Use of burosumab in two young children with X-linked hypophosphataemic rickets in Hong Kong: two case reports

Joanna YL Tung[1] *, MB, BS, FHKAM (Paediatrics), **Sammy Wong**[2], MB, ChB, FHKAM (Paediatrics), **Queenie WS See**[3], MB, BS, FHKAM (Paediatrics), **Joyce Chan**[4], MB, ChB, FHKAM (Radiology), **Evelyn Kuong**[5], MB, BS, FHKAM (Orthopaedics)

[1] *Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong SAR, China*
[2] *Department of Paediatrics and Adolescent Medicine, Alice Ho Miu Ling Nethersole Hospital, Hong Kong SAR, China*
[3] *Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*
[4] *Department of Radiology, Hong Kong Children's Hospital, Hong Kong SAR, China*
[5] *Department of Orthopaedics and Traumatology, Hong Kong Children's Hospital and Duchess of Kent Children's Hospital, Hong Kong SAR, China*

* Corresponding author: tyl404@ha.org.hk

This article was published on 26 Nov 2024 at www.hkmj.org.

Hong Kong Med J 2024;30:506–8
https://doi.org/10.12809/hkmj2311184

Case presentations

Two Chinese girls (22 months and 26 months of age [Case 1 and Case 2, respectively]) presented in August 2021 and November 2021 with progressive bowing of the lower limbs since infancy. Neither had any significant family history. Physical examination revealed rachitic deformity, waddling gait, and short stature. Further investigations showed hypophosphataemia, isolated hyperphosphaturia and a high serum alkaline phosphatase (ALP) level with normal serum calcium, 25(OH) vitamin D, and parathyroid hormone levels. Characteristic clinical and radiographical findings suggestive of hypophosphataemic rickets were also evident (Fig). Molecular testing confirmed a diagnosis of X-linked hypophosphataemia (XLH) with heterozygous pathogenic *PHEX* (phosphate-regulating endopeptidase homologue on the X chromosome) variants detected in both patients [Case 1: c.2104C>T, p.(Arg702); Case 2: (c.1699c>T) (Arg567)]. Neither set of parents was affected. Both girls were commenced on conventional treatment with phosphate solution and alfacalcidol for around 3 months with only fair improvement. They were then started on burosumab at a starting dose of 0.8 mg/kg every 2 weeks, titrated up to 2 mg/kg (20 mg) 4 months later based on fasting serum phosphate level. Despite maximum doses of burosumab, serum phosphate level remained slightly below the normal range for both patients. Nevertheless there was ongoing clinical improvement in ALP level, the ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate, growth velocity, and healing of rickets in both patients. After burosumab treatment for 24 months, both patients had significant clinical, biochemical, and radiological improvement (Table and Fig). They were followed up by the multidisciplinary team at the Hong Kong Children's Hospital. No treatment-related adverse reactions or disease-related complications (including skull deformities, dental abscess, and hearing problem) were observed.

Discussion

X-linked hypophosphataemia is the most common cause of genetic rickets, with a prevalence of 1:20 000 to 1:60 000.[1,2] It is caused by mutations in the *PHEX* gene and results in an increased level of the fibroblast growth factor 23 (FGF-23) hormone. This leads to impaired renal reabsorption of phosphate, low serum 1,25-dihydroxyvitamin D concentration, and reduced intestinal phosphate absorption, and ultimately, chronic hypophosphataemia. Patients typically present in early childhood with signs and symptoms of rickets and osteomalacia, progressive bowing deformities of the lower limbs, bone pain and stunted growth, as in our patients.

X-linked hypophosphataemia is conventionally treated with oral phosphate and active vitamin D analogues but this does not address the underlying pathogenesis and may only partially correct the biochemical derangement and skeletal deformities. Patients often require repeated orthopaedic procedures, eg, hemiepiphysiodesis or even multiple corrective osteotomies to maintain the mechanical axis of the lower limbs. Surgical correction is fraught with technical difficulties due to osteomalacia and there are high rates of recurrence. Moreover, conventional treatment is associated with long-term side-effects such as hyperparathyroidism and nephrocalcinosis.

Burosumab, a monoclonal antibody to FGF-23 for XLH treatment, was approved by the United States Food and Drug Administration[3] and the European Medicines Agency[4] in 2018. Subsequently, a phase III trial to evaluate 61 children with XLH

aged 1 to 12 years for 64 weeks[5] and another trial evaluating children with XLH aged 5 to 12 years for 160 weeks[6] further supported its safety and effectiveness in terms of improved total Rickets Severity Score and fasting serum phosphate level. These outcomes were also measured in our patients and similar improvements observed. With the approval of burosumab, there has been a paradigm shift in the treatment of XLH in Western countries. Nevertheless conventional treatment continues to be the norm in most parts of our region—partly attributed to the high cost of burosumab, and partly due to the lack of published regional experience with burosumab in the clinical setting.

In our patients, the dose of burosumab was titrated up slowly to the maximum dose based on age-specific fasting phosphate level, as per various clinical practice recommendations.[7,8] With the maximum dose, fasting serum phosphate level improved but failed to reach that of the age-specific normal range. Other secondary causes including vitamin D deficiency and hyperparathyroidism were excluded. Nevertheless improvement in other clinical parameters including serum ALP level, the ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate, growth velocity, and clinical and radiological evidence of rickets healing were observed. We have maintained our two patients on the same dose with ongoing clinical improvements observed. This is consistent with the recently published opinion based on early experience in seven European countries, recommending that a serum phosphate concentration below the age- and sex-specific range may be acceptable and the same maintenance dose continued as improvements in other clinical parameters are maintained.[9] This is based largely on expert opinion with no data on the proportion of patients who do not achieve a normalised phosphate level and no comparison of clinical outcomes.

X-linked hypophosphataemia is a rare, genetic multisystem disease. In addition to the skeletal manifestations, around two-thirds of affected individuals have associated dental and periodontal issues, such as spontaneous periapical abscesses, related to poor dentin mineralisation.[10] Some patients also have other complications including craniosynostosis and impaired hearing. Consequently, most guidelines recommend a multidisciplinary approach for this group of patients.[7,8] Despite treatment with burosumab, some complications cannot be mitigated. Dental abscess, a well-known complication in patients with XLH, has not been consistently shown to be ameliorated by burosumab treatment. In the phase 3 burosumab trial,[5] dental abscess was observed at a higher rate in the treatment group than the control arm. This implies that the pathophysiology of dental abscess is not mediated only by the FGF-23 pathway. This highlights the importance of a multidisciplinary approach

FIG. Clinical and radiological improvements of the two patients after burosumab treatment for 30 months. (a-d) Case 1. (e-h) Case 2. Before treatment ([c] and [g]), both patients had widening of growth plate with lucencies in the metaphyseal margins, with bowing seen in both the diaphyseal and metaphyseal bone. After treatment ([d] and [h]), there was a significant reduction in metaphyseal lucencies with improvement in bone density. Reduction in the width of the growth plates was observed. Extent of bowing of long bones also showed improvement after treatment

Abbreviation: AP Standing = anteroposterior standing

TABLE. Serial biochemical changes of the two patients after burosumab treatment for 30 months

	Case 1		Case 2	
	Pretreatment	Post-treatment	Pretreatment	Post-treatment
Age	22 months	3 years 10 months	26 months	4 years 2 months
PO_4, mmol/L*	0.69	1.10	0.71	1.23
ALP, U/L†	659	347	924	408
TmP/GFR, mmol/L	0.6	1.22	0.6	1.35
RSS	2	0.5	4	0.5
Growth velocity, cm/y	0.9	5.8	4.8	8.2
Adverse effects	Nil		Nil	

Abbreviations: ALP = alkaline phosphatase; PO_4 = phosphate; RSS = Rickets Severity Score; TmP/GFR = ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate

* Reference: 1.33-2.08 mmol/L

† Reference: 142-335 U/L

to the management of XLH, as recommended by recent international clinical practice guidelines[7] and regional consensus statements.[8] At the Hong Kong Children's Hospital, this group of patients is seen in the multidisciplinary bone clinic with input from a paediatric endocrinologist, orthopaedic surgeon, geneticist, dental surgeon, radiologist, and case manager (nurse practitioner). This orchestrated, coordinated multidisciplinary care is particularly important to maximise the effect and overall clinical outcome of burosumab treatment that remains remarkably expensive.

To the best of our knowledge, this is the first report of real-world experience of XLH treated with burosumab outside clinical trials in Asia. The target of a normal phosphate level may not be achievable in practice, and treatment response should also be guided by other clinical parameters. Further research into factors that affect the biochemical outcome and the clinical response of groups with different biochemical outcome is needed. A multidisciplinary approach should be adopted in the care of children with XLH.

Author contributions

Concept or design: JYL Tung.
Acquisition of data: JYL Tung.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: JYL Tung.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Declaration

Preliminary results for these two cases were presented as a poster at the 12th Asia Pacific Paediatric Endocrine Society Biennial Scientific Meeting 2022 (South Korea, 5-8 October 2022).

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

The patients were treated in accordance with the Declaration of Helsinki. Consent for all treatments, procedures, and consent for publication was obtained from parents of the patients.

References

1. 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;160:491-7.
2. Rafaelsen S, Johansson S, Ræder H, Bjerknes R. Hereditary hypophosphatemia in Norway: a retrospective population-based study of genotypes, phenotypes, and treatment complications. Eur J Endocrinol 2016;174:125-36.
3. United States Food and Drug Administration. FDA approves first therapy for rare inherited form of rickets, x-linked hypophosphatemia. 2018 Apr 17. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-therapy-rare-inherited-form-rickets-x-linked-hypophosphatemia. Accessed 28 Oct 2024.
4. European Medicines Agency. EU/3/14/1351—orphan designation for treatment of X-linked hypophosphataemia. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-14-1351. Accessed 28 Oct 2024.
5. Imel EA, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. Lancet 2019;393:2416-27.
6. Linglart A, Imel EA, Whyte MP, et al. Sustained efficacy and safety of burosumab, a monoclonal antibody to FGF23, in children with X-linked hypophosphatemia. J Clin Endocrinol Metab 2022;107:813-24.
7. Sandy JL, Simm PJ, Biggin A, et al. Clinical practice guidelines for paediatric X-linked hypophosphataemia in the era of burosumab. J Paediatr Child Health 2022;58:762-8.
8. Munns CF, Yoo HW, Jalaludin MY, et al. Asia-Pacific consensus recommendations on X-linked hypophosphatemia: diagnosis, multidisciplinary management, and transition from pediatric to adult care. JBMR Plus 2023;7:e10744.
9. Mughal MZ, Baroncelli GI, de Lucas-Collantes C, et al. Burosumab for X-linked hypophosphatemia in children and adolescents: opinion based on early experience in seven European countries. Front Endocrinol (Lausanne) 2023;13:1034580.
10. Baroncelli GI, Mora S. X-linked hypophosphatemic rickets: multisystemic disorder in children requiring multidisciplinary management. Front Endocrinol (Lausanne) 2021;12:688309.