Review Article

COVID-19 convalescent plasma: mechanisms of action and rationale for use: a narrative review

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Abstract: The use of convalescent plasma (CP) transfusions for patients with coronavirus disease 2019 (COVID-19) has gained great interest during the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic. This review aims at summarizing the literature on the potential mechanisms of action of COVID-19 CP (CCP) and the rationale for use. A narrative review of the literature was conducted using PubMed, Google Scholar, and the Cochrane Database through October 2020. The rationale of CCP deployment was based on historical use in other outbreaks and pandemics and the emergent need at the time of lack of proven therapies and vaccines. There are many proposed mechanisms of action including direct neutralization and suppression of viremia, antibody-dependent cellular cytotoxicity, modification of the inflammatory response, restoration of the coagulation factors, immunomodulation of the hypercoagulable state and the potential role of ABO naturally occurring iso-agglutinins. Many donor, product, and patient factors can impact the response to CCP, such as antibody titer in the CCP product, CCP dose, frequency of administration, the severity of underlying illness, and the timing of administration from time of disease onset. Based on current evidence, CCP appears to be safe. However, it remains unknown whether it impacts the improvement of clinical symptoms, time to death, and all-cause mortality. In conclusion, the use of CCP offers quick access as an empirical therapy when specific therapies are not available or under development. Ongoing clinical trials are expected to add to the breadth of knowledge on the safety and efficacy of CCP use in patients with COVID-19.

Keywords: Convalescent plasma (CP); neutralizing antibodies; severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); coronavirus disease 2019 (COVID-19); ABO blood group

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Introduction

In December 2019, the World Health Organization (WHO) was informed of cases of pneumonia of unknown etiology associated with exposures in a local seafood market in Wuhan city (1). The novel causative virus, later named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was found to be a strain of the *Coronaviridae* family, which also includes severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (2). The virus shares a 79.6% sequence identity to SARS-CoV and 96% identity to a bat coronavirus at the whole genome level (3). Compared to SARS and MERS, SARS-CoV-2 has an efficient human-to-human transmission and hence a higher pandemic potential (4,5). The coronavirus disease 2019 (COVID-19) pandemic has become within months a global

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health crisis, despite global public health responses aimed at containing the disease. As of 15th of November 2020, the WHO has been informed of 54,558,120 confirmed cases of COVID-19, with 1,320,148 deaths documented worldwide (6). Although most patients infected with SARS-CoV-2 experience mild to moderate symptoms that resolve in 6–10 days, almost 15–20% of patients develop severe illness characterized by an interstitial pneumonia and acute respiratory distress syndrome (ARDS) (7). The estimated overall rates of mortality per confirmed case in early reports from China were 4.5–12% (8,9). Although the estimated mortality rate of COVID-19 is lower than SARS and MERS, the number of deaths associated with COVID-19 has already surpassed those of SARS and MERS owing to the extremely high transmissibility of SARS-CoV-2 coronavirus (4).

As the pandemic continued to spread across the globe and given the historical use of convalescent plasma (CP) in other viral outbreaks and pandemics, COVID-19 CP (CCP) was quickly deployed in treating infected patients as an easily accessible source of anti-viral antibodies. Different organizations have released their recommendations on the collection and use of CCP. However, it is notable to mention that these guidance documents and recommendations were developed on an emergent basis based on the historical experience of convalescent sera and before any information is available on the safety and efficacy of CCP (10). The WHO recognizes CCP as an experimental therapy that needs to be evaluated in clinical studies to determine effectiveness and safety (11). The literature about CCP use is rapidly growing. This narrative review aims to summarize the published literature, and to provide an overview of the current knowledge on the potential mechanisms of action of CCP, the rationale for its use, and the donor and product factors that can implicate the recipient's response. We present the following article in accordance with the narrative review reporting checklist (available at http://dx.doi.org/10.21037/aob-2020-cp-01).

Methods

A native review of the literature was conducted using PubMed/MEDLINE, Google Scholar, and Cochrane Database. The literature was searched for published articles on the mechanisms of action of CCP and rationale for use, using a combination of the following keywords; "Convalescent plasma", "mechanism of action", "rationale for use", "Neutralizing antibodies", "ACE2 receptor", "SARS-CoV-2" or "Severe acute respiratory syndrome coronavirus 2", "COVID-19" or "coronavirus disease 2019", and "ABO blood group" from January through October 2020. Articles that specifically addressed the topic of interest were pulled and screened. After the first search, we included additional articles retrieved from a manual search of cited references. Relevant cited references therein were reviewed. The exclusion criteria included articles with no full text available and articles published in non-English-language.

Discussion

SARS-CoV-2 infection and COVID-19

The human-to-human transmission of SARS-CoV-2 is primarily mediated by respiratory droplets or aerosols. Structural and functional analysis of SARS-CoV-2 revealed that it uses the human angiotensin-converting enzyme 2 (ACE2) receptor to bind to human alveolar epithelial cells (12-14). This receptor is distributed across multiple organs and tissues, most notably the oral and nasal mucosa, nasopharynx, respiratory system, gastrointestinal tract, lymph nodes, thymus, bone marrow, heart, spleen, liver, kidney, bladder, and brain (15-17). In the early stages of the infection, SARS-CoV-2 entry is facilitated by high expression of ACE2 receptors on the mucosa of the oral cavity, including the epithelial cells of the tongue and nose (18,19). Virus replication takes place in the throat, and the incubation period lasts for 4–7 days (20). Peak viremia occurs within 2–5 days of symptom onset and pharyngeal virus shedding remains very high during the first week of symptoms (21). The expression of the ACE2 receptor on many cells, including alveolar epithelial cells and vascular endothelium, results in a profound immune response during COVID-19 infection (22).

SARS-CoV-2 has four major structural proteins: the spike protein (S), small envelope protein (E), matrix protein (M), and nucleocapsid protein (N) (23). Coronavirus entry into host cells is mediated by a transmembrane S protein that initiates cell fusion via attachment to the target receptor on the host cell surface. This is followed by the delivery of the viral nucleocapsid inside the target cell for subsequent replication (24). The S protein is comprised of two units that are responsible for binding to the host cell receptor (S_1 subunit), and fusion of the viral and cellular membrane (S_2 unit) (12). The receptor-binding domain (RBD) within the S_1 subunit directly interacts

with host receptors and contributes to the stabilization of the prefusion state of the membrane-anchored S_2 subunit (12,25,26). Further studies identified residues in the SARS-CoV-2 RBD that are essential for ACE2 binding, the majority of which are highly conserved or share similar side chain properties with those in the SARS-CoV RBD (27). However, SARS-CoV-2 RBD was also found to harbor a single mutation that significantly enhances its ACE2 binding affinity, suggesting an increased ability to infect and spread among humans (14). Some researchers reported this binding to be at a ~10–20-fold higher affinity than ACE2 binding to SARS-CoV S subunit (13,28,29). The higher binding affinity correlates with the higher potential of human-to-human disease transmission, disease severity, and overall viral replication (14). After attachment to ACE2, the transmembrane protease serine 2 (TMPRSS2) cleaves and primes the receptor-bound S protein to mediate fusion of the viral envelope with the membrane of the target cell in the host (30,31). This priming of the S protein allows the virus to enter the host cell through endocytosis or via direct fusion of the viral envelope with the host membrane (32).

During SARS-CoV-2 infection, it is hypothesized that the virus first attacks the organs that express ACE2 receptors. In a subset of patients, the viral infection progresses down the trachea to the lung targeting the epithelial lining of the lower airways owing to the substantial expression of ACE2 (33,34). As part of viral replication, the apoptotic response leads to epithelial cell death, diffuse alveolar damage, vascular leakage, edema, alveolar hemorrhage, local inflammation, and interstitial atypical pneumonia (35,36). It has been reported that ACE2 expression is sharply down-regulated shortly after virus entry, because of endocytosis of the receptor together with the virus, which leads to an increase in angiotensin II in lung tissue, and simulation of the type I angiotensin receptor (ATR1) (37,38). This mediates angiotensin II-induced vascular permeability and is hypothesized to contribute to organ injury in COVID-19 (39).

Viral entry to the cell promotes its proliferation and cell death, thereby incurring local and systemic inflammatory responses. The interaction between SARS-CoV-2 and the host induces the production of interferons, activation of natural killer (NK) cells, dendritic cells, macrophages, and neutrophils among other immune responses as reviewed elsewhere (40). During this phase, 20–30% of patients rapidly progress to ARDS with severe hypoxia and multi-organ failure. This stage is accompanied by a cytokine release syndrome (the 'cytokine storm') characterized by elevated levels of interleukins (IL) (including IL-6, IL-1β, IL-2, IL-10), granulocyte colony-stimulating factor (G-CSF), interferon-gamma (INF-γ), tumor necrosis factor (TNF-α), inducible protein 10 (IP-10, also known as CXCL10), and monocyte chemokines (CCL2, CCL7, CCL12) (41-44). Different reports estimated up to 10% fatality rates at this stage (45,46).

Growing evidence suggests that loss of vessel integrity during COVID-19 infection contributes to the initiation and propagation of ARDS by mediating diffuse endothelial inflammation, inflammatory cell recruitment, pulmonary infiltration, and endothelial cell death (47,48). This was evident from the histologic assessment of pulmonary vessels of patients with COVID-19, which showed widespread thrombosis and microangiopathy (47). After infecting pulmonary endothelial cells, endothelitis develops at least in a subset of critically ill patients, hence leading to diffuse endothelial inflammation and alteration in vascular hemostasis (48). Moreover, there is a widespread complement activation, especially in patients with severe COVID-19 as a major contributor to the acute phase response to eliminate the invading pathogen (49). Such complement activation adds to the endothelial cell injury and death with subsequent activation of the clotting cascade, resulting in microvascular thrombosis, pulmonary intravascular coagulopathy, and pulmonary hypertension (50). This is further aggravated by the pro-inflammatory cells, cytokines, and chemokines amplifying the vicious cycle of vessel coagulation and thrombosis. The expression of tissue factor (TF) by activated monocytes further stimulates the coagulation cascade and subsequent generation of thrombin (51). Therapeutic interventions that target the host hyper-immune response, complement activation, and systemic thrombosis are hypothesized to be promising in treating severe COVID-19 disease.

Several publications suggested that the ABO blood group may contribute to an increased susceptibility to acquire SARS-COV-2 infection among group A individuals compared to group O individuals (52-57). In addition, some of these observational studies suggested a higher risk of developing severe disease and need of hospitalization among group A individuals (52,53). However, conflicting findings were reported from other publications, which may be ascribed to different patient populations among other confounders (58,59). This can be related to the inclusion of randomly selected blood donors as controls for which there is an inherent risk of blood group O enrichment. A genome-wide association analysis performed in Spanish and

Italian centers on patients with severe COVID-19 disease with respiratory failure compared to population-derived controls detected cross-replicating association with two loci including rs67152 at chromosome 9q34.2, which coincided with the ABO blood group locus (60). This suggests that in addition to disease acquisition, the ABO blood group could also affect disease severity. A blood group specific analysis, corrected for age and sex, showed a higher risk of severe disease in blood group A and a protective effect in blood group O than in other blood groups. Group O Rh+ individuals significantly correlated with lower mortality in a meta-regression analysis including 8.9 million COVID-19 cases and 465,000 deaths of 101 different nations using their known blood group distribution (61).

The potential mechanism of the protective effect in group O individuals could be the possible interference of naturally-occurring anti-A isoagglutinins with the interaction of the virus S spike protein with the ACE2 receptor, hence preventing its entry into the lung endothelium, as previously studied in SARS-CoV infection (62,63). This is expected to be the case particularly given the similarity in the nucleic acid sequence and the ACE2 binding similarity between SARS-CoV and SARS-CoV-2 (14,27,32,64). Severe outcomes in group A individuals can also be explained by the higher levels of von Willebrand factor and factor VIII levels in individuals with blood group A, with a predisposition to cardiovascular complications (65). Another potential mechanism can be related to complement levels, as an association between COVID-19 prevalence and C3 and ACEI polymorphisms were previously described (66). There is a need for more studies to ascertain the association between the ABO blood group system and the risk of acquiring COVID-19 and disease severity in different patient populations.

CP—a historical perspective

The use of convalescent sera has been of particular interest in the last decades in the management and prevention of emerging viruses as a strategy of passive immunization (67). The introduction of the first serum therapies, initially extracted from animals after they had been rendered immune to the disease in question, was for the treatment of diphtheria and tetanus in the 1890s (68,69). Since then, plasma has been used emergently in epidemics where there is insufficient time or resources to generate immunoglobulin preparations. Historical data has reported the safety and efficacy of convalescent sera for use in other viral outbreaks and pandemics (67). This includes poliomyelitis (70), measles (71,72), mumps (73), and influenza (74). The Spanish influenza A (H1N1) of 1918 was the first viral pandemic for which convalescent blood products were reported to be potentially effective (75-79). A meta-analysis of 8 studies from 1918 to 1925 on the use of CP in a total of 1,703 patients with Spanish influenza A (H1N1) virus pandemic reported reduced mortality in patients who received CP (16% treated patients *vs.* 37% control) and lower mortality rates in patients treated early; namely within four days of pneumonia (80). However, the included studies were small and had many methodological limitations, and were variable in volume and dose of CP used. It is also noteworthy that historically, convalescent sera were developed in many cases without a mean to measure antibody titers.

Several decades later, CP treatment was deployed during the influenza A (H1N1) 2009 flu pandemic (81-83). In a prospective study by Hung *et al.*, 20 out of 93 patients with severe influenza A (H1N1) pdm09 infection were offered treatment with CP harvested by apheresis from patients recovering from the infection (81). Neutralizing antibody titers were measured, and a cut-off of ≥1:160 was used. Clinical outcome was compared between treated and untreated controls. Mortality in the treatment group was significantly lower than in the non-treatment group (20.0% *vs.* 54.8%; P=0.01). Multivariate analysis showed that plasma treatment reduced mortality (odds ratio, 0.20; 95% confidence interval, 0.06–0.69; P=0.011). Subgroup analysis of 44 patients demonstrated that CP treatment was associated with significantly lower viral load at days 3, 5, and 7, and lower IL-6, IL-10, and TNF-α compared with the control group (P<0.05). A multicenter prospective double-blinded randomized control trial (RCT) of using hyperimmune IV immunoglobulin fractionated from the collected CP versus intravenous immunoglobulin (IVIG) in the control arm was associated with significantly lower viral load and mortality within 5 days of symptom onset (84). However, several limitations concerning CP donation were reported, including donor failure to meet blood donation eligibility criteria, inability to make the apheresis appointment, failed laboratory tests, and insufficient neutralizing antibody titers (85).

Different studies assessed the use of CP during the SARS-CoV outbreak in 2003 (86-89). In a non-randomized study, 40 patients with progressive SARS-CoV disease refractory to ribavirin and methylprednisolone received either CP (n=19) or a further dose of methylprednisolone

(n=21) (87). Assessed outcomes revealed lower mortality (0% *vs.* 24%, P=0.049) and high day-22 discharge rate (73% *vs.* 19%, P=0.001) in the group that received CP compared to pulsed methylprednisolone. The authors reported poor clinical response in patients receiving CP after day 16. The largest study published included 80 patients with SARS in Hong Kong and reported that early treatment with CP with an antibody titer of 1:160 or more before day14 had improved outcomes for treated patients (86). The study revealed a higher day-22 discharge rate among patients who received CP before day 14 of illness (86). However, other investigators reported challenges with this approach and recommended a lower threshold of neutralizing antibodies of 1:80 or more, or selecting donors from patients who recovered from a severe illness (90).

A subsequent systematic review and meta-analysis of 32 studies assessed the effectiveness of CP for the treatment of severe acute respiratory infections, including Spanish influenza A (H1N1), influenza A (H1N1) pdm09, SARS-CoV, and avian influenza A (H5N1) (91). Although the data showed a reduction in the rates of mortality with no reports of serious adverse events or complications, it was evident that there are limited literature and a lack of high-quality studies to draw definitive conclusions. Moreover, although a subgroup analysis of viral load reduction has revealed significantly lower levels 3, 5, and 7 days after intensive care unit (ICU) admission, the confounding effects of concomitant treatments, including oseltamivir, zanamivir, and corticosteroids could not be excluded.

The WHO issued a guidance for the use of CP during the West African Ebola epidemic [2013–2016] due to the highly infectious nature of the virus, high associated case-fatality rate, and lack of proven therapies (92). A meta-analysis of clinical studies, including studies that utilized CP during the Ebola outbreak reported major limitations with the methodological design of existing studies and lack of randomization (93). The largest study was a non-randomized comparative study of 84 patients versus controls that reported a non-significant 7% decrease in mortality following two consecutive transfusions of 200–250 mL of ABO-compatible CP, albeit with unknown neutralizing antibody titers (94). No serious adverse events were reported in the patients who received CP. However, the investigators found that treatment with CP was feasible and acceptable to donors, patients, families, and health care providers. There are few reports on the use of CP in the MERS-CoV outbreak (86,89,90,95,96). A recent systematic review and meta-analysis of studies that reported outcomes for patients infected with SARS-CoV, H1N1 pdm09, H5N1, H1N1, avian influenza A (H7N9), Ebola virus, and SARS-CoV-2 show that CP treatment could reduce the risk of mortality, with a low incidence of adverse events (97).

CP—rational for use

The immediate availability of CCP offered use as an emergency intervention in several pandemics while specific treatments and vaccines are not yet available or under evaluation. The use of CCP was deployed for treating patients with SARS-CoV-2 infection in the early phases of the COVID-19 pandemic. CCP can be used for either treatment of patients with an active infection to reduce symptoms and mortality (98), or for prophylaxis for high-risk individuals; such as vulnerable individuals with underlying risk factors, healthcare providers, and those with a history of exposure to confirmed cases with COVID-19 infection. Such plasma may also be pooled and fractionated into hyperimmune immunoglobulin, which was used with success to treat other viral infections such as severe influenza A (H1N1) (84).

The ease of access to CP from recovered donors makes it an attractive therapeutic option, especially in the early stages of any pandemic. Moreover, considering the size of the pandemic, this therapeutic and preventive option could be rapidly made available when there is a sufficient number of potential donors who have recovered from COVID-19 and can donate CCP. It can also be deployed in different settings, including low and middle-income countries, which are most susceptible to being affected by devastating epidemics, although implementation can be limited by major organizational and technological challenges (10,99,100). CCP is obtained by apheresis or whole blood donation from a patient who has survived a previous infection and developed humoral immunity against the pathogen responsible for the disease of question. Apheresis is the preferred mode of the collection as it offers a larger volume collected per session and the absence of a decline in the hemoglobin level in the donor allowing for repeat collections. The WHO recommends that CCP should be used in RCTs to determine its safety and efficacy. In settings where the randomization of patients is not feasible, observational studies should be conducted with data on the characteristics of treated patients and pre-defined patient outcomes (11).

The use of CCP offers quick access as an empirical therapy when specific therapies are not available, especially

that the development of neutralizing antibody-based therapies and vaccines is a lengthy process (101). Moreover, the development of immunoglobulins has high costs of production, storage, and administration which could be prohibitive in some countries. Given the spectrum of pathogenic mechanisms involved in the development of severe COVID-19, ranging from immune hyperactivation to thromboembolic complications, it is unlikely that a single individual treatment will be effective. The multifactorial pathogenic nature of the disease indicates that multiple avenues of treatment might be required, and major effort should therefore be invested to determine the optimal timing and combinations in which these drugs should be administered to maximize their efficacy in severely ill patients with COVID-19. There is a need for high-quality clinical trials to assess the efficiency and safety of CCP use for therapeutic and prophylactic purposes.

CP—mechanisms of action

The precise mechanism of action of CCP is not fully understood. There are different mechanisms whereby CCP may offer a benefit in COVID-19. These can be immune and non-immune (102). The use of CCP offers means for the provision of passive and immediate antibody-mediated immunity (AMI) involving the administration of the neutralizing antibodies against the SARS-CoV-2 virus (98). AMI is classically associated with opsonization, toxin and viral neutralization, antibody-dependent cellular cytotoxicity (ADCC), complement activation, phagocytosis, and direct antimicrobial actions through the generation of oxidants (98,101,103). B cell antibodies can be immunomodulators; bridging the innate, acquired, cellular, and humoral immune responses (101). In addition, CCP contains other constitutes that can benefit the recipient. There is a need for further research to study the role of these mechanisms in viral clearance in COVID-19.

Immune mechanisms

Neutralization and suppression of viremia

Neutralizing antibodies provide an important immune defense against viral infections, through binding against a given virus and thereby neutralizing its infectivity directly (104). The presence of neutralizing antibodies in the plasma is proposed to reduce the viral infectivity by binding to the surface of the virus particles (virions), blocking viral attachment and entry to the infected cell (105). Neutralization is defined as a reduction in viral infectivity by the binding of antibodies to the surface of the viral virions, thereby blocking a step in the viral replication cycle (106). Neutralization assays measure the ability of sera to neutralize the infectivity of the virus in cell culture.

Neutralizing antibodies can be induced in convalescent patients and can provide an important specific immune defense against SARS-CoV infection (104,107). Experience from prior SARS-CoV coronavirus pandemic shows that convalescent sera contain neutralizing antibodies to the relevant virus (108). In COVID-19 infection, high levels of neutralizing antibodies are detected at about 10 days in both mild and severely ill patients, and remain stable thereafter (109). It was also shown that the levels of neutralizing antibodies were higher in the severe group (110). Considering that the coronavirus S protein mediates entry into host cells; it is the primary inducer and target for neutralizing antibodies upon infection. Particularly, RBD within S1 unit is the most crucial target. The antibody responses that target the immunodominant SARS-CoV-2 S protein, specifically those that target the RBD, are thought to be highly associated with virus neutralization by blocking the interaction between RBD and AEC2 receptor (111,112).

Early studies on CCP during the current pandemic demonstrated the presence of neutralizing antibodies in the plasma of recovered patients from COVID-19 (21). Studies have confirmed that up to 80% of recipients of CCP show a significant increase in antibody levels after transfusion (113). It has also been demonstrated that the administration of CCP containing these neutralizing antibodies to individuals with severe COVID-19 results in a rapid viral clearance by neutralizing the SARS-CoV-2 virus (114). The passive transfusion of anti-A blood group natural isoagglutinin, is another potential benefit, especially among elderly males who are known to experience reduction of isoagglutinin titers (115).

Antibody-dependent cellular cytotoxicity

Besides the neutralizing effect, non-neutralizing antibodies present in CCP may contribute to enhanced recovery (98). Non-neutralizing antibodies, such as immunoglobulin G (IgG) and immunoglobin M (IgM) can play an important role in prophylaxis and/or recovery through other antibody-dependent mechanisms (116). It is known that antibodies consist of two structural regions; a variable fragment (Fab) that mediates antigen binding, and a constant fragment (Fc) that mediates the biological properties of the immunoglobulin

molecule, such as serum half-life, interaction with cellular Fc receptors, and the ability to activate complement, and its downstream effector functions (101).

The Fc mediated antibody effect has been described in the Ebola virus and respiratory syncytial virus infection as a mean of antibody-mediated protection against viral infections (117,118). The interaction with Fc-receptors can lead to the killing of virus-infected cells through a variety of mechanisms, including ADCC and antibody-dependent cellular phagocytosis (ADCP) (98). ADCC is induced when the Fc domain of antibodies that are bound to viral proteins on the surface of virus-infected cells engage the Fc gamma receptors (FcγRs) on the innate effector cells. This interaction induces the release of cytotoxic granules resulting in the killing of infected cells (117). ADCP is the uptake of virus-antibody complexes or antibody-coated virus-infected cells by phagocytic cells, resulting in the clearance of the immune complexes from the infected host (117). The interaction with Fc-receptors can also lead to complement activation and complement-dependent cytotoxicity (CDC) (117).

Nonimmune mechanisms

Modification of inflammatory response and cytokine storm

In addition to neutralizing antibodies, collected CCP contains other proteins such as anti-inflammatory cytokines, natural antibodies, defensins, and other proteins that are obtained from the donor (119). As a result, it is hypothesized that the transfusion of CCP may provide further benefits such as immunomodulation via amelioration of the severe inflammatory response induced by the disease, which can reduce host damage (120). This is particularly the case with the over-activation of the immune system during COVID-19 and the development of the cytokine storm. It is hypothesized that CCP inhibits the formation of the inflammatory cytokine storm. Therefore, it is believed that it is most effective when administered prophylactically or used early after the onset of symptoms.

Complement activation largely contributes to the systematic inflammation and migration of the neutrophils to the lungs (121). There are several anti-inflammatory mechanisms by which IgG antibodies in IVIG reduce complement activation or interfere with the action of pro-inflammatory proteins, hence limiting the formation of complement complexes and the inflammatory effect (122). This potentially can be the case with CCP transfusion.

Restoration of coagulation factors and immunomodulation of the hypercoagulable state

Other constituents in CCP may also exert beneficial effects. It has been suggested that plasma components can provide other beneficial actions such as, restoration of the coagulation factors (123). It is possible that CCP provides procoagulant and antifibrinolytic factors that restore the endothelium glycocalyx and prevent excess vascular leakage. Moreover, it has been hypothesized that CCP might offer neutralization of autoantibodies in the recipient, similar to the effect of anti-idiotypic antibodies present in IVIG.

CP—factors impacting response

One important characteristic of antibody-based therapies is that their effectiveness decrease as the duration of infection increases, which can limit the application of such a therapeutic strategy to conditions where an early diagnosis can be made (124). When used for therapy, antibodies are most effective when administered shortly after symptom onset, as antibodies modify the initial inflammatory response. The reason for the temporal variation in efficacy could reflect that passive antibody works by neutralizing the initial inoculum, which is likely to be much smaller than that of established disease (125). As was shown when used in SARS-CoV disease, administration of CCP early in the disease would theoretically be more effective (86).

Considering that viremia peaks in the first week in most viral illnesses and seroconversion for most viruses occurs between 10 to 14 days, which is followed by the clearance of the virus, CCP is theoretically more effective if administered in the early stages of the disease, between 10–14 days, before the development of the cytokine storm (86,100). Data on COVID-19 patients indicate that seroconversion occurs after 7 days in 50% of patients, and by day 14 in all patients (21). Another study has shown that <40% of patients with COVID-19 had detectable antibodies (by enzyme-linked immunosorbent assay) within the first week of infection, increasing to 94% for IgM and 80% for IgG by day 15 after the onset of the disease (126). Some have recommended infusing CCP within the first 5 days of infection (111). Others proposed no later than 14 days post-infection or during the viremic and seroconversion stage (86). Many opted for collection after day 28 (11,127,128).

However, to achieve the desired effect, and for passive antibody therapy to be effective, a sufficient amount of antibodies must be administered (98). The efficacy of CCP therapy relies on a robust antibody response in CCP donors. The presence of an anti-SARS-CoV-2-neutralizing antibody at an adequate titer in the collected plasma is an important prerequisite. The challenge in using convalescent sera is that some CCP donors may not have high titers of neutralizing antibodies (90). Timing of donation relative to the resolution of symptoms and severity of illness could impact the antibody titer level in the donor at the time of donation (129). The titers in convalescent patients with H1N1 and MERS-CoV patients were found to correlate with viral load and severity of the viral illness (130,131). In COVID-19, male gender (reported to be at a greater risk for more severe COVID-19) (132), older age (113,133), and history of hospitalization (113) were found to be associated with increased antibody responses, and hence it has been suggested to use high antibody titer as a surrogate marker for worse clinical prognosis (126), and in the criteria of donor selection. At this time, the minimal cut-off of neutralizing antibodies and CCP doses to be effective is yet to be defined (100). A large study of 285 patients reported detectable IgG antibodies, using a magnetic chemiluminescence enzyme immunoassay (MCLIA) for virus-specific antibody detection, 17–19 days after symptom onset, while both IgG and IgM antibody titers were increasing during the first 3 weeks of symptom onset (134). Similar to other studies, IgG and IgM antibody titers were higher in the severe group when compared with the non-severe group.

Another challenge that can be encountered is that CCP donor may show no detectable antibodies with specificity toward RBD and S protein viral epitopes (133). Seroconversion studies in SARS-CoV infection have shown that there are temporal changes in S-specific and N-specific neutralizing antibody response and these may differ in patients who have either recovered or died. Patients who recovered had a higher and sustained increase in serum neutralizing antibody titers with anti-N protein-specific and anti-S glycoprotein-specific responses (135). A study assessing levels of antibodies among potential CCP donors using EUROIMMUN enzyme-linked immunosorbent assay that recognizes either IgG or IgA against the S1 domain reported a considerable heterogeneity in the antibody responses among the donors (136). Therefore, the specificity of the target of these antibodies is another factor to consider. If the correlation with outcomes in group O and B recipients is confirmed, titers of anti-A isoagglutinin would be another factor to impact response (137). Studies are ongoing to evaluate the correlation between isoagglutinin titers and outcomes in blood group O and B recipients of CCP (138).

CP—safety and efficacy

CCP was adopted quickly and widely during the pandemic without any strong evidence on safety or efficacy (100). None of the previous studies on CP use in other SARS viral infections did report a serious adverse event, although minor complications may be underreported in the literature (91). In a large study from the Mayo clinic, CCP has demonstrated safety with a low incidence of all serious adverse events within the first four hours of transfusion (139,140). The largest report on safety included data on 20,000 patients and reported transfusion reactions in 89 recipients of CCP (<1%). The 7-day mortality rate was 8.6%, including transfusion-associated circulatory overload (0.18%), severe allergic transfusion reaction (0.13%) and transfusion-related acute lung injury (0.10%) (139). The rate of thromboembolic/thrombotic events and cardiac events was also low (<1% and ~3% respectively), while the vast majority of these were judged to be unrelated to the CCP transfusion per se. The estimated 7-day mortality rate was higher among more critically ill mechanically ventilated patients, in patients admitted to the ICU, and in patients with septic shock or multiple organ dysfunction/failure (139).

As for efficacy, the initial case series reported effectiveness in treating critically ill patients with clinical improvement, reduced inflammation, and viral load (141-143). This was followed by the initiation of numerous studies and clinical trials worldwide for assessing the efficacy of therapeutic and prophylactic use of CCP. Two Cochrane reviews of these studies concluded that it remains very uncertain that CCP is effective or beneficial for admitted COVID-19 patients (144,145). The most recent Cochrane review included results from 1 RCT, 3 controlled non-randomized studies of interventions (NRSIs), and 10 non-controlled NRSIs with 5,443 participants, of whom 5,211 received CCP (145). The authors concluded that certainty remains unknown whether CCP has any effect on all-cause mortality at hospital discharge, has any effect on the improvement of clinical symptoms at seven days, or prolongs time to death. Moreover, there was limited information regarding adverse events, the majority of which were allergic or respiratory events. The review identified 98 ongoing studies evaluating

CCP and hyperimmune immunoglobulin, of which 50 are RCTs, projecting the upcoming wealth of information expected from the emerging literature.

Prophylaxis trials on the use of CCP in non-infected, but at-risk subjects including these with a history of exposure, are also being designed (146,147). The first trial is a randomized controlled double-blinded phase II trial that includes adult participants (18 years of age and older) with high-risk exposure within 96 hours as defined by the US Center of Disease Control. This trial aims to assess the efficacy of treatment at day 28 defined as development of SARS-CoV-2 infection (symptoms compatible with infection and/or positive molecular testing) regardless of disease severity and cumulative incidence of grade 3 & 4 and serious adverse events up to day 28 (146). The second trial includes children between 1 month and 18 years of age, determined to be at high risk for severe SARS-CoV-2 disease, including infants ≤1 year of age, immunocompromised kids, children with hemodynamically significant cardiac disease (e.g., congenital heart disease), or kids with underlying lung disease with chronic respiratory failure and with high-risk exposure. Susceptible children are defined as those with a history of exposure to a household member or in a day-care center to a person with a confirmed SARS-CoV-2 infection or with a clinically compatible disease, and randomization takes place within 96 hours of exposure (147).

CP—questions to be answered

To date, little is known about the effectiveness of CCP in treating COVID-19 patients. It is important to assess the effectiveness of CCP, considering the potential factors that determine efficacy. There is a need to determine which viral antigen epitopes elicit protective antibodies, and to estimate the required amount of antibody to use for therapy (101). It is also essential to understand the antibody characteristics and titers that can impact the response to the CCP. Results from longitudinal studies evaluating large numbers of serum samples from COVID-19 patients with a broad spectrum of clinical symptoms will be very informative to further assess the time for seroconversion and its correlation with disease severity and antibody titers. There is a need for more data to understand the dose-response effect of CCP transfusion among COVID-19 patients.

There are many identified gaps in knowledge around CCP use including patient eligibility criteria to receive CCP, best CCP dose, frequency of administration and timing, measures for assessment of response and outcomes, and application in pediatrics, neonates, and less resource countries (148). There is a need to develop international programs to facilitate access to CCP for patients in countries with limited resources. Moreover, many ethical considerations are required when establishing a CCP program including how to meet the demand with insufficient CCP supply, and when different competing needs are present, including compassionate use. It is worthwhile to mention that several neutralizing human monoclonal antibodies have been developed, and some are undergoing phase I clinical trials (112,149-154). These would avoid the limitations that are present with the use of CCP.

Conclusions

In conclusion, there are different potential mechanisms of actions for CCP in treating COVID-19. As SARS-CoV-2 spread worldwide, the deployment of different therapeutic and prophylactic strategies continues. The availability of therapeutic neutralizing antibodies against SARS-CoV-2 will offer benefits for the control of the current pandemic and the possible re-emergence of the virus in the future, and their development, therefore, remains a high priority. Until this is made available, CCP offers a therapeutic and prophylactic option. Based on the number of existing trials on the use of CCP, data from thousands of patients will be available in the near future. Time is of the essence to set up protocols for collection, preparation, and administration of CP to allow guidance for use in future emerging viral pandemics. Additional data on pathogenesis and immune response will aid in the further deployment of CCP in future viral threats.

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