Calcitriol Monotherapy for X-linked hypophosphatemia: Effects on Mineral Ions, Growth, and Skeletal Parameters

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Study design and participants: This HIPAA-compliant, prospective single-arm 12-month interventional clinical trial assessed calcitriol monotherapy for children and adults with XLH, was conducted between March 2019 and February 2024. The study was approved by the Partners Human Research Committee and registered on clinicaltrials.gov (NCT03748966). Informed consent was obtained from all adult participants and assent and parental consent were obtained for pediatric participants.

The primary endpoints were change in the serum phosphate concentration, nephrocalcinosis score, and radiographic rickets severity score (pediatric participants only). Secondary endpoints included change in height z-score in children and change in high-resolution peripheral quantitative computed tomography (HRpQCT) parameters in all subjects. Participants were evaluated at baseline and at 4, 6, 9, and 12 months. Laboratory testing was obtained at 1, 2, and 3 months, and calcitriol dose was titrated according to the schema described below. The baseline and 12-month visits were in-person; intervening visits could be in-person or virtual per participant preference due to Covid-19 pandemic restrictions. HRpQCT and renal ultrasound were performed at baseline and at 12 months. Rickets severity score was determined in pediatric participants at baseline, 4 months, and 12 months.

Participants with a clinical and/or genetic diagnosis of XLH were recruited for the study by investigators or referring physicians. Participants with average PTH >1.5-fold the upper limit of normal for the reference laboratory, average calcium ≥ 10.0 mg/dL, or 25(OH)D <20 ng/dL within the preceding 24 months were excluded. These 25(OHD) levels were used to rule out co-existing vitamin D deficiency. Additional exclusion criteria included chronic kidney disease

(defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2), allergy to calcitriol, pregnancy, lactation, current use of growth hormone therapy, use of diuretics, or skeletally active agents (including bisphosphonates, teriparatide, and progesterone-only contraceptive agents), use of cinacalcet or glucocorticoids within 2 weeks, and history of malignancy, significant history of poorly controlled psychiatric or substance use disorder, or significant cardiopulmonary disease. Participants were also excluded if there were no available laboratory values for serum calcium, phosphate, and creatinine within the 24 months prior to enrollment.

Calcitriol dose initiation and titration:

Washout: Participants taking phosphate and/or calcitriol stopped treatment 2 weeks prior to the baseline visit. One participant (XLH110) was treated with burosumab and was required to stop this medication 8 weeks prior to the baseline visit.

Initial dose: For participants not taking calcitriol prior to enrollment, calcitriol was initiated following the baseline visit at a dose of 20 ng/kg divided twice daily for pediatric participants and 0.25 mcg twice daily for adults. To determine the effects of optimization of calcitriol therapy, the initial dose was 50% higher than their individual pre-study dose for those already taking calcitriol.

Dose titration: Doses were titrated at the 1-month and 2-month follow-up visits based on fasting morning serum calcium (sCa) concentration and second-void urine calcium/creatinine ratio (UCa/Cr) according to the following schema: if sCa was in the normal range for the reference laboratory and UCa/Cr was ≤ 0.4, the calcitriol dose was increased by 25% (pediatric participants) or by 0.25 mcg/day (adults). If sCa was ≥0.5 mg/dl above the upper limit of normal

or if Uca/Cr ratio was >0.4, the calcitriol dose was decreased by 25% (pediatric participants) or by 0.25 mcg/day (adults).

Dose continuation: Participants remained on the dose of calcitriol established at the 3-month visit for the remainder of the 12-month trial unless a dose reduction was mandated based on elevated sCa or Uca/Cr observed on follow-up labs obtained at 4, 6, and 9 months. At the time of each study visit, participants were provided with a diary to record calcitriol intake which was reviewed at the subsequent visit along with current and past calcitriol prescription bottles to ascertain adherence. At each study visit, dietary intake of calcium in the form of calcium supplements and calcium rich foods were monitored, so as to not exceed the age-appropriate recommended daily allowance.

Demographics and anthropometrics: Participants were asked to self-identify their race. For pediatric participants, sitting and standing heights were measured on a stadiometer at baseline and 12 months to the nearest 0.1 cm. Z-scores for heights and sitting-standing height ratio were calculated[1-3].

Laboratory data: At all study visits (baseline, 4, 6, 9, and 12 months) and dose-titration time points (1, 2, and 3 months), serum calcium, phosphorus, and creatinine, and fasting second voided urine calcium, phosphate, and creatinine were evaluated. The urine calcium/creatinine ratio and tubular resorption of phosphate (TRP) were calculated using these measurements. At baseline and 12 months, fasting serum alkaline phosphatase, parathyroid hormone (PTH), 1,25D, and FGF23 were analyzed. Pre-study 25OHD levels were required to have been measured within 24 months of the baseline visit and were obtained from participants' primary endocrinologists.

At the baseline and 12-month visits, calcium, phosphate, creatinine, and urine studies were analyzed at Quest Diagnostics; labs at intervening visits were done at Quest or at participants' local laboratory facilities. Serum alkaline phosphatase and 1,25D were measured through Quest Laboratories, with 1,25D being measured by liquid chromatography/mass spectrometry. Serum PTH was measured by Quest Laboratories using the Roche ECLIA assay. Serum intact FGF23 was measured by ELISA (Kainos Laboratories, Inc., Tokyo, Japan, kindly performed by Dr. Karl Insogna at Yale University School of Medicine) (RRID AB_3105844).

Rickets assessment: For pediatric participants, anteroposterior bilateral knee and wrist x-rays were obtained at baseline, 4 months, and 12 months. Images were evaluated by an expert blinded to each participant using the Thacher rickets severity score, ranging from 0 for normal growth plates and 10 for the most severe rickets[4].

Renal imaging: Ultrasonography was obtained at baseline and 12 months by certified sonographers according to standard departmental protocol. Each scan was read by 2 fellowship trained radiologists blinded to participant and visit number on three separate occasions, for a total of 6 scores per scan. Each image was scored for nephrocalcinosis by a validated scale ranging from 0 (no nephrocalcinosis) to 3 (severe echogenicity of entire medullary pyramids). A score of 4 is given if overt stone formation is seen at the renal fornices[5, 6]. The mean of the 6 readings for each scan was used for analysis. The weighted kappa statistic between raters was 0.27 and the overall intraclass correlation was 0.55.

HRpQCT imaging: At baseline and 12 months, volumetric BMD and bone microarchitecture were evaluated at the distal and diaphyseal regions of the radius and tibia by high-resolution peripheral quantitative computed tomography (HRpQCT) (XtremeCT II; Scanco Medical AG, Brüttisellen, Switzerland)[7]. Analyzers of the scans were blinded to participant identities. The non-dominant side was scanned unless participants had a history of fracture or surgery of that region in which case the contralateral side was scanned. The scanned regions were 10.2 mm in length with an isotropic voxel size of 61 μm and were defined as a percentage of the individual participant's bone length (adult participants: 4% and 30% radius and 7% and 30% tibia; pediatric participants: 7% and 30% radius and 8% and 30% tibia). Some pediatric scans were inadvertently collected at the adult ROI; if the ROI was not matched between baseline and follow-up, the overlapping ROIs were analyzed by manual adjustment. For adult participants, ROIs of the distal radius and tibia at baseline and follow-up were matched by two-dimensional registration (distal radius common region 91-100%, distal tibia common region 91-100%, diaphyseal sites were not subjects to registration). Scans were graded on a 5-point scale for motion artifact; all scans had scores ≤ 3 and were thus included in the analysis[8]. Baseline metaphyseal scans were excluded in one pediatric participant as the adult ROI was used and there was no evaluable metaphyseal bone in the scan.

Manufacturer software was used to generate periosteal and endosteal contours with inspection and manual correction as necessary[9]. We measured total, cortical, and trabecular volumetric BMD, total area, cortical thickness and porosity. Failure load was estimated using microfinite element analysis of the HR-pQCT images by simulated application of a 1% compressive strain using a yield criterion of 2% critical volume and 7000 μstrain[10, 11].

HRpQCT scans were acquired, analyzed and reported in accordance with recommended guidelines[8].

Statistics and data analysis:

Power calculation: We anticipated requiring 7 pediatric and 7 adult XLH participants to achieve 90% power at an alpha of 0.05 to detect a 20% increase in serum phosphate above non-treatment baseline, in response to calcitriol, with a variation of 0.2 mg/dl, equivalent to a standard deviation of 12%. We additionally anticipated that we would require the same number of participants to achieve 90% power at an alpha of 0.05 to detect a 10% increase in TmP/GFR (ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate) in response to calcitriol with a variation of 0.3, equivalent to a standard deviation of 12%. To accommodate a 30% drop-out/non-compliance rate with the study protocol, we aimed to enroll 10 pediatric and 10 adult participants. Due to slow recruitment of pediatric participants associated with approval of burosumab just prior to study initiation as well as the Covid-19 pandemic, we enrolled fewer than anticipated pediatric participants.

We performed descriptive analyses summarizing pediatric and adult participants at baseline. Change in laboratory parameters, nephrocalcinosis score, HR-pQCT parameters, height z-score, and rickets severity score were evaluated with paired t-tests (Stata 18.0, StataCorp, College Station, TX). Given substantial differences in reference ranges for laboratory and HRpQCT

parameters, all analyses were performed separately in pediatric and adult cohorts. P values <0.05 were considered to be statistically significant.

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