COUNTER-COVID - Oral imatinib to prevent pulmonary vascular leak in Covid19 * a randomized, double-blind, placebo controlled, clinical trial in patients with severe Covid19 disease

Published: 25-03-2020
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To test whether treatment with oral imatinib reduce disease burden and consumption of medical resources.

Ethical review	Approved WMO
Status	Completed
Health condition type	Respiratory tract infections
Study type	Interventional

Summary

ID

NL-OMON49996

Source
ToetsingOnline

Brief title
CounterCovid Study

Condition

- Respiratory tract infections

Synonym
COVID-19 disease, Pulmonary edema

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: NWO/ZonMW;EU H2020 ,AMC foundation en VUmc Fonds

Intervention

Keyword: Coivd-19, Imatinib, Inflammatory vascular leak, Pulmonary edema

Outcome measures

Primary outcome

The main study parameter is the time to liberation from ventilation and

supplemental oxygen and alive during a 28 day period after randomization

Secondary outcome

- Secondary efficacy parameters

o 28-day mortality

o Need for ICU admission

o Length of ICU admission

o Need for invasive ventilation

o Days on ventilator

o Need for ECMO

o Need for non-invasive ventilation

o Length of non-invasive ventilation

o SpO2 at Day 1,2,3,4,5,7,9

o Fi O2 at Day 1,2,3,4,5,7,9

o SpO2/FiO2 at Day 1,2,3,4,5,7,9

o Length of oxygen suppletion

- Safety parameters

o Blood cell count Day 0,1,2,3,5,7,9

o Kidney function Day 0,1,2,3,5,7,9

o Liver enzymes Day 0,1,2,3,5,7,9

o NTproBNP at Day 0,1,2,3,5,7,9

o SAEs / AE

o ECG at Day 1,3,5,9

- Pharmacokinetics

o Study drug plasma levels at 4h, 8h, Day 1,3,5,7,9

o Albumin, AGP1 at Day 0,1,2,3,5,7,9

- Immune responses (subgroups of 50 patients per study arm)

o Host response plasma biomarkers on day 0, 5 and 9, and on the first day of any additional interventions (invasive ventilation, CT scanning, bronchoscopy).

o Neutrophil RNA sequencing, metabolomics and lipidomics on day 0 and 5

o Phenotypic and functional analysis of whole blood, peripheral blood mononuclear cells and polymorphonuclear leukocytes on day 0 and 5, and on the first day of additional interventions (invasive ventilation, CT scanning, bronchoscopy).

- Fibrotic responses (subgroups of 50 patients per study arm)

o Fibrotic plasma biomarkers on day 0, 5 and 9, and on the first day of any additional interventions (invasive ventilation, CT scanning, bronchoscopy)

Study description

Background summary

Covid19 is characterized by hypoxemic respiratory failure, caused by extensive vascular leak and pulmonary edema early in the course of disease. Although there is no proven therapy to reduce viral replication in Covid19, recent studies from our department have discovered that the tyrosine kinase inhibitor imatinib reinforces the endothelial barrier and prevents vascular leak in inflammatory conditions, while leaving the immune response intact. We hypothesize that reversing vascular leak is an effective approach to reduce disease burden and consumption of medical resources.

Study objective

To test whether treatment with oral imatinib reduce disease burden and consumption of medical resources.

Study design

Study design: A randomized, double-blind, placebo controlled, clinical trial.

Intervention

Intervention: The intervention group will receive a starting dose of 800mg oral imatinib once daily, followed by 400mg once daily during 9 days. The control group will receive a similar dosing schedule with a placebo.

Study burden and risks

Common side effects of imatinib include flushing, cough, flatulence, gastro-esophageal reflux, and gastritis. Relevant uncommon side effects include palpitations, cardiac failure, pleural effusion, acute renal failure, melena, chest pain and pancytopenia (although the pancytopenia was observed in patients in CML was shown to result from apoptosis of leukemic cells, and that repopulation with non-affected leucocytes was undisturbed under imatinib treatment). In general side effects are mild, and usually occur after chronic use. As the imatinib treatment in this study is relatively short (days) compared to the chronic use in CML (months-years), we anticipate that the side effects observed in CML studies are less frequent in the study proposed here. An extensive discussion of relevant side effect and imatinib toxicity is provided in the investigators brochure. Altogether, the potential benefit of preventing mechanical ventilation and reducing health care consumption outweighs the mild side effects observed in imatinib use.

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

- Age >18 years
- Hospital admission with proven SARS2-Covid19 infection
- Hypoxemic respiratory failure (SpaO2 <94% or, PaO2 <9kPa)
- Ability to give informed consent.

Exclusion criteria

- Pre-existing chronic pulmonary disease
- Former diagnosis of Interstitial pulmonary disease
- Former diagnosis of COPD 4 or FEV1<30%pred
- Previous DLCO <45%

- Total lung capacity (TLC) < 60% of predicted
- Lung cancer with non-surgical treatment in last year
- Chronic home oxygen treatment
- Pre-existing heart failure with a known left ventricular ejection fraction <40%
- Active treatment of hematological or non-hematological cancer with targeted, immuno- or chemotherapy or targeted radiotherpay in the last year
- Inability to provide informed consent
- Any subject who had received any investigational medication within 1 month prior to the start of this study or who is scheduled to receive another investigational drug during the course of this study
- Active liver disease, porphyria or elevations of serums transaminases >5 x ULN (upper limit of normal) or bilirubin > 1.5 x ULN
- History or suspicion of inability to cooperate adequately.
- White blood count < 4.0^109/l
- Hemoglobin < 6.0 mmol/l
- Thrombocytes < 100^109/l
- Pregnant femae subjects (pregnancy test will be performed in all women of childbearing age prior to inclusion)
- Breastfeeding female subjects
- Use of strong Cyp3A4 inductors, including the following drugs: Carbamazepine, efavirenz, enzalutamide, fenobarbital, fenytoine, hypericum, mitotaan, nevirapine, primidon, rifabutine, rifampicine
- Concomittant use of chloroquine or hydroxychloroquine.
- QTc >500msec at baseline.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	31-03-2020
Enrollment:	386
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	25-03-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-03-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-04-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
Other	2020-001236-10 (EUDRACT)
EudraCT	EUCTR2020-001236-10-NL
CCMO	NL73501.029.20

Study results

Date completed:	01-02-2021
Results posted:	21-07-2021
Actual enrolment:	386

First publication
17-06-2021