Pre-emptive tocilizumab in hypoxic COVID-19 patients, a prospective randomized trial

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The aim of the study is to assess whether early administration of the drug tocilizumab in SARS-CoV-2 infection (COVID19 - coronavirus) can prevent the risk of death and mechanical ventilation (assisted respiration by a ventilator).

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

Summary

ID

NL-OMON49824

Source
ToetsingOnline

Brief title
Pre-emptive tocilizumab in hypoxic COVID-19 patients

Condition

- Viral infectious disorders
- Upper respiratory tract disorders (excl infections)

Synonym
Corona, COVID-19

Research involving
Human

Sponsors and support

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

Intervention

Keyword: COVID-19, Hypoxic, Pre-emptive, Tocilizumab

Outcome measures

Primary outcome

- To assess in a randomized comparison the effect of pre-emptive tocilizumab in patients with hypoxia due to COVID-19 on 30-day mortality (from randomization)

Secondary outcome

- To asses in a randomized comparison days in hospital (calculated from randomisation)

-To asses in a randomized comparison the percentage of patients who need ICU care.

- To asses in a randomized comparison the percentage of patients who develop respiratory failure and need mechanical ventilation

- To asses in a randomized comparison the days on a ventilator.

- To asses in a randomized comparison normalisation of HRCT after resolution of disease

- To asses in a randomized comparison seroconversion 14 days after randomisation

- To identify potential biomarkers predictive of response (blood: cytokines (including Il-6 and IL-18), lymphopenia, CRP, ferritin, LDH, sCD25; nasal epithelial brushes: epithelial transcriptome immune response by bulk and single-cell RNA seq; faeces: microbiome, viral load), gender, age, co-morbidity and plasma levels tocilizumab by exploratory analysis.

- To assess safety and feasibility of pre-emptive use of tocilizumab (AE grade

4, increase in dyspnea according to CRS scale)

- To assess in a randomized comparison OS after 3 months (after randomization)

- To asses in a randomized comparison quality of life and pulmonary function

after 3 months (after randomization)

Study description

Background summary

Patients who develop respiratory failure with COVID-19 have a small chance (20%; with 8x IC capacity overload) to be eligible for invasive ventilation (capacity problem). This group of patients with respiratory failure who is not given invasive ventilation is likely to have very high (> 95%) mortality. However, the mortality of patients undergoing invasive ventilation is also high (approximately 50-60%) [Weiss et al. Lancet 2020, March 17].People who get respiratory problems do not get into trouble because they cannot clear the virus, but get into trouble because of the (uncontrolled) inflammatory response (see figure) [Mehta et al. Lancet 2020 March 13; Hasan et al. J Heart & Lung transpl. 2020 March]. The recently published clinical study, showing no effect of anti-viral therapy (Lopinavir * Ritonavir) in admitted patients with severe COVID-19, is in line with the belief that in the later stages of the disease, not the virus, but hyper- inflammation is the problem [A Trial of Lopinavir * Ritonavir in Adults Hospitalized with Severe Covid-19. Bin Cao, MD, et al. NEJM 2020]. This clinical picture is very similar to the cytokine release syndrome (CRS) as seen in cancer immunotherapy (eg, in the context of chimeric antigen receptor (CAR) T cell therapy and bi-specific antibody therapy).NB Experiences with UMCG patients with status after lung and liver transplantation who completed the SARS-CoV-2 virus and had a mild clinical picture fit this observation.

Study objective

The aim of the study is to assess whether early administration of the drug tocilizumab in SARS-CoV-2 infection (COVID19 - coronavirus) can prevent the risk of death and mechanical ventilation (assisted respiration by a ventilator).

Study design

This is a randomized open label phase II study.

Eligible patients will be randomized (after written informed consent) to standard care or intravenous tocilizumab.
Eligible patients who are randomized will receive intravenous tocilizumab 8 mg/kg (maximum dose 800 mg), infused over 1 hour. This dose can be repeated after 8 hours if the hypoxia is not resolved (still at dyspneu grade II according to CRS scale). Patients that are not randomized for intervention using tocilizumab will receive standard care.

Intervention

Patients in this study are treated with intravenous tociluzumab: 8 mg/kg (maximum dose 800 mg), which can be repeated at the same dose after 8 hours if the hypoxia has not improved

Study burden and risks

Allergic reactions during or after infusion can occur

Very common (incidence > 10%)
* upper respiratory tract infections with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache * high blood fat (cholesterol) levels.

Common (incidence 1-10 %)
* lung infection (pneumonia) * shingles (herpes zoster) * cold sores (oral herpes simplex), blisters * skin infection (cellulitis) sometimes with fever and chills * rash and itching, hives * allergic (hypersensitivity) reactions * eye infection (conjunctivitis) * headache, dizziness, high blood pressure * mouth ulcers, stomach pain * fluid retention (oedema) in the lower legs, weight increase * cough, shortness of breath * low white blood cell counts shown by blood tests (neutropenia, leucopenia) * abnormal liver function tests (increased transaminases) * increased bilirubin shown by blood tests * low fibrinogen levels in the blood (a protein involved in blood clotting).

Uncommon (< 1%)
* diverticulitis (fever, nausea, diarrhoea, constipation, stomach pain) * red swollen areas in the mouth * high blood fat (triglycerides) * stomach ulcer * kidney stones * underactive thyroid.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Patients 18 years and older
* Patients with a diagnosis of COVID-19 based on a compatible clinical presentation AND a positive SARS-CoV-2 PCR on a respiratory sample such as a nasopharyngeal swab, sputum, or BAL fluid
* Clinical features compatible with hyperinflammation:
- Hypoxia, without other explanation for hypoxia than COVID-19 OR
- ferritin >2000 *g/L or doubling of serum ferritin in 20-48 hours
Hypoxia is defined according to ASTCT CRS Consensus grading: grade II. [Lee DW, et al. BBMT 2019;25(4):625-638] Inclusion of patients already requiring oxygen administration prior to COVID-19 should be discussed with the study team.
* Not be pregnant
* Written informed consent.
* Patient is capable of giving informed consent.
* No known allergy to tocilizumab.

Exclusion criteria

Pregnancy

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-04-2020
Enrollment:	354
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	tocilizumab
Generic name:	tocilizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	03-04-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	14-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-05-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-05-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-07-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-09-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-01-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2020-001375-32-NL
CCMO	NL73560.042.20