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Understanding the effect of mepolizumab treatment on brain imaging and wellbeing in patients with severe asthma

Submission date 30/10/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 04/12/2023	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 23/04/2025	**Condition category** Respiratory	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
Many people with severe asthma experience anxiety, depression and problems with their thinking, which can affect a person's well-being. The relationship between asthma and these other factors is not understood. Uncontrolled asthma and medications might cause psychological problems, whilst mental health issues might make asthma worse.

Magnetic resonance imaging (MRI) scans have shown differences in brain structure and function between people with and without asthma. The extent of these changes seems to relate to the severity and control of a person’s asthma. A small number of studies have suggested that psychological treatments for people with asthma and depression can improve brain function. The full effects of asthma treatments on the brain require further investigation.

Mepolizumab is one of a group of new injectable asthma treatments that dramatically improves asthma control in 60% of people who are eligible for it. It reduces asthma flare-ups and the need for tablet steroids. It also improves asthma-related quality of life, but its effects on mental health and the brain have not been well studied.

This study aims to establish whether mepolizumab treatment improves the structure and function of patients' brains, whether mepolizumab treatment affects mental health and well-being and whether these effects are due directly to the mepolizumab, or secondary effects of improved asthma control.

Who can participate?
Patients aged 18+ with severe eosinophilic asthma due to start mepolizumab treatment. In addition, there will be a control group of patients aged 18+ with well-controlled mild-moderate asthma.

What does the study involve?
The study will involve completing approximately 45 minutes of questionnaires that will assess levels of anxiety, depression, well-being, sleep quality and cognition. Half of the patients will

have an MRI scan of the brain, which will assess both structure and function. The results of routinely collected data for patients with severe asthma will be recorded. For the control group, these data will not be available, so those patients will be asked questions related to their medical history, complete lung function tests and have a blood test. Patients who are starting mepolizumab will repeat the above measures after six months of treatment.

What are the possible benefits and risks of participating?
There are no direct personal benefits to participating in the study. Participants will be renumerated for their travel and time taken to complete the study. The output of the study is expected to improve the understanding of the interaction between asthma control and mental health issues, which could benefit many people with asthma in the future.

There are no significant risks of taking part in the study. Some people can feel claustrophobic in the MRI scanner, though not all participants need to have an MRI scan. Occasionally there is something seen on the MRI scan that requires further tests, in which case we will make arrangements for this.

Where is the study run from?
The University of Bristol Academic Respiratory Unit, North Bristol NHS Trust (UK)

When is the study starting and how long is it expected to run for?
September 2022 to November 2025

Who is funding the study?
GlaxoSmithKline

Who is the main contact?
Associate Professor James Dodd, James.dodd@nbt.nhs.uk

Contact information

Type(s)
Public

Contact name
Dr George Nava

Contact details
Airways Disease Clinical Research Fellow
North Bristol NHS Trust
2nd Floor, Learning and Research
Southmead Hospital
Bristol
United Kingdom
BS10 5NB
+44 (0)1174148040
pw20082@bristol.ac.uk

Type(s)
Scientific, Principal Investigator

Contact name
Dr James Dodd

ORCID ID
http://orcid.org/0000-0003-4805-5759

Contact details
Associate Professor of Respiratory Medicine & Honorary Consultant Respiratory Physician
Academic Respiratory Unit
University of Bristol
Learning and Research Building, Second Floor
Southmead Hospital
Bristol
United Kingdom
BS10 5NB
+44 (0)117 414 8114
james.dodd@nbt.nhs.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
328150

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 58072, IRAS 328150

Study information

Scientific Title
CONTENTed study: Characterisation Of Neuroimaging and wellbeing over Time in severe EosiNophilic asthma Treated with mepolizumab

Acronym
CONTENTed

Study objectives
Six months of mepolizumab treatment for severe eosinophilic asthma will improve brain tissue microstructure, resting functional activity, patient cognition and well-being.

Ethics approval required
Ethics approval required

Ethics approval(s)

Approved 10/10/2023, East Midlands- Leicester Central Research Ethics committee (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; None provided; leicestercentral.rec@hra.nhs.uk), ref: 23/EM/0195

Study design
Observational case-controlled study

Primary study design
Observational

Secondary study design
Case-control study

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Asthma

Interventions
This is a prospective observational study, which will use routinely collected data, enhanced with brain magnetic resonance imaging (MRI) and additional measures of cognition and well-being to address our primary question. Structural and functional brain MRI scans will be performed on 50 patients with severe eosinophilic asthma (SEA) before and six months after starting mepolizumab treatment. The null hypothesis is that there will be no difference in the brain images seen between these two-time points. Due to the large treatment effects of mepolizumab that are seen in patients with SEA, our alternative hypothesis is that brain imaging will change after six months of treatment.

There will be a control group of 25 patients with mild-moderate well-controlled asthma who will undergo brain imaging once only. This will allow us to understand whether there are imaging changes that are specific to those with severe asthma, and control for differences between healthy controls and patients with asthma that are not specific to SEA (for instance, the use of inhaled corticosteroids). Their imaging will also act as a proxy for disease remission (i.e. a therapeutic target). Mepolizumab is an important, established treatment for SEA and therefore constructing an interventional placebo-controlled study would be unethical.

In addition to the MRI study, participants will complete a series of psychological and neurocognitive assessments, and we will collect routine clinical data during their visits. This will allow us to interrogate the underlying mechanisms of any changes to the MR imaging that we discover. An additional 50 patients in the SEA group and 25 patients in the control (mild-moderate asthma) group will be recruited to complete the questionnaires and will have their clinical data collected.

Case selection: The normal clinical pathway is that patients with SEA are reviewed at the North Bristol NHS Trust (NBT) weekly complex airways clinic. From this clinic, patients will be referred to the regional Complex Airways Multidisciplinary Meeting (CAMDT) for consideration of mepolizumab therapy. If confirmed for mepolizumab, a face-to-face pre-biologic clinic appointment is arranged with the asthma specialist nursing team. Patients identified as eligible for mepolizumab therapy will be introduced to the CONTENTed study at the complex airways clinic and provided with a Participant Information Sheet (PIS). After MDT, if a decision is made to commence mepolizumab, patients will be contacted by telephone to inform them of this and will be asked if they would like to take part in the CONTENTed study in addition.

Participants will be offered the option to enter the full study, including MRI studies, or to only complete the pre- and post-mepolizumab questionnaires. If they opt to be included in the full study, an appointment will be arranged for them to attend for the MRI prior to their first mepolizumab dose. An MRI safety checklist will be completed by telephone prior to this to ensure eligibility. An electronic or telephone consent will be completed prior to the MRI appointment if a researcher cannot be present for the MRI scan. If an MRI appointment cannot be arranged prior to their first mepolizumab dose, they will be removed from the MRI arm of the study, but continue with the questionnaires. MRI enrolment will stop at 50 Cases.

Patients will attend their standard of care pre-biologic clinic, at which point they will also complete a written consent for the study if they were not in the MRI arm, and complete the questionnaires.

Participants will be followed up at a six-month mepolizumab review as part of routine clinical care, with repeated lung function. As part of the study, they will repeat their questionnaires +/- MRI brain.

Controls: Patients with mild-to-moderate well-controlled asthma will be identified through advertising in different locations including, North Bristol NHS Trust (NBT), University of Bristol staff and students, NBT outpatients and local GP practices.

Potential participants will be asked to contact us by email or telephone to arrange a screening appointment by telephone. A PIS will be sent digitally or posted to participants prior to this appointment according to patient preference. Enrolled participants will be invited to an appointment at Southmead Hospital at which they will complete the consent form, demographic and clinical details, the study questionnaires, lung function and a blood test for eosinophil count. Those opting to undergo the MRI brain will be provided with an appointment at UHBW for the MRI scan in addition to other study procedures. There will be no follow-up.

Intervention Type
Other

Phase
Not Specified

Primary outcome measure
Brain microstructural imaging (quasi-diffusion) measured with a magnetic resonance imaging brain scan at baseline (case and control) and after 6 months of mepolizumab treatment (case only)

Secondary outcome measures

The following secondary outcome measures will be assessed at baseline (case and control) and after 6 months of mepolizumab treatment (case only):

1. Resting-state functional MRI network measured using an MRI brain scan

2. Routine clinical measures:
2.1. Asthma exacerbation frequency/hospitalisation/intensive care unit admission measured using data extracted from medical records as an annualised frequency
2.2. Oral corticosteroid use, current and past measured using data extracted from medical records as annualised exacerbation frequency and total steroid burden
2.3. Asthma medication use measured using data extracted from medical records as changes to asthma medication over the 6-month period for Cases
2.4. FEV1 and FVC measured using spirometry
2.5. Airway inflammation measured using fractional exhaled nitric oxide
2.6. Blood eosinophil count measured using a blood test and standard laboratory methods
2.7. Side effects of mepolizumab and glucocorticoids measured using data extracted from medical records as the frequency of incidents reported by the patient

3. Cognitive, wellbeing and symptom perception scores:
3.1. Asthma control measured using the Asthma Control Questionnaire (ACQ-7)
3.2. Asthma-related quality of life measured using the Mini Asthma Quality of Life Questionnaire (Mini AQLQ)
3.3. Wellbeing measured using the Warwick-Edinburgh mental wellbeing scale
3.4. Depression measured using the Patient Health Questionnaire (PHQ-9)
3.5. Anxiety measured using the Generalised Anxiety Disorder Assessment (GAD-7)
3.6. Dyspnoa experience measured using the Multidimensional Dyspnea Profile (MDP)
3.7. Impact of the well-being of obstructive lung disease measured using the St George's Respiratory Questionnaire (SGRQ)
3.8. Cognition measured using the Montreal Cognitive Assessment (MoCA)
3.9. Illness perception measured using the Brief Illness Perception Questionnaire (Brief IPQ)
3.10. Sleep quality measured using the Athens Insomnia Scale (AIS)

Overall study start date
01/09/2022

Completion date
30/11/2025

Eligibility

Key inclusion criteria
Cases:
1. Aged 18+ years
2. Physician-diagnosed severe eosinophilic asthma eligible for mepolizumab therapy as per National Institute for Health and Care Excellence guidance 2017, satisfying one of the following criteria:
2.1. Peripheral blood eosinophils ≥300 cells per microlitre, with ≥4 exacerbations requiring oral corticosteroids in the previous 12 months or continuous oral corticosteroids of at least the equivalent of prednisolone 5 milligrams per day over the previous 6 months
2.2. Peripheral blood eosinophils ≥400 cells per microlitre, with ≥3 exacerbations requiring oral corticosteroids in the previous 12 months or continuous oral corticosteroids of at least the

equivalent of prednisolone 5 milligrams per day over the previous 6 months
3. A regional asthma MDT decision was made to start mepolizumab
4. The patient agrees to start mepolizumab and is able to provide written informed consent and participate in the study

Controls:
1. Aged 18+
2. Physician-diagnosed mild or moderate asthma for >3 months, GINA step 2-4
3. Well-controlled asthma defined by an Asthma Control Questionnaire–5 (ACQ-5) =/< 1.5
4. Participant is willing and able to give informed consent to take part in the study

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 150; UK Sample Size: 150

Key exclusion criteria
Cases
1. Current smoking, or a greater than 10 pack-year history of smoking in ex-smokers.
2. A diagnosis of an alternative lung disease, including, but not limited to, allergic bronchopulmonary aspergillosis, eosinophilic granulomatous polyangiitis, bronchiectasis or chronic obstructive pulmonary disease.
3. Previous anti-asthma biological therapies including mepolizumab, benralizumab, omalizumab, reslizumab and dupilimab.
4. Pregnancy/childbearing age not using contraception.
5. Alcohol and drug addiction.
6. CNS diseases the investigators consider would have a significant effect on outcomes – including stroke, MS, epilepsy, tumour or significant cognitive impairment (including dementia, or severe learning disabilities).
7. Participants with contraindications to MRI will not be able to take part in the MRI study, but can be recruited to complete the questionnaires.
8. Contraindications to completing pulmonary function tests.

Controls
1. Oral corticosteroid use in the last 3 months, or ≥3 oral corticosteroid courses in the last 12 months.
2. Current smoking, or a greater than 10 pack-year history of smoking in ex-smokers.
3. A diagnosis of an alternative lung disease, including, but not limited to, allergic bronchopulmonary aspergillosis, eosinophilic granulomatous polyangiitis, bronchiectasis, chronic obstructive pulmonary disease or interstitial lung disease.
4. Previous anti-asthma biological therapies including mepolizumab, benralizumab, omalizumab,

reslizumab, dupilumab or tezepelumab.
5. Pregnancy/childbearing age not using contraception.
6. Alcohol and drug addiction.
7. CNS diseases the investigators consider would have a significant effect on outcomes – including stroke, MS, epilepsy, tumour or significant cognitive impairment (including dementia, or severe learning disabilities).
8. Participants with contraindications to MRI will not be able to take part in the MRI study, but can be recruited to complete the questionnaires.
9. Contraindications to completing pulmonary function tests.

Date of first enrolment
05/12/2023

Date of final enrolment
31/05/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
North Bristol NHS Trust
Southmead Hospital
Southmead Road
Westbury-on-trym
Bristol
United Kingdom
BS10 5NB

Sponsor information

Organisation
North Bristol NHS Trust

Sponsor details
Research and Innovation
Level 3, Learning and Research Building
Southmead Hospital
Westbury-on-Trym
Bristol
England
United Kingdom
BS10 5NB

+44 (0)1174149330
researchsponsor@nbt.nhs.uk

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/036x6gt55

Funder(s)

Funder type
Industry

Funder Name
GlaxoSmithKline

Alternative Name(s)
GlaxoSmithKline plc., GSK plc., GSK

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned presentation at an international respiratory conference and publication in a high-impact peer-reviewed journal

Intention to publish date
30/05/2026

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