A randomized, double blinded clinical trial of convalescent plasma compared to standard plasma for treatment of hospitalized non-IC patients with COVID-19 infections

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To evaluate the efficacy of convalescent plasma compared to standard plasma to improve an ordinal outcome as primary endpoint: consisting of shorter than the average of 6 days hospital stay, no admission to the intensive care unit (ICU), no need for...

Ethical review	Approved WMO
Status	Pending
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON49946

Source
ToetsingOnline

Brief title
COV-PLAS

Condition

- Viral infectious disorders

Synonym
COVID-19

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: convalescent plasma, COVID-19 pandemic, virus inactivating and neutralizing antibodies

Outcome measures

Primary outcome

The estimated benefit in regard of the primary endpoint is a shift in the distribution of the scores towards less mortality, less mechanical ventilation, less ICU admission and shorter than the average of 6 days hospital stay. The primary endpoint will be analyzed using a Bayesian proportional odds model. Posterior probabilities will start to be computed after 20 patients have completed their follow-up and will be computed continuously afterwards. In this way, during the study, the trial statistician monitors if superiority of the treatment arm or inferiority of the control arm evolves. At that moment, the PI and the DSMB will be able to consider an earlier stop of the trial.

Primary objective:

To evaluate the efficacy of convalescent plasma compared to standard plasma on an ordinal outcome consisting of duration of hospital stay, admission to the intensive care unit (ICU), need for mechanical ventilation and mortality.

Secondary outcome

The other effectivity parameters that are monitored as secondary endpoints are :

- The ordinal endpoint at day 28 and 56.

- The combined mortality at and stay at the ICU at day 41,28 and 56

- The number of hospital days

Safety parameters monitored as secondary endpoints specifically looked at are possibly with plasma transfusion related side effects like: worsened respiration related to transfusion related acute lung injury (TRALI), circulatory overload by the plasma infusion (TACO), transfusion transmitted infections or allergic reactions caused by plasma proteins.

Study description

Background summary

The present COVID-19 pandemic overwhelmes the care-systems of the world and leads to high morbidity and mortality. No effective therapy or vaccination strategies are presently available, and outcome is largely dependent on a fast-enough clearance of the virus by the patients* own immune system. Most viral infections in this respect lead to a humoral immune response which consists out of the formation of virus inactivating and neutralizing antibodies. Also, patients that recover from COVID-19 infections show such antibodies in their plasma. Hence, assessing the potential therapeutic use of this plasma for transfusion and thus transfer of antibodies of cured patients to patients with active disease is logical and the aim of the present trial.

Study objective

To evaluate the efficacy of convalescent plasma compared to standard plasma to improve an ordinal outcome as primary endpoint: consisting of shorter than the average of 6 days hospital stay, no admission to the intensive care unit (ICU), no need for mechanical ventilation and survival. 2) To compare other efficacy parameters and safety of convalescent plasma versus standard plasma. 3) To evaluate the predictive value of co-morbidities and inflammation markers on endpoints. 4) To evaluate the predictive value plasma characteristics (e.g. titer and type of anti-Severe Acute Respiratory Disease-Coronavirus- 2 (SARS-CoV-2) titers) on endpoints. 5) To evaluate how convalescent plasma with anti-SARS-CoV-2 antibodies, modulates course and titres of anti-SARS-CoV-2 in patients prior to transfusion and thereafter on days 1, 2, 3 and every week up

to day 28 and at day 56 and how this compares to patients transfused with standard plasma. 6) Compare the rates, levels and duration of SARS-CoV-2 RNA in nasopharyngeal (NP) swabs using reverse transcription polymerase chain reaction (RT-PCR) amongst the convalescent plasma and the control (standard plasma) groups on days 1, 2, 3 and every week up to day 28 and at day 56.

Study design

This is a randomized, prospective, multicenter, double blinded phase 2/3 trial comparing efficacy and safety of anti-SARS-CoV-2 convalescent plasma vs standard plasma in maximally 3 days hospitalized COVID-19 patients that are not at or bound to be referred to the ICU.

Intervention

Enrolled patients will either receive convalescent thawed fresh frozen plasma 1 unit (250-325 ml) (=treatment group) or standard thawed fresh frozen plasma 1 unit (250-325 ml) (=control group).

Study burden and risks

All patients will receive 1 unit of plasma. Plasma itself has a well known but minor risk profile. Moreover, most of standard plasma associated side effects can be avoided by additional measures and exclusion of patients with risk factors e.g. for transfusion associated circulatory overload (TACO). Treatment with so called convalescent plasma with COVID-19 antibodies includes the same minor risk profile as standard plasma infusions, but is conceptually benefical for additional clearing virus for the transfused patients. However, possible disease excacerbation by the antibodies has also been suggested. A blinded and randomized approach comparing standard plasma with convalescent plasma is therefore chosen, moreover while unbiassed assessment of endpoints is guaranteed by this stragegy. except for minimal additional blood sampling : 27ml at t=1 (before plasmatransfusion), 28 en 56 days and 8 x6 ml t=1, 2,3,7,14,21, 28, 56 days = 48 ml in total 129 ml, and additional 7viral RNA assessing nose/pharyngeal swabs. For survival assessment also an on average 3 post-discharge (estimated to be applicable for most patients) visits at day 14, 28, 56 are needed. All other study-related screening and monitoring involves standard patient care and are according to the WHO/ ISARIC data-dictionary.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Maximal 3 days hospitalized patients at plasma infusion.
2. Age * 18 years and * 85 years
3. SARS-CoV-2 infection: confirmed by PCR (BAL, sputum, nasal and/or pharyngeal swap)
4. Symptoms not expected to lead to IC transfer within 6 hours of first plasma administration
5. Written informed consent including storing of specimen for future testing

Exclusion criteria

1. Accompanying diseases other than COVID-19 with an expected survival time of less than 12 months
2. Chronic obstructive lung disease (COPD), stage 4
3. Lung fibrosis with UIP pattern in CT und Severe emphysema
4. Chronic heart failure NYHA >= 3 and/or pre-existing reduction of left ventricular ejection fraction to * 30%
5. Cardiovascular failure requiring diuretics

6. Signs of severe coagulopathy : thrombocytopenia a/o prolongation of the PT/INR, PTT a/o elevation of D-dimer, a/o decreased fibrinogen level waardes ?
7. Liver cirrhosis Child C
8. Liver failure: Bilirubin > 5xULN and elevation of ALT /AST (at least one >10xULN).
9. Any history of severe adverse reactions to plasma proteins
10. Known deficiency of immunoglobulin A
11. Pregnancy
12. Breastfeeding women
13. Volume overload until sufficiently treated
14. Pulmonary edema
15. Participation in another clinical trial for treatment of COVID-19
16. Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator, would affect subject safety and/or compliance

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2020
Enrollment:	430
Type:	Anticipated

Ethics review

Approved WMO Date:	11-05-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	12-05-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	15-06-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 23835
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL73791.058.20
OMON	NL-OMON23835