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Switching from conventional therapy to burosumab injection has the potential to prevent nephrocalcinosis in patients with X-linked hypophosphatemic rickets

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Abstract

Objectives: X-linked hypophosphatemic rickets (XLH) is a congenital fibroblast growth factor (FGF)23-related metabolic bone disease that is treated with active vitamin D and phosphate as conventional therapies. Complications of these therapies include nephrocalcinosis (NC) caused by excessive urine calcium and phosphate concentrations. Recently, an anti-FGF23 antibody, burosumab, was developed and reported to be effective in poorly-controlled or severe XLH patients. This study aimed to reveal the impact of switching treatments in relatively well-controlled XLH children with the Rickets Severity Scale less than 2.0.

Methods: The effects of the two treatments in eight relatively well-controlled XLH children with a mean age of 10.4 ± 1.9 years were compared retrospectively for the same treatment duration (31 ± 11 months) before and after the baseline.

Results: Actual doses of alfacalcidol and phosphate as conventional therapy were 150.9 ± 43.9 ng/kg and 27.5 ± 6.3 mg/kg per day, respectively. Renal echography revealed spotty NC in 8/8 patients, but no aggravation of NC was detected by switching treatments. Switching treatments increased TmP/GFR ($p=0.002$) and %TRP ($p<0.001$), and improved the high urine calcium/creatinine ratio to the normal range ($p<0.001$) although both treatments controlled disease markers equally. Additionally, low

intact parathyroid hormone during conventional therapy was increased within the normal range by switching treatments.

Conclusions: Our results suggest that a high dose of alfacalcidol was needed to control the disease, but it caused hypercalciuria and NC. We concluded that switching treatments in relatively well-controlled XLH children improved renal phosphate reabsorption and decreased urine calcium excretion, and may have the potential to prevent NC.

Keywords: burosumab; hypercalciuria; nephrocalcinosis; neural phosphate; vitamin D; X-linked hypophosphatemic rickets.

Introduction

X-linked hypophosphatemic rickets (XLH) [OMIM#307800] is a congenital metabolic bone disease characterized by short stature, genu varum/valgum, fraying, or cupping in the metaphysis, and increased serum alkaline phosphatase (ALP), caused by hypophosphatemia [1–3]. XLH is caused by mutations in the *phosphate regulating neutral endopeptidase (PHEX)* gene [OMIM*300550] and is inherited as an X-chromosomal dominant trait [4]. Although the pathogenic mechanisms are not understood completely, the hypersecretion of fibroblast growth factor 23 (FGF23) in XLH patients decreases vitamin D activation and suppresses the reabsorption of phosphate (P) in renal tubules, leading to hypophosphatemia [5, 6].

Active vitamin D and phosphate are administered to XLH patients as conventional therapies to improve hypophosphatemia and rickets [7]. In adulthood, nephrocalcinosis (NC), nephrolithiasis, and impaired renal function occur in XLH patients as complications related to conventional therapy [8, 9]. NC is caused by hypercalciuria and excessive urine P concentration [10–12]. Because NC can cause nephrolithiasis, careful follow-up is essential [13, 14]. Although conventional therapy is moderately effective for

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XLH, oral active vitamin D and phosphate, or both, can promote or worsen NC related to drug-induced hypercalciuria in addition to the impaired reabsorption of phosphate by the disease itself [7, 15, 16].

Recently, an anti-FGF23 antibody, burosumab, was developed as a fundamental treatment for FGF23-related hypophosphatemic diseases [17–19]. Compared with conventional therapy, burosumab improved disease symptoms and clinical data in severe or poorly-controlled XLH patients, with the Rickets Severity Scale (RSS) of 2.0 or more, in a randomized controlled clinical trial (RCT) [20]. However, the effect of burosumab in relatively well-controlled XLH patients, with RSS below 2.0, by conventional therapy has not been evaluated thoroughly and the benefits of switching treatments are key clinical issues to be elucidated.

Patients and methods

Study design

This study aimed to reveal the impact of switching treatments from conventional therapy to burosumab in relatively well-controlled XLH children with RSS below 2.0.

We retrospectively analyzed the clinical data of pediatric XLH patients during conventional therapy and burosumab injection (Figure 1). Before initiating burosumab injection, we set the baseline after four weeks as the washout period for conventional therapy. Because the clinical severity or control status of XLH patients varies, the effects of the two treatments were compared for the same treatment duration (31 ± 11 months) in each patient before and after the baseline.

Patients

Overall, 28 XLH patients, 13 children, and 15 adults were treated with conventional therapy in our hospital. Because clinical trials for switching treatments to burosumab was for only pediatric patients, of these, informed consent was obtained from the parents of 13 pediatric XLH patients at enrollment to the RCT (UX023-CL301) [20] in December 2016, at enrollment to the self-injection trial (KRN23-003) in July 2017, and/or after burosumab approval in Japan in November 2019. Poorly-controlled XLH patients, with RSS of 2.0, participated in the RCT [20] and patients and/or parents/family members chose their own treatments. Two patients were enrolled in the RCT, five participated in the self-injection trial, and one initiated burosumab after its approval. Consequently, eight patients treated with burosumab were enrolled in

this study. Informed consent was obtained from all individual participants included in this study.

Treatments

For conventional therapy, 50–100 ng/kg per day of alfacalcidol (Alfarol[®], Chugai Pharmaceutical Co., Ltd., Tokyo, Japan, or Onealfa[®], Teijin Pharmaceutical Company, Tokyo, Japan) and/or 20–40 mg/kg per day of neural phosphate (Phosribbon[®] Combination granule, ZERIA Pharmaceutical Co., Ltd., Tokyo, Japan) were administered at diagnosis. We set the most important clinical goal as to control rickets. We adjusted the doses of the drugs monitoring bone X-rays and biochemical data particularly the serum ALP concentration. We also monitored the urine Ca/Cr ratio not to exceed about 0.3–0.4 mg/mg.

Burosumab (CRYSViTA[®] Subcutaneous Injection, Kyowa Kirin Co., Ltd, Tokyo, Japan) was administrated by subcutaneous injection at doses of 0.8–1.2 mg/kg every two weeks, adjusting in relation to serum P concentrations above 3.0 mg/dL which was the criterion of the clinical trials.

Data analysis

Biochemical analyses and bone X-rays were performed every 3–4 months and every six months, respectively, in the RCT (UX023-CL301) [20], in the following continuous administration trial (KRN23-004), in the self-injection trial (KRN23-003), or within clinical practice in our hospital. The RSS was used to evaluate rickets status as previously reported [21]. Briefly, rickets status in the metaphysis of four long bones (distal femur, proximal tibia, distal radius, and distal ulna) was scored from 0 (normal) to 10 (most severe). RSS was evaluated blindly by three specialists.

Renal echography was performed and the severity of NC was assessed as previously described on a scale of 0–4, with 0 indicating normal, 1 indicating mild echogenicity around the medullary pyramids border, 2 more intense echogenic rims with echoes faintly filling the entire pyramid, 3 uniformly intense echoes throughout the pyramid, and 4 indicating stone formation [7, 11, 22]. In a kidney indicating all severity including grade 0, high echoic dots may be detected (Figure 2). In this study, we diagnosed over three dots less than 3 mm in diameter in a kidney as mild spotty NC [23]. The severity of NC was also evaluated blindly by three specialists.

Genetic analysis of the *PHEX* gene was performed by direct sequencing.

Blood and urine tests were performed in a fasting state. Urine samples were the second urination of the day. Serum/urine concentrations of calcium (Ca) and creatinine (Cr) were measured in or after the clinical trials by Arsenazo III, an enzymatic method (sarcosine oxidase–peroxidase) (Aqua Auto Kinos Ca reagents, Kainos Laboratories, Inc., Tokyo, Japan; Serotec Ca-AL, Serotec Co., Ltd., Sapporo, Japan), and electrochemiluminescence immunoassay (ECLIA) (L system CRE, Sysmex Corporation, Kobe, Japan; Determiner L CRE, Hitachi Chemical Diagnostics Systems Co., Ltd.,

Figure 1: Schematic representation of study design.

Figure 2: Echographic analysis of kidney.

(A) Grade 1 of nephrocalcification in patient 1. (B) High echoic dots (arrows) considered as mild nephrocalcinosis in patient 5 grading 0.

Tokyo, Japan), respectively. Serum intact parathyroid hormone (iPTH) and 1,25-dihydroxy vitamin D [$1,25(\text{OH})_2\text{D}$], and FGF23 were measured by ECLIA (ECLusys PTH-intact: Roche Diagnostics K.K., Tokyo, Japan), double-antibody radioimmunoassay (RIA2) ($1,25(\text{OH})_2\text{D}$ RIA kit, Immunodiagnostic Systems Limited, Boldon, UK), and chemiluminescent enzyme immune assay (Determiner CL FGF23, Hitachi Chemical Diagnostics Systems Co., Ltd., Tokyo, Japan), respectively. Serum ALP activities were detected using the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) method (ALP2 Reagents, Roche Diagnostics Corporation, IN, USA) in the RCT [20] and the modified Japan Society of Clinical Chemistry Reference (JSCC) method for other data (CicaLiquid ALP, Kanto Kagaku Co. Inc., Tokyo, Japan) [24]. These methods cannot be directly compared, but the formula $x = 2.84 \times y$ ($x = \text{JSCC}$, $y = \text{IFSS}$) established by the Japan Society of Clinical Chemistry was used to estimate and compare values [25]. Serum and urine P were detected with different methods but the reference ranges were the same and considered comparable. Phosphate concentrations were measured by the molybdic acid direct method (IP-HR II, Fujifilm Wako Pure Chemical Corporation, Osaka, Japan) (reference range: 2.5–4.5 mg/dL) and the enzymatic method (UV-end) (IP reagent L “Kokusai”, Sysmex Corporation, Kobe, Japan) (reference range: 2.5–4.5 mg/dL), respectively, in the clinical trials and in our hospital.

Urine calcium extractions were analyzed in all patients using the spot urine Ca to urine Cr ratio (u-Ca/Cr) constantly, and by 24 h urine Ca extraction during the clinical trials. Consequently, the 24 h urine Ca extraction was evaluated total of 34 times in 7/8 patients. The maximal tubular reabsorption of phosphate per glomerular filtration rate (TmP/GFR) and tubular reabsorption of phosphate (%TRP) were calculated as follows: $\text{serum P} - (\text{urine P} \times \text{serum Cr}) / \text{urine Cr}$ (mg/dL), and $\{1 - (\text{urine P} \times \text{serum Cr} / \text{serum P} \times \text{urine Cr})\} \times 100$ (%), respectively.

Statistical analysis

The mean values of biochemical data and RSS were calculated for each patient during conventional therapy and burosumab treatment. To evaluate the course of serum and urine biochemical data, and X-rays, one-way analysis of variance (ANOVA) for repeated measures and general linear model repeated measures were performed. The mean values for baseline, conventional therapy, and burosumab were compared. Mauchly's sphericity test was applied and, if necessary, technical corrections were made using the Greenhouse–Geisser test. Multiple comparisons were analyzed by Bonferroni's test. Pearson's correlation coefficient was calculated to compare the correlation

between the two methods (spot sample and 24 h sample) for urine Ca extraction. All statistical analyses were performed using SPSS software V23.0 (IBM, Japan, Tokyo). A p-value <0.05 was considered statistically significant.

Ethical approval

This study was approved by the Medical Ethic Committee of JCHO Osaka Hospital (ID: 2020-04) for collection and analysis of the clinical data. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individuals included in this study.

Results

The backgrounds of the patients are summarized in Table 1. Two male patients were included in the eight participants (25%). Clinical diagnosis of XLH was determined at infancy (0.5 ± 0.2 years of age) and later it was confirmed by mutational analysis of the *PHEX* gene in all patients. The duration of conventional therapy was 9.8 ± 2.1 years and burosumab injection was started at 10.4 ± 1.9 years of age. At baseline, the mean height and BMI were -1.41 ± 0.75 SD (range: -0.64 to -2.52) and -0.84 ± 0.58 SD (range: -0.32 to -1.82), respectively. Patients were administrated alfacalcidol and phosphate as conventional therapies. The actual dose of alfacalcidol was 150.9 ± 43.9 ng/kg per day through the analysis period (range: 85–227). Oral phosphate was prescribed at 27.5 ± 6.3 mg/kg per day throughout the analysis period (range: 14.6–40.5) 3–4 times a day.

At baseline after four weeks of the washout period, the serum P and FGF23 concentrations were 2.3 ± 0.3 mg/dL and 247.8 ± 157.1 pg/mL, respectively (Table 2). Serum Ca, ALP, and $1,25(\text{OH})_2\text{D}$ were 9.8 ± 0.2 mg/dL, $1,564 \pm 177$ U/L,

Table 1: Backgrounds of the patients at initiation of burosumab.

Case no.	Gender	Age at diagnosis, years	Conventional therapy duration, years	Age, years	Height, SD	BMI, SD	Alfacalcidol, ng/kg/day	Phosphate, mg/kg/day
1	M	0.7	9.6	10.3	-2.52	-1.30	197 (197–227)	27.3 (21.9–32.8)
2	F	0.5	5.8	6.7	-1.51	-1.82	173 (171–208)	21.9 (18.8–25.9)
3	F	0.6	8.2	8.8	-1.54	-0.49	213 (207–217)	38.3 (26.0–38.7)
4	F	0.3	9.8	10.2	-2.09	-1.27	140 (140–154)	25.5 (25.5–40.5)
5	F	0.3	12.1	12.4	-0.72	-0.68	112 (112–127)	22.5 (25.5–30.8)
6	F	0.8	9.3	10.2	-0.42	-0.32	100 (85–104)	24.1 (16.0–25.0)
7	F	0.6	11.3	11.9	-0.64	-0.77	121 (96–146)	27.2 (24.3–28.2)
8	M	0.4	12.0	12.4	-1.81	-0.07	116 (110–123)	37.4 (36.8–37.4)
Average ± SD (range)		0.5 ± 0.2	9.8 ± 2.1	10.4 ± 1.9	-1.41 ± 0.75	-0.84 ± 0.58	150.9 ± 43.9 (85–227)	28.0 ± 6.4 (16.0–38.7)

Table 2: Clinical data at baseline.

Case no.	Ca, mg/dL	P, mg/dL	ALP, U/L	1,25-(OH) ₂ D, pg/mL	iPTH, pg/mL	FGF23, pg/mL	u-Ca/Cr, mg/mg	TmP/GFR, mg/dL	%TRP, %	RSS	Echography	
											NC grade	Spotty NC
1	10.0	2.4	1,645	12.4	50	219.9	0.0761	1.7	82.6	2.0	1	+
2	9.8	2.7	1,375	45.8	60	110.0	0.0203	1.8	79.2	2.0	0	+
3	9.5	1.9	1,772	81.4	52	560.2	0.0075	2.9	87.0	0.5	1	+
4	9.6	2.0	1,479	6.4	27	353.0	0.0947	2.4	87.0	1.0	1	+
5	9.8	2.2	1,579	27.5	22	88.0	0.0244	2.3	84.4	1.0	0	+
6	10.1	2.8	1,603	14.0	44	290.9	0.0924	1.5	78.6	0.5	1	+
7	9.4	2.1	1,284	79.4	53	242.6	0.0180	2.3	80.0	0	0	+
8	9.8	2.2	1,778	27.9	73.8	118.0	0.1070	2.0	90.7	2.0	0	+
Average ± SD		9.8 ± 0.2	2.3 ± 0.3	1,564 ± 177	36.9 ± 29.5	47.7 ± 16.8	247.8 ± 157.1	0.055 ± 0.041	2.1 ± 0.5	83.9 ± 4.7	1.1 ± 0.8	

SD, standard deviation; Ca, calcium; P, phosphate; ALP, alkaline phosphatase; 1,25-(OH)₂D, 1,25-dihydroxyvitamin D; iPTH, intact parathyroid hormone; FGF23, fibroblast growth factor 23; u-Ca/Cr, urine calcium/creatinine ratio; TmP/GFR, Maximal tubular reabsorption of phosphate per glomerular filtration rate; %TRP, tubular reabsorption of phosphate; RSS, rickets severity scale; FTA, fibro-tibia angle; NC, nephrocalcinosis.

and 36.9 ± 29.5 pg/mL, respectively. Urine extraction of Ca and renal reabsorption of P were assessed as the u-Ca/Cre (0.055 ± 0.041 mg/mg), and the TmP/GFR (2.1 ± 0.5 mg/dL) and %TRP ($87.6 \pm 6.1\%$), respectively. Bone X-rays to determine rickets status were analyzed by RSS as 1.1 ± 0.8 (range: 0.0–2.0). Abdominal echography revealed low-grade NC in four of eight patients (50%) and spotty calcifications were observed in all patients (Figure 2).

Burosumab was injected at 1.09 ± 0.38 mg/kg every two weeks (range: 0.64–2.04). Mean RSS scores tended to be improved by switching treatment from conventional therapy to burosumab, but this did not reach statistical significance ($F(2,12)=3.54$, $p=0.062$) (Figure 3). After switching treatments, renal echography was performed regularly and showed no aggravation of NC in any patients.

In both conventional therapy and burosumab injection, serum P ($F(2,14)=8.768$, $p=0.003$), ALP ($F(2,14)=4.385$, $p=0.033$), and $1,25(\text{OH})_2\text{D}$ ($F(2,14)=20.983$, $p<0.001$) were improved from baseline, but were not different between treatments (Supplementary Material). TmP/GFR and %TRP were unchanged by conventional therapy when compared with baseline, but they were significantly increased by burosumab injection: 78.4 ± 9.4 to $91.6 \pm 5.6\%$ ($F(2,12)=10.501$, $p=0.002$) and from 2.5 ± 0.6 to 3.0 ± 0.4 mg/dL ($F(2,12)=15.452$, $p<0.001$), respectively.

Switching treatments decreased serum Ca ($F(2,12)=4.536$, $p=0.034$) within the normal range and increased u-Ca/Cre to the normal range ($F(2,14)=28.639$, $p<0.001$) (Figure 4). Furthermore, suppressed serum iPTH during conventional therapy was increased within the normal range by washing out the treatment and during burosumab injection ($F(2,14)=0.548$, $p<0.001$) (Figure 4).

To analyze the reliability of spot urine samples, a comparison of spot u-Ca/Cre to 24 h urine Ca extraction was performed (Figure 5). Calcium extraction of spot urine samples correlated with that of 24 h urine samples ($r=0.61$, $p<0.001$).

Figure 3: Rickets severity scale (RSS) in bone X-rays.

Discussion

In the present study, burosumab improved the renal reabsorption of P (TmP/GFR and %TRP) compared to that at the baseline, which was unchanged by conventional therapy. These data demonstrate burosumab is a useful treatment for XLH and reproduced the results of a previous RCT [20].

Burosumab also tended to improve rickets in partly-controlled XLH children. A statistical difference was not detected in our study possibly because disease in our patients was already partly controlled. Indeed, RSS and height SD scores were relatively good during conventional therapy. To treat XLH children, we believe the most important goal is not to control biochemical defects but to control rickets in growing bones. Improved rickets should lead to good growth minimizing deformity of legs or short stature. Thus we adjusted doses of the drugs referring to X-rays paying attention to side effects including urine Ca extraction. Consequently, rickets in our patients were controlled with the conventional therapy instead of overdose active vitamin D. Large doses of active vitamin D increase the risk of hypercalciuria [15]. Although initial dose of alfacalcidol was recommended 30–50 ng/kg/day [26], actual clinical dose was reported 110 ± 0.04 ng/kg/day [27]. Overdoses of alfacalcidol in our patients may be in a gap between the recommendation and the clinical necessity. From this report, we could say that burosumab injection therapy dissolves this dilemma and is worth to be switched from the conventional therapy beyond the cost.

At baseline, frequent NC, increased serum Ca, and increased u-Ca/Cre were observed as possible side effects of the conventional therapy. Burosumab did not develop or worsen NC. Because the cutoff value of hypercalciuria in spot u-Ca/Cre has been reported to be 0.13–0.18 [28, 29], u-Ca/Cre during conventional therapy was often diagnosed as hypercalciuria. Switching treatments dissolved hypercalciuria to the normal range and may be useful for the reduction of side effects caused by conventional therapy although both treatments controlled disease markers equally (serum P, ALP, and $1,25(\text{OH})_2\text{D}$).

Intact PTH was increased within normal range after switching treatments. Because iPTH was already increased by washout of alfacalcidol administration, one possible cause may be a direct effect of hypervitaminosis D [30]. As the other possibility, endogenous PTH secretion may have been suppressed by excess serum Ca concentration provably because of the high dose of alfacalcidol. This assumption is partially supported by consequent hypercalciuria during the therapy. Through these ways, switching treatments can normalize serum iPTH levels.

Figure 4: The impact of switching treatments on calcium metabolism.

Switching treatments decreased serum Ca (A, B) and u-Ca/Cr (C, D) from 9.7 ± 0.4 to 9.5 ± 0.3 mg/dL ($p=0.015$), and from 0.359 ± 0.195 to 0.056 ± 0.044 mg/mg ($p=0.003$), respectively. On the other hand, iPTH (E, F) was increased from 25.9 ± 10.9 to 55.9 ± 15.3 pg/mL by switching treatments ($p<0.001$).

Figure 5: Correlation analysis of spot u-Ca/Cr and 24 h Ca extraction.

Spot u-Ca/Cr were correlated with urine Ca extraction in 24 h samples ($r=0.608$, $p<0.001$).

Hypercalciuria and high levels of urine P cause NC, and therefore oral vitamin D and phosphate may be major causes for developing NC in XLH patients treated with conventional therapy [12, 31–33]. The degree of NC varies from histologically subtle forms such as NC or Randall's plaque, which may not be detected by echography to advanced NC that is visible by X-rays [12, 34]. High echoic dots in the renal medulla should be assessed as mild NC although the echographic grading scale of NC judges them 0 (no abnormalities). To assess them in an objective manner, we set diagnostic criteria as over three dots less than 3 mm in diameter in a kidney. Several pathways for developing nephrolithiasis have been suggested and some

forms of NC lead to nephrolithiasis [12, 35, 36]. Consistent with our data, no past clinical studies have reported that burosumab induced or aggravated NC [37–39]. Thus, switching treatments, which decreased urine Ca and P extraction, is expected to decrease the risk of NC and nephrolithiasis.

In conclusion, this study demonstrated that burosumab improved renal P reabsorption in partly-controlled XLH children compared with conventional therapy. Because high doses of alfacalcidol and phosphate as conventional therapy were needed to control rickets in XLH children, switching treatments to burosumab injection can dissolve side effects associated with conventional therapy. Moreover, switching treatments decreased urine Ca extraction indicating it may have the potential to prevent NC.

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Competing interests: The authors declare that they have no conflict of interest.

Informed consent: Written informed consent was obtained from all individuals included in this study.

Ethical approval: This study was approved by the Medical Ethic Committee of JCHO Osaka Hospital (ID: 2020-04) for collection and analysis of the clinical data. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Serum and urine biochemical outcomes before and after switching treatments. Serum P (a, b), ALP (c, d), and 1,25-(OH)₂D (e, f) concentration were not changed 3.2 ± 0.7 vs. 3.2 ± 0.4 mg/dL, $1,229 \pm 371$ vs. $1,191 \pm 327$ IU/L, and 70.3 ± 24.1 vs. 65.0 ± 16.3 pg/mL in both the conventional therapy and burosumab, respectively, but improved comparing to baseline (BL). Renal P reabsorption were analyzed by TmP/GFR (g, h) and %TRP (i, j), and improved with burosumab from 2.5 ± 0.6 to 3.0 ± 0.5 mg/dL, and from 77.9 ± 9.3 to $90.6 \pm 5.3\%$, respectively.