COMPILE$_{home}$ (Continuous Monitoring of Pooled International trials of convalescent plasma for COVID-19 patients at home Consortium)

00467

Convalescent plasma for outpatients with early COVID-19, A randomized trial

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Background

Convalescent plasma (CP) for hospitalized patients with COVID-19 has not demonstrated clear benefits. This is in contrast to the clear value of monoclonal antibody therapy in outpatients in the first 7 days of symptoms. Large randomized trials on CP for outpatients with early COVID are lacking. We studied if CP benefits outpatients treated in the first 7 days of symptoms.

Aim

The aim of COMPILE$_{home}$ was to join forces between individual randomized trials that focus on CP for outpatients with COVID-19. This would not only help to reach conclusions on the potential benefits of CP faster but also increase the sample size and thus statistical power.

A simple and clinically relevant endpoint that could be derived from the study data from each individual trial was chosen (see methods) and a Bayesian adaptive individual patient data meta-analysis plan was implemented. While the individual studies continued to enroll, their data were pooled real-time and analyzed every 6 weeks using predefined stopping rules for efficacy.

Methods

Subjects were included when they had; 1) a PCR or antigen confirmed symptomatic COVID-19, 2) were not hospitalized or in the ER, 3) had symptoms for ≤7 days and 4) were 50 years or older.

Patients received one unit of 250-300 mL of plasma without SARS-CoV-2 antibodies or CP with a minimum level of SARS-CoV-2 Spike antibodies (minimum level as per individual study protocol). Neutralizing antibody titers from all donors were later converted to WHO international units as well.

Two primary endpoints were assessed:
- A 5-point ordinal scale assessed the speed of recovery as well as hospital admission, ICU admission and death up until day 28 (Table 2).
- A composite endpoint of hospital admission or death.

Secondary endpoints were:
- Time to full symptom resolution.
- Predefined subgroup analyses; 1) in patients who were SARS-CoV-2 IgG Spike antibody negative at baseline 2) in patients with ≤ 5 days versus >5 days of symptoms and 3) in patients treated with CP with a neutralizing antibody titer in IU/ml in the upper versus lower 50% of the range across all donors.

Analysis: Posterior probability of benefit analysis for both primary endpoints with stopping rules when $P(OR_{PE1}<1) \geq 0.985$ and $P(OR_{PE2}<1) \geq 0.80$ OR $P(OR_{PE2} < 1) \geq 0.975$. A proportional odds and logistic regression model was used for the first and second primary endpoint respectively. An OR < 1 means a better outcome with CP.

Results (1/2):

When 782 patients from 2 randomized trials had been enrolled, recruitment in both trials was discontinued as vaccination rates in adults had increased to >75% and hospital admissions had become limited.

The Bayesian posterior probability of benefit for the primary endpoint 1 and 2 at that time were 64.9% and 64.3% respectively.

Primary endpoint 1 (5-point ordinal scale): OR 0.936 (CI 0.667-1.311)
Primary endpoint 2 (Admission or death): OR 0.919 (CI 0.592-1.416)

Table 2 shows the distribution of patients across the 5-point scale.

Table 1. Baseline characteristics

Characteristics	CP (n=390)	Control (n=392)
Male sex – no. (%)	267 (68.5%)	255 (65.1%)
Age – median (IQR)	58 (53 – 64)	58 (54 – 65)
Number of comorbidities – median (IQR)	1 (0 – 2)	1 (0 – 2)
Days since first symptoms – median (IQR)	5 (4 – 6)	5 (4 – 6)
Anti S IgG positive at baseline – no. (%)	28 (7.7%)	24 (6.4%)

Disease severity scale	CP (n=390)	Control (n=392)
Recovered before day 8	74 (19.0%)	69 (17.6%)
Continued symptoms on day 8	282 (72.3%)	283 (72.2%)
Admitted to hospital but no invasive ventilation	31 (7.9%)	34 (8.7%)
Admitted to hospital and invasive ventilation	2 (0.5%)	4 (1.0%)
Death	1 (0.3%)	2 (0.5%)

Table 2. Distribution of outcome of the patients in the 28 days after inclusion across the 5-points disease severity scale

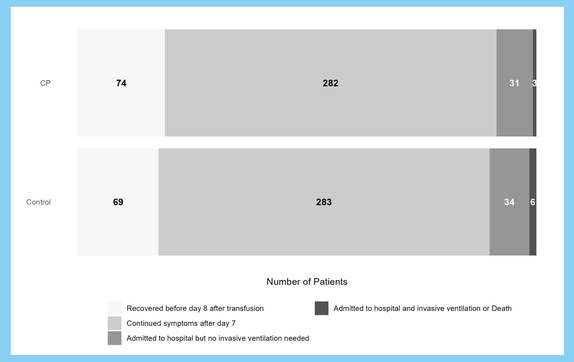


Figure 2. Distribution of the outcome of the patients in the 28 days after inclusion across the 5-points disease severity scale.

Results (2/2):

Secondary endpoint:
The OR in in the subgroup with ≤ 5 days of symptoms (OR 0.658) was lower than for those with > 5 days of symptoms (OR 1.427). (Figure 3)

No difference in time to full resolution of symptoms was seen (Figure 1).

The OR for patients who received CP with neutralizing antibody titers above or below the median titer were very similar. No difference was found when SARS-CoV-2 ELISA positive patients were excluded (Figure 3).

4 treatment related SAEs were observed.

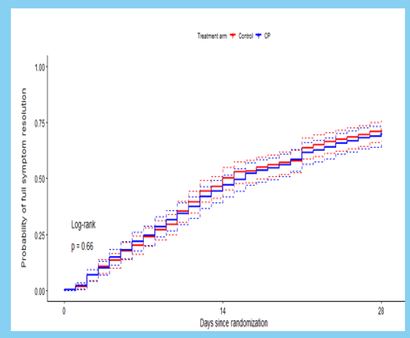


Figure 1. Time to resolution of symptoms

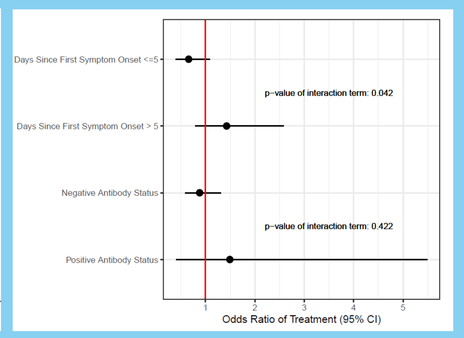


Figure 3. Results for predefined subgroups on the 5-point ordinal disease severity scale endpoint. Identical results were found for the endpoint of hospital admission or death

Conclusion

One unit of 250-300ml of CP given to outpatients in the first 7 days of symptoms did not improve the outcome of COVID-19. Higher doses (higher antibody titers or larger volumes) may be required to optimize this form of therapy(1). The potential benefit in those with 5 or fewer days of symptoms requires confirmation.

Financial support : ZONMW research grant nr. 10430062010001
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The full study report, protocol and statistical analysis plan can be downloaded at www.medxriv.org

More info about the COMPILE initiative can be found in Goldfeld K et al. Stat Med 2021 Oct 30 https://pubmed.ncbi.nlm.nih.gov/34164838/

1) Rijnders B, Huygens S, Mitja O. Evidence based dosing of convalescent plasma for COVID-19 in future trials. Clin Microb Infection 2022.