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REVIEW

Convalescent Plasma Therapy for COVID-19: State of the Art

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SUMMARY Convalescent plasma (CP) therapy has been used since the early 1900s to treat emerging infectious diseases; its efficacy was later associated with the evidence that polyclonal neutralizing antibodies can reduce the duration of viremia. Recent large outbreaks of viral diseases for which effective antivirals or vaccines are still lacking has renewed the interest in CP as a life-saving treatment. The ongoing COVID-19 pandemic has led to the scaling up of CP therapy to unprecedented levels. Compared with historical usage, pathogen reduction technologies have now added an extra layer of safety to the use of CP, and new manufacturing approaches are being explored. This review summarizes historical settings of application, with a focus on betacoronaviruses, and surveys current approaches for donor selection and CP collection, pooling technologies, pathogen inactivation systems, and banking of CP. We additionally list the ongoing registered clinical trials for CP throughout the world and discuss the trial results published thus far.

KEYWORDS Ebola virus disease, Middle East respiratory syndrome, antibody-dependent enhancement, convalescent blood product, convalescent plasma, convalescent whole blood, coronavirus disease 2019, enzyme-linked immunosorbent assay, intravenous immunoglobulins, plaque reduction neutralization test, SARS

INTRODUCTION

The recent COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1) has demonstrated the fragility of our health systems in tackling emergency situations related to the spread of new infectious agents that require the rapid development of effective care strategies. Unfortunately, there are several potentially pandemic viruses, such as flaviviruses (e.g., West Nile virus [WNV],

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dengue virus, and Zika virus) (2), chikungunya virus (3), influenza viruses A [e.g., A(H1N1) and A(H5N1)] (4), Ebola virus (EBOV) (5), and respiratory betacoronaviruses (SARS-CoV and Middle East respiratory syndrome-CoV [MERS-CoV]), which could put us in situations very similar to the situation with the current pandemic and which require the development of specific intervention protocols.

While vaccination strategy is undoubtedly a viable goal, development of a vaccine requires a time frame not compatible with an emergency situation. It is also a prophylactic approach that has no use in the therapeutic setting. On the other hand, the use of antivirals is valuable for the therapeutic setting (6, 7). For the limited number of antiviral agents currently available, unless provided free of charge to developing countries, financial cost is an issue. Additionally, manufacturing is hard to scale up in short time frames.

In situations in which the new pathogen is able to induce an immune response with the production of neutralizing antibodies, passive transfusion of convalescent blood products (CBPs), in particular, convalescent plasma (CP), has proven to be a winning and logistically feasible therapeutic strategy (8). CBPs can be manufactured by collecting whole blood or apheresis plasma from a convalescent donor. This approach has been used since 1900 (9), and previous experiences have been reported elsewhere (10).

The main accepted mechanism of action for CBP therapy is clearance of viremia, which typically happens 10 to 14 days after infection (11). So CBP has been typically administered after the appearance of early symptoms to maximize efficacy. Convalescent whole blood (CWB), in addition to antibodies, provides control of hemorrhagic events, as in Ebola virus disease, if transfusion occurs within 24 h to maintain viable platelets and clotting factors. Nevertheless, CP best fits settings where only antibodies are required.

In this review, we have described current technologies for CP collection, manufacturing, pathogen inactivation, and banking of CP. Then we have summarized historical settings of CBP application, with a specific focus on applications for COVID-19 and other future pandemics. Several articles included in this review are available as preprints which have not yet passed peer review, as indicated in the reference section.

CP DONOR RECRUITMENT STRATEGIES

Convalescent donor testing for neutralizing antibodies is mandatory in upstream donor selection. Donor selection is generally based on neutralizing antibody titer, as assessed with a plaque reduction neutralization test (PRNT) (12), which requires a viable isolate, replication-competent cell lines, and skilled personnel. Since PRNT takes time to be set up and requires expensive facilities, in resource-poor settings or in time-sensitive scenarios, collection based on a retrospective PRNT or, alternatively, on an enzyme-linked immunosorbent assay (ELISA) targeting the recombinant receptor binding domains (RBDs) of the viral antireceptor has often been implemented; under these circumstances, studies have suggested that ELISA ratios/indexes have good correlations with PRNT titers; e.g., the Euroimmun ELISA IgG score detected 60% of samples with PRNT titers of $>$1:100, with 100% specificity using a signal/cutoff reactivity index of 9.1 (13). The current understanding of neutralization suggests that the virus-blocking effect is related to the amount of antibodies against different epitopes coating the virion, whose stoichiometry is in turn affected by antibody concentration and affinity.

The donor should preferably live in the same area as the intended recipient(s) to allow consideration of mutations of the target viral antigens. SARS-CoV-2 S protein has already mutated after a few months of viral circulation (14), with one mutation outside the receptor-binding motif (23403A→G single nucleotide polymorphism, corresponding to a D614G amino acid change) currently defining a dominant clade (15) characterized by reduced S1 shedding and increased infectivity (16). Nevertheless, it should be considered that preferring indigenous donors could represent a drawback in areas with epidemics of other infectious diseases (e.g., malaria).

Three approaches are theoretically available to recruit CP donors, with each having pros and cons. The least cost-effective approach is screening the general regular blood

donor population for the presence of anti-SARS-CoV-2 antibodies. In areas of endemicity, such a strategy provides many fit donors with the additional benefit of seroprevalence study in the general population (80% of cases being asymptomatic) but requires a large budget.

Alternatively, recruitment of hospital-discharged patients is highly cost-effective (patients can be easily tested before discharge and tracked), but patients who have required hospitalization are highly likely to be elderly with comorbidities and, hence, unfit to donate.

The intermediate approach, whenever allowed by privacy regulations, is making calls to positive cases under home-based quarantine to solicit donations; given the large numbers of such cases, some of them are likely to be regular donors, and home-based convalescence suggests that they are fit enough to donate. Nevertheless, lessons from MERS (17) and preliminary evidence with COVID-19 (18–20) suggest that patients with mild symptoms may develop low-titer antibodies, making antibody titration even more important in the population-wide and home-based approaches. Plasma samples collected an average of 30 days after the onset of symptoms had undetectable half-maximal neutralizing titers in 18% of donors (21).

Under emergency settings, it has often happened that donors are not screened for high-titer neutralizing antibodies or that low-titer donations are collected; nevertheless, as soon as the urgent requests are satisfied and a buffer stock has been created, repeat donations should preferably focus on donors with high titers (22).

As recently suggested, plasmapheresis could additionally benefit the convalescent COVID-19 donor by reducing the prothrombotic state via the citrate-based anticoagulants administered during donation and by removal of high-molecular-weight viscous components (23).

In addition to interventional trials, in the United States several trials have been initiated to create registries (e.g., ClinicalTrials.gov registration no. NCT04359602) or collect plasma with titers of $>$1:64 from immune donors for banking purposes, without immediate reinfusion (e.g., trial NCT04360278, NCT04344977, or NCT04344015). These approaches should be encouraged to better face the next waves of the COVID-19 pandemic.

CONVALESCENT PLASMA AND PATHOGEN INACTIVATION

CP should be collected by apheresis in order to ensure larger volumes than available with whole-blood donations and more frequent donations and to avoid causing unnecessary anemia in the convalescent donor. Double filtration plasmapheresis (DFPP) using fractionation filter 2A20 is under investigation as an approach to increase IgG yield by 3 to 4 times (Table 1, trial NCT04346589 in Italy); since DFPP-derived plasma is not an ordinary blood component but, rather, a discard product, additional regulations could apply in different countries. A very exploratory approach is under investigation in a Chinese trial collecting immunoglobulins from convalescent donors by immunoadsorption (trial NCT04264858), which could be an alternative to plasma fractionation.

Technologies To Virally Reduce Plasma (Pathogen Inactivation)

Although neither the U.S. Food and Drug Administration (FDA) (24) nor the European Center for Disease Control (ECDC) is recommending pathogen reduction technologies (PRT) for CP (25), several national authorities consider that, under emergency settings, donor screening and conventional viral nucleic acid testing (NAT) (i.e., HIV, hepatitis C virus [HCV], and hepatitis B virus [HBV] NAT) would not be enough to ensure CP safety (12). Under this scenario, additional virological testing and PRT approximately double the final cost of the therapeutic dose. Several technologies for PRT have been approved and are currently marketed.

Solvent/detergent (S/D)-filtered plasma provides quick inactivation of $>$4 logs of most enveloped viruses; although the technology was developed and is widely used for large plasma pools, small-scale reduction has been reported. The technology relies on several steps: addition of 1% tri(*n*-butyl) phosphate–1% Triton X-45, elimination of solvent and detergent via oil extraction and filtration, and finally sterile filtration (26).

TABLE 1 Ongoing interventional clinical trials of convalescent plasma in COVID-19 patients[a]

Phase(s) and indication	Trial no.	Country	Study population (no. of participants per arm)[b]	Schedule (vs control arm)[c]	Donor titer[d]
I/II					
Exposed or confirmed children	NCT04377672	USA	30	5 ml/kg, equivalent to 1–2 U (200–250 ml/U)	>1:320
All patients with COVID-19	NCT04292340	China	15	NA	NA
	NCT04376788	Egypt	15	Exchange transfusion by venesection of 500 ml of blood replacement by 1 U of PRBC + 1 mg/kg methylene blue i.v. over 30 min + 200 ml of CP	NA
	NCT04345679	Hungary	20	1 U of CP (200 ml)	>1:320
	NCT04397523	North Macedonia	20	NA	>5 AU/ml
	NCT04356482	Mexico	90	Different amounts of CP	NA
	NCT04357106	Mexico	10	1 U of CP (200 ml)	NA
	NCT04384497	Sweden	50	Up to 7 infusions (200 ml each), dose-finding study	NA
	NCT04389944	Switzerland	15	2 U of CP (200 ml each)	NA
	NCT04343755	USA	55	NA	>1:64
	NCT04360486		EAP	NA	NA
	NCT04354831		131	1–2 U of CP (<7 ml/kg adjusted IBW)	NA
	NCT04408040		700	200–425 ml of CP	NA
	NCT04355897		100	500 ml	NA
Non-critically ill patients	NCT04332380	Colombia	10	2 U of CP (250 ml each)/24 h	NA
	NCT04375098	Chile	30	200 ml of CP on days 1 and 2	NA
	NCT04327349	Iran	30	NA	NA
	IRCT20200325046860N1	Iran	200	NA	NA
	NCT04365439	Switzerland	10	NA	NA
	NCT04374565	USA	29	2 U of CP (200 ml each) in 1–2 days	NA
Severe or critically ill patients	NCT04348877	Egypt	20	1 400-ml unit of CP	NA
	NCT04408209	Greece	60	3 doses of CP	NA
	NCT04346589	Italy	10	DFPP-collected CP	NA
	NCT04333355	Mexico	20	1–2 U of CP (250 ml/24 h)	NA
	NCT04352751	Pakistan	2,000	Children <35 kg, 15 ml/kg over 4–6 h; adults, <450–500 ml over 4–6 h	NA
	NCT04347681	Saudi Arabia	40	10–15 ml of CP/kg body wt	NA
	NCT04353206	USA	90	1–2 U of CP on days 0 and 6	NA
	NCT04343261		15	2 U of CP	NA
	NCT04388527		50	2 U of CP	NA
	NCT04389710		100	1–2 U of CP (200/600 ml)	NA
	NCT04338360		NA	1 U of CP (200/250 ml)	NA
	NCT04374370		EAP	1–2 U (200–400 ml/U), not to exceed 550 ml total	NA
	NCT04358211		EAP		>160
	NCT04363034		EAP up to 100		NA
	NCT04372368		EAP up to 150		NA
	NCT04340050		10	1 U of CP (300 ml)	NA
III					
Exposed within 96 h of enrollment and 120 h of receipt of plasma	NCT04323800	USA	150 (Exp, 75; Ctr, 75)	1 U of CP (200–250 ml) vs nonconvalescent plasma	>1:64
	NCT04390503		200 (Exp, 100; Ctr, 100)	1 U of CP (200–250 ml) vs 5% albumin i.v.	NA
All patients with COVID-19	NCT04377568	Canada	100	10 ml/kg, up to 500 ml, vs BSC	NA
	ChiCTR2000030039	China	90 (Exp, 30; Ctr, 60)	2 U of CP (200/500 ml/24 h) vs BSC	NA
	NCT04345289	Denmark	1,500 (6 arms)	1 600-ml unit of CP vs sarilumab vs baricitinib vs hydroxychloroquine vs injective placebo vs oral placebo	NA
	NCT04372979	France	80	2 U of 200–230 ml of CP vs nonconvalescent plasma	NA
	NCT04374487	India	100	Up to 3 200-ml doses of CP 24 h apart vs BSC	>1:40
	NCT04346446		40	1–3 U (200 ml) of CP vs nonconvalescent plasma	NA
	NCT04380935	Indonesia	60	NA vs BSC	NA
	IRCT20200310046736N1	Iran	45	CP vs PDIES	NA
	NCT04342182	Netherlands	426	1 U of CP (250 ml) vs BSC	NA
	NCT04366245	Spain	72	NA vs BSC	NA

(Continued on next page)

TABLE 1 (Continued)

Phase(s) and indication	Trial no.	Country	Study population (no. of participants per arm)[b]	Schedule (vs control arm)[c]	Donor titer[d]
	NCT04344535	USA	500	450–550 ml of CP vs BSC	>1:320
	NCT04333251		115	1–2 U of CP (250 ml/24) vs BSC	>1:64
	NCT04355767		206	1–2 U of CP (200–600 ml) vs placebo	>1:80
	NCT04373460		1344 (Exp, 772; Ctr, 772)	1 U of CP (200–250 ml) vs nonconvalescent plasma	≥1:320
	NCT04362176		500 (Exp, 250; Ctr, 250)	1 U of CP (250 ml at a rate of 500 ml/h) vs placebo	NA
	NCT04376034		240	1 (moderate) or 2 (severe) U of CP vs BSC	NA
Non-critically ill patients	NCT04356534	Bahrain	40 (Exp, 20; Ctr, 20)	2 U of CP, 200 ml each, over 2 h in 2 consecutive days vs BSC	NA
	NCT04348656	Canada	1,200	500 ml of CP within 12 h vs BSC	NA
	ChiCTR2000030702	China	50 (Exp, 25; Ctr, 25)	NA vs BSC	NA
	ChiCTR2000030929		80 (Exp, 30; Ctr, 30)	NA vs BSC	NA
	ChiCTR2000030010		100 (Exp, 50; Ctr, 50)	NA vs BSC	NA
	NCT04332835	Colombia	80	2 U of CP (250 ml/24 h) vs BSC	NA
	NCT04345991	France	120	Up to 4 U of CP (200–220 ml each) vs BSC	NA
	NCT04374526	Italy	182	200 ml/day for 3 consecutive days vs BSC	NA
	NCT04393727	Italy	126 (Exp, 63; Ctr, 63)	1 U (200 ml) of CP vs BSC	NA
	NCT04358783	Mexico	30 (Exp, 20; Ctr, 10)	1 U (200 ml) of CP vs BSC	NA
	NCT04345523	Spain	278 (Exp, 139; Ctr, 139)	CP vs BSC	NA
	NCT04364737	USA	300	1–2 U (250 ml each) vs i.v. placebo	NA
	NCT04361253		220	2 U of CP (250 ml each) within 24 h vs nonconvalescent plasma	NA
	NCT04397757		80 (Exp, 40; Ctr, NA)	2 U of CP vs BSC	NA
	NCT04359810		105 (Exp, 70; Ctr, 35)	1 U (200–250 ml) of CP vs nonconvalescent plasma	NA
Severe or critically ill patients	ChiCTR2000029850	China	20 (Exp, 10; Ctr, 10)	NA vs BSC	NA
	ChiCTR2000030179		100 (Exp, 50; Ctr, 50)	NA vs BSC	NA
	ChiCTR2000030627		30 (Exp, 15; Ctr, 15)	NA vs BSC	NA
	NCT04346446	India	40	1–3 U (200 ml each) of CP vs nonconvalescent plasma	NA
	NCT04385043	Italy	400 (Exp, 200; Ctr, 200)	NA vs BSC	NA
	NCT04381858	Mexico	500 (Exp, 340: Ctr, 160)	2 U (200 ml each) of CP vs polyclonal IVIg at 0.3 gr/kg/day (5 doses)	NA
	NCT04388410		250 (Exp, 125; Ctr, 125)	2 U of CP vs masked i.v. saline	NA
	NCT04405310		80 (Exp, 40; Ctr, 40)	1 U of CP vs 20% albumin	NA

[a]Trials included are listed in the World Health Organization International Clinical Trial Registry Platform (ICTRP) databases (https://www.who.int/docs/default-source/coronaviruse/covid-19-trials.xls; accessed 7 July 2020), NIH ClinicalTrials database (www.clinicaltrials.gov; accessed 7 July 2020), and Cytel Global Coronavirus COVID-19 Clinical Trial Tracker (www.covid-trials.org; accessed 7 July 2020).

[b]When the information was available, the numbers of participants in the experimental group (Exp) and control group (Ctr) are given in parentheses. EAP, expanded access program; NA, not available.

[c]NA, not available; PRBC, packed red blood cells; IBW, ideal body weight; BSC: best supportive care; PDIES, plasma-derived immunoglobulin-enriched solution; i.v., intravenous.

[d]AU, arbitrary units.

Filtration across 75- to 35-nm-pore-size hollow fibers could remove large viruses (such as betacoronaviruses) while preserving IgG (27), but this has not been implemented yet.

In recent years photoinactivation in the presence of a photosensitizer has become the standard for single-unit inactivation; approved technologies include combinations of methylene blue and visible light (28) (Theraflex), amotosalen (S-59) and UV A (29) (Intercept), and riboflavin and UV B (30) (Mirasol). These methods do not affect immunoglobulin activity.

Fatty acids are also an option. In 2002 it was reported that caprylic acid (31) and octanoic acid (32) were as effective as S/D at inactivating enveloped viruses.

Heat treatment of plasma has been used in the past (33, 34) but comes with a risk of aggregation of immunoglobulins (35, 36).

Pooling

Figure 1 represents how CP and intravenous immunoglobulin (IVIg) can be obtained under modern fractionation procedures. As per CP collection, two approaches can be pursued.

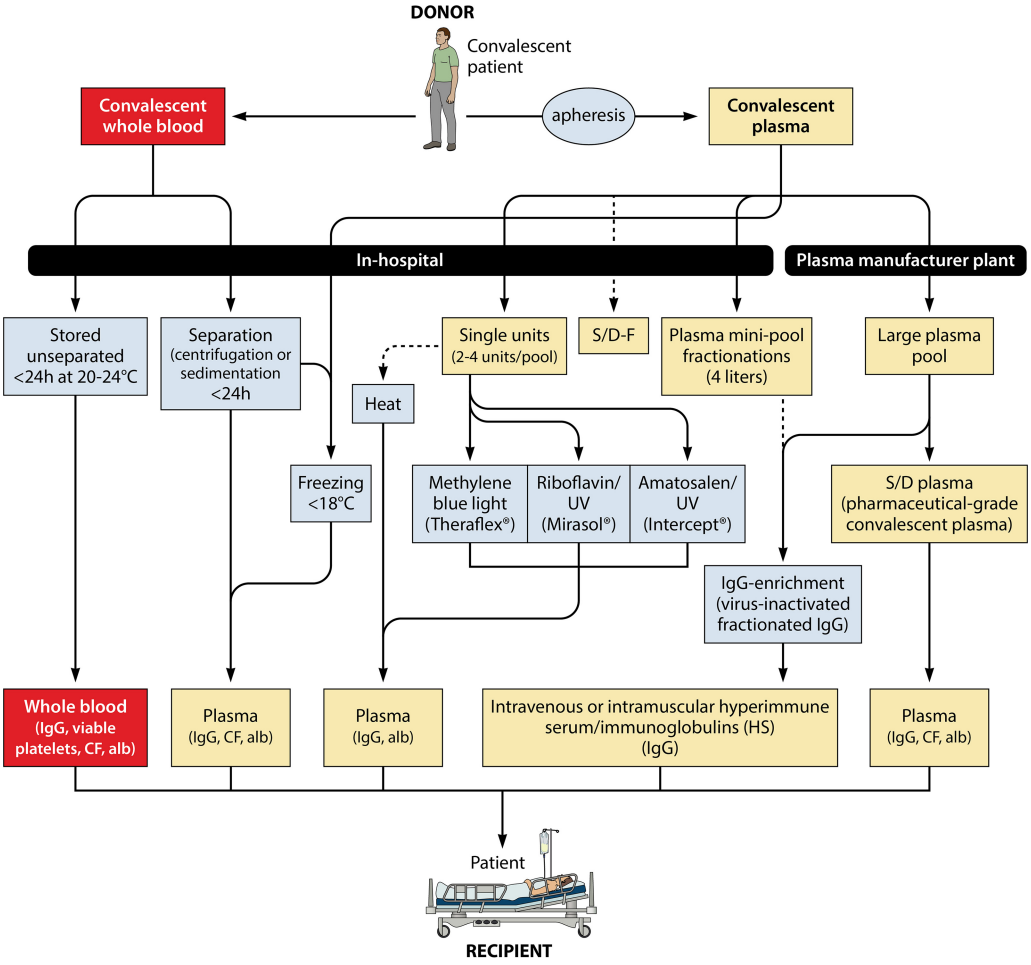

FIG 1 Summary of possible convalescent blood products (CBP). (Adapted from reference 153 with permission of Elsevier.)

Large-pool products. Pharmaceutical-grade facilities typically pool 100 to 2,500 donors to manufacture S/D-inactivated plasma. IVIgs are similarly prepared from pools of 2,000 to 4,000 liters of plasma (or 100 to 1,000 liters in the case of hyperimmune IVIg) (37, 38). Such volumes can hardly be obtained from CP donors, and timely creation of dedicated CP production chains pose difficult good manufacturing practice (GMP) issues within plasma vendor plants (38).

MPFS into immunoglobulins. In order to be economically sustainable, contract (private-run) fractionation typically requires well over 10,000 liters of plasma per year, and domestic (state-owned) fractionation typically requires over 100,000 to 200,000 liters per year in addition to starting up a fractionation facility. An "on-the-bench" minipool fractionation scale (MPFS) process (5 to 10 liters of plasma, i.e., approximately 20 recovered plasma units) using disposable devices and based on caprylic acid precipitation has been under development in Egypt since 2003 and has proved effective at purifying coagulation factors (39) and immunoglobulins (6-fold enrichment) (40). The same disposable bag system has also been combined with S/D reduction (26).

CP BANKING

CP can be either frozen or transfused as a fresh product. Aliquots of 200 to 300 ml can be easily achieved from a single unit using modern PRT kits. Banking CP at temperatures below −25°C (according to European Directorate for the Quality of Medicines [EDQM] or FDA guidelines for ordinary plasma for clinical use [41]) is encouraged in order to produce CP as an off-the-shelf, ready-to-use product. Most regulatory systems require that CP be tracked informatically as a blood component

different from ordinary plasma for clinical use. The final validation label should report that the donor has tested negative by PCR for the convalescent disorder and additional microbiological tests and should describe the inactivation method. A single cycle of freezing and thawing does not significantly affect the quantity or function of immunoglobulins (42). Given that COVID-19 AB blood group recipients can receive CP units only from scarce matched blood group AB donors, to increase the pool of compatible units several authors have recommended titration of anti-A and anti-B isoagglutinins and transfusion of low-titer ($<$1:32) non-ABO-compatible CP units (i.e., O, A, and B) to AB recipients (22, 43).

LESSONS FROM SARS

SARS-specific neutralizing antibodies usually persist for 2 years (44), and a decline in prevalence and titers occurs in the third year (45). Convalescent anti-SARS immunoglobulins were manufactured on a small scale (8, 46). Three infected health care workers with SARS progression despite the best supportive care (BSC) survived after transfusion with 500 ml of CP; viral load dropped to zero at 1 day after transfusion (47). Soo et al. reported in a retrospective nonrandomized trial that treatment with CP (titer of $>$1:160) in 19 patients was associated with a shorter hospital stay and lower mortality than continuing treatment with high-dose methylprednisolone (48). Amotosalen photochemical inactivation of apheresis platelet concentrates demonstrated a $>$6.2 $\log_{10}$ mean reduction of SARS-CoV (49). Theraflex reduces infectivity of SARS-CoV in plasma (50). Heating at 60°C for 15 to 30 min reduces SARS-CoV from plasma without cells (51), while maintaining 60°C for 10 h is required for plasma products (52). In addition, SARS-CoV was found to be sensitive to S/D (51, 53).

LESSONS FROM MERS

Antibody responses to MERS persist for less than 1 year, and the magnitude correlates with the duration of viral RNA shedding in sputum (but not with viral load). Patients with mild disease have very low antibody titers, making CP collection challenging in MERS convalescents (54). A study reported that only 2.7% (12 out of 443) exposed cases tested positive by ELISA, and only 75% of them had reactive microneutralization assay titers (17). CP with a PRNT titer of $\geq$1:80 provides clinical benefit in MERS (55). A case of transfusion-related acute lung injury (TRALI) following CP transfusion in a patient with MERS was reported (56, 57). MERS-CoV load in plasma was reduced by Theraflex (58), Intercept (59), Mirasol (60), and heating at 56°C for 25 min (61); in all cases, passaging of inactivated plasma in replication-competent cells showed no viral replication.

CONVALESCENT PLASMA FOR COVID-19

As soon as the COVID-19 pandemic appeared (62, 63), several authors suggested CP as a potential therapeutic agent (64, 65). Of interest, the most critically ill patients show prolonged viremia (strongly correlated with serum interleukin-6 [IL-6] levels) (10), which makes feasible therapeutic intervention with antiviral agents and immunoglobulins even at late stages. Viral shedding in survivors can last as long as 37 days (62), mandating SARS-CoV-2 RNA screening in CP donors. Serum IgM and IgA antibodies appear in COVID-19 patients as early as 5 days after symptom onset (66), while IgG can be detected at day 14 (67). IgGs are generally detected after 20 days (68, 69). Severely ill female patients generate IgG earlier and at higher titers (70, 71); the greatest part of the neutralizing antibody response has been shown to be associated with the IgG_1 and IgG_3 subclasses (72, 73). Duration of anti-SARS-CoV-2 antibodies in plasma is currently unknown; while the overall antibody responses for other betacoronaviruses typically declines after 6 to 12 months (74), SARS-specific neutralizing antibodies usually persist for 2 years (44). So, in the vast majority of countries, a suitable donor could donate 600 ml of plasma (equivalent to 3 therapeutic doses under most current trials) every 14 days for a minimum of 6 months. Up to 7 plasma donations have been proven not to decrease antibody titers in convalescent donors (18). In contrast to SARS and MERS

patients, most COVID-19 patients exhibit few or no symptoms and do not require hospitalization; this could suggest that the majority of convalescent donors are best sought in the general population although specific studies on antibody titers in mildly symptomatic patients suggest low titers (18–20).

SARS-CoV-2 is reduced by >3.4 logs by Mirasol (75) (and likely by other PRTs); nevertheless, SARS-CoV-2 viral RNA (vRNA) is detectable at low viral loads in a minority of serum samples collected in acute infection but is not associated with infectious SARS-CoV-2 (76). Intercept treatment has been proven not to reduce SARS-CoV-2 neutralizing antibody titers (77).

The main contraindications to CP therapy are allergy to plasma protein or sodium citrate, selective IgA deficiency (<70 mg/dl in patients 4 years old or older), leading to anaphylaxis from IgA-containing CP (78), or treatment with immunoglobulins in the last 30 days (because of a risk of developing serum sickness). As in many other trial settings, concurrent viral or bacterial infections, thrombosis, poor compliance, short life expectancy (e.g., multiple-organ failure), and pregnancy or breastfeeding are also contraindications (79).

In an early case series from China, five patients under mechanical ventilation (4 of 5 with no preexisting medical conditions) received transfusions of CP with an ELISA IgG titer of >1:1,000 and a PRNT titer of >40 at days 10 to 22 after admission. Four patients recovered from acute respiratory disease syndrome (ARDS), and three were weaned from mechanical ventilation within 2 weeks of treatment, with the remaining patients being stable (80).

Another Chinese pilot study (ChiCTR2000030046) of 10 critically ill patients showed that one dose of 200 ml of CP with a neutralizing antibody titer of >1:640 resulted in an undetectable viral load in 7 patients, with radiological and clinical improvement (81).

A third series of 6 cases with COVID-19 pneumonia in Wuhan showed that a single 200-ml dose of CP (with titers of anti-S antibodies determined by chemiluminescent immunoassay [CLIA] only) administered at a late stage led to viral clearance in 2 patients and radiological resolution in 5 patients (82). Pei et al. reported successful treatment of 2 out of 3 patients with 200- to 500-ml doses of CP (83). Recovery from mechanical ventilation was also reported by Zhang et al. in a single patient after antibodies in CP were titrated with an anti-N protein ELISA (84). No improvement in mortality despite viral clearance was reported in a retrospective observational study recruiting 6 late-stage, critically ill patients treated with gold-immunochromatography-titrated CP, compared to results in 13 untreated controls (85). One case of recovery in a centenarian patient who received 2 CP units (S-RBD-specific IgG titer of >1:640) was also reported (86).

Many more case reports and small case series are accumulating in the literature; successful treatment was reported in 3 cases with ARDS and mechanical ventilation using two 250-ml CP doses (titrated with ELISA only) in South Korea (43, 87), in 2 cases from Iraq (88), in 8 out 10 severe cases from Mexico (89), in 20 out of 26 severe cases from Turkey (90), in a kidney transplant recipient from China (91), in a case with severe aplastic anemia in Poland (92), in a case with X-linked agammaglobulinemia in Spain (93), and in 1 patient with marginal-zone lymphoma treated with bendamustine and rituximab in the United Kingdom (94). Centers in the United States reported successful treatment with CP in 18 out of 20 patients in a series (95), in 27 out of 31 patients with severe to life-threatening disease in another series (96), in one case with myelodysplastic syndrome (97), in a critically ill obstetric patient (in combination with remdesivir) (98), and in an allogeneic stem cell transplant recipient (99).

In a single-arm phase II trial (NCT04321421 [100]) run in Lombardy, 49 patients with moderate to severe disease were treated with up to 3 units of PRT-treated CP (250 to 300 ml/48 h) having neutralizing antibody titers of ≥1:160 in 96% of cases. Importantly, the viral inoculum was 50 50% tissue culture infective doses ($TCID_{50}$) instead of the usual 100 $TCID_{50}$. Seven-day mortality was 6% versus 16% in a historical cohort. One case of TRALI was reported (101).

In a large case series from Wuhan, 138 patients were transfused with 200 to 1,200 ml

of CP at a median of 45 days after symptom onset and experienced a 50% lower intensive care unit (ICU) admission rate and mortality than the group treated with best supportive care. Responders had higher lymphocyte counts, lower neutrophil counts, and lower lactate dehydrogenase (LDH), type B natriuretic peptide (BNP), urea nitrogen, procalcitonin, glucose, and C-reactive protein (CRP) levels. Complete data on neutralizing antibody titers in COVID-19 convalescent plasma (CCP) units were not available, but responders tended to have received CP units with higher antibody levels (102).

In the first retrospective, randomized controlled trial published to date, 39 patients in New York with severe COVID-19 were transfused with 2 units of ABO-type matched CP with anti-Spike antibody titers of ≥1:320 (measured by a two-step Spike protein-directed ELISA). CP recipients were more likely than control patients to not increase their supplemental oxygen requirements by posttransfusion day 14 (odds ratio [OR], 0.86), but survival improved only for nonintubated patients (hazard ratio [HR], 0.19) (103).

Another prospective, multicenter randomized controlled trial from China (ChiCTR2000029757) enrolled 103 patients with severe to life-threatening COVID-19. The study was underpowered because of earlier than expected (200 cases) termination. CP (9 to 13 ml/kg from donors with S-RBD IgG titer of ≥1:640) was associated with a negative SARS-CoV-2 PCR test at 72 h in 87.2% of the CP group versus 37.5% of the BSC group, but clinical improvement at 28 days was statistically different only in patients with severe, but not in life-threatening, disease (104).

Table 1 lists the other ongoing CP trials in COVID-19 patients collected from different web portals. The United States has developed a specific platform for facilitating clinical trials (https://ccpp19.org/), while the International Society of Blood Transfusion created a resource library (https://isbtweb.org/coronaoutbreak/covid-19-convalescent-plasma-document-library/). At the same time, in the United States an expanded-access program (EAP) has been approved by the FDA and coordinated by Mayo Clinic and has led to treatment of more than 30,000 patients as of 8 July 2020 (https://www.uscovidplasma.org). A preliminary report on the first 20,000 patients (66% from intensive care units) confirms safety (<1% severe adverse events and 14.9% mortality at 14 days) and suggests a benefit compared to results with historical cohorts, especially if CP is administered before mechanical ventilation (105, 106); donor titers were not disclosed, and evidently some donations were not titrated before reinfusion. Largely similar data have been reported from a 25-patient case series from Houston, Texas, where CP has been used as an emerging investigational new drug (eIND) (107).

Typically, 1 or 2 doses of 200 ml are administered (if 2 doses are used, they are administered at least 12 h apart), with infusion rates of 100 to 200 ml/h. The cumulative dose should be targeted according to body weight and antibody titer (22).

Several authors have suggested plasma exchange with CP (i.e., high-volume therapeutic plasmapheresis followed by CP transfusion) rather than CP transfusion alone in order to clear proinflammatory cytokines from the bloodstream (108, 109), and several successful case reports deploying nonconvalescent plasma have been reported (110–112). One randomized controlled trial (NCT04374539) is ongoing in patients with severe COVID-19, but unfortunately no trial to date is testing plasmapheresis followed by CP.

Unfortunately, most trials in westernized countries (in contrast to ones ongoing in China) have no control arm, which will impair efficacy interpretation. When present, the control arm consists of the best supportive care alone (typically oxygen and hydroxychloroquine at 400 mg twice a day [b.i.d.] for 10 days) or combined with intravenous placebo or standard (nonconvalescent) plasma (eventually of pharmaceutical grade). Since other plasma components (e.g., aspecific immunoglobulins or isoagglutinins; see below) could contribute to clinical benefit, the latter approach is ideal for dissecting the specific contribution of neutralizing antibodies although concerns could be raised by the prothrombotic nature of COVID-19 pathology (see Side Benefits from CP in COVID-19, below). Even using a placebo control in late-stage patients (refractory to former lines) could pose some ethical concerns because it denies treatment opportunities to an unresponsive disease. Future trials should investigate combined antiviral and CP therapies.

Notably, several plasma manufacturers are attempting to develop SARS-CoV-2-specific hyperimmune sera (e.g., Takeda's TAK-888 merged with Biotest, BPL, LFB, Octapharma, and CSL Behring into the Convalescent Plasma Coalition [113]; Kedrion and Kamada have joint ventures [81]).

MONITORING RESPONSE TO CP TREATMENT

CP is considered an experimental therapy, and, as such, phase 3 randomized controlled trials should be encouraged. Despite this recommendation, in emergency settings phase 2 trials are usually started, hampering efficacy analysis. Response in published trials is generally measured clinically (PaO_2/FiO_2 ratio) or radiologically according to target organs. Nevertheless, surrogate endpoints can include anti-SARS-CoV-2 antibody titer or absolute lymphocyte count increases in recipients, as well as decreases in recipients' SARS-CoV-2 viral load or IL-6 levels. Whenever quantitative PCR is not available, cycle threshold (C_T) value increases in qualitative PCR after transfusion could be a proxy for reduced viral load.

CONCERNS

The first concern is transfusion-transmitted infection (TTI). Modern performance improvement (PI) technologies, combined with NAT, reduce the risk for contracting additional TTIs. Most regulatory systems require additional tests (e.g., for hepatitis A virus [HAV] RNA, hepatitis E virus [HEV] RNA, or parvovirus B19 DNA) to be performed on CP for additional transfusion safety. CBP obtained from donors in the United Kingdom may be problematic for a couple of reasons. Currently, CBP obtained from individuals who lived for at least 6 months in the United Kingdom during the 1980-1996 outbreak of "mad cow disease" (bovine spongiform encephalopathy [BSE]) may not be acceptable in some countries (114) or by some individuals. In addition, there is a now a recognized risk of hepatitis E the within the U.K. blood donor population (115), most likely due to the consumption of poorly cooked pork products (116, 117), for which screening has only relatively recently been initiated (71). Although this does not preclude such SARS-CoV-2 convalescent plasma/serum from being used therapeutically within the United Kingdom, these other risks should be considered during larger clinical trials or with compassionate use in individual patients. Respiratory betacoronaviruses produce only a mild and transient viremia. With SARS-CoV, limited replication in lymphocytes (118) leads to significant risk only for recipients of blood products with high concentrations of donor lymphocytes (peripheral blood stem cells, bone marrow, granulocyte concentrates, etc.). Preliminary reports have shown that SARS-CoV-2 viremia persists only in critically ill patients (10).

The second concern is TRALI, which can be life-threatening in patients who are already suffering from ALI. Male donors are usually preferred in order to avoid the risk of transfusing anti-HLA/HNA/HPA antibodies from parous women. In the case of COVID-19, where female patients have been shown to have higher IgG levels, this could be detrimental, and anti-HLA/HNA/HPA antibody screening could be implemented.

Antibody-dependent enhancement (ADE) is also a theoretical concern related to passive or active antibodies (targeting S protein domains other than the RBD) facilitating IgG-coated virion entry into macrophages via Fcγ receptors and/or complement receptors (119, 120), leading to activation of the RNA sensing Toll-like receptors (TLR) 3, 7, and 8 and finally to elevated production of tumor necrosis factor (TNF) and IL-6 (a so-called cytokine storm). ELISAs discriminating the difference between total and RBD-binding antibodies could be useful to inspect the occurrence of ADE. Genetic polymorphisms (e.g., FcγRIIa [121]) can also contribute to ADE. To date, potential evidence supporting a role for ADE in COVID-19 include the following: (i) the correlation between disease severity and total anti-SARS-CoV-2 antibody levels (70, 122–124), including neutralizing antibodies (125, 126); (ii) the low prevalence of symptoms in COVID-19 patients younger than 20 (who have likely not been primed by infection with the other common cross-reacting coronavirus 229E or OC43 or anyway have low-affinity anti-coronavirus IgG [127, 128]); (iii) the occurrence, in SARS, of ADE at low antibody titers *in vitro* (129) and

correlation in patients of high IgG titers and early seroconversion with disease severity (130). Overall, these findings raise concerns for usage of low-titer CP units (131). Other evidence is the high level of afucosylated IgG against S protein, facilitating FcR binding, that is produced in the most severely ill patients (132, 133).

A last, COVID-19-specific, concern is worsening of the underlying coagulopathy (134) from clotting factors in transfused plasma (not only CP but also nonconvalescent plasma in control arms); since this has not been reported to date, it remains a theoretical concern.

SIDE BENEFITS FROM CP IN COVID-19

Obviously, patients with humoral immune deficiencies can benefit from polyclonal antibodies contained in CP, and patients with hemorrhagic diathesis can benefit from clotting factors.

Plasma is also likely to contain antibodies against other common betacoronaviruses associated with the common cold, which have been shown to cross-react with SARS-CoV-2 antigens in intravenous immunoglobulin (IVIg) preparations (135), likely stemming from recent infection with another human betacoronavirus (128). Accordingly, IVIg led to clinical and radiological recovery in 3 Chinese patients with severe COVID-19 (136), and the same team is now leading a randomized controlled trial (NCT04261426).

After demonstration that blood group O health care workers were less likely to become infected with SARS-CoV (137), a research group proved that anti-A blood group natural isoagglutinins (which can also be found in CP plasma from blood group O and B donors) inhibit SARS-CoV entry into competent cells (138). Such binding could opsonize virions and induce complement-mediated neutralization (139). Since SARS-CoV-2 uses the same receptor as SARS-CoV, anti-A isoagglutinins are expected to have similar effects against SARS-CoV-2 (140); accordingly, clusters of glycosylation sites exist proximal to the receptor-binding motif of the S protein from both SARS-CoV (141) and SARS-CoV-2 (142). Several publications showed that the odds ratio for acquiring COVID-19 is higher in blood group A than in blood group O (143–147), and one showed the ABO gene polymorphism to be the most significant at predicting severity of COVID-19 (147). COVID-19 has more severe clinical presentations and outcomes in the elderly and in males; intriguingly, elderly males are known to experience reductions in isoagglutinin titers (148, 149). Although alternative explanations exist (150, 151), studies are hence ongoing to evaluate correlations between isoagglutinin titers and outcomes in blood group O and B patients (152). If the correlations are confirmed, while preserving ABO match compatibility, blood group O and B donors for CP in COVID-19 could be preferred, and their anti-A isoagglutinin titers should be tested.

CONCLUSIONS

CP manufacturing should be considered among the first responses during a pandemic while antivirals and vaccines are tested. Despite huge competition from trials employing small molecules, multicenter randomized controlled trials should be encouraged in order to establish efficacy and provide hints about the most effective schedule (timing and dose).

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