RESEARCH ARTICLE

Post-trial follow-up after a randomized clinical trial of COVID-19 convalescent plasma [version 1; peer review: awaiting peer review]

Ignacio Esteban1,2, María Teresa Panighetti1,3, Fernando P. Polack1

1INFANT Foundation, Buenos Aires, Argentina
2Johns Hopkins Bloomberg School of Public Health, Baltimore, USA
3SAMIC Pediatric Hospital ‘Prof. Dr. Juan P. Garrahan’, Buenos Aires, Argentina

Abstract

Background:
COVID-19 convalescent plasma (CP) proved to be a safe acute intervention, however, the long-term clinical effects of COVID-19 CP are to date unknown. CP might have a prospective negative effect by down-regulating the inflammatory response suppressing antibody formation and promoting autoantibodies against interferons. Our objective was to establish the long-term safety profile of COVID-19 CP and determine if its administration increases the risk for further respiratory infections in older adults.

Methods:
All participants included in the intention to treat analysis of a randomized clinical trial evaluating the efficacy of COVID-19 CP in older adults were invited to participate in this post-trial follow-up study.

Patients were strictly followed for at least 6 months after randomization. The primary endpoint was the number of patients with clinically confirmed acute respiratory infections (ARIs). Secondary endpoints included all-cause mortality, time to first respiratory infection, SARS-CoV-2 re-infection, adverse events, and persistence of COVID-19 symptoms after initial infection.

Results:
142 patients were included in the study (total retention rate=92.8%). The mean age was 77.2 years (SD=8.6) and the median duration of follow-up was 10.4 months (IQR=1.63), with no differences among groups. 20 patients had a clinically confirmed ARI during the study. No differences were observed between groups in the proportion of ARIs (CP=11/72 and Placebo=9/70, p-value=0.678) and in the probability of ARI-free survival between groups (log-rank test p-value=0.63).

No differences emerged when comparing groups regarding secondary endpoints.
Conclusions:
COVID-19 convalescent plasma remains a safe intervention without increasing the risk of acute respiratory infection or other clinical consequences in the long term.

Keywords
convalescent plasma, COVID-19, post-trial, follow-up, safety, elderly.

This article is included in the Coronavirus (COVID-19) collection.
Introduction

COVID-19 convalescent plasma (CP) is one of the most studied pharmacological strategies during the pandemic. In a recent double-blind, randomized, placebo-controlled trial we showed that early administration of high-titer CP against SARS-CoV-2 to mildly ill infected older adults was a safe therapeutic intervention and reduced the progression to COVID-19 severe respiratory disease (relative risk = 0.52; 95% confidence interval 0.29 to 0.94; p-value = 0.03) and a relative risk reduction of 48%.

The most widely accepted theory on how CP acts in SARS-CoV-2 infection is by neutralizing antibodies inhibiting viral entry and amplification, mediating viral clearance, activating complement, enhancing the dependent cellular phagocytosis, and cytotoxicity, and providing anti-inflammatory cytokines.

However, CP may also have a long-term negative effect by down-regulating the inflammatory response (a decrease in activated, effector, and memory CD4+ T cells, a decrease in activated and effector CD8+ T cells, and a decrease of naïve B cells), suppressing antibody formation and promoting autoantibodies against interferons.

COVID-19 CP proved to be a safe intervention with <1% severe adverse events immediately after its administration. Nevertheless, the long-term clinical effects of COVID-19 CP are to date understudied.

Our objective was to establish the long-term safety profile of COVID-19 CP and determine if its administration increases the risk for further respiratory infections in older adults.

Methods

Study population

The study by Libster et. al. included 160 mildly symptomatic participants infected with SARS-CoV-2 who were 75 years of age or older, or between 65 and 74 years of age with at least one coexisting comorbidity (hypertension, diabetes, obesity, chronic renal failure, cardiovascular disease, and COPD). Participants were randomized 1:1 to receive 250 ml of convalescent plasma (with an IgG titer > 1:1000 against SARS-CoV-2 spike protein) or 250 ml of placebo (0.9% normal saline) in less than 72 hours since the onset of symptoms. Next, they were strictly followed for 15 days to evaluate the development of severe respiratory disease.

All patients included in the intention to treat (ITT) analysis of the original RCT study were invited to participate in a prospective cohort to assess for clinical differences over time among the CP and the placebo groups.

Ethics and consent

This follow-up study was part of the original protocol and was approved by the institutional review boards of each participating institution and the state of Buenos Aires (Comité de Ética Central de la Provincia de Buenos Aires, reference number: 2919–2129–2020, approved 15/5/2020; Clínica y Maternidad Suizo Argentina – Comité de Ética en Investigación, reference number: 1912, approved 19/6/2020; Swiss Medical Group, Clínica Olivos, approved 18/6/2020; Sanatorio Finochietto, approved 10/6/2020; Centro Gallego de Buenos Aires, Comité de Ética en Investigación Clínica, reference number: 1651/55/2020, approved 18/6/2020; Sanatorio Sagrado Corazon-OSECAC, approved 19/6/2020).

All participants or their legal guardians signed an informed consent and provided verbal consent during follow-up.

Study procedure

At the end of their participation in the RCT, all participants were instructed to communicate with the research team and report any adverse event, the onset of new symptoms, any confirmed diagnosis, and/or any visit to the health system. In addition, previously trained physicians using pre-designed questionnaires (available in section Data availability) phone-called all participants to assess for the variables and outcomes of interest at 3 and 6 months after randomization, and conducted a final contact between 7–10 months for data quality assurance. Data collection occurred between June 2020 and June 2021 in the city of Buenos Aires and Buenos Aires State, Argentina.

The primary endpoint of the follow-up study was the number of patients with clinically confirmed acute respiratory infections (ARIs) defined by the diagnosis of at least one of the following: pneumonia, upper respiratory infection, bronchitis, pharyngitis, or acute otitis media.

Secondary endpoints included all-cause mortality, time to first respiratory infection, SARS-CoV-2 confirmed re-infection, adverse events probably related to investigational product, and persistence of COVID-19 symptoms after initial infection.

Statistical analysis

Differences between participants were compared using the Student t-test and Chi-squared test, where appropriate. A p-value <0.05 was considered statistically significant. Time to first respiratory infection was assessed using the Kaplan-Meier method, and the log-rank test to assess for differences among groups (CP and placebo). We conducted a subgroup analysis by modified intention to treat (mITT) as in the original study excluding those randomized to CP but did finally not receive it, and by those receiving a higher SARS-CoV-2 S IgG titer in donor plasma (using 1:3200 as a cutoff point). Stata/SE 13 package for IBM-PC (Stata Corp) was used for analysis and figure creation.

Results

From the initial RCT that included a total of 160 patients in the ITT analysis (CP=80 and Placebo=80) and 154 in the mITT (CP=76 and Placebo=78), 153 were eligible to participate in the study (6 died during the original study and 1 withdrew consent). 142 patients were included in the follow-up study. 10 patients were lost to follow-up and 1 patient did not want to participate in the follow-up study, resulting in a total retention rate of 92.8% (CP=92.3% vs Placebo=93.3%) (Figure 1).
The mean age of included participants was 77.2 years (SD 8.6), and their median duration of follow-up was 10.4 months (IQR 1.63), with no differences among groups, with 10.3 months (IQR 1.68) and 10.42 months (IQR 1.6) for the CP and placebo groups respectively (t-value (df 140) = -0.35, p-value=0.724). No treatment switching was evidenced during the follow-up time. 89% of the participants (n=127) received a COVID-19 vaccine during the study with a median time to the first dose of 8.8 months (IQR 2.2).

14% of the participants (n=20) had a clinically confirmed ARI during the study. No differences were observed between groups (CP=11/72 and Placebo=9/70, χ² =0.17, p-value=0.678). The median time to first ARI was 8.63 months (IQR 7.13) for the CP group and 9.2 months (IQR 7.53) for the placebo. No statistically significant differences were observed in the probability of ARI-free survival between groups (log-rank test p-value=0.63) (Figure 2).

There were no statistically significant differences in the number of participants with ARI when comparing within the mITT subgroup (CP=10/69 and Placebo=9/68, χ² =0.045, p-value=0.831) or when comparing those who received SARS-CoV-2 S IgG titer in donor plasma ≥1:3200 vs. placebo (CP=3/34 and Placebo=9/70, χ² =0.36, p-value=0.546). All secondary endpoints remained stable with no difference by treatment in the subgroup analyses (data not shown).

**Discussion**

In this post-trial follow-up study of an RCT of COVID-19 convalescent plasma in older adults, CP did not increase the risk for acute respiratory infections in the long-term follow-up. Furthermore, no differences were observed between groups (CP vs placebo) when assessing for time to first acute respiratory infection, adverse events, SARS-CoV-2 reinfections, all-cause mortality, and persistence of COVID-19 symptoms. In addition, all endpoints remained stable showing no difference in the subgroup analyses.

To our knowledge, this is the first post-trial follow-up after an RCT of COVID-19 CP assessing for long-term consequences of its administration. COVID-19 convalescent plasma remains a safe intervention with no clinical consequences in the long term.

A recent randomized clinical trial with control plasma by Sullivan et al. supports the hypothesis of our original study that
Figure 2. Acute respiratory infections free survival curves over follow-up time by treatment group. ARI = Acute Respiratory Infection. Placebo (solid line). COVID-19 convalescent plasma (dashed line).

COVID-19 CP should be administered early in the course of the disease and to those presenting mild symptoms. In this study, COVID-19 CP presented a relative risk reduction of 54% in COVID-19 related hospitalization within 28 days after transfusion, which increased to 79.9% in those with ≤ 5 days of symptoms. However, no differences were found between groups when comparing patients already vaccinated.

Our study adds evidence to the long-term safety of COVID-19 CP. This intervention might have now a lesser role as a strategy against SARS-CoV-2, however, our study supports an early and coordinated evaluation of convalescent plasma use in future pandemics.

Data availability

Extended data


This project contains the Stata do-file.

figshare: Codebook. https://doi.org/10.6084/m9.figshare.20349534

This project contains the database codebook.


This project contains the data collection instruments and questionnaires in English.

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

References


