'BATMAN' antibiotics against amyloid angiopathy: a placebo-controlled, randomized, double-blind study of minocycline for sporadic and hereditary cerebral amyloid angiopathy.

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To prove in a randomized clinical trial in a translational setting that minocycline treatment (duration 3 months) can decrease markers of neuroinflammation and the gelatinase pathway in the cerebrospinal fluid (CSF) of patients with HCHWA-D (n=30)...

Ethical review	Approved WMO
Status	Completed
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON54550

Source
ToetsingOnline

Brief title
BATMAN

Condition

- Central nervous system vascular disorders

Synonym
CAA, cerebral amyloid angiopathy

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: NWO,Hersenstichting

Intervention

Keyword: CAA, cerebral amyloid angiopathy, minocycline, RCT

Outcome measures

Primary outcome

Markers of neuroinflammation and the gelatinase pathway in the CSF.

Secondary outcome

The effect of minocycline on microvascular CAA markers on 7 Tesla MRI.

Study description

Background summary

Cerebral Amyloid Angiopathy (CAA) is a disease caused by accumulation of the protein amyloid-beta in the leptomeningeal arteries, cortical arterioles and capillaries of the brain. It is one of the major causes of ICH and vascular dementia in the elderly. Approximately 60% of all lobar (cortical) ICHs are CAA related.1 Most CAA cases are sporadic but a few familial forms exist. Around the Dutch village Katwijk (near Leiden) several families suffer from hereditary Dutch type Cerebral Amyloid Angiopathy (D-CAA), also known as: Hereditary Cerebral Hemorrhage With Amyloidosis - Dutch type (HCHWA-D), an autosomal dominant familial form of CAA. D-CAA, like sporadic-CAA is characterized by recurrent ICH and dementia, although we showed that its disease course is more aggressive.2 Currently, there is no treatment for D-CAA or sporadic CAA. Presence of amyloid-beta induces a chronic state of cerebral inflammation by activating reactive astrocytes, microglia and pro-inflammatory substances.3, 4 We will perform a randomized clinical trial with minocycline. Minocycline is an antibiotic of the tetracycline family and known to modulate inflammation, gelatinase activity and angiogenesis, which we know are central mechanisms in CAA-pathology.

Study objective

To prove in a randomized clinical trial in a translational setting that

minocycline treatment (duration 3 months) can decrease markers of neuroinflammation and the gelatinase pathway in the cerebrospinal fluid (CSF) of patients with HCHWA-D (n=30) and sporadic-CAA (n=30).

Study design

The study design is a randomized double-blind placebo-controlled trial.

Intervention

60 patients will be randomized and receive either placebo or minocycline treatment (15 sCAA placebo, 15 sCAA minocycline, 15 D-CAA placebo and 15 D-CAA minocycline).

Study burden and risks

Blood withdrawal and lumbar punctures are routine procedures at the Department of Neurology. Lumbar puncture will be performed by experienced physicians. We will use atraumatic spinal needles to reduce the risk of post-lumbar puncture headache. Patients will be informed extensively about the potential risks of these procedures, after which written informed consent will be obtained. The risks of MRI are minimal (risk of everyday life), because there are no consequences to the health of the participant. Contra-indications will be carefully investigated per subject, burden will be kept at a minimum by using short protocols. There is no direct benefit for the patients except for more insight in the possible effect of minocycline on CAA.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age >=18 years for HCHWA-D and age >=50 years for sporadic-CAA
- Probable-CAA according to the Boston criteria 2.0, or genetically proven D-CAA
- <= 2 ICH (occurrence of ICHs at least 1 year ago) and presence of >= 2 lobar microbleeds +/-cortical superficial siderosis
- Presence of deep microbleeds is allowed if
- There is presence of cortical superficial siderosis, or
- >=10 lobar microbleeds are present for every deep microbleed
- Written informed consent

Exclusion criteria

- Previous allergic reactions to minocycline
- Modified Rankin Score >=3
- Contraindications, such as:
- Contraindications for 7T MRI as determined by the 7Tesla safety committee. Examples of possible contra-indications are: claustrophobia, pacemakers and defibrillators, nerve stimulators, intracranial clips, intraorbital or intraocular metallic fragments, cochlear implants, ferromagnetic implants, hydrocephalus pump, intra-uterine device, permanent make-up, tattoos above the shoulders.
- Specific contraindications for fMRI: seizure within prior year, photosensitive epilepsy, noncorrectable visual impairment.
- Contraindications for lumbar puncture: compression of the spinal cord, signs and symptoms of increased intracranial pressure, local infections of the skin at the puncture site, a coagulopathy including use of anti-coagulant drugs (INR>=1.8) or thrombocytopenia (<40).

(Use of acetylsalicylic acid, NSAIDs, COX2 inhibitors or low-molecular-weight heparin are no contraindications for lumbar puncture.)
- Pregnancy/breast feeding
- Liver/renal failure
- Use of antibiotics <1 month
- SLE or other diseases known to generate inflammatory responses
- Previous/current/planned use of retinoids (since this is related to increasing risk of increased intracranial pressure)
- Current use of anaesthetics like methoxyflurane, agents inhibiting peristalsis, barbiturates, carbamazepine or fenytoïne

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	02-12-2020
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Minocycline
Generic name:	Minocycline
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-08-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	01-10-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	16-11-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	25-01-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	08-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	04-08-2021
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-06-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	10-09-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	01-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-004786-41-NL
CCMO	NL71513.058.20