Production and Quality Assurance of Human Polyclonal Hyperimmune Immunoglobulins against SARS-CoV-2

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Highlights

- Anti-Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) human hyperimmune Immunoglobulin (HIG) is a passive polyclonal immunotherapy of potential value to treat COVID-19.

- HIG can be fractionated from pooled convalescent plasma (CP) donations or plasma donated by vaccinated donors

- HIG has advantages over a regular convalescent plasma product due to its standardized and controlled high neutralizing antibody content and its increased virus safety.

- Donor selection, collection, and testing of plasma for HIG production should comply with testing requirements for COVID-19 donations and general requirements of plasma for fractionation.

- The fractionation of plasma rich in SARS-CoV-2 antibodies should meet good manufacturing practices to ensure quality, safety, and consistency of HIG.

Production and Quality Assurance of Human Polyclonal Hyperimmune Immunoglobulins against SARS-CoV-2

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has highlighted the potential therapeutic value of early passive polyclonal immunotherapy using high-titer convalescent plasma (CCP). Human polyclonal hyperimmune immunoglobulin (HIG) has several advantages over CCP. Unlike CCP, HIG can provide standardized and controlled antibody content. It is also subjected to robust pathogen reduction rendering it virally safe and is purified by technologies demonstrated to preserve immunoglobulin neutralization capacity and Fc fragment integrity. This document provides an overview of current practices and guidance for the collection and testing of plasma rich in antibodies against Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) and its industrial fractionation for the manufacture of quality-assured and safe HIG. Considerations are also given to the production of HIG preparations in low- and middle-income countries.

Keywords: COVID-19; passive immunotherapy; convalescent plasma; SARS-CoV-2; human hyperimmune immunoglobulins.

Background and introduction

Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) emerged rapidly in December 2019, spurring a historic pandemic that has yet to relent, as virus variants continue to spread. At the time of this writing, there have been over 525 million reported cases of SARS-CoV-2 infection and more than 6.2 million deaths from the associated Coronavirus Disease 2019 (COVID-19) [1]. Treatment options at the outset of the pandemic were understandably few and included early passive polyclonal immunotherapies including COVID-19 convalescent plasma (CCP) and hyperimmune immunoglobulin (HIG). Early reports of benefit of COVID-19 convalescent plasma (CCP) [i.e. plasma collected from those who have recovered from COVID-19] in China [2, 3] led to transfusion of CCP on a unprecedent scale, most notably in the United States (US) where CCP was administered both through a federally funded expanded access program, as well as through several observational studies and clinical trials that sought to evaluate the safety and efficacy of CCP [4].

CCP was extensively characterized and used for COVID-19 treatment in a number of clinical trials with conflicting results [5-9], but signals of efficacy were observed in some vulnerable populations [10-12]. Two key elements appear central to the efficacy of CCP: the titer of neutralising antibodies and timing of administration relative to symptom onset [12]. Unfortunately, the overwhelming majority of studies of CCP to date have evaluated patients with severe (i.e., late stage) COVID-19, while the data have since shown that timing of administration should be early relative to symptom onset i.e., the collective data show little benefit of CCP administration in moderate to late-stage disease [13]. In a multicenter, double-blind, randomized, controlled trial, that evaluated the efficacy of CCP, as compared with control plasma, within 9 days after the onset of symptoms in symptomatic mostly unvaccinated adult patients, the administration of CPP reduced the risk of disease progression leading to hospitalization [12].

From the early stages of the COVID-19 pandemic, CCP was deployed rapidly, drawing on an extant blood collection infrastructure that is widely available [14]. That ease of access extends to remote and low resource settings [15, 16]. CCP antibody content is polyclonal, which is potentially advantageous given SARS-COV-2 virus evolution during the pandemic where selected monoclonal antibodies (mAbs) were rendered ineffective [17, 18].

Unlike CCP, hyperimmune immunoglobulin (HIG), which is produced by pooling large numbers of units of donor plasma, enables standardization of dosing. Further, routine application of virus reduction technologies, validated as part of regulatory requirements to preserve immunoglobulin neutralization capacity and Fc fragment integrity, ensures low infectious risk, and preserved therapeutic efficacy. Nonetheless, standardization requires production from massive pools of plasma, requiring

months before HIG could be evaluated. At time of writing, large studies pertaining to the use of anti-SARS-CoV-2 HIG have been limited. No evidence of clinical benefit was seen from the administration of anti-SARS-CoV-2 HIG together with remdesivir in symptomatic hospitalized COVID-19 patients without acute end-organ failure [19]. However, HIG passive immunotherapy may still be beneficial in earlier disease stages of COVID-19 or in specific populations [10-12].

The primary therapeutic value of HIG made from multiple donors with anti-SARS-CoV-2 antibodies, as compared to single-donor CCP plasma donation, is the polyvalence of antibodies that is expected to enhance the antiviral activities [20]. This polyvalence may help overcome viral mutations leading to a higher degree of resistance to neutralizing antibodies [21]. Diversity in anti-SARS-CoV-2 antibodies may confer broader antiviral activities through a more potent targeting viral epitopes and engagement of complementary mechanisms of cellular defence [22]. Processing CCP into HIG results in a highly purified immunoglobulin G (IgG) product with more concentrated neutralising antibody activity. HIG administration results in a treatment supplying a larger dose of antibodies per unit of volume, which can contribute to reducing the risks of side effects in patients. Indeed, the fractionation process of plasma includes purification and concentration steps that result in a final product containing over 10-fold the concentration in total and anti-SARS-CoV-2 IgG compared to the starting CCP pool [22].

In this manuscript, we sought to contextualize the individual roles of CCP and human plasma-derived HIG in preventing hospitalization or progression of disease in patients with SARS-CoV-2 infection in high income as well as in LMICs and provide points to consider for the collection and testing of plasma rich in SARS-CoV-2 antibodies as well as production and quality assurance of human polyclonal plasma-derived anti-SARS-CoV-2 HIG.

Donor selection

HIG can be prepared from plasma that has been collected from convalescent or/and vaccinated donors. Based on the experience with the production of other therapeutic human HIG, such as hepatitis B or rabies immunoglobulins, it is expected that plasma from vaccinated donors, without a documented history of infections, can be qualified as plasma donors to manufacture HIG. An advantage of using plasma collected from very recently infected individuals (vaccinated or not) for HIG preparation is that it may provide anti-SARS-CoV-2 antibodies against emerging variants. Donor selection criteria overlap those used for the collection and transfusion of CCP. In particular, testing for relevant transfusion-transmitted infections by serology and nucleic acid testing must be performed by the blood establishment or the fractionator, in line with the requirements of the local jurisdiction. The plasma for

fractionation should meet the quality and safety specifications as defined by the plasma fractionator in compliance with regulations in place.

Convalescent plasma

Plasma that is collected from coronavirus disease 2019 (COVID-19) convalescent individuals can be used therapeutically either as transfusion of convalescent plasma or through the manufacture of HIG. Plasma with high titers of SARS-CoV-2 binding antibodies (which correlate reasonably well with high neutralising antibody titers) are preferred [12, 23]. However, due to the variety of assays used to characterize CCP in different clinical trials and the lack of calibration of these assays against international standards, it has not been possible to define the attributes of high-titer CCP. The introduction of the WHO International Reference Panel to allow the calibration of assays against arbitrary units will help standardise the definition of CCP characteristics in terms of binding and neutralizing Ab titers. Still, little information on the collection of potent units is currently available [24]. CCP for therapeutic purposes or for HIG preparation is collected from individuals whose plasma contains anti-SARS-CoV-2 antibodies and who should meet all donor eligibility criteria.

Criteria and deferral periods for donating plasma for HIG overlap those established for CCP donations [25, 26], although recommendations could eventually change as new information becomes available on any possible risk of virus infectivity from collected blood [25, 27, 28]. To minimize the risk of transfusion-related acute lung injury (TRALI), donors who donate plasma for transfusion, including CCP, should be either male donors, female donors who have never been pregnant, or female donors who have been tested since their most recent pregnancy and have negative results for human leukocyte antigen HLA antibodies [22, 25, 26, 29]. However, for the manufacture of HIG, plasma donated by females may in principle be used for fractionation into HIG, as is the case to produce any polyvalent or HIG. Using plasma from female donors for fractionation has not been associated with an increasing occurrence of TRALI following treatments with polyvalent immunoglobulins, although rare adverse events of TRALI have been reported [30].

Vaccinated donors

As the pandemics progresses, the number of vaccinated individuals (who may also be regular blood donors) is continuing to increase and can facilitate the supply of plasma containing high levels of

SARS-CoV-2 antibodies for transfusion or fractionation [31-34]. US and EU legislations allow vaccinated donors to donate CCP if they have recovered from SARS-CoV-2 infection. According to FDA requirements, individuals who have received authorised, licenced, or investigational COVID-19 vaccination can currently donate CCP for transfusion only if they have had symptoms of COVID-19 and a positive test result from an approved/cleared or authorized test by FDA *AND* received COVID-19 vaccine after diagnosis of COVID-19 *AND* are within 6 months after completed resolution of COVID-19 symptoms [26]. Administration of COVID-19 vaccines to boost the immunity of CP donors would need to be conducted within a clinical trial [25, 26].

The humoral response elicited after vaccination (one or two doses in previously infected individuals and two or three doses in never-infected (*naïve*) individuals) is higher than the response seen in convalescent donors early after infection [35-37]. Individuals with pre-existing immunity exhibit an antibody response to the first BTN 162b2 vaccine dose that is similar to or higher than that of naïve individuals after the second dose [38]. Individuals previously infected with SARS-CoV-2 have significantly higher reactogenicity [38, 39], even when vaccinated with only one dose [40].

The SARS-CoV-2 vaccines that are currently licensed induce antibodies to the spike protein of the virus (S) only. As a result, the ratio of anti-N versus anti-S antibodies in normal immunoglobulin products is a useful factor to discriminate the relative contributions of vaccines and COVID-19 infection in the plasma donors pool [41]. The neutralising and Fc-mediated activities in donated plasma from vaccinated individuals are higher than those measured in CCP collected early after disease resolution [37, 42]. Using vaccinated donors as donors of source plasma would largely preserve the high neutralising antibody titers in the final product since viral neutralization should be less dependent on IgM compared to IgG owing to the maturation of the adaptive immune response.

Recent studies revealed a clear advantage of the longer interval between the first two doses of vaccine on the level of SARS-CoV-2 antibody levels and neutralising antibody titers [43, 44], despite the fact that the impact of dosing interval on vaccinated previously infected individuals was less pronounced than in naïve individuals. However, hybrid immunity (natural infection plus vaccination) led to the strongest cross-reactive neutralisation against variants of concern [43]. Fc-mediated activity was greater in previously infected individuals who received two doses of the vaccine, and was comparable between previously infected individuals who received only one dose and naïve individuals who received two doses [37]. Altogether these observations suggest that vaccinated previously infected individuals represent ideal plasma donors for HIG preparation, followed by fully vaccinated naïve individuals with an extended interval between the two doses. As for CCP, a decline in antibody titer is observed after vaccination [45] indicating that a window period for plasma collection from vaccinated donors should be defined.

Plasma fractionators may have specific selection and testing requirements. One plasma fractionator enrolled donors of plasma for fractionation if they have evidence of previous SARS-CoV-2 infection through positive nucleic acid amplification testing (NAT), positive antigen test or, alternatively, SARS-CoV-2 antibody test [22]. The minimum acceptable cut-off level in SARS-CoV-2 antibodies in individual donations of plasma for fractionation depends upon the targeted minimum antibody titer in the manufacturing plasma pool taking into account the enrichment and concentration factors achieved during fractionation, and the targeted neutralization titer of the final product.

Plasma collection procedure

Typically, hyperimmune plasma for fractionation is preferably collected by apheresis, rather than whole blood donations. Apheresis plasma collection follows local regulations that specify volume (e.g., 600-880 mL) and frequency (e.g., 24 times/year) of donations [22]. The optimal duration and frequency for donating CCP after an infection or a vaccination is not established. It should be noted that currently, and for regulatory reasons, plasma subjected to a pathogen reduction treatment licensed for clinical plasma transfusion (e.g. psoralen/UVA, methylene blue/light, riboflavin/UV, or solvent/detergent), cannot be used for fractionation into HIG.

Testing for SARS-CoV-2 titer in plasma for fractionation into HIG

Testing of SARS-CoV-2 antibodies

Guidance from the European Commission recommends that "SARS-CoV-2 antibodies should be measured in a sample obtained from a donor before or during donation, or from donated plasma for fractionation after donation. The volume of the specimen should be sufficient for repeat testing and tests approved at the national level or validated by nationally recognized virology or public health institutions or laboratories should be used" [25]. A wide range of immunoassays with different readouts exists to measure the humoral response to SARS-CoV-2 infection or vaccination. Many assays target spike protein or its receptor binding domain (RBD). The most frequently employed methods are immunosorbent assays, such as enzyme-linked immunosorbent assays (ELISA). A virus neutralisation test or a binding antibody test can be used to determine the titer of neutralising antibodies in vitro directly or indirectly. The FDA established a cut-off criteria to qualify high titer plasma based on the assay used

for testing [46]. Studies have shown that titers of anti-S protein IgG antibodies (anti-spike ectodomain (ECD) and anti-RBD) correlate well with the titers of virus neutralising antibodies in vitro [41, 43, 47-49]. Thus, binding antibody testing may be used as a surrogate test for neutralising antibody activity [46]. Donor's weight, time between disease onset and serial plasma collection, and anti-SARS-CoV-2 IgG and IgM levels are important predictors for neutralising antibody titers [50].

The World Health Organization (WHO) offers an international reference panel to allow the calibration of assays to arbitrary units (IU/mL for neutralising antibodies and BAU/mL for binding antibodies), and facilitate comparison of data regardless of the assay used [51]. Assays to directly measure viral neutralization are not easy to perform in routine laboratory analyses. Surrogate assays for neutralization have been proposed but their performance was not better than those of commercial or in-house assays measuring S- or RBD- binding antibodies [48, 52]. Nevertheless, at least one commercial neutralization surrogate assay has been calibrated with the WHO standards [53], which will allow comparison of plasma potency measured with this or other neutralization assays, as long as these assays are also calibrated with the same WHO standards.

As for neutralization, the evaluation of Fc-mediated effector function requires more complex assays. It has been shown that Fc-mediated effector functions of SARS-CoV-2 antibodies are most strongly correlated with FcγR-binding antibodies and with RBD-specific IgG1 and IgG3 antibodies [54]. Therefore, assays to measure RBD-binding IgG antibodies (or IgG1/IgG3 if more accuracy is required) could be used to select plasma with high Fc-mediated activity. In fact, selection of plasma with high titers of anti-RBD IgG antibodies using a single (and simple) antibody binding assay with results preferably expressed in WHO international units, should be sufficient to ensure the presence of acceptable levels of neutralising and Fc-mediated activities for anti-SARS-CoV-2 HIG preparation.

Importance of neutralization and Fc-mediated activity in selecting plasma

A clinical trial highlighted the importance of IgG Fc-mediated activity for the efficacy of CCP [55], supporting studies in animal models of SARS-CoV-2 infection which revealed the role of both neutralising and Fc-mediated activities of monoclonal antibodies to SARS-CoV-2 for optimal therapeutic efficacy [56-58]. Therefore, HIG should preferably contain high titers of SARS-CoV-2 binding antibodies with good neutralising and Fc-mediated activities for maximal efficacy.

Two groups reported the preparation of HIG using plasma from convalescent individuals who had a confirmed SARS-CoV-2 infection and a positive SARS-CoV-2 antibody test [22, 29]. Convalescent individuals developed variable levels of anti-SARS-CoV-2 binding antibodies with also variable (and

sometimes low) levels of neutralising and Fc-mediated activities [59-61]. Follow-up studies revealed waning of antibodies over time to reach, in some cases, undetectable levels [42, 62, 63], indicating the need to qualify donors and to define a window period for the collection of suitable CCP after disease resolution for HIG preparation.

Although IgM may play an important role in neutralising activity in CCP [64], its activity declines rapidly after COVID-19 resolution due to the rapid waning of SARS-CoV-2 antibodies of IgM isotype compared to other isotypes [42, 65]. IgA also contributes to the neutralising activity of SARS-Co-V-2 antibodies [64, 66]. Consequently, a portion of neutralising activity present in the starting plasma pool might be lost during fractionation of plasma into anti-SARS-CoV-2 HIG containing only IgG [22]. In contrast, Fc-mediated effector functions which are mediated by IgG (namely IgG1 and IgG3) will be retained in an HIG product.

Other tests performed on plasma for fractionation into HIG

Testing for relevant transfusion-transmitted infections by serological and/or nucleic acid tests, approved by the fractionator should be performed, and the donation found to be compliant with the specifications. Furthermore, plasma fractionators typically perform virus testing of minipools of plasma prior to industrial pooling by nucleic acid testing for human immune deficiency virus (HIV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Hepatitis A virus (HAV), and parvovirus B19 to reduce the risk of window phase donations and further lower the viral load challenge in the manufacturing plasma pool. Fractionators should comply with all other plasma fractionation requirements as set out in Pharmacopoeia, their national regulatory authorities, international regulatory guidance [67], or following WHO recommendations.

Plasma fractionation and product specifications

Industrial-scale fractionation

Industrial fractionation of pooled CCP donations containing neutralising antibodies against SARS-CoV-2 allows obtaining a polyclonal HIG preparation with a standardized antibody content and

consistent formulation. Plasma for fractionation is typically collected from a network of collection centers covering a large geographic area [22]. The broad diversity in the donor source and the mix of antibodies may provide a potent neutralization potency against various virus variants and epitopes. The standardized immunoglobulin preparation should facilitate therapeutic or prophylactic application for COVID-19.

Most industrial plasma fractionation methods that are validated for the production of HIG and can be implemented to prepare convalescent immunoglobulins combine ethanol fractionation, caprylic acid treatment, and chromatography [22, 68]. Such processes segregate the immunoglobulin G fraction from other plasma proteins, including IgA and IgM. Procedures are validated and monitored to remove or avoid the generation of unwanted contaminants (isoagglutinins, aggregates, prekallicrein activator, activated factor XI, endotoxins), which, if present, could lead to a range of rare adverse events that can be deleterious to the recipients [68, 69]. The fractionation processes also combine various dedicated steps (solvent/detergent, low pH incubation, pasteurization, and/or nanofiltration) validated to inactivate or remove enveloped and non-enveloped viruses without altering the functionality of the IgG molecule as part of regulatory requirements [68, 70]. The purified immunoglobulin G is concentrated at least five to ten-fold compared to the starting plasma to reach a concentration of 50 to 100 mg/mL, making it suitable for low-volume intravenous administration. This implies that 25 mL of an HIG preparation contain a mean anti-SARS-CoV-2 antibodies equivalent to 125 to 250 mL of CCP. Preparations with higher concentration, close to 200 mg/mL, could even be considered in principle for prophylaxis in exposed individuals in sub-cutaneous formulations. Each immunoglobulin brand has its characteristics and safety profile depending on the manufacturing process and formulation [71].

Limitations in the ability of the industrial plasma fractionation industry to manufacture SARS-CoV-2 and other convalescent immunoglobulins have surfaced. The logistics required to accumulate several convalescent donations sufficient to reach the necessary volume of plasma needed for industrial fractionation (typically 1000-4000L at the stage of the plasma pool) has delayed the availability of immunoglobulin batches for clinical trials. Ensuring proper process segregation of the fractionation of CCP alongside that of licensed plasma products is an issue that can be addressed using a pilot-scale facility dedicated to the manufacture of convalescent immunoglobulins. Disrupting routine manufacturing schedules is an issue posed by the production of convalescent immunoglobulins as it may affect the supply of routinely manufactured plasma-derived medicinal products [22].

Specifications of SARS-CoV-2 hyperimmune immunoglobulins

The final immunoglobulin preparations must comply with fixed quality specifications to ensure molecular integrity, optimal quality, and transfusion safety [68]. A validated assay for SARS-CoV-2 neutralization capacity and SARS-CoV-2 antibody titer should be implemented and expressed using the WHO international reference units. Recently, two studies on immune correlates of protection using data from COVID-19 vaccine efficacy trials have provided binding and neutralizing Ab titers expressed in standardized WHO units (BAU/ml and UI/ml respectively) for 90% vaccine efficacy [72, 73]. These data can help define specifications for plasma donor selection rather than using various assay cut-offs. They can be used as a guide to establish the BAU/ml and IU/ml levels of final HIG products required to yield protective titers after infusion into recipients. The three highest anti-SARS-CoV-2 neutralising immunoglobulin lots released in July 2021 by Gammagard, Liquid; Baxalta, US Inc., Lexington, MA were manufactured from recovered plasma with a geometric mean potency of 4,740 IU/mL (range 4,605-5,022 IU/mL) significantly higher than the lots manufactured from source plasma with a geometric mean potency of 1,045 IU/mL (range 157 – 3,256 IU/mL) [33]. The higher SARS-CoV-2 antibody titers of immunoglobin lots manufactured from recovered plasma may result from the comparatively higher age of whole blood donors versus plasma donors. Advanced age is a risk factor for more severe COVID-19 and results in stronger immune responses and higher antibody titers [24, 33]. Dosing of the HIG to patients may vary based on the anti-SARS-CoV-2 antibody titer of the preparation. In current and past clinical studies, doses corresponding to 10 to 40 g of total IgG have been administered intravenously [19].

Safety and efficacy of anti-SARS-CoV-2 hyperimmune immunoglobulins

The experience accumulated with administering various immunoglobulins products, polyvalent and hyperimmune, over the past decades can help delineate the expected safety profile of anti-SARS-CoV-2 HIG prepared using the same fractionation processes. Although normal human plasma-derived immunoglobulins have a relatively good safety profile, adverse events may occur in a few percent of patients [71]. The occurrence of adverse events depends on different variables such as the age of the patient, underlying disease conditions (e.g., renal disease), dose and rate of infusion, and specific characteristics and formulation of the immunoglobulin product transfused. The safety profile of immunoglobulin preparations to treat SARS-CoV-2 infections should be analyzed considering the clinical profile and severity of COVID-19 disease. Severe COVID 19 patients may experience severe inflammation, hyperviscosity, hypercoagulablity, fever, and other adverse events. Anti-SARS-CoV-2 HIG prepared by new fractionation processes should also meet the essential safety criteria highlighted below.

Anti-SARS-CoV-2 HIG should be virtually exempt from risks of virus transmissions thanks to the complementary safety measures implemented all along the production chain, including (a) donors screening, (b) serological and nucleic acid testing of donations against the major blood-borne viruses, and last but not least, (c) “orthogonal” virus inactivation and removal treatments [74].

The risks for hemolytic events due to elevated titers of isoagglutinins can be controlled by (a) exclusion of the donations with high anti-A or anti-B titers from the starting plasma pool, (b) introduction of a dedicated affinity chromatographic step designed to remove isoagglutinins [75-77], and (c) control of anti-A or anti-B titers in intermediate fractions and final batches [68]. The product should have no or limited amount of protein aggregates that can be responsible for anaphylactic reactions. Anti-SARS-CoV-2 HIG should be devoid of proteolytic activity (a consequence of prekallicrein activator or thrombin-like proteases generated during fractionation) [68, 78, 79] which could result in hypotensive and procoagulant side-effects, respectively, using advanced and well-monitored purification methods. The preparation should have an endotoxins within strict specifications to avoid inducing fever in patients.

The safety profile of Anti-SARS-CoV-2 HIG should be looked at carefully in the context of the multifaceted pathophysiological abnormalities presented by severely affected COVID-19 patients admitted to ICU and considering the dose of immunoglobulins transfused. It seems especially relevant to ensure absence of procoagulant activated factor XI and other thrombogenic factors in HIG to avoid the occurrence of thromboembolism in severe COVID-19 patients with a hypercoagulable state [78-81].

Rare events may also occur. Depending upon the fractionation process implemented, anti-SARS-CoV-2 HIG may also contain a variable amount of IgA. Specific care should apply if transfusing HIG with high residual IgA to COVID-19 patients with both IgA deficiency and anti-IgA antibodies, as they may develop anaphylactic reactions [82]. Approximately 30% of individuals with IgA deficiency have anti-IgA antibodies, but a lower proportion appear to develop anaphylactic reactions when receiving intravenous immunoglobulins [71]. Occurrence of such anaphylactic reactions may also reflect the presence of plasma impurities, other than IgA, not eliminated during the manufacturing process of immunoglobulins [83]. Finally, the administration of anti-SARS-CoV-2 HIG as passive immunotherapy should consider the potential risk of inducing an antibody-dependent enhancement of the disease (ADE) [84], a serious complications which was reported in various viral infections [85]. In the last decades, ADE has not been reported when using HIG against HBV, HAV, chickenpox, rabies, and other viral infections [84]. CCP administration has not been associated with an increased risk of ADE [86].

At the time of writing, and due to the limited number of published clinical studies and the small number of patients enrolled, the safety and efficacy of anti-SARS-CoV-2 HIG prepared using traditional fractionation methods remain uncertain. Data from a multicentre, randomized, placebo-controlled clinical trial conducted by the ITAC Study Group have recently been published [19]. Five

hundred ninety-three hospitalized COVID-19 patients symptomatic for up to 12 days were randomly assigned to receive a single dose (400 mg/kg body weight or 40 g maximum) of one of four anti-SARS-CoV-2 HIG product or saline placebo, in addition to standard of care, including remdesivir. More infusion reactions were recorded in the group receiving anti-SARS-CoV-2 HIG than placebo. The study has also identified an increase in adverse events (particularly respiratory failure) in patients with neutralizing antibodies receiving the HIG, versus those without antibodies [19]. This observation raises questions on the possible negative effects of the administration of anti-SARS-CoV-2 HIG in patients with pre-existing neutralizing antibodies [87]. These adverse events do not seem specific to a particular brand of anti-SARS-CoV-2 HIG since this study used four different products. Based on previous literature, the authors of the study hypothesized the cause of these adverse events: (a) presence of IgG against the whole transmembrane spike protein, (b) pre-existing antibodies to type I interferons, or (c) development of antibody-dependent enhancement [19]. The study did not find any clinical benefits linked to the administration of these HIG products in these hospitalized patients. Data on the outcomes of a study in outpatients with COVID-19 infection are pending (NCT04910269; [88])

Therefore, further controlled studies are therefore needed to delineate the specific safety profile of anti-SARS-CoV-2 HIG and determine whether these immunoglobulins should, as recommended for CCP, be used at the early onset of the disease and patients without anti-SARS-CoV-2 antibodies.

Feasibility in low- and middle-income countries

In the absence of industrial plasma fractionation facility in many LMIC, alternative preparation methods of immunoglobulins have been explored. Minipool caprylic acid fractionation and virus inactivation of immunoglobulins, using a bag system has proven to be feasible in LMIC such as Egypt [89, 90]. A similar process applied on 4-8 L plasma pools was used to prepare clinical anti-SARS-CoV-2 HIG containing IgA, IgM, and IgG in Pakistan [29]. This preparation was reported by the authors to be safe, increased chances of survival and decreased risk of disease progression in a small phase I/II randomized controlled single-blinded trial conducted in either severely or critically ill patients with acute respiratory distress syndrome (ARDS) [91].

Of note, the additional infrastructure for donor qualification and plasma processing into HIG is often missing in LMIC. HIG production ability would be most often reserved to the most advanced local blood establishments, provided they receive sufficient financial support from local government to comply with good manufacturing practices and are supervised by a knowledgeable independent regulatory authority. Efforts supported by WHO, within the “Action framework to ensure advance universal access to safe, effective and quality assured blood products 2020-2023” [92], to provide

"Guidance on increasing supplied of plasma-derived medicinal products in LMIC through fractionation of domestic plasma" by stepwise actions [93] is consistent with the goal of establishing quality-assured local manufacture of safe plasma protein products, including immunoglobulins [94].

Potential alternative to large-pool hyperimmune immunoglobulin product

A potential alternative to single-donor CCP and purified pooled HIG is pooled SD-treated plasma. Depending upon legislations, pooled SD-plasma manufactured from about 100 to 2000 plasma donations can be available within a short time-frame, e.g after the appearance of new variants, and should provide a higher standardized and polyclonal source of immunoglobins than single-donor CCP, while containing a physiological mix of IgG, IgA, and IgM.

Conclusions

It is established that several human plasma-derived HIG, such as those licensed and on the WHO Model List of Essential Medicines [95] are effective in the prevention and treatment of several infectious diseases. The current pandemic has demonstrated that it is feasible to prepare human plasma-derived anti-SARS-CoV-2 HIG. However, whether such polyvalent HIG preparations are safe and beneficial to assist specifically the management or prevention of COVID-19 upon exposure remains to be demonstrated in well-designed randomized clinical trials. Therefore, controlled clinical trials are needed to define the impact of product specification, and optimal timing and dose of administration in patients infected with SARS-CoV-2. The authors hope that this manuscript provide relevant guidance for the production, quality assurance, and clinical evaluation of HIG when passive immunotherapy against SARS-CoV-2 appears justified.

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Conflict of interest

The authors declare no conflict of interest in relation to this manuscript.

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Appendix

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