Journal of Endocrinological Investigation (2025) 48:2199–2228
https://doi.org/10.1007/s40618-025-02611-7

CONSENSUS STATEMENT

Experts' consensus on the management and treatment of individuals with X-linked hypophosphatemia across lifespan

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Received: 26 January 2025 / Accepted: 13 May 2025 / Published online: 1 July 2025

Abstract

Purpose X-linked hypophosphatemia (XLH) is a rare hereditary skeletal disorder that may be very disabling and significantly impacting the quality of life throughout the lifespan. The aim of this document was to inform stakeholders about the lifelong impact, management, and treatment of individuals with XLH, especially focusing on the new therapeutic approach with burosumab.

Methods From October 2023 to April 2024, a multidisciplinary working group of Italian experts on bone and mineral metabolism convened periodic online meetings. Statements were formulated identifying the most relevant studies, including randomized controlled trials, international guidelines based on GRADE criteria, and systematic reviews, and the experts' opinions.

Results The panel of experts provided "consensus statements" on the clinical management of individuals with XLH across lifespan. Five main issues were identified: (1) clinical and biochemical diagnosis of individuals with XLH and monitoring of the progression of the disease; (2) effects of conventional treatment with phosphate supplements and active vitamin D metabolites; (3) effects of the treatment with burosumab; (4) multidisciplinary approach and management of individuals with XLH; (5) consensus statement for transition from pediatric to adult care in individuals with XLH.

Conclusion Individuals with XLH often experience unmet needs throughout life; a multidisciplinary approach involving different specialists, is recommended. The new treatment with burosumab can provide an effective and safety therapeutic option in reducing the burden of the disease in both children and adults. Therefore, awareness about the XLH disease should be increased among stakeholders. The criteria and reimbursement policies of burosumab should be revised.

Keywords Burosumab · Conventional treatment · FGF23 · Osteomalacia · Rickets · XLH

Introduction

X-linked hypophosphatemia (XLH, OMIM 307800) is a rare hereditary, lifelong and progressive skeletal disorder occurring with an estimated incidence as between 1.33 and 4.8 per 100,000 persons [1–5]. XLH is caused by *PHEX* (*Phosphate Regulating Gene with Homologies to Endopeptidases on the X chromosome*) gene mutations that result in elevated circulating fibroblast growth factor 23 (FGF23) concentration [6]. The excessive production of FGF23 stimulates urinary phosphate wasting and renal 24-hydroxylase activity and reduces renal 1α-hydroxylase activity with insufficient production of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), resulting in hyperphosphaturia and hypophosphatemia [6].

Clinical manifestations of XLH vary in severity, even among affected individuals in the same kindred. XLH

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progresses throughout lifespan and a multidisciplinary approach involving different specialists is recommended [7–15].

Early diagnosis and long-term treatment are crucial for managing individuals with XLH. Recently, burosumab, a recombinant human IgG1 monoclonal antibody targeting FGF23, changed the therapeutic approach in individuals with XLH, improving phosphate metabolism, muscular and osteoarticular symptoms, skeletal abnormalities, and quality of life (QoL) [16]. However, access at burosumab treatment remains challenging for many individuals with XLH.

The aim of this document is to provide stakeholders about the lifelong impact and the management of individuals with XLH. It also aims to analyze the safety and the efficacy of conventional treatment with phosphate supplements (Pi) and active vitamin D metabolites compared to burosumab. The panel of experts provided"consensus statements"on the clinical management of individuals with XLH throughout lifespan. Moreover, some suggestions are proposed for the treatment of persons with XLH during transition from pediatric to adult services.

Methods

From October 2023 to April 2024, a Multidisciplinary Working Group of Italian experts from the Bone and Mineral Metabolism Group of the Italian Society of Pediatric Endocrinology and Diabetology (SIEDP), Italian Society of Endocrinology (SIE), Italian Society of Pediatric Nephrology (SINePe), and Italian Society of Nephrology (SIN), including 9 pediatric endocrinologists, 2 pediatric nephrologists, 15 endocrinologists, 1 nephrologist and 1 internist convened periodic meetings and 6 teleconferences to discuss key issues related to the management and treatment of individuals with XLH and formalized Experts'Consensus Statements based on their expertise and the main literature evidence on five topics: (1) clinical and biochemical diagnosis of individuals with XLH across lifespan; (2) effects of conventional treatment with Pi and active vitamin D metabolites; (3) effects of the treatment with burosumab; (4) multidisciplinary approach and management of individuals with XLH; (5) consensus statement for transition from pediatric to adult care in individuals with XLH.

A scientific literature review was carried out in PubMed (MEDLINE) according the PRISMA guidelines. Randomized controlled trials, international guidelines based on GRADE criteria, consensus statements, systematic reviews, meta-analysis, and clinical trials were considered for inclusion. The following key MeSH terms were used to identify suitable studies: X-linked hypophosphatemic rickets; X-linked hypophosphatemia; hypophosphatemic rickets; burosumab; burosumab treatment; hypophosphatemic osteomalacia; pediatric XLH; children XLH; adult XLH; conventional therapy; conventional treatment; XLH outcomes. The PubMed database was searched until 30 October 2023. A second and third PubMed database search was done on 30 March 2024 and 30 November 2024, respectively, using the same MeSH terms to incorporate new evidence obtained during the guideline process. A final search was done on 20 February 2025 using the same MeSH terms. To identify publications meeting the inclusion criteria, the members of the multidisciplinary group critically reviewed all the full text articles selected in the first-pass screening to verify whether they carried relevant data according to the identified main study topics. Moreover, two authors (GB and SC) independently reviewed the search screening results, and the data extracted from the examined studies. Abstracts were not included in literature review. No publication date limit was used. Subsequently, a Delphi technique was applied to build consensus for each draft statement. All the experts participated in six rounds of online voting; the experts provided their agreements on each draft statement, by an agree/disagree scale, and submitted their comments for writing all the statements. Consensus for all the assessments was based on experts' clinical practice by at least 80% of participants. All the statements were performed on clinical expertise and literature data, taking into consideration especially the studies with GRADE methodology.

Aim 1: Clinical and biochemical diagnosis of individuals with XLH across lifespan

The clinical manifestations of XLH vary according to the age at diagnosis, severity of disease, and efficacy of treatment. Clinical phenotype changes with the progression of disease across lifespan and may be influenced by the adverse effects of conventional treatment. Figure 1 describes the phenotype throughout the lifespan in individuals living with XLH. The severity of the phenotype does not correlate with the underlying genotype [2, 17, 18].

Clinical diagnosis in infants, children, and adolescents

Medical history, physical examination, biochemical findings, and X-ray examination have a key role for the diagnosis. Length and weight at birth are usually normal. Stunted growth with body disproportion, swelling of the wrists, knees, or ankles, and skeletal muscle weakness may be early signs of XLH [11, 13–15, 19, 20]. Sixty percent of individuals with XLH showed frontal bossing and mild to severe craniosynostosis [20–22]. When the infant starts

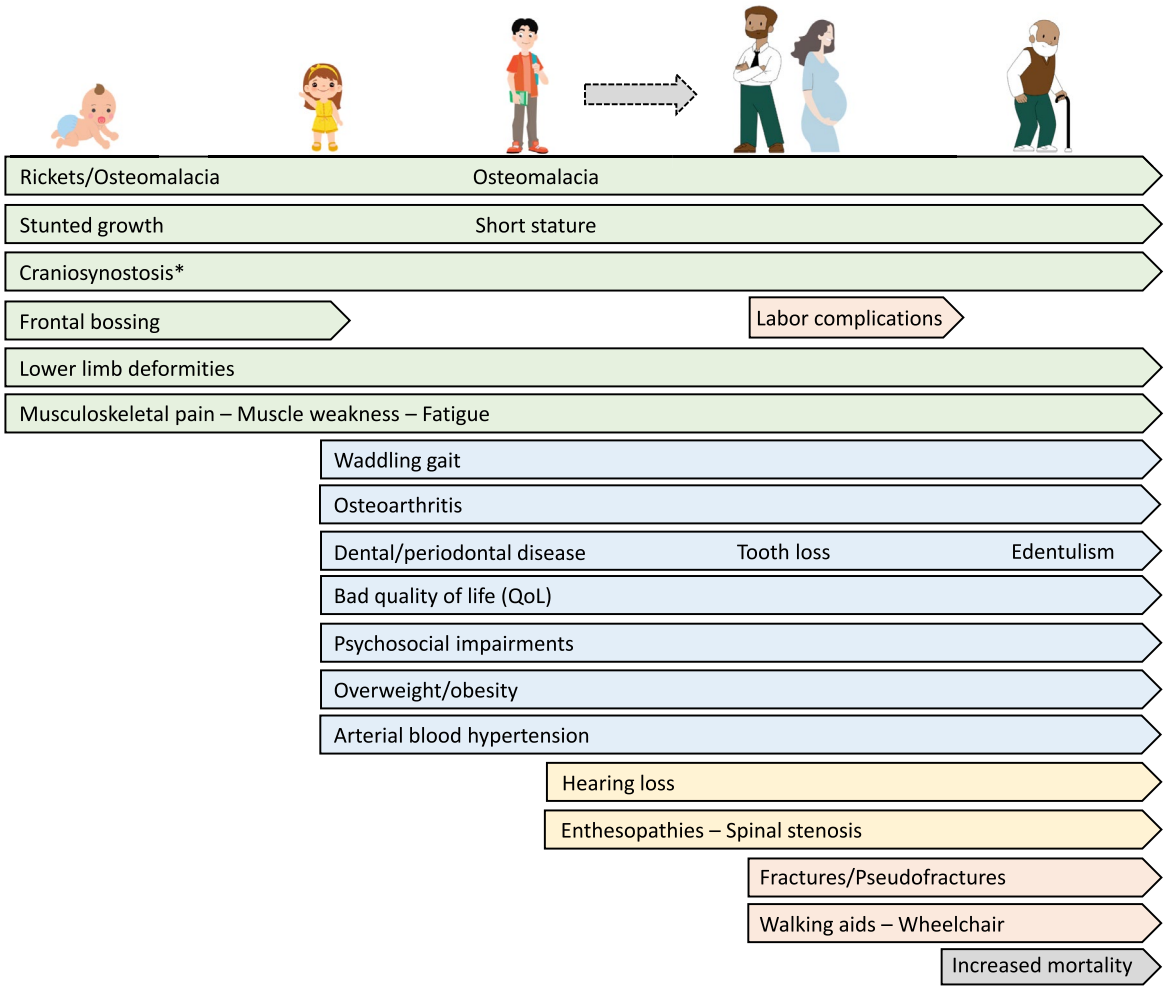

Fig. 1 Phenotype throughout the lifespan in individuals living with XLH. Note the progression and the occurrence of some symptoms along the life. Infant: 0–1 year; child: > 1–12 years; adolescent: > 12–17 years; adult: 18 + years; elderly: 65 + years. Possible complications caused by conventional treatment are not reported. The mechanisms of the development of overweight/obesity and hypertension are not defined, and it is not clear if they are related to conventional treatment or disease itself. *It may be associated with Arnold-Chiari malformation. Light grey arrow represents the transition phase from adolescence to young adulthood

walking progressive bowing of lower limbs (genu-varum, genu-valgum, or combined genu-varum/valgum) associated with waddling gait, femoral and tibial torsion (intoeing or extoeing), and frequent falls usually occur [11, 13–15, 19, 23, 24]. Figure 2 shows the typical phenotype and radiological lesions in children with XLH.

In infants with a familial history of XLH, diagnosis may be confirmed within the first weeks of life by genetic analysis of the *PHEX* gene. Diagnosis of XLH may be delayed in infants with a de novo mutation of the *PHEX* gene, as the skeletal signs are like those observed in children with nutritional vitamin D deficiency rickets or other forms of rickets. Eighty-five to 90% of individuals harboured an identified germinal *PHEX* mutation, which can be inherited or de novo [17]. However, no genetic defect is found in about 10% of individuals, and mosaicism may be observed for de novo *PHEX* gene mutations [25]. More than 330 different *PHEX* gene mutations have been described to date, including nonsense, missense, deletions, duplications, insertions and splice mutations, unevenly distributed along the *PHEX* gene with three regions having a high mutation density [17, 26].

In adolescents with XLH, skeletal deformities which occurred during childhood progressively worse, and most individuals require orthopedic surgery because of unresolved or partially corrected childhood deformities [27, 28]. New cumulative deficits such as osteoarthritis, enthesopathies, and spinal stenosis, leading to severe pain, stiffness and decreased physical activity usually occur [28–32].

Pseudofractures (wide and transverse lucent bands due to a build-up of osteoid with condensation of bone along the borders), as an expression of osteomalacia, are very rare in

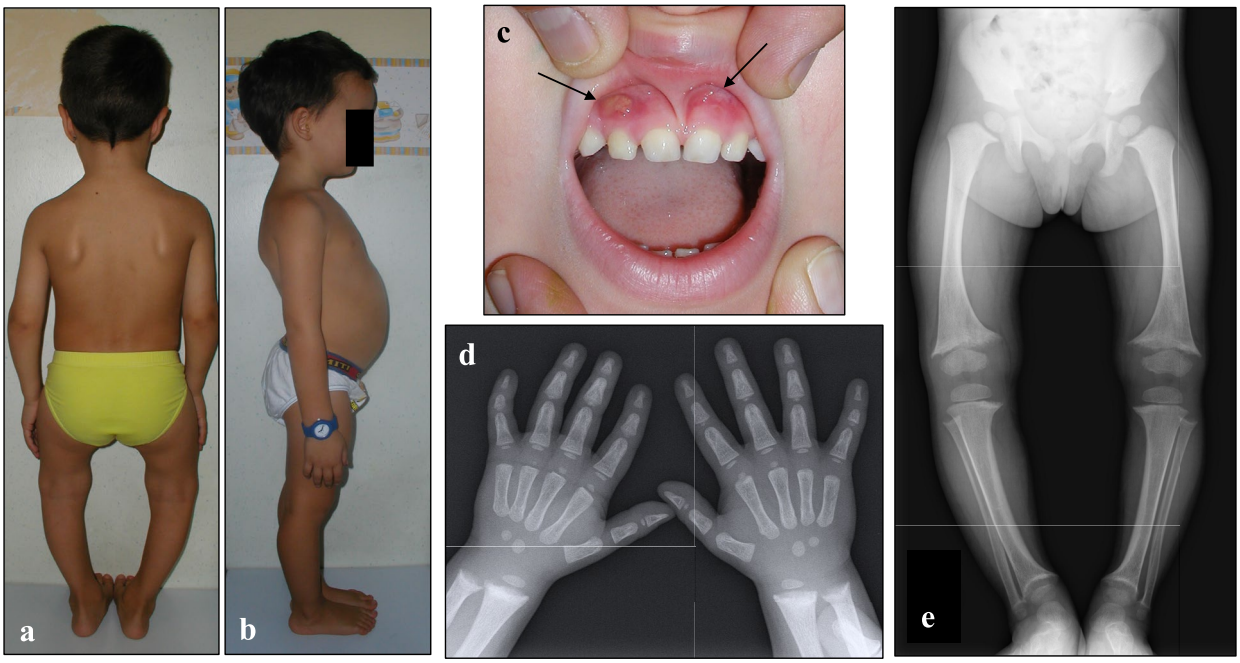

Fig. 2 Typical phenotype and radiological lesions in children with XLH. **a** Severe short stature (−4.6 Z-score) with body disproportion and genu-varum in a 6.5-year-old male. **b** Severe short stature (−3.0 Z-score) with body disproportion, exaggerated lordotic posture to compensate for the anterior bowing of the lower limbs, and craniosynostosis in a 6-year-old male. **c** Spontaneous gingival fistulae (black arrows) corresponding to deciduous left and right maxillary lateral incisors in a 4.3-year-old male. **d** X-ray features of the wrist in a 1.8-year-old female: widening and fraying of the epiphyseal plate and metaphyseal concavity of the ulna. **e** X-ray features of the lower limbs in a 2.1-year-old female: genu-varum and distal medial femoral and tibial bowing with widening and fraying of the distal epiphyseal plate of the femur and tibia and of the proximal epiphyseal plate of fibula and medial epiphyseal plate of the tibia

children and adolescents with XLH [33, 34]. A Dutch observational registry on XLH study reported the occurrence of pseudofractures in three children at a mean age of 6.5 years [35].

In children with XLH, dental development is usually delayed, and eruption patterns are abnormal. Dental malocclusions are common, such as an open bite, maxillary retrognathism and impacted or ectopic maxillary canines [36–40]. In addition, dental and periodontal lesions, including recurrent gingival abscesses with periapical fistulae, mainly in incisors and canines, without evidence of trauma or dental decay are common findings in children with XLH (Fig. 2) [36–38]. Recurrent abscesses are reported in 25 [4, 39] to 75% [41] of children with XLH. Enlarged pulps chambers with altered shape and morphology and prominent pulp horns into the tooth crown in primary and secondary molars are typical lesions observed by orthopantomography [41, 42]. These lesions, associated with a poor dentin mineralization, may predispose to recurrent abscesses with fistulae [36, 37, 41]. Impaired oral health may reduce QoL [43].

Hearing loss has been reported in 6.9% of children with XLH [35], but criteria to identify those at risk are not defined [44].

Increased prevalence of overweight and obesity has been detected in about one-third of children and adolescents with XLH [45–47]. The duration of conventional treatment and a decline in ATP production inducing increased food intake or a decreased thermogenesis with an impaired energy expenditure have been suggested to have a role in the development of weight gain in XLH [45]. Leptin concentrations were lower in children but not in adolescents with XLH so that their role in the higher prevalence of obesity is unclear [47]. Adolescents and adults with XLH are prone to develop obesity partly because chronic bone and joint complications decrease the propensity to exercise, and they are often not able to practice any sporting activity because bone and joint pain significantly reduce their physical abilities [20, 48]. Moreover, higher body mass index (BMI) has been associated with lower ankle power and disturbances of biomechanical function, worsening the weight bearing effect on lower extremities [49].

Psychological impact of XLH becomes prominent in adolescents as they become increasingly aware of the physical limitations associated with their lifelong condition [50, 51]. An awareness of short stature and the presence of dental and periodontal abscesses may significantly affect a child's feeling of self-esteem, impairing his/her QoL, and preventing their full integration in society [40, 52].

Clinical diagnosis in adults

Adults with XLH commonly develop enthesopathies, that have been reported in 33% of individuals with XLH aged < 30 years and 100% in those aged ≥ 30 years [53, 54]. Spinal enthesopathies have been described in 84% of adults with XLH above 40 years of age [55], and they progress in up to 52.9% in a mean follow-up of 6 years [56].

The early appearance of radiological signs of arthrosis, mostly affecting joints of lower limbs, has been observed in 25% of adults with XLH aged < 40 and in 58% aged > 40 [55]. Up to 7.5% of adults with XLH are also at risk of spinal kyphosis and scoliosis [35, 57] and up to 20% of spinal stenosis [13, 58]. Symptomatic spinal cord compression due to spinal stenosis can be severe and can occur at multiple levels, requiring neurosurgical posterior decompression [58]. Hip deformities were observed in 12.5% of adults with XLH; severe hip and knee deformities frequently required orthopedic interventions, including hip and knee prosthesis [35]. Osteophytes, enthesopathies, and spinal stenosis increased with age, beginning at the age of 30 [59].

Pseudofractures have been reported in 20–45% of adults with XLH, most commonly (69%) between 30 and 50 years of age [13, 27, 53, 54, 59]. The prevalence is higher in men than in women, with rates of 53% and 39%, respectively [54]. Fractures involve more commonly lower limb skeletal segments including hip and femur, also in young adults with XLH. Bone mineral density (BMD) measured by DXA is usually increased at lumbar spine due to calcification of yellow ligaments and osteoarthritis of the spine. Therefore, BMD may be not useful for the management of patients with XLH.

Overall, osteomalacia, enthesopathies, arthrosis, axial spondylarthritis, and pseudofractures can cause chronic musculoskeletal pain, significantly impairing physical activity and limiting QoL in individuals with XLH [7, 19, 29, 59–62]. Bone pain may occur with or without the evidence of pseudofractures [63]. Almost all adults with XLH (97%) complain of bone pain or joint stiffness, with walking difficulty and functional limitation [59]; up to 70% regularly take analgesics [27, 62, 64, 65], up to 45% opioids [27, 65], and antidepressants [64]. Moreover, untreated symptomatic adults with XLH showed degenerative joint disease, bone pain, and dental abscesses associated with histological signs of osteomalacia [53]. Moderate to severe osteomalacia has been detected by histomorphometry in asymptomatic adults [66]. These data suggest that both untreated and conventional treated adults with XLH have chronic hypophosphatemia with osteomalacia, which is usually associated with bone pain, even in absence of pseudofractures. The occurrence of pseudofractures is always associated with osteomalacia.

Adults with XLH usually have worse oral health than healthy population and especially suffer from endodontic conditions, including periodontitis, tooth decay, and dental abscesses leading to early tooth loss [32, 55, 67, 68]. In a survey assessing disease burden, dental abscesses were present in 82% of adults with XLH [59], and dental infections were diagnosed in 60–70% [69, 70]. Male adults had a higher risk of poor oral health than females with XLH [67], as reported in children [41].

Hearing alterations are more frequently seen in adults than in children and adolescents (48–82% and 9%, respectively), with the most common cause being sensorineural hearing loss, that is often asymmetric [64].

Cardiovascular involvement has been suggested in adults with XLH, although data are conflicting, with a possible increase in the risk of early-onset hypertension and left ventricular hypertrophy [71, 72]. Other studies failed in detecting cardiovascular impairment [73, 74]. A role of nephrocalcinosis, hyperparathyroidism and high FGF23 concentration in the development of hypertension and left ventricular hypertrophy has been hypothesized [71, 72] but not confirmed.

Overweight or obesity has been reported in 29–35% and 21–57% in adults with XLH [47, 75], respectively; 66% were receiving conventional treatment [75] or were being treated with burosumab [47]. Fasting glucose, glucose tolerance, prevalence of type 2 diabetes, and serum leptin concentration did not differ between XLH adults and matched controls [47, 75].

Biochemical phenotype in XLH

Laboratory assessment is crucial to establish the underlying cause of hypophosphatemia and it is useful in making the differential diagnoses among the various forms of renal phosphate wasting. When osteomalacia is present, tumor induced osteomalacia (TIO) should be considered in differential diagnosis [28, 63, 76]. TIO differs from XLH for some clinical features. Several imaging techniques may be used to detect causative tumors, including plain radiographs, computed tomography, magnetic resonance, octreotide scanning, and combined positron emission tomography/computed tomography [63]. However, tumor detection is successful in approximately 50% of instances, leading to delayed diagnosis for the remaining cases, which are found upon retesting after a few years [63].

Serum phosphate concentration

Hypophosphatemia persists throughout life and is a biomarker in persons with XLH. The degree of hypophosphatemia is

not correlated with the severity of the skeletal lesions and does not have a prognostic value [77, 78].

Interpretation of serum phosphate concentration is crucial for the diagnosis of XLH as it progressively declines from infancy to post puberty [79–81] and is higher in pediatric ages compared with adulthood [79]. Clinicians should be pay attention as many clinical laboratories do not report age-appropriate normal ranges for serum phosphate concentration resulting in missed or delayed diagnoses of hypophosphatemia in children and adolescents. Serum phosphate reference range for age and sex is reported in Supplemental Table S1.

Tubular maximum reabsorption of phosphate/glomerular filtration rate (Tmp/GFR)

TmP/GFR is an accurate parameter for the diagnosis of XLH. In infants, children, and adolescents, TmP/GFR should be calculated by using the formula suggested by Stark et al. [82] and Brodhel et al. [83], as the nomogram of Walton-Bijvoet [84] deriving from findings in adults, does not represent a direct measurement, and children have higher serum phosphate concentration and lower GFRs than adults [82, 83]. There are no differences between morning fasting and non-fasting values, so that this is an important option in infants and children [82]. The nomogram of Walton-Bijvoet is appropriate for TmP/GFR assessment in adults [84]. Of note, other proximal or distal tubular wasting disorders should be excluded [28, 58, 76, 85].

Serum alkaline phosphatase (ALP) activity

Serum total ALP is a reliable and cost-effective biomarker of rickets and osteomalacia reflecting an impaired growth plate and bone matrix mineralization [86]. Bone-specific ALP (BALP) measurement should be preferred in adults with XLH given that approximately 50% of circulating total ALP originates from hepatocytes [87]. BALP may be considered as a surrogate of bone healing in individuals with XLH receiving conventional treatment [88] or burosumab [89]. Nonetheless, some adults with XLH may have normal values of BALP associated with osteomalacia [64, 90, 91].

Circulating parathyroid hormone (PTH) concentration

At diagnosis, individuals with XLH have normal or slightly elevated PTH concentration [11, 88]. In individuals with XLH receiving conventional treatment the recurrent stimulation of parathyroid glands by oral Pi boluses has long been thought to be the main physiopathological mechanism responsible of increased serum PTH concentration [14, 88, 92]. A deficient synthesis of $1,25(OH)_2D$ induced by FGF23 excess could contribute to the development of hyperparathyroidism as $1,25(OH)_2D$ is a known inhibitor of parathyroid cell proliferation [93]. Moreover, the relative abundance of *PHEX* transcripts in the human parathyroid cells may have a role in the inactivation of PTH [94].

Regular assessment of circulating PTH concentration is essential to prevent the occurrence of secondary or tertiary hyperparathyroidism [14, 19, 58, 85, 88, 92].

Serum vitamin D metabolites

Serum 25-hydroxyvitamin D (25OHD) concentration is normal in individuals with XLH, unless affected by factors such as sunlight exposure, nutrition, and maternal vitamin D status [9, 15]. $1,25(OH)_2D$ synthesis is impaired in individuals with XLH [95–97] due to excessive production of FGF23 that suppresses transcription of *CYP27B1*/1α-hydroxylase and activates transcription of *CYP24A1*/24-hydroxylase in proximal renal tubules [98].

Circulating FGF23 concentration

Measurement of circulating FGF23 concentration represents a useful tool in separating FGF23-mediated from non-FGF23-mediated hypophosphatemic disorders. High FGF23 concentration has been found in both hereditary and acquired forms of hypophosphatemic rickets [7, 14, 15, 28, 58, 85, 88, 99]. Increased FGF23 concentration in XLH is the results of inactivating mutations in the *PHEX* gene, likely via increased concentration of acidic serine aspartate-rich-MEPE-associated protein (ASARM) peptide [7]. Chronological age and pubertal development are main determinants of intact FGF23 plasma concentration in healthy infants, children, and adolescents [80]. Moreover, the cut-off of intact FGF23 concentration between healthy subjects and individuals with XLH varies from 25.5 pg/mL to 40 pg/mL according to the method used for its measurement [80, 100–102].

Serum calcium concentration and urinary calcium excretion

They are normal in individuals with XLH [11, 14, 88]; they may be useful for differential diagnosis with other forms of rickets or osteomalacia [11, 14, 58, 88] and for monitoring potential adverse effects related to long-term conventional treatment. Urinary calcium excretion can be measured in morning urine spotting in children and in 24 h-urine collection in adults.

Statement 1. XLH should be considered in the diagnostic evaluation of growth retardation in pediatric patients through linear growth and body proportion assessment.

Statement 2. The diagnosis of XLH can be suspected in presence of rickets, short disproportionate stature, reduced serum phosphate concentration, increased ALP activity and FGF23 concentration.

Statement 3. Measurement of FGF23 concentration may be useful to distinguish FGF23-mediated from non-FGF23-mediated hypophosphatemic disorders.

Statement 4. (a) biochemical parameters (serum and urinary phosphate, calcium, and creatinine, TmP/GFR, ALP or BALP activity, PTH, FGF23, 25OHD, and 1,25$(OH)_2$D) should be evaluated at the same time; (b) biochemical parameters should be carefully interpreted according to age and sex and concomitant conditions or ongoing treatments.

Statement 5. Genetic analysis for variants of the *PHEX* gene should be considered in all children with non-related nutritional rickets.

Statement 6. Expert dentists and psychologists must be part of the multidisciplinary team caring for individuals with XLH.

Statement 7. Adults with XLH should be examined for bone and muscle pain, hearing loss, oral health, weight, and cardiovascular risk.

Aim 2: Effects of conventional treatment with Pi and active vitamin D metabolites

During the 70 s individuals with XLH had received large amounts of vitamin D (> 50,000 IU per day) [103], resulting in poor clinical outcomes and development of severe complications including impaired renal function and secondary or tertiary hyperparathyroidism [104]. From the early 80 s onwards, individuals with XLH have been treated with the so-called"conventional treatment"(or"standard therapy") based on the combination of Pi and an active metabolite of vitamin D (calcitriol or alfacalcidol) [19, 58, 88, 104]. This treatment led to significant improvements in linear growth, skeletal deformities, and bone mineralization in comparison with vitamin D (non-active metabolite) or Pi alone or in combination [104].

The aims of treatment in infants, children, and adolescents with XLH are the healing of rickets and osteomalacia, and the improvement of leg deformities, linear growth, dental and periodontal lesions, bone and muscular pain, and QoL. However, conventional treatment does not correct the underlying pathogenesis or normalize fasting serum phosphate concentration, and outcomes depend on timing of diagnosis and severity of disease, as well as tolerance and compliance with the treatment [11, 14, 15, 19, 78, 88, 105].

Treatment in adults with XLH aims to heal osteomalacia and its related symptoms, including bone pain, pseudofractures, and muscle weakness, as well as dental and periodontal disease and QoL. However, in most cases these aims are partially achieved [30, 32, 59, 60, 62, 64, 88, 106, 107]. Several adults with XLH did not receive any treatment during childhood, and in most of them the diagnosis was delayed.

Though active vitamin D metabolites are the choice in conventional treatment, low vitamin D status, diagnosed as serum 25OHD < 20 ng/mL, should be ruled out and, when occurring, treated with cholecalciferol supplementation.

From infancy to growth completion

Conventional treatment requires balancing the benefits of treatment with potential risks of overtreatment. Doses of Pi and active vitamin D metabolites should be titrated up to the maximum tolerance, without the occurrence of clinical and biochemical adverse effects (Supplemental Table S2). The compliance with conventional treatment may be poor due to the development of gastrointestinal symptoms, such as diarrhea, bloody stools, and abdominal pain; compliance may improve by reducing the dose of oral Pi [20, 88, 108]. Potential adverse events that may arise during conventional treatment are reported in Supplemental Table S3.

Biochemical parameters useful for titrating the dose of conventional treatment include serum ALP activity, serum calcium, circulating PTH concentration, and urinary calcium excretion. However, only the reduction of serum ALP activity is a useful marker of the efficacy of conventional treatment. Increased serum calcium and PTH concentration, and urinary calcium excretion may reflect overtreatment with Pi and/or active vitamin D metabolites, suggesting a reduction of the dose of Pi and/or active vitamin D metabolites [14, 19, 55, 88, 108] (Supplemental Table S3).

Assessment of linear growth and growth velocity, and the amount of correction of lower limbs deformities may be additional clinical findings for adjusting the dose of conventional treatment [19, 20, 55, 88, 108].

Serum phosphate and TmP/GFR correction, and 1,25$(OH_2$D production

Conventional treatment may be associated with a mild but transient increase in serum phosphate concentration which rapidly declines (1 h) after an oral phosphate dose has

been taken [109]. Despite multiple daily Pi doses, serum phosphate concentration can fluctuate considerably during the day, precluding its use for dose adjustment [13, 88]. Conventional treatment does not improve TmP/GFR and serum $1,25(OH)_2D$ concentration [110, 111]. Therefore, these parameters are not useful for monitoring the effects of therapy.

Bone mineralization and skeletal deformities

Conventional treatment reduces the amount of unmineralized osteoid but did not lead to mineralization of the bone tissue immediately adjacent to osteocytes (periosteocytic lesions) that occur in individuals with XLH [66, 90]. Similarly, conventional treatment increases bone mineralization of the forearm shaft but does not normalize it [112]. Periosteocytic lesions are likely to be caused by mineralization inhibitors such as osteopontin and pyrophosphate that accumulate around osteocyte lacunae as an indirect consequence of *PHEX* mutations [113, 114], because of FGF23 excess in osteocytes rather than hypophosphatemia [112].

In most children and adolescents with XLH, conventional treatment cannot fully normalize the skeletal deformities of the lower limbs, which require surgical corrections [8, 11, 115–117]. In severe cases, skeletal deformities worsen during adulthood. Even with close monitoring up to 90% of children and adolescents with XLH required surgery to correct bone deformities [59, 115, 118, 119]. A recurrence rate of 90% after the first corrective osteotomy and 60% after a second procedure has been reported, despite adequate treatment [120].

Linear growth

The effect of conventional treatment on linear growth is variable and is influenced by age at diagnosis, treatment regimen, and compliance with the treatment. However, in most children linear growth is unsatisfactory, and some children remain unresponsive [121, 122]. This may be because the correction of serum phosphate concentration is not adequate or because mechanisms other than hypophosphatemia are involved, including *PHEX* gene deficiency by FGF23 suppression of chondrocyte proliferation and maturation [123].

Growth retardation in children with XLH receiving conventional treatment is already evident in the first years of life and is mainly caused by a reduced growth of the lower limbs [122, 124]. Growth retardation in children younger than 1 year of age is similar between males and females, whereas, after the age of 5, stunting is more pronounced in boys than in girls (- 3.0 ±1.0 Z-score and—2.1 ±1.3 Z-score, respectively) [122]. Although conventional treatment may improve rickets and skeletal deformities, its effect on linear growth may be insufficient and final height is often below −2.0 Z-score of normal reference values [19, 53, 124–127]. Final height was reduced in individuals with XLH regardless of the age at which conventional treatment was begun [121]. However, a good compliance with the conventional treatment may improve final height [128]. Overall, the introduction of the conventional treatment in the late 70 s was associated with an improvement of final height in individuals with XLH, more in women than in men (−1.7 ± 1.1 Z-score and −2.1 ± 1.2 Z-score, $P < 0.002$, respectively) [129].

Recombinant human growth hormone (rhGH) in association with conventional treatment may increase short-term linear growth in children with XLH [11]. Although the effects on final height are not conclusive [130–134], two studies [130, 134] showed a positive effect of rhGH associated with conventional treatment on final height. Makitie et al. [135] found that rhGH treatment alone for 12 months in children and adolescents who discontinued conventional treatment, improved linear growth, serum phosphate and $1,25(OH)_2D$ concentrations, and normalized PTH concentration, but pre-existing skeletal deformities worsened. Routine treatment with rhGH for children and adolescents with XLH is not recommended [14, 15], but we suggest considering rhGH therapy as an option for improving short stature in the context of severe forms of XLH, evaluating case-by-case. The dose and duration of rhGH is not well defined. Likely, high doses of rhGH may be needed to promote growth in children with XLH [134]. Maximum rhGH dose is approximately 70 µg/kg/day and should be adjusted for serum IGF-1 concentration; rhGH treatment should be continued for at least 2 yrs to assess its effect on growth [134].

Enthesopathic disease

Few data on the development of enthesopathic disease in children and adolescents with XLH are available. Enthesopathic disease was reported in 45% of individuals with XLH aged less than 20 years; enthesopathies were evident in both treated and untreated subjects, suggesting that the disorder is an age-dependent process unrelated to previous or ongoing treatment [136]. Enthesopathy begins with the calcification of tendon and ligament insertion sites but progresses to the development of osteophytes, often bridging between adjacent bones [57]. Usually, pain due to enthesopathies is located at the tendons. Likely, the conventional treatment in children and adolescents with XLH have little impact in preventing enthesopathies [57].

Bone, joint and muscle pain, and QoL

Bone pain occurred in up to 33.3% and joint pain in 56.7% of children with XLH receiving conventional treatment; muscle pain and joint stiffness or restricted range of motion were reported in 60% and 38%, respectively [59]. Similarly, bone and joint pain were recorded in 68%, muscle pain in 46%, and motor delay or reduced activity in 35% of individuals with XLH before 18 years; use of mobility aid was detected in 4% of children [4]. Delayed walking, unusual gait or way of walking/running, muscle weakness, and use of a walking device was present in 44%, 84%, 30%, and 10% of children, respectively [59, 137].

Adolescents with XLH receiving conventional treatment showed high scores of Western Ontario and McMaster University (WOMAC) Osteoarthritis Index and Graded Chronic Pain Scale-Revised [138]. Both painful symptoms and difficulties with age-appropriate gross motor activities, such as walking, running, and jumping significantly affect QoL in children and adolescents with XLH [10, 13, 14, 39, 137–139].

Oral health

Conventional treatment may have a beneficial impact on oral health in children and adolescents with XLH [19, 140], suggesting that hypophosphatemia plays a role in interglobular dentin formation. However, other studies showed that dental and periodontal lesions were incompletely reversed by conventional treatment, and the occurrence of dental abscesses continued into the adult age [30, 37, 41, 52]. These results may indicate that the abnormal dentinogenesis could be related, at least in part, to the effects of the *PHEX* gene mutation on dentin formation and mineralization [41].

Adverse effects

Conventional treatment may be associated with adverse effects due to the administration of high doses of Pi and/or active vitamin D metabolites [14, 15, 88, 108, 141–143]. Some studies have shown that increased urinary calcium excretion promoted nephrocalcinosis in up to 30–70% of individuals with XLH [2, 4, 35, 108, 144, 145]. Nephrocalcinosis was detected more often in children (56%) than in adults (26%) and it was mainly related to hyperphosphaturia due to high doses of Pi supplements [146]. However, a recent analysis reported nephrocalcinosis more often in adults (38%) than in children (22%) previously treated with conventional treatment [145].

Most children and adolescents with XLH who had received conventional treatment develop hypercalcemia, and secondary or tertiary hyperparathyroidism [11, 14, 15, 115, 141, 142]. Secondary hyperparathyroidism was reported in more than 80% of children with XLH [115, 143]. Bosman et al. [35] showed normocalcemic and hypercalcemic hyperparathyroidism in 68.2% and 9.1%, respectively. Tertiary hyperparathyroidism was detected in 4.5% of children and adolescents with XLH [143]. Few children with XLH underwent parathyroidectomy due to tertiary hyperparathyroidism [142].

An abnormal increase in diastolic blood pressure has been reported in more than 90% of children and adolescents with XLH receiving conventional treatment; moreover, left ventricular hypertrophy was diagnosed by electrocardiogram in 23% and by ultrasonography in 54% of children with XLH; however, all children were asymptomatic [71]. Alon et al. [147] showed that hypertension was closely associated with secondary/tertiary hyperparathyroidism in 73% of children with XLH. It remains unclear whether cardiovascular abnormalities in XLH are primary manifestations of the disease or complications arising from conventional treatment.

Recommendations for the follow-up in children and adolescents with XLH receiving conventional treatment according to some guidelines [8, 14, 15, 19, 20, 58, 88, 148–150] and authors' expertise are reported in Table 1.

Statement 8. Serum phosphate concentration is not useful to titrate the dose of conventional treatment.

Statement 9. Serum ALP activity is useful to titrate the dose of conventional treatment.

Statement 10. rhGH therapy may be an option for improving linear growth in children with severe short stature, on a case-by-case basis.

Statement 11. QoL may be a useful framework to assess the clinical efficacy of conventional treatment.

Statement 12. Conventional treatment is associated with a high frequency of adverse effects.

Statement 13. Conventional treatment should be considered only when burosumab cannot be administered.

In adulthood

Before the approval of burosumab for XLH treatment, conventional treatment was usually started at diagnosis and was continued until growth completion. Thereafter, there is no consensus on whether conventional treatment should be continued into adulthood although the practice has often been to maintain treatment particularly in adults who experienced symptoms of osteomalacia [14, 19, 58]. Cessation

Table 1 Recommendations for the follow-up in infants, children, and adolescents with XLH receiving conventional treatment or burosumab

	Timing in infants, children, and adolescents
Clinical assessments	
Clinical and auxological examination[a]	< 5 yrs, 1–3 mo; > 5 yrs, 3–6 mo
Odontostomatological examination	Twice yearly[b] or based on clinical symptoms
Orthopedic examination	Once a yr[c] or based on clinical symptoms
Neurological examination[d]	< 5 yrs, 1–3 mo; prepuberty, 3–6 mo; puberty, 3 mo
ENT examination	> 8 yrs, 1 st evaluation in all children and adolescents even if they are apparently asymptomatic; hearing evaluation if symptoms of hearing difficulties are detected
Reumathological examination	> 5 yrs, based on clinical symptoms; every 12 mo during puberty or based on clinical symptoms
Psycological consultation	> 5 yrs, based on clinical symptoms; every 6–12 mo during puberty and transition or based on clinical symptoms
Musculoskeletal function[e]	If feasible, every 6–12 mo
Biochemical assessments	
Serum concentration of calcium, phosphate, creatinine, ALP (BALP is available), and PTH	CT: every 3–6 mo; more frequent checks if dosage is increased. BT: every 3–4 mo or based on clinical and biochemical pattern
Serum 25OHD and $1,25(OH)_2D$	CT: not needed[f]. BT: every 3–4 mo[g], mainly during the winter mo
Urinary calcium, phosphate, creatinine[h]	CT and BT: every 3–6 mo; more frequent checks if dosage is increased
Imaging assessments	
X-ray of wrists[i], knees[i], standing lower limbs[j]	Every 1–2 yrs or based on clinical signs
X-ray periapical or orthopantomogram	Based on clinical symptoms
Renal ultrasonography	CT: once a yr or every 6 mo if nephrocalcinosis is diagnosed BT: every 1–2 yrs or once a yr if preexisting nephrocalcinosis
Cardiac ultrasonography	If elevated and persistent BP is documented (> 95° percentile)
Brain/spine magnetic resonance imaging	In presence of craniosynostosis or skull shape malformation, headache, neurological symptoms or visual disturbances, or suspected spinal stenosis based on clinical simptoms
Other assessments	

Table 1 (continued)

	Timing in infants, children, and adolescents
QoL	> 5 yrs, every yr[k]
Genetic counseling	During transition to adolescence

Adapted and modified from Refs. [8, 14, 15, 19, 20, 58, 88, 148–150, 177], and authors' expertise

Abbreviations: ALP, alkaline phosphatase; BALP, bone-specific alkaline phosphatase; BP, blood pressure; BT, burosumab treatment; CT, conventional treatment; PTH, parathyroid hormone; QoL, quality of life

[a]Including length/height, weight, body mass index, head circumference with skull shape description (at least up to 5–6 yrs), pubertal stage in children and adolescents, intercondylar and intermalleolar distance, blood pressure; presence of signs of rickets, pain, stiffness, fatigue

[b]After tooth eruption

[c]After initiation of walking

[d]In presence of craniosynostosis, spinal stenosis, Arnold-Chiari type 1 malformation, or occurrence of neurogical symptoms

[e]The most appropriate test/s for children and adolescents is/are not defined

[f]Measurement of serum 25OHD concentration and vitamin D treatment is not indicated in individuals receiving active vitamin D metabolites

[g]Adequate body stores of serum 25OHD (> 20 ng/ml; 50 nmol/L) may facilitate burosumab-mediated $1,25(OH)_2D$ synthesis and to prevent secondary hyperparathyroidism and associated phosphaturia [149]. Some authors suggest to assess serum 25OHD concentration annually [14, 15]. Measurement of serum $1,25(OH)_2D$ concentration is not recommended by some authors [150], whereas others suggest to measure it at least every 12 mo on burosumab treatment [14]

[h]To assess urinary calcium excretion as calcium/creatinine ratio or calcium excretion 24 h in individuals with very low urinary creatinine levels due to low muscle mass [14, 15], and TmP/GFR

[i]To assess rickets severity score and estimation of bone age

[j]To assess and quantify the degree of varism or valgism, and the mechanical axis. In case of orthopedic surgery additional X-rays may be required

[k]Assessed by using age-appropriate and disease-validate scales for children and adolescents. The most appropriate timing is not defined

of conventional treatment at the end of skeletal growth is often related to a high risk of the occurrence of side effects [108, 151].

Conventional treatment is not generally recommended in asymptomatic adults with XLH, unless they develop pseudofractures, even without symptoms [14, 19, 58]. However, bone fractures/pseudofractures, can occur two to ten years after cessation of conventional treatment [152]. When treatment is considered, lower doses of Pi and active vitamin D metabolites are recommended compared to those used in children (Supplemental Table S2).

Bone mineralization and skeletal deformities

Conventional treatment is recommended in symptomatic adults with XLH experiencing musculoskeletal pain, pseudofractures, biochemical evidence of osteomalacia with an increase in BALP activity, dental and periodontal issues, or when orthopaedic or dental surgery are planned [13, 14, 58, 88]. However, conventional treatment does not decrease or prevent the development of osteoarthritis, enthesopathies or hearing loss [14, 58, 69].

Oral health

The extension of conventional treatment for XLH into adulthood may have beneficial for the prevention of dental abscesses [69].

Pregnancy and lactation

Few data are available on the administration of conventional treatment in pregnant and lactating women with XLH. Although the treatment regimen remains undefined, the doses of Pi and active vitamin D metabolites usually suggested in adults with XLH (Supplemental Table S2) may be safe and effective during pregnancy and lactation [12, 14, 19, 58]. Recent guidelines suggested treating pregnant women with XLH in the last trimester [14].

Adverse effects

The clinical benefit of conventional therapy in adults with XLH is limited and poor tolerance and severe complications, such as hyperparathyroidism and nephrocalcinosis, are common [14, 51, 58, 63, 88, 143, 146]. Total or subtotal parathyroidectomy with autografting of parathyroid tissue fragments into the muscle of the forearm is suggested when hyperparathyroidism occurs [92, 143, 153].

Hypertension and left ventricular hypertrophy have been suggested as early cardiovascular complications in adults with XLH, while secondary hyperparathyroidism, renal dysfunction, and nephrocalcinosis, often associated with high doses of conventional treatment, are suspected as major risk factors for the cardiovascular side effects [72, 154]. However, these cardiovascular complications were not confirmed in other studies [72, 74].

Adverse events that may develop during conventional treatment in adults with XLH and suggested changes are summarized in Supplemental Table S3.

Statement 14. Conventional treatment should be considered in symptomatic adults with XLH or who are planning orthopaedic or dental surgery, and during pregnancy/lactation.

Aim 3: Efficacy of burosumab compared with conventional treatment

Burosumab has been developed to reduce the effects of FGF23 excess by binding directly to FGF23. Burosumab inhibits FGF23 signaling, thereby increasing tubular phosphate reabsorption and stimulating intestinal phosphate absorption through increased $1,25(OH)_2D$ synthesis [155]. As a result, serum phosphate concentration and bone mineralization improve. While conventional treatment should be considered primarily as a symptomatic therapy, burosumab directly counteracts the effects of excessive production of FGF23, which is the main pathogenetic known mechanism in individuals with XLH.

Efficacy and safety of burosumab, and comparison with conventional treatment in children and adolescents

Clinical trials, retrospective investigations, and case series demonstrated greater efficacy of burosumab on phosphate retention, skeletal abnormalities, physical function, muscle-bone pain, and QoL in comparison with conventional treatment [89, 138, 156–176] (Supplemental Table S4). Besides, only a randomized controlled clinical trial demonstrated the superiority of burosumab treatment to conventional therapy [157]. Considering the clear benefits reported in clinical trials, burosumab treatment should be considered in all eligible children with XLH [12, 14, 177].

Serum phosphate and TmP/GFR correction, and $1,25(OH)_2D$ production

In children with XLH aged 1–12 years, burosumab has proven to be much more effective than conventional treatment to improve serum phosphate concentration and TmP/GFR [157, 163, 168]. It has been also observed that prior Pi or active vitamin D did not influence treatment response after switching to burosumab among children with XLH and active radiographic rickets [168]. Moreover, serum phosphate concentration and TmP/GFR after 12 months treatment with burosumab did not differ between children and adolescents [167]. The positive effect of burosumab on phosphate metabolism has been demonstrated to persist up to 88 weeks [171] and 160 weeks [160]. Furthermore, it has been demonstrated that burosumab treatment improved serum phosphate concentration and TmP/GFR in adolescents with XLH enrolled near the transition age [138]. All studies showed that serum $1,25(OH)_2D$ concentration improved significantly during burosumab treatment (Supplemental Table S4). These data support long-term efficacy of burosumab in improving phosphate metabolism and $1,25(OH)_2D$ production in children and adolescents with XLH.

Bone mineralization and skeletal deformities

All studies with burosumab demonstrated an improvement of bone mineralization and severity of rickets in children with XLH (Supplemental Table S4). Burosumab was more effective in reducing serum ALP activity and improving signs of rickets than conventional treatment [157, 163, 168].

Few data are available on the effects of burosumab on lower limb deformities in children and adolescents with XLH. Mindler et al. [178] showed that one year of burosumab was associated with persistent maltorsion and frontal axis deviation despite improved rickets; however, some cases demonstrated relatively fast correction by guided growth procedures during burosumab treatment, resembling rates of correction reported in healthy children and compared to literature data [179, 180]. Sawamura et al. [181] found that younger individuals with more severe bone deformities showed significant improvement in lower limb alignment after one-year treatment with burosumab, suggesting that burosumab may delay or avoid the need for surgical intervention. It is conceivable that improvements in rickets severity and lower limb deformities may reduce the need for corrective orthopedic surgery, but this has not yet been systematically assessed. A recent review reported (moderate certainty) that burosumab may prevent lower limb deformity and may improve QoL compared to conventional therapy [16].

Linear growth

The main studies evaluating the effect of burosumab on linear growth are summarized in Supplemental Table S5. In most studies linear growth improved [89, 156, 157, 160, 162–164, 166, 172], while in others it did not change [161, 167, 169, 171, 175] or improved only in some individuals [158]. Two meta-analyses reported inconclusive results revealing high heterogeneity of the effect of burosumab on linear growth [182, 183], whereas a recent review showed (low certainty) that burosumab may increase height and

enhance the burden of symptoms related to chronic hypophosphatemia [16]. Data at final height in children with XLH who had received burosumab from the diagnosis will be crucial for drawing definitive conclusions about its true impact on linear growth.

In children and adolescents with XLH treated with a combination of rhGH and burosumab for 12 months a significant height change was found compared with those receiving burosumab alone [184]. Further and longer studies are required to examine the role of rhGH in addition to burosumab in children with XLH.

Enthesopathic disease

No data are available on the development of enthesopathy in children and adolescents with XLH treated with burosumab.

Bone, joint, muscle pain, and QoL

Few studies examined the effects of burosumab on QoL in children. It has been clearly demonstrated that burosumab reduced stress, bone pain, and fatigue, and improved physical health as well as increasing acceptance by peers and promoting a positive school experience [138, 159, 173, 177]. However, all the benefits of burosumab on phosphate metabolism and QoL were lost after its discontinuation in adolescents with XLH near the transition to adulthood [138, 176]. This may suggest that continuing burosumab after the completion of skeletal growth is required to maintain the clinical benefits during the transition to young adulthood.

Oral health

A variable risk of dental abscesses during burosumab has been reported. Some studies showed a reduced prevalence of dental abscesses in children with XLH treated with burosumab compared with those receiving conventional treatment [185], whereas others reported unchanged [156] or increased prevalence [157] of dental abscesses. Dental abscesses were not found in younger children but were present in 53% of older children [163], and in two out of five adolescents with XLH [158].

In children and adolescents with XLH, the pulp-coronal height ratio decreased, while pulp-coronal width ratio unchanged after 3 years of burosumab [164]. No difference in pulp/tooth ratio and in the width of the pulp chamber was found in children and adolescents with XLH treated with conventional treatment or burosumab [42]. These data suggest that both treatments do not fully restore the hypomineralization of the teeth. Noteworthy, these results were from short controlled trials or studies involving a small number of subjects.

Adverse events

Clinical trials with burosumab in children and adolescents with XLH did not report any short-term serious adverse event leading to the discontinuation of treatment. The most common adverse events were a transient reaction at the injection site (50–57%), headache (54%), pain in the extremities (10–42%), and reduction of serum 25OHD concentration (28%) [89, 148, 156, 157, 160, 161].

A post-authorization safety 10-year retrospective and prospective cohort study in 67 children and adolescents with XLH using data embedded within the International XLH Registry [186] and a systematic review [182] confirmed the efficacy and safety of burosumab.

Palojan et al. [162] described a child with XLH previously treated with conventional treatment who developed nephrocalcinosis on burosumab therapy. Olivotto et al. [172] found a complete resolution of nephrocalcinosis after one year of burosumab in one child and an improvement in another. Two systematic reviews and meta-analyses did not find changes in nephrocalcinosis score in the burosumab arm [182, 183]. Furthermore, switching from conventional treatment to burosumab may have the potential to prevent nephrocalcinosis reducing urine calcium excretion and improving tubular phosphate reabsorption [175, 187].

Zhukouskaya et al. [188] showed that about 10% of individuals with XLH developed secondary hyperparathyroidism after three years of burosumab treatment; they were the older in the case series and had significantly higher PTH concentrations at baseline; no case of tertiary hyperparathyroidism occurred. Recently, Padidela et al. [189] reported the occurrence of tertiary hyperparathyroidism after 3–4 years of burosumab in two females with XLH, that required parathyroidectomy. Higher post-dose phosphate levels or a direct effect of *PHEX* mutation on the parathyroid gland could have triggered PTH secretion.

A multicentric study showed that adolescents with XLH treated with burosumab had an increased BMI and lower systolic blood pressure than those receiving conventional treatment [46], but these results were not confirmed in other studies [172, 173]. A normal cardiac function was shown during burosumab treatment [172, 190, 191]. Simpson et al. [47] found lower serum insulin concentration in 2–10-year-old children with XLH treated with burosumab than in controls, but its pathogenetic role is unknown.

In summary, burosumab shows a good safety profile and good compliance in children and adolescents with XLH. Hypercalcemia, hypercalciuria, and nephrocalcinosis, may be less with burosumab than with conventional therapy, while the occurrence of secondary/tertiary hyperparathyroidism during burosumab needed further evaluation.

Statement 15. Recommendations for the follow-up of children and adolescents with XLH receiving conventional treatment or burosumab are reported in Table 1.

Statement 16. Recommendations and suggestions for the management of burosumab treatment in children and adolescents with XLH are summarized in Table 2.

Efficacy and safety of burosumab and comparison with conventional treatment in adults

Burosumab showed a good safety profile and efficacy in adults with XLH raising serum phosphate concentration into the lower normal range and increasing serum $1,25(OH)_2D$ concentration; moreover, burosumab reduced stiffness, pain and fatigue, and improved physical function [14, 192, 193]. Nevertheless, a recent systematic review reported that burosumab had little or no benefit in improving worst pain based on direct measurements using the BPI-SF scale (moderate certainty), but it showed an improvement in fracture and pseudofracture healing in adults with XLH compared with no treatment [194]. Some evidence demonstrated that the benefits of burosumab were lost when treatment was interrupted and recovered over time when treatment was resumed [193].

Mineral and bone metabolic parameters

During burosumab treatment, in 94.1% of the adults with XLH serum phosphate concentration normalized against 7.6% in the placebo group; increased TmP/GFR was evident only in subjects receiving burosumab [195, 196]. These results were confirmed by other studies [154, 182, 192, 197–200]. Similarly, serum $1,25(OH)_2D$ concentration increased in adults with XLH treated with burosumab, while no changes were detected in those receiving placebo or previously treated with conventional treatment [182, 195–203].

Serum PTH concentration decreased during burosumab treatment and increased in the group of individuals receiving conventional treatment [196]. No variation of serum PTH concentration during burosumab was found by other studies [183, 197, 198, 201–203].

Serum BALP activity increased during the first weeks of burosumab treatment compared with baseline [199, 203] or placebo [196] reflecting the activation of skeletal remodeling; subsequently, serum BALP activity progressively declined [193, 199, 203]. A meta-analysis on serum BALP activity did not show any change before and after burosumab treatment [183], while a progressive decline was found by Arcidiacono et al. [200]. Serum concentration of C-terminal telopeptide and procollagen type 1 N-terminal propeptide had a similar pattern of serum BALP activity in adults with XLH reflecting an increased bone turnover [195, 196, 199, 200, 202].

Osteomalacia

Burosumab treatment was associated with improvements in histomorphometric parameters of osteomalacia in adults with XLH by 48 weeks compared to baseline [202].

Enthesopathies and osteoarthritis

Currently, there is no evidence that burosumab treatment ameliorates enthesopathies and osteoarthritis. When initiated in adulthood, burosumab is unlikely to reverse established osteoarthritis; nevertheless, starting treatment before osteoarthritis could prevent joint degeneration [58]. Similarly, burosumab could prevent the development of enthesopathies and/or spinal stenosis if these are not present yet, or in an early stage of development [58]. Michigami et al. [174] described four new cases of ectopic calcifications in individuals with XLH after 6 months of burosumab treatment; however, at baseline a higher proportion of XLH adults with ectopic calcifications was present in the burosumab-treated group (64%) than in the non-burosumab group (26.7%), representing a possible bias.

Bone, joint, muscle pain, and QoL

Several studies on QoL in adults with XLH treated with burosumab have shown an improvement of clinical symptoms and physical function, pain, stiffness, fatigue, mobility, and muscle strength [68, 154, 192, 193, 196, 198, 200, 203–206].

Fracture/pseudofracture healing

Randomized, double-blind, and placebo-controlled trials demonstrated that burosumab treatment for 24 weeks was associated with full healing of nearly half of the fractures identified at baseline in adults with XLH; the odds of healing a fracture for the participants treated with burosumab was 16.8-fold greater than for those receiving placebo [195, 202]. By week 48, 63.1% of baseline fractures/pseudofractures healed fully with burosumab, compared with 35.2% with burosumab after placebo [202]. A recent pharmacodynamic exposure–response analysis showed a relationship between burosumab treatment and a reduction in fracture counts in adults with XLH suggesting that the degree of serum phosphate increase during burosumab was important in reducing the rate of new fractures [207].

Table 2 Main recommendations and suggestions for the management of burosumab treatment in individuals with XLH

Recommendations	Children and adolescents (> 1 yr)[a]	Adults
Before burosumab administration	Conventional treatment must be stopped at least 1 wk before to start burosumab treatment	
Burosumab treatment option	• It should be considered, if approved and appropriate, as the first-line option of treatment, mainly if profound rickets is evident (RSS ≥2) or if it is present an insufficient skeletal response[b] or significant side effects to conventional treatment	• It should be considered, if approved an appropriate, as a second-line treatment in individuals with insufficient response[c] or intolerant to conventional treatment
Burosumab starting dose[d]	• 0.8 mg/kg per 14 days, s.c.; dose should be rounded to the nearest 10 mg	• 1.0 mg/kg every 28 days, s.c.; dose should be rounded to the nearest 10 mg up to a maximum dose of 90 mg
Burosumab titration dose	• After initiation of burosumab, fasting serum P concentration should be measured every 2 wk for the first mo of treatment; every 4 wk for the following 2 mo and thereafter as appropriate • Fasting serum P concentration should also be measured 2 wk after any dose adjustment. If fasting serum P concentration is within the reference range for age the same dose should be maintained • Serum P concentration peak is achieved after 7–11 days after burosumab injection • After achieving a steady state of serum P concentration, which can be assumed after 3–4 mo on a stable dosage, fasting serum P concentration should be measured preferentially directly before injections to detect underdosing	• After initiation of burosumab, fasting serum P concentration should be measured every 2 wk for the first mo of treatment; every 4 wk for the following 2 mo and thereafter as appropriate • Serum P concentration peak is achieved after 7–11 days after burosumab injection
Burosumab dose adjustment	• If fasting serum P concentration is below the reference range for age the dose may be increased stepwise by 0.4 mg/kg. Maximum dose 2 mg/kg per 14 days. The maximum dose is 90 mg • If fasting serum P concentration is above the reference range for age the next dose should be withheld, and fasting serum P concentration reassessed within 2 wk • Fasting serum P concentration must be below the reference range for age to restart burosumab at half of the previous dose, rounding the amount to the nearest 10 mg	• If fasting serum P concentration is above the reference range for age the next dose should be withheld, and fasting serum Pi concentration reassessed within 2 wk. Burosumab can be restarted at approximately half the previous dose when serum P concentration is below the normal range
Fasting serum P concentration target	To decrease the risk for ectopic mineralization fasting serum P concentration should be targeted in the lower end of the normal reference range for age	
Biochemical parameters to monitor the efficacy of burosumab	• Serum P concentration should be maintained around the age- and sex-specific lower limit of normal • Serum P concentration below the age- and sex-specific lower limit of normal may be acceptable if there is a sustained decrease in serum ALP activity, improvement of rickets, and the subject is responding clinically	• Serum P concentration should be maintained around the lower limit of normal • Serum P concentration below the age- and sex-specific lower limit of normal may be acceptable if there is a sustained decrease in bone pain and serum ALP activity, and there is a reduction in analgesic use from baseline
Criteria for a satisfactory response to burosumab[e]	• Within 6 mo: significant improvement of serum P concentration and TmP/GFR (low-normal range for age should be considered an adequate target), reduction in serum ALP activity, bone pain[f], and RSS; within 24 mo: progressive improvement of leg deformities in growing children, serum ALP activity in the age-related normal range, and normal growth velocity (> 25 th percentile for age and sex)	Within 6 mo: significant improvement of serum P concentration and TmP/GFR (low-normal range should be considered an adequate target), and musculoskeletal pain; within 12 months: improvement of musculoskeletal pain, stiffness, signs of osteomalacia including radiological lesions (e.g. pseudofractures), and total or bone specific serum ALP activity
Burosumab duration of treatment	• Children who have started burosumab should continue treatment throughout adolescence until the closure of the growth plate	• Review the efficacy of burosumab annually within a multidisciplinary team and consider continuing the treatment if average pain is improved and there is a reduction in analgesic use from baseline. Otherwise burosumab should be discontinued
Contraindications	• Association with conventional treatment or calcimimetic drugs, severe renal impairment, pregnancy[g], lactation[g], sexually active adolescents/women without adequate contraception, hypersensitivity, occurrence of severe adverse reactions	
Suggestions		

Table 2 (continued)

Recommendations	Children and adolescents (> 1 yr)[a]	Adults
Vitamin D status	• Serum 25OHD concentration should be maintained ≥20 ng/mL	• Vitamin D supplements in case of vitamin D deficiency
Calcium intake	• Adequate dietary calcium intake is required to allow the rickets healing[h] • Calcium supplements should never be associated with Pi supplements	• Adequate dietary calcium intake is required to allow bone health
Burosumab continuity in transition	Continued and uninterrupted treatment may be indicated to sustain the clinical benefits achieved in adolescence: 1.0 mg/kg every 28 days, s.c.; dose should be rounded to the nearest 10 mg	

Abbreviations ALP, alkaline phosphatase; BALP: bone isoenzyme of alkaline phosphatase; 25OHD, 25-hydroxyvitamin D; P, phosphate; RSS, rickets severity score

[a]In USA burosumab treatment may be initiated at 0.8 mg/kg per 14 days in infants older than 6 mo and weighed > 10 kg and at 1 mg/kg per 14 days in infants weighed < 10 kg. Maximum dose is 2 mg/kg per 14 days or 90 mg per 14 days. Burosumab doses should be rounded to the nearest 10 mg in infants weighed > 10 kg and to the nearest 1 mg in infants weighed < 10 kg

[b]defined as the lack of achievement of significant improvement of rickets activity, including bone pain, and serum ALP activity within 12 mo, and significant improvement of leg deformities and normal growth velocity (> 25 th percentile for age and sex) within 24 mo of conventional treatment [14]

[c]defined as the lack of achievement of significant improvement of musculoskeletal pain, stiffness, signs of osteomalacia including radiological lesions (e.g. pseudofractures) and normalization of total serum ALP or BALP activity, if elevated, within 24 mo of conventional treatment [14]

[d]Vials of 10, 20, 30 mg/mL solution. The maximum volume per injection site is 1.5 mL. When more than 1.5 mL is required on a given dosing day, the total volume must be split and administered at two or more different injection sites. Injection sites should be rotated and carefully monitored for signs of potential reactions

[e]Criteria suggested by Haffner et al. [14] and authors' expertise. However, the improvement of leg deformities in some growing children may be delayed and growth velocity may be subnormal although the improvement of serum P concentration, TmP/GFR values, and serum ALP activity are satisfactory. Continuation of burosumab treatment is recommended in these individuals, by authors' expertise

[f]It may be difficult to quantify in the first 2–3 yrs of life

[g]Burosumab should be discontinued when pregnancy is planned or identified, and conventional treatment is recommended. Contraception is recommended in women of childbearing potential receiving burosumab. Burosumab is not indicated during breast-feeding as no safety data are available; conventional treatment does not represent a contraindication during breast-feeding [14]

[h]Suggested by Kamenicky et al. [13], and Haffner et al. [14]

Oral health

Few data on the oral health effects of burosumab in adults with XLH are available. A significant reduction in dental infections during burosumab treatment periods compared with those without treatment or with conventional treatment has been reported [70]. However, a recent systematic review documented, with low certainty, that burosumab may increase dental abscess risk [194].

Adverse events

A long-term study with burosumab up to 96 weeks showed that body weight did not change by more than 20% from the baseline assessment [193. Burosumab treatment was not associated with hyperparathyroidism or the development or progression of renal or cardiac ectopic mineralization [195, 197, 199, 202]. Furthermore, some data suggested that there was an indication (low certainty) of a reduced likelihood of parathyroidectomy among adults with XLH receiving burosumab [194]. Nephrocalcinosis scores did not change from baseline by more than one grade up to 48 weeks of treatment [151]. Restless legs syndrome was more frequently observed in the treated group (11.8%) than in the placebo group (7.6%) [195].

Statement 17. Recommendations and suggestions for the management of burosumab treatment in adults with XLH are summarized in Table 2.

Statement 18. Recommendations for the follow-up of adults with XLH receiving conventional treatment or burosumab are reported in Table 3

Aim 4: Multidisciplinary approach and management of individuals with XLH

XLH is a progressive and multisystemic bone disorder that requires the evaluation by several specialists throughout a individual's life. Clinical signs and symptoms vary according to age and some complications, including those related to chronic conventional treatment, develop from childhood and adolescence become more evident in adults. Management of individuals with XLH involves several assessments by a multidisciplinary team, including endocrinologists,

Table 3 Recommendations for the follow-up in adults with XLH receiving conventional treatment or burosumab

	Timing in adults
Clinical assessments	
Clinical examination[a]	Every 6–12 mo
Odontostomatological examination	Twice yearly
Orthopedic examination	Once a yr[b]
Neurological examination[c]	Every 6–12 mo or based on clinical symptoms
ENT examination	Hearing assessment if symptoms of hearing difficulties are detected
Reumathological examination	Once a yr or based on clinical symptoms
Psycological consultation	Based on clinical symptoms[d]
Musculoskeletal function	Once a yr
Biochemical assessments	
Serum concentration of calcium, phosphate, creatinine, BALP, and PTH	CT: every 3–6 mo; more frequent checks if dosage is increased. BT: every 3–4 mo or based on clinical and biochemical pattern
Serum 25OHD and $1,25(OH)_2D$	CT: not needed[e]. BT: every 3–4 mo[f], mainly during the winter mo
Urinary calcium, phosphate, creatinine[g]	CT and BT: every 3–6 mo; more frequent checks if dosage is increased
Imaging assessments	
X-ray of pelvis, knees, standing lower limbs or other skeletal sites[h]	Based on clinical symptoms
X-ray periapical or orthopantomogram	Based on clinical symptoms
Renal ultrasonography	CT: once a yr or every 6 mo if nephrocalcinosis is diagnosed. BT: every 1–2 yrs or once a yr if preexisting nephrocalcinosis
Cardiac ultrasonography	If elevated and persistent BP is documented (> 95° percentile)
Brain/spine magnetic resonance imaging	In presence of craniosynostosis or skull shape malformation, headache, neurological symptoms or visual disturbances, or suspected spinal stenosis based on clinical simptoms
Other assessments	
QoL	Every 2 yrs
Genetic counseling	In women planning pregnancy or are pregnant along with opinion their partners, and for women planning pregnancy or are pregnant with their XLH partners

Adapted and modified from Refs. [14, 19, 58, 88], and authors' expertise

Abbreviations BALP, bone-specific alkaline phosphatase; BP, blood pressure; BT, burosumab treatment; CT, conventional treatment; PTH, parathyroid hormone; QoL, quality of life

[a]Including height, weight, body mass index, intercondylar and intermalleolar distance, blood pressure; presence of bone deformities, pain, stiffness, fatigue

[b]If symptomatic

[c]In presence of craniosynostosis, spinal stenosis, Arnold-Chiari type 1 malformation, or occurrence of neurogical symptoms

[d]Psychiatric consultation should be required based on symptoms

[e]Measurement of serum 25OHD concentration and vitamin D treatment is not indicated in individuals receiving active vitamin D metabolites

[f]Measurement of serum 25OHD concentration is recommended yearly by some authors [14]. Measurement of serum $1,25(OH)_2D$ concentration is not recommended by some authors [150], whereas others suggest to measure it at least every 12 mo on burosumab treatment [14]

[g]To assess urinary calcium excretion 24 h or in individuals with very low urinary creatinine levels due to low muscle mass [14], and TmP/GFR

[h]To assess the development, extension, and severity of bone deformities, enthesopathies, osteoarthritis, or pseudofractures. The skeletal sites should be examined according to clinical symptoms

nephrologists, orthopedic surgeons, neurologists, odontostomatologists, rehabilitation physicians, physical therapists, and others. The timing and type of evaluation vary according to age and regiment of treatment (Tables 1 and 3).

Some studies indicated that telemedicine became an integral component of the management of individuals with XLH, particularly in those who live far from the referral center [208–210]. Physicians may communicate with individuals with XLH or their caregivers by e-mail, phone calls, or social media. Some clinical parameters, including anthropometric data, PROs assessment, and the occurrence of adverse events, require remote monitoring by photographs and videos. Albeit with some limitations, telemedicine and other digital technologies may have a role in treating the individuals with XLH when hospital admissions are restricted [12].

Statement 19. XLH requires a regular multidisciplinary approach coordinated by a metabolic bone disease specialist.

Aim 5: Consensus statements for transition from pediatric to adult care in individuals with XLH

The transition period usually allows the adolescent with a chronic or a rare disease to gradually assume the responsibilities as an adult. Transition from the pediatric to adult care includes adapting to a different care context and leaves familiar pediatric care teams. To enable the adolescent to successfully complete this process the transition should be carefully planned and implemented in steps [209–212]. Three main areas of competency have been well defined for transition of individuals with XLH: (1) person foundational knowledge of their disease and the healthcare process; (2) accurate information for transitioning from pediatric to adult care, including scheduled timelines; (3) supportive behaviors that promote active engagement [209, 211]. Moreover, the effective transition from pediatric to adult care needs the attainment of 3 critical items: (1) start the transition early; (2) close collaboration between the pediatric team leader and adult-centered providers; (3) introduce the individual with XLH. Details for each item are reported in Table 4. Giannini et al. [28] emphasized that the transition to adult care is a shared responsibility between the pediatric and adult healthcare teams because XLH involves lifelong multi-organ morbidities changing with age.

Table 4 Suggestions for approaching the transition from pediatric to adult care in individuals with XLH

Start the transition early
• Develop self-management skills
• Establish partnership among sick individuals, family, and health providers
• Sick individual and parents/caregivers may require psychologic supports and resources
• Multidisciplinary approach involving sick individual, and his/her family is required
Collaboration between pediatric"team leader"and adult-centered providers
• Planning the preparation and discuss the optimal time of transition case-by-case
• Prepare transition passport including all the medical data, including genetic counseling
• Continue collaborations between pediatric"team leader"and adult-centered providers also after the transition
• Patients'associations should be involved actively in the transition care pathway
Introduce the individual with XLH
• Schedule meetings between pediatric"team leader"and adults services according to the individual with XLH
• Let the individual with XLH speak according to her/his needs and put her/him at easy
• Ensure that adult specialists understand the medical history, treatment regimens, and complications that have occurred over the years of caring for the patient
• Reassure the individual with XLH and parents/caregivers that continuity of care will be guaranteed

Adapted and modified from Refs. [209–212], and authors' expertise

The pathway for transition requires some tools to assess person knowledge of his/her disease by using questionnaires and individualized training provided by an experienced pediatrician. The transfer to adult care can be organized via a specific care coordinator. More details on the transition pathway from pediatric to adult care have been reported [12, 28, 51, 209, 210, 212].

The cut-off age for transition of care in persons with XLH has a wide range (14–26 years) across countries [12, 15, 209, 210, 212]. In Italy, transition of care usually occurs after 18 years. Some factors may influence the timing of transition of care in various countries, including the will of individual and parents/caregivers, culturally accepted age when adolescent assert their independence from their parents/caregivers, health care setting, and the availability of well-defined pathways for care. Transition readiness tracking can begin when adolescents with XLH are approximately age 12 years, and the timing introducing transition of care should begin some years (2–4 years) before the transition process happens [12, 209, 210, 212]. However, timelines for introducing transition should be individualized according to the individual's readiness for transition of care.

Statement 20. A tailored pathway for transition of adolescents with XLH should be prepared to facilitate the effective transfer from pediatric- to adult-focused health care.

Statement 21. A multidisciplinary team including parents and caregivers should support adolescents with XLH during the transition from pediatric to adult care.

Role of associations of individuals with XLH during the transition from pediatric to adult care

Associations of people with XLH, such as the XLH Network in the US (https://xlhnetwork.org/) and XLHuk in the UK (https://xlhuk.org/), can play a pivotal role in supporting individuals throughout the transition process. They collaborate with both family and medical team to ensure continuous care and guidance. Moreover, the International XLH Alliance established to amplify the voices of individuals with XLH and set a global multidisciplinary standard of care and research published a poster with twelve recommendations including the transitional care (https://xlhalliance.org/wp-content/uploads/2021/10/XLH_Infographic_Poster_A4.pdf) and a very extensive and detailed toolkit to approach the transition in individuals with XLH (https://xlhnetwork.org

/wp-content/uploads/2023/04/XLH_TRANSITIONS_TOOLKIT.pdf).

The Italian Association Supporting Hereditary Metabolic Diseases (AISMME, https://www.aismme.org/), a member of XLHalliance.org, provided a free of charge psychological support project (online and/or in person) for parents/caregivers and individuals with XLH (Aurora Project, https://www.aismme.org/images/progetti/progetto-aurora+xlh/ProgettoAurora+XLH.pdf).

Statement 22. XLH associations should support adolescents with XLH during the transition from pediatric to adult care.

Treatment of individuals with XLH during transition

The evidence of osteomalacia by bone histomorphometry in asymptomatic individuals with XLH, aged 16–47 years, who stopped the treatment for at least 5 years, confirmed the persistence of skeletal disease after epiphyseal closure [66, 104]. Furthermore, it cannot be excluded that asymptomatic adolescents become symptomatic individuals during transition upon discontinuation of conventional treatment. Since XLH continues throughout life, it is conceivable to continue the therapy during the transition from adolescence to adulthood, without discontinuation, to prevent osteomalacia and the associated pseudofractures, bone pain, and dental and periodontal lesions [14, 15, 69, 149, 150].

Conventional treatment

As suggested in adults, conventional treatment is not usually recommended in asymptomatic individuals with XLH during transition. Nevertheless, a regular clinical and biochemical follow-up is recommended after discontinuation of conventional treatment as some individuals with XLH may become symptomatic or develop complications in young adulthood.

Guidelines for using conventional treatment during the transition from pediatric to adult care in individuals with XLH are very scant. There is a trend to continue the conventional treatment in adolescents approaching transition, particularly in those who show active symptoms or when orthopedic surgery is needed [14, 88]. When orthopedic surgery is programmed and conventional treatment has been ceased, the treatment should be restarted at least 3–6 months before the surgery and should be continued for 6–9 months afterwards [88]. The duration of treatment should be prolonged according to clinical signs and symptoms. Suggested criteria for continuation or cessation of conventional treatment in individuals with XLH during transition are reported in Table 5. In asymptomatic individuals with XLH becoming symptomatic or displaying one of the suggested criteria for therapy continuation, conventional treatment should be restarted.

Table 5 Suggested criteria for continuation of conventional treatment in individuals with XLH during transition from adolescence to adulthood care

Treatment should be continued[a]	Treatment cessation
• Moderate-severe cases	• Mild cases
• Symptomatic	• Asymptomatic
• Active and recurrent dental and/or periodontal lesions	• No dental and/or periodontal lesions
• Orthopedic surgery needed	• Orthopedic surgery not needed
• Persistence of increased serum ALP or BALP activity	• Normal serum ALP or BALP activity
• Severe reduction of QoL	• Normal or mild reduction of QoL

Abbreviations: ALP, alkaline phosphatase; BALP, bone-specific alkaline phosphatase; QoL, quality of life

[a]Conventional treatment is not recommended in individuals showing persistent or worsening secondary hyperparathyroidism, tertiary hyperparathyroidism, impaired renal function, nephrocalcinosis, or poor tolerance of Pi supplements. In poor responders to conventional treatment (based on clinical and biochemical features) the administration of burosumab should be taken into consideration

When conventional treatment is continued during transition, the dose of Pi and active vitamin D metabolites should be significantly decreased to reduce the risk of exacerbating preexisting secondary hyperparathyroidism or triggering its onset. Although there are no detailed indications on the dosage of conventional treatment after the epiphyseal closure and during the transition, based on experts' clinical experience, a reduction of approximately 40–50% of the dose of Pi and active vitamin D metabolites over a period of 1 to 3 years is suggested. A further 20–30% reduction of both calcitriol or alfacalcidol and Pi may be needed according to the individual tolerance, biochemical data, and kidney ultrasonography till the dose usually administered in adults with XLH (Supplemental Table S2).

Statement 23. Conventional treatment should be continued during the transition in symptomatic individuals with XLH.

Statement 24. The dosage of conventional treatment should be gradually reduced during the transition.

Burosumab treatment

There are few data on the effects and dosing regimens of burosumab in individuals with XLH transitioning from pediatric to adult care. No randomized controlled trial has compared the effects of burosumab against the conventional therapy during transition. In adolescents with XLH approaching the transition, who had previously received

conventional treatment with poor benefits, a positive effect of burosumab on bone lesions, phosphate metabolism, serum ALP activity, serum $1,25(OH)_2D$ concentration, and PROs has been shown [138]. The evidence that all the benefits acquired during burosumab were lost after the interruption of treatment suggested that burosumab should be continued during the transition.

It is opinion of the experts' panel that adolescents with severe XLH who have received conventional treatment with poor benefits and/or showing persistence of increased serum ALP activity, active dental and periodontal lesions, reduced QoL, or poor tolerance of Pi, should start burosumab during transition. Furthermore, burosumab may be an option if conventional treatment is contraindicated, as in individuals with persistent or worsening secondary hyperparathyroidism, tertiary hyperparathyroidism, or nephrocalcinosis.

Two recent international consensus suggested to continue burosumab treatment for at least several years following epiphyseal closure to optimize peak bone mass [14, 15], although no data are available to confirm this proposal.

During transition, the optimal dose and timing for conversion from Q2 W to Q4 W dosing of burosumab remains to be defined. The attainment of final height or the complete ossification of growth plates may be main criteria for switching from pediatrics to adult regimen of treatment [149, 150, 160]. Nevertheless, it has been suggested that may be reasonable to consider transitioning to monthly dosing within 1–2 years following fusion of the growth plates [15]. Further studies are needed to establish the best regimen of treatment with burosumab during transition.

Statement 25. Burosumab treatment should be continued without interruption during transition.

Statement 26. The dosage of burosumab should be switched to the dose indicated in adults with XLH during transition.

Statement 27. In individuals with XLH who did not respond to conventional treatment during the transition, or conventional treatment is contraindicated, burosumab should be recommended.

Access and reimbursement criteria to burosumab treatment

Regulatory and reimbursement restrictions for burosumab treatment in individuals with XLH vary in European countries. Criteria for burosumab treatment in children, adolescents, and adults are related to disease severity or inadequate response or complications to conventional treatment [51]. In some countries, all children above 1 year with a confirmed diagnosis of XLH, radiographic evidence of bone disease and a growing skeleton are eligible for burosumab as first-line treatment [149]. However, in many European countries, burosumab is discontinued once longitudinal growth ceases because of a gap between regulatory approval and reimbursement of therapy [149].

In the US, the Food and Drug Administration has approved burosumab for treatment of children with XLH aging 6 months and older as well as adults [148]. In Japan, burosumab has been approved for treatment of all FGF23-related hypophosphatemic rickets and osteomalacia [170]. In many European countries, burosumab is licensed for adults, but it is not reimbursed [51]. These discrepancies among countries highlight an inequality among European citizens, advocating action for equal access to care.

In Italy, reimbursement for burosumab by the Italian Medicine Agency (AIFA, Agenzia Italiana del Farmaco) ceases upon the complete ossification of growth plate. Therefore, most of benefits acquired with burosumab treatment during childhood and adolescence were lost in the transition period [138]. The main criterion indicated by AIFA for reimbursment of burosumab after the complete ossification of growth plate and in adults with XLH is the evidence of an active fracture/pseudofracture occurring in individuals previously treated with conventional therapy (https://www.aifa.gov.it/documents/20142/847786/Determina CRYSVITA_GUn.71_24-3–2023.pdf). However, it should be considered that the occurrence of active fractures/pseudofractures is a very rare event in children and adolescents (see Section"Clinical diagnosis in infants, children, and adolescents") and may occur in less than half of the osteomalacic adults with XLH (see Section"Clinical diagnosis in adults"). As a result, almost all the young individuals with XLH during the transition, as well as most of adults with XLH, are unable to continue or to start burosumab treatment due to the lack of fracture/pseudofractures. Furthermore, in adults with XLH, reimbursement of burosumab ends at the age of 65. Although no data are currently available on the treatment of adults with XLH beyond this age, those who have shown benefits from burosumab therapy are likely to experience further benefits, such as prevention of osteomalacia and the related risk of fractures/pseudofractures, and improved muscle and joint pain and QoL, by continuing burosumab beyond the age of 65. Therefore, the experts' panel believes that the reimbursement criteria for burosumab should be revised to ensure that the benefits gained from burosumab treatment during childhood and adolescence or prior to age 65, are not lost.

Conclusions

XLH is a rare, multisystemic, and progressive skeletal disorder that may be very disabling and significantly impacting the QoL throughout the lifespan. Hypophosphatemia persists lifelong.

The clinical phenotype of XLH varies among children, adolescents, and adults. When not effectively managed in childhood, deformities at lower limbs can worsen in adulthood. Adults with XLH are at risk of further complications, including osteomalacia, fractures/pseudofractures, enthesopathies, osteoarthritis, spinal stenosis, hearing loss, and complications related to the conventional treatment, such as hyperparathyroidism and nephrocalcinosis.

In children, burosumab leads to greater improvement in phosphate metabolism, rickets and linear growth than conventional treatment. Therefore, burosumab should be considered as first-line treatment in children and adolescents with XLH, and it should be continued during transition.

In adults, burosumab is generally considered as a second-line therapy according to current guidelines. Burosumab treatment should be offered to individuals with fractures/pseudofractures, severe osteomalacic disease, severely reduced mobility, and poor dental status, who did not respond or experiencing severe adverse events to conventional treatment. However, in some countries commercial arrangements and reimbursement of burosumab in adults with XLH are restricted by specific criteria, which should be re-evaluated in light of the cost/benefit ratio.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40618-025-02611-7.

Acknowledgements This work is generated within the European Reference Networks for Rare Bone Diseases (BOND-ERN), Rare Endocrine Conditions (ENDO-ERN), and Rare Kidney Diseases (ERKNET). C.P. and G.S. are Representatives of BOND-ERN; B.G.I., D.I.N., and D.F. are BOND-ERN members. B.M.L., D.I.N., G.A., M.S., P.M., P.M., R.V., R.R.M., and S.S. are ENDO-ERN members. E.F. and R.B. are ERKNET members.

Funding This manuscript has been supported by Italian Ministry of Health - Ricerca Corrente.

Declarations

Conflict of interest All Authors have no conflict of interest to declare.

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