A placebo-controlled, double-blind randomized trial evaluating the effect of etidronate in young patients with pseudoxanthoma elasticum on ectopic mineralization.

Published: 16-12-2021
Last updated: 09-11-2024

This study has been transitioned to CTIS with ID 2024-512133-33-00 check the CTIS register for the current data. Primary Objective To determine if 24 months of treatment with etidronate halts the progression of arterial calcification in the legs and…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Retina, choroid and vitreous haemorrhages and vascular disorders
Study type	Interventional

Summary

ID

NL-OMON54216

Source
ToetsingOnline

Brief title
TEMP-PREVENT

Condition

- Retina, choroid and vitreous haemorrhages and vascular disorders
- Epidermal and dermal conditions
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Grönblad-Strandberg syndrome, Pseudoxantoma elasticum

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: via diverse stichtingen en fondsen.

Intervention

Keyword: Ectopic mineralization, Etidronate, Pseudoxanthoma elasticum, Therapy

Outcome measures

Primary outcome

Arterial calcification in the legs and carotid syphons measured on low dose Ct scan.

Secondary outcome

1. To determine the effect of 24 months of treatment with etidronate on functional ophthalmological measurements, such as visual acuity and contrast sensitivity compared to placebo.

2. To determine if 24 months of treatment with etidronate halts the progression of normalized reflectivity in Bruch*s membrane as measured with SD-optical coherence tomography, compared to placebo.

3. To determine the effect of 24 months of treatment with etidronate on structural ophthalmological measurements, on fundus photography, (infrared (IR) and autofluorescence (FAF)) and OCT-angiography (OCTA).

4. To determine if 24 months of treatment with etidronate affects the intracranial velocity pulsatility index as measured with MRI.

5. To determine if 24 months of treatment with etidronate halts the progression of elastin degradation and of calcification in the skin in dermatological

observation of skin biopsies, compared to placebo.

6. To determine the effect of 24 months of treatment with etidronate on inorganic pyrophosphate an desmosine compared to placebo.

7. To determine if 24 months of treatment with etidronate halts leads to changes in vascular measurements (carotid intima-media thickness, pulse wave velocity on ultrasound, ankle brachial index, 6 minute walking test and WELCH questionnaire) compared to placebo.

8. To determine if 24 months of treatment with etidronate leads to decreased occurrence of major adverse cardiovascular events (stroke, TIA, myocardial infarction or cardiovascular death) compared to placebo.

9. To determine if 24 months of treatment with etidronate leads to improved reported quality of life amd physical functioning, as measured with the EQ-5D, PROMIS 10, PROMIS PF and USER P compared to placebo.

10. To determine if 24 months of treatment with etidronate leads to better results on cognitive tests compared to placebo.

11. To determine if 24 months of treatment with etidronate leads to observed differences in safety measures: changes in plasma calcium, phosphate measured via laboratory assessment, and number of anti-VEGF injections used.

Study description

Background summary

Pseudoxanthoma elasticum is a genetic disease caused by mutations in the ABCC6 gene. These mutations result in reduced levels of inorganic pyrophosphate, a strong inhibitor of ectopic calcification. PXE is characterized by a typical pattern of progressive degradation and calcification of elastin fibers in the

skin, the medial layer of small- and medium sized arteries and the Bruch*s membrane of the retina. This results clinically in skin disorders (pseudoxanthoma*s), peripheral arterial disease, gastric bleeding and stroke. The progressive calcification of the Bruch*s membrane results in peau d* orange, angioid streaks, choroidal neovascularizations (CNV*s) and macular atrophy.

The bisphosphonate etidronate is a molecular homologue of pyrophosphate, which therefore has the potential to substitute the loss of pyrophosphate that is seen in PXE. It has been on the market for over 40 years and has a well-established safety profile. Based upon positive results from animal studies, studies in related genetic disorders, and trials in patients with renal disease, we recently conducted a double blind, randomized, placebo-controlled clinical trial (RCT) in PXE patients. This Treatment of Ectopic Mineralization in PXE (TEMP)-trial (protocol ID: NL47602.041.15) showed that one year of treatment with etidronate was safe, and reduced calcifications of the leg arteries and of other vascular beds compared to placebo in PXE patients with arterial calcifications. As no other systemic treatment for PXE exists, this established etidronate as a very promising therapeutic option.

The TEMP trial focused on reduction of progression of clinical manifestations in patients with already manifest arterial calcifications. However, if etidronate is effective in young patients with little to no arterial calcification to prevent calcification from arising is not yet systematically assessed.

Therefore, the TEMP-prevent trial aims to investigate the effect of etidronate on the progression of arterial calcification in the legs and the carotid artery.

Study objective

This study has been transitioned to CTIS with ID 2024-512133-33-00 check the CTIS register for the current data.

Primary Objective
To determine if 24 months of treatment with etidronate halts the progression of arterial calcification in the legs and carotid siphons.

Secondary Objectives
1. To determine the effect of 24 months of treatment with etidronate on functional ophthalmological measurements, such as visual acuity and contrast sensitivity compared to placebo.
2. To determine if 24 months of treatment with etidronate halts the progression of normalized reflectivity in Bruch*s membrane as measured with SD-optical coherence tomography, compared to placebo.
3. To determine the effect of 24 months of treatment with etidronate on

structural ophthalmological measurements, on fundus photography, (infrared (IR) and autofluorescence (FAF)) and OCT-angiography (OCTA).
4. To determine if 24 months of treatment with etidronate affects the intracranial velocity pulsatility index as measured with MRI.
5. To determine if 24 months of treatment with etidronate halts the progression of elastin degradation and of calcification in the skin in dermatological observation of skin biopsies, compared to placebo.
6. To determine the effect of 24 months of treatment with etidronate on inorganic pyrophosphate an desmosine compared to placebo.
7. To determine if 24 months of treatment with etidronate halts leads to changes in vascular measurements (carotid intima-media thickness, pulse wave velocity on ultrasound, ankle brachial index, 6 minute walking test and WELCH questionnaire) compared to placebo.
8. To determine if 24 months of treatment with etidronate leads to decreased occurrence of major adverse cardiovascular events (stroke, TIA, myocardial infarction or cardiovascular death) compared to placebo.
9. To determine if 24 months of treatment with etidronate leads to improved reported quality of life amd physical functioning, as measured with the EQ-5D, PROMIS 10, PROMIS PF and USER P compared to placebo.
10. To determine if 24 months of treatment with etidronate leads to better results on cognitive tests compared to placebo.
11. To determine if 24 months of treatment with etidronate leads to observed differences in safety measures: changes in plasma calcium, phosphate measured via laboratory assessment, and number of anti-VEGF injections used.

Study design

Randomised, double blind, placebo controlled clinical trial.

Intervention

Etidronate versus placebo

Study burden and risks

Every participant will visit the UMC Utrecht 3 times during this study (screening and M0, M12, M24). A low-dose CT scan of the neck and the legs will be performed two times (M0 + M24). The effective dose of radiation is 2.84 mSV pro person. In theory the additional radiation increases the risk on malignancy in the future. Dermatological measurements are performed by a punch biopsy. Laboratorial results are measured by venipuncture. Apart from the usual risk (hematoma, pain and swelling, bleeding, vagal reaction, infection or allergic reaction to local anesthesia), there is no additional risk in these research operations. The 7Tesla MRI-scanner that is used in this study is not CE-marked, and is only used for research. In previous studies with this MRI-scanner there were no problems regarding subject safety.

Because of the know safety of etidronate and the long term experience with this pharmaceutical, the overall risk of the TEMP-prevent is deemed low.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Be between 18 years and 55 years.
- Have a definitive diagnosis of PXE according to the Plomp criteria, which confirm a diagnosis of PXE when at least two (or more) criteria not belonging to the same category (skin, eye, genetic) are met:
1. Skin
a. Yellowish papules and/or plaques on the lateral side of the neck and/or flexural areas of the body or

b. Increase of morphologically altered elastin with fragmentation, clumping and calcification of elastic fibers in a skin biopsy taken.
2. Eye
a. Peau d'orange of the retina or
b. One or more angioid streaks (AS), each at least as long as one disk diameter. When in doubt, fluorescein or indocyanine green angiography of the fundus is needed for confirmation.
3. Genetics
a. A pathogenic mutation of both alleles of the ABCC6 gene or
b. A first-degree relative (parent, sibling or child) who meets independently the diagnostic criteria for definitive PXE

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. Patients that are unable or unwilling to sign for informed consent.
2. Pregnant, lactating, or fertile women who might wish to become pregnant within three years.
3. Patients with an estimated glomerular filtration rate below 30 ml/min/1.73m2 according to the CKD-EPI equation.
4. Patients with a known abnormality of the oesophagus that would interfere with passage of the drug (e.g. oesophagus stenosis).
5. Patients with chronic diarrhoea (> 1 month).
6. Patients with osteomalacia.
7. Patients with hypocalcaemia (calcium <;2.20 mmol/L corrected for albumin)*
8. Patients with a vitamin D deficiency (<35 nmol/L)*
9. Patients that used a bisphosphonate in the last 5 years
10. Patients with known sensitivity to etidronate.
11. Any other medical or social condition that, at the discretion 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.
* After correction a patient is again suitable for participation, as long as inclusion criteria are met.

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-04-2023
Enrollment:	76
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	16-12-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	05-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-04-2023

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	16-06-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-04-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-04-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-07-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-07-2024
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	CTIS2024-512133-33-00
EudraCT	EUCTR2021-000434-34-NL
CCMO	NL75350.041.21