A multiple dosing study to demonstrate the safety, tolerability, pharmacokinetics and efficacy potential of intravenously administered ANXV (a recombinant human Annexin A5) in patients with confirmed moderate to severe COVID-19; The CO-ANNEXIN Study.

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Primary Objective:To evaluate the efficacy potential, safety and tolerability of intravenously administered ANXV, in ascending doses, and two different dosing regimens, in patients with confirmed moderate to severe COVID-19.Secondary Objectives:To...

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

Summary

ID

NL-OMON51226

Source
ToetsingOnline

Brief title
The CO-ANNEXIN STUDY

Condition

- Autoimmune disorders
- Viral infectious disorders
- Pulmonary vascular disorders

Synonym
COVID-19 pneumonia; SARS-COV-2 infection

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: 175.000,Annexin Pharmaceuticals AB

Intervention

Keyword: ANNEXIN A5, Anticoagulation, COVID-19, Immuno-thrombosis

Outcome measures

Primary outcome

Main study parameter/endpoint:

Efficacy potential:

• Assessment of activated coagulation factors in complex with antithrombin

before each ANXV administration, and at 5, 20, 90, 240 and 480 min after the

ending of each ANXV administration. Complexes are FXIa:AT, FIXa:AT and FXa:AT.

• Assessment of cytokine and inflammatory profile at baseline, at 16 and 32

hours after last ANXV administration. (CRP, IFN-*, TNF*, IL-1*, IL- 6, IL-10

and IL-18).

• Assessment of coagulation profile at baseline, and at 16 and 32 hours after

the start of the first ANXV administration. Endpoints: Absolute D-dimer -

(Fibrin Equivalent units); aPTT (Activated Partial Thromboplastin time) -

seconds; fibrinogen (g/L); INR

• Assessment of complement C5a levels at baseline, and at 16 and 32 hours after

the start of the first ANXV administration

• Assessment of the presence or absence of free histones in plasma.

• 28-day all cause mortality

• Patient free of shortness of breath (respiratory rate <20/min) and in absence of oxygen supply.

• Patient free of fever (fever > 37,50°C)

• Change from baseline in ALT and AST

• Change from baseline in lymphocyte count

• Change from baseline in neutrophil count

Frequency, intensity and seriousness of adverse events (AEs):

• Infusion reactions to IMP, including hypersensitivity or anaphylactic reactions.

• Clinically relevant changes from baseline in:

• Vital signs (blood pressure, pulse, body temperature, respiratory rate, pulse oximetry, FiO2)

• Physical examination

• Safety laboratory parameters

• ADA

• Electrocardiogram (ECG)

• Imaging (on indication, for instance in case suspicion of thromboembolic-or hemorrhagic event)

Secondary outcome

Pharmaco-kinetic parameters:

• Area under the plasma concentration vs time curve from time zero extrapolated

to infinity (AUCinf)

• AUC from time zero to time of last quantifiable analyte concentration

(AUClast)

• Observed maximum concentration (Cmax)

• Time to Cmax (Tmax)

• Terminal slope of a semi-logarithmic concentration-time curve (*z)

• Terminal half-life (T*)

• Clearance (CL)

• Volume of distribution (Vz)

• Dose proportionality after a single dose, based on AUC and Cmax

Study description

Background summary

Within the past 14 months over 3,0 million people have been reported deceased due to COVID-19, a novel clinical entity caused by severe acute respiratory syndrome due to infection with the coronavirus-2 (SARS CoV-2). No specific anti-viral treatment is available against SARS CoV-2.
We recently demonstrated that the pathogenesis of severe COVID-19 involves the innate immune system and the coagulation cascade, explaining the high incidence of thrombotic complications and vasculopathy1. The crosstalk between activated neutrophils and the coagulation cascade, also coined immuno-thrombosis, appeared to amplify thrombogenesis and injury of blood vessels.
Recently the DAMP PS has indeed been linked to the pathogenic mechanisms involved in COVID-19. Hence, PS is a promising therapeutic target for treatment of COVID-19.
Annexin A5 is a human anticoagulant protein that was discovered at the Maastricht University.
ANXV is a recombinant human Annexin A5 currently in development for treatment of acute immuno-thrombotic vascular disease, including retinal vein occlusion.
ANXV suppresses the catalytic activity of phosphatidylserine (PS). PS is exposed by activated, injured and dying cells and, thereby, functions as a danger associated molecular pattern (DAMPs), which are immunomodulatory molecules, activating proinflammatory and prothrombotic signaling cascades.

ANXV binds PS with high affinity, and thereby dampens this downstream immuno-thrombotic cascade.
We hypothesize that ANXV administered to patients with moderate to severe COVID-19 infection will prevent clinical deterioration and reduce the need for invasive ventilation, and thereby mortality. To address this hypothesis, a single centre proof of concept clinical trial is proposed to assess the safety, tolerability and efficacy potential of ANXV in hospitalised adult patients with moderate to severe COVID-19 who are receiving high flow nasal oxygen (HFNO). Observations from this study, including efficacy indicators, will be informative for and thus guide near future randomised controlled studies with multiple dosing, which will be considered immediately pending the results from this study.

Study objective

Primary Objective:
To evaluate the efficacy potential, safety and tolerability of intravenously administered ANXV, in ascending doses, and two different dosing regimens, in patients with confirmed moderate to severe COVID-19.

Secondary Objectives:
To determine the PK profile of intravenously administered ANXV, in ascending doses, and two different dosing regimens, in patients with confirmed moderate to severe COVID-19.

Study design

The trial aims to enroll 12 patients who are admitted with moderate to severe COVID-19, over a 6-month inclusion period.
It is an interventional, open-label, standard of care-controlled trial, to evaluate the safety, tolerability, pharmacokinetics and clinical efficacy of multiple intravenous dosing with ANXV, and two dosing regimens, in patients with confirmed moderate to severe COVID-19.
Recruitment takes place among the patients who are admitted to the medium care or intensive care unit of our referral hospital because of moderate to severe COVID-19. All patients for the purpose of this study are receiving high flow nasal oxygen (optiflow). After admission the treating physician will inform the patient about the study. Depending on the patient*s acceptance to hear more about this study, a member of the research or study team will further inform the patient about the outline of the study. The patient will receive a written patient information brochure and will be given a maximum of 48 hours to decide whether or not to participate.
Baseline measurements will be performed and baseline blood samples will be taken. All patients will receive optimal COVID-19 related treatment, according to the local protocol.
Directly following the completion of all baseline measurements, the first

intravenous dose of ANXV will be administered. The following doses are proposed to be tested in Cohort 1 in the study: 1 mg total dose/60 min (starting dose), 1 mg total dose/15 min, 2 mg total dose /60 min, 2 mg total dose/ 15 min. Only after the evaluation of the safety data, the study will be extended to Cohort 2 with 4 mg total dose/60 min and 4 mg total dose/15 min.
The study aims to evaluate 6 subjects in Cohort 1 and 6 subjects in Cohort 2.
As control group for we will include data from 16 subjects with moderate to severe COVID-19 wo received standard of care with no ANXV nor placebo administration. In these patients we previously collected blood samples as part of our biomarker study in COVID-19. (Annexin and extracellular histon3 are novel biomarkers for the progression of COVID-19. A bridging opportunity towards new treatment strategies. METC 2020-1325)
Safety evaluation and dose escalation will be done per subject. The starting dose will be 1 mg per subject administered intravenously as a slow (60 min), and subsequently after eight hours fast (15 min) infusion. This first and the second dose level of ANXV are expected to be well tolerated based on the NOAEL obtained in pre-clinical toxicology studies and on safety and tolerability data from in human healthy volunteers. The dose will be incrementally escalated to 6.0 mg and 8.0 mg total dose per subject, in Cohort 1 and Cohort 2, respectively.

Intervention

The first 6 consecutive patients will receive 1 mg ANXV i.v. in 60 minutes, (t=0) and 1 mg ANXVV i.v. in 15 minutes (t=8h), on day 1.
The next day these 6 patients, in case there have been no safety issues, will receive 2 mg ANXV i.v. in 60 minutes (t=0), followed by 2 mg ANXV i.v. in 15 minutes (t=8h).
In case no safety issues arise, a second cohort of 6 patients will be included. They will receive 4 mg ANXV i.v. in 60 minutes on day 1, followed by 4 mg ANXV i.v. on day 2.

Study burden and risks

The current study potentially contributes to the development of a novel and promising class of medication to treat patients with moderate to severe damage caused by the immuno-thrombotic cascade incited by the SARS-CoV-2 virus infection. ANXV is based on the cellular protein Annexin A5, that binds the danger molecule PS. Participation in this study, based on the above-mentioned mode of action of the test compound, could result (being the leading hypothesis) in dampening of the inflammatory cascade, also described as immuno-thrombosis, which in its turn may result in a better clinical outcome. However, as this is the first administration of ANXV in COVID-19 patients, the optimal dosing regimen is presently unknown. All patients will receive optimal standard care. Based on the available data, the dose of ANXV that is chosen in this study is considered safe.

During the study there will be more sampling of blood than anticipated during usual care, but the total volume of blood taken will be safe.
ANXV could potentially induce side effects, including headache, dizziness, heartburn, tremor, muscle ache and spasms.
During this study, several invasive sample collections will be performed, including blood sample collection. These measurements could be associated with local hematoma or bruise development. However, due to the state-of-the-art techniques, risks for infection or prolonged bleeding will be minimized.
All non-invasive measurements performed in this study are part of standard clinical care for patients with COVID-19, in their particular stage of disease.
Blood pressure and heart rate measurements will be performed by means of an automatic inflat-able cuff. These measurements might feel a bit uncomfortable, but do not induce detrimental health effects.

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

1. Patients hospitalized for laboratory documented SARS-CoV2 infection (qRT-PCR).
2. Males between 18 and 75 years or Females of non-reproductive age or capacity, i.e post-menopausal or sterile, and between 18 and 75 years.
3. Signed informed consent by patient
4. Hospitalized with a resting oxygen saturation on room air of <92 %, AND receiving high flow nasal oxygen.
5. Elevated LDH (>350U/L, n=97-247 U/l)
6. Mentally Competent

Exclusion criteria

1. Subject requiring mechanical ventilation/ extracorporeal membrane oxygenation and in-tubated for mechanical ventilation.
2. Severe COPD, defined by continuous use of long-acting bronchodilators or inhaled/oral corticosteroids for > 2 months in the home situation.
3. Subject with severe renal impairment (eGFR < 30 ml/min)
4. Subjects on chronic dialysis.
5. Subject with an active malignancy within the last three months, and/or a risk of mortality >50% within 6 months.
6. Bleeding Risk:
a. Clinical: Active bleeding; head trauma, intracranial surgery or stroke within 3 months; history of intracerebral arteriovenous malformation, cerebral aneurysm or mass lesions of the central nervous system; cerebral haemorrhage; history of a bleeding diatheses; gastrointestinal bleeding within 6 weeks; presence of an epidural or spinal catheter; contraindication for IV therapeutic UFH.
b. Laboratory: Platelet count <50 x109/L, INR >3.0 or baseline aPTT >=45 seconds prior to enrolment.
7. Use of any of the following treatments: UFH to treat a thrombotic event within 12 hours before enrolment; thrombolytic therapy within 3 previous days;
8. Confirmed antiphospholipid syndrome, systemic lupus erythematosus and other auto-immune diseases (at discretion of PI)
9. Confirmed thalassemias (e.g sickle cell disease)
10. Cardiopulmonary resuscitation in previous 7 days.
11. Liver failure defined as Child-Pugh Score Class C.
12. Abnormal liver function (AST >5xULN, ALT >5xULN)
13. Life expectancy of <24 hours
14. Treating physician refusal.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2021
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	not yet available
Generic name:	Annexin A5

Ethics review

Approved WMO

Date:	10-12-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	23-12-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-09-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-09-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2021-002200-12-NL
CCMO	NL77746.068.21
Other	nog niet bekend