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Switching off leakage and inflammation in small brain blood vessels

Submission date 24/09/2018	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 01/10/2018	**Overall study status** Completed	
Last Edited 18/04/2024	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
Cerebral small vessel disease (abnormalities related to small blood vessels in the brain) is a major cause of stroke and dementia in the UK. The causes of progression of the disease are not completely understood. Recently leakiness of the blood brain barrier has been proposed as a mechanism, which itself may cause inflammation of the brain. If we can understand what causes progression of the disease it may be possible to target treatments to reduce these processes and, therefore, progression. A previous study showed that differences between patients and healthy people can be detected in both blood brain barrier leakiness and neuroinflammation (inflammation of the nervous tissue). The aim of this study is to assess whether minocycline, an antibiotic which has been shown to inhibit the processes that cause inflammation and leakiness in animals, can have the same effect in humans.

Who can participate?
Patients aged 18 years and over with small vessel disease

What does the study involve?
Participants are randomly allocated to be treated with either minocycline or a placebo (dummy drug). MRI and PET imaging is performed before treatment starts and after three months and the amount of leakiness and inflammation is measured to see whether they differ between the groups. MRI images are also acquired after 12 months to see if the treatment has reduced the accrual of damage to the brain. Cognitive tests are also performed at the start of the study and after 12 months.

What are the possible benefits and risks of participating?
There is no direct benefit to participants, but it will provide useful information on the role of inflammation in small vessel disease, and how this can be influenced by the use of minocycline.

Where is the study run from?
Addenbrooke's Hospital (UK)

When is the study starting and how long is it expected to run for?
March 2018 to June 2023

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Mrs Laurence Loubiere
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Contact information

Type(s)
Scientific

Contact name
Mrs Laurence Loubiere

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
CPMS 39159

Study information

Scientific Title
MINocyclinE to Reduce inflammation and blood brain barrier leakage in small Vessel diseAse (MINERVA) - A treatment trial

Acronym
MINERVA

Study objectives
Cerebral small vessel disease (SVD) is a major cause of stroke and dementia in the UK. The causes of progression of the disease are not completely understood. Recently leakiness of the

blood brain barrier has been proposed as a mechanism, which itself may cause inflammation of the brain. If we can understand what causes progression of the disease it may be possible to target treatments to reduce these processes and, therefore, progression.

Our previous observational study showed that we can detect differences between SVD patients and controls in both blood brain barrier leakiness and neuroinflammation. This double-blind randomised controlled trial will assess whether a drug, minocycline, an antibiotic, which has been shown to inhibit the processes that cause inflammation and leakiness in animals, can have the same effect in man.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/10/2018, NRES Committee East of England Cambridge Central (Royal Standard Place, Nottingham, NG1 6FS; +44 (0)207 104 8107/+44 (0)207 104 8234; nrescommittee.eastofengland-cambridgecentral@nhs.net), ref: 18/EE/0237

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

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 patient information sheet

Health condition(s) or problem(s) studied
Cerebral small vessel disease

Interventions
Current intervention as of 21/11/2019:
This project is a double blind randomised clinical trial which uses MRI and PET imaging at baseline and three months to study blood brain barrier permeability and neuroinflammation and how it is affected by minocycline.

The trialists will recruit 44 small vessel disease subjects split equally two treatment arms, minocycline and placebo taken orally at 100 mg bd of minocycline and an equivalent placebo. They will undergo conventional and gadolinium contrast agent enhanced MRI, PET imaging with [11C]PK11195, cognitive assessment, clinical assessment and phlebotomy at baseline and again at three months.

The MHRA have reviewed the protocol and classified the study as a non-CTIMP. This is because minocycline is a well-recognised drug which is being used in this context as an experimental probe to reduce inflammation and blood brain barrier permeability.

In more detail all subjects will undergo at baseline:
1. Screening. During routine clinical care consultations patients will be approached by their consultant if they are felt to be appropriate for the project. The suitability of participants will be assessed against the inclusion and exclusion criteria. Those who are eligible will be provided with a participant information sheet and the study will be explained by a trained researcher.The participant will then be asked to consent to participate in the study by completing a consent form. They will be given a copy of the consent and PIS to take away.
2. Blood collection. All participants who have not had their renal function measured will have a blood sample taken to calculate their renal function. If this is below an acceptable level (an eGFR =<59 ml/min/1.73m2) they will not be able to be a part of the study.
3. Cognitive and clinical assessment. All subjects who are eligible and who have consented will be asked to attend the clinic at Addenbrooke's for cognitive testing and clinical assessment. This will include collection of demographic data as well as cardiovascular risk factors and medical history as well as an estimate of disability. Cognitive assessment consists of a battery of tests that will provide information about the subject's cognitive ability including memory and attention tests as well as questionnaires about their mood and their fatigue experienced. These tests will take up to 90 minutes.
4. MRI and PET imaging. Subjects will undergo MRI and PET scanning at the same time using a dual-modality PET/MR scanner. The MRI protocol will include conventional MRI sequences as well as contrast enhanced MRI which is used to determine the permeability of the blood brain barrier. This will involve the insertion of a canula to allow the administration of the contrast agent during the MRI scan. The PET scan will involve the administration of a radioactive ligand [11C]PK11195 immediately prior to the scan. Scanning will take approximately 90 minutes.
5. During the fitting of the canula blood samples will be taken to perform serum analysis for endothelial dysfunction and inflammatory markers.
6. Randomisation, subjects will be assigned at random, using an online randomisation tool, to one of the two treatment arms.
7. Treatment. The subjects will then take the assigned treatment for three months
8. Follow-up testing and imaging. Three months after the first scan participants will be asked back to repeat the scanning to investigate change in this over the study period. The scanning will again last 90 minutes and further blood samples will be taken at this point.
9. Follow-up testing and imaging. A further follow-up scan will be performed after 12 months. This will comprise of non-contrast MRI only and take around 35 minutes. Cognitive testing will also be repeated at this time-point.

Previous intervention:
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Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome measure
The co-primary endpoints are:
1. Blood brain barrier permeability (white matter permeability) measured using MRI at baseline

and 3 months
2. Microglial activation ([11C]-PK11195 binding) measured using PET of 'hot-spots' of binding in the white matter at baseline and 3 months

Secondary outcome measures
Current secondary outcome measures as of 25/02/2019:
1. Volume of tissue with abnormal BBB permeability and/or neuro-inflammation at baseline and 3 months
2. Blood endothelial and inflammatory markers (CRP, ICAM1, MMP9, thrombomodulin) at baseline and 3 months
3. Cognitive outcome measures at baseline and 12 months:
3.1. Working Memory (WM), measured using digit span
3.2. Episodic (Long Term) Memory (LTM), measured using logical memory I & II and visual reproduction I & II from the WMS-IV battery
3.3. Processing Speed (PS), measured using digit symbol substitution, B-MIPB speed of information processing task, and the grooved pegboard task
3.4. Executive Function (EF), measured using trail-making test (part B), single letter (FAS) verbal fluency, and the Wisconsin card sort test
3.5 Mood assessment (Apathy and Depression) measured using the Geriatric Depression Scale (Long Form, GDS-30)

Previous secondary outcome measures:
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2. Blood endothelial and inflammatory markers (CRP, ICAM1, MMP9, thrombomodulin) at baseline and 3 months
3. Cognitive outcome measures at baseline, 3 months and 12 months:
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3.2. Episodic (Long Term) Memory (LTM), measured using logical memory I & II and visual reproduction I & II from the WMS-IV battery
3.3. Processing Speed (PS), measured using digit symbol substitution, B-MIPB speed of information processing task, and the grooved pegboard task
3.4. Executive Function (EF), measured using trail-making test (part B), single letter (FAS) verbal fluency, and the Wisconsin card sort test

Overall study start date
26/03/2018

Completion date
30/06/2023

Eligibility

Key inclusion criteria
1. Clinical evidence of cerebral small vessel disease as evidenced by one or more of;
1.1. A lacunar stroke syndrome (e.g., pure motor stroke, pure sensory stroke, sensorimotor stroke or ataxic hemiparesis, or clumsy hand dysarthria syndrome) with a corresponding acute lacunar infarct on diffusion weighted imaging (DWI) for cases imaged (clinically) within 3 weeks of stroke or an anatomically compatible lacunar infarct on FLAIR/T1 MRI for cases imaged later after stroke (<=1.5 cm diameter)
1.2. Symptoms of cognitive impairment

1.3. Gait apraxia
2. Confluent white matter hyper-intensities on T2 weighted MRI
3. If a past history of stroke at least 3 months after last stroke to exclude BBB changes secondary to acute infarction

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 44; UK Sample Size: 44

Total final enrolment
48

Key exclusion criteria
Current exclusion criteria as of 21/11/2019:
1. Unable/unwilling to consent
2. MMSE <21 (for consent issues)
3. Age <18 years
4. Lacunar infarcts >1.5 cm – as many of these are striatocapsular infarcts caused by embolism
5. Evidence of cortical stroke
6. Any stroke cause other than SVD including:
6.1. Cardioembolic source
6.2. Carotid or vertebral stenosis > 50% measured on NASCET criteria
7. Estimated glomerular filtration rate (eGFR) =<59 ml/min/1.73m2 within past 3 months. Estimated GFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation:
186 x (Creatinine / 88.4)1.154 x (Age) - 0.203 x (0.742 if female) x (1.210 if black)
8. Contraindications to taking part in MRI study, e.g., pacemaker
9. Inability to lie still in the PET/MR scanner for up to 75 minutes
10. Women who are of childbearing age, pregnant or breastfeeding
11. Meeting exclusions related to minocycline consumption, in particular:
11.1. Allergic to minocycline hydrochloride or other similar antibiotics
11.2. Have had complete kidney failure
11.3. Suffer from myasthenia gravis, have impaired liver or kidney function or have systemic lupus erythematosus (SLE)
11.4. Suffer from increased pressure in the skull
11.5. Are sensitive to sunlight or artificial light (e.g. sunbeds)
12. Taking medication contra-indicated to minocycline

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Date of first enrolment
29/04/2019

Date of final enrolment
15/06/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Addenbrooke's Hospital
Hills Rd
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

Sponsor details

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United Kingdom
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+44 (0)1223 217418
research@addenbrookes.nhs.uk

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council; Grant Codes: MR/N026896/1

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

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

Intention to publish date
30/11/2023

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?
Protocol article		17/05/2022	29/11/2022	Yes	No
HRA research summary			28/06/2023	No	No
Results article		17/04/2024	18/04/2024	Yes	No