A randomized, placebo-controlled, double blind trial to study the effects of Etidronate on ectopic CALCIfication in FAhr*s Disease or syndrome.

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This study has been transitioned to CTIS with ID 2024-512300-19-00 check the CTIS register for the current data. The objective is to determine whether etidronate can halt or attenuate disease progression in patients with Fahr*s disease or syndrome...

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

Summary

ID

NL-OMON53560

Source
ToetsingOnline

Brief title
CALCIFADE trial

Condition

- Central nervous system vascular disorders

Synonym
Fahr's disease, primary familial brain calcification

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Hersenstichting

Intervention

Keyword: basal gangla diseases, calcification, calcinosis, rare diseases

Outcome measures

Primary outcome

Primary outcome: change in cognitive functioning of patients with Fahr*s disease or syndrome treated with etidronate or placebo between baseline and 12 months after baseline.

Secondary outcome

Secondary outcomes: change in mobility, psychiatric symptoms, daily functioning, quality of life, and calcification in the brain of patients with Fahr*s disease or syndrome treated with etidronate or placebo between baseline and 12 months after baseline.

Study description

Background summary

Fahr*s disease, also known as primary familial brain calcification, is a rare, monogenetic disease in which patients present with bilateral vessel associated calcifications in the basal ganglia in the absence of other secondary causes of brain calcifications. When a secondary cause is identified (e.g. parathyroid disease), the term Fahr*s syndrome is used. The calcifications are visible on a computed tomography scan. Dominantly-inherited Fahr*s disease is associated with mutations in four genes; SLC20A2, XPR1, PDGFB and PDGFRB. Recessively inherited Fahr*s disease is associated with mutations in MYORG and JAM2. Mutations in the known genes account for half of patients, suggesting genetic heterogeneity, with new genes yet to be discovered. The clinical presentation of Fahr*s disease or syndrome is heterogeneous comprising of neuropsychiatric signs (e.g. depression, anxiety), cognitive decline, mobility disorders (e.g. Parkinsonism) and various other signs (e.g. migraine, pain). The symptoms start at an age between 30 and 50 years and are (slowly) progressive. Symptomatic

patients have an increased risk for dependence in activities of daily living and impaired quality of life.
Mutations in several genes linked to Fahr*s disease are related to the calcium/phosphate homeostasis. Similar monogenetic, rare calcifying diseases of arteries in other parts of the body are also caused by a disturbance in the calcium/phosphate homeostasis. Lack of inorganic pyrophosphate (PPi) is the central problem. PPi is the strongest inhibitor of ectopic calcification in the body. These diseases are successfully treated with etidronate, a stable analog of PPi and a well known bisphosphonate that has been used widely. Presently, the rare genetic diseases Pseudoxanthoma Elasticum (PXE), Generalized Arterial Calcification of Infancy (GACI) and Arterial Calcification due to CD73 deficiency (ACDC) are successfully treated with this medication.
Currently, disease-modifying therapies are not available for patients with Fahr*s disease or syndrome. Now the time has come to investigate the effectiveness of treatment with etidronate in patients with Fahr*s disease or syndrome in a randomized controlled trial.

Study objective

This study has been transitioned to CTIS with ID 2024-512300-19-00 check the CTIS register for the current data.

The objective is to determine whether etidronate can halt or attenuate disease progression in patients with Fahr*s disease or syndrome.

Study design

Randomized, placebo controlled, double blind trial.

Intervention

Treatment with etidronate during one year (cyclical 20 mg/kg for 2 weeks on and 10 weeks off) or placebo.

Study burden and risks

Each patient will visit the UMCU three times during the 13 month duration of the study. At baseline (two times) and after 12 months of follow-up, visits are planned for laboratory tests, neuropsychological assessment, and tests for mobility, neuropsychiatric functioning, daily functioning, and quality of life.
At baseline and at 12 months a CT scan of the brain will be made. For the entire study protocol, the effective dosage is approximately 4 mSv. This radiation theoretically could marginally increase the lifetime risk of developing cancer. At three and six months, patients will be scheduled for telephone consultation for evaluation of treatment compliance and side effects.
The study drug is a known and safe drug, generally well tolerated and side

effects are mostly mild. The most commonly reported side effects are transient musculoskeletal pain and gastrointestinal side effects like dyspepsia. A rare side effect is osteonecrosis of the jaw. Patients who have dental disease or use certain drugs (chemotherapeutic or anti-inflammatory drugs) have a higher risk for this side effect. To reduce this risk, the physician at the expert center will perform a medication review and check the dental status before starting treatment. Though treatment with etidronate in patients with Fahr*s disease or syndrome is promising, until effectiveness of this treatment is proven in this trial we can not assume that research participants gain individual benefit from their participation in the study. However, the study is expected to open up a new promising treatment for patients with Fahr*s disease or syndrome, a disease for which at the moment no effective therapy exists, using a well-known drug with good safety profile.

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

1. Age of 18 years or over.
2. Clinical diagnosis of Fahr*s disease or syndrome. No international accepted diagnostic criteria for Fahr*s disease or syndrome exist yet. It is diagnosed mostly based on the clinical presentation. For the present study the following criteria are used:
a. Clinical symptoms consistent with a clinical diagnosis of Fahr*s disease or syndrome.
b. Bilateral calcifications of the basal ganglia as seen on the CT scan of the head. To rule out basal ganglia calcifications due to aging, a CT based calcification score will be used as proposed by Nicolas et al. Calcification is graded from 0 (no calcification) to 5 (serious and confluent) in specific locations of the brain; lenticular, caudate, thalamus nuclei, subcortical white matter, cortex, cerebellar hemispheres, vermis, midbrain, pons, and medulla. The total calcification score (ranging from 0 to 80) is obtained by adding all location-specific points, where a score higher than the age-specific threshold points at Fahr's disease or syndrome.

Furthermore, the next criteria are supportive for the clinical diagnosis of Fahr's disease:
c. Frequently, the family history is consistent with autosomal dominant inheritance. A positive family history with at least one relative in the first or second degree with symptoms of Fahr*s disease is supportive for the clinical diagnosis of Fahr*s disease.
d. The presence of a (likely) pathogenic mutation in one of the Fahr*s disease-related genes is supportive for the clinical diagnosis of Fahr*s disease. Mutations in up to now four known genes are associated with an autosomal dominant pattern of inheritance: SLC20A2 (OMIM#213600), XPR1 (OMIM#616413), PDGFB (OMIM#615483), and PDGFRB (OMIM#615007). Autosomal recessively inherited PFBC is associated with mutations in two genes: MYORG (OMIM#618317) and JAM2 (OMIM#618824).

Exclusion criteria

1. Unable or unwilling to sign an informed consent.
2. Severe renal impairment (estimated creatinine clearance/eGFR of <30 ml/min/1.73m2 calculated using CKD-EPI equation).
3. Contraindication to receiving oral medication.
4. Known abnormality of the esophagus that would interfere with the passage of the drug.
5. Known sensitivity to etidronate.
6. Pregnancy, women with an active pregnancy wish <1 year, or women who are breastfeeding at the time of inclusion.

7. Any other medical or social condition that, in the opinion of the Principal Investigator, might put the subject at risk of harm during the study or might adversely affect the interpretation of the study data.
8. Use of bisphosphonate during the last 5 years.
9. Hypocalcemia (calcium <2.20 mmol/L)*.
10. 25-OH vitamin D deficiency <35 nmol/L)*.
*After correcting the hypocalcemia or vitamin D deficiency, a participant is again suitable for participation in the CALCIFADE trial, as long as the participant meets the inclusion criteria.

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:	Recruiting
Start date (anticipated):	03-04-2023
Enrollment:	98
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	etidronate
Generic name:	etidronate

Ethics review

Approved WMO Date:	18-01-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-03-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	23-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-06-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-07-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-07-2024
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2024-512300-19-00
EudraCT	EUCTR2022-003299-17-NL
CCMO	NL83131.041.22