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Effect of N-acetylcysteine on COVID-19 treatment

Submission date	Recruitment status	[X] Prospectively registered
11/07/2020	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
19/07/2020	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
03/08/2020	Infections and Infestations	[_] 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.
COVID-19 mortality and morbidity are linked to cytokine storms and unregulated immune /inflammatory host response. N-acetylcysteine (NAC) has anti-inflammatory, antioxidant, antiviral, and anticoagulant and platelet-inhibiting properties and a very good safety profile. It has been widely used for more than 50 years as a prescribed drug and is approved as an over-the-counter dietary supplement. It is on the WHO list of essential medications which includes the safest and most effective medications needed in a healthcare system. It is well-tolerated, inexpensive, safe and listed in FDA- Category B for use in pregnancy. NAC could be used in the treatment and/or prevention of acute viral respiratory infections including COVID-19 but no COVID-19 specific trial has proved this yet. The aim of this study is to find out whether NAC has an effect on COVID-19 patients by reducing and regulating the inflammatory response and therefore the progression from mild/moderate to severe disease.

Who can participate?
Patients aged 18 and over, admitted to the hospital with confirmed COVID-19, (added 20/07 /2020) on oxygen therapy.

What does the study involve?
After consent is obtained from participants, they will be assigned into one of two groups, the treatment group and the control group. If they were allocated to the treatment group, the study drug prescribed will be N-acetylcysteine 150 mg/kg twice a day for 14 days, orally or into a vein (IV). If they are allocated to the control group, the study drug prescribed will be normal saline (salt water). The treating physician could decide to switch the drug to IV if it is more appropriate to their case. This is in addition to the standard treatment provided in the center to the patient's clinical needs. The patients' outcome results and the result of blood investigations, usually done during the admission, will be collected daily from hospital medical records and from the study diary during the hospital admission until the discharge.

What are the possible benefits and risks of participating?
Taking part in this study may or may not make the patient's health better and does not guarantee that patients will be COVID-19 free. While doctors hope that the results of this study may increase understanding of the disease and its treatment, there is no proof of this yet. Patients will be able to know the results of this study at the end of the study period. N-acetylcysteine is generally a safe drug. Possible side effects include pruritus, rash, urticaria (1% to 3%), diarrhea, nausea vomiting (2% to 7%), anaphylactoid reactions with IV (0.1% to 0.2%). Anaphylactoid reactions have been described with IV NAC including rash, flushing, erythema, vomiting, hypotension, wheezing and/or shortness of breath. This reaction is not considered an allergy. Acute flushing and erythema of the skin have been reported to resolve spontaneously even with continued use, However, symptoms of anaphylactoid reactions can also be treated with antihistamines or by holding the infusion until symptoms dissipate and then restart the infusion at a slower rate. Caution is advised when administering to patients with asthma or a history of bronchospasm to avoid anaphylactoid reactions. Acetylcysteine is category B in US FDA for pregnancy use (no risk shown in animal studies or non-controlled human studies). Studies testing NAC on pregnant women after 24 weeks gestation resulted in no major risk for them or their babies. Acetylcysteine crosses the placenta. It is unknown if Acetylcysteine is excreted in breast milk. Normal saline fluid is generally a safe drug. It is a medication that has been widely used for more than 150 years. It is an over the counter drug used as a dehydration treatment and it is in World Health Organization List of Essential Medications which include the safest and most effective medicines needed in a health system. There are no reported side effects. It is safe to be used during pregnancy, for lactating mothers and for children.

Where is the study run from?
1. King Saud University Medical City (Saudi Arabia)
2. Ministry of Health - Kingdom of Saudi Arabia (added 03/08/2020)
3. Ministry of Health -Sultanate Oman (added 03/08/2020)

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

Who is funding the study?
Investigator initiated, and sponsored by King Saud University Medical City (Saudi Arabia)

Who is the main contact?
Dr Baian Al-Abdulbaqi
Balabdulbaqi@ksu.edu.sa

Contact information

Type(s)
Scientific

Contact name
Dr Baian Alabdulbaqi

ORCID ID
http://orcid.org/0000-0003-3153-1915

Contact details
Riyadh
Riyadh
Saudi Arabia
678354040
+966 (0)14671079
Balabdulbaqi@ksu.edu

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
NCT04455243

Secondary identifying numbers
E-20-4934

Study information

Scientific Title
Inflammatory regulation effect of N-acetylcysteine on COVID-19 treatment, pilot, double blinded randomized placebo controlled multicenter clinical trial

Acronym
INFECT-19

Study objectives
Early use of N-acetylcysteine (NAC) in COVID-19 patients would play a favorable role in reducing and regulating the inflammatory response and therefore the progression from mild/moderate to severe disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 30/06/2020 by King Saud University Medical City Institutional Review Board (3rd Floor Room 317, Block 22 (near Theatre C), King Saud University College of Medicine and King

Khalid University Hospital, PO Box 7805 Riyadh, 11472 K.S.A.; +966 (0)11 469 1531; +966 (0)11 469 1532; rdeocampo@ksu.edu.sa; irb.medksu@hotmail.com), ref: E-20-4934
2. Approved 20/07/2020, Ministry of Health - Kingdom of Saudi Arabia-Central Institutional Review Board (PO Box 7805 Riyadh, 11472 K.S.A; +966 (0)11 212 5555 ext 4337 1; haziz@moh.gov.sa), ref: E-20-146E
3. Approved 20/07/2020, Ministry of Health - Sultanate Oman Research and ethical review and approval center (PO Box 393, Postal Code 100, Muscat, Oman; +968 22357254; mohrerac@gmail.com), ref: MOH/CSR/20/23522

Study design
Adaptive pilot double-blinded randomized placebo-controlled multi-center clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please contact Directctu@ksu.edu.sa to request a participant information sheet

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

Interventions
Randomization will be stratified by:
1. Center
2. COVID-19 clinical severity stage
Allocation to the intervention group and the control group will be in a 1:1 ratio. Randomization will be blocked in a randomly permuted block size.

The intervention group will receive N-Acetylcysteine (NAC) 150 mg/kg every 12 hours for 14 days of admission in addition to the standard of care.
The primary route is oral, but the treating team has the option to start or switch to IV Infusion over 1 hour if:
1. The patient can’t tolerate orally.
2. The patient is in shock and gastrointestinal absorption is thought to be impaired.

The control group will receive matching normal saline placebo administered in the same schedule and volume as NAC in addition to the standard of care implemented in the hospitals for COVID-19 management.

Participants will be followed until they are discharged. No specific laboratory/radiological investigation is required. The result of their usual lab, symptoms progression, clinical severity and outcomes will be collected on a daily basis during hospitalization until discharge.

Intervention Type
Drug

Phase
Phase III/IV

Drug/device/biological/vaccine name(s)
N-Acetylcysteine (NAC)

Primary outcome measure
Time to recovery: day of recovery is defined as the first day on which one of the following three categories from the Ordinal scale on clinical improvement per WHO blueprint in COVID-19 therapeutic trials:
1. Hospitalized, not requiring supplemental oxygen
2. Not hospitalized, limitation on activities and/or requiring home oxygen
3. Not hospitalized, no limitations on activities
Measured using patient's medical records until discharge

Secondary outcome measures
Measured using patient's medical records until discharge, unless stated otherwise:
1. Improvement of clinical severity assessed using an ordinal scale:
1.1. Time to an improvement of one category from Day 1
1.2. Time to an improvement of two categories from Day 1
1.3. Mean change in the ordinal scale from Day 1 to Days 3
1.4. Mean change in the ordinal scale from Day 1 to Days 5
1.5. Mean change in the ordinal scale from Day 1 to Days 7
1.6. Mean change in the ordinal scale from Day 1 to Days 14
1.7. Mean change in the ordinal scale from Day 1 to Days 28
1.8. Mean change in the ordinal scale from Day 1 to discharge
2. Oxygenation needs during hospital admission:
2.1. Duration in days of supplemental oxygen
2.2. Incidence of non-invasive ventilation/high flow oxygen
2.3. Duration in days of non-invasive/high flow oxygen
2.4. Incidence of invasive mechanical ventilation
2.5. Duration in days of invasive mechanical ventilation
3. End organ damage during hospital admission:
3.1. Incidence of pressor
3.2. Duration in days of pressor
3.3. Incidence of HD
3.4. Duration in days of HD
3.5. Incidence ECMO
3.6. Duration in days of ECMO
4. Symptoms duration in days up to discharge
5. Time to first negative PCR test result in days
6. Improvement of inflammatory markers
3. Days of hospitalization

4. Incidence and duration of ICU admission
5. Mortality: the number and percentage of participants who die by day 28, will be presented by treatment arm (denominator for the percentages will be the number of participants in the safety population in each treatment arm)

Overall study start date
21/03/2020

Completion date
01/10/2021

Eligibility

Key inclusion criteria
1. Adults (above 18 years)
2. Admitted to the hospital
3. Confirmed COVID-19 patient by RT-PCR test from any specimen (nasal, throat swab, sputum, etc)
4. On oxygen supplement (Category 4, 5, 6, 7 on the ordinal scale)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
1180

Key exclusion criteria
1. Active indication and use of NAC
2. Known allergy to NAC
3. In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of provision of treatment e.g. patients on ECMO at time of randomization
4. Patients enrolled in other investigational drug studies are not eligible for our study

Date of first enrolment
01/09/2020

Date of final enrolment
01/09/2021

Locations

Countries of recruitment
Oman

Saudi Arabia

Study participating centre
King Saud University Medical City
Alderiya
PO Box 7805
Riyadh
Saudi Arabia
11472

Study participating centre
Ministry of Health - Kingdom of Saudi Arabia
PO Box 7805
Riyadh
Saudi Arabia
11472

Study participating centre
Ministry of Health -Sultanate Oman
Muscat
Oman
100

Sponsor information

Organisation
King Saud Medical City

Sponsor details
King Saud University Medical City
Riyadh
Saudi Arabia
PO Box 7805, Riyadh 11472
+966 (0)543333281
directctu@ksu.edu.sa

Sponsor type
Hospital/treatment centre

Website
https://medicalcity.ksu.edu.sa/en

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Prince Naif Bin Abdulaziz Health Research Center

Results and Publications

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

Intention to publish date
01/10/2022

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Baian Alabdulbaqi (balabdulbaqi@ksu.edu.sa). All of the individual participant data collected during the trial, after identification, will be available immediately following publication with no end date and can be used for any purpose.
Analysis Plan, Informed Consent Form, Clinical Study Report, and Analytic Code will be available for anyone who wishes to access the data.

IPD sharing plan summary
Available on request