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The effects of burosumab on growth, nephrocalcinosis and cardiovascular outcomes in children with X-linked hypophosphatemia: a single-center experience

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Abstract

Purpose X-linked hypophosphatemia (XLH) is the most common cause of inherited rickets. It is characterized by chronic hypophosphatemia due to increased levels of Fibroblast Growth Factor 23 hormone (FGF23), renal phosphate wasting, and decreased renal vitamin D hydroxylation. Burosumab, an anti-FGF23 antibody, was approved in 2018 for XLH children.

Methods This retrospective single-center study assessed the progression of clinical, biological, renal, and cardiovascular outcomes of XLH patients who started burosumab before 18 years of age, between July 2018 and June 2022.

Results In total, 12 children began burosumab treatment at a median age of 10.1(2.7–14.7) years, after 7.6 (1.1–11.3) years of conventional therapy. The last follow-up was 2.7(0.8–4.7) years after burosumab initiation, with 10 patients with at least 2 years of follow-up. Regarding the progression of anthropometric parameters, only height SDS significantly increased from baseline at the last follow-up. Regarding the biological parameters, as expected, at 12 months after starting burosumab and at the last follow-up, phosphate and alkaline phosphatase levels significantly improved. Although not significant, there was a trend towards an early increase of osteocalcin and crosslaps during the first months of therapy. Before starting burosumab, 5 patients (42%) had nephrocalcinosis (1 stage 1, 4 stage 2). One patient displayed a complete resolution of nephrocalcinosis after 1 year of treatment, and one patient showed improvement of nephrocalcinosis. No nephrocalcinosis appeared in a patient while being treated with burosumab. Cardiac ultrasounds remained normal in all.

Conclusion Our real-life data confirm that burosumab improves outcomes in XLH children, including nephrocalcinosis and growth.

Keywords Burosumab, X-linked hypophosphatemia, Rickets, Nephrocalcinosis, Growth

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Introduction

X-linked hypophosphatemia (XLH) is a rare genetic disease, due to an inactivating *PHEX* mutation, characterized by increased levels of Fibroblast Growth Factor 23 (FGF23), renal phosphate wasting, chronic hypophosphatemia and decreased 1-25OH_2 dihydroxyvitamin D (1-25-OH_2-D) [9]. XLH is associated with delayed gait development, lower limb deformities, growth retardation, craniosynostosis, and dental abscesses [9].

Conventional medical management (Standard of Care, SoC) is based on phosphate supplementation and active vitamin D analogs. SoC is often insufficient for growth and bone symptoms, whilst increasing the risk of nephrocalcinosis (NC) and secondary hyperparathyroidism [9]. Burosumab, an anti-FGF23 antibody, was approved in 2018 for XLH children aged 1–18 years. Burosumab restores renal phosphate reabsorption and stimulates endogenous calcitriol synthesis, with sustained control of phosphate and alkaline phosphatase (ALP), and a favorable safety profile [11].

Even though more real-life series are published in pediatrics [8, 12, 13], some key questions remain open, notably the progression of NC and cardiovascular parameters. Thus, we aimed to provide real-life data on burosumab use in XLH children, with a focus on these outcomes.

Patients and methods

This single-center retrospective study assessed the progression of clinical and biological parameters of genetically-confirmed XLH children who started burosumab before 18 years, between July 2018 and June 2022. In France in 2018, we could not treat all patients with burosumab, only the most severe ones (i.e., late diagnosis after 8 years of age, nephrocalcinosis, dental complications, hyperparathyroidism, neurosurgical complications, persisting deformations after 1 year of SoC). Since 2018, things have progressively changed, and we can now treat less severe forms of XLH. As such, there was a modification of practice with time. That being said, we still have patients receiving SoC in our center, mainly the youngest ones. In clinical practice, we often discuss the introduction of burosumab at the beginning of puberty to optimize the peak bone mass. Concerning the dose, we usually begin at 0.4 mg/kg, and have the objective to reach phosphate levels within the lower normal limit for age, with monthly titration if appropriate.

The following clinical data were collected from electronic medical records: weight, height, body mass index (BMI), blood pressure, age at diagnosis, duration of SoC, burosumab doses, concomitant recombinant growth hormone therapy (rhGH) if any, and global clinical description of XLH (neurosurgical complications, NC). All parameters were expressed in absolute values and as standard deviation scores (SDS) or percentiles for age, gender, and/or height, as previously described [2, 3].

Routine bone biomarkers were collected: creatinine to calculate glomerular filtration rate (eGFR) by the 2009-Schwartz formula, calcium, phosphate (absolute and SDS for age) [1], PTH (normal 15–65 ng/L), total alkaline phosphatase (ALP), 25 OH vitamin D (25-D) and 1-25-OH_2-D (normal 69–200 pmol/L), osteocalcin, crosslaps, and bone alkaline phosphatase. Spot urine samples were used to assess urinary calcium, creatinine, and phosphate to obtain calcium/creatinine ratio and tubular maximum phosphate reabsorption per GFR (TmP/GFR) [6]. Other routine biomarkers were analyzed, notably insulin-like growth factor (IGF-1) and hemoglobin. Of note, patients are usually seen in clinics a few days before the next injection of burosumab, to obtain phosphate "trough" levels.

Calcium intake was regularly assessed by a specialized pediatric dietician and expressed as % of the recommended intake for age [4].

Routine imaging consisted of renal and cardiac ultrasounds at baseline and every 1–2 years afterward, with at least one skeletal X-ray on the wrist before burosumab therapy. Skeletal X-rays were performed afterwards only when clinically indicated, to avoid unnecessary radiation exposure, so that we cannot present the modification of RSS scoring. The same experienced pediatric radiologist retrospectively reviewed renal ultrasounds.

Because of the low number of patients, we only compared the results between baseline and 1 year, and between baseline and last follow-up, using non-parametric paired Wilcoxon tests (SPSS software). Results are presented as median (range). This retrospective series was approved by the *Comité d'Ethique des Hospices Civils de Lyon* (2/9/2021, 21_519).

Results

In total, 12 children began burosumab at a median age of 10.1(2.7–14.7) years, after 7.6(1.1–11.3) years of SoC. The last follow-up was 2.7(0.8–4.7) years after burosumab initiation, with 10 patients having at least 2 years of follow-up. Two patients received concomitant rhGH. Five patients (42%) displayed neurological complications (craniosynostosis, Chiari, and/or syringomyelia), but only one patient underwent neurosurgery before burosumab.

Burosumab starting and last follow-up doses were 0.4(0.2–0.8) and 1.1(0.2–1.9) mg/kg/2 weeks, respectively. One teenage boy was given injections every 3 weeks because of a "too good" response on phosphate levels even with low doses. Raw values for weight, height, and BMI significantly increased but when normalized for age and gender, only height SDS significantly increased from baseline to the last follow-up.

Serum phosphate levels (raw and normalized values) and TmP/GFR significantly improved. Total ALP progressively decreased over time whilst 1-25-OH_2-D increased. No significant differences were observed for calcium, urinary calcium, urinary calcium/creatinine ratio, PTH, and hemoglobin. Despite native vitamin D supplementation, 25D levels decreased. Although not significant, there was a trend towards an early increase of osteocalcin and crosslaps during the first months of therapy. We observed significantly increased creatinine levels and decreased eGFR under burosumab.

Regarding cardiovascular outcomes, both absolute and normalized systolic blood pressure significantly increased whilst diastolic blood pressure did not change. Cardiac ultrasounds were normal in all patients before burosumab, and during follow-up.

Before starting burosumab, 5 patients (42 %) had NC. It completely disappeared in one patient, and improved in one. No patient developed NC whilst receiving burosumab. One patient worsened NC (stage 2 to 3), but he had genetically confirmed XLH with another genetic abnormality in FGF10.

Table 1 summarizes all these data and Figs. 1 and 2 illustrate the progression of the most important parameters. No significant side effects were reported, except pain and redness at injection sites.

Discussion

This retrospective study aimed to provide real-life data on burosumab use after switching from SoC in 12 children, with a follow-up of more than 2 years in 10. We confirm that burosumab improves outcomes in XLH children, including biological control, growth, and safety profile. Data on NC and cardiovascular parameters are novel.

Data on growth under burosumab are conflicting, with initial disappointing results (mainly in short-term studies), but also promising results in the most recent data [11, 13]. Here we observe a significant beneficial effect on height SDS only at the last follow-up, but standardized weight and BMI did not change. Since obesity/overweight is a complication of XLH [14], still of unclear pathophysiology [5], we could have expected improved standardized BMI with burosumab. However, BMI is not only the reflection of fat mass, but also muscle mass, which may improve with burosumab; unfortunately Dual X-ray Absorptiometry (DXA) assessment of lean and fat mass was not performed here. We did not have enough power to evaluate the effect of combined burosumab and rhGH in the two patients who received both therapies. One observational study has analyzed the effects of rhGH in children who were switched from SoC to burosumab. Treatment with rhGH resulted in a sustained increase in height *z*-score (0.2 ± 0.1) during the first year in which the treatment switch occurred while no significant changes were observed in XLH controls treated only with burosumab [7]. Here we had an overall positive effect of burosumab on growth with a longer follow-up. Taken together, these data suggest that treatment with rhGH of short children with XLH might be beneficial to improve final adult height.

As previously published, phosphate, TmP/GFR, and ALP significantly improved. No significant differences were observed for other biomarkers of phosphate/calcium metabolism. From our experience in real life, we suggest that regular monitoring of calcium intake by dieticians was beneficial: slightly increased PTH levels were often seen in case of insufficient calcium intake that normalized or near-normalized when providing normal calcium intake for age: temporary calcium supplementation was prescribed in three patients during follow-up to achieve age-specific recommend calcium intake because nutritional intake was not sufficient [4]. Burosumab improves phosphate metabolism, allowing the child to mineralize his/her skeleton. Hydroxyapatite consists of both calcium and phosphate: in case of calcium deficiency (that will not necessarily be seen in circulating calcium levels) [4], PTH levels slightly increase. Therefore, optimizing nutritional calcium in children receiving burosumab seems crucial. Despite the regular 25 D levels assessment and further cholecalciferol prescription, 25-D levels decreased over time, however mostly remaining within the target range. This provides a rationale to regularly assess 25D levels, to avoid even mild secondary hyperparathyroidism. In any case, we propose that these children with an underlying bone disease at least follow the national guidelines proposed in general pediatric populations, namely in France a supplementation in all children between 0 and 18 years (400 to 800 IU per day), with a doubling of doses in presence of risk factors for vitamin D deficiency (i.e., obesity, dark skin, vegan diet and/or absence of sun exposure) [4]. In contrast, the use of active vitamin D analogs is contra-indicated in patients receiving burosumab, and none of the patients received alfacalcidol after the switch to burosumab.

Because of the growing evidence of a strong association between FGF23 and iron metabolism, notably in autosomal dominant hypophosphatemic rickets [10], we sought to assess the trends in hemoglobin levels, without seeing any significant difference over time. Last, similarly to what we already described in the XLH21 study [5], we again find a trend towards glomerular hyperfiltration (as defined by increased eGFR) in XLH patients at baseline, with a significant decrease of eGFR overtime here, albeit in the normal range. We cannot confirm the link between FGF23 and

Table 1 Clinical and biological parameters of burosumab

	Baseline	M3	M6	M9	M12	M24	M36	Last follow-up
Number of patients	12	12	12	12	11	10	7	12
Age (years)	10.1 (2.7/ 14.7)	10.4 (3.1/15)	10.7 (3.3/15.2)	10.9 (3.5/15.5)	12 (3.9/15.9)	13.1 (4.7/16.4)	14.4 (4.9/17)	14.2 (4.7/18)
Skeletal age (years)	10.0 (2.0/ 13.6)							
Duration of standard of care therapy (years)	7.6 (1.1/11.3)							
Dose burosumab (mg/kg/dose)	0.4 (0.2/0.8)	0.94 (0.12/1.6)	1.1 (0.2/2.3)	1.14 (0.21/2.2)	1.14* (0.2/2.2)	1.2 (0.2/1.9)	1.25 (0.5/1.7)	1.1* (0.2/1.9)
Time under burosumab therapy (years)								2.7 (0.6/4.7)
Nutritional calcium intake (mg/day)	848 (536/2075)				1188* (860/1270)	1175 (538/1600)	1000 (600/1600)	1125 (500/1600)
Nutritional calcium intake (% DRI)	90 (48/173)				110* (75/244)	100 (59/140)	100 (52/140)	104.3 (43/163)
Body weight (kg)	33.2 (12.2/76)	34.7 (12.6/84.6)	35.6 (13/88.4)	36.8 (13.5/– 89)	40* (13.8/91.2)	44.2 (16.1/100.7)	51 (33/99.8)	50.9* (16.1/–101.5)
Body weight (SDS)	0.07 (– 0.6/3.1)	0.07 (– 1.1/3.8)	0.3 (– 1.1/4)	0.28 (– 1/3.9)	0.2 (– 1.2/4)	– 0.2 (– 0.9/2.8)	– 0.9 (– 1.5/2.7)	0.1 (– 0.9/2.7)
Height (m)	1.32 (0.84/1.65)	1.34 (0.86/1.67)	1.36 (0.88/1.68)	1.37 (0.88/1.70)	1.43* (0.91/1.70)	1.46 (0.96/1.73)	1.51 (1.29/1.75)	1.50* (0.96/1.76)
Height (SDS)	– 1.5 (– 2.9/– 0.3)	– 1.47 (– 3/– 0.2)	– 1.5 (– 2.9/– 0.3)	– 1.5 (– 3/– 0.1)	– 1.3 (– 2.8/0.9)	– 1.35 (– 2.5/1)	– 1.4 (– 2.9/– 0.2)	– 0.8* (– 2.5/1)
Body mass index (kg/m^2)	18.9 (17.3/30.1)	19.8 (17.0/32.2)	19.6 (16.8/32.9)	19.6 (17.4/32.9)	20.2* (16.7/32.9)	20.6 (17.5/33.6)	22.2 (19.8/32.6)	20.7* (17.5/32.6)
Body mass index (percentile)	85 (22/99)	73 (11/99)	79 (24/99)	72.5 (24/99)	79 (28/99)	86 (43/99)	82 (53/99)	85 (22/99)
Systolic blood pressure (mmHg)	103 (91/121)	108.5 (95/119)	112.5 (95/126)	105.5 (87/121)	115* (97/118)	107.5 (103/129)	118 (108/125)	114.5* (101/132)
Systolic blood pressure (percentile)	69 (8/95)	81 (19/97)	82 (27/98)	73.5 (9/95)	79* (56/99)	70 (31/93)	83.5 (63/96)	74.5* (56/98)
Diastolic blood pressure (mmHg)	63 (56/80)	61.5 (50/81)	63 (50/77)	61.5 (50/86)	65 (53/77)	67 (54/74)	64 (59/72)	62 (54/73)
Diastolic blood pressure (percentile)	78 (25/97)	64.5 (17/97)	76 (11/98)	57.5 (9/98)	76 (39/97)	73 (22/89)	56 (23/77)	54.5 (22/89)
Creatinine (µmol/L)	38 (23/48)	40 (25/50)	38 (23/57)	42 (23/57)	44* (28/55)	39 (25/62)	49 (39/68)	48* (25/68)
eGFR (mL/min per 1.73 m^2)	133 (110/160)	125 (107/156)	127 (99/149)	127 (109/159)	119* (110/148)	128 (102/163)	110 (89/131)	114* (89/140)
Hb (g/dL)	143 (113/150)	134 (111/157)	133 (114/146)	37 (120/149)	132 (120/148)	131 (104/154)	129 (124/162)	131 (104/162)
Ca (mmol/L)	2.44 (2.34/2.63)	2.41 (2.29/2.54)	2.43 (2.23/2.65)	2.48 (2.23/2.66)	2.42 (2.28/2.54)	2.38 (2.21/2.68)	2.45 (2.27/2.55)	2.42 (2.23/2.51)
Phosphate (mmol/L)	0.75 (0.52/0.98)	1.03 (0.83/1.27)	1.04 (0.79/1.31)	1.03 (0.88/1.23)	1.01* (0.88/1.16)	0.96 (0.82/1.29)	1.00 (0.89/1.11)	1.02* (0.82/1.29)
Phosphate SDS	– 4.1 (– 5.9/– 3.2)	– 2.7 (– 4.6/– 1.8)	– 2.7 (– 4.2/– 1.1)	– 2.3 (– 4.2/1.4)	– 2.5* (– 4.6/– 2.1)	– 2.9 (– 4.5/– 1.8)	– 2.3 (– 3.5/– 1.4)	– 2.2* (– 4.5/– 1.5)
PTH (ng/L)	44 (22/92)	54 (21/95)	54 (29/123)	58 (26/85)	53 (28/86)	53 (11/72)	42 (30/94)	45 (30/144)
25OH D (nmol/L)	81 (66/113)	89 (34/128)	69 (44/113)	62 (49/85)	85 (59/96)	78 (49/111)	62 (45/92)	72* (45/108)
Total ALP (UI/L)	496 (264/768)	409 (223/678)	372 (194/727)	371 (155/691)	342* (145/645)	239 (83/489)	135 (65/224)	221* (67/489)
Total ALP (SDS)	1.35 (0.95/2.53)	1.10 (0.80/2.40)	0.95 (0.69/2.15)	0.84 (0.55/1.88)	1.33 (0.63/3.55)	0.96 (0.49/3.41)	0.52 (0.26/1.75)	0.88 (0.03/3.41)

Table 1 (continued)

	Baseline	M3	M6	M9	M12	M24	M36	Last follow-up
1-25$(OH)_2$D (pmol/L)	95 (18/160)	182 (101/322)	199 (149/313)	186 (124/232)	170* (113/286)	155 (125/212)	160 (122/190)	172* (99/219)
Osteocalcin (µg/L)	75 (40/174)	142 (64/297)	137 (97/194)	147 (104/208)	101 (61/186)	106 (42/202)	75 (32/ 202)	80 (31/202)
Crosslaps (pg/mL)	2297 (1743/4382)	3528 (2202/4640	3187 (2796/4089))	3548 (948/4856)	2682 (1544/4069)	2454 (1191/4264)	1262 (513/4047)	1352 (513/2672)
Bone ALP (µg/L)	119 (51/220)	164 (46/224)	163 (32/257)	78 (11/286)	105 (48/224)	77 (25/166)	34 (18/62)	64 (18/166)
IGF1 (µg/L)	277 (65/619)	240 (59/365)	340 (97/601)	398 (107/ 597)	311* (71/465)	349 (102/477)	464 (450/477)	376 (173/477)
Urinary calcium (mmol/L)	1.9 (0.2/5)	1.6 (0.3/3.4)	1 (0.3/4.8)	2 (1.1/3.8)	1.9 (0.1/4.1)	3.8 (2.7/5.2)	2.3 (1.3/5.8)	2.8 (0.9/8.5)
Urinary calcium/creatinine ratio (mmol/mmol)	0.31 (0.01/1.53)	0.22 (0.03/0.54)	0.09 (0.01/0.43)	0.15 (0.11/0.24)	0.17 (0.02/0.49)	0.30 (0.14/0.42)	0.24 (0.13/0.44)	0.25 (0.10/0.80)
TmP/GFR (mmol/L)	0.69 (0.43/1.05)	1.06 (0.81/1.48)	1.24 (0.97/1.39)	0.93 (0.91/0.95)	1.18* (0.98/1.48)	1.05 (0.87/1.81)	1.09 (0.82/1.18)	1.08* (0.82/ 1.81)
TmP/GFR (SDS)	− 2.00 (− 3.83/− 1.17)	− 0.87 (− 2.10/1.01)	− 0.29 (− 1.55/1.39)	− 0.65 (− 1.50/0.13)	− 0.53* (− 1.86/0.21)	− 0.57 (− 1.38/1.05)	− 0.76 (− 1.46/− 0.13)	− 0.86* (3.43/1.05)
Nephrocalcinosis (%)	42				36	22	40	33
Description of nephrocalcinosis (NC)	No NC, *N* = 7 Stage 1, *N* = 1 Stage 2, *N* = 4 Stage 3, *N* = 0				No NC, *N* = 7 Stage 1, *N* = 0 Stage 2, *N* = 3 Stage 3, *N* = 1	No NC, *N* = 7 Stage 1, *N* = 0 Stage 2, *N* = 2 Stage 3, *N* = 0	No NC, *N* = 3 Stage 1, *N* = 1 Stage 2, *N* = 1 Stage 3, *N* = 0	No NC, *N* = 8 Stage 1, *N* = 1 Stage 2, *N* = 2 Stage 3, *N* = 1

Results are presented as median (min/max). When *, $p < 0.05$ when performing paired Wilcoxon non-parametric tests between burosumab initiation and 1 year of follow-up, and between burosumab initiation and last follow-up

DRI dietary reference intake, *SDS* standard deviation score, *eGFR* estimated glomerular filtration rate, *Hb* hemoglobin, *ABV* average blood volume, *Ca* calcium, *PTH* parathyroid hormone, *25 OH D* 25 hydroxyvitamin D, *total ALP* total alkaline phosphatase, *1,25 $(OH)_2D$* 1,25 dihydroxyvitamin D, *bone ALP* bone alkaline phosphatase, *IGF1* insulin-like growth factor 1, *TmP/GFR* mean ratio of tubular maximum reabsorption rate of phosphate to glomerular filtration rate, *NC* nephrocalcinosis, *N* number

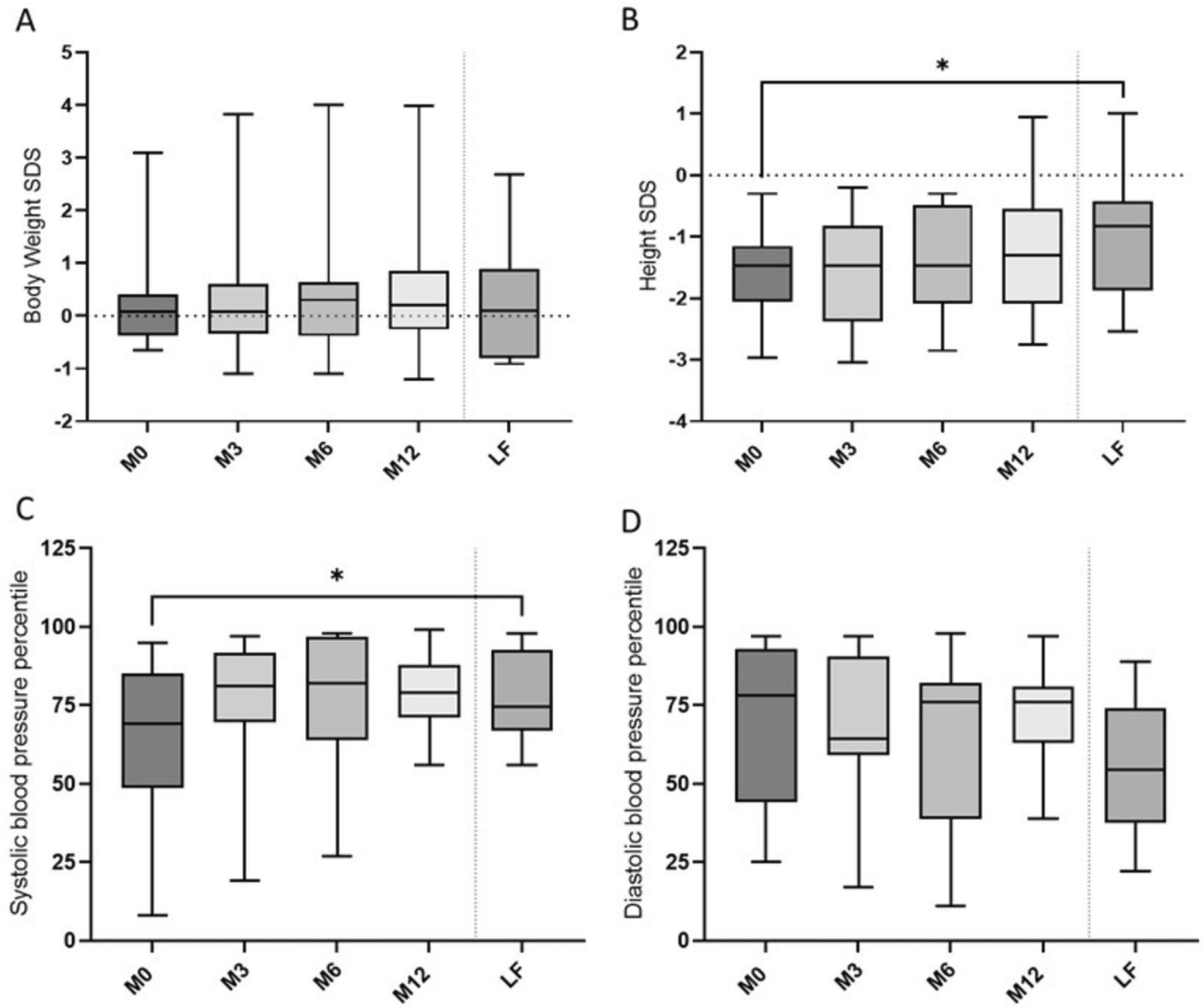

Fig. 1 Graphical representation of the progression of the most important clinical parameters under burosumab. **A** Bodyweight SDS. **B** Height SDS. **C** Systolic blood pressure percentile SDS; **D** Diastolic blood pressure percentile. M0: baseline; M3: 3 months; M6: 6 months; M12: 1 year; LF: last follow-up 2.7(0.8–4.7) years after burosumab initiation

hyperfiltration. Alternatively, the increase in muscle mass by burosumab may also increase creatinine levels, and therefore mathematically decrease eGFR. Cystatin C may help answer this intriguing question.

FGF23 also has extra-skeletal effects, notably on the cardiovascular system [5], through different mechanisms: direct cardiac hypertrophy, decreased 1-25-OH_2-D that will in turn stimulate the renin/angiotensin system, hypertension through increased tubular sodium reabsorption, inflammation, and iron deficiency [2, 3]. Based on our previous study comparing two groups of XLH patients and showing lower blood pressure in XLH patients receiving burosumab compared to SoC [5], we hypothesized that we would see decreased blood pressure over time. However, the XLH21 trial was a clinical prospective trial with a procedural assessment of blood pressure, whilst we present here real-life data. Importantly, no patient displayed left ventricular hypertrophy at baseline, and cardiac ultrasound remained normal in all patients (performed at least every 2 years in each patient). Ambulatory blood pressure monitoring could be of great interest in this clinical setting.

There is almost no data on NC progression under burosumab, except the description in the long-term data of the industry-sponsored trial of improvement (but no disappearance) of NC in 3 children [11]. Here, we see one improvement but also one complete

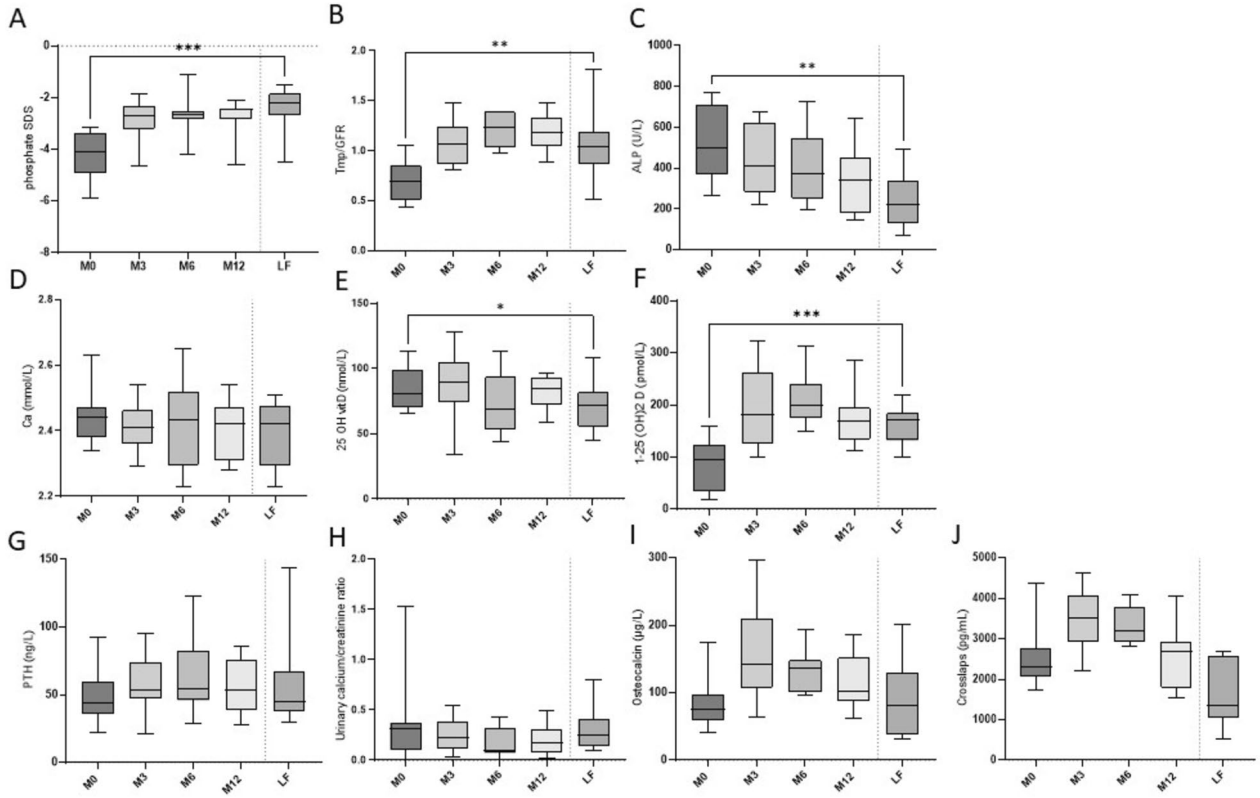

Fig. 2 Graphical representation of the progression of the most important clinical parameters under burosumab. **A** Phosphate SDS. **B** TmP/GFR. **C** ALP. **D** Calcium. **E** 25 D. **F** 1-25 (OH)2-D. **G** PTH. **H** Urinary calcium/creatinine ratio. **I** Osteocalcin. **J** Crosslaps. M0: baseline; M3: 3 months; M6: 6 months; M12: 1 year; LF: last follow-up 2.7(0.8–4.7) years after burosumab initiation

resolution of NC under therapy; however, NC worsened in the patient with XLH and FGF10 variant. The fact that the urinary calcium/creatinine ratio did not change over time may appear intriguing, but urinary calcium excretion also depends on sodium and protein nutritional intake, hypercalciuria being frequent even in healthy teenagers [4]. As described in other diseases, the time to correct NC once the risk factors disappear (i.e., mainly the use of vitamin D analogs and phosphate supplementation with SoC) may take time. Patients should be reminded of the basics to prevent urine oversaturation, notably sufficient hydration, and a protein- and sodium-controlled diet. It remains to be proved in the (very) long-term that improvement of nephrocalcinosis may improve renal outcomes, and notably the risk of chronic kidney disease.

Last, we unfortunately did not have enough data to quantitatively assess physical activity and quality of life in these patients, but they all reported an improvement in their physical ability, improved compliance, and never asked to withdraw treatment despite the closer biological follow-up at treatment initiation. Standardized assessment of such parameters as well as patients' reported outcomes measures (PROMs) would be of great interest in the future.

Conclusion

We present here a well-characterized cohort of pediatric XLH with a follow-up of more than 2 years in most patients. Our real-life data confirm that burosumab improves outcomes in XLH children, including nephrocalcinosis and growth, with a good safety profile.

Authors' contributions

JB designed the study, analyzed the data, edited the manuscript, and took responsibility for the entire content of the manuscript. BO and ED performed the data collection. BO wrote the first draft of the manuscript. SC performed the retrospective review of all renal ultrasounds. SF prepared the administrative paperwork, did the statistical analyses, and prepared the Supplemental figures. ABT and ADM edited the manuscript and followed patients in a clinical routine. All authors reviewed and approved the manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are not publicly available due to confidential data but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This retrospective series was approved by the Comité d'Ethique des Hospices Civils de Lyon (2/9/2021, 21_519).

Consent for publication
Not applicable

Competing interests
JB received consulting, research, and speaker fees from Kyowa Kirin. The rest of the authors have no conflict of interest to declare.

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