A Randomised Open-Label Trial of Early, Very High-Titre Convalescent Plasma Therapy in Clinically Vulnerable Individuals with Mild COVID-19

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To determine whether convalescent plasma collected from donors who have recovered from COVID-19 and who have a very high titre of anti-SARS-CoV-2 antibodies reduce the risk of hospitalization or death due to COVID-19 in patients with early symptoms...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON51772

Source
ToetsingOnline

Brief title
COVIC-19

Condition

- Immune disorders NEC
- Viral infectious disorders
- Respiratory tract infections

Synonym
corona virus, COVID-19, SARS-CoV-2

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,ZONMW,EU funding is aangevraagd maar nog niet toegezegd. Op dit moment worden de kosten door de nationale sponsor gedragen.

Intervention

Keyword: convalescent, COVID-19, immunocompromised, plasma

Outcome measures

Primary outcome

Proportion of participants with (1) at least one overnight stay in hospital for

progressive COVID-19 symptoms , or (2) who died, by day 28 after

randomisation.

Secondary outcome

Secondary endpoints:

- Proportion of patients with hospitalisation for progressive COVID-19

symptoms, or death by day 14 after randomisation

- Proportion of patients with hospitalisation for progressive COVID-19 symptoms

requiring O2 support*, or death by day 14 and 28 after randomisation

- All-cause mortality by day 28, 90 and 180 after randomisation

- Proportion of patients with supplemental oxygen by day 14 and 28 after

randomisation

- Proportion of patients with non-invasive ventilation by day 14 and 28 after

randomisation

- Proportion of patients with intubation and mechanical ventilation by day 14

and 28 after randomisation

- Change in 10-point WHO Clinical Progression Scale score at 14 and 28 days after randomisation

- Duration of hospital admission censored at 28 days after randomisation

- Proportion of patients with ITU admission by day 14 and 28 after randomisation

- Duration of ITU admission censored at 28 days after randomisation

- Proportion of patients with long COVID-19 symptoms and time to recovery assessed by questionnaire at days 28 and 180 post randomisation

- Health-related quality of life assessed using the EQ-5D-5L at 28 and 180 days after randomisation

- Number of serious Adverse Events at 72 hours after randomisation (Grade 3/4 adverse events and AE unexpected for their nature, onset, evolution, severity or frequency)

- Arterial and venous thromboembolic events at 28, 90 and 180 days after randomization

* O2 support requirement based on O2 saturation level on room air <= 93 % and/or Respiratory Rate > 30)

Exploratory endpoints:

- Change in SARS-CoV-2 RNA level (Polymerase chain reaction, Cycle Threshold value) in oral or nose/throat swab samples at days 3, 14, 28 and 180 after randomisation (cohort 2 only)

- Change in anti-SARS-CoV-2 spike antibody levels in blood at days 14 and 28 after randomisation

- SARS-CoV-2 whole genome sequence analysis in oral or nose/throat swab samples

at day 1 and 28 after randomisation

- Proportion and clinical characteristics of patients with cultivable virus at

day 28, hospitalisation and day 180

- Virus sequence variation and cultivability over time, overall and in

individuals receiving vs not receiving CP

Study description

Background summary

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic has caused more than 5 million deaths worldwide. Mortality is 40% or more for patients from clinically vulnerable groups admitted to hospital. Therefore, treatment is urgently needed soon after symptom onset, to prevent progression to severe disease and hospitalization. This is especially important in clinically vulnerable patients who are at high risk of prolonged hospitalization or death due to COVID-19.
Furthermore, patients with immunosuppression usage or a immunodeficiency have been disproportionately affected by the COVID-19 pandemic, and often present with a persistent SARS-CoV-2 infection and may shed viable SARS-CoV-2 for months. Vulnerable patients may belong to subgroups less likely to respond well to vaccination.

We will evaluate the efficacy of convalescent plasma collected from donors with high-titer neutralizing SARS-CoV-2 antibodies in reducing the risk of hospitalization in people with early onset COVID-19 compared to standard care. We will do this through a randomized, open-label two-arm trial in clinically vulnerable patients that will provide robust comparative efficacy data in groups most likely to benefit from early treatment. We will assess virologic parameters by sequentially measuring SARS-CoV-2 RNA and virus viability in oropharyngeal samples, antibody levels and viral sequence variation.

Study objective

To determine whether convalescent plasma collected from donors who have recovered from COVID-19 and who have a very high titre of anti-SARS-CoV-2 antibodies reduce the risk of hospitalization or death due to COVID-19 in patients with early symptoms of acute COVID-19 who are vulnerable to this

disease compared to standard of care.

Study design

Multicenter, randomized, open-label, adaptive superiority trial: convalescent plasma with a very high neutralizing titer versus standard care in 2 cohorts of vulnerable patients (cohort 1: elderly (>= 70 years) and younger with comorbidities, cohort 2: immunosuppressed patients).

Study phase: phase 3
Randomization: 1:1 (standard of care + convalescent plasma vs. standard of care) stratified by center and by patient cohort
Sample Size: minimum of 340 per cohort and maximum of 1020 per cohort depending on the interim analysis
Study duration: step 1: 18 months; step 2: 18 to 30 months
Study setting: outpatient setting with recruitment and inclusion in the study at the hospital

Intervention

Two units of high antibody titre COVID-19 convalescent plasma to individuals randomised to the intervention group, 2 units from 2 different donors, preferably transfused on the same day.

Study burden and risks

Known potential risks are mostly those associated with the transfusion of plasma. Adverse effects associated with plasma transfusion CCP include allergy, febrile reactions, transfusion-related circulatory overload (TACO) and Transfusion Related Acute Lung Injury (TRALI).
Data show that convalescent plasma is well tolerated. In a Cochrane review, amongst 20 000 people with COVID-19 receiving convalescent plasma in non* controlled non*randomized studies of interventions and for whom adverse events were recorded, there were 63 deaths of which 12 were possibly and 1 probably related to transfusion (13/20622, 0.06%). There were 146 serious adverse events within 4 hours and 1136 serious adverse events within 7 days post-transfusion; predominantly allergic, respiratory, thrombotic or cardiac events (1282/20 000, 6.4%). Four RCTs observed severe or serious transfusion*related adverse events in 0 to 1.3% of participants receiving convalescent plasma, including severe transfusion*associated dyspnea, and probably*transfusion*related deaths. The reported studies pertaining to early convalescent plasma administration in mildly ill vulnerable COVID-19 patients (as for patients to be included in COVIC-19) reported no adverse events, or adverse events occurring with similar frequency in the control groups.

Early transfusion of high titer convalescent plasma in vulnerable patients may

significantly reduce the risk of disease worsening and need for hospitalization. Severe COVID-19 disease in vulnerable patients such as elderly patients, less elderly with comorbidities or patients with immunodeficiency remains associated with significant morbidity and mortality. Furthermore, immunosuppressed patients, least likely to benefit from a SARS-CoV-2 vaccine, are at risk of prolonged (>2 months) shedding and pose a risk of sustained onward transmission or selection of variants and so may gain additional benefits from early therapeutic intervention. Additionally, reducing the need for hospitalization will also reduce the burden on the healthcare system at time of crisis.
To the difference of anti-SARS-CoV-2 monoclonal antibodies, convalescent plasma may be readily available and adapted in the presence of an emerging immune-resistant SARS-CoV-2 variant or in case of a pandemic involving a novel pathogen. The polyclonal antibody content of convalescent plasma could make this an ideal passive immunotherapy for treatment of patients infected by new variants.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

's-Gravendijkwal 230
Rotterdam 3015CE
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

's-Gravendijkwal 230
Rotterdam 3015CE
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Overall:
- SARS-CoV-2 RNA detected in a specimen, <= 7 days after onset of symptoms
- Symptoms of COVID-19
- Clinical status not requiring admission to hospital for COVID-19 disease and oxygen support
- Ability to transfuse (per randomisation) within 7 days after onset of symptoms
- Signed written informed consent

Additional to cohort 1:
Men or women, 70 years or older OR under 70 years with significant comorbidities resulting in a "COVID-age" of 70 years or more according to the ALAMA risk calculator.

Additional to cohort 2:
Men or women, >=18 years of age with extremely high risk. Including patients with acquired immune deficiencies OR primary lymphoid immune deficiencies OR without detectable seroconversion >= 3 weeks after complete vaccination schedule with an approved vaccine.

Exclusion criteria

Overall:
- Age < 16 years
- Prior or concurrent treatment for COVID-19 (unless listed as authorized specific treatment in protocol)
- History of documented SARS-CoV-2 infection in the last 90 days prior to enrollment
- Contraindication to receiving convalescent plasma including previous history of transfusion-related acute lung injury (TRALI) or moderate or severe allergic reaction to blood components
- Known participant objection to receiving plasma products
- Refusal to participate expressed by patient or legally authorised representative
- Pregnancy

Additional to cohort 1:
- Prior anti-SARS-CoV-2 immunization

- Primary or acquired immune deficiency listed below (see cohort 2)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-10-2022
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	02-08-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05271929
CCMO	NL81485.078.22

Study results

Date completed: 28-06-2024

Summary results
Trial ended prematurely