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Etidronate for Prevention of Ectopic Mineralization in Patients With Pseudoxanthoma Elasticum

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ABSTRACT

BACKGROUND In pseudoxanthoma elasticum (PXE), low pyrophosphate levels may cause ectopic mineralization, leading to skin changes, visual impairment, and peripheral arterial disease.

OBJECTIVES The authors hypothesized that etidronate, a pyrophosphate analog, might reduce ectopic mineralization in PXE.

METHODS In the Treatment of Ectopic Mineralization in Pseudoxanthoma Elasticum trial, adults with PXE and leg arterial calcifications (n = 74) were randomly assigned to etidronate or placebo (cyclical 20 mg/kg for 2 weeks every 12 weeks). The primary outcome was ectopic mineralization, quantified with ^{18}fluoride positron emission tomography scans as femoral arterial wall target-to-background ratios ($TBR_{femoral}$). Secondary outcomes were computed tomography arterial calcification and ophthalmological changes. Safety outcomes were bone density, serum calcium, and phosphate.

RESULTS During 12 months of follow-up, the $TBR_{femoral}$ increased 6% (interquartile range [IQR]: −12% to 25%) in the etidronate group and 7% (IQR: −9% to 32%) in the placebo group (p = 0.465). Arterial calcification decreased 4% (IQR: −11% to 7%) in the etidronate group and increased 8% (IQR: −1% to 20%) in the placebo group (p = 0.001). Etidronate treatment was associated with significantly fewer subretinal neovascularization events (1 vs. 9, p = 0.007). Bone density decreased 4% ± 12% in the etidronate group and 6% ± 9% in the placebo group (p = 0.374). Hypocalcemia (<2.20 mmol/l) occurred in 3 versus 1 patient (8.1% vs. 2.7%, p = 0.304). Eighteen patients (48.6%) treated with etidronate, compared with 0 patients treated with placebo (p < 0.001), experienced hyperphosphatemia (>1.5 mmol/l) and recovered spontaneously.

CONCLUSIONS In patients with PXE, etidronate reduced arterial calcification and subretinal neovascularization events but did not lower femoral ^{18}fluoride sodium positron emission tomography activity compared with placebo, without important safety issues. (Treatment of Ectopic Mineralization in Pseudoxanthoma elasticum; NTR5180) (J Am Coll Cardiol 2018;71:1117–26) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

^{18}F-NaF PET = ^{18}fluoride sodium positron emission tomography

ALT = alanine transaminase

AST = aspartate transaminase

BCVA = best corrected visual acuity

CT = computed tomography

eGFR = estimated glomerular filtration rate

IMT = intima-media thickness

IQR = interquartile range

PPi = inorganic pyrophosphate

PWV = pulse wave velocity

PXE = pseudoxanthoma elasticum

SF-36 = Short Form 36

$TBR_{femoral}$ = femoral arterial wall target-to-background ratio

VEGF = vascular endothelial growth factor

Pseudoxanthoma elasticum (PXE, OMIM #264800) is an autosomal recessive systemic calcification disorder. PXE is characterized by skin involvement (e.g., yellowish papules/plaques), eye involvement (e.g., angioid streaks), and vascular involvement (arterial calcification), and has a considerable morbidity, including severe visual impairment and blindness, peripheral arterial disease, ischemic stroke, and vascular dementia (1,2). The prevalence is approximately 1:25,000 to 100,000 (2). To prevent progression of visual impairment caused by choroidal neovascularization in patients with PXE, injections with antivascular endothelial growth factor (VEGF) are used (3); however, there is no specific and preventive treatment available for patients with PXE.

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PXE is caused by mutations in the *ABCC6* gene and associated with ectopic mineralization of elastic fibers in the skin, the Bruch membrane beneath the retina, and the medial layer of arteries (4). Recently, major steps have been made in deciphering the etiology of PXE. *ABCC6* mutations have been shown to result in reduced adenosine triphosphate secretion in the liver causing low levels of inorganic pyrophosphate (PPi) (5). PPi is a strong inhibitor of ectopic mineralization (6–8). The decreased levels of PPi in PXE may therefore cause the ectopic mineralization in PXE (9).

Bisphosphonates, well-established drugs for the treatment of osteoporosis and bone metastases, are stable PPi analogs and could thus stimulate the inhibitory effects on ectopic mineralization (10). In fact, bisphosphonates have been shown to reduce soft tissue calcifications in rats even before their effect on bone resorption was known (11). Of the currently available bisphosphonates, etidronate may have the largest potential to delay ectopic mineralization given its predominant inhibition of calcium precipitation and hydroxyapatite binding. This is different from newer bisphosphonates, such as alendronate, which predominantly inhibit osteoclasts (12,13).

Several nonrandomized and uncontrolled reports describe beneficial effects of etidronate in patients with rare diseases with ectopic mineralization resulting from a deficiency in PPi homeostasis. In patients with basal ganglia calcifications or primary brain calcifications (OMIM #213600), treatment with etidronate alleviates neurological symptoms (12,14). In generalized arterial calcification of infancy (OMIM #208000) etidronate treatment reduces arterial calcification and is associated with improved survival (15,16). Generalized arterial calcification of infancy can be seen as an aggressive form of PXE with a considerable overlap in genotype and phenotype (17,18). Treatment with etidronate in PXE mouse models results in prevention of ectopic mineralization and in alterations in bone microarchitecture (19,20). The effectiveness of etidronate remains to be established in patients with PXE in a randomized, placebo-controlled trial.

We therefore hypothesized that synthetic PPi supplementation with etidronate treatment could reduce ectopic mineralization in patients with PXE. To be able to investigate this hypothesis in a randomized, placebo-controlled trial, we used femoral arterial wall ^{18}fluoride sodium positron emission tomography (^{18}F-NaF PET) activity and computed tomography (CT)-based femoral calcium scores as markers of ectopic mineralization (21–25). Imaging with ^{18}F-NaF PET may be more sensitive to changes in ectopic mineralization compared with traditional CT because it is believed to be able to visualize the active and ongoing calcification process and discriminate between the active and the more indolent calcifications (22,26).

Here, we report the results of the Treatment of Ectopic Mineralization in Pseudoxanthoma elasticum (TEMP) trial in which we set out to investigate the effectiveness and safety of 1 year's treatment with etidronate (cyclical 20 mg/kg for 2 weeks every 12 weeks) on ectopic mineralization among participants with PXE.

METHODS

TRIAL DESIGN AND STUDY POPULATION. The TEMP trial was a single-center, randomized, double-blind, placebo-controlled trial conducted in the PXE expertise center at the University Medical Center Utrecht, the Netherlands. Participants eligible for participation had a confirmed clinical diagnosis of PXE, were ≥18 years of age, and had evidence of arterial calcification on a CT scan of the legs that was acquired in all patients during the first visit in our center. PXE was diagnosed if 2 of the following were present: skin involvement (e.g., yellowish papules/plaques), eye involvement (e.g., angioid streaks), and genetically confirmation (biallelic *ABCC6* mutations) (1). Exclusion criteria were severe renal impairment, known abnormality of the esophagus, known sensitivity to etidronate, use of bisphosphonates during the past 5 years, osteomalacia, chronic diarrhea, pregnancy, claustrophobia, hypocalcemia (calcium <2.20 mmol/l), and vitamin D