Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Why should we use convalescent plasma for COVID-19?

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Coronavirus, an enveloped virus belonging to the family of *Coronaviridae* which initially caused enzootic infections, has shown in the last decades to be capable of crossing the species barrier causing severe epidemics in humans. A novel flu-like coronavirus, emerging towards the end of 2019 and subsequently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2, the virus that causes Coronavirus Disease 2019 [COVID-19]) has been associated with an epidemic initially focused in Wuhan, China [1]. From there, SARS-CoV-2 has spread quickly throughout China, infecting many thousands of people and causing more than 4,500 deaths [2]. However, in a globalize world, it immediately became well clear that this fearsome infection could not be confined to China only, but soon it spread to neighboring Asian countries and immediately after to more than 201 countries around the world, where more than 3,200,000 individuals have contracted SARS-CoV-2 and more than 230,000 of them have deceased (data updated on May 3, 2020) [2]. On march 11, WHO declared the rapidly spreading coronavirus outbreak a pandemic and Italy is currently the country with the highest number of cases of SARS-CoV-2 infection after USA and this has generated an unprecedented health and social emergency. Unfortunately, no standardized therapy does exist for COVID-19 and a number of drugs for the use in patients with life-threatening COVID-19 are currently being investigated in a number of non-randomized or randomized trials. These agents include steroids, chloroquine, antiviral and anti-inflammatory agents [3]. In addition, experiences from previous coronavirus epidemics indicate that convalescent plasma collected from recovered COVID-19 patients, containing antibodies specific against SARS-CoV-2 that can be delivered from donors to patients, could be a potentially effective therapeutic weapon [4].

Before SARS-CoV-2, the use of convalescent plasma has been investigated, with reported positive outcomes, in outbreaks of other viral infections, including the 1918 Spanish H1N1 influenza A pandemic and, more recently, the 2003 Avian H5N1 influenza A epidemic, the 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1 influenza pandemic, the 2012 Middle East Respiratory Syndrome (MERS)-CoV epidemic, and the 2014 Ebola epidemic [5]. Pertaining to the respiratory CoV infections, a number of studies have been conducted during the past decade to evaluate the clinical effectiveness of convalescent plasma. A systematic review and exploratory meta-analysis performed in 2015 identified 32 studies of SARS coronavirus infection and severe influenza. These studies involved 699 treated patients and 568 untreated controls [6]. In the pooled analysis of the data, the review revealed the evidence for a consistent reduction in mortality in the group treated with plasma therapy compared with that receiving placebo or no therapy (odds ratio, 0.25; 95% CI:0.14–0.45 with a low degree of heterogeneity: $I^2 = 0\%$) [6]. Only few reports have been published so far on the use of convalescent plasma in COVID-19 patients. Shen and colleagues reported a case series of 5 critically ill patients, all receiving convalescent plasma containing SARS-CoV-2 antibodies (titer > 1:1000) and a neutralization titer greater than 40, administered between day 10 and 22 of admission [7]. Following transfusion, 4 out of 5 patients experienced increases in viral antibody titers, decreases in SARS-CoV-2 viral loads, and normalization of temperature and resolution of acute respiratory distress syndrome (ARDS) [7]. Duan and colleagues presented a series of 10 severely ill COVID-19 patients, all receiving a 200 mL transfusion of convalescent plasma with high titers of neutralizing antibody (>1:640) at a median of 16.5 days [8]. The primary endpoint was safety, which was demonstrated as all patients tolerated plasma transfusion without severe adverse events. The secondary endpoints included improvement of clinical symptoms and of laboratory values from day 3 post-infusion. They reported increase neutralizing antibody titer, oxygen saturation and lymphocyte count and decrease in C-reactive protein, SARS-CoV-2 viral load and lung lesions on radiological examination [8]. Zhang and colleagues described retrospectively 4 critically ill patients who were transfused with 200-2400 mL of convalescent plasma ranging from day 11 to day 18 of admission [9]. All the patients (including a pregnant woman) recovered from the SARS-CoV-2 infection. Finally, Zeng and colleagues tested the role of convalescent plasma in 6 critically end-stage COVID-19 patients [10]. Although the blood component, which was transfused at a median of 21.5 days after first detection of viral shedding, led to the discontinuation of the SARS-CoV-2 shedding by 3 days after infusion, it was not able to improve the survival in these patients with advanced disease (5/6 and 14/15 deaths in the convalescent plasma group and control group, respectively). Based on the results of this trial, the authors concluded the convalescent plasma should be used in an early phase of the disease to obtain the best effect [10].

Following these first reports on the successful use of convalescent plasma in COVID-19 patients in China and considering the efficacy of this treatment in previous severe viral epidemics and the absence of standardized treatments, the Food and Drug Administration (FDA) approved the use of convalescent plasma to treat critically ill patients on

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26 march 2020 and this action has fueled the planning of several trials. A research performed on May 4, 2020 on clinicaltrials.gov (https://clinicaltrials.gov) with the terms “convalescent plasma and COVID-19” showed 38 active ongoing trials on the use of convalescent plasma in COVID-19 patients, heterogeneous in term of study design and outcomes’ criteria: 14 of them are randomized versus other approaches (2 studies versus placebo, 5 studies versus standard fresh frozen plasma and 7 versus various pharmacologic agents including hydroxychloroquine and antiviral drugs). Also our group, in collaboration with University of Pavia, has given a contribute to this research. Indeed, considering the dramatic situation and the high lethality rate of COVID-19 in Italy, we have planned an interventional single-arm trial (NCT04321421) to produce hyperimmune plasma for treating critical patients with COVID-19. The results of these numerous trials are greatly awaited as they will permit to respond to the many still unanswered issues regarding convalescent plasma, including donors’ selection (i.e., age, gender, diagnosis of SARS-Cov-2 infection and of recovery, anti-SARS-CoV-2 antibody titer required for plasma donation), plasma collection and biologic qualification (number, volume and frequency of donations, infectious disease markers and pathogen inactivation) and treatment and disease characteristics (i.e., dose and timing of convalescent plasma infused and stage of the disease at which to start convalescent plasma treatment).

There is currently great interest towards the use of passive immunotherapy by means of transfusion of convalescent plasma from recovered COVID-19 patients documented by the high number of ongoing trials and of reviews/perspectives/commentaries published every day. The results of such trials will help us to elucidate the still unanswered issues listed above and related to convalescent plasma collection, biologic validation and treatment modalities. Meanwhile, the data arising from previous coronaviruses epidemics and from COVID-19 case series, although limited, strongly encourage clinicians and investigators to treat COVID-19 patients, particularly at an early stage of the disease, also with convalescent plasma in the frame of registered protocols.

Declaration of Competing Interest

None.

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Massimo Franchini*
Department of Hematology and Transfusion Medicine, Carlo Poma Hospital, ASST, 46100 Mantova, Italy
E-mail address: massimo.franchini@asst-mantova.it.

* Corresponding author.