

LETTER

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Recombinant human C1 esterase inhibitor (conestat alfa) in the prevention of severe SARS-CoV-2 infection in hospitalized patients with COVID-19: A structured summary of a study protocol for a randomized, parallel-group, open-label, multi-center pilot trial (PROTECT-COVID-19)

Pascal Urwyler¹, Panteleimon Charitos¹, Stephan Moser¹, Ingmar A. F. M. Heijnen², Marten Trendelenburg^{1,3}, Reto Thoma⁴, Johannes Sumer⁴, Adrián Camacho-Ortiz⁵, Marcelo R. Bacci⁶, Lars C. Huber⁷, Melina Stüssi-Helbling⁷, Werner C. Albrich⁴, Parham Sendi^{8,9} and Michael Osthoff^{1,3*} 

Abstract

Objectives: Conestat alfa, a recombinant human C1 esterase inhibitor, is a multi-target inhibitor of inflammatory cascades including the complement, the kinin-kallikrein and the contact activation system. The study objective is to investigate the efficacy and safety of conestat alfa in improving disease severity and short-term outcome in COVID-19 patients with pulmonary disease.

Trial design: This study is an investigator-initiated, randomized (2:1 ratio), open-label, parallel-group, controlled, multi-center, phase 2a clinical trial.

Participants: This trial is conducted in 3 hospitals in Switzerland, 1 hospital in Brazil and 1 hospital in Mexico (academic and non-academic). All patients with confirmed SARS-CoV-2 infection requiring hospitalization for at least 3 calendar days for severe COVID-19 will be screened for study eligibility.

Inclusion criteria:

- Signed informed consent
- Age 18-85 years
- Evidence of pulmonary involvement on CT scan or X-ray of the chest

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* Correspondence: Michael.Osthoff@usb.ch

¹Division of Internal Medicine, University Hospital Basel, Basel, Switzerland

³Department of Clinical Research and Department of Biomedicine, University of Basel, Basel, Switzerland

Full list of author information is available at the end of the article



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- Duration of symptoms associated with COVID-19 \leq 10 days
- At least one of the following risk factors for progression to mechanical ventilation on the day of enrolment:
 - 1) Arterial hypertension
 - 2) \geq 50 years
 - 3) Obesity (BMI \geq 30 kg/m²)
 - 4) History of cardiovascular disease
 - 5) Chronic pulmonary disease
 - 6) Chronic renal disease
 - 7) C-reactive protein > 35mg/L
 - 8) Oxygen saturation at rest of \leq 94% when breathing ambient air

Exclusion criteria:

- Incapacity or inability to provide informed consent
- Contraindications to the class of drugs under investigation (C1 esterase inhibitor)
- Treatment with tocilizumab or another IL-6R or IL-6 inhibitor before enrolment
- History or suspicion of allergy to rabbits
- Pregnancy or breast feeding
- Active or anticipated treatment with any other complement inhibitor
- Liver cirrhosis (any Child-Pugh score)
- Admission to an ICU on the day or anticipated within the next 24 hours of enrolment
- Invasive or non-invasive ventilation
- Participation in another study with any investigational drug within the 30 days prior to enrolment
- Enrolment of the study investigators, their family members, employees and other closely related or dependent persons

Intervention and comparator: Patients randomized to the experimental arm will receive conestat alfa in addition to standard of care (SOC). Conestat alfa (8400 U followed by 4200 U every 8 hours) will be administered as a slow intravenous injection (5-10 minutes) over a 72-hour period (i.e. 9 administrations in total). The first conestat alfa treatment will be administered on the day of enrolment. The control group will receive SOC only. SOC treatment will be administered according to local institutional guidelines, including supplemental oxygen, antibiotics, corticosteroids, remdesivir, and anticoagulation.

Main outcomes: The primary endpoint of this trial is disease severity on day 7 after enrolment assessed by an adapted WHO Ordinal Scale for Clinical Improvement (score 0 will be omitted and score 6 and 7 will be combined) from 1 (no limitation of activities) to 7 (death).

Secondary outcomes include (i) the time to clinical improvement (time from randomization to an improvement of two points on the WHO ordinal scale or discharge from hospital) within 14 days after enrolment, (ii) the proportion of participants alive and not having required invasive or non-invasive ventilation at 14 days after enrolment and (iii) the proportion of subjects without an acute lung injury (defined by PaO₂/FiO₂ ratio of \leq 300mmHg) within 14 days after enrolment.

Exploratory outcomes include virological clearance, C1 esterase inhibitor pharmacokinetics and changes in routine laboratory parameters and inflammatory proteins.

Randomisation: Subjects will be randomised in a 2:1 ratio to treatment with conestat alfa in addition to SOC or SOC only. Randomization is performed via an interactive web response system (SecuTrial®).

Blinding (masking): In this open-label trial, participants, caregivers and outcome assessors are not blinded to group assignment.

Numbers to be randomised (sample size): We will randomise approximately 120 individuals (80 in the active treatment arm, 40 in the SOC group). Two interim analyses after 40 and 80 patients are planned according to the Pocock adjusted levels $\alpha_p = 0.0221$. The results of the interim analysis will allow adjustment of the sample size (Lehmacher, Wassmer, 1999).

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Trial Status: PROTECT-COVID-19 protocol version 3.0 (July 07 2020). Participant recruitment started on July 30 2020 in one center (Basel, Switzerland, first participant included on August 06 2020). In four of five study centers patients are actively recruited. Participation of the fifth study center (Mexico) is anticipated by mid December 2020. Completion of trial recruitment depends on the development of the SARS-CoV-2 pandemic.

Trial registration: Clinicaltrials.gov, number: [NCT04414631](https://clinicaltrials.gov/ct2/show/study/NCT04414631), registered on 4 June 2020

Full protocol: The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest of expediting dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol.

Keywords: COVID-19, randomized trial, protocol, C1 esterase inhibitor, complement system, kallikrein kinin system, contact activation system

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13063-020-04976-x>.

Additional file 1. Full Study Protocol.

Acknowledgements

Not applicable.

Authors' contributions

PU, PS, MT and MO designed the study; PU and MO drafted the first version of the study protocol, PS and MT were involved in the revision of the protocol. PU, PC, SM, IH, MT, RT, JS, ACO, MB, LH, MSH, WA, PS and MO are involved in the ongoing conduction of the study and data acquisition. PU and MO drafted the first version of this manuscript, whilst all authors intellectually contributed and revised this manuscript. All authors have read and approved the final manuscript for publication.

Funding

Supported by the Swiss National Science Foundation (SNSF) within the framework of the National Research Programme "Covid-19" (NRP 78) Grant-N° 40780_198403, an unconditional research grant including free investigational medicinal product of Pharming Biotechnologies B.V., Leiden, The Netherlands, and departmental funds of MO (University Hospital Basel). Pharming Biotechnologies B.V. was involved in the design of the study at an initial stage and in the organization of the study in Brazil and Mexico. The funders will have no role in collection, management, analysis and interpretation of the data, preparation of the manuscript, or the decision to submit the manuscript for publication.

Availability of data and materials

All co-authors will have access to the original dataset. The data will be available from the author on reasonable request by email.

Ethics approval and consent to participate

The study has been approved in Switzerland by the lead ethics committee «Ethikkommission Nordwest- und Zentralschweiz» (EKNZ) and the local ethics committees «Ethikkommission Ostschweiz» (EKOS) and «Kantonale Ethikkommission Zürich» (reference number 2020- 01252) on 07.07.2020 (https://ongoingprojects.swissethics.ch/runningProjects_list.php?q=%28PI~contains~osthoff%29&orderby=dBASECID)

The study has been approved by the National Research Ethics Commission (Comissão Nacional de Ética Em Pesquisa, CONEP) (reference number 4.284.895) on September 18 2020.

The study has been approved in Mexico by the Comisión Federal Para La Protección Contra Riesgos Sanitarios (COFEPRIS) (reference number 203301410A0200/2020) on November 03 2020.

We hereby certify that this trial has received ethical approval from the ethical committees mentioned above. We will obtain written informed consent from all participants prior to inclusion in the study. This study will be conducted in compliance with the protocol, the current version of the

Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

Consent for publication

Not applicable.

Competing interests

MT reports receiving grants from the Swiss National Science Foundation, and having research collaborations with Roche, Novartis, and Idorsia outside the submitted work.

WCA reports receiving fees and research grants from A. Vogel AG and fees for attendance of advisory boards to MSD and Vifor Pharma that were paid to his institution outside the submitted work.

MO reports receiving consulting fees from Pharming Biotechnologies B.V. during the conduct of the study and grants from Pharming Biotechnologies B.V. outside the submitted work.

LH reports receiving consulting fees from GlaxoSmithKline and Novartis during the conduct of the study but unrelated to this trial.

All other authors have declared no competing interests.

Author details

¹Division of Internal Medicine, University Hospital Basel, Basel, Switzerland. ²Division of Medical Immunology, Laboratory Medicine, University Hospital Basel, Basel, Switzerland. ³Department of Clinical Research and Department of Biomedicine, University of Basel, Basel, Switzerland. ⁴Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland. ⁵Hospital Universitario Dr. José Eleuterio González, Facultad de Medicina, Universidad Autónoma de Nuevo León, Monterrey, Mexico. ⁶Department of General Practice, Centro Universitário em Saúde do ABC, Santo André, SP, Brazil. ⁷Clinic for Internal Medicine, City Hospital Triemli, Zurich, Switzerland. ⁸Department of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland. ⁹Institute for Infectious Diseases, University of Bern, Bern, Switzerland.

Received: 8 December 2020 Accepted: 14 December 2020

Published online: 04 January 2021

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.