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Safety and efficacy of burosumab in improving phosphate metabolism, bone health, and quality of life in adolescents with X-linked hypophosphatemic rickets

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ABSTRACT

Background and objective: X-linked hypophosphatemic rickets (XLH) is due to loss-of-function mutations in the phosphate-regulating endopeptidase homologue on the X chromosome (*PHEX*) that lead to increased fibroblast growth factor 23 (FGF23) production. FGF23 excess causes renal phosphate wasting and insufficient 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) synthesis with reduced intestinal phosphate absorption, ultimately resulting in chronic hypophosphatemia.

Children with XLH show typical skeletal lesions of rickets, deformities of the lower limbs, stunted growth with disproportionate short stature, bone pain, and physical dysfunctions.

Burosumab, a fully human IgG1 monoclonal antibody that binds to FGF23 to inhibit its activity, is more effective to improve the biochemical and clinical signs of XLH than conventional treatment with phosphate supplements and vitamin D active metabolites. Data on adolescents with XLH during the transition period to young adulthood are few.

In this prospective case series, we aimed to assess safety and efficacy of burosumab in adolescents with XLH who discontinued long-term conventional therapy.

Methods: Five Caucasian adolescents (4 males, 1 female; mean age 15.4 ± 1.5 years) with XLH were recruited and switched from conventional treatment to burosumab (0.8–1.2 mg/kg, s. c. QW2). Burosumab was continued for 12–48 months and, once discontinued, patients were followed-up for 6–12 months. In all patients, serum calcium, phosphate, alkaline phosphatase (ALP), parathyroid hormone (PTH), and $1,25(OH)_2D$ levels, and renal tubular reabsorption of phosphate (TmP/GFR) values were assessed at entry and during burosumab. Intact FGF23 plasma levels were measured at entry. Patient-reported outcomes (PROs) were assessed at entry and every 3–6 months to evaluate the impact of low extremity pain, stiffness, and difficulties performing daily activities.

Results: At entry, all patients showed hypophosphatemia, increased intact FGF23 levels, reduced TmP/GFR, insufficient $1,25(OH)_2D$ levels, and in four out of five increased ALP levels. Two patients had radiological signs of rickets. During burosumab, all patients showed a significant increase in serum phosphate and $1,25(OH)_2D$ levels, and in TmP/GFR values ($P < 0.05$ - $P < 0.0001$). Serum ALP levels significantly declined ($P < 0.05$) to normal values. No changes of serum calcium and PTH levels (P=NS) were found during burosumab. PROs significantly improved ($P < 0.02$ - $P < 0.0001$) in all patients. Four patients discontinued burosumab when they turned 18 or 19, whereas one continued the treatment since he was still younger than 18 during the study period. Four patients who suspended burosumab showed a rapid decline in serum phosphate and $1,25(OH)_2D$ levels and in TmP/

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GFR values; serum ALP levels increased, and PROs progressively worsened with a significant reduction in quality of life. These consequences were not observed in the patient who continued burosumab treatment.
Discussion: Our data showed that conventional treatment improved only in part the signs and symptoms of XLH. Burosumab was well tolerated and was effective in improving phosphate metabolism, bone health, and PROs. All the benefits of burosumab were lost after its discontinuation. These results suggested that continuing burosumab is required to achieve and maintain the clinical benefits of the treatment during the transition to young adulthood in patients with XLH.

1. Introduction

X-linked hypophosphatemic rickets (XLH, MIM 307800) is a rare, lifelong, and progressive metabolic bone disorder with a estimated prevalence of 1:20,000–60,000 (Beck-Nielsen et al., 2009; Rafaelsen et al., 2016). XLH represents the commonest inherited form of rickets and it is due to loss-of-function mutations in the phosphate-regulating endopeptidase homologue on the X chromosome (*PHEX*) gene which is expressed in osteocytes and odontoblasts. *PHEX* mutation results in excess circulating fibroblast growth factor 23 (FGF23) levels which cause renal phosphate wasting and insufficient 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) production with reduced intestinal phosphate absorption (Beck-Nielsen et al., 2019). The hallmark biochemical findings of patients with XLH include hypophosphatemia, increased alkaline phosphatase (ALP) and FGF23 levels, normal or slightly elevated parathyroid hormone (PTH) levels, normocalcemia, and reduced 1,25 $(OH)_2$D levels for the degree of hypophosphatemia (Baroncelli and Mora, 2021).

Children with XLH show the typical skeletal lesions of rickets and osteomalacia with progressive bowing deformities of the lower limbs, stunted growth with disproportionate short stature, bone pain, and physical dysfunctions (Baroncelli and Mora, 2021). Moreover, dentinal and periodontal abnormalities causing recurrent periapical abscesses with fistulae of both deciduous and permanent teeth affect the majority of children and adults with XLH (Baroncelli et al., 2021; Nguyen et al., 2022). Adults with XLH may have early loss of teeth (Nguyen et al., 2022).

Conventional treatment for children with XLH includes a combination of phosphate supplements and active vitamin D metabolites, such as alfacalcidol or calcitriol. Although this approach has been a mainstay for the treatment of XLH since the early 1980s, it is cumbersome, does not completely correct the skeletal abnormalities and is associated with considerable toxicity, including hypercalcemia, nephrocalcinosis, and secondary or tertiary hyperparathyroidism (Imel, 2021). Moreover, optimal dosage of phosphate supplements and vitamin D active metabolites does not prevent orthopedic surgery in the majority of patients (Imel, 2021).

The recent approval of burosumab, a fully human IgG1 monoclonal antibody to FGF23, has provided a new targeted treatment option for patients with XLH. Burosumab treatment has demonstrated improvement of rickets, lower limb deformities, and growth in children and adolescents with XLH, including during randomized controlled trials compared with conventional therapy (Imel, 2021; Carpenter et al., 2017; Imel et al., 2019; Ward et al., 2022; Ewert et al., 2023). However, there are few data of burosumab treatment specifically in adolescents approaching the transition phase to adulthood, leaving a critical knowledge gap in how to adequately deal with this patient population.

This study aimed to assess the safety and the effects of burosumab treatment on phosphate metabolism, skeletal abnormalities, and bone health in adolescents with XLH previously receiving long-term conventional therapy.

2. Patients data

2.1. Patient reports

Five Caucasian patients with XLH (4 males and 1 female) aged 15.4 ± 1.5 years were recruited at the Pediatric Endocrine Unit of the University Hospital of Pisa, Italy. The diagnosis of XLH was established by clinical, biochemical, and radiographic criteria, and was confirmed by *PHEX* gene mutation. Age at diagnosis was 2.6 ± 1.6 years (range 0.1–4.4 years). Sporadic *PHEX* gene mutation was demonstrated in three patients and familial inheritance in two. Karyotype was 46, XY in all males and 46, XX in the female. All patients had normal weight and length at birth and had normal renal and liver function. All patients received the conventional treatment with inorganic oral phosphate salts (doses titrated up to 35–40 mg elemental phosphorus/kg/d, in four to six divided doses) as Joulie's solution during infancy; thereafter, they received tablets (Reducto Spezial®, Temmler Pharma/Hormosan Pharma, Germany). Phosphate supplements were given in combination with alfacalcidol during infancy or calcitriol during childhood and adolescence (doses titrated up to 25–38 ng/kg/d, once a day for alfacalcidol; and in two or three divided doses for calcitriol) from the time of diagnosis. No patient developed nephrocalcinosis or secondary/tertiary hyperparathyroidism during the conventional treatment.

All patients discontinued the conventional treatment (calcitriol and phosphate supplements) 10–15 days before starting burosumab. In all patients, burosumab 0.8 mg/kg was administered via subcutaneous (sc) injection Q2W in the first month; subsequently, in all patients burosumab 1.2 mg/kg QW2 was administered up to 18 years of age. In all patients, burosumab was obtained with the authorization of the National Italian Medicines Agency Fund (AIFA Fund 5%) that provided the therapy up to the age of 18. One patient continued burosumab (1 mg/kg) QW4 after 18 for 12 months by compassionate use obtained by Kyowa-Kirin and authorized by the local Ethics Committee.

Each dose of burosumab was rounded to the nearest 10 mg, up to a maximum of 90 mg. Burosumab was administered via s.c. injection to the upper arms, upper thighs, buttocks, or any quadrant of the abdomen; the site was rotated with each injection. The maximum volume per injection was 1.5 mL (45 mg).

2.2. Study design

This is a prospective observational study. In all patients fasting serum levels of phosphate, calcium, total ALP, intact PTH, and 1,25$(OH)_2$D, maximum rate of renal tubular reabsorption of phosphate normalized to the glomerular filtration rate (TmP/GFR), and 24-h urine calcium excretion were assessed at entry, after 7–10 days, 1 month, and then every 3 months during burosumab treatment, and at 6–12 months after its discontinuation. Intact FGF23 plasma levels were measured at entry. In all patients, electrocardiogram, echocardiogram, and renal ultrasound were assessed at entry and every 6 months.

The severity of rickets was evaluated at entry and during burosumab treatment when appropriate. In addition, to evaluate the impact of low extremity pain, stiffness, and difficulties performing daily activities, patient-reported outcomes (PROs) were assessed at entry and every 3–6 months during burosumab treatment and after its discontinuation.

Safety measurements included the assessment of the incidence and

severity of all the adverse events occurring during burosumab treatment.

The study protocol was approved by the ethics committee for human investigation of the Department of Obstetrics, Gynecology and Pediatrics of the University Hospital of Pisa. All parents, and the patients when appropriate, provided informed consent to perform the study. The study was conducted according to the Declaration of Helsinki II and the Good Clinical Practice guidelines.

3. Methods

Height was measured by a calibrated wall-mounted Harpenden stadiometer and expressed as Z-score according to Freeman et al. (1995). Serum phosphate, calcium, creatinine, and ALP levels, as well as urinary phosphate and creatinine values were assessed within 1 h from sampling by an automated analyser. Twenty-four hours urine calcium sample was measured within 3 h from sampling by an automated analyser. Plasma EDTA samples for the measurement of intact FGF23 and intact PTH, and serum samples for $1,25(OH)_2D$, were separated within 2 h from sampling and stored at −20 °C until assayed; all the measurements were performed within 7 days from sampling.

Intact FGF23 and PTH plasma levels were assessed by immunochemiluminescent sandwich assay (DiaSorin, Saluggia, Italy). Serum $1,25(OH)_2D$ levels were measured by radioimmunoassay (^{125}I, Immunodiagnostic Systems Holdings Ltd, UK).

Urine samples for the calculation of TmP/GFR ratio were obtained from the second voluntary voiding in the morning and collected no more than 2 h after the previous voiding. The TmP/GFR was calculated as filtered phosphate per 100 ml GF excreted phosphate per 100 ml glomerular filtration by the following equation: Pp - (Up x PCr/UCr), where GFR was measured as creatinine clearance and Pp, Up, PCr, and UCr refer to the serum and urinary concentrations of phosphate and creatinine, respectively, as suggested by Stark et al. (1986).

For all measurements, inter-assay variability was less than 8% and intra-assay variability was less than 5%.

Rickets severity score (RSS) was assessed by the method of Thacher et al. (2019) that is based on the degree of metaphyseal fraying, concavity, and the proportion of the growth plate affected; separate scores for the wrist (maximum score 4) and knee (maximum score 6) were calculated and a total RSS from 0 to 10 was obtained, where higher scores represent greater severity of rickets.

PROs were assessed using the full Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire (Bellamy, 2012) designed for the assessment of lower-extremity pain and Graded Chronic Pain Scale-Revised (GCPS-R) to generate a disability score (Von et al., 2020).

WOMAC score is the result of three subscales, such as pain, stiffness, and physical function that include 5, 2, and 17 items, respectively. Briefly, each scale uses the following descriptors for all items: none, mild moderate, severe, and extreme. These correspond to an ordinal scale of 0–4. The scores are summed for items in each subscale, with possible ranges as follows: pain = 0 - 20, stiffness = 0–8, and physical function = 0 - 68. A total WOMAC score is created by summing the items for all three subscales (0–96). WOMAC score is a well-validated and reliable (Cronbach's α: pain subscale = 0.89; physical function subscale = 0.97) instrument (Fullwood et al., 2021).

GCPS-R was adapted for the age of the patients, and the "ability to work" was substituted with the "opportunity to play sport". GCPS-R identifies persons with chronic pain and grades chronic pain severity (mild, bothersome, high impact chronic pain). High-impact chronic pain is defined by sustained pain-related limitations in work/play sport, social and self-care activities (Von et al., 2020). GCPS-R employs two simple questions to identify chronic pain and high-impact chronic pain. Three main items Pain, Enjoyment, and General Activities (PEG) were assessed to evaluate GCPS-R. A PEG summary score of 12 or greater, up to 30 (i.e. equivalent to an average score of 4 or greater across the 3 items) was defined as moderate to severe chronic pain, while a PEG score of 11 or less was classified as mild chronic pain.

3.1. Statistical analysis

The results are expressed as means ± SD, as well as single values in each patient. When appropriate, changes in the biochemical parameters during burosumab treatment compared to the values at entry were performed with the non-parametric Wilcoxon's (Mann-Whitney) rank sum test. All statistical analyses were carried out using the SPSS (Statistical Package of Social Sciences, Chicago, IL, USA) for Windows software program. A P value < 0.05 was considered significant.

4. Results

4.1. Clinical and biochemical data at entry

Data at entry for each patient are summarized in Table 1. All but one patient had short stature. All patients showed reduced serum phosphate levels, reduced or inappropriately normal serum $1,25(OH)_2D$ levels for the degree of hypophosphatemia and low values of TmP/GFR. All but one patient had increased serum ALP and intact plasma FGF23 levels. Serum PTH levels were normal in two patients and slightly above the normal limit in three patients. All patients had normocalcemia (9.4 ± 0.4 mg/dL). All patients received conventional treatment since XLH diagnosis with good compliance.

RSS was 0 in three patients (patients 2, 4, and 5) and increased in two (patients 1 and 3).

Womac index was high in each patient with a mean of 71.2 ± 8.1. GCPS-R was in the range moderate to severe in all patients (25.0 ± 2.3).

4.2. Clinical and biochemical data during burosumab and after its discontinuation

Burosumab treatment ranged from 12 to 48 months (Table 1). Three patients discontinued burosumab when they reached 18 according to the cessation of the AIFA Fund 5%. One patient stopped burosumab at the age of 19 due to discontinuation of the program for compassionate use (patient 4, Table 1). Only a patient continued burosumab at the time of the study as he was not yet 18 years old (patient 3, Table 1). Two patients (patients 1 and 4, Table 1) were followed up for a further 6 months and two (patients 2 and 5, Table 1) for a further 12 months after the suspension of burosumab.

In all patients, a significant increase in serum phosphate (2.9 ± 0.2 mg/dL; $P < 0.0001$) and $1,25(OH)_2D$ levels (42.5 ± 8.5 pg/mL; $P < 0.001$), and TmP/GFR values (2.4 ± 0.2 mg/dL; $P < 0.01$) was found after 7–10 days of burosumab treatment. Similar data were observed after 1 month of burosumab for all three parameters (*data not shown*).

In all patients, serum phosphate levels remained over the limit of normal for age at 3, 6, and 12 months of burosumab treatment; after burosumab discontinuation, serum phosphate levels declined to pretreatment values (Fig. 1a).

All patients showed a significant increase of TmP/GFR values at 3, 6, and 12 months of burosumab treatment, with values that were above or near the lower limit of normal for age. TmP/GFR declined to pretreatment values after burosumab discontinuation (Fig. 1b).

In all patients, serum $1,25(OH)_2D$ levels increased significantly at 3, 6, and 12 months of burosumab treatment; in one patient serum $1,25(OH)_2D$ levels were above the upper limit of normal in two measurements after 12 months of treatment. In patients who stopped the treatment serum $1,25(OH)_2D$ levels declined rapidly and in three out of four dropped below the lower limit of normal (Fig. 1c).

Serum ALP levels did not change after 7–10 days and 1 month of burosumab treatment (439 ± 138 IU/L and 425 ± 131 IU/L, respectively; P═NS) in comparison with the levels at entry into the study. In all patients, serum ALP levels progressively declined at 3, 6, and 12 months

Table 1
Clinical and biochemical data at entry into the study, duration of conventional and burosumab treatment, and *PHEX* gene mutation.

Case/Sex	Age at diagnosis years	Age at entry years	CT years	BT months	Height Z-Score	P mg/dL	TmP mg/dL	FGF23 pg/mL	ALP IU/L	PTH pg/mL	1,25 $(OH)_2D$ pg/mL	RSS	*PHEX* gene mutation
1/M	0.1	14	13.9	48	−2.3	1.6	1.7	256.3	589	51.5	32.2	1	c.1645C > T
2/F	1.4	16.8	15.3	12	−2.2	2.1	2.0	78.1	221	46.8	24.7	0	c.1616_1617delCC
3/M	3.5	13.3	9.8	42	−3.4	1.8	1.8	168.3	604	38.6	21.7	2.5	c.1041_1042insT
4/M	3.6	16	12.4	36	−1.2	1.9	1.9	147.8	450	37.5	27.5	0	c.2239C > T
5/M	4.4	17	12.5	12	−2.6	1.7	1.4	149.0	396	43.6	14.7	0	c.118+1G > A
Mean	2.6	15.4	12.8	2.8	−2.3	1.8	1.8	159.9	452	43.6	24.2	0.7	
SD	1.6	1.5	1.8	1.5	0.7	0.2	0.2	57.1	140	5.2	5.9	1.0	
Normal values						2.5–4.5	2.7–3.9[a]	19.8–91.1[b]; 15.6–87.3[c]	<390[d] <130[e]	8–40	25–110	0	

Familial form: patients 1 and 4. CT: conventional treatment; BT: burosumab treatment; RSS: Rickets Severity Score.
[a] From ref .13.
[b] Puberty (patients 1, 3, and 4), from ref. 23.
[c] Post-puberty (patients 2 and 5), from ref. 23.
[d] Upper limit in puberty.
[e] Upper limit in adulthood.

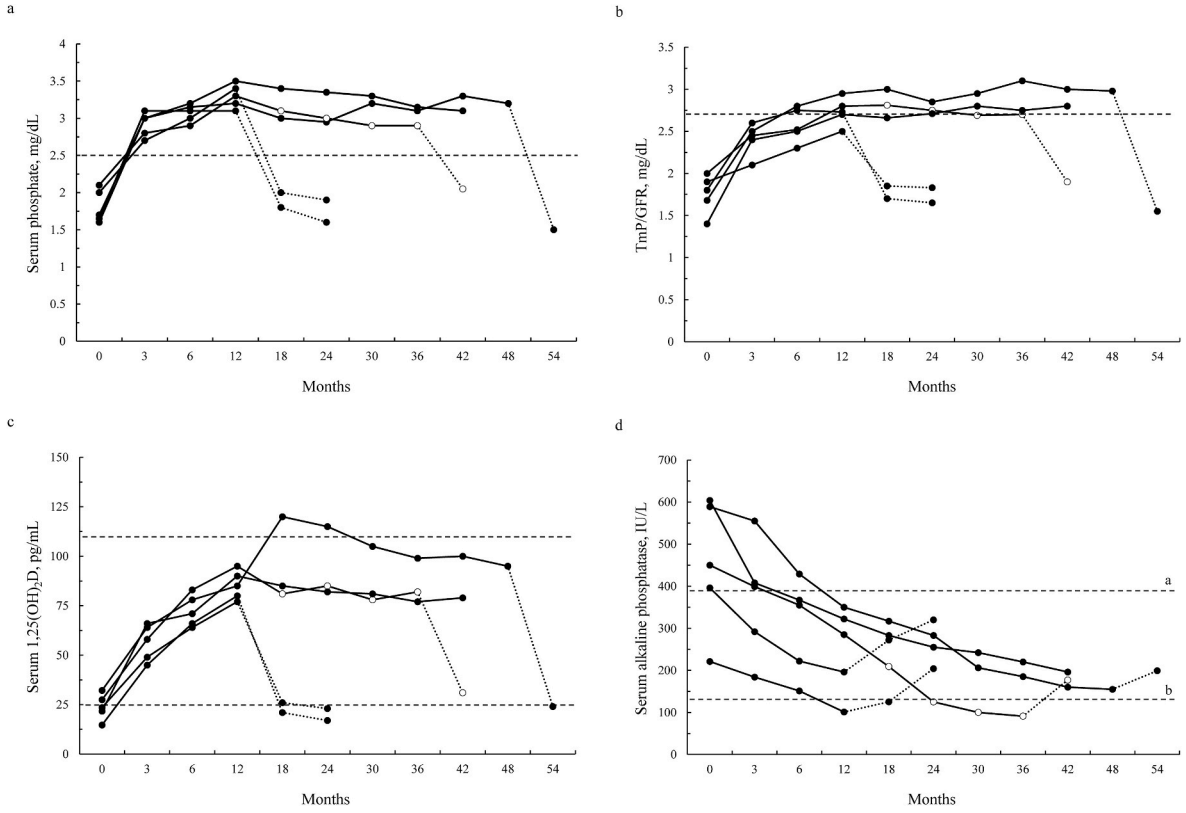

Fig. 1. Changes in serum phosphate levels (panel a), TmP/GFR values (panel b), serum 1,25$(OH)_2D$ levels (panel c), and serum alkaline phosphatase levels (panel d) in each patient during burosumab treatment.
Dashed line indicates the lower limit of normal for serum phosphate and TmP/GFR; the upper limit of normal in puberty (a) and in adulthood (b) for serum alkaline phosphatase; and the range of normal for 1,25$(OH)_2D$. Continuous line indicates burosumab treatment. Dotted line indicates burosumab discontinuation. White circles show the patient who switched burosumab from 1.2 mg/kg QW2 to 1 mg/kg QW4. $P < 0.0001$ at 3, 6, and 12 months of treatment vs baseline for serum phosphate and 1,25$(OH)_2D$ levels. $P < 0.01$ at 3, $P < 0.0001$ at 6 and 12 months of treatment vs baseline for TmP/GFR values. $P < 0.05$ at 12 months of treatment vs baseline for serum alkaline phosphatase levels.

of burosumab treatment, including in the patient who had normal values at entry. Serum ALP levels increased again in patients who stopped the treatment (Fig. 1d).

Serum levels of calcium and PTH did not show any significant (P═NS) change during burosumab treatment (9.5 ± 0.4 mg/dL and 38.5 ± 4.9 pg/mL, respectively) in comparison with the values at entry. Serum PTH levels were above the normal limit in two patients (patient 1, 45.1 pg/mL and patient 4, 42.0 pg/mL).

A significant decrease in the WOMAC index was found in all patients during burosumab treatment; WOMAC index rapidly increased in the patients who discontinued the treatment (Fig. 2a). All patients reported that bone pain and difficulty in physical function reappeared about 2–3 months after discontinuation of burosumab and progressively worsened.

A significant decrease in GCPS-R was reported in all patients during

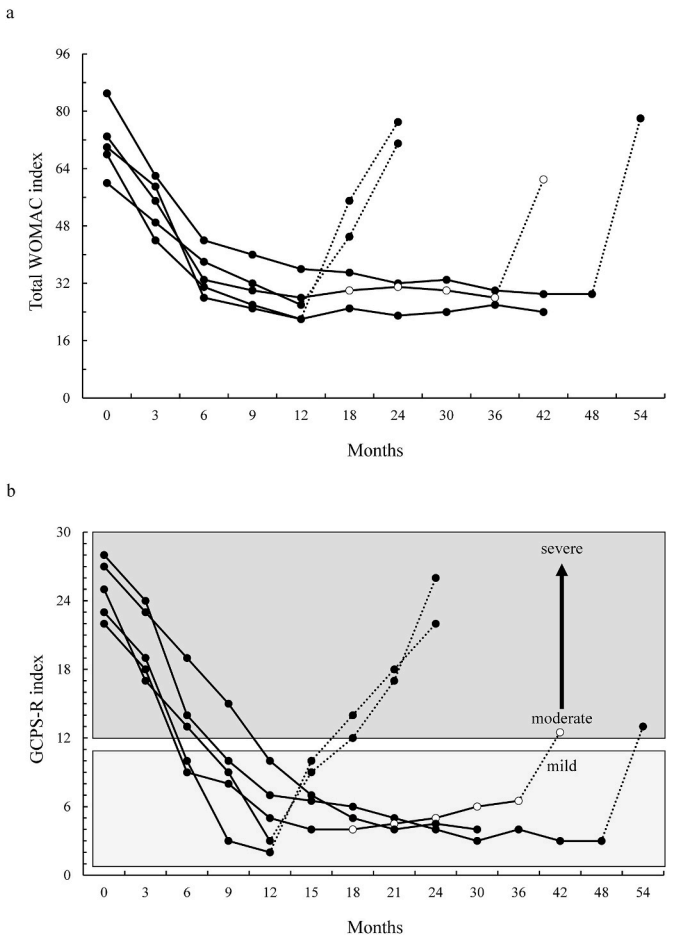

Fig. 2. Changes of total Womac index (panel a) and GCPS-R index (panel b) in each patient during burosumab treatment.
Panel b: the upper grey box represents moderate to severe values; the lower light grey box represents mild values. Cut-off between moderate to severe box and mild box is 11.
Continuous line indicates burosumab treatment. Dotted line indicates burosumab discontinuation.
White circles represent the patient who switched burosumab from 1.2 mg/kg QW2 to 1 mg/kg QW4. $P < 0.01$ at 3, $P < 0.0001$ at 6, 9, and 12 months of treatment vs baseline for WOMAC index.
$P < 0.02$ at 3, $P < 0.001$ at 6, $P < 0.0001$ at 9 and 12 months of treatment vs baseline for GCPS-R index.

burosumab treatment. After 12 months of treatment, all patients showed a value of GCPS-R in the range of mild chronic pain. After burosumab discontinuation, all patients had a rapid increase in bone pain referred to as severe and similar to that they suffered before burosumab treatment (Fig. 2b).

RSS improved during burosumab treatment in both patients 1 and 3; RSS was 0 after 12 and 18 months of burosumab in patients 1 and 3, respectively. In Fig. 3 is depicted the radiographic evolution of the mechanical axis and the lower limb deformities during burosumab treatment up to the complete growth plate fusion in patient 3. In the other three patients, X-ray of the legs was assessed after stopping burosumab; RSS have remained 0 and no signs of osteomalacia, including pseudofractures, were evident.

In all patients, after burosumab discontinuation some signs of depression occurred, such as continuous low mood or sadness, feeling hopeless and helpless, and having low self-esteem. Psychological support was needed for both patients and parents. The resurgence of all the symptoms of the disease, including severe and continuous bone pain and functional disability, forced the patients to chronic self-administration of nonsteroidal anti-inflammatory drugs to have partial pain relief.

4.3. *Adverse effects during burosumab treatment*

No patient showed side effects during burosumab treatment. None of the patients developed hypercalcemia or hyperphosphatemia, nephrocalcinosis, or cardiac abnormalities during burosumab treatment. In all patients, 24 h urinary calcium excretion was normal during burosumab therapy (*data not shown*). Burosumab treatment was well tolerated, and no patient reported a local reaction at the site of s.c. injection.

5. Discussion

XLH presents differently throughout the lifespan. Affected children show rickets, skeletal deformities mainly at lower limbs, short stature, physical dysfunction, and bone pain (Baroncelli and Mora, 2021; Carpenter et al., 2017). Adolescents and adults commonly experience unresolved complications from infancy and childhood, as the consequences of orthopedic surgeries for the correction of lower limb deformities, along with new cumulative deficits such as osteoarthritis, enthesopathies and spinal stenosis, leading to severe pain, stiffness and decreased physical activity, with a progressive burden of disease and a reduction in quality-of-life (QoL) (Chesher et al., 2018; Skrinar et al., 2019; Mindler et al., 2022). The occurrence of pseudofractures also strongly affects mobility in adult patients (Chesher et al., 2018).

Few data of burosumab treatment addressing the transition period from adolescence to adulthood are available. A recent study of Ewert et al. (2023) examined XLH patients with a mean age of 13.7 years treated with burosmab for 12 months, showing that the treatment was effective in increasing serum phosphate levels and TmP/GFR values, and in normalizing serum ALP.

Although our patients had received conventional treatment for many years with good compliance they showed hypophosphatemia with reduced TmP/GFR, increased ALP levels (in all but one), and insufficient serum levels of $1,25(OH)_2D$. Two patients still showed radiographic signs of rickets at entry, and all but one had short stature. Moreover, all patients had high values of WOMAC index and GCPS-R indicating that they suffered severe chronic pain, stiffness, and physical dysfunction. These data suggested that conventional treatment had only partial effectiveness, even though the compliance was good, and/or that they were affected by a severe form of the disease. However, significant variability in terms of individual response and in the dose required for optimal effect has been reported (Imel, 2021; Mughal et al., 2023). Additionally, the therapeutic benefit of the conventional treatment may be limited by its effect of further increasing FGF23 levels (Imel et al., 2010). At entry into the study, intact FGF23 plasma levels were above the normal limit in all but one patient. However, we recently demonstrated that hypophosphatemia associated with intact FGF23 plasma concentration greater than 40 pg/mL may be a crucial marker for the early diagnosis of XLH in pediatric patients (Baroncelli et al., 2024).

Recent studies showed that long-term burosumab treatment was effective in improving phosphate metabolism and muscular complication, and reducing the severity of rickets and disability in children with XLH from 1 to 12 years (Imel et al., 2019; Ward et al., 2022; Carpenter et al., 2018; Whyte et al., 2019; Linglart et al., 2022) and from 12 to 16 (Ewert et al., 2023; Ramos et al., 2020). Burosumab was usually well tolerated and none of the children in the clinical trials stopped the treatment (Imel, 2021; Linglart et al., 2022). Moreover, a long-term (160 weeks) study reported that no child showed hyperphosphatemia or had clinically meaningful increases in serum calcium levels, urine calcium excretion, or circulating PTH (Linglart et al., 2022), as we found in our patients.

Significantly greater clinical improvements were shown in rickets severity, growth, and biochemistries among children with XLH treated with burosumab compared with those continuing conventional therapy

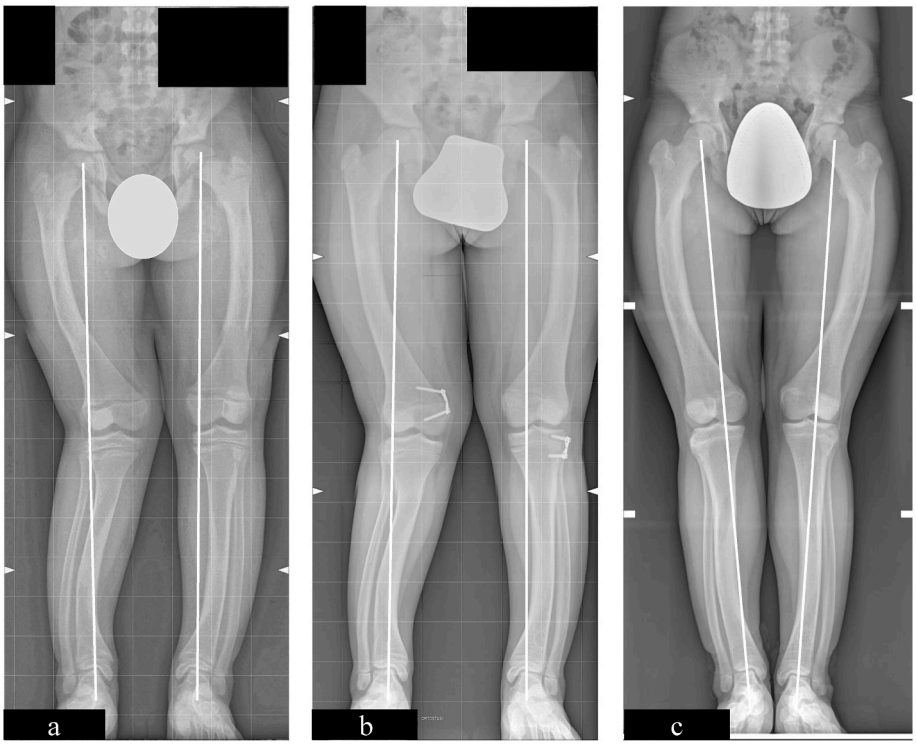

Fig. 3. Evolution of the skeletal lesions of rickets and mechanical axis at the lower limbs during conventional treatment and burosumab in patient n. 3.
a: age 13.3, at entry, after 9.8 years of conventional treatment. RSS 2.5 assessed at knees. The limb malalignment is more evident on the right side with lateralization of the patella. Lower limb dysmetria.
b: age 14.8, after 18 months of burosumab treatment. RSS = 0 at both knees. The limb malalignment was substantially unchanged, but lower limb dysmetria slightly improved. Guided growth with hemiepiphysiodesis: eight-plate were positioned at the medial side of the right distal femur and at the lateral side of the left proximal tibia at the age of 13.6 years.
c: age 17, after 42 months of burosumab treatment. Physeal closure at both femur and tibia. No signs of rickets were evident. Mechanical axis and lower limb dysmetria improved. A mild genu-varum remained at the right knee, with bilateral lateralization of the patella. Eight-plates were removed at the age of 15.1 years. The white lines represent the mechanical axis.

(Imel et al., 2019, 2023; Ward et al., 2022). Therefore, for children who are having persistent rickets, bone pain, and failure to correct ALP during conventional therapy, as occurred in our patients, a switch to burosumab should be considered (Mughal et al., 2023).

In our patients, a positive effect of burosumab on phosphate metabolism was documented, and it was associated with improvement of PROs, similarly to what has been shown in randomized controlled trials in both children 1–12 years (Padidela et al., 2021) and adults with XLH (Portale et al., 2019; Brandi et al., 2022).

The efficacy of burosumab in children, adolescents, and adults with XLH may be explained by the mechanism of action of burosumab in improving the deficiency of serum phosphate by directly binding to FGF23 and inhibiting its signaling, increasing tubular phosphate reabsorption, and stimulating $1,25(OH)_2D$ synthesis with increased gastrointestinal phosphate absorption (Imel, 2021; Padidela et al., 2021).

In adults with XLH, Kameniky et al. (2023) showed that the benefits of burosumab on clinical laboratory tests of efficacy, PROs, and ambulatory function were lost if the treatment was interrupted, and serum phosphate levels returned to baseline. However, all the benefits of burosumab returned with the reinstatement of treatment (Kamenicky et al., 2023). These results suggested that continued treatment with burosumab is required to maintain serum phosphate within the normal range and to maintain the benefits in mitigating pain, stiffness and fatigue, and improving physical function and mobility. Our results in adolescents documented the same consequences on phosphate metabolism and bone health reported in adults with XLH after burosumab discontinuation.

In our patients, the improvement in phosphate metabolism and physical function, as well as the reduced bone pain were associated with extremely positive psychological and emotional impacts on patients themselves and their parents. It was an experience they had never had before that changed their approach to life. Nevertheless, the discontinuation of burosumab caused a psychological shock in both patients and parents.

A recent expert opinion-based consensus (Mughal et al., 2023) suggested that, if feasible, children with XLH should start treatment with burosumab as early as possible, particularly if they have profound rickets (RSS $\geq$2), and should continue treatment without cessation throughout adolescence and where possible into adulthood, to improve clinical outcomes and slowing/halting the progression of the disease. Moreover, following growth plate closure in adolescents with XLH radiographic assessment of rickets is no longer relevant for monitoring improvements. Therefore, PROs used in adults may also be reliable to monitor treatment response in adolescents (Mughal et al., 2023), as we found in our patients.

A limiting factor of our study is the small number of enrolled patients. However, the results were quite consistent, adding some information in adolescents with XLH receiving burosumab treatment near the transition to young adulthood.

In conclusion, our data showed that conventional treatment may change only in part the evolution of the disease. Adolescents with XLH approaching the transition to young adulthood who changed to burosumab treatment from conventional therapy had significant improvements in phosphate metabolism, bone health, and QoL. All the benefits of burosumab treatment were lost after the interruption of treatment, suggesting that it is a real effect. Moreover, burosumab cessation was associated with psychological and emotional discomfort. Therefore, continued and uninterrupted burosumab treatment appears necessary to

sustain the clinical benefits of treatment, including the QoL, during the transition to young adulthood in patients with XLH. Burosumab was well tolerated and all the patients expressed the will to continue the treatment.

Further studies are needed to evaluate if the continuation of burosumab treatment after adolescence may prevent or reduce the prevalence of some of the main complications of the disease, including enthesopathy and pseudofractures later in life.

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CRediT authorship contribution statement

Giampiero I. Baroncelli: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Anna Grandone:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Antonio Aversa:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Maria Rita Sessa:** Validation, Methodology, Formal analysis, Conceptualization. **Caterina Pelosini:** Validation, Methodology, Formal analysis, Conceptualization. **Angela Michelucci:** Validation, Methodology, Formal analysis, Conceptualization. **Benedetta Toschi:** Validation, Methodology, Formal analysis, Conceptualization. **Mario Manca:** Visualization, Validation, Methodology, Data curation, Conceptualization. **Alessandro Isola:** Visualization, Validation, Methodology, Formal analysis, Conceptualization. **Pasquale Comberiati:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

Data will be made available on request.

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