ISRCTN11713182 https://doi.org/10.1186/ISRCTN11713182

Testing the effectiveness of almitrine bismesylate in the treatment of COVID-19

Submission date
27/11/2020

Recruitment status
No longer recruiting

Registration date
02/12/2020

Overall study status
Completed

Last Edited
02/12/2020

Condition category
Infections and Infestations

[X] 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 April 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.
In COVID-19 some patients have difficulty transferring oxygen from lungs into the blood. This leads to low blood oxygen levels (also known as hypoxaemia). One possible reason for this difficulty in transferring oxygen is that the coronavirus might affect the way the blood vessels change their size to regulate the distribution of blood flow within the lung.
In lung diseases associated with other infections, including those caused by other viruses, a drug called almitrine has been found to improve the way the blood vessels regulate blood flow and to help the lung transfer of oxygen into the blood. It is not known whether almitrine will have this effect in COVID-19, but if it does, it may be beneficial for patients.
This study is designed primarily to see whether taking almitrine for 7 days can improve the levels of oxygen in the bloodstream of patients with COVID-19 while in hospital, and reduce the need for oxygen therapy and other forms of breathing support.

Who can participate?
Patients admitted to hospital with confirmed COVID-19

What does the study involve?
All standard COVID clinical care will be given and in addition participants will be randomly allocated to receive the study drug or placebo capsules given every 4 hours for up to 7 days. This will include doses during the night.

What are the possible benefits and risks of participating?
The major purpose of this study is to understand more about the effects of almitrine in COVID-19, in the hope that this may benefit people in the future. However, it is possible that almitrine will increase oxygen levels in the blood and help speed up recovery.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
April 2020 to September 2021

Who is funding the study?
LifeArc (UK)

Who is the main contact?
Unfortunately, this study is not recruiting public volunteers at this time. This is because the research isn't ready for volunteers yet or the researchers are directly identifying volunteers in certain areas or hospitals. Please do not contact the research team as they will not be able to respond. For more information about COVID-19 research, visit the Be Part of Research homepage.

Contact information

Type(s)
Scientific

Contact name
Dr Nick Talbot

ORCID ID
https://orcid.org/0000-0002-9186-8950

Contact details
Department of Physiology, Anatomy & Genetics
University of Oxford and Oxford University Hospitals NHS Foundation Trust
Oxford
United Kingdom
OX1 3PT

Additional identifiers

Clinical Trials Information System (CTIS)
2020-002567-57

Integrated Research Application System (IRAS)

282381

Central Portfolio Management System (CPMS)
47241

Study information

Scientific Title
To determine whether administration of almitrine bismesylate can ameliorate hypoxaemia in COVID-19 and augment the effectiveness of supplementary oxygen therapy and respiratory support

Study objectives
Between December 2019 and September 2020, over 37 million cases of coronavirus disease 2019 (COVID-19) were reported worldwide, with over 1 million deaths. Over the same period in the UK, over 143,000 patients were admitted to hospital with COVID-19, and >40,000 patients have died after testing positive for the causative virus, the majority of whom died from COVID-19 pneumonia. Although some new treatments (e.g. dexamethasone, remdesivir) have been shown to be effective in hospitalised patients (Bai et al, 2020), the mortality of moderate-severe disease remains high, and further waves of infection are expected. Additional effective therapies are urgently required.

Coronavirus disease 2019 (COVID-19) pneumonia presents with an unusual clinical picture of severe hypoxia without other features of classical acute respiratory distress syndrome (ARDS). There is growing evidence to suggest that an important and specific feature of COVID-19 is the loss of a protective physiological mechanism called hypoxic pulmonary vasoconstriction (HPV), which normally diverts blood flow away from diseased areas of the lung. Loss of this mechanism would explain the unusually severe hypoxaemia (low blood oxygen levels) that characterises COVID-19, and which often leads to a requirement for supplementary oxygen or other forms of respiratory support.

Almitrine bismesylate is the only licenced drug known to enhance HPV. It was previously licenced for the treatment of chronic obstructive pulmonary disease (COPD) and ARDS. Although its efficacy in these conditions, in which HPV may well be operating normally, are relatively modest, there is a strong rationale for believing that its effects in COVID-19 pneumonia, in which HPV appears to be impaired, would be much greater. This rationale, combined with promising case series data in patients (Losser et al, 2020, Barthelemy et al, 2020, Huette et al, 2020, Cardinale et al, 2020; Caplan et al 2020), has led to numerous calls for prospective clinical trials of this compound in COVID-19 (e.g. Archer et al, 2020; Bendjelid et al, 2020; Caplan et al, 2020).

The current trial will randomise patients with moderate to severe COVID-19 pneumonia to receive one week of oral almitrine bismesylate or placebo. The primary aim is to determine whether almitrine improves blood oxygen levels and reduces the need for respiratory support. It is funded by a major (>£400,000) award from the charity LifeArc, in recognition of the novelty of the therapeutic approach, and the potential for rapid deployment of almitrine for the treatment of COVID-19.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/11/2020, North West – Liverpool Central REC, 3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8197, +44 (0)2071048387; liverpoolcentral.rec@hra.nhs.uk), REC ref: 20/NW/0415

Primary study design
Interventional

Study design
Randomized; Interventional; Design type: Treatment, Drug

Study type(s)
Treatment

Health condition(s) or problem(s) studied
COVID-19 (SARS-CoV-2 infection)

Interventions
Design
Participants will receive an oral/via NG tube course for 7 days of the drug (56 patients) or control (56 patients) and will be studied over a 7-day period to see whether the type of respiratory support increases, stays constant, or decreases during that time period.

Participants will be approached for entry into the trial if they experiencing symptoms of COVID-19. They must fulfil the inclusion/exclusion criteria for entry. Females of childbearing potential will have to undertake a urine pregnancy test prior to inclusion. Those participants unable to consent for themselves, written consent will be sought from a legal representative. Participants will be randomised using a bespoke computer software package and will be blinded to their trial treatment along with their treating physician and all members of the trial teams. As part of the trial, participants will be asked to have blood samples taken on a daily basis for plasma almitrine levels, lactate and liver function tests for 7 days whilst on trial treatment. Participants will also have their level of respiratory support recorded.

Interventions
All participants will be given a loading oral dose of 100 mg almitrine/placebo, followed by 50 mg almitrine/placebo 4 hourly for 7 days.

Sub-study (30 participants in total): Arterial blood sampling from existing arterial catheter before drug administration and then hourly for 4 hours after drug administration (for arterial oxygen and for plasma almitrine levels).

Pharmacokinetics/dose
Physiological sub-study: Prior studies (Reyes et al, 1988; Prost et al, 1991; Esnault et al, 2019) used an intravenous infusion of either 0.25 mg/kg or 0.5 mg/kg of almitrine as a test dose in acute respiratory distress syndrome (ARDS), and then measured the response at 1 h after the start of the infusion. Using the pharmacokinetic model of Stavchansky et al (1989a) and an oral bioavailability of 0.7 (Bromet et al, 1983; Gordon, 1995), fig. 1A (ADDENDUM) illustrates that a single 100 mg oral dose of almitrine should result in a very similar plasma level to that obtained with an intravenous test dose of 0.5 mg/kg.

Main study: Although some prior studies (B'Chir et al, 1998; Esnault et al, 2019) have used higher infusion rates, Servier give an infusion rate of 2–4 µg/kg/min for the management of severe ARDS. Using the pharmacokinetic model of Stavchansky et al (1989a), an infusion at 2 µg/kg/min fairly rapidly results in plasma levels above those at which a good response in oxygenation was observed with the single test dose. This suggests the lower dose is sufficient. Fig. 1B also illustrates that a 100 mg loading dose of almitrine, followed by 50 mg 4 hourly, results in a plasma profile that reasonably mimics that of an infusion at 2 µg/kg/min.

In relation to maximum plasma levels, it is of note that even if the oral availability were 100%, simulation shows that the plasma profile remains well below that of Servier's upper 4 µg/kg/min infusion rate (the profile follows an infusion rate of ~3 µg/kg/min). Furthermore, at 1 week, the predicted plasma concentration of almitrine is still below the median measured in COPD patients (~500 ng/ml) who received chronic treatment with almitrine at the lower of two dose regimens (50 mg twice daily - the higher dose regime was 100 mg twice daily) (Stavchansky et al, 1989b).

Statistical considerations:
The primary outcome is the level of respiratory support given over the seven days of treatment. The outcome will be assessed daily using an ordinal scale. The primary analysis of this outcome will be using a mixed-effects ordinal logistic regression model. Results will be presented as a common odds ratio (from proportional odds model) over time. The primary time-point will be at 7 days. The model will include treatment arm and minimisation factors as covariates.

The same data will be additionally analysed using time-to-event approaches, by assessing both 'time-to-escalation' and 'time-to-de-escalation' by assessing changes in respiratory support with respect to the baseline level. These outcomes will be analysed using Cox Proportional Hazards models, again adjusting for treatment arm and minimisation factors. Results will be summarised with a hazard ratio, 95% confidence interval and associated p-value. The researchers will also analyse time to all-cause mortality, and time to discharge, in the same fashion.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Almitrine bismesylate

Primary outcome(s)
Level of respiratory support measured using an ordinal scale at baseline and days 1-7

Key secondary outcome(s)
1. Time to de-escalation of respiratory support, measured at baseline and days 1-7
2. Daily circulating almitrine levels measured by taking daily blood samples for storage at baseline and days 1-7
3. Mortality captured via medical records/phone follow up at 30 days

Completion date
30/09/2021

Eligibility

Key inclusion criteria
1. Hospitalised patients
2. Male or female, aged 18 and above
3. Clinically confident or proven COVID-19 disease* who require respiratory support** and who have not undergone significant de-escalation of respiratory support*** (i.e. are not in a recovery phase)
4. Female participants of childbearing potential must be willing to use effective contraception for two weeks after the final dose of IMP. Women will be advised to use a hormonal method, an intrauterine device (IUD) or intrauterine system (IUS), a barrier method or abstinence.

*A clinically confident diagnosis is made where there is either swab positivity for COVID-19, or where the clinical presentation (including any of symptoms, clinical chemistry (e.g. raised D-dimer, raised CRP) and radiology (CXR, CT or ultrasound findings)) is consistent with likely COVID-19 infection. A pre-planned subgroup analysis will compare the primary outcome for those with swab positive and "clinically likely" disease.

**At the time of recruitment, patients will be at least moderate oxygen therapy (> 4 l/min O_2 flow to mask or nasal cannulae; FiO_2 > 0.3 for Venturi mask) to maintain pulse oximeter saturation, SpO_2, in the target range set by the treating clinician. Other higher levels of oxygen support (including higher doses of oxygen, non-invasive respiratory support (continuous positive airway pressure (CPAP), high-flow nasal oxygen, or bi-level non-invasive positive pressure ventilation (NIPPV)) and invasive mechanical ventilation via an endotracheal tube can all be included, but patients are excluded if they have received > 72 hours of invasive mechanical ventilation during their current illness.

***De-escalation of respiratory support is defined as a significant reduction in respiratory support that maintains saturation within the treating physicians' target range within 24 hours of inclusion to this study. A significant reduction is any change in the mode of oxygen delivery (i.e. intubated to non-invasive ventilation, non-invasive ventilation to standard oxygen therapy, or reduction of standard "wall" oxygen of more than 3 litres/min). Changes less than this will not be considered to be significant.

Additional inclusion criteria for the physiological sub-study:
1. Arterial line in place for clinical care
2. Receiving either non-invasive respiratory support or invasive mechanical ventilation for which the inspired oxygen fraction can be measured

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Female participant who is pregnant, lactating or planning pregnancy during the course of the trial (women of childbearing potential as determined by the clinician must have a negative urine pregnancy test)
2. Pre-existing significant liver disease or a baseline AST or ALT which is >3x the upper limit of normal
3. A previously established diagnosis of significant pulmonary hypertension defined as a resting pulmonary artery pressure of >50 mmHg on right heart catheter or echocardiography
4. Received invasive mechanical ventilation for > 72 h during current illness, at the time of recruitment into the study
5. In the clinicians' view, expected to survive < 24 hours
6. Patients who, in the absence of COVID-19, would be unable to give informed consent
7. Hypersensitivity to almitrine
8. A previously established diagnosis of right ventricular dysfunction that is clinically significant in the opinion of the treating physician
9. Hyperlactataemia (lactate >2mM)

Date of first enrolment
21/12/2020

Date of final enrolment
31/03/2021

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre
Royal Berkshire NHS Foundation Trust
London Road
Reading
United Kingdom
RG1 5AN

Study participating centre
University Hospital of Wales
Heath Park Way

Cardiff
United Kingdom
CF14 4XW

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
LifeArc

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No
Protocol file	version V3.0	28/10/2020	02/12/2020	No	No