

## Review Article

# Management of X-linked hypophosphatemic rickets: a review

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**Received:** 05 August 2020

**Accepted:** 05 September 2020

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### ABSTRACT

There are two types of management in X-linked hypophosphatemic rickets (XLH), out of which the main stay of treatment is conventional treatment which includes combination of oral phosphate supplements and active vitamin D (calcitriol or alfacalcidol) after the diagnosis is established. Although, conventional treatment with phosphate supplementation and active vitamin D might improve the rickets and control the renal phosphate excretion but it has significant risk of high calcium excretion in the urine and thereby increases the risk of nephrocalcinosis. The other emerging treatment is burosumab therapy which is human monoclonal IgG1 antibody against fibroblast growth factor 23 (FGF 23) for the treatment of XLH in children  $\geq 1$  year of age and in adolescents and is found to be effective in improving rickets without major adverse events. In this review, modalities for XLH treatment over the past and the near future will be discussed along with clinical manifestations and investigations.

**Keywords:** FGF 23, PTH, XLH

### INTRODUCTION

XLH is one of the hereditary rickets manifested by low serum phosphate, decreased intestinal absorption of calcium and joint deformities.<sup>1,2</sup> Due to scarcity of information and the lack of treatment guidelines which frequently lead to missed diagnoses or mismanagement. Therefore, a review of all available literature is needed to have the guidelines for the treatment of XLH with children. In this review, outline the current evidence and provide recommendations on features of the XLH, including new treatment methods, to improve knowledge and provide guidance for management.

There are two types of management in XLH, out of which the main stay of treatment is conventional treatment which includes combination of oral phosphate supplements and active vitamin D as soon as diagnosis is established.<sup>2-5</sup> It is well evident that initial and early management is associated with good outcomes. In children, healing of rickets is determined by the normalization of alkaline phosphatase levels and improvement in radiological signs. Also early

management promotes growth, reduces bone pain, and improves leg deformities.<sup>1-7</sup>

The cornerstone in managing XLH is the conventional treatment with active vitamin D (calcitriol or alfacalcidol) in addition to oral phosphate supplements to prevent secondary hyperparathyroidism and increase phosphate absorption from the gut.<sup>1,2</sup> However, higher doses of active vitamin D although improves growth and bone healing but are associated with significant risk of increased calcium excretion in urine and nephrocalcinosis. On the other side, decreased doses of vitamin D are usually associated with low intestinal calcium absorption and poorly controlled rickets. Thus, conventional management should be adjusted to keep PTH (parathyroid hormone) levels within the normal range (10-65 pg/ml in children) to prevent the orthopedic complications.<sup>2,8-12</sup>

The other emerging treatment is burosumab therapy which is human monoclonal IgG1 antibody against fibroblast growth factor 23 (FGF 23) for the treatment of XLH in children  $\geq 1$  year of age and in adolescents and is

found to be effective in improving rickets without major adverse events and in 2018 received approval from European Medicines Agency (EMA), and USA (United States of America) Food and Drug Administration (FDA).<sup>1-3</sup>

### Clinical manifestations

Children usually manifests with short stature, features of rickets affecting mainly lower limbs. Moreover, some of the children may present with delayed walking, lower limb deformities (varus deformity or valgus deformity) along with (intoeing or extoeing), widening of the wrist, reduced growth velocity, disproportionate short stature, dental abscesses and abnormal skull shape.<sup>2-4</sup>

### Investigations

The salient features of XLH are hypophosphatemia due to renal phosphate wasting, increased alkaline phosphatase (ALP) levels and elevated intact FGF23 levels. The urinary phosphate wasting should be assessed by calculating the tubular maximum reabsorption of phosphate per glomerular filtration rate (TmP/GFR).<sup>1,2,5</sup>

The list of biochemical tests, including serum levels of phosphate, calcium, alkaline phosphatase, parathyroid hormone, 25 (OH) vitamin D (25 hydroxyvitamin D), 1, 25 (OH)<sub>2</sub> Vitamin D (1, 25-dihydroxyvitamin D<sub>3</sub>) and creatinine, and urinary levels of calcium, phosphate and creatinine by use of a spot urine test for calculation of the tubular maximum reabsorption of phosphate per glomerular filtration rate (TmP/GFR) and urinary calcium: creatinine ratio.<sup>2,13-17</sup> The confirmation of the biochemical and clinical diagnosis of XLH is by genetic analysis of the PHEX gene in children. Moreover, renal ultrasound should be monitored for nephrocalcinosis.<sup>1-3</sup>

**Table 1: Biochemical features of XLH.**

Laboratory value	XLH	Nutritional rickets
Serum phosphorous	↓	↓
TmP/GFR	↓	↑
Urinary phosphorous	↑	↑
ALP	↑	↑↑
Serum calcium	Normal or ↑	Normal or ↓
PTH	Normal or ↑	↑↑
1,25 (OH) <sub>2</sub> D	Inappropriately normal or ↓	↓
25 (OH)D	Normal	↓
FGF 23	Inappropriately normal or ↑	Normal or ↓

TmP/GFR-tubular maximum reabsorption of phosphate per glomerular filtration rate; ALP- Alkaline phosphatase; PTH- Parathyroid hormone; 1, 25 (OH)<sub>2</sub> D-1, 25- dihydroxyvitamin D<sub>3</sub>; 25 (OH) D-25 hydroxyvitamin D; FGF 23- Fibroblast growth factor 23.

Other important radiological diagnostic features supports the diagnosis are rachitic lesions are characterized by cupped and flared metaphysis and widened and irregular physes (growth plates) of the long bones.<sup>2,5,18-21</sup>

### TREATMENT

Includes conventional medical management and emerging medical management.

#### Conventional medical management

The main stays in conventional management in treating children with XLH are combination of active vitamin D and oral phosphate supplements.<sup>2</sup> The treatment guideline varies significantly among children and it depends on the severity of the phenotype and no agreement exists on the optimal dose of oral phosphate. However, starting doses of 20-60 mg/kg body weight daily (0.7-2.0 mmol/kg daily).<sup>1,2,5</sup>

The phosphate supplements are available as liquid formulation or as tablets containing sodium-based and/or potassium-based salt and should be given as frequently as possible, for example, 4-6 times per day in children as the phosphate concentrations return to baseline in 1.5 hours.<sup>1,2</sup> On the other side, higher phosphate doses may cause diarrhea and gastrointestinal discomfort.<sup>2</sup> Therefore, there should be fine balance between optimal dose and the side effects.

Also active vitamin D should be started along with phosphate supplements in order to prevent secondary hyperparathyroidism and increase phosphate absorption from the gut and the dosage recommended is calcitriol of 20-30 ng/kg body weight daily or alfacalcidol of 30-50 ng/kg body weight daily or at 0.5 µg daily of calcitriol or 1 µg of alfacalcidol in patients >12 months old and adjusted on the basis of clinical and biochemical responses.<sup>2,5</sup> Calcitriol can be given in one or two doses per day, whereas alfacalcidol should be give once per day owing to its longer half-life.<sup>1,2,5,22</sup>

**Table 2: Monitoring and dose regulating.**

Biochemical finding	Dose regulating
<b>Hypercalciuria, normal serum calcium</b>	↓ calcitriol, and/or ↑ phosphate
<b>Hypercalcemia</b>	↓ calcitriol or discontinue both medications if hypercalcemia
<b>↑ PTH</b>	↑ calcitriol, and/or ↓ phosphate
<b>Lack of radiographic response or inappropriate growth deceleration</b>	↑ calcitriol or phosphate, as tolerated and within weight based guidelines
<b>Hypophosphatemia</b>	Increase carefully phosphate supplements and need to closely monitor as hyperparathyroidism may occur.

The aim of the treatment is to keep serum phosphate >1 mmol/L, PTH within the normal range (10–65 pg/ml in children), ALP (<500 U/L), normal calcium 2.25–2.5 mmol/l and normal urinary calcium creatinine ratio according to age centiles.<sup>2,5,22</sup>

### **Emerging medical management**

#### *Burosumab therapy in children*

The pathogenesis in XLH is caused by excessive levels and activity of FGF23. Burosumab is a recombinant fully human monoclonal IgG1 antibody, against FGF23 planned to block excess FGF23 activity in children. It further increases the phosphate reabsorption and production of vitamin D from the kidney.<sup>1,2,5</sup>

Burosumab therapy was approved in children following encouraging results from the previous trials. Thomas et al conducted an open-label, phase 2 trials in 52 children with X-linked hypophosphatemia and concluded that renal tubular phosphate reabsorption significantly improved along with linear growth, and physical function.<sup>3</sup> Moreover, Erik et al conducted the open-label, randomized, active controlled, phase 3 trial compared the efficacy and safety of burosumab with conventional treatment which also supports the above recommendations.<sup>1</sup> Results of the trials testing burosumab in a total of 61 pediatric children aged between 1–12 years with severe XLH illustrated greater clinical improvements in rickets severity, growth and biochemistries among children with XLH.<sup>1–3,22–25</sup>

In children, approved starting dose of 0.4 mg/kg body weight and 0.8 mg/kg body weight, respectively, given every 2 weeks. Starting with a dose of 0.4 mg/kg body weight as this dose might be sufficient. The dose should be titrated in increments of 0.4 mg/kg body weight in order to raise fasting serum phosphate levels within the lower end of the normal reference range for age, with a maximum dosage of 2.0 mg/kg body weight (maximum dose 90 mg).<sup>1,2,5</sup> In pediatric trials, the average maintenance dose was 1 mg/kg body weight. The side effects observed with burosumab therapy were injection-site reactions, headache and pain in the extremities.<sup>2,5,22</sup>

Burosumab should not be given along with conventional treatment, when serum phosphate levels are within the age-related normal reference range before initiation of treatment or in the presence of severe renal failure.<sup>2,5</sup> The dose should be discontinued if serum phosphate level is above the higher range of normal and can be restarted at approximately half of the previous dose when serum phosphate concentration is below the normal range.<sup>1,2,5</sup>

The most important is monitoring and follow up during and after burosumab therapy and monitoring of fasting serum phosphate levels during the titration period between injections, ideally 7–11 days after the last injection, to avoid inadvertently causing

hyperphosphatasemia.<sup>2,3</sup> Moreover after 3 months of stable dosage, suggest monitoring serum levels of phosphate preferentially directly before injections to detect hypophosphatemia.<sup>1–3,22</sup>

### **CONCLUSION**

To conclude, burosumab therapy was more effective than continuing conventional therapy in improving rickets, growth, lower limb deformity and mobility in children with XLH as evident in open-label active-controlled randomized trials. Moreover, this review article also highlights the importance of emerging modalities of managing XLH in children in order to prevent the adverse effects associated with conventional treatments. However, we need further randomized, double-blind, controlled trial study with more adequate samples and meta-analysis needed especially in children.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not required*

### **REFERENCES**

1. Imel EA, Glorieux FH, Whyte MP, Munns CF, Ward LM, Nilsson O, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. *Lancet*. 2019;393(10189):2416–27.
2. Haffner D, Emma F, Eastwood DM, Duplan MB, Bacchetta J, Schnabel D, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat Rev Nephrol*. 2019;15:435–55.
3. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Mineral Res*. 2015;30(2):394.
4. Pettifor JM. What's new in hypophosphataemic rickets? *Eur J Pediatr*. 2008;167:493–9.
5. Beck-Nielsen SS, Brock-Jacobsen B, Gram J, Brixen K, Jensen TK. Incidence and prevalence of nutritional and hereditary rickets in southern Denmark *Eur J Endocrinol*. 2009;160(3):491–7.
6. Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*. 2006;444:770–4.
7. Rasmussen H, Pechet M, Anast C, Mazur A, Gertner J, Broadus AE. Long-term treatment of familial hypophosphatemic rickets with oral phosphate and 1 alpha-hydroxyvitamin D3. *J Pediatr*. 1981;99:16–25.
8. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J Bone Miner Res*. 2004;19:429–35.

9. The ADHR Consortium. Autosomal dominant hypophosphatemic rickets is associated with mutations in FGF-23. *Nat Genet.* 2000;26:345-8.
10. Farrow EG, White KE. Recent advances in renal phosphate handling. *Nat Rev Nephrol.* 2010;6:207-17.
11. Sullivan W, Carpenter TO, Glorieux F, Travers R, Insogna K. A prospective trial of phosphate and 1,25-dihydroxyvitamin D<sub>3</sub> therapy on symptomatic adults with X-linked hypophosphatemic rickets. *J Clin Endocrinol Metab.* 1992 75:879-85.
12. Tsuru N, Chan JC, Chinchilli VM. Renal hypophosphatemic rickets. Growth and mineral metabolism after treatment with calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>) and phosphate supplementation. *Am J Dis Child.* 1987;141:108-10.
13. Petersen DJ, Boniface AM, Schranck FW, Rupich RC, Whyte MP. X-linked hypophosphatemic rickets: a study (with literature review) of linear growth response to calcitriol and phosphate therapy. *J Bone Miner Res.* 1992;7:583-90.
14. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest.* 2006;116:2062-72.
15. Aono Y, Yamazaki Y, Yasutake J, Kawata T, Hasegawa H, Urakawa I, et al. Therapeutic effects of anti-FGF23 antibodies in hypophosphatemic rickets/osteomalacia. *J Bone Miner Res.* 2009;24:1879-88.
16. Verge CF, Lam A, Simpson JM, Cowell CT, Howard NJ, Silink M. Effects of therapy in X-linked hypophosphatemic rickets. *N Engl J Med.* 1991;325:1843-8.
17. Ward LM, Gaboury IL, Adhani MZ, Lotkin S. Vitamin D-deficiency rickets among children in Canada. *Canadian Med Assoc J.* 2007;177:161-6.
18. Thacher TD, Fischer PR, Strand MA, Pettifor JM. Nutritional rickets around the world: causes and future directions. *Ann Trop Paediatr.* 2006;26:1-16.
19. Harrell RM, Lyles KW, Harrelson JM, Friedman NE, Drezner MK. Healing of bone disease in X-linked hypophosphatemic rickets/osteomalacia. Induction and maintenance with phosphorus and calcitriol. *J Clin Invest.* 1985;75:1858-68.
20. Mughal Z. Rickets in childhood. *Semin Musculoskel Radiol.* 2002;6:183-90.
21. Santos F, Fuente R, Mejia N, Mantecon L, Gil-Peña H, Ordoñez FA. Hypophosphatemia and growth. *Pediatr Nephrol.* 2013;28(4):595-603.
22. Whyte MP, Carpenter TO, Gottesman GS, Mao M, Skrinar A, San Martin J, et al. Efficacy and safety of burosumab in children aged 1–4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial. *Lancet Diabetes Endocrinol.* 2019;7(3):189-99.
23. Lamb YN. Burosumab: first global approval. *Drugs.* 2018;78:707-14.
24. Linglart A, Biosse-Duplan M, Briot K, Chaussain C, Esterle L, Guillaume-Czitrom S, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect.* 2014;3(1):R13-30.
25. West CD, Blanton JC, Silverman FN, Holland NH. Use of phosphate salts as an adjunct to vitamin D in the treatment of hypophosphatemic vitamin D refractory rickets. *J Pediatr.* 1964;64:469-77.

**Cite this article as:** Azar M. Management of X-linked hypophosphatemic rickets: a review. *Int J Res Med Sci* 2020;8:3761-4.