Title: Burosumab for pediatric X-linked hypophosphatemia

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Abstract:

Purpose of Review: X-linked hypophosphatemia (XLH) is the most common genetic cause of rickets. This review describes advances in management of XLH using burosumab which was FDA approved for treating children with XLH in 2018.

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Recent findings: Elevated FGF23 in XLH leads to systemic hypophosphatemia and several musculoskeletal manifestations, including rachitic bone deformities, impaired growth, dental abscesses, insufficiency fractures, osteoarthritis, and enthesopathy, with lifelong consequences for physical function and quality of life. Burosumab treatment has demonstrated clinical improvement of rickets and growth in children, including during a randomized controlled trial compared with conventional therapy. Burosumab also improved pseudofracture healing in adults.

Summary: Burosumab led to greater improvement in rickets and growth than conventional therapy. However, many questions remain regarding the impact of burosumab for several outcomes, including final height, nephrocalcinosis, dental disease, enthesopathy and surgical interventions.

Introduction

Although X-linked hypophosphatemia (XLH) is a rare metabolic bone disease, it is the most common genetic cause of hypophosphatemia and rickets[1]. XLH is caused by one of several hundred mutations in *PHEX*[2, 3], which is expressed in osteocytes and odontoblasts[4]. Deficiency of PHEX causes elevated *FGF23* gene expression and production of intact FGF23[5]. FGF23 interacts with FGF receptors and the co-receptor α-klotho in the renal tubule, downregulating surface expression of the sodium phosphate co-transporters NPT2a and NPT2c, which leads to renal phosphate wasting, and consequent systemic hypophosphatemia[6-8]. FGF23 activity also decreases 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] in two ways: through decreased conversion from 25-hydroxyvitamin D via 1α-hydroxylase (CYP27), and increased catabolism through 24-hydroxylase (CYP24)[7]. Thus, the 1,25$(OH)_2$D concentration is generally "inappropriately" low or normal compared to the expected physiologic response to hypophosphatemia (which should normally raise 1,25$(OH)_2$D). Additional consequences of PHEX deficiency include accumulation of osteopontin, a mineralization inhibitor [9].

The net effect of these biochemical abnormalities is to cause hypophosphatemia at the growth plate chondrocytes as well as at the osteoid surface, resulting in impaired hypertrophic chondrocyte apoptosis and decreasing the mineral apposition rate, and the manifestations of rickets and osteomalacia [10, 11]. The rachitic abnormalities progressively lead to skeletal deformation, most prominent in the long bones of the lower extremities, which can present with varus or valgus abnormalities and hence gait abnormalities and short stature[12]. The magnitude of these skeletal abnormalities can vary widely between individual patients, even within the same family. However, short stature persists in most patients and the deviation from normal worsens as children age and go through puberty, with the mean adult height being typically below -2 SD from the normal population mean[13]. The growth of the lower limbs is impaired disproportionate to the trunk growth impairment. Additional features of XLH include cranial bone abnormalities such as frontal bossing, Chiari malformation, and effects on hearing. Muscle weakness and lower limb deformities alter gait and impair physical function, even in children [12]. Indeed, the Rickets Severity Score (RSS) is predictive of severity of other clinical features including

impairments in growth, impairments in the distance walked in 6 minutes, self-reported pain, and physical function scores [14]. Children frequently require surgical intervention to correct lower limb bowing and torsion abnormalities [1].

Hypophosphatemia in XLH is lifelong, thus adults with XLH remain at risk for psuedofractures and bone pain from osteomalacia. Adults with XLH remain are generally short due to childhood growth impairments and have ongoing issues related to the remaining skeletal deformities at the end of growth contributing to altered gait. However additional features such as enthesopathy, osteoarthritis and spinal stenosis are common features of adults with XLH [15-18]. These several features impact mobility and physical function among adults with XLH[19, 20].

Conventional therapy for XLH

The goals of treatment for XLH are to heal rickets, improve skeletal deformities and growth, as well as bone pain and mobility. Although historically XLH was classified as a "vitamin D resistant rickets" based on the ineffectiveness of using nutritional vitamin D as treatment, with the current knowledge of molecular genetics, this term really should be abandoned, as there is no evidence of resistance of the vitamin D receptor to vitamin D in this disorder. The conventional therapy for XLH for many years has involved treatment with high doses of an active form of vitamin D such as calcitriol or alfacacidol, in combination with high doses of phosphate salts, which combat the target effects of FGF23 to lower serum phosphorus and $1,25(OH)_2D$ [21, 1]. Dose recommendations and titrations for conventional therapy have been thoroughly detailed elsewhere, with calcitriol doses commonly of 20-40 ng/kg per day or alfacalcidol 30-50 ng/kg per day, and phosphate salts of 20-60 mg/kg per day [21, 1]. Doses of calcitriol and phosphate must be divided and spread throughout the day (typically four times a day for phosphate). Higher daily doses are sometimes required, and it is important not to think of this treatment as merely supplementation, as there are real side effects requiring careful monitoring.

Conventional therapy improves rickets and growth in children, and osteomalacia in adults, but with significant variability in terms of individual response and in the doses required for optimal effect.

Indeed, as an indicator of the effectiveness of conventional therapy, during enrollment for one of the clinical trials of burosumab in children, 45% of the children screened were excluded due to insufficient severity of rickets at screening after conventional therapy[22]. There is good evidence that at least growth outcomes are improved when conventional treatment is started younger than one year of age[23]. However, short stature remains prevalent and orthopedic corrective surgeries are often necessary.

Conventional therapy attempts to address the consequences of excess FGF23 (low phosphate and $1,25(OH)_2D$) but does not block the effects of FGF23 and in fact multiple studies have demonstrated increases in FGF23 during conventional therapy of XLH[24, 25]. Conventional therapy does not improve the tubular reabsorption of phosphorus in patients with XLH[21, 1]. As a result, renal phosphate losses persist and even increase during conventional therapy, which may contribute both to some of the limitations of conventional therapy and also its complications, specifically nephrocalcinosis.

Important challenges of conventional therapy include difficulties with complying with regimens requiring multiple doses every day, and the gastrointestinal side effects of phosphate salts, as well as well as frequent occurrence of nephrocalcinosis and hyperparathyroidism[21, 1]. Nephrocalcinosis is reported in up to 50-80% of XLH patients in some studies, and appears to be related at least in part to hypercalciuria[54-57]. There is little data on the impact of nephrocalcinosis on development of subsequent chronic kidney disease. Most patients develop secondary hyperparathyroidism at some point in time, which often is transient, while 25-30% of adults and 4 % of children develop tertiary hyperparathyroidism, which can present even years after stopping conventional therapy[26]. Tertiary hyperparathyroidism requires surgical intervention, usually with three and a half gland resection. Cincalcet use has been reported in several cases though the results have been mixed[26]. Overall, treating XLH requires frequent laboratory monitoring and careful dose adjustments to optimize effect and minimize adverse events in growing children.

Burusomab for XLH

Clinical trial evidence

The strategy of blocking FGF23 using monoclonal antibodies has been demonstrated in the hyp mouse model of XLH to improve renal phosphorus transport, serum phosphorus and to increase $1,25(OH)_2D$[27, 28]. In addition, the mice had improvements in growth, rickets, osteomalacia and muscle strength[27, 28].

Burosumab is a fully human IgG1 monoclonal antibody that binds to FGF23 to inhibit its activity, which was recently approved as monotherapy for the treatment of XLH by the FDA, EMA and other regulatory institutions. Based on the results from clinical trials, burosumab dosing in adults is 1 mg/kg every 4 weeks subcutaneously, while in children the dose is typically 0.8 to 1.2 mg/kg every 2 weeks[22, 29, 30]. Because burosumab binds FGF23 and hence increases renal tubular phosphorus reabsorption and serum phosphorus, dosing can be titrated to target the serum phosphorus level to be in the normal range, while dose decreases are sometimes required to avoid hyperphosphatemia. The first multi-dose phase 2 trial in adults demonstrated increases in TmP/GFR (which peaked about 7 days after dose), serum phosphorus (which peaked 3-7 days after dose) and $1,25(OH)_2D$ (with peak 3-7 days after dosing) [31]. By 4 weeks post dose, these values had decreased to a trough effect, which generally remained higher than baseline, especially for serum phosphorus. Pharmacokinetic studies demonstrated the burosumab half-life to be 13-19 days [32].

Three clinical trials of burosumab were conducted in children (Table 1). In all trials patients stopped conventional therapy for a washout period prior to initiating burosumab. These trials confirmed the expected biochemical response to FGF23 blockade, as well as beneficial effects on the skeletal targets of therapy. For all trials radiographs were scored by raters blinded to treatment. Changes in rickets were assessed according to the RSS (which is a scale from 0-10, with 0 indicating no rickets and 10 being the most severe)[33] and the Radiographic Global Impression of Change (RGI-C) score [which is an ordinal scale from -3 (severe worsening) to +3 (complete healing), with 0 indicating no change from baseline][34]. The RGI-C methodology was also applied to assessment of changes in lower limb deformity.

The first phase 2 trial randomized 52 children ages 5-12 years with XLH to receive burosumab every 2 weeks vs every 4 weeks, starting at low doses and titrating to higher doses based on serum phosphorus concentration[35]. This trial demonstrated post dose increases in serum phosphorus, TmP/GFR and $1,25(OH)_2D$. Dosing every 2 weeks provided better phosphorus levels with less of a trough effect. The primary endpoint was change in RSS. The mean RSS decreased from 1.9 to 0.8 with dosing every 2 weeks, and from 1.7 to 0.9 with dosing every 4 weeks. Thus, the magnitude of improvement in RSS was greater with every 2 week dosing than every 4 week dosing over a 64 week period. The LS mean RGI-C score was +1.57 in the combined groups at week 64. The RGI-C indicated substantial healing in 54% (scores of +2 or more). This trial also demonstrated improvements in alkaline phosphatase. Small improvements in height Z-score were also seen by week 64 (mean change +0.19 in the every 2 week dosing group, and +0.12 in the every 4 week dosing group). A subset of patients (about half of the population) had baseline impairments in 6 minute walking distance and patient reported outcomes scores which also improved during the trial [35].

It should be acknowledged that in this first pediatric trial dosing, especially in the first cohort of this trial, started very small (0.1 mg/kg every 2 weeks and 0.2 mg/kg every 4 weeks to be titrated over time) compared to the higher doses reached by the end of this trial and then used in later studies. Thus, the early subtherapeutic doses in many patients may have limited the total changes seen. This trial established the pediatric dosing interval as well as the per kg dose range to be pursued in subsequent studies and for registration.

In a small phase 2 trial in young children age 1-4 years, 13 children with XLH were enrolled with dosing 0.8 mg/kg subcutaneously every 2 weeks, with potential titration up to 1.2 mg/kg every 2 weeks if needed based on serum phosphorus concentration[36]. The mean RSS decreased from 2.9 at baseline to 1.2 at week 40 and 0.9 at week 64 ($p<0.0001$). This corresponded to improvements in the Radiographic Global Impression of Change (RGI-C) score. The LS mean RGI-C was +2.3 by week 40 and + 2.2 at week 64 ($p<0.0001$). All patients achieved an RGI-C of +2 or greater corresponding to substantial healing of rickets. The lower limb deformity RGI-C was +1.6 at week 64 ($p<0.0001$) While this younger age

group did not increase in height Z-score, treatment appeared to blunt the usual decline in height Z-scores typically seen after age 1-2 years[36].

The pediatric phase 3 randomized controlled trial was the only burosumab trial to compare the effects of switching to burosumab to the effects of continuing conventional therapy[22]. Children with XLH ages 1-12 years were required to have RSS of 2 or higher despite treatment with conventional therapy to enroll. Randomization was stratified by RSS and by age over and under 5 years of age. Sixty-one children were enrolled with mean RSS of 3.2 and mean duration of prior conventional therapy of 4.3 years in the group randomized to continue conventional therapy and 3.3 years in the group randomized to burosumab. This study demonstrated that mean fasting serum phosphorus remained low in the conventional therapy arm, while it normalized in those randomized to burosumab at 1 week post the first dose, with mean values remaining in the target range at measured timepoints throughout the trial. This study also confirmed that conventional therapy did not improve TmP/GFR, while burosumab increased TmP/GFR.

By week 40 there were significant differences between groups in terms of changes in rickets [22]. The primary outcome was the global RGI-C for rickets at week 40. The burosumab group had a least squares (LS) mean global RGI-C of +1.9 compared to +0.8 with conventional therapy ($p<0.0001$) at week 40 and at +2.1 and +1.0, respectively ($P<0.0001$) at week 64. In this trial 87% of those treated with burosumab achieved an RGI-C of +2 or more at week 64, compared to only 19% of conventional therapy patients. The LS mean change in RSS was a decrease of -2.2 with burosumab vs -1.0 with conventional therapy. Lower limb deformity also improved though to a lesser degree during this time frame (LS mean lower limb RGI-C +1.3 with burosumab and +0.3 with conventional therapy). The length/height Z-score increased in the burosumab treated group (LS mean change + 0.17) but was unchanged in the conventional therapy group (+0.02) [22].

Collectively these trials indicate that burosumab improves the biochemical and skeletal features of XLH in children between the ages of 1 and 12 years at enrollment. Nearly all the children in this clinical trial program had been treated with prior conventional therapy (2 patients in the first phase 2 trial

were not on conventional therapy before enrollment, all others in the three trials had prior conventional therapy) [22, 36, 35]. Thus, switching from conventional therapy to burosumab resulted in improvements in rickets, while the randomized controlled trial confirmed that switching led to greater improvements than continuing on conventional therapy[22]. In a post-hoc analysis of this trial, patients receiving burosumab had greater improvements in rickets than those on conventional therapy regardless of whether the on-study phosphate doses were >40 mg/kg or ≤40 mg/kg or whether active vitamin D doses were higher (alfacalcidol >60 ng/kg or calcitriol >30 ng/kg), or lower (alfacalcidol ≤60 ng/kg or calcitriol ≤30 ng/kg). Similarly, patients receiving burosumab improved similarly regardless of whether their pre-trial phosphate and active vitamin D doses were in the higher or lower dose groupings [37].

Pseudofractures are common in XLH, especially among adults. There are no fracture related trial data in children with burosumab. However, the placebo controlled trial of burosumab in adults with XLH enrolled patients having chronic pain (with the brief pain inventory worst pain score of ≥4), and at baseline 52% had one or more active fractures or psuedofractures (for a total of 156 such fractures)[15, 29] The placebo control period lasted 24 weeks. By week 24, 43% of the active fractures or psuedofractures had completely healed in the burosumab group compared with only 7.7% in the placebo group. After 24 weeks all patients switched to open label burosumab. By the end of 48 weeks of treatment with burosumab, 63.1% of active fractures and psuedofractures had completely healed. There were also improvements in pain and stiffness in these adults.

The fracture data unfortunately were not compared to conventional therapy, but to a placebo. It is not surprising that some treatment is better than no treatment in osteomalacia. However, many of these patients were receiving conventional therapy before enrolling in this trial and still had these fractures that were unhealed at baseline (the proportion is not entirely clear from the study publications). This fits with clinical experience that psuedofractures are often symptomatic for long periods of time and take a long time to heal with conventional therapy. The fact that by 48 weeks of burosumab only 63.1 % had completely healed is another indicator of the chronic nature of these lesions and time required to heal with medical therapy.

Side effects of burosumab

During the burosumab clinical trials, several adverse events were described among adults and children. Transient injection site reactions were common in children, affecting 52-57% [35, 22, 36], though these were less common in adults (11.8%) [15]. Some individuals only had injection site reactions intermittently. Fevers were also common in children, though this can be difficult to interpret as routine illnesses in children commonly involve fevers. Hypersensitivity reactions were more common in children on burosumab (38%) than those on conventional therapy (19%), but were low in adults on burosumab or placebo (5.9% and 6.1%)[15, 22]. These were not thought to be due to burosumab and importantly, none of the children in the clinical trials stopped burosumab for these symptoms during the primary study periods.

Restless legs syndrome was noted in the adult clinical trials in both the burosumab group (11.8%) and the placebo group (7.6%)[15]. Restless legs symptoms do appear to be a common in adults with XLH (untreated or during treatment with conventional therapy), but this symptom has also developed or increased during burosumab treatment (personal observation from the author's practice- EI). There was no difference between groups regarding change in nephrocalcinosis during the relatively short treatment periods of the controlled clinical trials in children or adults [22, 38].

Dental abscesses remained common during treatment with burosumab, and were actually more frequent in the burosumab treated group than with conventional therapy in children over 64 weeks, or in adults vs placebo over 24 weeks. Dental abscesses and periodontal disease remain common in children or adults with XLH even on conventional therapy. In a recent abstract both $1,25(OH)_2D$ and anti-FGF23 antibody improved dentin-cementum volumes about 20% in hyp mice but volumes remained dramatically lower than in the wild-type mice while the mineral density of these tissues did not improve[39]. This is consistent with evidence that the dental phenotype is not merely due to changes in FGF23, phosphorus and $1,25(OH)_2D$ in XLH [9].

Costs of burosumab

The annual cost of treating with burosumab is many times more expensive than treating with conventional therapy. Though the cost will vary by age, dose, formulation and local drug prices and pharmacy markups, as well as additional costs to administer the drug for burosumab, one can safely estimate that the annual cost of burosumab is well over 100 times greater than the cost of conventional therapy. Due to the high cost of burosumab it is expected that virtually no one would be able to pay for burosumab out of pocket, restricting access to those patients who have third party payors (medical insurance or government health systems) that agree to provide coverage of this medication. This can lead to disparities in access based on socioeconomic status, health insurance or country or region of the world. To the extent that burosumab has some potential (though not fully proven) to decrease lifetime disability those disparities related to socioeconomic status could be compounded across a patient's lifetime. To complicate matters, patients with lower socioeconomic status may also sometimes have difficulties accessing and paying for conventional therapy and the tests necessary for monitoring it.

To the author's knowledge, no formal peer-reviewed studies have been published regarding cost-benefit analysis, specifically taking into account the expense of the various treatment options for XLH along with the expense of various complications of XLH (or of its treatment), including surgical procedures, quality of life, disability, etc. In an analysis submitted to Canadian regulatory authorities by Kyowa Kirin Limited, the base estimate of the incremental cost in Canadian dollars per quality adjusted life-years for burosumab treatment during pediatric years or during adult years was estimated at $1,364,863 and $1,119,456, respectively [40]. Currently such analyses require a lot of assumptions about effect size and are somewhat hampered by substantial unknowns (outlined in the next section) regarding the magnitude of effect of long-term treatment during childhood (encompassing the full period of growth for example), or during adulthood, as studies to date of burosumab have been comparatively short, and unable to measure some outcomes that would be important long term. The cost-benefit ratio likely varies between those with milder versus more severe musculoskeletal disease manifestations and further studies

are needed. Thus, some authors have proposed to initiate patients on conventional therapy and use burosumab when response is inadequate [41, 42].

Unknowns about burosumab.

The clinical trials of burosumab in children have left many remaining questions. No study has systematically evaluated the transition from pediatric to adult dosing regimens among adolescents treated with burosumab. Similarly, no trial has evaluated continuing treatment versus discontinuation during this time period with monitoring for development of symptoms (as has long been a standard practice with conventional therapy). Importantly, though the pediatric trials indicated some improvement in height Z-score with burosumab, it will be several years before the height impact of treating from early childhood through the end of growth is known. No trial has been long enough to assess this effect. While it is possible that the improvements in rickets and lower limb deformity observed in the pediatric trials may influence the need for corrective orthopedic surgery, this has also not been systematically assessed, and will require long term studies of beginning treatment at young ages to determine.

The action of burosumab to decrease phosphaturia might possibly decrease the risk of nephrocalcinosis. However, the best information from the trials merely can suggest that over short term treatment with burosumab, nephrocalcinosis is probably not increased over conventional therapy. However, since one potential risk of burosumab is over treatment resulting in hyperphosphatemia, and there is an increase in $1,25(OH)_2D$ (sometimes to supraphysiologic levels) transiently after dosing, there likely will still be some risk for nephrocalcinosis. Whether or not this is less than the risk with conventional therapy still remains to be seen. Thus, monitoring for nephrocalcinosis remains an important consideration during treatment with either conventional therapy of burosumab.

The long term influence of burosumab on the morbidities of XLH during adulthood also are not yet known. Some aspects of adult symptoms are related to osteomalacia, psuedofractures and bone pain, which are addressed during treatment with burosumab. However, the adult burden of disease is also due to enthesopathy, osteoarthritis and frequent occurrence of spinal stenosis all of which begin even during the third decade in some patients[20]. The mechanism of enthesopathy in XLH remains uncertain, but so

far there is no evidence that treatment with conventional therapy or with burosumab beneficially impacts the development or progression of enthesopathy, or of spinal stenosis which can result. Improvements in skeletal limb deformities during childhood could potentially influence development of adult osteoarthritis. Very long-term studies are needed to be able to address these questions. Given these unknowns, it is important to avoid misleading our patients regarding the benefits and risks of burosumab.

Conclusion.

Children with XLH may be treated with either conventional therapy or with burosumab. Some will respond well to conventional therapy and if these patients are not experiencing adverse events, then continuation with conventional therapy is reasonable. However, rickets and skeletal deformity are poorly controlled with conventional therapy in many patients with XLH, while long term side effects of nephrocalcinosis and hyperparathyroidism remain important considerations. Burosumab does improve rickets to a greater degree than conventional therapy and its every 2 week injections are easier to administer as compared to multiple oral doses of conventional therapy per day, and hence is an effective option for children regardless of the degree of severity of rickets (and is the only FDA approved therapy for XLH). However, frequent laboratory monitoring is necessary for safe and effective treatment with either conventional therapy or burosumab. Several questions remain regarding the long-term effects of burosumab, which will hopefully be determined over the next several years.

Table 1. Radiographic outcomes in children after 64 weeks in clinical trials of burosumab.

Study	Age at enrollment	N	Dosing	RSS at baseline Mean ± SD (range)	RSS at 64 weeks Mean ± SD	RSS change from baseline LS mean [SE]	Global RGI-C at 64 weeks Mean [SE]	Global RGI-C ≥2 at 64 weeks (%)	Lower limb deformity RGI-C at 64 weeks
Carpenter et al. [35]	5-12 years	26	Burosumab Q2W (initially 0.1 mg/kg, titrated to mean 0.98 mg/kg)	1.9 ± 1.2 (0–4.5)	0.8 ± 0.6	-1.00 [0.11]	+1.56 [0.11]	58%	+0.5 [0.1] [a]
		26	Burosumab Q4W (initially 0.2 mg/kg, titrated to mean 1.5 mg/kg)	1.7 ± 1.0 (0–3.0)	0.9 ± 0.5	-0.84 [0.10]	+1.58 [0.11]	50%	See above [a]
Whyte et al.[36]	1-4 years	13	Burosumab 0.8-1.2 mg/kg Q2W	2.9 ± 1.4 (1.0-6.5)	0.9 ± 0.5 [b]	–2.0 [0.1]	+2.2 [0.1]	100%	+1.6 [0.1]
Imel et al.[22]	1-12 years	29	Burosumab 0.8-1.2 mg/kg Q2W	3.2 ± 1.0	1.0 ± 0.7 [b]	–2.2 [0.1]	+2.1 [0.1]	87%	+1.3 [0.2]
		32	Phosphate and active vitamin D	3.2 ± 1.1	2.2 ± 0.8 [b]	–1.0 [0.2]	+1.0 [0.1]	19%	+0.3 [0.1]

[a] The lower limb deformity score for this trial was only reported for the combined group including those dosed Q2W and Q4W together.

[b] These numbers were not expressly stated in the text, but were estimated for the table from the graphs in the original publications.

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