Allogeneic convalescent plasma transfusion results in clinical improvement in critically ill patients with COVID-19:
Two experiences in México.

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The outbreak of the novel coronavirus disease (COVID-19) caused by the new SARS-CoV-2 virus is indeed a pandemic threat to global public health. Although the pandemic´s epicenter was initially located in Wuhan, China in December 2019, the disease has spread worldwide and millions of lives have been affected not only by the disease but by the economic consequences of compulsory isolation / quarantine (1). To date, no specific therapeutic agents or vaccines for COVID-19 are available; several options such as remdesivir, hydroxycloroquine, lopinavir/ritonavir

and others are currently under investigation, but their antiviral efficacy has not been fully proven (2). The use of convalescent plasma (CoPla) was recommended as empirical treatment of Ebola in 2014 and later, in the management of the Middle East respiratory syndrome, SARS-CoV, H5N1 avian influenza and H1N1 influenza (3-4). CoPla has been recently used in the treatment of patients with COVID-19 in China (3-4) and was found to be safe and effective; in addition, it is affordable, a key requirement in low and middle-income economies. Based on these concepts, we designed protocols to treat patients with severe forms of COVID-19 in México with CoPla, and registered both in www.clinicaltrials.gov. The results obtained in two of these studies are here summarized.

Study number 1 (Puebla, México) [www.clinicaltrials.gov NCT4357106](www.clinicaltrials.gov) (5)

Objective: To study the safety and outcomes of the administration of CoPla to individuals with severe COVID-19 in an academic medical center.

Methods: Ten patients were prospectively treated with plasma from COVID-19 convalescent donors.

Results: Over 8 days, the sequential organ failure assessment (SOFA) score dropped significantly in all patients, from 3 to 1.5 (p=0.014); the Kirby index (PaO2/FiO2) score increased from 124 to 255, (p<0.0001), body temperature decreased significantly from 38.1 to 36.9 °C (p=0.0058) and ferritin levels also dropped significantly from 1736.6 to 1061.8 ng/ml (p=0.0001). Chest X-rays improved in 7/10 cases and in 6/10, computerized tomography scans also revealed

improvement of the lung injury. Decreases in C-reactive protein and D-dimer levels were also observed. Three of five patients on mechanical ventilation support could be extubated, nine were transferred to conventional hospital floors and six were sent home; two patients died. The administration of CoPla had no side effects and the 24-day overall survival was 77%.

Conclusions: Although other treatments were also administered to the patients and as a result data are difficult to interpret, it seems that the addition of CoPla improved pulmonary function. This study was funded by the *Consejo de Ciencia y Tecnología del Estado de Puebla*. Puebla, Mexico.

Study number 2 (Monterrey, México). www.clinicaltrials.gov NCT 04358783.

The second study is a randomized one. One group will receive Copla and the other just placebo and the best therapy available. This is a double blind study, we have just started and until now 14 patients have been included. No results are now available because of the blinded protocol.

Previous studies have reported the merit of CoPla in several infectious diseases (2-4) and specifically, in COVID-19 (3). In these studies, critically ill patients due to infection by the SARS-CoV-2 virus and with a Kirby index below 300 reflecting severe pulmonary injury, received CoPla. Most patients had a positive result, defined as the improvement in both their clinical course and in the surrogate markers of the disease (5). Since the patients were receiving other treatments, it is difficult to

conclude that the CoPla infusion was fully responsible for the improvement in pulmonary function and in the patients´ clinical course. It is clear that these two studies have several limitations: 1) The number of patients is low; 2) The results cannot be generalized; 3) In only one of the studies a control group is included 4) There are several confounding factors, mainly the other treatments administered in conjunction with the CoPla; 5) The inclusion criteria are limited since only severely ill patients were included. Be that as it may, these studies suggest that the administration of CoPla may result in improvement in both respiratory function and in the clinical course of COVID-19 patients. Although the numbers are small, the intervention confirms previous experiences (3). Adding CoPla to the treatment of critically ill patients with COVID-19 may be useful and it is both affordable and safe, but we need more detailed information in order to define the role of this practical therapeutic intervention. In a recent study from China (6), patients were randomized for Copla and best therapy in comparison with just the best therapy available. The results showed that there is no significant difference, but a potential benefit was observed in severely ill patients and there is a reasonable hope that high titer antibody against SARS-CoV-2 may have antiviral efficay and a role in the treatment of COVID-19 patients.
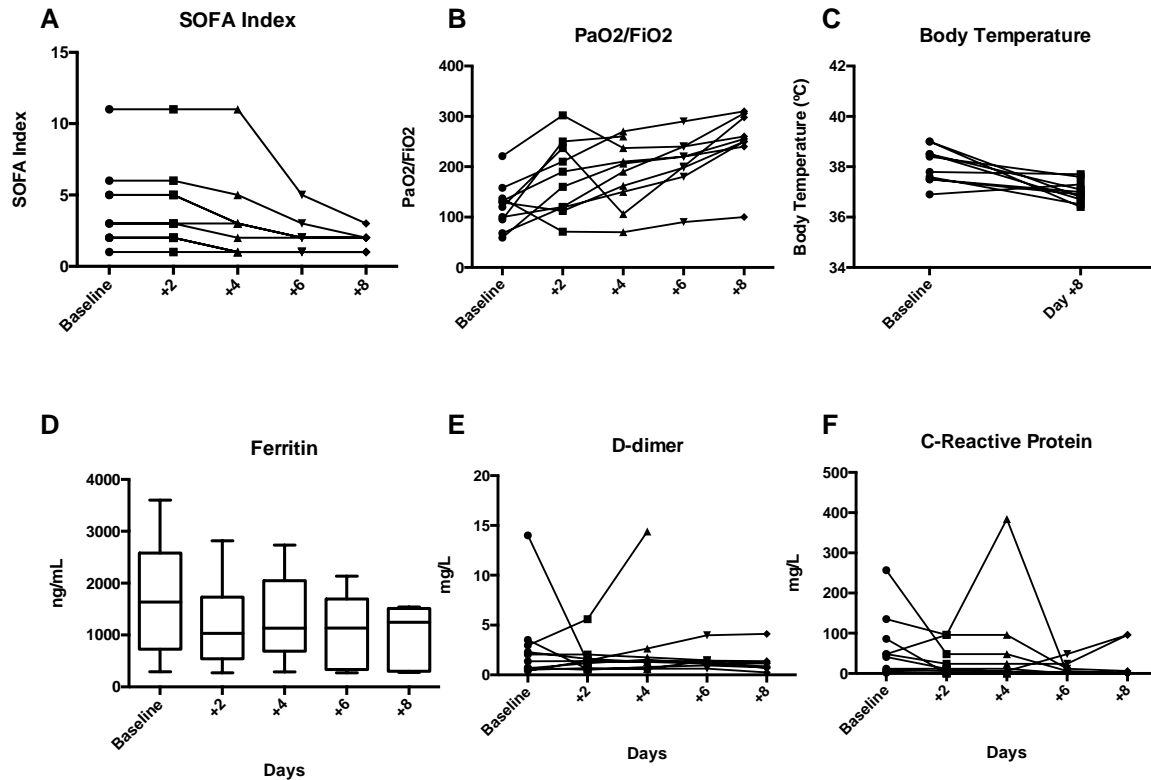
Figure 1. Changes after plasma infusion in the 10 patients described in study number 1: Panel A depicts the significant drop of the SOFA index; panel B shows the significant increase in the Kirby index (pO2/FiO2); panel C shows the significant decrease in body temperature and panel D shows the significant drop in serum ferritin levels. Panels E and F indicate the drops in D-dimers and C-reactive protein, which are not significant

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