populations may not be generalizable to pediatric patients. Although SARS-CoV-2 generally appears to cause milder disease in children,[48] some do develop severe disease (including those with comorbidities and/or immunosuppression) and may benefit from CP if shown to be effective.[49]

What is the role of CP among other antibody therapies for COVID-19?
Blood-component alternatives to CP include hyperimmune globulin, which has potential advantages over CP such as a more standardized product (antibody titer), pathogen inactivation, lower volume, and easier storage. However, due to the necessity to pool large volumes of plasma and manufacture the product, there are inherent delays in its availability. Hyperimmune globulin preparations for COVID-19 are being manufactured globally, with trials under way.[50] Monoclonal antibodies targeting SARS-CoV-2 are entering clinical trials, although data are not yet available on efficacy or safety.[51,52] Polyclonal immunoglobulins for IV (IVIG) or subcutaneous use likely already do, or soon will, contain anti–SARS-CoV-2 antibodies given rising rates of antibody positivity among blood donors.[39,40,53,54] IVIG is already being used in the treatment of COVID-19, although evidence of benefit is limited.[50,54] There is preclinical evidence that platelet-derived IgG may be more potent at viral neutralization than plasma IgG, raising the question of whether platelets could be a novel method of delivering passive immune therapy.[55]

Therapeutic plasma exchange (TPE) is being studied in trials in critically ill COVID-19 patients; however, the rationale for this treatment is not related to passive immunity but rather removal of potentially harmful circulating cytokines and other molecules, and replacement of protective plasma proteins to maintain microcirculatory flow and prevent vascular leak.[56] However, unless CP is used, TPE may lead to reduction in circulating antibodies directed at SARS-CoV-2.[57]

What can we do better now, and for the next time?

Recent achievements in COVID-19 clinical practice and research present opportunities to learn and improve. A high priority for the future should be opening and completing high-quality trials faster.[41,57-59] Examples of the success of large, simple, pragmatic studies for COVID-19 are RECOVERY and SOLIDARITY (ISRCTN8397115),[60] which combined have randomized >45 000 patients to date. The opportunity to add CP "domains" to established multi-interventional platform trials was taken with RECOVERY and REMAP-CAP. International collaboration on trial design (such as agreement on universal end points measured in standardized ways) and management (such as common protocols) will permit comparability of results.[59,61] By working through these networks, duplication of effort and cost can be avoided when setting up independent studies in each country. Additionally, there can be flexibility in completing trials that are started: new sites can join quickly as a pandemic spreads, and recruitment can be stopped if cases decline locally (without compromising trial completion as other locations take over recruitment) or seamlessly reactivated if there are "second (or later) waves."

Standardized protocols for CP collection, characterization, and use (developed by blood establishments and hospitals in SARS-CoV-2 and other recent epidemics and enabled through international blood supplier networks, research collaborations, and the World Health Organization) can be further harmonized and activated quickly when needed in the future.[11,19,20,41,61-63]

Data sharing of meta-analyses of individual patient data from completed trials as well as reports on the experiences of blood establishments that collect CP is becoming more widespread, even prior to study completion and analysis.[64,65] International hemovigilance definitions can facilitate comparison of adverse event reporting, and hemovigilance systems established in many countries can support vigilance for potential emerging adverse reactions related to CP, during and after completion of clinical trials.

Availability of patient, product, and blood-donor samples in biorepositories will enable important correlative studies to better understand the mechanism(s) of action of CP and other therapies, and support laboratory quality-assurance activities.

Implications for blood services and blood donors

While considering the potential role for CP in helping patients, we should not forget our responsibility for the welfare of blood donors, who are community volunteers and have themselves recently recovered from illness. Blood establishments have implemented a range of public health measures to protect donors and staff, and to enable safe donation and preparation of CP. This can be very challenging at times when measures to contain an infectious outbreak substantially affect blood center operations and efforts to maintain sufficiency in other blood products.[66-69] Logistical issues such as delays in access to CP for clinical trials have been reported.[68,69]

Conclusions

CP may be of benefit for patients with COVID-19, but more information on both efficacy and safety is needed.[41,58,70] Results from randomized trials are essential, and are starting to appear in the peer-reviewed literature. Harmonization of approaches in elements of study design (eg, use of standardized end points) and management (eg, use of common protocols for characterization of CP) will greatly assist interpretation of results. National and international collaborative studies are under way and will provide detailed product characterizations as well as clinical outcome and cost data. Available information is continuously being summarized and continually updated, including through a series of living Cochrane reviews and coordinated data-sharing activities.[34,64] Professional guidance to date has largely been based on first principles (including, importantly to "first do no harm") and experience with CP in other settings, and will transition to evidence-based guidelines as data become available.[58,71,72] In the future, availability of established trial platforms will help us open and complete high-quality trials sooner and at lower cost, and obtain better answers faster.

Authorship

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