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

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Passive immunotherapy with plasma derived from convalescent patients recovering from SARS-CoV-2 infection can be a promising approach in the treatment of COVID-19 patients. It is important that blood establishments are ready to satisfy requests for immune plasma by defining the requirements applicable to plasma donors and the standards for preparation, qualification, storage, distribution, and control of product use. This Position paper aims to give recommendations on the biological characteristics of a plasma preparation from convalescent donors and to support the evaluation of this therapeutic approach in more rigorous investigations.

Keywords: COVID-19, immune plasma.

INTRODUCTION

Passive immunotherapy with plasma derived from patients who have recovered from SARS-CoV-2 infection can be a promising approach in the treatment of COVID-19 patients, as suggested by recent experiences¹⁻³ and discussed in two very recent important editorials¹⁴⁻¹⁵. The use of convalescent plasma has a high level of safety, as documented in previous reports of its use over the years⁴. Therefore, different countries, including the USA⁵, Italy⁶ and the Netherlands⁷, have started collecting convalescent plasma for the treatment of COVID-19 patients and others will follow over the next few days. Because of this, many clinical trials are now ongoing, as reported in recent updates from the World Health Organization (WHO)⁸ and also by the US National Institutes of Health (NIH)⁹. These protocols are expected to clarify the actual role (if any) of immune plasma in improving the 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 were to demonstrate its therapeutic efficacy. The increase could be even more pronounced in cases of limited access to other therapeutic options due to the possible shortage of some drugs, as recently highlighted by some regional health authorities¹⁰. Therefore, it is now of the utmost importance that blood establishments prepare themselves in order to be ready 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 the preparation, qualification, storage and distribution of the product, in compliance with Good Manufacturing Practices and with European and
national legislation, while maintaining due consideration of its safety and appropriate use.

This Position paper is not a protocol for the treatment of patients with COVID-19 by means of convalescent plasma; under almost all legal jurisdictions, clinical protocols and trials require the approval of local or national ethical committees, and sometimes also of national competent authorities on blood or drugs. In the present phase of pandemic, we are aware of the fact that in Italy (and, in fact, across the world) hospital clinicians have been urging transfusion services to provide immune plasma for its possible use in the treatment of COVID-19 patients. We need to support the possibility of evaluating this therapeutic approach as part of more rigorous investigations. To this purpose, these recommendations on the biological characteristics of a plasma preparation from convalescent donors will help to facilitate a future comparison between studies.

REQUIREMENTS FOR DONORS

At the moment, a possible source of immune plasma is provided by patients with a very recent documented infection by SARS-CoV-2 who volunteer, after informed consent, to undergo apheresis procedures to collect plasma specifically for the treatment of severe SARS-CoV-2 infections. This target population requires careful management because they may not completely satisfy the selection criteria set out under Italian legislation enforcing European directives. Any waiver to the legislation in force can involve the age of the donor and the deferral period after clinical recovery, which is 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 Europe. Finally, we must take into consideration the fact that we will collect plasma for clinical use from patients who, in the majority of cases, were not regular blood donors, and as such do not have a previously compiled safety profile. All the remaining selection criteria must be applied, and these must include, above all, the exclusion of donors with previous history of pregnancy and/or blood transfusion.

Plasma will be collected by apheresis from patients who have recently recovered from laboratory confirmed infection by SARS-CoV-2, who were either hospitalised or who self-isolated at home, with the following characteristics:

- collected at least 14 days after clinical recovery of the patient (no symptoms) and after a negative result of two NAT tests on nasopharyngeal swab and on serum/plasma performed 24 hours apart, following recovery, or prior to discharge if hospitalised;
- a further negative result of a NAT test on nasopharyngeal swab and on serum/plasma, performed 14 days after the first one (although this is not mandatory, and is not required by the majority of protocols in place);
- an adequate serum titre of specific neutralising antibodies (>160 by enzyme immunoassay [EIA] or the equivalent with other methods, as previously suggested).

It should be pointed out that these people are selected to donate immune plasma because they are patients convalescing from COVID-19. The scope of the plasma collection is only related to its use for COVID-19 patients and not as plasma for clinical use. However, as from now, we can expect to have an enormous 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 amount of post-donation information we have been receiving over these last few days on the presentation of fever and a cough, but also considering the high number of asymptomatic carriers of the virus. As soon as serology testing becomes available, the demonstration in their sera of an antibody titre >160 by EIA (or equivalent with other methods) will represent a unique pool of donors providing immune plasma because they are regular blood donors and are fully compliant with the selection criteria for plasma donation, and because we can establish an adequate interval (28 days) from the resolution of symptoms to the donation. Therefore, this second group of people can become an important and numerically significant source of immune plasma that will not require any waiver from legal provisions covering donor selection. Their recruitment can easily follow screening for SARS-CoV-2 (followed by titration of the antibody) in the population of donors at the time of the donation. This could also provide a deeper insight into the epidemiology of the disease outside the context of a severe clinical disease leading to hospitalisation of patients.
PRODUCT STANDARD
Regarding product standard, a previous reference is offered by the definition of a standard for immune plasma that was published during the MERS epidemic in 2015. When dealing with convalescent patients who were not previously blood donors, collected units should initially be tested according to the Italian legislation for plasma intended for clinical transfusion (HIV, HCV, HBV NAT and serology testing, syphilis). Convalescent patients, both first-time donors and regular donors, should be tested as required by Italian legislation; regarding plasma from first-time donors (patients who are recovering from the virus), it is advisable to further test by for HAV and PVB19 by NAT, as well as to treat the units through pathogen reduction technologies. This would probably not be necessary if the plasma is collected from regular 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 and IgM) and neutralising antibody titre (>160 by EIA or equivalent with other methods; see above). This is intended to provide an approximate estimate of the amount of immunoglobulins administered to the patients, which will allow a subsequent comparison between dose and effectiveness.

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

Standard for product labelling and traceability
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 its exclusive use in the treatment of COVID-19 patients and to assure complete traceability.

Pooling plasma
The use of hyperimmune immunoglobulin concentrates, derived from plasma of immunised donors, is likely to be an even more effective method for administering specific antibodies and is the subject of current research by pharmaceutical companies. However, in the medium term, the availability of immune plasma from regular donors who have fully recovered from the virus could allow the preparation of units of human plasma pooled and treated for virus inactivation, according to the standards set out by the European Pharmacopoeia. This would allow hyperimmune plasma to be produced with a known and standardised antibody titre. A preliminary discussion with pharmaceutical companies and with the national competent authority (in the case of Italy, the AIFA) is clearly necessary.

INDICATIONS AND INSTRUCTIONS FOR USE
Indications
There is no conclusive evidence to enable us to establish the indications for this product. According to preliminary results in the literature, and from the consensus reached among experts (mainly relating to the experience so far in Asia), eligible patients must have laboratory confirmed COVID-19 (preferably NAT positive but seronegative) and must have severe or rapidly progressing, or immediately life-threatening COVID-19. It would, however, be advisable to carry out a controlled study of the use of immune plasma also in patients at an earlier stage of the disease.

Many clinical studies which have been presented so far require a severity stratification based on clinical and/or biological parameters, such as:
• respiratory frequency ≥30/min;
• PaO2/FiO2 <300 mm Hg in oxygen;
• blood oxygen saturation ≤93%;
• tracheal intubation with mechanical ventilation;
• Sequential Organ Failure Assessment (SOFA) score;
• length of stay in the Intensive Care Unit (ICU);
• length of hospital stay.

Volume and posology
Volume and posology are based on schedules of administration that have been defined in previous epidemics and on consensus among experts, as there is still no conclusive evidence. An administration of volumes of from 200 to 600 mL of immune plasma (roughly corresponding to 8-10 mL/kg, with a maximum of 600 mL) once per day and up to three consecutive days is suggested. This scheme could then be repeated once. Higher volumes could be contraindicated due to the risk of transfusion-associated circulatory overload (TACO).

Time of administration
Early start of 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 2 weeks.
Administration of immune plasma does not seem to be effective after 3 weeks of the onset of the disease.

**Drug interaction**
Up to now, no synergic or negative effects in the interaction with other drugs used in the treatment of COVID-19 have been described. In the absence of any firm conclusions, immune plasma can be administered on the basis of locally approved protocols.

**Adverse reactions**
Clinicians must be aware that all adverse reactions and contraindications described for the administration of human plasma can also occur in treatment with this product. In particular, blood establishments should remind treating physicians about:

- the absolute contraindication of administering human plasma to patients with a complete IgA deficit. (We recommend testing for IgA before starting administration of plasma);
- to proceed with caution due to the possible onset of TACO.

Another risk that has been hypothesised in an animal model is related to a possible decrease in the immune response of the patient against the virus due to the passive immunisation following antibody administration with plasma, leaving patients more susceptible to reinfection. This event must clearly be taken into consideration and evaluated\(^\text{20}\).

This product is indicated for off-label clinical use of plasma and must be used with caution.

**FINAL RECOMMENDATIONS**
We recommend blood establishments to obtain the informed consent of blood donors for their sera to be stored after donation so an epidemiological evaluation can be made as soon as validated serology testing becomes available.

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

The Authors declare no conflicts of interest.