

Convalescent Plasma

“Position paper” on the preparation of immune plasma to be used in the treatment of patients with COVID-19.



Società Italiana di Medicina Trasfusionale e Immunoematologia



SIdEM

Società Italiana di Emaferesi e Manipolazione Cellulare

“Position paper” on the preparation of immune plasma to be used in the treatment of patients with COVID-19.

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Introduction

Passive immunotherapy with plasma derived from patients that have recovered from SARS-CoV-2 infection can be a promising approach in the treatment of COVID-19 patients, as suggested by recent experiences ^{1, 2, 3} and discussed in two very recent relevant editorials ^{4, 5}. The use of convalescent plasma has a high level of safety, as documented in any previous situation of its use during the last years ⁶. Therefore, collection of convalescent plasma for the treatment of COVID-19 patients has started in different countries (among which the USA ⁷, Italy ⁸ and the Netherlands ⁹) and others will follow in the very next days. Due to this, many clinical trials are ongoing, as regularly updated by the WHO (<http://apps.who.int/trialsearch/default.aspx>) and also by the NIH (<https://clinicaltrials.gov/ct2/home>). These protocols are expected to clarify the effective role (if any) of immune plasma in improving prognosis of patients affected by severe forms of the disease and we cannot exclude a rapid and sustained increase in the request for this product, if clinical trials would demonstrate its therapeutic efficacy; the increase could be even more pronounced in case of a limited access to other therapeutic options due to the possible shortage of some drugs (as recently highlighted by some regional health authorities ¹⁰).

Therefore, it is now of utmost importance that Blood Establishments are prepared to satisfy requests for “hyperimmune plasma” or “convalescent plasma”, by defining the requirements for the recruitment and the selection of plasma donors and the standards for preparation, qualification, storage and distribution of the product, in compliance with Good Manufacturing Practices and with European and national legislation, without neglecting its safe and appropriate use.

This “position paper” is not a protocol for the treatment of patients with COVID-19 by means of convalescent plasma: clinical protocols and trials require in almost all jurisdictions an approval by local or national ethical committees and sometimes also by national Competent Authorities on blood or drugs. In the present phase of pandemic, we are aware that in Italy (as well as in the rest of the world) Transfusion Services have been urged by clinicians in hospitals to provide immune

plasma for a possible utilization in the therapy of COVID-19 patients. We need to support the possibility of evaluating this therapeutic approach in more rigorous investigations. To this purpose, these recommendations on biological characteristics of a plasma preparation from convalescent donors can be helpful, to make future comparison among studies easier.

Requirements to the donors

The attention for a possible source of immune plasma is drawn, at present, by patients with a very recent documented infection by SARS-CoV-2 who volunteer, upon informed consent, to undergo apheresis procedures as to collect plasma specifically intended for therapy of severe infections by SARS-CoV-2. This target population requires some caution because of some exceptions with respect to the standards defined by the selection criteria defined by Italian legislation enforcing European directives¹¹; this derogation can be referred to the age of the donor and to the deferral period after clinical recovery (probably less than twice the incubation period, as suggested by the “Guide for preparation, use and quality assurance of blood component”, published by the EDQM - Council of Europe¹²); finally we must be aware of the fact that we will collect plasma for clinical use from patients that, in the majority of cases, have not been previously regular blood donors, thus lacking a previous safety profile. All the remaining selection criteria must be applied, first of all the exclusion of donors with previous history of pregnancy and/or blood transfusion.

Plasma will be collected by apheresis from patients recently recovered from laboratory confirmed infection by SARS-CoV-2 (either hospitalized or self-isolated at home) with the following characteristics:

- at least 14 days from clinical recovery of the patient (no symptoms) and from a negative result of two NAT test on nasopharyngeal swab and on serum/plasma, performed 24 hours apart, following recovery or prior to discharge if hospitalized;
- not mandatory (and not required by the majority of protocols in place) is a further negative result of a NAT testing on nasopharyngeal swab and on serum/plasma, performed 14 days after the first one;
- an adequate serum titer of neutralizing specific antibodies (> 160 by EIA method or equivalent with other methods, as previously suggested^{13, 14, 15}).

It should be pointed out that these persons are selected to donate immune plasma because they are COVID-19 convalescent patients: the scope of plasma collection is only related to the use for COVID-19 patients and not as a plasma for clinical use. However, from now on, we can expect a

huge number of people who have recovered from an asymptomatic infection (or from a disease with minor clinical signs); many among them are probably regular blood donors, as suggested by the number of post-donation information we are receiving in these days on fever and cough appearance, but also considering the high number of asymptomatic carriers of the virus. As soon as a serology testing will be available, the demonstration in their sera of an antibody titer > 160 by EIA method (or equivalent with other methods) will represent a unique pool of immune plasma providing donors because they are regular blood donors, they are fully compliant with the selection criteria for plasma donation, and an adequate interval (28 days) can separate the resolution of symptoms from the donation. Therefore, this second group of persons can become a relevant source of immune plasma, not requiring any derogation from legal provisions on donor selection. Their recruitment can easily follow a screening for SARS-CoV-2 (eventually followed by a titration of the antibody) in the population of donors at the time of the donation. This could also contribute to have a deeper insight in the epidemiology of the disease outside the context of a severe clinical disease leading to hospitalization of patients.

Standard for the product

A previous reference is offered by the definition of standard for immune plasma that have already been published during the MERS epidemic in 2015 ⁷.

When dealing with convalescent patients, not previously blood donors, collected units should be initially tested as required by the Italian legislation for plasma intended for clinical transfusion (HIV, HCV, HBV NAT and serology testing, syphilis); moreover, it is advisable to further test by NAT for HAV e PVB19 and to treat the units by pathogen reduction technologies. This could be probably not necessary when collecting plasma from donors who meet the criteria of Italian and European legislation for blood donation and are already regular voluntary donors. A negative result of NAT testing for SARS-CoV-2 is also clearly expected in both cases.

On each plasma unit it is advisable to determine the total content of immunoglobulins (IgG, IgA e IgM) and neutralizing specific antibody titer (> 160 by EIA method or equivalent with other methods as previously discussed); this is intended to have a rough evaluation of the amount of immunoglobulins administered to the patients, which will allow subsequent comparison between dose and effectiveness.

Due to the schedule of administration (see later), it is suggested to freeze and store the units in aliquots of around 300ml.

Standard for labelling and traceability of the product

When the collection of plasma is intended solely for administering anti SARS-CoV-2 antibodies to patients, it is advisable to label the product with a specific ISBT or UNI code, in order to allow the exclusive use for the therapy of COVID-19 patients and to assure a full traceability.

Pooling of plasma

The use of hyperimmune immunoglobulin concentrates (derived from plasma of immunized donors), is likely to be an even more effective method for administering specific antibodies and this is at present a field of research for pharmaceutical companies; however, in the medium term period, the availability of immune plasma from regular donors fully recovered could allow the preparation of units of human plasma pooled and treated for virus inactivation, with the standard described by the European Pharmacopoeia (Monograph n. 1646). This would allow production of hyperimmune plasma with known and standardized antibody titre. A preliminary discussion with pharmaceutical companies and with the National Competent Authority (AIFA, in Italy) is clearly necessary.

Indications and instructions for use

Indications

There is no conclusive evidence for the indications of this product. As a preliminary result from the literature and from consensus among experts (mainly related to experiences made until now in Asia), eligible patients must have laboratory confirmed COVID-19 (better if NAT positive but seronegative) and must have severe or rapidly progressive or immediately life-threatening COVID-19. It would be however advisable to consider, in a controlled study, the use of immune plasma also in patients in an earlier stage of the disease.

Many clinical studies which have been presented until now require a severity stratification base on clinical and /or biological parameters ¹⁶ as:

- respiratory frequency $\geq 30/\text{min}$,
- $\text{PaO}_2/\text{FiO}_2 < 300\text{mm Hg}$ in oxygen
- blood oxygen saturation $\leq 93\%$
- tracheal intubation with mechanical ventilation
- Sequential Organ Failure Assessment (SOFA) score

- ICU length of stay
- Hospital length of stay

Volume and posology

Also for volume and posology there is no conclusive evidence until now and the first trials are based on schedules of administration defined in previous epidemics ^{1, 2, 8, 17} and on consensus among experts and suggest an administration of volumes from 200 to 600mL of immune plasma (roughly corresponding to 8 to 10mL/Kg, with a maximum of 600mL) once per day and up to three consecutive days. This scheme can be eventually repeated once. Higher volumes could be contraindicated due to the risk of transfusion associated circulatory overload.

Time for administration

An early onset of the therapy with immune plasma: the optimal period is within 7 days from the onset of symptoms but the therapy seems to be effective also within two weeks. Administration of immune plasma does not seem to be effective after 3 weeks from the onset of the disease.

Drug interaction

Until now there are no descriptions of synergic or negative effects in the interaction with other drugs used in the treatment of COVID-19. In the absence of any conclusion, immune plasma can be administered on the basis of locally approved protocol.

Adverse reactions

Clinicians must be aware that all adverse reactions and contraindications described for the administration of human plasma can take place also in the treatment with this product; in particular Blood Establishments should remind to treating physicians:

- the absolute contraindication of administering human plasma to patients with a complete IgA deficit (we recommend to test for IgA before the beginning of plasma administration)
- the caution for a possible onset of transfusion associated circulatory overload (TACO).

Another risk (hypothesized in an animal model) is related to a possible decrease of the immune response of the patient against the virus due to the passive immunization following antibody administration with plasma, leaving patients more susceptible to reinfection. This event must be clearly taken into account and evaluated ¹⁸.

A caution on the use of this product must be done due to the fact that this is an off label indication in the clinical use of plasma.

Final recommendations

We recommend Blood Establishments to obtain an informed consent from blood donors in order to store their sera after donation, as to make possible epidemiologic evaluation as soon as validated serology testing will be available.

We also recommend to collect any data from donors, possibly related to SARS-CoV-2 infection, that could be useful for subsequent epidemiological analysis (e.g. blood collection and deferral during pandemic, number and characteristics of post-donation information, results from look-back, when performed, etc.).

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