

Switching off leakage and inflammation in small brain blood vessels

Submission date 24/09/2018	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 01/10/2018	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 18/04/2024	Condition category Circulatory System	<input type="checkbox"/> Individual participant data

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
lhl31@medschl.cam.ac.uk

Contact information

Type(s)
Scientific

Contact name
Mrs Laurence Loubiere

Contact details
Stroke Research group, Dept of Clinical Neurosciences
R3, Box 83, Cambridge Biomedical Campus
Cambridge
United Kingdom
CB2 0QQ
+44 (0)1223 217695
lhl31@medschl.cam.ac.uk

Additional identifiers

Protocol serial number
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

Study type(s)

Treatment

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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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 an estimate of their pre-morbid IQ. These tests will take up to 90 minutes.

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Intervention Type

Drug

Phase

Not Applicable

Drug/device/biological/vaccine name(s)

Minocycline

Primary outcome(s)

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

Key secondary outcome(s)

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)

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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

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

Healthy volunteers allowed

No

Age group

Adult

Sex

All

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:
$$186 \times (\text{Creatinine} / 88.4)^{1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$
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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17. Taking medication contra-indicated to minocycline

Date of first enrolment

29/04/2019

Date of final enrolment

15/06/2022

Locations

Countries of recruitment

United Kingdom

England

Study participating centre

Addenbrooke's Hospital

Hills Rd

Cambridge

United Kingdom

CB2 0QQ

Sponsor information

Organisation

Cambridge University Hospitals NHS Foundation Trust

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

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?
Results article	Participant information sheet	17/04/2024	18/04/2024	Yes	No
Protocol article		17/05/2022	29/11/2022	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet		11/11/2025	11/11/2025	No	Yes