

Regulatory considerations on authorization of the use of
convalescent plasma (PC) to address the COVID-19
emergency, 22 April 2020

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Summary

Since the last century, passive immunization has been used for the prevention and treatment of some human infectious diseases. The serum of convalescent patients is the treatment of choice in cases of Argentine Hemorrhagic Fever. In addition, it was used during outbreaks of Ebola in Africa and also during the SARS and MERS outbreaks, as no other therapeutic options existed.

Experience to date with the use of convalescent plasma for the treatment of COVID-19 is limited, but preliminary results indicate potential usefulness. Several controlled clinical trials are underway, to collect more quality scientific evidence to confirm the safety and efficacy of this intervention. In this context, the recommendations foresee its use under experimental conditions within the regulatory framework of each country. Moreover, there are challenges for large-scale collection, processing, and distribution of plasma from convalescent patients to meet potential clinical needs. Some published guidance exists for the collection and use of plasma from convalescent patients in infectious disease cases and Ebola outbreaks and even in the current COVID-19 situation.

Background

On 11 March 2020, with more than 118,000 cases in 114 countries and 4,291 deaths, WHO characterized the COVID-19 situation as a pandemic (1). As of the date of this document, April 2020, there is no approved etiological treatment (or vaccine) for COVID-19. The current treatment includes support care and monitoring for mild disease and oxygen therapy and mechanical ventilation for the most aggressive phase, among others (2).

Serum therapies have been used successfully in the past to treat many bacterial and viral infectious diseases even before their therapeutic effect was known (3). It is the treatment of choice in Junin virus infections, and in recent outbreaks of diseases such as Ebola convalescent plasma has been part of the therapeutic response for managing this type of events (4-6).

Different types of blood products have been used (under the general term “convalescent blood products”) to achieve artificially acquired passive immunity: convalescent whole blood (CWB), convalescent plasma (CP), or convalescent serum (CS); pooled human immunoglobulin (Ig) for intravenous or intramuscular administration; high-titer human Ig; and polyclonal or monoclonal antibodies (7).

Convalescent plasma has been identified as one experimental therapy for treatment of COVID-19, (8) and various clinical studies are under way (9-11). From an ethical standpoint, it is a moral obligation to conduct research on treatments for COVID-19 as quickly as possible in order to produce the necessary evidence to respond to the pandemic (12,13). Some countries, based on the experience of previous outbreaks and emergencies and in line with relevant ethical guidelines, have justified the use of convalescent plasma as an

unproven intervention in extraordinary situations and in a context of “monitored emergency use of unregistered and investigational interventions” (MEURI) (14,15).

The experimental use of convalescent plasma is not currently a conventional treatment (16) for COVID-19 and there is limited evidence of its usefulness (17,18). Such experimental use means that approved protocols for controlled tests should be followed to ensure that technical requirements are met, and ethical principles observed (12-15). Furthermore, a detailed assessment of risks and benefits should be carried out, ensuring that the relevant services have sufficient capacity to safely extract, process, store, and administer the blood derivatives used, with quality assurance (16).

Objective

The objective of this document is to offer recommendations and references for the collection and experimental use of plasma from “convalescent” COVID-19 donors, taking into account relevant issues such as the need to ensure the safety of the donors, patients, and health personnel involved in the process and the need to obtain safe, quality blood products. An additional objective is to facilitate the production of quality scientific evidence for the use of this product in epidemic situations. Other products, such as small-scale immunoglobulin concentrates or purified immunoglobulins, are not discussed in this document.

Rationale for considering the use of convalescent plasma

The transfusion of convalescent plasma (CP) has received renewed attention with the emergence of COVID-19 (SARS-CoV-2) (8,13,15,16), although the evidence accumulated to date is not robust enough or of the necessary quality for this treatment to be deemed effective, either alone or in combination with other treatments. The available evidence comes mainly from non-randomized research designs with high risk of bias (3). Hence, the safety and efficacy of CP must be assessed in the context of randomized clinical trials (RCT) that are robust, well designed, approved by ethics committees, and specific to COVID-19 treatment (9-11,15).

Given the circumstances of the current COVID-19 pandemic—i.e., considerable mortality and no proven treatment option or preventive vaccine—it is a global public health priority to consider potentially useful options. Appropriate experimental designs can help confirm evidence of the usefulness of these options. In this case, previous knowledge of passive immunization, supported by recent prior experience (3-6,17-21), could show that using plasma from COVID-19 patients (obtained from persons recovering from the disease) may be effective in treating or preventing SARS-CoV-2 infection.

Research on the topic should also consider comorbidities and the multiple treatment and intervention variables associated with hospitalized COVID-19 patients, including the use of corticosteroids, antibiotics for associated infections, and experimental drugs such as antivirals, biologicals, IGIV, and others under study (7). In addition, research initiatives should consider and provide for appropriate procedures to avoid the risk of transfusion-transmitted infections (TTI) such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), as well as the real threat of transfusion-transmitted infections to blood services

personnel (16). At the same time, such research should make it possible to assess the infrastructure and capacity of blood services to collect and manage PC inventories to meet needs. Research results could also inform the infrastructure and processes needed to make this intervention feasible in health care services, so that it can then become one of the options for preparing for the management of future epidemic events like the current one (22).

General considerations

a) Regarding the clinical use of convalescent plasma

An experimental approach based on a research protocol or a protocol for monitored emergency use (after evaluation and approval by an ethics committee)—rather than an uncertain medical practice approach to empirical use of convalescent plasma to treat COVID-19 ((2,8,12,13)—will generate greater benefits in terms of patient safety and the compilation of useful scientific information.

Such an approach should be based on the following considerations:

- The safety and efficacy of convalescent plasma in the context of this epidemic are currently unproven. The collection and clinical use of this product should therefore be managed in accordance with ethical principles (including informed consent of donors and patients), with appropriate institutional approval of the proposed research protocol and suitable conditions for processing and analysis of the plasma. It is also important to commit to gathering and reporting the outcomes achieved, regardless of whether they are positive or negative with respect to the efficacy and safety of the intervention (12-14,16).
- A mechanism or organized program and the oversight of a regulatory authority should allow the safe use of the CP and to determine the level of efficacy of this therapy (16)
- All donor selection criteria should be followed to prevent transfusion-transmitted diseases and ensure donor safety and product quality in accordance with international guidelines (16).
- Institutions that have the capacity to perform convalescent plasma collection without disrupting standard collection, processing, and distribution operations, should be selected to ensure that the obtention of CP does not affect the availability of blood for other events requiring transfusion.
- **A protocol should be developed that reflects these recommendations and others that are relevant in the light of current scientific evidence.** Specific protocols may be found in:
Ministerio de Sanidad. Comité Científico para la Seguridad Transfusional. España. Recomendaciones para la obtención de plasma de donantes convalecientes de COVID-19, 2020. https://www.msccbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/COVID-19_RecPlasma_donantes.pdf
Mayo Clinic. Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19. <https://www.uscovidplasma.org/pdf/20-003312%20COVID-19%20Plasma%20EAP%20Version%202.0.pdf>
National COVID-19 Convalescent Plasma Project. <https://ccpp19.org/>

b) Regarding the blood services dedicated to the collection, processing and distribution of CP

- The responsible institutions should be authorized by the competent national regulatory authority and should have trained staff operating under standard operation procedures, national norms for good manufacturing and laboratory practices that comply with internationally recognized standards in order to guarantee the safety of the donors and receptors (23).
- These should be institutions that routinely collect and prepare blood and plasma in accordance with national or international quality guidelines (23).
- The institutions designated for collection and processing of this product should be identified.
- All criteria for donor selection should be applied to ensure TTI prevention in recipients, donor safety and product quality in accordance with international guidelines.
- In this regard, CP should be tested and must be negative for all markers that detect TTI defined by the national norm.

c) Regarding the donors, the collection, processing and labelling of CP

- Donors should meet all eligibility criteria set out in national standards, in addition to being confirmed as patients who have had COVID-19 (laboratory confirmation or presence of SARS-CoV-2 antibodies).
- Donations should be obtained from patients with confirmed COVID-19 infection who have been symptom-free for 14 days before donating blood and who have negative results for COVID-19, after 2 nasopharyngeal swab specimens at least 48 hours apart (molecular test), or in a blood molecular diagnostic test, or in patients who have completed 1 month after full recovery from a confirmed infection with the COVID-19 virus (15,24-26).
- It may be appropriate to select male or female donors who have never been pregnant or to ensure testing for the presence of anti-HLA and anti-granulocyte antibodies present in the plasma of women who have been pregnant, to minimize the risk of an acute lung injury caused by transfusion (TRALI) (16).
- Plasma should be tested and should be negative for all infectious agents transmissible by transfusion, such as human immunodeficiency virus (HIV), hepatitis B or C virus (HBV, HCV), syphilis, and any other diseases identified under national standards.
- The use of plasma treated for pathogen reduction is recommended (UV, detergent solvent or another approved for use in plasma), or plasma kept in quarantine (27).
- If possible, anti-Sars-CoV-2 antibodies in donated plasma should be titrated. If neutralizing antibody titers cannot be obtained in advance, a sample of the donated convalescent plasma should be stored for later determination.
- Traceability of the product throughout the transfusion chain from donor to recipient should be ensured.
- Labeling in addition to the requirements defined in local regulations should indicate its experimental use, and special considerations if applied, such as molecular polymerase chain reaction or nucleic acid detection (PCR or NAT) tests with Negative results for SARS-CoV-2, or if the plasma has been treated for pathogen reduction or inactivated or quarantined and the expiration date (15,16,28).

- The donation interval should protect donor health and be appropriate to the method used (extraction of whole blood or apheresis). The other components obtained in the whole blood extraction procedure will not be used for transfusion use.
- Storage, transportation, and handling conditions should be similar to those established for the handling of other plasma products, with clear identification and separation of plasma for experimental use (5,29)
- The shelf life of convalescent plasma should be determined based on the protocol for experimental use and the storage temperature (-18°C or colder, 1-year shelf life) (thawed plasma at 2–6°C, 24-hour shelf life) (29).
- Convalescent plasma released for experimental use should be ABO-compatible with the potential recipient.

d) Regarding the criteria for the inclusion of patients to be treated

The types of patients to be treated should be defined and priorities should be set for the clinical use of convalescent plasma (patients recently admitted or who have been symptomatic for only a few days, as opposed to patients with advanced disease, and ultimately even health personnel). Various studies have found that passive immunotherapy is usually more effective when administered early in the course of the disease (8,19,30) and that passive immunity can be achieved with smaller doses than are required for the treatment of established disease. Empirical studies suggest that its use in the first days following onset of symptoms or hospitalization can lead to a better response (16,19,27).

e) Regarding the monitoring of outcomes focused on determining products safety and efficacy and on rapid communication of best practices

Patient outcome monitoring and reporting should include indicators of safety and efficacy (16). Some outcome indicators might include: mortality, length of hospital stay, viral load or time to a negative SARS-CoV-2 (18) molecular test, and the occurrence of adverse events such as TRALI, chill reactions and possible exacerbation of symptoms in some critically ill patients, allergic reactions, and circulatory overload (30-32).

Additional recommendations and variants on what are proposed here can be found in the documents listed below. In particular, please consult the WHO Blood Regulators Network (BRN) Position Paper on “Use of Convalescent Plasma, Serum or Immune Globulin Concentrates as an Element in Response to an Emerging Virus” (2017) (16).

Glossary

Apheresis

The process by which one or more blood components are selectively obtained from a donor by withdrawing whole blood, separating it by centrifugation and/or filtration into its components, and returning those not required to the donor.

Convalescent blood products:

Blood products used to achieve artificially acquired passive immunity, such as: convalescent whole blood (CWB), convalescent plasma (CP), or convalescent serum (CS); pooled human immunoglobulin (Ig) for intravenous or intramuscular administration; high-titer human Ig; and polyclonal or monoclonal antibodies.

Good manufacturing practice (GMP)

All elements in the established practice that will collectively lead to final products or services that consistently meet appropriate specifications and compliance with defined regulations

Nucleic acid amplification techniques (NAT)

A testing method to detect the presence of a targeted area of a defined microbial genome that uses amplification techniques such as polymerase chain reaction (PCR).

Quarantine

The status of starting or packaging materials, intermediate, bulk or finished products that are isolated physically or by other means while a decision is awaited on their release for use or rejection.

Quarantine FFP

Quarantine FFP can be released once the donor has been re-tested, at least for HBsAg, anti-HIV and anti-HCV, with negative results after a defined period of time that is designed to exclude the risk associated with the window period.

Pathogen reduced (PR)

A term applied to a blood component that has been prepared following the use of PRT.

Pathogen reduction technologies (PRT)

Procedures that irreversibly impede proliferation of pathogens, either by removal or inactivation with physical and/or chemical methods.

Plasmapheresis

The process by which plasma is selectively obtained from a donor, by separating plasma from whole blood by centrifugation or filtration and returning the other components to the donor.

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