2018

Burosumab therapy in children with x-linked hypophosphatemia

Thomas O. Carpenter
Yale University School of Medicine

Michael P. Whyte
Washington University School of Medicine in St. Louis

Erik A. Imel
Indiana University School of Medicine

Annemieke M. Boot
University of Groningen

Wolfgang Hogler
Birmingham Children's Hospital

See next page for additional authors

ORIGINAL ARTICLE

Burosumab Therapy in Children with X-Linked Hypophosphatemia

Thomas O. Carpenter, M.D., Michael P. Whyte, M.D., Erik A. Imel, M.D., Annemieke M. Boot, M.D., Ph.D., Wolfgang Högler, M.D., Agnès Linglart, M.D., Ph.D., Raja Padidela, M.D., William van't Hoff, M.D., Meng Mao, Ph.D., Chao-Yin Chen, Ph.D., Alison Skrinar, Ph.D., Emil Kakkis, M.D., Ph.D., Javier San Martin, M.D., and Anthony A. Portale, M.D.

ABSTRACT

BACKGROUND

X-linked hypophosphatemia is characterized by increased secretion of fibroblast growth factor 23 (FGF-23), which leads to hypophosphatemia and consequently rickets, osteomalacia, and skeletal deformities. We investigated burosumab, a monoclonal antibody that targets FGF-23, in patients with X-linked hypophosphatemia.

METHODS

In an open-label, phase 2 trial, we randomly assigned 52 children with X-linked hypophosphatemia, in a 1:1 ratio, to receive subcutaneous burosumab either every 2 weeks or every 4 weeks; the dose was adjusted to achieve a serum phosphorus level at the low end of the normal range. The primary end point was the change from baseline to weeks 40 and 64 in the Thacher rickets severity total score (ranging from 0 to 10, with higher scores indicating greater disease severity). In addition, the Radiographic Global Impression of Change was used to evaluate rachitic changes from baseline to week 40 and to week 64. Additional end points were changes in pharmacodynamic markers, linear growth, physical ability, and patient-reported outcomes and the incidence of adverse events.

RESULTS

The mean Thacher rickets severity total score decreased from 1.9 at baseline to 0.8 at week 40 with every-2-week dosing and from 1.7 at baseline to 1.1 at week 40 with every-4-week dosing ($P<0.001$ for both comparisons); these improvements persisted at week 64. The mean serum phosphorus level increased after the first dose in both groups, and more than half the patients in both groups had levels within the normal range (3.2 to 6.1 mg per deciliter [1.0 to 2.0 mmol per liter]) by week 6. Stable serum phosphorus levels were maintained through week 64 with every-2-week dosing. Renal tubular phosphate reabsorption increased from baseline in both groups, with an overall mean increase of 0.98 mg per deciliter (0.32 mmol per liter). The mean dose of burosumab at week 40 was 0.98 mg per kilogram of body weight with every-2-week dosing and 1.50 mg per kilogram with every-4-week dosing. Across both groups, the mean serum alkaline phosphatase level decreased from 459 U per liter at baseline to 369 U per liter at week 64. The mean standing-height z score increased in both groups, with greater improvement seen at all time points with every-2-week dosing (an increase from baseline of 0.19 at week 64) than with every-4-week dosing (an increase from baseline of 0.12 at week 64). Physical ability improved and pain decreased. Nearly all the adverse events were mild or moderate in severity.

CONCLUSIONS

In children with X-linked hypophosphatemia, treatment with burosumab improved renal tubular phosphate reabsorption, serum phosphorus levels, linear growth, and physical function and reduced pain and the severity of rickets. (Funded by Ultragenyx Pharmaceutical and Kyowa Hakko Kirin; ClinicalTrials.gov number, NCT02163577; EudraCT number, 2014-000406-35).

From Yale University School of Medicine, New Haven, CT (T.O.C.); Shriners Hospital for Children and Division of Bone and Mineral Diseases, Department of Internal Medicine, Washington University School of Medicine, St. Louis (M.P.W.); Indiana University School of Medicine, Indianapolis (E.A.I.); University of Groningen, Groningen, the Netherlands (A.M.B.); Birmingham Children's Hospital, Birmingham (W. Högler), Royal Manchester Children's Hospital, Manchester (R.P.), and Great Ormond Street Hospital, London (W. van't Hoff) — all in the United Kingdom; Assistance Publique–Hôpitaux de Paris Hôpital Bicêtre, Paris (A.L.); and Ultragenyx Pharmaceutical, Novato (M.M., C.-Y.C., A.S., E.K., J.S.M.), and University of California at San Francisco, San Francisco (A.A.P.) — both in California. Address reprint requests to Dr. Carpenter at Yale University School of Medicine, Department of Pediatrics (Endocrinology), P.O. Box 208064, New Haven, CT 06520-8064, or at thomas.carpenter@yale.edu.

N Engl J Med 2018;378:1987-98.
DOI: 10.1056/NEJMoa1714641

A Quick Take is available at NEJM.org

X-linked hypophosphatemia, a disorder of renal phosphate wasting and the most common heritable form of rickets, is caused by loss-of-function mutations in the gene encoding phosphate-regulating endopeptidase homolog X-linked (*PHEX*), which results in excess circulating fibroblast growth factor 23 (FGF-23).[1] FGF-23 is the primary regulator of phosphate homeostasis and acts by controlling phosphate reabsorption in the kidney.[2] Excess FGF-23 impairs renal phosphate reabsorption, which leads to hypophosphatemia, and decreases the synthesis of the active metabolite of vitamin D, 1,25-dihydroxyvitamin D (also known as $1,25[OH]_2D$). Chronic hypophosphatemia leads to rickets and osteomalacia, which often result in stunted growth, lower-limb deformity, pain, and physical dysfunction that can limit daily activities.[1,3-5]

Conventional therapy for X-linked hypophosphatemia consists of multiple daily doses of oral phosphate salts and vitamin D metabolites or analogues as replacement therapy.[6] This treatment, which has been in place for approximately four decades, transiently increases serum phosphorus levels; however, it is associated with incomplete healing of rickets, residual skeletal deformity, persistent short stature, gastrointestinal side effects, and risks of metabolic and endocrine abnormalities such as hypercalciuria, nephrocalcinosis, and hyperparathyroidism.[1,5,7-12]

Burosumab is a recombinant human IgG1 monoclonal antibody that targets FGF-23.[13,14] In phase 1 and 2 trials involving adults with X-linked hypophosphatemia, treatment with burosumab, administered at doses of up to 1 mg per kilogram of body weight every 4 weeks, improved renal tubular phosphate reabsorption, thereby increasing serum phosphorus to normal levels, and increased serum 1,25-dihydroxyvitamin D levels.[13-15] Here, we report the results of a clinical trial that evaluated the efficacy and safety of burosumab in pediatric patients with X-linked hypophosphatemia.

Methods

Patients

Children between 5 and 12 years of age were eligible for participation if they had received a diagnosis of X-linked hypophosphatemia; if they had active rickets at growth plates, bowing of the femur or tibia, or both; and if their pubertal stage was classified as Tanner stage 2 or lower (with stages ranging from 1 to 5 and higher stages indicating more advanced pubertal development). X-linked hypophosphatemia was confirmed either by the presence of the *PHEX* mutation in the patient or a directly related family member or by a serum intact FGF-23 level of more than 30 pg per milliliter.[16,17] Additional inclusion criteria were a fasting serum phosphorus level of 2.8 mg or less per deciliter (0.90 mmol per liter) and a standing height below the 50th percentile for age and sex on the basis of local normative data from the United States or Europe. After the initial 36 patients were enrolled, another 16 patients were enrolled to provide additional safety and efficacy data. The 16 additional patients were required to have a Thacher rickets severity total score of at least 1.5 at the knee.[18] Thacher rickets severity total score ranges from 0 (no rickets) to 10 (severe rickets); scores between 0 and 5 are typically observed in children with the form of rickets assessed in this trial. All the participants discontinued the conventional therapy they were receiving for X-linked hypophosphatemia for the duration of the trial. Key exclusion criteria were the use of vitamin D metabolites or analogues within 14 days before screening; the use of oral phosphate supplements, aluminum hydroxide antacids, systemic glucocorticoids, or thiazide diuretics within 7 days before screening; the use of growth hormone therapy within 3 months before screening; nephrocalcinosis of grade 3 or higher as assessed by renal ultrasonography[19]; hypocalcemia or hypercalcemia; tertiary hyperparathyroidism as determined by the investigator; or the use of calcimimetic agents within 2 months before screening.

Trial Design

In this randomized, open-label, parallel-group, phase 2 trial, we investigated the efficacy and safety of burosumab in children with X-linked hypophosphatemia at nine sites in the United States and Europe (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients were randomly assigned, in a 1:1 ratio, to receive burosumab subcutaneously every 2 weeks or every 4 weeks during a 16-week dose-escalation period, followed by a 48-week treatment period, for a total of 64 weeks of treatment. Patients had the option to enroll in

an open-label extension. Enrollment of the initial 36 patients could include no more than 20 boys or 20 girls.

After the initial doses of burosumab (0.1 mg per kilogram every 2 weeks or 0.2 mg per kilogram every 4 weeks) were administered and no severe side effects were observed, patients were assigned sequentially to receive escalating doses (0.2 or 0.3 mg per kilogram every 2 weeks, or 0.4 or 0.6 mg per kilogram every 4 weeks). During the dose-escalation period, the dose was adjusted according to the patient's fasting serum phosphorus level 2 weeks after administration, with a goal of attaining a phosphorus level at the low end of the normal range (see the Supplementary Appendix).

TRIAL END POINTS

The primary end point was the change from baseline (with baseline scores determined according to radiographs obtained at screening) to week 40 and week 64 in the Thacher rickets severity total score, as determined by an independent central reader who was unaware of the treatment assignments; scores reflected combined assessments of prespecified radiographic abnormalities at the wrist and knee.[18] In addition, the Radiographic Global Impression of Change was used to evaluate rachitic changes from baseline to week 40 and to week 64; three radiologists who were unaware of the treatment assignments each provided scores, which were subsequently averaged. The Radiographic Global Impression of Change scale is a tool that enables a side-by-side comparison of radiographs obtained before and after treatment and is based on a 7-point ordinal scale that ranges from 3 (complete healing) to −3 (severe worsening). An assessment of deformities of the legs was also performed with the use of the Radiographic Global Impression of Change scale.[20]

Secondary end points included the change from baseline in the following pharmacodynamic variables: the renal tubular phosphate reabsorption (expressed as the ratio of the maximum rate of tubular reabsorption of phosphate to the glomerular filtration rate), the serum phosphorus level, the serum 1,25-dihydroxyvitamin D level, and the serum alkaline phosphatase level (a marker of rachitic activity); all serum and urine samples for these assessments were obtained during fasting.[18,21-24] Additional details of the trial methods and the timing of assessments are available in the Supplementary Text section and Table S1 in the Supplementary Appendix. We also assessed the height-for-age z score, physical ability (as evaluated with the use of the 6-minute walk test), and patient-reported pain and functional disability (as measured with the use of the Pediatric Orthopedic Society of North America Pediatric Outcomes Data Collection Instrument; normative scores range from 0 to 100, with higher scores indicating better functioning or less pain).[25-27]

All reported adverse events and serious adverse events were tabulated. Changes in levels of serum calcium and serum intact parathyroid hormone and in urinary excretion of calcium were determined. Urinary phosphorus was measured to calculate the ratio of the maximum rate of tubular reabsorption of phosphate to the glomerular filtration rate. Serial assessments of the development of both immunoreactive and neutralizing antibodies to burosumab were performed. Evidence of ectopic calcification was evaluated by renal and cardiac ultrasonography.[19]

TRIAL OVERSIGHT

The institutional review board at each participating site approved the protocol, available at NEJM.org. Parents or guardians provided written informed consent for their children to participate, and when age-appropriate, the patient's assent was obtained before participation. An external data and safety monitoring committee monitored patient safety. The trial investigators and the sponsors, Ultragenyx Pharmaceutical and Kyowa Hakko Kirin, designed the trial and collected, analyzed, and interpreted the data. The authors made the decision to submit the manuscript for publication and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The manuscript was written by the authors with medical writing support from the sponsors.

STATISTICAL ANALYSIS

For all the analyses of pharmacodynamic markers, P values were calculated for the mean change from baseline to week 40 with the use of paired Student's t-tests. For the analysis of the Thacher rickets severity total score, we calculated P values and 95% confidence intervals for the least-squares mean change from baseline to week 40 using

the generalized estimating equation approach, which included regimen, trial visit, baseline Thacher rickets severity total score, and the interaction between regimen and trial visit as categorical variables, with an exchangeable covariance structure. All other assessments were reported as means and standard deviations, least-squares means and standard errors, or changes from baseline. For the analyses of the Thacher rickets severity total score, serum phosphorus level, renal tubular phosphate reabsorption, 1,25-dihydroxyvitamin D level, and serum alkaline phosphatase level, P values for the mean change from baseline in each dosing group at week 40 are presented as nominal P values.

We estimated that a sample of 50 patients would provide the trial with at least 90% power to detect a mean (±SD) change from baseline of 0.5±0.5 in the Thacher rickets severity total score. Nominal two-sided P values of 0.05 or less were considered to indicate statistical significance.

RESULTS

PATIENTS

A total of 79 children were screened, of whom 52 (66%) were eligible for participation and were randomly assigned to receive burosumab either every 2 weeks or every 4 weeks (26 patients in each group). All 52 patients completed 64 weeks of treatment, were included in the efficacy and safety analyses, and continued into the extension period.

Overall, the demographic and clinical characteristics of the two groups were similar at baseline, although standing height was slightly greater in the every-2-week dosing group (Table 1). At baseline, patients had persistent rickets, bowing of the femur or tibia, or both, as well as short stature, even though 96% had received previous conventional therapy for X-linked hypophosphatemia for a mean of 6.9 years. At baseline, 94% of the patients had active rickets at growth plate sites (Thacher rickets severity total score >0). Baseline radiographs revealed that many patients had metaphyseal abnormalities at the distal femur (lucency, 98%; separation, 100%; fraying, 89%; and concavity, 89%), proximal tibia (lucency, 89%; separation, 85%; fraying, 67%; and concavity, 79%), distal ulna (lucency, 85%; separation, 73%; fraying, 54%; and concavity, 83%), and distal radius (lucency, 60%; separation, 50%; fraying, 35%; and concavity, 39%).

EFFICACY

By week 40, rickets was significantly ameliorated, with a mean Thacher rickets severity total score of 0.8 in the every-2-week dosing group and 1.1 in the every-4-week dosing group (least-squares mean change, –1.1 with every-2-week dosing and –0.7 with every-4-week dosing; P<0.001 for both comparisons) (Fig. 1A, and Table S2 in the Supplementary Appendix); these improvements were maintained at week 64. The reductions in the Thacher rickets severity total score were greater among the 34 patients who had a Thacher rickets severity total score of 1.5 or higher at baseline, with a least-squares mean change at week 40 of –1.7 with every-2-week dosing and –1.3 with every-4-week dosing (Fig. 1A, and Table S3 in the Supplementary Appendix).

The Radiographic Global Impression of Change global score at week 40 also indicated reduction in the severity of rickets with both dosing regimens (Fig. 1B, and Table S2 in the Supplementary Appendix). Substantial healing of rickets (change from baseline represented by a score of ≥2.0) was achieved in 28 of 52 patients (54%) at week 40 (18 of 26 patients in the every 2-week-dosing group and 10 of 26 patients in the every-4-week dosing group) and also in 28 of 52 patients (54%) at week 64 (15 of 26 patients in the every 2-week-dosing group and 13 of 26 patients in the every-4-week dosing group). Among the 17 patients who had a Thacher rickets severity total score of 1.5 or higher at baseline and were receiving burosumab every 2 weeks, 16 patients (94%) showed substantial healing at week 40 (Fig. 1B, and Table S3 in the Supplementary Appendix). Furthermore, when the Radiographic Global Impression of Change scale was used to assess overall deformities of the legs, a modest improvement was observed at week 64 in all 52 patients (mean [±SE] score representative of change, 0.5±0.1).

The mean fasting serum phosphorus level increased from baseline in both groups at all time points, with an overall mean increase of 0.75 mg per deciliter (0.24 mmol per liter; a 34% increase) (Fig. 2A) at week 40 and 0.84 mg per deciliter (0.27 mmol per liter; a 38% increase) at

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	Burosumab Every 2 Weeks (N=26)	Burosumab Every 4 Weeks (N=26)	All Patients (N=52)
Age — yr			
Mean	8.7±1.7	8.3±2.0	8.5±1.9
Range	5–12	5–12	5–12
Male sex — no. (%)	12 (46)	12 (46)	24 (46)
White race — no. (%)†	23 (88)	23 (88)	46 (88)
Weight — kg	31.9±7.9	29.1±10.7	30.5±9.4
Standing height			
z Score	−1.7±1.0	−2.1±1.0	−1.9±1.00
Percentile for age and sex	11.1±13.8	6.2±8.2	8.7±11.5
Geographic region — no. (%)			
United States	17 (65)	19 (73)	36 (69)
Europe	9 (35)	7 (27)	16 (31)
Previous conventional therapy for X-linked hypophosphatemia — no. (%)	24 (92)	26 (100)	50 (96)
Duration of conventional therapy — yr	7.0±2.1	6.7±2.6	6.9±2.4
Age when conventional therapy was initiated — yr	2.2±1.5	1.9±1.2	2.1±1.3
Renal tubular phosphate reabsorption — mg/dl‡§	2.2±0.5	2.0 ±0.3	2.1±0.4
Serum phosphorus — mg/dl§	2.4±0.4	2.3±0.3	2.3±0.4
Serum 1,25-dihydroxyvitamin D — pg/ml§	41.3±22.0	41.4±15.3	41.3±18.7
Serum alkaline phosphatase — U/liter§	462±110	456±101	459±105
Thacher rickets severity total score¶			
Mean	1.9±1.2	1.7±1.0	1.8±1.1
Range	0–4.5	0–3.0	0–4.5
Positive for pathogenic *PHEX* mutation — no. (%)‖	23 (88)	22 (85)	45 (87)
Nephrocalcinosis grade — no. (%)**			
0	17 (65)	17 (65)	34 (65)
1	6 (23)	5 (19)	11 (21)
2	3 (12)	4 (15)	7 (13)

* Plus–minus values are means ±SD. To convert the values for renal tubular phosphate reabsorption to millimoles per liter, multiply by 0.3229. To convert the values for serum phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for serum 1,25-dihydroxyvitamin D to picomoles per liter, multiply by 2.6. Percentages may not sum to 100 because of rounding.

† Race was determined by parent or caregiver report.

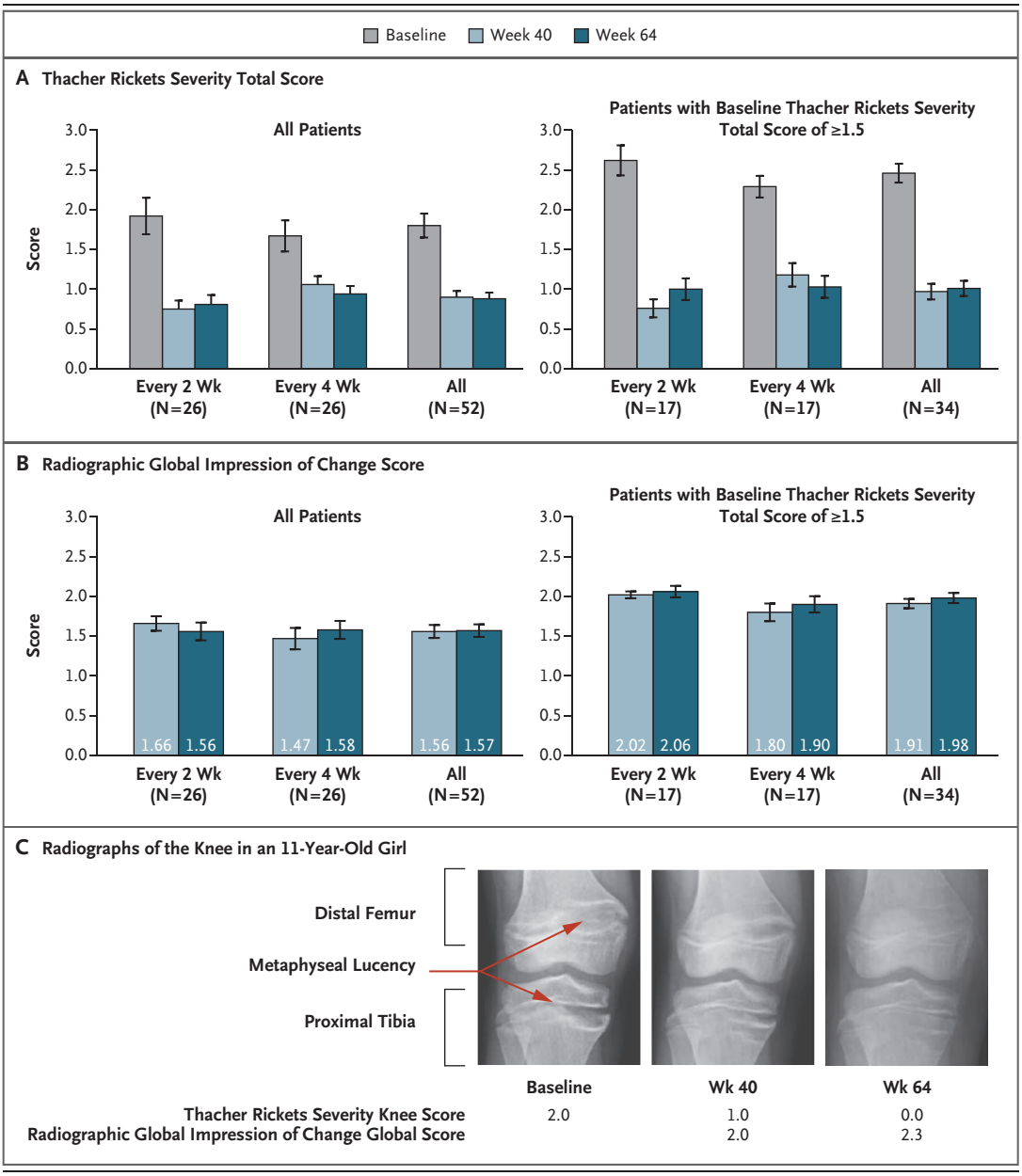
‡ Renal tubular phosphate reabsorption is expressed as the ratio of the maximum rate of tubular reabsorption of phosphate to the glomerular filtration rate.

§ Serum and urine samples for pharmacodynamic assessments were obtained during fasting.

¶ The baseline mean Thacher rickets severity total score (scores range from 0 [no rickets] to 10 [severe rickets]; scores between 0 and 5 are typically observed in children with the form of rickets assessed in this trial) for the 16 patients who enrolled after enrollment of the initial 36 patients was 2.63±0.72.

‖ One patient had a variant in *PHEX* that was considered to be probably pathogenic, and four patients had variants in *PHEX* of unknown significance. No mutation in *PHEX* was identified in two patients; however, the analysis of mutations in *PHEX* cannot capture all possible mutations that alter *PHEX* activity. The seven patients who were not positive for pathogenic mutations in *PHEX* had a clinical diagnosis of X-linked hypophosphatemia and had a baseline serum intact FGF-23 level of more than 30 pg per milliliter.

** Values range from 0 (normal) to 4 (stone formation).



week 64. By week 6, more than half the patients in both groups had serum phosphorus levels within the normal range (3.2 to 6.1 mg per deciliter [1.0 to 2.0 mmol per liter]). Every-2-week dosing was associated with sustained mean increases in serum phosphorus levels during the treatment period, whereas every-4-week dosing showed fluctuations over time. No patients in either group had a serum phosphorus level above the upper limit of the normal range at any time during the trial.

The renal tubular phosphate reabsorption increased from baseline in both groups at all time points, with an overall mean increase of 0.98 mg per deciliter (0.32 mmol per liter; a 51% increase) (Fig. 2B) at week 40 and 1.01 mg per deciliter (0.33 mmol per liter; a 51% increase) at week 64. The mean serum 1,25-dihydroxyvitamin D level increased from baseline in both groups at all time points, with an overall mean increase of 23 pg per milliliter (60 pmol per liter; a 99% increase) (Fig. 2C) at week 40 and 18 pg per milliliter (46 pmol per liter; a 78% increase) at week 64. The mean serum alkaline phosphatase level decreased from baseline by 90 U per liter overall at week 64 (a 20% decrease) (Fig. 2D).

Figure 1 (facing page). Effects of Burosumab on Rickets Scores.

Panel A shows the mean Thacher rickets severity total score (scores range from 0 [no rickets] to 10 [severe rickets]; scores between 0 and 5 are typically observed in children with the form of rickets assessed in this trial). All 52 patients were included in the analyses at week 40 and at week 64. A significant decrease in the Thacher rickets severity total score was seen at week 40 in both dosing groups ($P<0.001$) on the basis of the generalized estimating equation model. Panel B shows the least-squares mean Radiographic Global Impression of Change score (representing the degree of change from baseline) at week 40 and week 64. The Radiographic Global Impression of Change scale is a tool that enables a side-by-side comparison of radiographs obtained before and after treatment and is based on a 7-point ordinal scale: 3 (complete healing), 2 (substantial healing), 1 (minimal healing), 0 (unchanged), –1 (minimal worsening), –2 (moderate worsening), and –3 (severe worsening). Scores for the Thacher rickets severity total score and the Radiographic Global Impression of Change are shown for all patients and for the subgroup of patients who had a Thacher rickets severity total score of 1.5 or higher at baseline (indicating more severe rickets). I bars in Panels A and B indicate standard errors. Panel C shows a set of radiographs of the knee from an 11-year-old girl who had been receiving conventional therapy for 9 years before she was enrolled in the trial and was randomly assigned to receive burosumab every 2 weeks. The baseline image shows metaphyseal lucencies of the distal femur and proximal tibia. By week 64, the abnormalities were completely healed (Thacher rickets severity total score of 0). The Radiographic Global Impression of Change score for the knee at week 64 was 2.3, which indicated substantial healing of rickets.

The mean standing-height z score increased from baseline in both groups, with greater improvement seen at all time points with every-2-week dosing (an increase from baseline of 0.19 at week 64) than with every-4-week dosing (an increase from baseline of 0.12 at week 64). Results are shown in Table 2, and in Figure S2A in the Supplementary Appendix.

Across both groups, walking distance in the 6-minute walk test was increased from baseline both at week 40 and at week 64 (Table 2). A total of 24 of the 52 patients (46%) had an impairment (defined as a walking distance that was <80% of the predicted normal distance) at baseline. Among these patients, the 6-minute walk test distance increased from 68% of the predicted normal distance (408 m) at baseline to 79% of the predicted distance (487 m) at week 64 (an increase of 10%; least-squares mean increase in distance walked, 77 m); greater increases were seen among the 14 patients who received the drug every 2 weeks (12% increase; least-squares mean increase in distance walked, 96 m) than among the 10 patients who received the drug every 4 weeks (8% increase; least-squares mean increase in distance walked, 58 m) (Fig. S2B in the Supplementary Appendix).

The baseline mean scores for the sports and physical functioning domain and the pain and comfort domain of the Pediatric Outcomes Data Collection Instrument were low, defined as less than 1 SD below the normal population mean.[28] Functional ability improved and pain decreased in both groups (Table 2). Among the 28 patients (54% of the 52 patients) who had greater functional impairment (defined as a score of <40 on the Global Functioning Scale) at baseline, the score on the sports and physical functioning domain increased by a mean of 15.6 at week 64, and the score on the pain and comfort domain increased by a mean of 13.4 at week 64. The results for the upper extremity, transfer and basic mobility, and happiness domains are described in the Supplementary Appendix.

SAFETY

Adverse events were reported in all 52 patients (Table 3). One patient who received burosumab every 4 weeks was hospitalized for serious adverse events of fever and myalgia, both of which were assessed as being moderate in severity and possibly related to burosumab. The fever resolved within 24 hours after onset, the myalgia resolved within 8 days, and the patient continued to receive treatment without recurrence of a similar event. A total of 17 of the 26 patients (65%) in the every-2-week dosing group and 13 of the 26 patients (50%) in the every-4-week dosing group had an injection-site reaction; these reactions were considered to be mild, were limited to the skin, and lasted no more than 1 or 2 days. Other common adverse events across the two dosing groups were headache (26 patients), cough (23 patients), nasopharyngitis (21 patients), and pain in an arm or leg (21 patients). No patients died, discontinued the trial regimen, or had dose-limiting toxic effects. All adverse events reported during the trial were mild or moderate in severity, with the exception of a tooth abscess (in 1 patient) and a rash (in 1 patient); both events were considered by the investigator to be unrelated to the trial treatment.

No noteworthy changes in the levels of serum

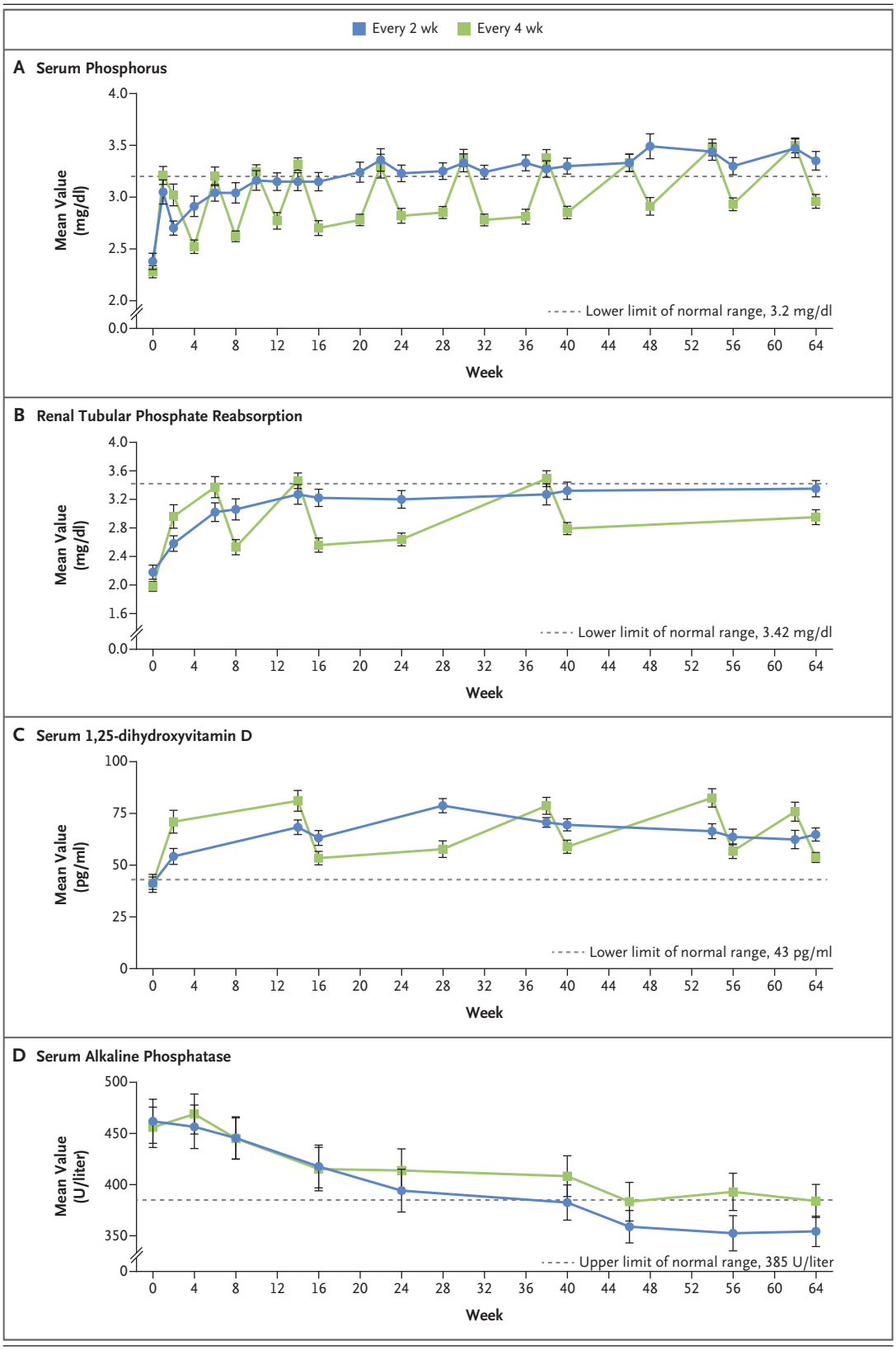


Table 2. Effects of Burosumab on Height, Physical Functioning, and Patient-Reported Outcomes.

Assessment	Burosumab Every 2 Weeks (N=26)	Burosumab Every 4 Weeks (N=26)	All Patients (N=52)
Standing-height z score*			
Baseline	−1.72±1.03	−2.05±0.96	−1.89±1.00
Week 64	−1.54±1.13	−1.92±0.84	−1.73±1.00
Change from baseline	0.19±0.05	0.12±0.06	0.15±0.04
6-Minute walk test†			
Baseline			
Percentage of predicted distance	79.32±2.60	81.42±2.96	80.37±1.96
Distance (m)	479.9±16.6	486.4±21.3	483.1±13.4
Week 64			
Percentage of predicted distance	85.00±2.03	84.74±2.67	84.87±1.66
Change from baseline in percentage of predicted distance — percentage points	5.69±2.02	3.32±1.96	4.50±1.41
Distance (m)	533.85±11.51	525.85±17.56	529.85±10.41
Change from baseline in distance (m)	52.67±8.82	40.59±9.57	46.63±6.48
Sports and physical functioning, normative score*‡			
Baseline	34.6±15.7	32.2±19.3	33.4±17.4
Week 64	41.7±15.7	42.8±13.7	42.2±14.6
Change from baseline	7.7±2.6	9.8±2.5	8.8±1.8
Pain and comfort scale, normative score*‡			
Baseline	35.2±15.3	34.8±16.8	35.0±15.9
Week 64	41.0±17.0	43.0±11.5	42.0±14.5
Change from baseline	5.6±2.9	7.7±2.1	6.7±1.8
Global functioning, normative score*‡			
Baseline	37.5±14.0	35.6±17.2	36.6±15.5
Week 64	43.1±16.1	45.1±11.2	44.1±13.8
Change from baseline	6.0±2.7	8.7±2.0	7.4±1.7

* Plus–minus values at baseline and at week 64 are means ±SD. Plus–minus values for the change from baseline are least-squares means ±SE.
† Plus–minus values for the percentage of predicted distance and for distance are means ±SE. Plus–minus values for the change from baseline are least-squares means ±SE.
‡ This variable was assessed with the use of the Pediatric Orthopedic Society of North America Pediatric Outcomes Data Collection Instrument. The mean (±SD) population normative score is 50±10; higher scores indicate better functioning or less pain.

Figure 2 (facing page). Effects of Burosumab on Pharmacodynamic Variables.

All serum and urine samples were obtained during fasting. A significant mean increase from baseline to week 40 in serum phosphorus level (Panel A), the renal tubular phosphate reabsorption (expressed as the ratio of the maximum rate of tubular reabsorption of phosphate to the glomerular filtration rate) (Panel B), and serum 1,25-dihydroxyvitamin D level (Panel C) was seen among the 26 patients in each group ($P<0.001$). With respect to the serum alkaline phosphatase level (Panel D), there was a significant mean decrease from baseline to week 40 with every-2-week dosing (26 patients, $P<0.001$) and with every-4-week dosing (26 patients, $P=0.002$). Graphs displayed in SI units are available in Figure S5 in the Supplementary Appendix. The reference range for serum alkaline phosphatase was provided by Covance Laboratories, and the reference ranges for the remaining variables were obtained from published articles: serum phosphorus, from Lockitch et al.[24]; renal tubular phosphate reabsorption, from Kruse et al.[23]; and 1,25-dihydroxyvitamin D, from Chesney et al.[22] I bars indicate standard errors.

Table 3. Adverse Events and Antibody Results.

Variable	Burosumab Every 2 Weeks (N=26)	Burosumab Every 4 Weeks (N=26)	All Patients (N=52)
		no. of patients (%)	
Any adverse event	26 (100)	26 (100)	52 (100)
Adverse events with ≥15% incidence in both groups combined			
Injection-site reaction*	17 (65.4)	13 (50.0)	30 (57.7)
Headache	16 (61.5)	10 (38.5)	26 (50.0)
Cough	15 (57.7)	8 (30.8)	23 (44.2)
Nasopharyngitis	8 (30.8)	13 (50.0)	21 (40.4)
Pain in extremity	9 (34.6)	12 (46.2)	21 (40.4)
Upper respiratory tract infection	9 (34.6)	9 (34.6)	18 (34.6)
Vomiting	10 (38.5)	8 (30.8)	18 (34.6)
Arthralgia	7 (26.9)	10 (38.5)	17 (32.7)
Pyrexia	8 (30.8)	8 (30.8)	16 (30.8)
Rash	7 (26.9)	6 (23.1)	13 (25.0)
Seasonal allergy	5 (19.2)	8 (30.8)	13 (25.0)
Abdominal pain, upper	4 (15.4)	5 (19.2)	9 (17.3)
Oropharyngeal pain	3 (11.5)	6 (23.1)	9 (17.3)
Diarrhea	3 (11.5)	5 (19.2)	8 (15.4)
Nasal congestion	4 (15.4)	4 (15.4)	8 (15.4)
Nausea	5 (19.2)	3 (11.5)	8 (15.4)
Rhinorrhea	2 (7.7)	6 (23.1)	8 (15.4)
Serious adverse event	0	1 (3.8)	1 (1.9)
Leading to discontinuation of trial regimen	0	0	0
Resulting in death	0	0	0
Presence of antibody to burosumab	0	0	0

* This category includes the following reactions at the injection site: erythema, swelling, rash, pruritus, bruising, pain, discoloration, hematoma, hemorrhage, macule, and urticaria.

calcium, urinary calcium, or serum intact parathyroid hormone were observed (Figs. S3 and S4 in the Supplementary Appendix), and no notable changes in vital signs occurred. Mild elevations in serum amylase levels, primarily the salivary isoenzyme, were detected in 13 patients at screening and in 26 patients during at least one of nine total assessments through week 64. None of the elevations were associated with symptoms. Evaluation of renal ultrasonographic images to detect nephrocalcinosis revealed no change from baseline in renal ultrasound scores (0 [normal] to 4 [stone formation][19,29]) in 21 patients in each group; of the remaining patients, 1 patient in each group had a decrease in score from 1 to 0 and 3 patients in each group had an increase in score from 0 to 1, 1 to 2, or 2 to 3. Ultrasonographic data from 2 patients were missing. No patient had a change in renal ultrasound score of more than 1 point. Renal function remained normal. There was no evidence of ectopic myocardial mineralization on echocardiography. No antibodies to burosumab were detected at any postbaseline visits. The mean dose of burosumab at week 40 was 0.98 mg per kilogram with every-2-week dosing and 1.50 mg per kilogram with every-4-week dosing.

DISCUSSION

In the current trial, inhibition of FGF-23 activity with burosumab, a recombinant human IgG1 monoclonal antibody, was associated with an increase in renal tubular phosphate reabsorption

and the correction of hypophosphatemia in children with X-linked hypophosphatemia. The improvement in phosphate metabolism corresponded to a decrease in the severity of rickets. The healing of rickets probably contributed to concurrent improvements in growth and physical activity and a reduction in pain.

Treatment with burosumab administered once every 2 weeks provided a sustained increase in the serum phosphorus level to normal or near-normal levels after the dose was adjusted to approximately 1 mg per kilogram, whereas every-4-week dosing was associated with lower levels of serum phosphorus at the end of the dose interval. Pharmacodynamic results showed a plateaued treatment response, which suggested that feedback mechanisms may stabilize the levels of serum phosphorus and 1,25-dihydroxyvitamin D when the duration of exposure is longer or the dose levels are higher. Every-2-week dosing resulted in substantial healing of rickets in nearly all the children who had more severe rickets at baseline. These results indicate that burosumab at a dose of approximately 1.0 mg per kilogram administered every 2 weeks is an appropriate regimen for improving renal tubular phosphate reabsorption and clinical outcomes in children with X-linked hypophosphatemia.

Small but significant amelioration of leg deformity, as assessed by scores on the Radiographic Global Impression of Change, were observed. Studies in animals suggest that normalization of the ambient phosphate milieu may correct the disrupted cellular organization of the rachitic growth plate to allow for improved growth.[30-33]

In children with X-linked hypophosphatemia, ongoing management of the disease is critical to elicit the best possible skeletal outcomes; therefore, a placebo control group was deemed to be unacceptable, given the duration of the current trial. An active control group was not included in the trial owing to the lack of clinical data regarding burosumab or conventional therapy and to the considerable variability in the application of conventional therapy.[1] Despite the lack of a control group, the consistent improvement in the fasting serum phosphorus response that was observed in all the patients coincided with improvements in multiple related efficacy end points, including amelioration of rickets, increase in linear growth, improvement in physical ability, and reduction in pain. These findings suggest a therapeutic benefit in a pediatric population with X-linked hypophosphatemia in which almost all the patients had previously received conventional therapy with limited clinical improvement. On the basis of the findings from this trial, a phase 3 trial (ClinicalTrials.gov number, NCT02915705), which is ongoing, was designed to investigate the efficacy and safety of burosumab as compared with conventional therapy.

No clinically significant safety findings with burosumab were observed during the current trial. The most commonly reported adverse events were either typical for children or were common manifestations of X-linked hypophosphatemia.[1,34-38] Hyperphosphatemia was not observed in any patient during treatment. Moreover, no noteworthy changes in levels of serum calcium, urinary calcium, or serum intact parathyroid hormone were noted, and no antibodies to burosumab were detected after treatment.

For more than 40 years, treatment for X-linked hypophosphatemia has consisted of multiple daily doses of oral phosphate salts and active vitamin D. This approach is often difficult to maintain, particularly in younger patients, owing to the burdens of multiple daily dosing, parental surveillance, and suboptimal phosphate preparations.[5] The limitations of conventional therapy are evidenced by the persistence of rickets observed in radiographs obtained at screening in this trial despite the patients having received therapy for X-linked hypophosphatemia at academic specialty centers for multiple years.[1,5,6] By targeting a central pathophysiological defect in X-linked hypophosphatemia (i.e., excess FGF-23), burosumab improved phosphate homeostasis and decreased the severity of rickets.

The research was carried out at the National Institute for Health Research/Wellcome Birmingham Clinical Research Facility (Birmingham, United Kingdom). The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health.

Supported by Ultragenyx Pharmaceutical and Kyowa Hakko Kirin.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients and their parents and caregivers; the health care professionals who participated in this trial, including Marian Hart, Amy Reeves, Karen Mack, Eric Cox, Connie Sullivan, Stuart Warden, Michelle Hepburn, Elizabeth A. Olear, Joanne Walker, Vinodhini Lakshman, Melissa Fang, and Jessie Chen; the following sub-investigators: Anya Rothenbuler, Claire Morel-Bouvattier, Valentina Gracchi, Farzana Perwad, Linda DiMeglio, Munro Peacock, Gary S. Gottesman, Zulf Mughal, Karl Insogna, Clemens Bergwitz, Detlef Bockenhaur, Wesley Hayes, Nick Shaw, Vrinda Saraff, and Sophia Sakka; and Ting Chang, Ph.D., and Catherine Woods, Ph.D., of Ultragenyx Pharmaceutical for medical writing support.

REFERENCES

1. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. J Bone Miner Res 2011;26:1381-8.
2. Liu S, Quarles LD. How fibroblast growth factor 23 works. J Am Soc Nephrol 2007;18:1637-47.
3. Reid IR, Hardy DC, Murphy WA, Teitelbaum SL, Bergfeld MA, Whyte MP. X-linked hypophosphatemia: a clinical, biochemical, and histopathologic assessment of morbidity in adults. Medicine (Baltimore) 1989;68:336-52.
4. Lee JY, Imel EA. The changing face of hypophosphatemic disorders in the FGF-23 era. Pediatr Endocrinol Rev 2013; 10:Suppl 2:367-79.
5. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. Endocr Connect 2014;3:R13-R30.
6. Glorieux FH, Marie PJ, Pettifor JM, Delvin EE. Bone response to phosphate salts, ergocalciferol, and calcitriol in hypophosphatemic vitamin D-resistant rickets. N Engl J Med 1980;303:1023-31.
7. Petersen DJ, Boniface AM, Schranck FW, Rupich RC, Whyte MP. X-linked hypophosphatemic rickets: a study (with literature review) of linear growth response to calcitriol and phosphate therapy. J Bone Miner Res 1992;7:583-97.
8. Mäkitie O, Doria A, Kooh SW, Cole WG, Daneman A, Sochett E. Early treatment improves growth and biochemical and radiographic outcome in X-linked hypophosphatemic rickets. J Clin Endocrinol Metab 2003;88:3591-7.
9. Nielsen LH, Rahbek ET, Beck-Nielsen SS, Christesen HT. Treatment of hypophosphataemic rickets in children remains a challenge. Dan Med J 2014;61:A4874.
10. Rafaelsen S, Johansson S, Ræder H, Bjerknes R. Hereditary hypophosphatemia in Norway: a retrospective population-based study of genotypes, phenotypes, and treatment complications. Eur J Endocrinol 2016;174:125-36.
11. Santos F, Fuente R, Mejia N, Mantecon L, Gil-Peña H, Ordoñez FA. Hypophosphatemia and growth. Pediatr Nephrol 2013;28:595-603.
12. Zivičnjak M, Schnabel D, Billing H, et al. Age-related stature and linear body segments in children with X-linked hypophosphatemic rickets. Pediatr Nephrol 2011;26:223-31.
13. Carpenter TO, Imel EA, Ruppe MD, et al. Randomized trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia. J Clin Invest 2014;124:1587-97.
14. Imel EA, Zhang X, Ruppe MD, et al. Prolonged correction of serum phosphorus in adults with X-linked hypophosphatemia using monthly doses of KRN23. J Clin Endocrinol Metab 2015;100:2565-73.
15. Ruppe M, Peacock M, Weber T, et al. Clinical and radiographic characteristics of adult X-linked hypophosphatemia (XLH) in a cohort of patients treated with KRN23, an antibody to FGF23. Presented at the ASBMR 2016 Annual Meeting, Atlanta, September 16–19, 2016:MO0319. abstract.
16. Endo I, Fukumoto S, Ozono K, et al. Nationwide survey of fibroblast growth factor 23 (FGF23)-related hypophosphatemic diseases in Japan: prevalence, biochemical data and treatment. Endocr J 2015;62:811-6 .
17. Endo I, Fukumoto S, Ozono K, et al. Clinical usefulness of measurement of fibroblast growth factor 23 (FGF23) in hypophosphatemic patients: proposal of diagnostic criteria using FGF23 measurement. Bone 2008;42:1235-9.
18. Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Manaster BJ, Reading JC. Radiographic scoring method for the assessment of the severity of nutritional rickets. J Trop Pediatr 2000;46:132-9.
19. Verge CF, Lam A, Simpson JM, Cowell CT, Howard NJ, Silink M. Effects of therapy in X-linked hypophosphatemic rickets. N Engl J Med 1991;325:1843-8.
20. Whyte MP, Fujita KP, Moseley S, Thompson DD, McAlister WH. Validation of a novel scoring system for changes in skeletal manifestations of hypophosphatasia in newborns, infants, and children: the Radiographic Global Impression of Change scale. J Bone Miner Res 2018;33: 868-74.
21. Carpenter TO, Shaw NJ, Portale AA, Ward LM, Abrams SA, Pettifor JM. Rickets. Nat Rev Dis Primers 2017;3:17101.
22. Chesney RW, Rosen JF, Hamstra AJ, DeLuca HF. Serum 1,25-dihydroxyvitamin D levels in normal children and in vitamin D disorders. Am J Dis Child 1980; 134:135-9.
23. Kruse K, Kracht U, Göpfert G. Renal threshold phosphate concentration (TmPO4/GFR). Arch Dis Child 1982;57: 217-23.
24. Lockitch G, Halstead AC, Albersheim S, MacCallum C, Quigley G. Age- and sex-specific pediatric reference intervals for biochemistry analytes as measured with the Ektachem-700 analyzer. Clin Chem 1988;34:1622-5.
25. Daltroy LH, Liang MH, Fossel AH, Goldberg MJ. The POSNA pediatric musculoskeletal functional health questionnaire: report on reliability, validity, and sensitivity to change. J Pediatr Orthop 1998;18:561-71.
26. Flegal KM, Cole TJ. Construction of LMS parameters for the Centers for Disease Control and Prevention 2000 growth charts. Natl Health Stat Report 2013;11: 1-3.
27. Geiger R, Strasak A, Treml B, et al. Six-minute walk test in children and adolescents. J Pediatr 2007;150:395-9.
28. Klepper SE. Measures of pediatric function: Child Health Assessment Questionnaire (C-HAQ), Juvenile Arthritis Functional Assessment Scale (JAFAS), Pediatric Outcomes Data Collection Instrument (PODCI), and Activities Scale for Kids (ASK). Arthritis Care Res (Hoboken) 2011; 63:Suppl 11:S371-S382.
29. Patriquin H, Robitaille P. Renal calcium deposition in children: sonographic demonstration of the Anderson-Carr progression. AJR Am J Roentgenol 1986;146: 1253-6.
30. Sabbagh Y, Carpenter TO, Demay MB. Hypophosphatemia leads to rickets by impairing caspase-mediated apoptosis of hypertrophic chondrocytes. Proc Natl Acad Sci U S A 2005;102:9637-42.
31. Aono Y, Yamazaki Y, Yasutake J, et al. Therapeutic effects of anti-FGF23 antibodies in hypophosphatemic rickets/osteomalacia. J Bone Miner Res 2009;24: 1879-88.
32. Aono Y, Hasegawa H, Yamazaki Y, et al. Anti-FGF-23 neutralizing antibodies ameliorate muscle weakness and decreased spontaneous movement of Hyp mice. J Bone Miner Res 2011;26:803-10.
33. Li YC, Amling M, Pirro AE, et al. Normalization of mineral ion homeostasis by dietary means prevents hyperparathyroidism, rickets, and osteomalacia, but not alopecia in vitamin D receptor-ablated mice. Endocrinology 1998;139:4391-6.
34. Morrell DC. Symptom interpretation in general practice. J R Coll Gen Pract 1972;22:297-309.
35. Hay AD, Heron J, Ness A. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study. Fam Pract 2005;22:367-74.
36. Antonaci F, Voiticovschi-Iosob C, Di Stefano AL, Galli F, Ozge A, Balottin U. The evolution of headache from childhood to adulthood: a review of the literature. J Headache Pain 2014;15:15.
37. Abu-Arafeh I, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. Dev Med Child Neurol 2010;52: 1088-97.
38. Clifford RD, Radford M, Howell JB, Holgate ST. Prevalence of respiratory symptoms among 7 and 11 year old schoolchildren and association with asthma. Arch Dis Child 1989;64:1118-25.