TEMP trial

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Pseudoxanthoma elasticum (PXE) is a rare autosomal recessive disorder affecting primarily the skin, the eyes and the vascular system (tunica media calcifications) with a considerable morbidity and possibly premature mortality. PXE is caused by...

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON27089

Bron
NTR

Verkorte titel
TEMP

Aandoening

Pseudoxanthoma elasticum, ectopic mineralization

Ondersteuning

Primaire sponsor: University Medical Center Utrecht
Department of Vascular Medicine
Heidelberglaan 100
3584 CX Utrecht
The Netherlands
Overige ondersteuning: Vrienden van UMC Utrecht, Oogsvereniging, Innovatiefonds zorgverzekeraars.

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

The percentage change in 18F-NaF uptake in the leg arteries after 12 months of treatment with etidronate 20 mg/kg compared with placebo.

Toelichting onderzoek

Achtergrond van het onderzoek

SUMMARY

Rationale: Pseudoxanthoma elasticum (PXE) is a rare autosomal recessive disorder affecting primarily the skin, the eyes and the vascular system (tunica media calcifications) with a considerable morbidity and possibly premature 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. A decreased inorganic pyrophosphate level has been shown to be related both to ABCC6 mutations and the occurrence of ectopic mineralization. In PXE animal models treatment with inorganic pyrophosphate and inorganic 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. 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 CD73 (ACDC), another genetic disease in which vascular calcifications of the tunica media develop. Like in GACI and ACDC, 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 have been found in studies in patients with GACI now the time has come to investigate the effectiveness of treatment with bisphosphonates in patients with PXE in a randomized controlled trial.

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 inorganic pyrophosphate.

Study design: Randomized placebo-controlled trial.

Study population: 74 PXE patients >18 years with evidence of arterial calcification.

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

Main study parameters/endpoints: Primary endpoint: the percentage change in 18F-NaF uptake in the leg arteries after 12 months of treatment with etidronate 20 mg/kg compared with placebo.

Secondary endpoints: the percentage change in 18F-NaF uptake after 12 months treatment in other arteries than the leg arteries, ophthalmological changes after 12 months, changes in vascular stiffness after 12 months, changes in bone mineral density after 12 months, changes in quality of life and changes in serum calcium and phosphate.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Each patient will visit the UMC Utrecht six times during 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). 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 for patients with PXE, a disease for which at the moment no effective therapy exists, using a well-known drug with good safety profile.

Doel van het onderzoek

Pseudoxanthoma elasticum (PXE) is a rare autosomal recessive disorder affecting primarily the skin, the eyes and the vascular system (tunica media calcifications) with a considerable morbidity and possibly premature 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. A decreased inorganic pyrophosphate level has been shown to be related both to ABCC6 mutations and the occurrence of ectopic mineralization. In PXE animal models treatment with inorganic pyrophosphate and inorganic 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. 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 CD73 (ACDC), another genetic disease in which vascular calcifications of the tunica media develop. Like in GACI and ACDC, 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 have been found in studies in patients with GACI now the time has come to investigate the effectiveness of treatment with bisphosphonates in patients with PXE in a randomized controlled trial.

Onderzoeksopzet

3 months, 6 months, 9 months and 12 months

Onderzoeksproduct en/of interventie

Etidronate 20 mg/kg

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Age 18 and older.

2. Clinical diagnosis of PXE. For the present study the revised criteria for diagnosis of PXE from Plomp et al (2010) (41) will be used. At least two (or more) criteria not belonging to the same (skin, eye, genetic) category should be present for inclusion.

a. Skin

i. Yellowish papules and/or plaques on the lateral side of the neck and/or flexural areas of the body

or

ii. Increase of morphologically altered elastin with fragmentation, clumping and calcification of elastic fibers in a skin biopsy taken.

b. Eye

i. Peau d'orange of the retina; or

ii. 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.

c. Genetics

i. A pathogenic mutation of both alleles of the ABCC6 gene; or

ii. A first-degree relative (parent, sibling or child) who meets independently the diagnostic criteria for definitive PXE

3. Evidence of arterial calcification (increased vascular stiffness (increased pulse wave

velocity and/or increased augmentation index) and/or vascular calcifications on CT-scan).

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek

Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	01-07-2015
Aantal proefpersonen:	74
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	12-05-2015
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 41676
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL4956
NTR-old	NTR5180
CCMO	NL47602.041.15
OMON	NL-OMON41676

Resultaten