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Review

Treatment of X-Linked Hypophosphatemia in Children

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Abstract: The conventional treatment for X-linked hypophosphatemia (XLH), consisting of phosphorus supplementation and a biologically active form of vitamin D (alfacalcidol or calcitriol), is used to treat rickets and leg deformities and promote growth. However, patients' adult height often remains less than −2 SD. Moreover, adverse events, such as renal calcification and hyperparathyroidism, may occur. The main pathology in XLH is caused by excessive production of fibroblast growth factor 23 (FGF23). Several studies have demonstrated that treatment with burosumab, a blocking neutralizing antibody against FGF23, is better than conventional therapy for severe XLH and has no serious, short-term side effects. Thus, treatment with burosumab may be an option for severe XLH. The present article reviews the conventional and burosumab therapies. In addition to the fact that the long-term efficacy of antibody-based treatment has not been demonstrated, there are other, unresolved issues concerning the burosumab treatment of XLH.

Keywords: phosphorus; active form of Vitamin D; renal calcification; fibroblast growth factor 23 (FGF23); burosumab

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1. Introduction

Hereditary hypo-phosphatemic disorders caused by elevated fibroblast growth factor-23 (FGF23) includes X-linked hypo-phosphatemic rickets (XLH) and autosomal-dominant hypo-phosphatemic rickets (ADHR) [1–4]. Osteoblasts and osteocytes produce and secrete FGF23, which binds to KLOTHO-FGF receptor 1 (FGFR1) in the target organs [3,4]. FGF23 suppresses the expression of type 2a and 2c sodium-phosphate cotransporters in renal proximal tubules, inhibiting phosphate reabsorption [3,4]. Moreover, FGF23 downregulates the expression of 1α-hydroxylase (CYP27B1), which converts 25-hydroxyvitamin D to 1, 25 $(OH)_2$ hydroxyvitamin D [3,4]. Thus, the symptoms of XLH and ADHR consist of rickets, short stature, osteo-malacia, bone pain, and dental diseases caused by renal phosphate wasting and low or inappropriately normal 1, 25 $(OH)_2$-hydroxyvitamin D levels [1,2].

The frequency of XLH is 1.7 per 100,000 children [1–3]. XLH arises from mutations of the phosphate-regulating endopeptidase homolog X-linked (PHEX) gene (Xp22.11), and its inheritance is X-linked dominant [3,4]. Males and females are equally affected, but the clinical severity is often variable even in familial cases [3,4]. The PHEX protein, a protease expressed in osteocytes and odontoblasts, does not degrade FGF23 [3,4]. Although the exact mechanism underlying elevated FGF23 in XLH is not completely understood, it is speculated that the sensing of phosphate in osteocytes may be disturbed [3,4].

The treatment target in X-linked hypophosphatemia (XLH) in childhood is to improve rickets, restore growth, alleviate bone pain, improve physical activity, and maintain dental health [1,2,5–9]. Infants in whom the condition is diagnosed at birth via family screening should be treated as soon as possible, as the outcomes are better the earlier therapy is begun [1,2,10].

The conventional therapy for XLH consists of oral phosphorus supplementation and alfacalcidol or calcitriol [1,2,5–9]. Recently burosumab, an IgG1 monoclonal antibody

targeting FGF23, was developed and authorized for use by the European Medicines Agency and Food and Drug Administration [1–3,10–12], and several studies of its use in the treatment of severe XLH have already been published [13–17].

The present review provides a descriptive summary of oral phosphorus supplementation and alfacalcidol or calcitriol therapy, issues related to this treatment, and the prospects of burosumab as an alternative therapy for XLH.

2. Conventional Therapy

As mentioned above, the conventional therapy for XLH consists of oral phosphorus supplementation and alfacalcidol or calcitriol. Oral phosphorus supplementation compensates for renal phosphate wasting, and alfacalcidol or calcitriol compensates for impaired 1, 25 $(OH)_2$-hydroxyvitamin D production caused by excess fibroblast growth factor 23 (FGF23) [1,2,18].

The phosphorus is administered in the form of a sodium-based and/or potassium-based salt preparation. Table 1 summarizes the dosage of phosphorus and alfacalcidol or calcitriol [7].

Table 1. Dosage of phosphorus and alfacalcidol or calcitriol.

	Dose (Ref. [2])	Number of Doses per Day
Phosphorus	20–60 mg/kg/day (initial dose)	4–6 times/day
Alfacalcidol	0.03–0.05 mg/kg/day	Once a day
Calcitriol	0.02–0.03 mg/kg/day	One or two doses

Oral phosphorus 20–60 mg/kg/day is recommended as the initial dosage, depending on the age of the patient and the severity of the clinical symptoms [1,2]. It may be advisable to begin with a low dosage. However, to avoid gastrointestinal side effects, such as abdominal pain and diarrhea, and hyperparathyroidism, the dosage should not exceed 80 mg/kg/day [1,2]. When phosphorus is administered orally, it is poorly absorbed by the intestinal tract and returns to the original value after a few hours [2]. Therefore, multiple, daily doses of phosphorus are needed. In children, four to six divided doses daily are preferable [2]. The serum phosphate level should not be used to adjust the dosage of phosphorus supplementation [2].

Alfacalcidol or calcitriol is administered with oral phosphorus supplementation to compensate for impaired 1, 25 $(OH)_2$ hydroxyvitamin D production caused by excess FGF23 [1,2,5–8]. Alfacalcidol and calcitriol increase the absorption of phosphorus from the intestines. Initially, alfacalcidol 0.03–0.05 mg/kg/day should be administered once daily, and calcitriol 0.02–0.03 mg/kg/day could be administered in one or two doses daily [2]. The alfacalcidol and calcitriol dosage are often higher in toddlers and adolescents than in children [1,2,5,6] and should be adjusted so that it does not exceed (0.35 mg/mg) in urinary calcium/creatine [2]. If necessary, water intake is recommended to reduce the urinary calcium concentration [1]. Calculating the dosage should also take into consideration the degree of ALP decrease as well [1,2]. While administering a large amount of alfacalcidol or calcitriol is effective for improving rickets and growth velocity, it can lead to hypercalcemia, increased urinary calcium excretion, and renal calcification [1,2,5–8]. However, if the dosage is too low, it will be ineffective in improving rickets or the growth velocity. Thus, fine-tuning the alfacalcidol and calcitriol dosage is often difficult.

Regarding adult height, Miyamoto et al. [19] reported that the adult height of patients with XLH who received conventional therapy was −1.69 SD. Linglart et al. [8,20] reported that the mean adult height in female and male patients with XLH was −1.3 SD and −1.9 SD, respectively. However, 25–40% of patients with well-controlled XLH show an adult height below −2 SD despite receiving optimized conventional therapy [21–26].

Cheung et al. [27] reported that pediatric patients with conventional therapy showed lower cortical volumetric bone mineral density (vBMD) of the radius as determined by pe-

ripheral quantitative computed tomography (pQCT) than control subjects. Neto et al. [28] also reported a lower vBMD of the radius and tibia in pediatric patients with conventional therapy. In Hyp mice, early supplementation with calcitriol and phosphate improved bone microarchitecture on micro-CT to a greater extent than in non-treated Hyp mice [29]. In Hyp mice, the abnormal PHEX function may directly cause the cartilage abnormalities [30,31]. Taken together, conventional therapy may be only partially effective for bone mineralization.

3. Possible Complications under Conventional Therapy

Three to five phosphorus doses are normally administered. Phosphorus supplementation stimulates the gastrointestinal system and can cause diarrhea [1,2], possibly leading to decreased compliance. Furthermore, alfacalcidol and calcitriol have a relatively narrow therapeutic window, as mentioned previously, and may thus increase urinary calcium excretion. Increased urinary calcium excretion and hyper-phosphaturia lead to nephrocalcinosis and nephrolithiasis [3–6]. Renal calcification reportedly occurs in 30–70% of patients with XLH [1,32–34] as a manifestation of secondary hyperparathyroidism [1,2,8,35–37], which is caused by the high dose of oral phosphorus and/or an active form of vitamin D. In addition, FGF23 contributes to the progression of secondary hyperparathyroidism by reducing 1, 25 $(OH)_2$ hydroxyvitamin D synthesis and subsequently decreasing active intestinal calcium transport [1,2,8]. Furthermore, hyperparathyroidism in XLH patients has been reported to cause hypertension [36,37]. According to Alon et al. [36]. eight of 41 patients with XLH aged 20–29 years experienced hypertension during treatment. Secondary and tertiary hyperparathyroidism were observed in all eight of these patients, and nephrocalcinosis was observed in seven patients. Nakamura et al. [37] also reported that six of 22 adult patients with XLH experienced hypertension, and that the average age at hypertension onset was 29 years. All six patients had secondary or tertiary hyperparathyroidism, and two patients had renal dysfunction. Monitoring of blood pressure is necessary for XLH patients with hyperparathyroidism.

4. Clinical Trials of Burosumab

As mentioned above, the conventional therapy is effective, but leg deformities and diminished adult height persist in some patients with XLH despite long-term therapy.

Recently, burosumab, an anti-FGF23 antibody, was developed as a drug for decreasing excess FGF23 [3,11,12], which is central to the pathology of XLH [1–3]. Burosumab is a recombinant immunoglobulin G1 monoclonal antibody that binds intact and fragmented FGF23 at the N-terminal domain [12]. N-terminal antibodies to FGF23 can prevent the interaction of FGF23 and FGF receptor 1c [12]. Blood levels of burosumab peak in seven to 11 days on average, and its half-life in blood is 16 to 19 days [38,39]. The pharmacokinetics are the same for adults and children [39].

Aono et al. [12] reported the effects of antiFGF23 antibody in Hyp mice. The antibodies were administered to 4-week-old mice once a week for one month. As a result, the serum phosphate and 1, 25 $(OH)_2$ hydroxyvitamin D levels increased. Improvement of bone deformities and mineralization were observed. Blocking FGF23 with antibodies can cause a rapid increase in 1, 25 $(OH)_2$ hydroxyvitamin D, leading to hypercalcemia and possible renal calcification. However, in the previously cited study of Hyp mice, no nephrocalcinosis was observed.

Table 2 summarizes the results of several clinical trials of burosumab [13–17]. In all the trials, changes in rickets were assessed using the Rickets Severity Score (RSS) and Radiographic Global Impression of Change (RGI-C). The RSS consists of ten sores, with 0 indicating no rickets, and 10 indicating the greatest severity [40]. The RGI-C is an ordinal scale in which −3 indicates severe exacerbation and +3 indicates a complete cure [41].

Table 2. The effect on radiographic changes and height change of burosumab.

	Ref [13]	Ref [14]	Ref [15]	Ref [16] [1]	Ref [17]
Number of patients (age)	52 (5–12 years)	13 (1–4 year)	61 (1–12 years)	52 (5–12 years)	15 (1–12 years)
Burosumab dose	N = 26 Q2W [2] (initial 0.1 mg/kg, titrated to mean 0.98 mg/kg) N = 26 Q4W [3] (initial 0.2 mg/kg, titrated mean 1.5 mg/kg)	0.8–1.2 mg/kg Q2W	N = 29 Burosumab 0.8–1.2 mg/kg Q2W N = 32 Conventional therapy	0.8–1.2 mg/kg Q2W	0.8–1.2 mg/kg Q2W
Change of RSS Mean ± SD	At base line Q2W 1.9 ± 1.2 Q4W 1.7 ± 1.0 At 64 weeks Q2W 0.8 ± 0.6 Q4W 0.9 ± 0.5	At base line 2.9 ± 1.2 At 64 weeks 0.9 ± 0.5 [4]	At base line Burosumab 3.2 ± 1.1 Conventional therapy 3.2 ± 1.0 At 64 weeks Burosumab 1.0 ± 0.7 [4] Conventional therapy 2.2 ± 0.8 [4]	At 160 weeks RSS decreased in 41/52 patients	At base line 1.3 ± 1.2
Change of RGC-I LSM [5] ± SE	Q2W 0.8 ± 0.6 at 64 weeks Q4W 0.9 ± 0.5 at 64 weeks	0.9 ± 0.5 (RGI-C score ≧+2 13/13) patients) [6]	Burosumab at 64 weeks 1.0 ± 0.7 [4] (RGI-C score ≧+2 25/29 patients) [6] Conventional at 64 weeks 2.2 ± 0.8 [4] (RGI-C score ≧+2 6/32 patients)	LSM (SE) from base line to week 160 +1.89 ± 0.1 (RGI-C score ≧+2 23/41 patients at 160 weeks) [6]	Global RGC-I At 40 weeks 1.5 ± 0.8 At the end of treatment (average 121.7 weeks) 2.1 ± 0.7
Effect on length of height change after burosumab	Mean change of height Z score Q2W +0.19 at 64 weeks Q4W +0.12 at 64 weeks	Mean (SD) recumbent length or standing height Z score −1.38 ± 1.1 at base line −1.64 ± 1.09 at 63 weeks	LSM (SE) at 64 weeks Burosumab 0.17 ± 0.07 Conventional therapy 0.02 ± 0.04	Mean (SD) height Z score Q4W→Q2W −2.05 ± 0.96 at base line −1.85 ± 0.85 at 160 weeks Q2W→Q2W −1.72 ± 1.03 at base line −1.38 ± 1.06 at 160 weeks	No change of height Z score from baseline

[1]. Shown here is a study examining the continued treatment of the 52 patients previously enrolled in a study by Carpenter et al. [13] with burosumab for up to 160 weeks. [2]. Q2W, every two weeks. [3]. Q4W, every four weeks. [4]. These data were provided by ref. [42]. [5]. LSM, lean squared mean. [6]. The number of patients with ≧ 2 points at the end of the study.

The first, open-label, uncontrolled study included 52 patients with XLH (aged 5–12 years) who were followed to week 64 [13]. All the patients switched from the conventional therapy to burosumab. At base line, 94% of the patients had active rickets (RSS > 0). The subjects were divided into biweekly and four-weekly administration groups. The initial dosage was 0.1 mg/kg in the biweekly group and 0.2 mg/kg in the four-weekly group. The dosage was gradually increased to reach the lower limit of the reference value for fasting serum phosphorus level by age at week 2 after administration.

Increased serum phosphorus, renal phosphate reabsorption, 1, 25 (OH) 2D, and decreased serum ALP were observed in both groups. The mean fasting serum phosphorus level initially increased from the baseline value at all time-points in both groups and was able to be maintained in the biweekly group during the treatment period whereas in the four-weekly group it decreased steadily even at week 64 until the next dose.

While the biweekly group showed a decrease in the mean RSS, the four-weekly group showed a smaller decrease, indicating greater improvement in the former group. A small increase in the mean standing height Z score was also observed in the biweekly group and the four-weekly group. Furthermore, the score for physical functioning and pain improved in both groups. Based on these findings, burosumab was considered effective for children with XLH, and biweekly administration of burosumab was considered most appropriate.

Secondly, an open-label study of 13 patients (aged 1 to 4 years) [14] switching conventional therapy to burosumab treatment at baseline found that 12 of the patients had a RSS of

at least 1.5, indicating severe rickets. As a result, the RSS improved by week 64. However, the length and height Z scores worsened. The authors stated that a precise assessment of length and height can be difficult at this age; however, most patients' height Z score continued to follow the growth curves.

Third, a randomized control study enrolled 61 children with XLH (aged 1 to 12 years) with an RSS score > 2 (relatively severe) who switched from the conventional therapy to burosumab or continued the conventional therapy [15]. The patients in both groups had already received the conventional therapy for an average of 4.3 years and 3.3 years, respectively. Burosumab administration was begun at 0.8 mg/kg every two weeks, then increased to 1.2 mg/kg.

At week 64, improvement in RGC-I and RSS was better in the burosumab group than in the conventional therapy group. The increase in the length and height Z scores at week 64 was also significantly greater in the burosumab group than in the conventional therapy group. Therefore, in patients with relatively severe XLH, burosumab is more effective than conventional therapy.

A study which examined continuation of burosumab therapy in the 52 patients previously enrolled in a study by Carpenter et al. [13] for up to 160 weeks [16] was reported. Most patients showed improvement in radiographic findings of rickets. Although the height Z score improved, the change from the baseline was moderate.

Namba et al. [17] recently reported the results of a Phase 3 and 4 open-label trial. Fifteen children (aged 1 to 12 years) received an average of six years of the conventional therapy. As in previous reports, RSS, RGI-S and growth rate tended to improve at week 124.

5. Safety of Burosumab

No previous studies based on clinical trials reported any short-term serious adverse events leading to the discontinuation of burosumab [13–16]. A recent, longitudinal study reported that adverse events related to burosumab occurred in 73% of the patients enrolled [16]. The most common adverse event was a reaction at the injection site [13–17], which occurred in about half the patients receiving burosumab but resolved one to two days after the injection. The second most common burosumab-related adverse event was pain in the extremities (10%). One patient experienced two serious adverse events requiring hospitalization (fever and muscle pain at week 48 and headache at week 182) but the therapy was nonetheless continued [16].

Six patients were positive for antidrug antibodies at the baseline while 40 patients remained negative for the 160-week course [16]. Three of the six patients with antidrug antibodies were also positive for neutralizing antibody. These patients experienced a reaction at the injection site but achieved improved RSS and maintained their serum phosphorus level. None of the patients had increased serum calcium, excessive urinary calcium excretion or increased serum PTH even after 160 weeks of therapy [16].

A study comparing burosumab with the conventional therapy found no renal calcification or hyperparathyroidism in a burosumab-therapy group [15] but reported a higher number of dental abscesses in this group than in a conventional therapy group [15], corroborating previous findings of the efficacy of the conventional therapy against dental diseases [1,2,8]. Further study is needed to clarify these issues.

6. Indications for Burosumab Treatment in Children

A recent consensus statement has suggested that burosumab therapy should be considered as the first-line therapy in children with XLH aged 1 year or older (6 months in some countries, such as the USA) and adolescents with radiographic findings of bone disease [2]. The consensus also recommended that the treatment be continued until epiphyseal closure [2]. While clinical trials have so far shown burosumab to be more effective than conventional therapy in severe XLH, the effect of burosumab on mild XLH is still unknown. Further, the annual cost of burosumab therapy is enormous (about US $200,000). Therefore, conventional therapy should be attempted first in mild cases [2].

The initial burosumab dosage is 0.8 mg/kg administered subcutaneously every two weeks [2]. The dosage should be adjusted so that the fasting serum phosphorus concentration is at the lower end of the normal reference range by age [2]. The fasting phosphate level should be measured 12–14 days after the injection to avoid hyperphosphatemia [2].

7. Future Prospects for Burosumab Treatment

Table 3 summarizes the unsolved questions in burosumab therapy.

Table 3. Open questions to be considered in burosumab treatment.

- Treatment of infants
- Biochemical markers for dose setting (fasting serum phosphorus level, tubular reabsorption of phosphorus, urine calcium/creatinine, PTH, etc.)
- Long-term effect on healing of rickets, adult height, dental health, bone pain, and physical function
- Long-term safety

Further, long-term follow up is needed to assess the long-term impact of the therapy on rickets, adult height, and safety.

8. Summary

The present review summarized the current methods of treating XLH. The conventional therapy consisting of phosphorus supplementation and alfacalcidol or calcitriol is effective for improving rickets and growth rate, but some patients fail to respond adequately, resulting in leg deformities and reduced adult height. Moreover, adverse events sometimes occur with the conventional therapy. Burosumab is more effective than the conventional therapy in severe XLH, but some unresolved issues, including the fact that final height data have not yet been collected, remain. More evidence from future studies should clarify these issues.

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