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To study the treatment of COVID-19 with severe viral pneumonia by using purified stem cell exosomes

Submission date
03/05/2020

Recruitment status
No longer recruiting

Registration date
02/06/2020

Overall study status
Completed

Last Edited
08/06/2020

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
COVID-19 is a condition caused by the coronavirus (called SARS-CoV-2) that was first identified in late 2019. This virus can infect the respiratory (breathing) system. Some people do not have symptoms but can carry the virus and pass it on to others. People who have developed the condition may develop a fever and/or a continuous cough among other symptoms. This can develop into pneumonia. Pneumonia is a chest infection where the small air pockets of the lungs, called alveoli, fill with liquid and make it more difficult to breathe.

In 2020, the virus has spread to many countries around the world and neither a vaccine against the virus or specific treatment for COVID-19 has yet been developed. As of March 2020, it is advised that people minimize travel and social contact, and regularly wash their hands to reduce the spread of the virus.

Groups who are at a higher risk from infection with the virus, and therefore of developing COVID-19, include people aged over 70 years, people who have long-term health conditions (such as asthma or diabetes), people who have a weakened immune system and people who are pregnant. People in these groups, and people who might come into contact with them, can reduce this risk by following the up-to-date advice to reduce the spread of the virus.

COVID-19, the viral respiratory illness that results from SARS-Cov-2 infection, initially presents with mild symptoms for several days concurrent with the highest levels of viral shedding suggesting that the virus itself does not cause significant cytopathic damage.
The inflammatory damage of COVID-19 follows as the natural immune response to the virus results in the release of high levels of inflammatory mediators.
Elderly individuals are at particular risk because of their diminished immune response, reduced ability to repair the damaged epithelium, and reduced mucociliary clearance, which allows the virus to spread to the alveoli more readily.
Inflammatory mediators (cytokines and chemokines) released by type II alveolar epithelial cells increase vasodilation, leukocyte adhesion and capillary permeability.
The persistent immune response, despite falling viral titers in this inflammatory phase, leads to

progressive tissue injury, suggesting that the inflammatory damage is greater than the viral cytopathic damage. Exosomes derived from mesenchymal stem cells have the capacity to efficiently interfere with the production of inflammatory macrophages since they are specifically ingested. This exosome treatment is highly likely preferential to treat COVID-19.

Who can participate?
COVID-19 patients requiring invasive mechanical ventilation for respiratory failure due to pneumonia, or requiring treatment with vasopressors.

What does the study involve?
Participants will be randomly allocated to receive either the experimental drug or placebo and will be followed up for six months. Both the participant and the treatment team will not know which treatment has been allocated.

What are the possible benefits and risks of participating?
The possible benefits of participating in this clinical trial are improved respiration of COVID-19 disease, the shortened time needed for mechanical ventilation, improved signs of hypercytokinemia and inflammation, accelerated immune response against CoV-2 and decreased probability and severity of post COVID-19 associated lung fibrosis. The possible risks of participating in this clinical trial are: non-responsiveness or only weak response to the anti-inflammatory effects by exosome administration, and minor response patterns regarding respiration and lung fibrosis.

Where is the study run from?
Ulm University Hospital (Germany)

When is the study starting and how long is it expected to run for?
April 2020 to December 2020

Who is funding the study?
Ulm University Hospital (Germany)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2020-002326-90

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
89081

Study information

Scientific Title
Rationale and investigational study for the treatment of COVID-19 with severe viral pneumonia with isolated, placental, mesenchymal stem cell exosomes

Acronym
XoGloCoV2

Study objectives
Determine safety and efficacy of isolated, placental, mesenchymal stem cell-derived extracellular vesicles for treatment of COVID-19 viral pneumonia.
1. Reduced days of ventilation in COVID-19 patients?
2. Is the time of COVID-19 related lymphopenia less and/ or less severe?
3. Are frequencies and severities of COVID-19 associated lung fibrosis improved?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, Ethikkommission der Universität Ulm (Inst. für Geschichte, Theorie und Ethik der Medizin, Parkstraße 11, 3. OG, 89073 Ulm, Germany; +49 (0)731 500 33720; no email provided), ref: 123/20

Study design
Interventional randomized parallel trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
No participant information sheet available

Health condition(s) or problem(s) studied
Hypercytokinemia in patients with COVID-19 and severe respiratory distress syndrome (SARS) due to CoV-2 infection

Interventions
With both subject and the evaluating physician blinded, subjects will be administered the investigational drug injection and placebo (saline) injection at Visit 1 (Day 0), by a non-evaluating (unblinded) study site staff member and will be followed up and re-evaluated by a blinded evaluating physician at Visit 2 (Day 1), Visit 3 (Day 7), Visit 4 (Day 14), Visit 5 (Day 21), Visit 6 (Day 30), Visit 7 (Day 60), Visit 8 (Day 90), visit 9 (day 120), and visit 10 (day 180).
At each visit, participants (and accompanying caregivers) will be informed/reminded about study design, responsibilities, and possible adverse events.

Intervention:
Intravenous infusion of purified exosomes, XoGlo®, which are isolated, neonatal, mesenchymal stem cell-derived extracellular vesicles at a dose of 0.2 mg/kg each in a total of 15ml on day 1 and day 3.
Control:
15ml of saline, i.v. on Day 1 and Day 3

Intervention Type
Biological/Vaccine

Phase
Phase II

Drug/device/biological/vaccine name(s)
XoGlo

Primary outcome measure
1. Safety and adverse events measured using i.v. administration of 0.2mg/kg of placental, mesenchymal stem cell-derived exosome preparations (KTA 100,= XoGlo®) at day 1 and day 3
2. Improved respiration measured using PaO2/FiO2 at day 1, 2, and onwards daily

Secondary outcome measures
1. Mechanical ventilator and vasopressors treatment-free days (number of days that a patient is alive and free from mechanical ventilation and vasopressors) over 28 days.
2. Percentage of patients alive and free of mechanical ventilation at Day 29
3. Ventilator free days (VFD) over 28 days. VFD are defined as one point for each day during the measurement period that are both alive and free of mechanical ventilation.
4. Percentage of patients alive and free of vasopressors at Day 29

5. Vasopressor treatment-free days over 28 days defined as one point for each day during the measurement period that subjects are both alive and free of vasopressors.
6. Time to end of invasive mechanical ventilation
7. Time to end of invasive and/or non-invasive mechanical ventilation
8. Time to end of vasopressors treatment
9. sVP-ARDS-COVID-19 Clinical Response at Day 14±2 assessed as follows:
9.1. Cure: complete resolution of pneumonia signs and symptoms present at baseline, no new symptoms or complications attributable to the pneumonia.
9.2. Non-response: any of the following:
9.2.1. Failure related to pneumonia: Persistence/progression of baseline signs/symptoms of pneumonia; or baseline radiographic abnormalities after at least 2 days of treatment; or development of new pulmonary/extra pulmonary findings consistent with active infection, or development of new pulmonary infection or extrapulmonary infection requiring antimicrobial therapy; or persistence/progression of baseline signs/symptoms of severe sepsis; or development of new signs/symptoms of severe sepsis; or death due to sepsis
9.2.2. Failure unrelated to pneumonia: Any other cause of clinical response failure than in the investigator's judgement is unrelated to the index pneumonia (myocardial infarction, pulmonary thromboembolism, sepsis of urinary origin, etc.).
9.2.3. Indeterminate: extenuating circumstances precluding classification to one of the above
10. Clinical response at Day 8-10 and Day 29 or early discontinuation:
10.1. Time to sVP-ARDS-COVID-19 cure
10.2. Duration of antiviral treatment
10.3. Rate of pneumonia recurrence/reinfection after clinical cure
10.4. Pneumonia recurrence is defined as a new acute clinical episode of pneumonia, after clinical cure of the episode that qualified the patient for the study, based on the presence of two relevant signs (fever, tachypoea, leukocytosis, or hypoxemia) and radiographic findings of new pulmonary infiltrates or clinically significant worsening of previous ones. If a pathogen isolated in the recurrent episode is phenotypically different from the one isolated in the previous episode this will be considered as reinfection.
11. Time to recurrence/reinfection of pneumonia after clinical cure at sVP-ARDS-COVID-19 clinical response assessments.
12. Survival 28-day all-cause mortality
13. 28-day sVP-ARDS-COVID-19-associated mortality
14. Survival at Day 7, 14, 29, and 90 visits
15. Time to death
16. Time to discharge from ICU
17. Time to discharge from hospital
18. Length of stay in ICU and hospital after randomisation
19. Number of ICU-free days over 28 days
20. Changes in Sepsis-related Organ Failure
21. Assessment score daily during stay at ICU
22. Changes on chest X-ray assessed at Screening, and then as medically required with at least one CXR per sVP-ARDS-COVID-19 clinical response assessment until clinical cure from Day 1 to Day 28 and for pneumonia recurrence/reinfection assessment.
23. Evolution of partial pressure of oxygen/fraction inspired oxygen (PaO2/FiO2) daily until Day 7.
24. Need of mechanical ventilation or need for non-invasive ventilation 12 hours after the second XoGlo infusion.
25. Use of rescue antibiotics i.e. addition or change of antibiotic treatments due to the occurrence of antibiotic resistance posterior to microbiology results at baseline or insufficient efficacy during the course of the study
26. Cell responses on Day 0 Pre-dose and Days 7, 14 and 29 or early discontinuation:

26.1. Cell proliferative capacity in the presence and absence of stimulation
26.2. Cell activation status (phenotype pro/anti-inflammatory monocytes, pro/antiinflammatory T cells, HLADR, CD69)
26.3. Secretion assay of peripheral blood mononuclear cells in response to stimulation
26.4. Evaluation of RNA expression profiles of blood leukocytes on Screening, Day 0 Post-dose, Day 2, Day 3 Post-dose and Days 7 and 14 or early discontinuation (only if early termination [ET] is before V9 [Day 14]).
26.5. Evaluation of plasma concentrations of biomarkers on Screening, Day 0 Post-dose, Day 2, Day 3 Post-dose, and Days 7 and 14 or early discontinuation (only if ET is before V9 [Day 14]).
26.6. Protein biomarkers may include, but are not restricted to: TNF-α, IL-1, IL-6, IL-8, IL-10, IL-17, soluble triggering receptor expressed on myeloid cells 1, C-reactive protein, plasminogen activator inhibitor-1, protein C, sE selectin, angiopoietin-1, and angiopoietin-2, troponin-I

Overall study start date
26/04/2020

Completion date
31/12/2020

Eligibility

Key inclusion criteria
1. COVID-19 patients requiring invasive mechanical ventilation for respiratory failure due to pneumonia
2. Requiring treatment with vasopressors
3. Requiring artificial ventilation and PaO2/FiO2 < 300 mmHg

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
64

Key exclusion criteria
1. Recent administration of hydroxychloroquine, chloroquine, or steroids
2. Recent administration of tocilizumab (IL-6 antibody)
3. Hospital acquired (HAP)-, Health Care acquired (HCAP)- or Ventilator associated-pneumonia (VAP)
4. Pneumonia exclusively of bacterial or fungal origin* bacterial pneumonia co-infected with viruses and/or other microorganisms may be entered into the study. *Due to the short time window (up to 18 hours) between fulfillment of severity criteria (ie initiation of invasive mechanical ventilation or vasopressors administration, whichever comes first) and the start of the first dose of study treatment, patients with a pneumonia of suspected viral origin by any established standard diagnostic method routinely applied at the study site (eg oral swap antigen

test, rt-PCR) can be entered into the study (confirmation of viral origin must be obtained afterwards)
5. Known or suspected Pneumocystis jirovecii (formerly known as Pneumocystis carinii) pneumonia
6. Aspiration pneumonia
7. Known active tuberculosis
8. A history of post-obstructive pneumonia
9. Cystic fibrosis
10. Any chronic lung disease requiring oxygen therapy at home
11. Presence of infection in another organ location caused by same pathogen (eg
12. Pneumococcal meningitis in the context of pneumococcal pneumonia)
13. Expected to have rapidly fatal disease within 72 hours after randomization
14. Inability to maintain a mean arterial pressure 50 mmHg prior to Screening despite the presence of vasopressors and intravenous fluids
15. Not expected to survive for 3 months due to other pre-existing medical conditions such as end-stage neoplasm or other diseases
16. A history of malignancy in the 5 years prior to screening, except for successfully surgically treated non-melanoma skin malignancies
17. Known primary immunodeficiency disorder or with HIV infection and acquired immune deficiency syndrome (AIDS) with CD4 count <200 cells/mm3 or not receiving highly active antiretroviral therapy (HAART) for HIV
18. Receiving immunosuppressant therapy (including chronic treatment with anti-TNFα) or on chronic high doses of steroids (single administration of 2 mg/kg body weight or 20 mg/day of prednisone or equivalent for 2 weeks)
19. Granulocyotopenia, not due to sepsis, as evidenced by leukocyte absolute neutrophil count <500 per µL>21 days prior to onset of pneumonia symptoms
20. Received stem cell therapy, or allogeneic transplantation (organ or bone marrow transplant) within the past 6 months
21. Receiving treatment with a biological agent (eg antibodies, cells), immunotherapy or plasma exchange treatment within the last 8 weeks
22. A known liver function impairment associated with liver cirrhosis (Child Pugh C) or known esophageal varices
23. Hospitalized within the previous 15 days
24. Conditions resulting in a New York Heart Association or Canadian Cardiovascular Society Class IV functional status
25. End-stage neuromuscular disorders (eg motor neuron diseases, myasthenia gravis, etc) or cerebral disorders that impair weaning
26. Patients with quadriplegia (traumatic or otherwise)
27. Patients who have received any other investigational drugs for treatment

Date of first enrolment
01/06/2020

Date of final enrolment
31/12/2020

Locations

Countries of recruitment
Germany

Study participating centre
Ulm University Hospital
Albert-Einsgtein-Allee 23
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Sponsor information

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Kimera Labs

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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05emabm63

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Ulm University Hospital

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date

01/08/2020

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file		08/05/2020	08/06/2020	No	No