TRANSFUSION MEDICINE AND TRANSFUSION COMPLICATIONS

Position paper

Position paper on the use of COVID-19 convalescent plasma: an update

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INTRODUCTION

Soon after the start of the coronavirus disease 19 (COVID-19) pandemic, in the absence of a vaccine and specific treatments, the collection and storage of plasma from donors who had had COVID-19 was considered promising for evaluation in clinical studies or as a starting material for the manufacture of experimental anti-SARS-CoV-2 hyperimmune immunoglobulins[1]. Early non-randomised studies[2-5] suggested the safety and potential efficacy of transfusions of COVID-19 convalescent plasma (CCP) as a treatment for hospitalised patients. Driven by these observations, extensive donation campaigns were implemented, and many patients started to be treated worldwide, in the context of expanded access programmes. However, the initial enthusiasm was tempered as good quality randomised trials and systematic reviews were published. It is now agreed that CCP treatment, although safe, is ineffective for the treatment of most hospitalised COVID-19 patients.

In the COVID-19 pandemic, Italy was hit very early and hard[6]. CCP collection and clinical use were authorised and regulated by the Italian National Blood Centre (*Centro Nazionale Sangue*, CNS) since mid-March 2020[7]. A position paper on the preparation and use of CCP, written by Italian Society for Transfusion Medicine and Immunohaematology (SIMTI), and the Italian Society for Haemapheresis and Cell Manipulation (SIdEM), was published in May 2020[8]. After almost one year, the two scientific societies felt the importance of updating their recommendations in the light of accumulated scientific evidence.

METHODS

The writing committee analysed published data to reach a consensus for best practice recommendations. A formal systematic review was not conducted and position statements were formulated as interim expert recommendations, independently of Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

STANDARD OF PRODUCT

A consensus document on the preparation of CCP was published recently by the CNS[9], and is the national reference for the standard of product.

CCP can be obtained by apheresis or separated from a standard whole blood donation. Although apheresis has been frequently preferred because of the higher yield of product and shorter interval between donations, some blood centres proposed convincing organisational models based on anti-SARS- CoV-2 antibody screening and preparation of fresh-frozen CCP units from whole blood donations. CCP is stored in aliquots of 200 mL (fractionation) to 300 mL (apheresis)[10].

On the basis of the existing evidence (see paragraph below), CCP units should be qualified for clinical use only if they contain high titres of anti-SARS-CoV-2 antibodies,

as determined by either neutralising or binding antibody tests. Unfortunately, an international standardised unit for "titre" is not yet available, nor is there currently any calibration possible to reliably compare titres among different studies[9,10]. However, a summary on how to interpret results of different serological assays in relation to corresponding anti-SARS-CoV-2 neutralising titres has been provided by the CNS[9].

SAFETY, EFFICACY, AND CLINICAL INDICATIONS OF COVID-19 CONVALESCENT PLASMA

The possibility of using CCP to treat viral infections is based on several historical precedents[11]. However, the usage of CCP has not been as widespread as during the COVID-19 pandemic, and its efficacy has never been studied in such detail. Since the beginning of the COVID-19 pandemic (spring 2020), access to CCP treatment was granted by clinical trials and by expanded access programmes, both in Europe and in the USA. At the time of writing, more than 720,000 CCP units had been distributed to hospitals in the context of the US federal programmes[12]. In Italy, almost 17,000 CCP units have been transfused according to the data monitored by the CNS[13].

Early evidence of the clinical safety and efficacy of CCP came mainly from non-controlled studies, and from retrospective, indirect evaluations using expanded access data[2-5,14]. Overall, these studies showed that the frequency of adverse transfusion reactions was not higher than that related to plasma transfusions administered for other clinical indications. In addition, they suggested that transfusion of CCP containing high titres of neutralising antibodies was potentially effective in reducing mortality, disease progression and hospital stay of hospitalised patients, especially if treatment was administered earlier in the clinical course[10]. Data on safety were subsequently corroborated by data collected in 20,000 patients, showing a low rate of serious adverse events (<1% of all transfusions), which were mostly unrelated to the plasma transfusion *per se*[15].

Since summer 2020, data from several randomised clinical trials have become available. Remarkably, these data did not confirm the effectiveness suggested by observational studies. In the first randomised controlled trial of transfusion in severely or critically ill patients in China, treatment had not significantly reduced the time to clinical improvement within 28 days, although the trial was terminated early and may have been underpowered to detect a statistically significant difference[16]. The PLACID study[17], a randomised controlled trial involving large numbers of patients, showed a lack of efficacy of CCP transfusion in preventing mortality and clinical progression. However, a possible limitation of the PLACID trial was that the patients mostly received plasma units containing low (or unmeasured) titres of neutralising antibody (median 1:40). In a high quality clinical trial, Simonovich *et al.*[18] studied 333 patients with severe COVID-19, who were randomised 2:1 to receive high-titre CCP or placebo. Remarkably, no significant differences were observed in the clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo.

Similar results emerged from two important adaptive randomised trials conducted in UK, the RECOVERY and REMAP-CAP trials. On January 18, a summary of the results of CCP treatment within these two trials was reported by the UK National Institute for Health Research[19], while peer-reviewed publication was still pending. In the RECOVERY trial[20], a preliminary analysis from almost 10,500 patients randomised in the convalescent plasma arm showed no significant difference in the primary endpoint of 28-day mortality (18% with CCP treatments *vs* 18% with usual care alone), and the study therefore closed recruitment to its convalescent plasma treatment arm. In the REMAP-CAP study[21], the analysis of 912 critically ill patients showed that CCP had no impact on mortality or days in the Intensive Care Unit. Thus, the convalescent plasma arm of the REMAP-CAP study was halted.

Very recently, the results of TSUNAMI, an Italian randomised controlled study promoted by the Italian National Institute of Health (ISS) and Italian Drug Agency (AIFA), were disclosed[22] prior to publication. The trial compared the effect of convalescent plasma with high titres of neutralising antibodies (≥1:160) associated with standard therapy *vs* standard therapy alone in patients with COVID-19 and pneumonia with mild to moderate ventilatory impairment. The study included 487 patients from 27 clinical centres distributed throughout Italy. The results did not show a benefit of CCP treatment in terms of reducing the risk of respiratory worsening or death in the first 30 days.

In agreement with clinical trial results, a meta-analysis including data from 1,060 patients in four peer-reviewed randomised controlled trials and 10,722

Blood Transfus 2021; 19: 277-80 DOI 10.2450/2021.0150-21

patients from six other publicly available randomised controlled trials failed to demonstrate a decrease in all-cause mortality or any benefit for other clinical outcomes among patients receiving CCP, as compared to those receiving placebo or standard care[23].

So far, CCP has been primarily used in the attempt to improve the clinical course of disease in individuals who have already become ill. However, it is reasonable to hypothesise that some efficacy can be obtained in terms of prevention of disease progression in those who have very early infection and mild symptoms[11].

In this regard, Joyner and colleagues[24] found a dose-response relationship between anti-SARS-CoV-2 IgG antibody levels and improved outcomes (30-day mortality: with high-titre plasma, 22%; with medium-titre plasma, 27%; with low-titre plasma, 30%). Furthermore, Libster *et al.*[25] recently reported finding in 160 older patients (>65 years) who were randomised to receive either high-titre convalescent plasma or placebo very early in the course of the disease (i.e., within 72 hour of symptom onset). In this study, the relative risk of disease progression in patients treated with convalescent plasma was 0.52 (95% confidence interval: 0.29-0.94). Data on mortality were not reported; however, these results suggest that early administration of high-titre convalescent plasma against SARS-CoV-2 to mildly ill infected older adults may reduce the progression of COVID-19.

Nevertheless, these promising results were challenged by those emerging from the Clinical Trial of COVID-19 Convalescent Plasma of Outpatients (C3PO)[26]. Early in March 2021, the National Institutes of Health halted this trial because an interim analysis suggested that results were unlikely to demonstrate that CCP prevents progression from mild to severe illness in at-risk non-hospitalised participants, even if treated relatively early (i.e. within 1 week of the onset of symptoms). On the basis of the negative results accumulating from clinical trials, programmes of plasma donations were halted or temporarily deferred in the USA and UK.

STUDIES ON PLASMA-DERIVED HYPERIMMUNE IMMUNOGLOBULIN MEDICINES

Plasma donations collected from subjects with resolved SARS-CoV-2 infection have also been considered as starting material for the manufacture of experimental hyperimmune immunoglobulins[1]. The potential advantages of hyperimmune immunoglobulins over CCP include lower infectious risk due to the standard pathogen-reduction treatment, a lower volume of administration, standardised titre of antibody content, easier storage and shipping conditions, and the possibility of intramuscular or subcutaneous administration.

A special consortium of world-leading plasma product manufacturers -The CoVIg-19 Plasma Alliance- was formed in April 2020 with the aim of developing an investigational unbranded polyclonal anti-SARS-CoV-2 hyperimmune globulin. This product, known as CoVIg-19, is a pharmaceutical preparation that contains purified, standardised and concentrated levels of convalescent antibodies. The results of a National Institutes of Health-sponsored phase III clinical trial (ITAC), aimed to determine whether the administration of CoVIg-19 could reduce the risk of disease progression when added to standard-of-care treatment in hospitalised patients at risk of serious complications, were very recently announced[27]. Treatment was proven to be safe. Nevertheless, efficacy endpoints were not met. With the ITAC trial failing, the CoVIg-19 Plasma Alliance is closing[27]. At the moment, hyperimmune immunoglobulin preparations are not licensed for clinical use.

CONCLUSIONS AND RECOMMENDATIONS

In summary, the evidence accumulated so far from high quality randomised studies and meta-analyses indicates that CCP treatment is ineffective in hospitalised patients, and should no longer be administered. Starting new research trials in such patients is not warranted, as more than 100 ongoing trials are at risk of being terminated early or never published[23].

Further studies in the field should be conducted using high-titres CCP units, as early as possible in the course of the disease. In particular, it remains to be established whether CCP administration can prevent disease progression and death in at-risk, non-hospitalised subjects with early infection (i.e. <3 days from clinical onset) and mild symptoms. However, meeting these conditions outside clinical trials may be challenging, in part due to organisational issues.

Results from trials conducted in immunosuppressed individuals, who are unable to mount an anti-SARS-CoV-2 antibody response, are also underway.

Until new data become publicly available, the use of CCP

outside clinical trials (e.g. for compassionate use) should only be considered in individual patients with similar characteristics to those described above. Decisions should be taken after multidisciplinary evaluation, carefully balancing potential risks and benefits.

After the publication of trials not demonstrating efficacy in hospitalised COVID-19 patients, the clinical use of CCP rapidly declined worldwide, including in Italy. Furthermore, the emergence of new viral variants raises the problem of the potential ineffectiveness of plasma collected from donors who were infected with different SARS-CoV-2 strains[28]. Decisions on whether and how to continue CCP donation campaigns will need to be taken by national/regional health authorities, taking into account costs and needs, including the request of CCP stocks by plasma manufacturers for the preparation of anti-SARS-CoV-2 hyperimmune immunoglobulins, and the possible use in the case of future flares of the COVID-19 pandemic.

The Authors declare no conflicts of interest.

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