Efficacy and Safety of COVID-19 Convalescent Plasma in Hospitalized Patients

A Randomized Clinical Trial (CONTAIN COVID-19)

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BACKGROUND

NYC was the initial epicenter of COVID-19 pandemic in the U.S. The absence of effective therapies prompted COVID-19 convalescent plasma (CCP) use because of biological plausibility and historical success of convalescent plasma in prior pandemic. There is clinical equipoise for CCP use in patients hospitalized with COVID-19.

OBJECTIVES

To determine the safety and efficacy of CCP compared with placebo (saline solution) in hospitalized patients with COVID-19 receiving noninvasive supplemental oxygen.

METHODS

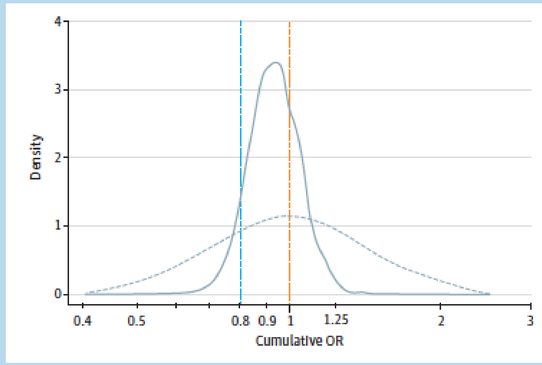
- CONTAIN COVID-19, a randomized, double-blind, placebo-controlled trial of CCP was conducted at 21 US hospitals from April 17, 2020, to March 15, 2021.
- Eligible patients were adults ≥18 years hospitalized for ≤3 days or with symptoms of respiratory illness for ≤7 days who required noninvasive O_2 supplementation and had a positive nasopharyngeal SARS-CoV-2 RT-PCR.
- Exclusion criteria were receipt of pooled immunoglobulin, contraindication to transfusion, invasive MV or ECMO, volume overload, and receipt of a COVID-19 vaccine.
- The primary outcome was participant scores on the 11-point World Health Organization (WHO) Ordinal Scale for Clinical Improvement on day 14 after randomization; the secondary outcome was WHO scores determined on day 28.
- Subgroups were analyzed with respect to age, baseline WHO score, concomitant medications, symptom duration, CCP SARS-CoV-2 titer, baseline SARS-CoV-2 serostatus, and enrollment quarter.
- Outcomes were analyzed using a bayesian proportional cumulative odds model. Efficacy of CCP was defined as a posterior probability of cumulative adjusted odds ratio (cOR)<1 of ≥95% and a clinically meaningful effect as P(cOR<0.8)≥50%.

RESULTS

Table. Demographic and Clinical Characteristics of the Patients at Randomization

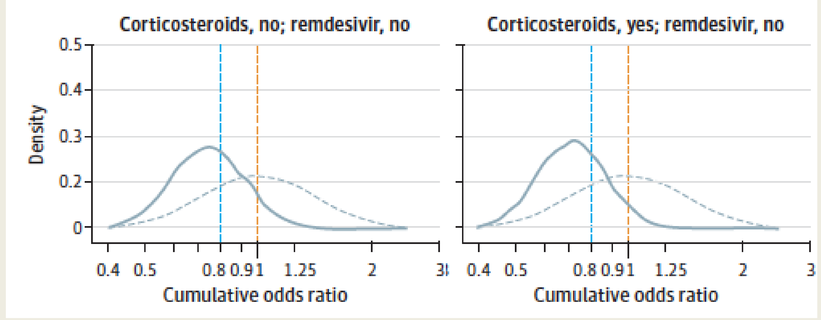
	Placebo (n=473)	CCP (n=468)
Age (years, IQR)	64 (54 – 74)	62 (51 – 72)
Sex, women (%)	42.5	39.3
Hispanic (%)	40.2	39.1
Non-Hispanic Black (%)	13.3	14.7
BMI (median, IQR)	29.7 (25.8 – 35.5)	31.0 (26.5 – 36.3)
WHO score 5 (low flow O2) (%)	72.1	70.9
Symptom onset to randomization (median days, IQR)	7.0 (4.0 – 9.0)	7.0 (4.0 – 9.0)
Hypertension (%)	60.5	60.9
Cardiovascular (%)	45.5	40.4
Seropositive at baseline (%)	68.8	64.4

Figure 1. Posterior Distributions of Cumulative Odds Ratio for World Health Organization Scores 14 Days After Randomization



The dashed curve represents the prior distribution assumption for the OR, and the solid curve represents the estimated posterior probability distribution of the OR. The area under solid curve totals 1, and the area to the left of the dashed orange line represents P(OR<1).

Figure 2. Posterior distribution of cOR for WHO scores 14 days after randomization by Remdesivir and Corticosteroids use



Participants

- From Apr 2020, to Mar 2021, 13,027 participants were evaluated; 941 were randomized. Median age was 63 yrs, 59% men, 41% women, and 72% had prerandomization WHO scores of 5 (requiring oxygen by mask or nasal prongs). 40% were Hispanic, 14.0% non-Hispanic Black, and 33.8% non-Hispanic White. Median time from symptom onset to randomization was 7 days (Table).
- 98.2% completed the study and 1.8% withdrew.

Primary and Secondary outcomes

- The primary (WHO scores on day 14) and secondary (WHO scores on day 28) outcomes, adjusted for prespecified covariates, did not meet prespecified definitions of efficacy.
- At day 14, the cOR was 0.94, P(cOR<1) = 72% and P(cOR<0.8) = 8% (Figure 1)
- At day 28, the cOR was 0.92, P(cOR<1) = 76% and P(cOR<0.8) = 10%.

Subgroup analyses

- At day 28, the cOR for participants enrolled in Apr-Jun 2020 was 0.72, P(cOR<1)=93%, in Jul-Sept 2020 was 0.83, P(cOR<1)=77%, in Oct-Dec 2020 was 0.99, P(cOR<1)=52%, and in Jan-Mar 2021 was 1.18, P(cOR<1)=19%.
- At day 14, the cOR for participants not receiving remdesivir or corticosteroids was 0.74, P(cOR<1)=92% and, for those receiving corticosteroids but not remdesivir, 0.71, P(cOR<1)=95% (Figure 2).
- There were no significant associations between CCP EC_{50} or neutralizing titer, or participant serostatus and clinical outcome.

CONCLUSIONS

Limitations

- The primary outcome at day 14 was likely too early for a disease now known to have a prolonged course.
- There were heterogeneous treatment effects over time, perhaps related to changing patient characteristics, treatment options, and other factors.
- CCP obtained in the NYC area was used in non-NY sites and may not have matched local viral species, and emergence of SARS-CoV-2 variants may have reduced CCP efficacy over time.

Conclusions

- The primary outcome did not meet the prespecified definition for CCP efficacy. CCP was safe and well tolerated.
- A possible benefit of CCP was observed early in the pandemic when higher titer CCP was used and corticosteroids and remdesivir were not in use.
- CCP may be a feasible treatment option at the beginning of a pandemic or when other therapies are not in use or available.

REFERENCES: Ortigoza, Yoon, Goldfeld, et al. *JAMA Intern Med.* 2022;182(2); Casadevall and Pirofski, *J Clin Invest*. 2020;130(4); Joyner, Carter, et al. *N Engl J Med*. 2021; Yoon, Bartash, et al. *JCI Insight*. 2021;6(4)

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