ISRCTN16059833 https://doi.org/10.1186/ISRCTN16059833

Investigating the effect of azithromycin on gullet function in patients with long-term respiratory disease

Submission date
16/09/2022

Recruitment status
No longer recruiting

Registration date
16/12/2022

Overall study status
Completed

Last Edited
19/06/2024

Condition category
Respiratory

[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
Symptoms such as cough, wheeze, and breathlessness are among the most common reasons for patients to visit their general practitioner or emergency department in the United Kingdom, accounting for up to 20% of healthcare visits. Such symptoms are known to have a profound impact on the ability of such patients to live a fulfilled life, as they can often render people unable to work and socialise. Patients are often left with lasting symptoms despite being treated with all currently recommended therapies, suggesting that there is ample reason to keep searching for new treatments for patients with chronic lung disease.

Azithromycin is a type of antibiotic which has been found to improve symptoms and reduce flare-ups of common diseases such as asthma and chronic obstructive pulmonary disease (COPD). The reason why it works is still unclear. Many people believe in one of two theories, either that it decreases the number of bacteria in the lungs or that it reduces inflammation in the lungs and the upper airways. Neither of these theories is proven and there has been a different mechanism suggested, although it has been much less studied. Azithromycin is thought to encourage the body to move food and fluid through the gut more quickly, and this may help to prevent small food particles and stomach to reflux into the airways. It has been shown that lung damage can occur when gut contents enter the airways, which may contribute to the symptoms of patients with chronic lung disease.

Who can participate?
Adult patients diagnosed with a respiratory condition

What does the study involve?
In this study, we will test the effect of azithromycin on the gut in patients with chronic lung diseases. We will measure the strength of a patient's swallow by measuring the pressures in their gullet, using high-resolution oesophageal manometry (HROM), before and after treatment, in people being started on azithromycin as part of their routine care. We will also measure the effect that azithromycin has on their symptoms and observe whether there is a relationship between the strength of their swallow and their symptoms.

At the end of this study, we will hope to better understand the way in which azithromycin helps to improve the symptoms of patients with chronic lung diseases. We also hope to open the door to investigating the effect of other drugs that improve gut function in patients with chronic lung diseases.

What are the possible benefits and risks of participating?
There will be the inconvenience of travelling to the clinical trials unit on 3 separate occasions, we will attempt to assuage this by offering a broad range of time options for participants to attend and helping them with travel arrangements whenever possible. Travel expenses will be reimbursed for up to £10 per study visit.

HROM is generally seen as an uncomfortable procedure and can sometimes give patients a runny nose or sore throat, advice will be given to help these symptoms. The investigations will be carried out by expert technicians with many years of experience, minimising any risks.

We will be asking participants to carry around a mobile cough recording device, either a smartwatch or a dedicated mobile phone device, which may be cumbersome. We endeavour to provide all participants with smartwatches as this will minimise the impact on participants' daily lives. We will give all participants training in how to use and carry the devices in order for them to be as discrete as possible to minimise the interruption to their normal daily life.

Where is the study run from?
Hull University Teaching Hospitals NHS Trust, Castle Hill Hospital (United Kingdom)

When is the study starting and how long is it expected to run for?
September 2022 to August 2024

Who is funding the study?
Hull University Teaching Hospitals NHS Trust (United Kingdom)

Who is the main contact?
Dr Dominic Sykes, dominic.sykes2@nhs.net

Contact information

Type(s)
Scientific

Contact name
Dr James Illingworth

Contact details
R&D
First floor
Castle Hill Hospital
Cottingham
United Kingdom
HU16 5JQ
+44 (0)1482 461903 77
james.illingworth3@nhs.net

Type(s)
Scientific

Contact name
Dr Dominic Sykes

Contact details
Academic Respiratory medicine
Daisy Building
Castle Hill Hospital
Cottingham
United Kingdom
HU16 5JQ
+44 (0)1482 461795 77
dominic.sykes2@nhs.net

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1006318

ClinicalTrials.gov number
NCT05469555

Secondary identifying numbers
IRAS 1006318

Study information

Scientific Title
Exploring the effect of azithromycin on oesophageal motility and respiratory symptoms in patients with chronic respiratory disease: a prospective observational study

Study objectives
Azithromycin (an antibiotic) improves symptoms and reduces flare-ups of diseases such as asthma and chronic obstructive pulmonary disease (COPD). The reason why it works is unclear. Many people believe that it either decreases the number of bacteria in the lungs or reduces inflammation in the lungs and the upper airways. Neither theory is proven. Another possible mechanism that has been much less studied is that azithromycin encourages the body to move food and fluid through the gut more quickly, thus preventing reflux and aspiration of small food particles and stomach acid. It has been shown that lung damage can occur when gut contents enter the airways, which may contribute to chronic lung disease patients' symptoms

In this study, we will test the effect of azithromycin on the gut in patients with chronic lung diseases. We will measure the strength of a patient's swallow by measuring the pressures in their gullet, using high-resolution oesophageal manometry (HROM), before and after

To display the effect of azithromycin on symptoms in patients with chronic respiratory disease and how this relates to an improvement in oesophageal function.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 15/12/2022, MHRA (10 South Colonnade, Canary Wharf, London, E14 4PU, UK; +44 (0)20 3080 6000; info@mhra.gov.uk), ref: CTA 21411/0261/001-0001
2. Approved 15/12/2022, North East - Newcastle & North Tyneside 2 Research Ethics Committee (NHS BT Blood Donor Centre, Holland Drive, Newcastle upon Tyne, Tyne and Wear, NE2 4NQ, UK; +44 (0)2071048086, (0)2071048140; newcastlenorthtyneside2.rec@hra.nhs.uk), ref: 22/NE/0194

Study design
Randomized controlled study

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 use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Ashtma, cough, lung fibrosis, COPD

Interventions
All patients who are being started on azithromycin as part of routine clinical care will be investigated with high-resolution oesophageal manometry prior to the commencement of azithromycin. All patients will then receive 1 month of azithromycin 250 mg OD treatment before having a second high-resolution oesophageal manometry investigation performed. At that point, participation in the trial is finished.

Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome measure

1. Eligibility to consent ratio, defined as the ratio of participants deemed eligible to participate in the study to the number of those who provide consent to take part, measured using an examination of recruitment records i.e. looking at how many patients were approached to how many patients provided informed consent at 1 year
2. Recruitment rate, defined as the number of participants successfully recruited per month, measured using recruitment records i.e. looking at how many patients were recruited to the study each month at 1 year
3. Participant retention to follow-up, defined as the proportion of those participants who consent to take part that complete all study measures to follow-up, measured using the patient database and recording how many patients completed all study measures to 30 days at 1 year
4. Acceptability of assessment, defined as the proportion of participants who judge the study investigations, principally high-resolution oesophageal manometry (HROM), to be acceptable measured using the study experience questionnaire at 1 year

Secondary outcome measures

1. Distal contractile integrity, defined as the effect of azithromycin on the contraction vigour and swallow coordination, measured using high-resolution oesophageal manometry (HROM) before and 1 month after initiation of azithromycin as part of routine clinical care. Measured in mmHg/sec/cm.
2. Lower oesophageal sphincter pressure, defined as the effect of azithromycin on the pressure of the lower oesophageal sphincter as measured using HROM before and 1 month after initiation of azithromycin as part of routine clinical care. Measured in mmHg.
3. Distal latency, defined as the effect of azithromycin on the timeframe of the wave from the beginning of the swallow to an inflection of the peristaltic axis, measured using HROM before and 1 month after initiation of azithromycin as part of routine clinical care. Measured in seconds.
4. Integrated relaxation pressure, defined as the effect of azithromycin on the oesophageal pressure topography metric that is used for assessing the adequacy of oesophagogastric junction relaxation, measured using HROM before and 1 month after initiation of azithromycin as part of routine clinical care. Measured in seconds.
5. Chicago Classification version 4.0, defined as a composite classification based on all HROM measurements at 1 month
6. Symptoms of reflux measured using the Hull Airway Reflux questionnaire, a Likert scale questionnaire at 1 month
7. Symptom burden measured using a 5-point Likert validated tool assessing breathlessness, cough, and sputum scale at 1 month
8. Breathlessness measured using the MRC dyspnoea scale at 1 month
9. Cough severity measured using a visual analogue scale at 1 month
10. Symptom burden measured using a COPD Assessment test (COPD patients only) at 1 month
11. Symptom burden measured using an Asthma control questionnaire (asthma patients only) at 1 month
12. Breathlessness severity measured using a Numerical rating scale at 1 month
13. Impact of cough on physical, social, and psychological welfare of the patient measured using the Leicester Cough Questionnaire at 1 month
14. Impact of overall health, daily life, and well-being in patients with obstructive airways disease measured using the St. George's Respiratory Questionnaire at 1 month
15. Impact of interstitial lung disease on quality of life and health status measured using the King's Brief Interstitial Lung Disease Questionnaire (interstitial lung disease patients only) at 1

month
16. Relationship between oesophageal motility and symptoms examined measured using statistical analysis at 1 month

Overall study start date
13/09/2022

Completion date
01/08/2024

Eligibility

Key inclusion criteria
1. Males and females aged ≥18 years
2. Have a diagnosis of chronic respiratory disease (COPD, asthma, interstitial lung disease, chronic cough, cystic fibrosis, and/or bronchiectasis) confirmed by a respiratory consultant
3. Exhibit symptoms consistent with airway reflux, demonstrated by a score ≥14 on the Hull Airways Reflux Questionnaire
4. Are being initiated on azithromycin as part of routine clinical care, as judged by their usual respiratory clinician. This will include all common treatment regimes, 250mg once daily, 250mg three times per week, and 500mg three time per week.
5. Are willing and able to consent to all study procedures

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
30

Total final enrolment
30

Key exclusion criteria
1. Previous treatment with long-term macrolides in the past 3 months
2. Unable to be investigated with HROM due to contraindications such as anatomical abnormalities or diseases of the oesophagus or unwilling/ unable to be investigated with HROM based on the clinical judgement of the investigators due to the severity of lung disease
3. Have another cardiorespiratory cause for their symptoms (such as heart failure or lung cancer)
4. Women of childbearing potential not using effective means of contraception
5. Are unable or unwilling to consent to or complete the study procedures

Date of first enrolment
06/01/2023

Date of final enrolment
07/05/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Castle Hill Hospital
Castle Road
Cottingham
United Kingdom
HU16 5JQ

Sponsor information

Organisation
Hull University Teaching Hospitals NHS Trust

Sponsor details
1st floor
Daisy building
Castle Hill Hospital
Cottingham
England
United Kingdom
HU16 5JQ
+44 (0)1482 461903
hyp-tr.development.research@nhs.net

Sponsor type
Hospital/treatment centre

Website
http://www.nhs.uk/Services/hospitals/Overview/DefaultView.aspx?id=1998

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Hull University Teaching Hospitals NHS Trust

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Conference presentation
3. Primary data will be anonymised and will be available on request

Intention to publish date
01/10/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from:
Dominic Sykes
dominic.sykes2@nhs.net
Excel file
Shared with any research professionals by Dr Dominic Sykes.
For secondary analysis or as part of meta-analyses.
All data will be anonymised.
No ethical or legal restrictions.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 4	18/01/2023	11/12/2023	No	No