LEADING ARTICLE

New Developments in the Treatment of X-Linked Hypophosphataemia: Implications for Clinical Management

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Abstract

X-linked hypophosphataemia (XLH) is due to mutations in phosphate-regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*) and represents the most common heritable form of rickets. In this condition, the hormone fibroblast growth factor 23 (FGF23) is produced in excessive amounts for still unknown reasons, and causes renal phosphate wasting and suppression of 1,25-dihydroxyvitamin D, leading to low serum phosphate concentrations. Prolonged hypophosphataemia decreases apoptosis of hypertrophic chondrocytes in growth plates (causing rickets) and decreases mineralisation of existing bone (causing osteomalacia). In contrast to historical conventional treatment with oral phosphate supplements and active vitamin D for the last 50 years, the new anti-FGF23 antibody treatment (burosumab) targets the primary pathology by blocking FGF23, thereby restoring phosphate homeostasis. In this review, we describe the changes in treatment monitoring, treatment targets and long-term treatment goals, including future opportunities and challenges in the treatment of XLH in children.

1 Introduction

Rickets is a disorder of growing bones characterised by defective mineralisation of growth plates and bone tissue. Solar and nutritional vitamin D and/or nutritional calcium deficiency are the most common causes of rickets, whilst so-called vitamin D-*dependent* forms of rickets (genetic defects in calcitriol synthesis or action) and hypophosphataemic rickets are the rarest. By increasing intestinal absorption, calcitriol, also called active vitamin D or 1,25-dihydroxyvitamin D $(1,25[OH]_2D)$, serves as the principal supplier of the major minerals calcium and phosphorus to mineralisation sites. However, vitamin D or calcitriol concentrations are not causative and fundamental to hypomineralisation; the reduced availability of phosphate is, irrespective of its origin.

This review is focused on X-linked hypophosphataemia (XLH), the most common heritable form of rickets and osteomalacia. Various disorders result in renal phosphate wasting; however, XLH due to mutation in phosphate-regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*) is the commonest cause. The review aims to highlight the changes in treatment monitoring, treatment targets and long-term treatment goals brought about by new drug development, and future challenges in managing XLH.

2 Phosphate Function and Regulation

Phosphate is a key metabolic factor for cellular energy metabolism and membrane stability and is the main component of hydroxyapatite in bone. Eighty per cent of phosphate in the body is bound in bone as hydroxyapatite. Serum phosphate levels (representing 2–3% of the total body phosphate pool) are maintained by hormonal regulation of its intestinal absorption, renal reabsorption and bone resorption. The solute carrier 34 (SLC34) subfamily of sodium-phosphate co-transporters (NPT) mediate the absorption in the gut

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(SLC34A2 for NPT2b) and in the renal tubules (SLC34A1 for NPT2a and SLC34A3 for NPT2c) [1, 2].

Three key hormones regulate phosphate homeostasis: calcitriol, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). Via NPT upregulation, calcitriol enhances absorption of phosphate both from the intestine and reabsorption from the renal tubule. In healthy subjects, hypophosphataemia and PTH induce 1-alpha hydroxylase activity (calcitriol synthesis). Elevated PTH reduces NPT2a expression in the renal tubules [3, 4] and promotes phosphate excretion, and also increases bone resorption via stimulation of osteoclasts [5, 6].

In the kidneys, glomerular filtration of phosphate occurs by passive diffusion, whereas the reabsorption in the proximal tubule is NPT mediated, leading to 70% of filtered phosphate being reabsorbed [7]. It is here that FGF23, a polypeptide hormone historically called phosphatonin, has its principal action. FGF23 is secreted by osteocytes and acts in conjunction with the fibroblast growth factor receptor 1c (FGFR1c)/α-klotho co-receptor at the basolateral membrane of the renal tubules, promoting renal phosphate loss by internalisation and destruction of NPT2a and NPT2c co-transporters at the apical membrane (Fig. 1a) [8]. FGF23 also leads to reduced calcitriol production by (1) inhibiting renal 1-alpha hydroxylase via suppression of cytochrome p450 27B1 (CYP27B1) and (2) enhanced calcitriol breakdown via stimulation of CYP24A1 [9]. Thus physiologically, FGF23 prevents undue elevation of serum phosphate levels. In XLH, the *PHEX* gene mutation, via unclear mechanisms, causes FGF23 excess, which is the key to the pathophysiology of rickets development.

3 Types of Hypophosphataemic Rickets

There are various causes of hypophosphataemic rickets and or osteomalacia (Table 1), most of which have a genetic basis. Apart from a few conditions causing global proximal renal tubular dysfunction, most disorders affect NPT2a- and NPT2c-mediated renal phosphate reabsorption. A genetic defect in NPT2c function is responsible for hereditary hypophosphataemic rickets with hypercalciuria (HHRH), where FGF23 levels are appropriately suppressed and calcitriol levels elevated. In primary renal tubular defects associated with hyperphosphaturia, FGF23 is also appropriately suppressed in an attempt to conserve phosphate and enhance calcitriol production and intestinal calcium absorption. Contrary to this, FGF23 production is increased in XLH (Table 1). The mechanisms of disease remain unknown for several conditions.
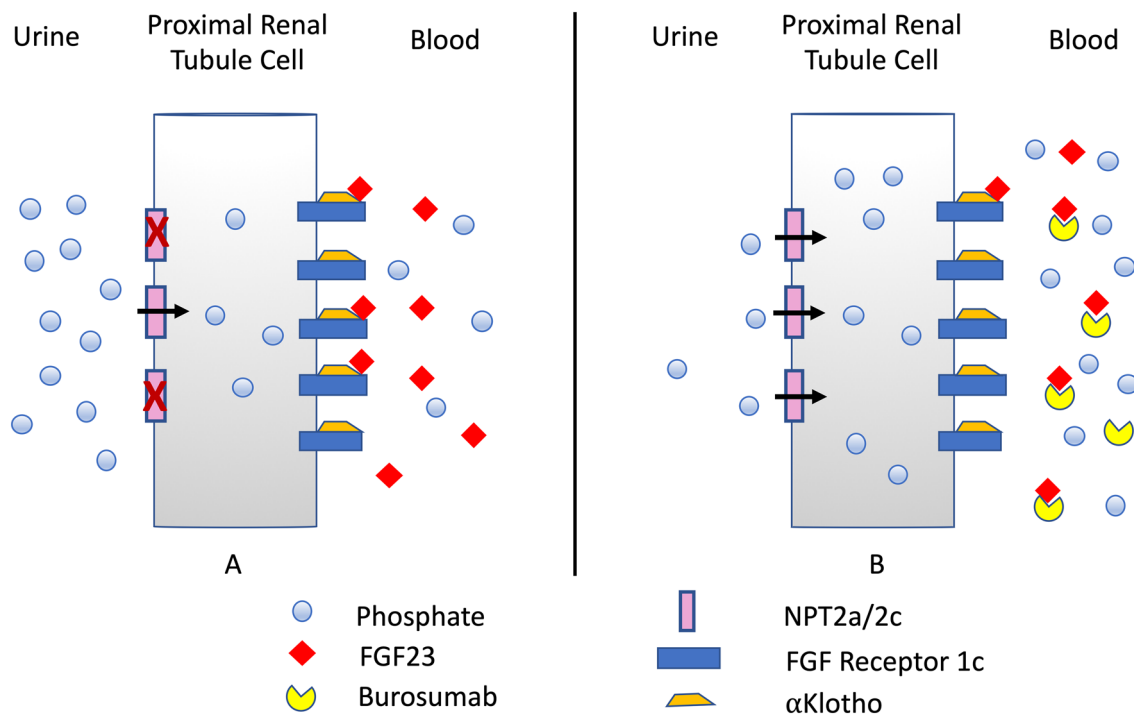

Fig. 1 a Renal phosphate wasting in X-linked hypophosphataemia. Reduced phosphate reabsorption in the proximal renal tubule is due to excessive FGF23, which stimulates the FGFR1c/α-klotho co-receptor complex at the basolateral membrane, resulting in reduced expression of sodium phosphate co-transporter NPT2a and NPT2c at the apical membrane. b Mechanism of action of burosumab: binding to excess FGF23 and thereby facilitating renal phosphate reabsorption from the proximal renal tubule. *FGF23* fibroblast growth factor 23, *FGFR1c* fibroblast growth factor receptor 1c, *NPT* sodium-phosphate co-transporter

Table 1 Types of hypophosphataemia based on pathophysiology

Type	Cause/genetic basis	FGF23 levels	Pathogenesis
Group I: Excess FGF23 production/action			
ADHR	*FGF23*	↑	Resistance of FGF23 to proteolytic cleavage, resulting in prolonged action [10]. Iron deficiency likely cause of disease manifestation through increased FGF23 expression [11]
XLH	*PHEX*	↑	↑ FGF23 expression in bone [12]
ARHR 1	*DMP1* (dentin matrix protein)	↑	*DMP1* encodes a bone matrix protein; mutation results in ↑ FGF23 by unclear mechanisms [13]
ARHR 2	*ENPP1* (ectonucleotide pyrophosphatase/ phosphodiesterase)	↑	ENPP1 generates extracellular pyrophosphate. The mechanism for ↑ FGF23 is unclear; however, the same mutation is also implicated in GACI [14]
ARHR 3	*FAM20C* (family with sequence similarity 20C)	↑	*FAM20C* encodes GEF-CK, a phosphorylation enzyme. This phosphorylation defect is the proposed mechanism for ↑ FGF23 [15]
Group II: Defective renal tubular phosphate reabsorption due to defective NPT2c			
HHRH	*SLC34A3*	↓	↑ $1,25(OH)_2D$, defective $NPT2_C$ function, hypercalciuria and nephrocalcinosis [7]
Group III: Acquired disorders of excess FGF23			
TIO	Paraneoplastic syndrome	↑	FGF23 production from mesenchymal tumoural cells [16]
Group IV: Phosphate loss due to global renal tubular dysfunction			
Proximal tubular dysfunction	*CLCN5*: Dent's disease *Xq26.1*: Lowe syndrome *Xq26*: Fanconi's syndrome *CTNS*: Cystinosis	Normal or ↑	Proximal renal tubulopathy, ↓ $1,25(OH)_2D$
Group V: Drug-induced hypophosphataemia			
1	Aluminium containing antacids	↓	Binding of phosphate causing reduced absorption [17]
2	Elemental infant formula	↓	Reduced bioavailability[a] of phosphate [18, 19]
3	Sodium valproate, cisplatin, ifosfamide, tenofovir, deferasirox	↓	Proximal tubular dysfunction (drug-induced Fanconi's syndrome) [20]
4	Intravenous iron preparations	↓	↑ FGF23 mediated phosphate loss [21]
5	Imatinib mesylate	↑	Inhibition of PDGF receptors on osteoblasts and osteoclasts [22]

Representation of various causes of hypophosphataemic rickets/osteomalacia based on pathophysiology of phosphate loss and co-relation with FGF23 levels

ADHR autosomal dominant hypophosphataemic rickets, *ARHR* autosomal recessive hypophosphataemic rickets, *FGF23* fibroblast growth factor 23, *GACI* generalised arterial calcification of infancy, *GEF-CK* golgi-enriched fraction casein kinase, *HHRH* hereditary hypophosphataemic rickets with hypercalciuria, *NPT* sodium-phosphate co-transporter, *PDGF* platelet-derived growth factor, *PHEX* phosphate-regulating gene with homologies to endopeptidases on the X chromosome, *SLC34* solute carrier 34, *TIO* tumour-induced (or oncogenic) osteomalacia, *XLH* X-linked hypophosphataemic rickets

[a]The reported cases were infants and children on Neocate® feed

4 Genetics of XLH

X-linked hypophosphataemic rickets has an incidence of approximately 1:20,000 live births and is the most common inherited form of phosphopenic rickets [23]. Over 300 pathogenic *PHEX* mutations have been reported to date [24], which have a dominant effect manifesting disease even in females. Hence the condition commonly runs in families. Since the *PHEX* gene is located on the X chromosome, an affected mother will have a 50% chance of having affected children, and an affected father will pass on the condition to all his daughters, but none of his sons.

The first milestone in the understanding of XLH came from studies in the *hyp* mouse [25] in the 1970s, the murine

homologue of XLH. *PHEX* was first identified in the late 1990s [26]. In 2000/2001, FGF23 was first described to be associated with phosphate wasting in autosomal dominant hypophosphataemic rickets (ADHR) [27] and tumour-induced (or oncogenic) osteomalacia (TIO) [16]. To date, the exact mechanism of FGF23 excess in XLH remains to be identified. However, within a decade, phase 1 clinical trials of anti-FGF23 antibody KRN-23 (burosumab) were underway [28].

5 Clinical Features and Diagnosis

There are two types of presentation: familial cases that are diagnosed during pregnancy or soon after birth and de novo cases, which are diagnosed later. In the former case, a known gene mutation in an affected parent enables early diagnosis and thus early treatment intervention in the offspring [29]. The latter cases often present during infancy and toddler years with bony deformities including genu varum, frontal bossing, widened wrists and ankles and dental abscesses [29, 30]. Biochemistry typically reveals low serum phosphate and elevated serum alkaline phosphatase (ALP) activity. In de novo cases, serum 25OH vitamin D needs to be normalised before the diagnosis of XLH can be confirmed. Whilst renal calcium reabsorption remains intact, serum PTH tends to be at the upper limit of normal or elevated. Paired measurement of serum and urinary phosphate and creatinine, with calculation of the maximum tubular phosphate reabsorption rate per glomerular filtration rate (TmP/GFR), clinches the diagnosis [31]. The diagnosis of rickets is confirmed by radiological features showing growth plate widening with metaphyseal flaring and fraying at the knee and wrist. Confirmatory genetic testing is recommended, especially in the absence of a family history.

Prompt diagnosis and early initiation of treatment are absolutely essential for good long-term outcomes, in particular, final height and correction of leg bowing. Clinical features in adults are bone pain, pathological fractures, pseudofractures, osteoarthritis and enthesopathy, and are reviewed in detail elsewhere [32].

6 Treatment

The objectives of XLH treatment include healing rickets, improving leg deformities and avoiding orthopaedic surgery, maximising growth potential, improving bone and teeth mineralisation, alleviating pain, improving muscle function and reducing long-term complications (including those encountered in adulthood). Treatment is usually initiated at the time of diagnosis and continued at least until growth completion.

Disease severity is not the same in all children, and some respond better to treatment than others.

6.1 Medical Management

6.1.1 Conventional Treatment

The conventional approach to treatment since the 1970s includes measures to counteract the results of FGF23 excess with multiple daily doses of oral phosphate supplements and active vitamin D analogues. Doses reported in the literature vary widely depending on individual patient requirements and medical expertise. Recommended dosages vary from 20 to 60 mg/kg/day for phosphate supplements, and 1–3 μg/day for alfacalcidol or 0.2–1.5 μg/day for calcitriol. Higher doses are often required during phases of rapid growth, i.e. infancy and puberty [29, 30, 33]. Due to the constant renal phosphate wasting, the recommended oral phosphate dosing is up to 5 times a day. To avoid gastrointestinal side effects, clinicians tend to start with low doses and build these up over time. The challenges often faced with conventional treatment include variable compliance and poor tolerability including gastrointestinal symptoms such as diarrhoea and abdominal cramps (Fig. 2). Phosphate supplements are available in solution form for very young patients and powder or effervescent tablets for older children. Similarly, alfacalcidol is available both in solution and capsule forms.

6.1.1.1 Treatment Monitoring Treatment is titrated based on the changes in serum ALP, PTH, severity of rickets on knee and hand X-rays, leg bowing and growth velocity. Much in contrast to burosumab therapy, conventional therapy must not be titrated towards normal serum phosphate levels. Attempts to do so result in side effects and secondary and tertiary hyperparathyroidism. PTH elevations should trigger a reduction in phosphate doses or increase in alfacalcidol. Evidence of hypercalciuria should lead to a reduction in alfacalcidol doses. Calcium excretion is assessed by calcium/creatinine ratio measured via spot urine sample in children younger than 5 years old and preferably by 24-h urinary excretion in older children. Also, annual renal ultrasounds are recommended to monitor for nephrocalcinosis [34]. Maintaining satisfactory 25OH vitamin D levels is also recommended. Of note, orthopaedic interventions that correct leg deformities may give a false sense of treatment efficacy whilst limiting growth potential; therefore, rickets activity should be systematically assessed at all times [29].

Treatment is continued at least until completion of growth. There is currently no consensus on continuation of conventional treatment into adulthood, although often the practice is to do so at least in patients who are symptomatic from the ensuing osteomalacia that inevitably follows treatment cessation.
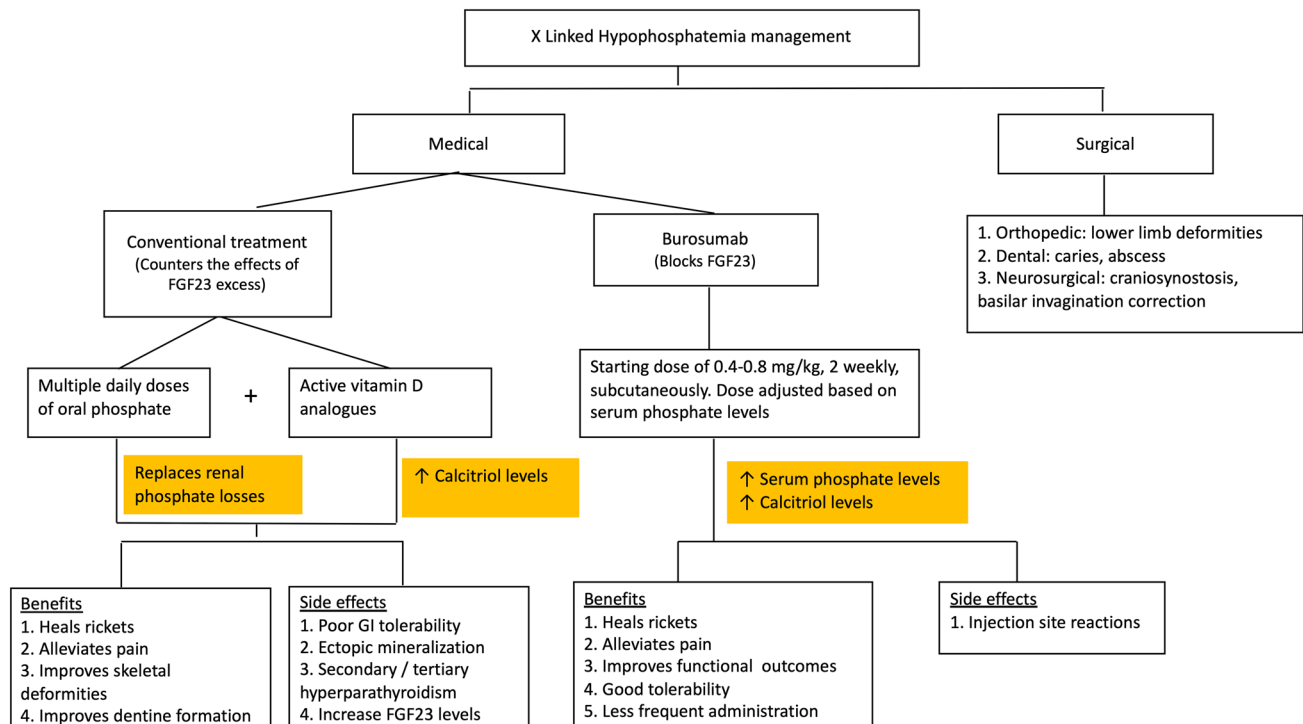
Fig. 2 Flowchart outlining the medical and surgical management of X-linked hypophosphataemia in children. *FGF23* fibroblast growth factor 23, *GI* gastrointestinal

6.1.2 Anti-FGF23 Monoclonal Antibody (Burosumab)

Burosumab is a recombinant, human monoclonal IgG1 antibody that targets FGF23. By counteracting FGF23 excess, it restores the action of renal NPT co-transporters, thereby improving phosphate reabsorption and normalising serum phosphate levels (Fig. 1b). Burosumab is the first targeted drug therapy in XLH which addresses the underlying mechanism of the condition. This FGF23 antibody was first used in a phase 1 dose-finding study in 38 adult XLH patients, and demonstrated an increase in serum phosphate, $1,25(OH)_2D_3$ and TmP/GFR, with an acceptable safety and tolerability profile [28].

The landmark phase 2 and phase 3 studies in children that followed led to market approval by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2018. Starting in 2016, two open-label, multicentre, phase 2 studies confirmed the safety and efficacy of burosumab in children aged 5–12 years [35] and those aged 1–4 years [36]. The first study included a 16-week dose titration regimen, targeting the lower end of the normal serum phosphate range, and compared 2-weekly and 4-weekly dosing. The trial demonstrated superiority of 2-weekly injections and an average dose requirement of 0.8 mg/kg/dose. Similar treatment efficacy and safety was demonstrated in a separate phase 2 study in children aged 1–4 years, using a starting dose of 0.8 mg/kg/dose subcutaneously every

2 weeks and titration upwards based on serum phosphate levels [36]. Both studies, at week 64, demonstrated improvement in serum phosphate levels, radiological rickets severity and growth, and the latter study also demonstrated an improvement in leg deformity assessed by a visual global impression of change score used by independent radiologists.

In 2019, an active-controlled, open-label, phase 3 trial was published, conducted in 61 children with genetically confirmed XLH and a Thacher rickets severity score of 2 or above [37]. Children were randomised to either receive conventional treatment or burosumab (0.8 mg/kg, every 2 weeks, subcutaneously). At 64 weeks, significantly greater improvements were noted in children on burosumab compared to conventional treatment with regard to radiological rickets healing, phosphate, ALP and calcitriol concentrations, TmP/GFR, growth and functional outcomes [6-min walk distance (6MWD)] (Fig. 2) [38].

In adults with XLH, a double-blind, controlled trial compared 1 mg/kg of burosumab versus matching placebo subcutaneously 4-weekly for the first 24 weeks, followed by a treatment continuation period where all participants received burosumab for a further 24 weeks. The group that received burosumab from the start, versus those given placebo, demonstrated better healing of active insufficiency fractures. Complete fracture resolution was observed in 43.1% of burosumab patients versus 7.7% of placebo recipients at week 24; also a clinically significant and sustained improvement

in pain, stiffness and functional outcomes (6MWD) was observed in the group that received burosumab [39].

6.1.2.1 Side Effects Burosumab is generally a well-tolerated drug, with a good safety profile. The most common side effect recorded in drug trials was injection site reactions (57.7%); these were localised, lasting for a few hours, and resolved spontaneously. Other reported adverse events in children, notably deemed unrelated to the drug by the investigators, included headache, vomiting, pyrexia, pain in extremities and a fall in 25OH vitamin D levels. There was no evidence of hyperphosphataemia or ectopic mineralisation in the trials [35].

6.1.2.2 Drug Licence Burosumab was approved as monotherapy in 2018 by the EMA (conditionally) and by the FDA (fully). The EMA conditionally approved use of burosumab in children aged 1 year and older with radiographic evidence of bone disease, through adolescence during skeletal growth. The EMA-approved starting dosage is 0.4 mg/kg subcutaneously every 2 weeks in children, with 0.8 mg/kg (rounded up to the nearest 10 mg) as typical maintenance dosing and a maximum dose of 90 mg. The FDA-approved starting dosage is 0.8 mg/kg every 2 weeks in children aged 1 year and older and 1 mg/kg every 4 weeks in adults, with a maximum dose of 90 mg [40].

6.1.2.3 Treatment Recommendations Based on the product information, fasting serum phosphate levels should be measured before initiating burosumab, following a 7-day washout period if the patient was previously on conventional treatment. Serum phosphate should be monitored on a 2-weekly basis for the first month, 4-weekly for the following 2 months and at the clinician's discretion thereafter. Also recommended is checking serum phosphate levels 4 weeks after each dose change (in increments of 0.4 mg/kg), but also rounding of doses to the nearest 10 mg. The target is a serum phosphate level at the lower end of the normal reference range. The most useful biomarkers for treatment monitoring include serum ALP, TmP/GFR, and knee and wrist X-rays. Periodic measurement of urine calcium and phosphate along with renal ultrasound 6-monthly for the first year and annually thereafter is recommended in children until further evidence arises [34].

6.1.2.4 The Unknowns Various aspects of burosumab therapy in XLH are yet to be explored, including whether specific groups of children with XLH respond better than others and whether such response can be predicted. As with other high-cost drugs, national bodies or health insurers need to negotiate the drug price and determine which centres they will allow to prescribe the drug and which criteria will be used to start burosumab versus conventional therapy, in

consultation with paediatric bone experts. Whether starting treatment in childhood mitigates XLH-related complications in adulthood is a long-term question that will take a long time to answer. The effect of burosumab on prevention of dental complications of XLH, craniosynostosis and muscle weakness as well as long-term safety needs further clinical studies, ideally in treatment registries such as the European Registries for Rare Endocrine Conditions [41]. More studies assessing disease burden [42] and treatment options in adults are required.

7 Old and New Drugs with Treatment-Adjunct Potential

7.1 Growth Hormone

There are very few published studies evaluating the role of recombinant human growth hormone (GH) in children with XLH. In a small group of short children with XLH ($n = 19$), Rothenbuhler et al. demonstrated substantial improvement in height SDS (baseline vs 2 year: -2.35 ± 0.8 vs -1.2 ± 1 SDS; $p = 0.04$) on high GH dose (67 µg/kg/day) given alongside conventional XLH therapy. Growth response to GH was better in prepubertal compared to pubertal children with XLH. An earlier, randomised, open-label study looking at very short children with XLH ($n = 16$) had shown a substantial growth response from -3.3 height SDS at baseline, which improved by $+1.1$ SDS during 3 years on GH treatment ($p < 0.05$ vs baseline) [43]. However, a more recent follow-up analysis of this study cohort ($n = 11$) has shown no significant difference in adult final height in the GH-treated group versus controls (-2.4 ± 0.7 vs -3.3 ± 1.2; $p = 0.082$) [44]. Due to the paucity of evidence demonstrating definite benefit of GH therapy in improving growth, this treatment cannot currently be recommended as an adjunct therapy in routine clinical practice.

7.2 MAPK Inhibitors

A recent study in a young *hyp* mice model demonstrated that the combination of MAPK inhibitor, which heals rickets and improves growth plate organisation, along with GH could be a promising new therapy in treating children with XLH. However, such therapy would need exploration via clinical trials in humans [45].

7.3 Cinacalcet

Conventional treatment can result in elevated PTH levels and further stimulated FGF23 production. A small study in eight patients with XLH (age 6–19 years) well controlled on conventional treatment demonstrated that a single dose

of cinacalcet reduced serum PTH and FGF23 levels and increased serum phosphate concentrations substantially more than a phosphate dose alone [46]. No further studies have since been conducted.

7.4 Calcitonin

Calcitonin is presumed to work through activated receptors on osteocytes which regulate FGF23 production and through stimulating 1α-hydroxylase production [47]. A single subcutaneous dose of salmon calcitonin in a prospective, randomised, double-blinded, placebo-controlled trial in seven adult patients with XLH showed significant reductions in FGF23 concentrations ($p < 0.001$) for 16 h, with a transient increase in serum phosphate levels. No significant change in FGF23 was noted in controls [48]. A similar biochemical effect was not demonstrated in a randomised, controlled, 3-month trial of 400 IU of nasal calcitonin in adult patients with XLH [49].

7.5 Summary

None of these potential treatment options have been trialled in children and therefore cannot be recommended for routine clinical use.

8 Involvement of Other Specialists in Multidisciplinary Care

Rare diseases such as XLH should not be managed in isolation; they should instead be managed by multidisciplinary teams with the necessary expertise in tertiary centres, consisting of paediatric bone specialists or nephrologists, orthopaedic surgeons, geneticists, dentists, neurosurgeons, radiologists, physiotherapists, occupational therapists, psychologists, social workers and nurse specialists, to achieve the best possible outcomes.

8.1 Orthopaedic

Despite optimal medical management with conventional treatment, a substantial proportion of patients have worsening lower limb deformities and require surgical correction (25–65%) [50]. The commonest intervention is growth modulation with hemiepiphysiodesis (eight plates) as this procedure is minimally invasive [51]. Some of the deformities may require osteotomies and fixation by various methods such as K-wire and casting, intramedullary nails or external fixators [52, 53]. Whilst burosumab may have greater potential to improve leg deformities than conventional therapy [38], its role in preventing skeletal complications and orthopaedic surgery will have to be determined in future studies.

8.2 Dental

Recurrent dental abscesses, dental fissures and sinus tract formation, delayed eruption of deciduous and permanent dentition, defects in dentin mineralisation, thin enamel and increased risk of periodontal disease are among some of the dental complications in XLH [54–56]. Treatment with oral phosphate supplements and alfacalcidol has shown to improve dentin development and mineralisation. Also, continuation of treatment into adulthood is associated with reduced frequency of periodontitis [57]. The beneficial effects of burosumab on dental outcomes needs systematic assessment in future studies.

8.3 Neurosurgical

XLH is associated with craniosynostosis due to the premature fusion of the skull sutures. Also, Chiari 1 malformations and syringomyelia are known associations. Although routine brain imaging is not performed in this subgroup of children, monitoring head circumference through serial measurements, performing brain magnetic resonance imaging (MRI) and involving the paediatric neurosurgical team as indicated is recommended [58, 59].

9 Conclusion

XLH is a rare complex disease mainly affecting the musculoskeletal system. Early diagnosis and treatment is vital to achieve good long term outcomes. Conventional therapy with multiple daily doses of oral phosphate and active vitamin D analogues was the mainstay in treatment until recently. The newly introduced burosumab therapy targeting FGF23 is very promising not just for XLH but for a whole range of other conditions with FGF23 excess such as TIO, ADHR, and ARHR. Although this drug has very good safety and tolerability profiles along with favourable skeletal and functional outcomes in the short term, its long-term outcomes are yet to be established. This rare condition requires management by a tertiary multidisciplinary team with the necessary expertise to achieve the best possible outcomes for the child.

Compliance with Ethical Standards

Conflict of interest VS and WH were investigators for clinical studies sponsored by Ultragenyx and received honoraria and travel support

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