Treatment of Ectopic Mineralization in Pseudoxanthoma Elasticum.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac and vascular disorders congenital
Study type	Interventional

Summary

ID

NL-OMON41676

Source
ToetsingOnline

Brief title
TEMP trial.

Condition

- Cardiac and vascular disorders congenital
- Retina, choroid and vitreous haemorrhages and vascular disorders
- Vascular disorders NEC

Synonym
Pseudoxanthoma Elasticum

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Innovatiefonds Zorgverzekeraars;Vrienden UMC Utrecht;Oogvereniging.

Intervention

Keyword: Etidronic Acid, Pseudoxanthoma Elasticum, Vacular Calcification

Outcome measures

Primary outcome

The primary endpoint is the percentage change in 18F-NaF-uptake after 12 months treatment with etidronate 20 mg/kg compared with placebo.

Secondary outcome

Secondary endpoints are the percentage change in 18F-NaF-uptake in other arteries than the femoral artery, ophthalmological changes , changes in vascular stiffness, changes in bone mineral density, dermatological changes, changes in quality of life and changes in serum calcium and phosphate, changes in MRI brain lesions, vascular brain flow, pulsatility and brain tissue perfusion, changes in cognitive function.

Study description

Background summary

Pseudoxanthoma elasticum (PXE) is a rare autosomal recessive disorder affecting primarily the skin, the eyes and the vascular system with a considerable morbidity and occasional mortality. PXE is caused by mutations in the ABCC6 gene leading to mineralization of elastic fibers in the skin, the Bruch*s membrane of the retina and the vasculature. Decreased pyrophosphate levels has been shown to be related both to ABCC6 mutations and the occurrence of ectopic mineralization. In animal models treatment with pyrophosphate and pyrophosphate analogues such as bisphosphonates has been proven to inhibit mineralization. Studies in generalized arterial calcification of infancy (GACI), a mineralization disorder genetically and phenotypically similar to PXE, suggest that treatment with bisphosphonates is very effective on resolution of calcification of blood vessels and is associated with improved survival. Also in patients without PXE bisphosphonates have been shown to be able to stabilize vascular calcifications. Also, in age-related macular degeneration

bisphosphonates can reduce the choroidal neovascularization. Based on these positive findings, a clinical trial is now evaluating the effectiveness on arterial calcification and safety of the bisphosphonate etidronate in patients with Arterial Calcifications due to Deficiency in SD73 (ACDC), another genetic disease in which vascular calcifications of the tunica media develop. Like in GACI, treatment with bisphosphonates is a potentially effective treatment in PXE. After the effectiveness of treatment with bisphosphonates in PXE in animal models has been established and promising results has been found in studies in patients with GACI, a disease from the same clinical spectrum as PXE, now the time has come to investigate the effectiveness of treatment with bisphosphonates in patients with PXE in a randomized controlled trial.

Study objective

The main objective is to determine if bisphosphonate therapy with etidronate leads to stabilization or attenuation of ongoing calcification in the leg arteries as quantified by 18F-sodium fluoride(18F-NaF) PET-CT imaging in patients with PXE. Secondary objectives are to determine if bisphosphonate therapy with etidronate leads to changes in calcium scores of the peripheral arteries, attenuation of ongoing calcification in other arteries than the leg arteries, ophthalmological changes, dermatological changes, changes in vascular stiffness, changes in bone mineral density, changes in quality of life, changes in serum calcium and phosphate and changes in pyrophosphate, changes in MRI brain laesions, vascular brain flow, pulsatility and brain tissue perfusion, changes in cognitive function.

Study design

Randomized placebo-controlled trial

Intervention

Subjects will be randomized to either treatment with etidronate during one year (cyclical 20 mg/kg for 2 weeks on and 10 weeks of) or placebo.

Study burden and risks

Each patient will visit the UMC Utrecht six times for the 12 month duration of the study. At baseline and after 12 months a *whole-body* 18F-NaF PET-CT scan will be made. After 6 months of follow-up a conventional CT-scan will be performed. For the entire study protocol, the effective dosage is approximately 13.6 mSv. This radiation theoretically could marginally increase the lifetime risk of developing cancer. During the study follow-up visits are planned each 3 months for ophthalmological evaluation (M0, M3, M6, M9, M12), non-invasive evaluation of vascular stiffness (M0, M12), laboratory evaluations (M0, M3, M6, M9, M12), and quality of life questionnaire (M0, M12). Additionaly participants

will undergo cognitive testing and MRI brain imaging with contrast at M0 and M12. Twelve months etidronate use carries a potential health risk (estimated as medium risk). Though treatment with etidronate in PXE patients 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 in patients with PXE, a disease for which at the moment no 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. All patients should be at least 18 years old.
2. A participant must meet the revised diagnostic criteria of Plomp et al. for the diagnosis of

PXE
3. In all patients evidence of arterial calcification should be available.

Exclusion criteria

1. Subjects who are 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. Known abnormality of the esophagus that would interfere with the passage of the drug, such as a oesophagus stenosis.
4. Patients with osteomalacy
5. Patients with chronic diarrhea (>1 month)
6. Known sensitivity to etidronate.;7. Pregnant, lactating or fertile women who might wish to become pregnant within three years.
8. 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.
9. Use of bisphosphonate during last 5 years.
10. Hypocalcemia (calcium <2,20 mmol/L and ionised calcium < 1.15)*.
11. Vitamin D deficiency <35 nmol/L*.
*After correcting the hypocalcemia or vitamin D deficiency a participant is again suitable for participation in the TEMP 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: Recruitment stopped

Start date (anticipated):	13-10-2015
Enrollment:	74
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ostopor
Generic name:	etidronic acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	06-05-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 27089
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2013-005620-41-NL
CCMO	NL47602.041.15
OMON	NL-OMON27089