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Mini-Review

Systematic Review: Efficacy of Medical Therapy on Outcomes Important to Pediatric Patients With X-Linked Hypophosphatemia

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Abstract

Objective: To examine the evidence addressing the management of X-linked hypophosphatemia (XLH) in children to inform treatment recommendations.

Methods: We searched Embase, MEDLINE, Web of Science, and Cochrane Central up to May 2023. Eligible studies included randomized controlled trials (RCTs) and observational studies of individuals younger than 18 years with clinically or genetically confirmed XLH. Manuscripts comparing burosumab to either no treatment or conventional therapy (phosphate and active vitamin D) or evaluating conventional therapy to no treatment were included. Two reviewers independently determined eligibility, extracted data, and assessed risk of bias (RoB). GRADE methodology was used to assess evidence certainty.

Results: We screened 4114 records and assessed 254 full texts. One RCT and one post hoc study proved eligible when comparing burosumab to conventional therapy or no treatment. The open-label RCT was at high RoB, with certainty of evidence ranging from moderate to very low. Burosumab, compared to conventional therapy, probably prevents lower limb deformity and improves physical health quality of life (QoL) (moderate certainty). Burosumab may increase height and enhance the burden of symptoms related to chronic hypophosphatemia (low certainty). Burosumab probably increases treatment-emergent adverse events (moderate certainty) and may increase dental abscesses (low certainty). One observational study assessing conventional therapy vs no treatment was at high RoB, providing very low certainty evidence regarding the impact of conventional therapy on final height.

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Conclusion: Our review indicates that burosumab likely provides benefits to children by preventing lower limb deformity and improving physical health QoL while potentially increasing height. However, burosumab may also increase adverse events. Our review found limited evidence regarding the impact of conventional therapy compared to no treatment on final height. Further research is required to understand the long-term effect of medical therapy in children.

Key Words: pediatric XLH, children XLH, efficacy, burosumab, conventional therapy, patient-important outcomes

Abbreviations: 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; 6MWT, 6-minute walking test; ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23; GFR, glomerular filtration rate; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; MD, mean difference; MID, minimal important difference; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; QoL, quality of life; RCT, randomized controlled trial; RoB, risk of bias; SR, systematic review; TmP/GFR, tubular maximum reabsorption of phosphate to glomerular filtration rate; XLH, X-linked hypophosphatemia.

X-linked hypophosphatemia (XLH, OMIM 307800) is a rare genetic disorder caused by inactivating variants in the phosphate regulating gene with homology to endopeptidases (*PHEX)* gene. *PHEX* encodes a metalloprotease that cleaves small peptides and is involved in fibroblast growth factor 23 (FGF23) regulation by an unknown mechanism. Consequently, FGF23 levels are elevated in patients with XLH, which impairs proximal renal phosphate reabsorption and reduces 1-α–hydroxylation of 25-hydroxyvitamin D (25(OH)D) to 1,25 dihydroxy vitamin D ($1,25(OH)_2D$), the latter of which normally stimulates phosphate absorption in the gut by upregulating the expression of the sodium-phosphate cotransporter (NaPi-IIb) in the brush border membrane of enterocytes. The combined renal phosphate wasting and decreased gastrointestinal absorption of phosphate in XLH ultimately lead to hypophosphatemia (1). The recorded prevalence of XLH in children based on a population-based cohort from the United Kingdom is estimated to be 15.1 per million (95% CI, 11.3-20.1) (2). Children present with lower limb deformities, rickets, impaired mineralization of the bones and teeth, and other clinical features. Early diagnosis and management may optimize growth, prevent bone deformities, and improve outcomes such as quality of life (QoL). Despite the lack of studies describing the natural history of the disease and long-term consequences, the burden of disease observed in the adult XLH patient population suggests that late diagnosis and delayed treatment are associated with adverse outcomes (3, 4). Conventional therapy consisted of phosphate salts and active vitamin D replacement, whereas more recent advances in treatment include a fully human monoclonal antibody to FGF23 (burosumab). This review comprises 2 systematic reviews (SRs). The first review aims to assess the relative impact of burosumab in children with XLH compared to conventional therapy or no treatment on various patient-important outcomes; these include: (i) musculoskeletal pain; (ii) mobility; (iii) QoL (encompassing mental, physical and social aspects); (iv) fatigue; (v) symptomatic fractures; (vi) fracture healing; (vii) dental manifestations, such as abscesses and maxillofacial cellulitis; (viii) skeletal deformities, such as genu varum and genu valgum in lower limbs and skull deformities; (ix) parathyroidectomy; (x) corrective surgeries including osteotomy, guided growth surgery and cranial vault surgery; (xi) auditory manifestations including hearing loss or tinnitus; and (xii) final height. The second SR aims to evaluate the impact of conventional therapy compared to no treatment on those same outcomes.

Methodology

The protocols of these two SRs were registered a priori at PROSPERO (registration number CRD42023416689 and CRD42023416713). We refer to the SR addressing burosumab vs conventional therapy or no treatment as $SR_{Bmab\ vs\ Pi/D\ or\ no\ Rx}$ and the SR addressing conventional therapy vs no treatment as $SR_{Pi/D\ vs\ no\ Rx}$. We adhered to PRISMA reporting guidelines (5) and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) for assessing certainty of evidence (6).

Search Strategy

An experienced health sciences librarian (R.C., see "Acknowledgments") led the development of the search strategy for the PICO (patient, intervention, comparison, outcome) questions of the two SRs. The search was conducted from inception to May 2023 in 4 databases: MEDLINE, Web of Science, EMBASE, and Cochrane Central. The search utilized the following keywords: *X-linked hypophosphatemia*, *X-linked hypophosphatemic rickets*, *familial hypophosphatemia*, *XLH*, *PHEX Phosphate Regulating Neutral Endopeptidase/or PHEX*, *burosumab*, *active vitamin D*, *calcitriol*, *alfacalcidol*, *phosphate*, and *anti-FGF23 antibody*. The complete search strategy is published online (7).

Eligibility Criteria

SR on burosumab vs conventional therapy or no treatment

Eligible studies included randomized controlled trials (RCTs) involving children (age < 18 years) diagnosed with XLH. The diagnosis was based on a pathogenic variant in the *PHEX* gene or clinical features such as a family history of an X-linked dominant inheritance pattern. Additional criteria included biochemical evidence of chronic hypophosphatemia secondary to renal phosphate wasting, low ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR), elevated alkaline phosphatase (ALP) or radiographic evidence of rickets. Eligible studies compared burosumab either to conventional therapy (phosphate salts and active vitamin D) or to no treatment.

SR on conventional therapy vs no treatment

Eligible studies included the same patient population but instead compared conventional therapy to no treatment, including RCTs and observational studies.

For both SRs, studies were excluded if they: (i) were intervention studies of ≤ 4 weeks' duration; (ii) reported on adults or mixed populations of children and adults where distinguishing between those < 18 years old and ≥ 18 years old was not possible; or (iii) were published in languages other than English.

Screening Citations and Extracting Data

We compiled the findings from the database searches using a reference manager (EndNote) and removed all duplicates. Two reviewers (D.A. and F.A.) independently assessed articles for eligibility based on the titles and abstracts using Covidence. Any citations deemed potentially suitable by either reviewer

underwent full-text evaluation. Articles meeting the eligibility criteria were then thoroughly reviewed in full text. A third reviewer with experience in research methods (R.M.) resolved the conflict.

Reviewers independently extracted data using standardized templates, including pairs (D.A. and S.H., D.A. and F.A.). These templates included information such as the author and publication year, study design and characteristics, sample size, patient demographics (age, sex, body mass index), treatment details, duration of follow-up, and patient-important and surrogate outcomes.

Risk of Bias and Certainty of Evidence

Two reviewers conducted the risk of bias (RoB) assessment in duplicate; a third reviewer resolved any persistent disagreements. To inform the RoB assessments for RCTs, we utilized the Cochrane risk-of-bias tool 1, modified by McMaster University's CLARITY group (8). This includes random sequence generation, allocation concealment, blinding of participants, healthcare providers, outcome adjudicators, and missing outcome data. There are 4 levels of RoB (definitely high, probably high, probably low, and low). If a study exhibits a definitely or probably high RoB in any domain, it is categorized as having a high RoB overall. Further, if a study demonstrates probably low RoB across all domains, there remains some concern in each domain, though small. In such instances, it is still considered to be at RoB. It is crucial to note that this does not imply bias per se but rather a susceptibility to bias.

To inform the RoB assessments for cohort studies, we used the modified Ottawa-Newcastle scale across 8 domains: selection bias, exposure to intervention, outcome measurements both at the start and end of trial, assessment of prognostic features, appropriate adjustment of prognostic imbalances, adequacy of follow-up, and similarity of intervention between groups (9, 10).

We used the GRADE methodology to assess the certainty of evidence as high, moderate, low, or very low. The certainty of evidence is defined as the adequacy to support a particular decision or recommendation. RCTs begin as high-certainty evidence but may be downrated by one or more in each of 5 categories of limitations: RoB, inconsistency, imprecision, indirectness, and publication bias (6). To study the impact of missing outcome data concerning RoB, we considered imputing missing data using plausible worst cases, assuming worse event rates among patients who were lost to follow-up (eg, sensitivity analyses) and reporting the impact of missing data on the results and conclusions of the SR (11).

We created summary of findings (SoF) tables using optimal formats in the MAGIC app, which included relative and absolute effects (12).

Outcomes of Interest and Measure of Effect

We outlined specific outcomes at the outset. We focused on patient-important outcomes, such as variables impacting their feelings, functional status, or survival. The guideline international working group (IWG) members, along with a patient partner (E.M.) and input from the methodology team, chose these outcomes. We considered the following outcomes as critical: symptomatic fractures, fracture healing, musculoskeletal pain, serious adverse events related to treatment, skeletal deformities (eg, genu varum, genu valgum), skull deformity (eg, craniosynostosis), and orthopedic corrective surgeries (osteotomy, guided growth surgery, cranial vault surgery). We considered the following outcomes as important: treatment-related adverse events, mobility, QoL (mental, physical, and social), fatigue, dental manifestations (eg, abscesses, maxillofacial cellulitis), parathyroidectomy, impact on final height and auditory findings (hearing loss or tinnitus).

We also incorporated surrogate outcomes, such as laboratory measurements, radiographic images, physical signs, or other measures that were not direct indicators of clinical benefit but could predict benefits significant to patients. We assessed the presence of hypertension, secondary and tertiary hyperparathyroidism, changes in serum phosphorus levels (hypophosphatemia), raised serum ALP, radiographic evidence of nephrocalcinosis/nephrolithiasis, joint and ligament damage (including enthesopathy, joint space narrowing indicating cartilage damage, osteophytes and facet joint hypertrophy), rickets severity score, estimated GFR, and the ratio of TmP/GFR.

Given the rarity of the disease, direct evidence concerning how therapy impacts several outcomes important to patients is scarce. Consequently, we inferred the effects of burosumab on these outcomes using surrogate measures, making indirect assessments. Specifically, we inferred reductions in the risk of parathyroidectomy based on reductions in intact parathyroid hormone (iPTH) levels (since data on parathyroidectomy were lacking); risk of progression to chronic kidney disease based on radiographic improvement in nephrocalcinosis score (since data on renal function and dialysis were lacking) and improvement in the overall burden of symptoms related to chronic hypophosphatemia indicated by improvement in serum phosphorus level, TmP/GFR, and reductions in serum ALP. We appropriately reduced our certainty in these assessments given the serious indirectness and the very serious indirectness in the latter-most inference.

We assessed dichotomous outcomes using relative risk and continuous outcomes with mean difference (MD); for specific outcomes with available minimal important differences (MID) for patients with XLH, we applied MID. Specifically, when measuring pain with the PROMIS instrument, where a lower score indicates less pain, we applied an MID of 2 (13, 14).

For assessing mobility using the 6-minute walking test (6MWT), we used an MID of a 7% increase in the distance walked over 6 minutes as a percentage of the predicted distance. This percentage was drawn from studies involving patients with respiratory, cardiovascular, or musculoskeletal diseases, which were compared to changes observed in patients with Morquio A syndrome during the 6MWT (15). We specifically relied on the MID utilized in patients with musculoskeletal diseases. The literature review revealed a mean MID of 7% change (range, 3%-15%) in studies employing anchor-based methods and a 9% change (range, 4%-16%) using distribution-based methods (15).

When evaluating physical health QoL with the SF-10 Health Survey (PHS-10), where higher scores signify better physical health, we applied an MID of 2 (16). For psychosocial health QoL, also measured by the SF-10 (PSS-10), where higher scores denote better psychosocial health, we used an MID of 1. In surrogate measures, we also deemed a 5% reduction in serum ALP significant for patients.

Results

Study Selection

This systematic search for both reviews revealed 7043 citations, of which 4114 were screened after removing duplicates. After

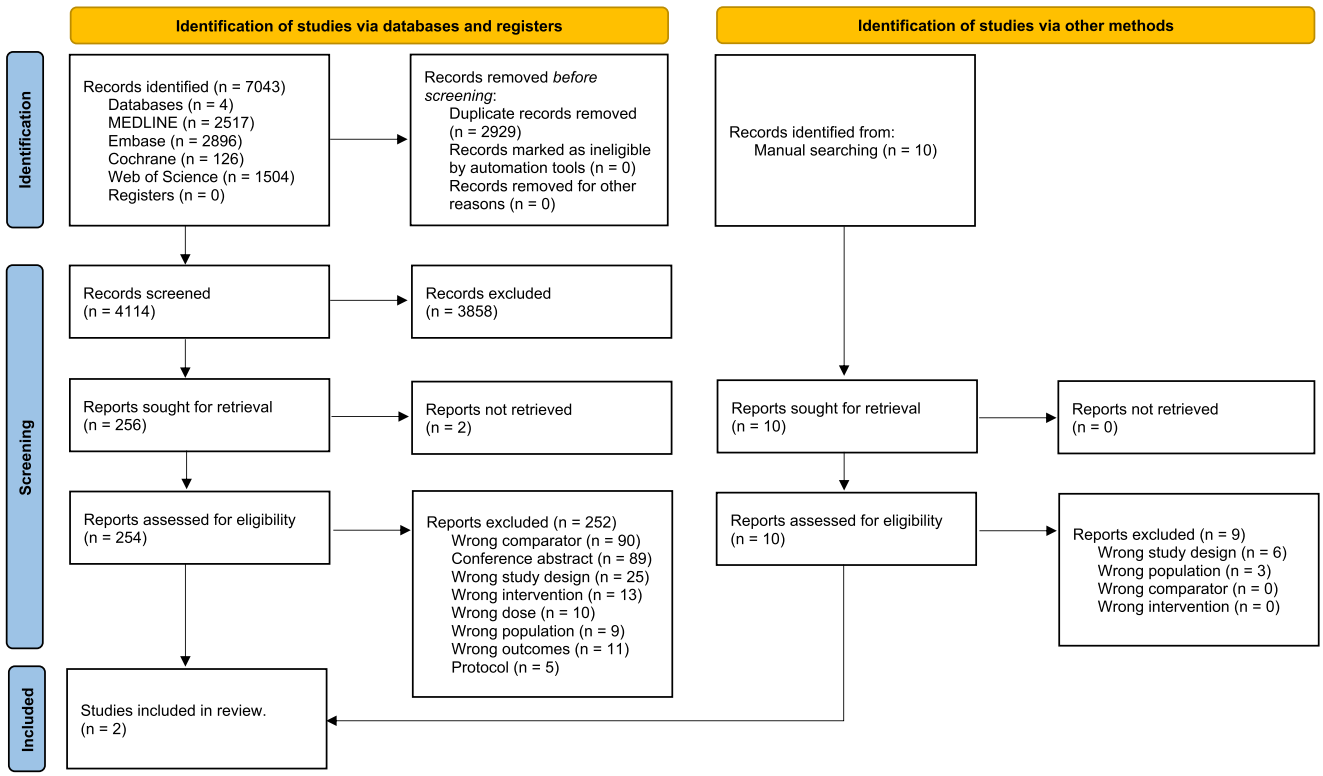

Figure 1. PRISMA 2020 flow diagram for SR addressing the impact of burosumab vs conventional therapy.

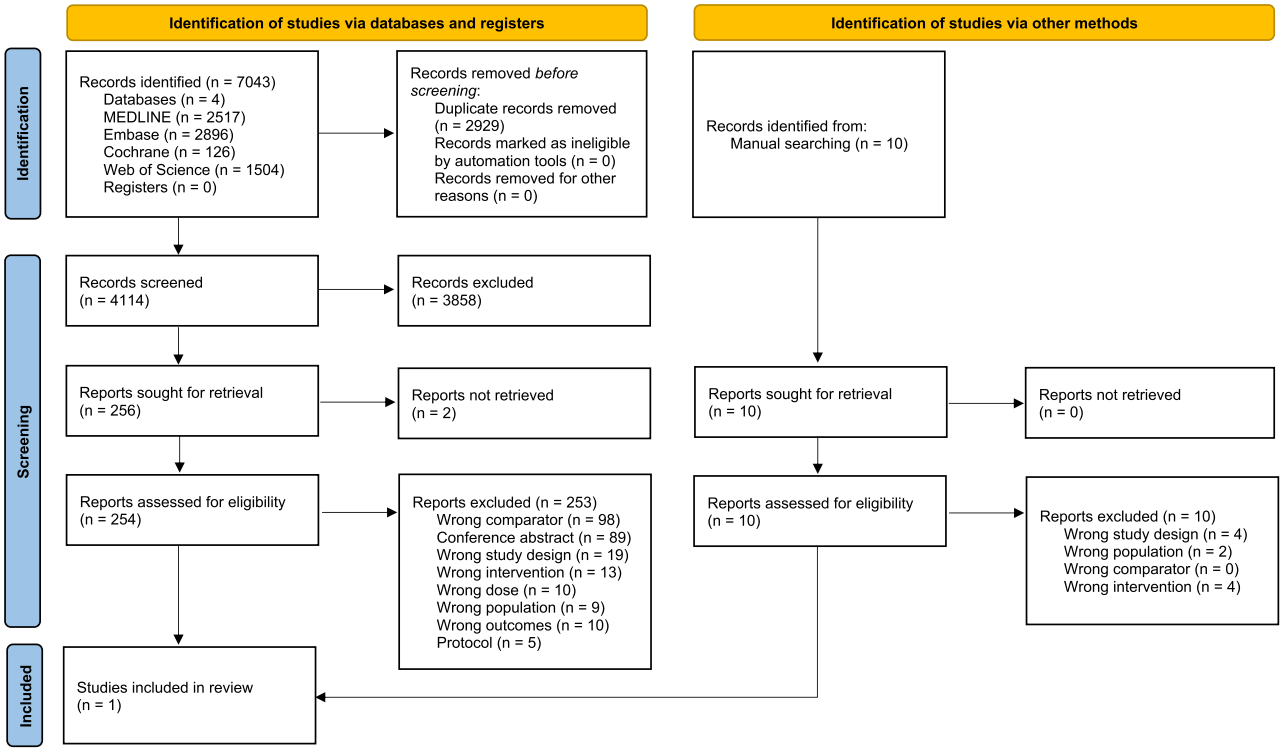

Figure 2. PRISMA 2020 flow diagram for SR addressing the impact of conventional therapy vs no treatment.

assessing 4114 records and excluding 3858 based on title and abstract, we evaluated 254 reports in full text for eligibility. We conducted a secondary manual search that identified 10 additional records, all assessed in full text, but none met the inclusion criteria (see Figs. 1 and 2, PRISMA). In $SR_{Bmab\ vs\ Pi/D\ or\ no\ Rx}$, 1 RCT and 1 post hoc analysis of the RCT met our eligibility

Table 1. Characteristics of included studies

ID	Author, year	Population	Country, site	Study design	Sample size			Inclusion criteria	Exclusion criteria	Intervention	Follow-up
					Intervention	Control	Total				
$SR_{Bmab\ vs\ Pi/D\ or\ no\ Rx}$											
1	Imel, 2019 (17)	Children 1-12 years	United States, Japan, United Kingdom, Canada, Sweden, Korea, and Australia	Randomized, active-controlled, open-label, phase 3 trial	29	32	61	Total Thacher rickets severity score of at least 2·0, fasting serum phosphorus lower than 0·97 mmol/L (3·0 mg/dL), confirmed *PHEX* mutation or variant of unknown significance in the patient or a family member with appropriate X-linked dominant inheritance, and receipt of conventional therapy for at least 6 consecutive months for children < 3 years or at least 12 consecutive months for children older than 3 years	Tanner stage ≥4; height >50th percentile for age and sex, based on country-specific norms; use of growth hormone therapy within 12 months prior to screening; plasma parathyroid hormone >19 pmol/L (180 pg/mL); hypo- or hypercalcemia; renal ultrasound indicating nephrocalcinosis of Grade 4 (on a scale of 0-4)10; and planned orthopedic surgery	Burosumab	64 weeks
2	Padidela, 2021 (18)			Post hoc of #1	15	20	35	Children ≥ 5 years old		Burosumab	64 weeks
$SR_{Pi/D\ vs.\ no\ Rx}$											
1	Del Pino, 2022 (19)	Children < 18 years	Argentina	Retrospective	14	29	43	all patients diagnosed with hereditary hypophosphatemic rickets, attending multidisciplinary team at Hospital Garrahan, in Argentina between 1992 and 2019	No patient was excluded	Pi + active vit D	7.5 years (0.77)

Table 2. Studies excluded from systematic review, and reason for exclusion

No.	Study	Title and description	Reason for exclusion
SR on burosumab vs conventional therapy or no treatment			
1	Gadion, 2022 (20)	Burosumab and Dental Abscesses in Children With X-Linked Hypophosphatemia.	With only 1 observational study and 1 RCT (17) meeting our inclusion criteria, the RCT was the study that we included. It is not possible to pool the dental data from the observational study with that of the RCT and in this case meta-analysis was not possible.
2	Imel, 2023 (21)	Burosumab Versus Phosphate/Active Vitamin D in Pediatric X-Linked Hypophosphatemia: A Sub-group Analysis by Dose Level.	Post hoc analysis of included RCT (17), no additional data on outcomes of interest.
3	Akta, 2023 (22)	The ankle in XLH: Reduced Motion, Power and Quality of Life.	Cross-sectional study, same as reason (No.1).
4	Ward, 2022 (23)	Effect of Burosumab Compared with Conventional Therapy on Younger vs Older Children With X-linked Hypophosphatemia. Post hoc analysis of included RCT (17); compared surrogate outcomes between older (≥5 years) and younger children (<5 years).	Post hoc analysis of included RCT (17), no additional data on outcomes of interest.
5	Ariceta G, 2023 (24)	The International X-Linked Hypophosphatemia (XLH) Registry: First Interim Analysis of Baseline Demographic, Genetic and Clinical Data. Baseline characteristics of children treated with conventional therapy and burosumab; ongoing international, multicenter, non-interventional clinical study for children < 18 years; n = 165 (burosumab), n = 114 (conventional therapy), and 2 untreated.	Observational, offered baseline data only.
6	Baronio, 2023 (25)	X-Linked Hypophosphatemic Rickets: Cases Series and Literature Review With a Focus on Neurosurgical Management.	Case series.
7	Barros, 2023 (26)	X-Linked Hypophosphatemia in 4 Generations Due to an Exon 13-15 Duplication in *PHEX*, in the Absence of the c.*231A>G Variant.	Case series.
8	Demirbaş, 2023 (27)	A Novel PHEX Mutation in A Case Followed Up With A Diagnosis of X-Linked Hypophosphatemic Rickets.	Case study.
9	Ewert, 2023 (28)	Effects of Burosumab Treatment on Mineral Metabolism in Children and Adolescents With X-linked Hypophosphatemia. A prospective national registry from Germany, involved 65 children, 28 adolescents with XLH.	Prospective, single-arm study.
SR on conventional therapy vs no treatment			
1	Verge, 1991 (29)	Effects of Therapy In X-Linked Hypophosphatemic Rickets. Retrospective study from Australia involved children 1 to 16 years; n = 19 (conventional therapy) and 16 (no treatment).	No outcome data on controls other than baseline.
2	Cheung, 2013 (30)	Cortical and Trabecular Bone Density in X-Linked Hypophosphatemic Rickets. Cross-sectional study from Canada in children < 18 years; n = 21 (conventional therapy) and 6 (no treatment).	Mixed patient population; unable to separate adults data vs children, especially when assessing the impact of intervention vs no intervention on outcomes of interest.
3	Grote, 2023 (31)	Predicting Rates of Angular Correction After Hemiepiphysiodesis in Patients With X-Linked Hypophosphatemic Rickets.	Retrospective, control group does not have XLH.
4	Taylor, 1995 (32)	Nephrocalcinosis in X-Linked Hypophosphatemia: Effect of Treatment Versus Disease. Interventional study from the United States; involved adults and children; n = 8 (conventional therapy) and 4 (no treatment).	Provided baseline data only.

Abbreviations: RCT, randomized controlled trial; XLH, X-linked hypophosphatemia.

criteria (17, 18). In $SR_{Pi/D\ vs\ no\ Rx}$, 1 observational study met our eligibility criteria (19). Table 1 presents the characteristics of the included studies, and Table 2 presents the excluded studies and reasons for exclusion.

Study and Patient Characteristics

SR on Burosumab vs Conventional Therapy or no Treatment

The primary analysis ultimately included 1 randomized, active-controlled, open-label trial that involved 61 children with XLH, of whom 29 were randomized after a 7-day conventional therapy washout period to receive burosumab and 32 continued on conventional therapy (alfacalcidol 40-60 ng/kg/day or calcitriol 20-30 ng/kg/day, and phosphate salts 20-60 mg/kg/day divided into 3-5 doses per day), and were followed for 64 weeks (17). This RCT was funded by Ultragenyx Pharmaceutical Inc. and Kyowa Kirin International who were responsible for the study design, management, monitoring, pharmacovigilance, statistical and data analysis, and supply of burosumab (17). The second study is a post hoc analysis of the trial, focusing on a subset of patients aged 5 years or older (18). It evaluated patient-reported outcomes, including pain, fatigue, and physical and psychosocial

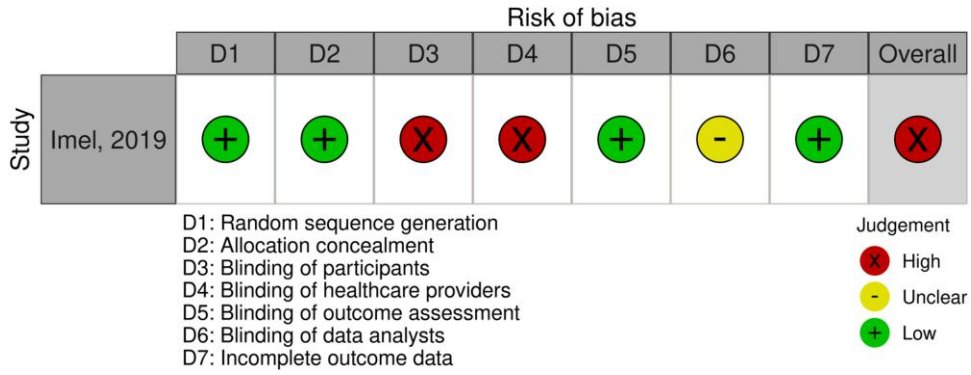

Figure 3. Risk of bias assessment of SR comparing burosumab to conventional therapy (RCT) (17).

health. The mean (SD) age of included children in the post hoc study was 8.5 (2.2) years, and 45.7% were female.

SR on Conventional Therapy vs no Treatment

Table 1 also displays one observational study that met our eligibility criteria for the SR addressing the impact of conventional therapy compared to no treatment (19). The study is retrospective, involving 43 children followed over 7.5 ± 0.77 years. In this study, all children were treated with conventional therapy and were divided into "good compliance" and "poor compliance" groups. We considered those with poor compliance as controls. There were 14 patients in the intervention group and 29 in the control. Poor compliance was defined as a patient who did not come to the appointment and did not pick up the medication supplied either by the hospital or an outpatient supplier or if a patient reported having not taken medication during follow-up.

Risk of Bias of Included Studies and Quality of Evidence

SR on Burosumab vs Conventional Therapy or no Treatment

This open-label RCT (17) demonstrated high RoB in two domains of the modified Cochrane RoB tool 1: blinding of participants and healthcare providers. This resulted in an overall high RoB (Fig. 3).

The post hoc analysis of this RCT (18) demonstrated a high RoB in 3 domains of the modified Newcastle-Ottawa quality assessment scale, including outcome of interest not present at the start of the trial, confidence in outcome assessment, and similar co-interventions in each group. Following the RoB assessment, we generated a summary of findings (SoF) table addressing the impact of burosumab compared to conventional therapy on patient-important outcomes in children (Table 3).

SR on Conventional Therapy vs no Treatment

This SR proved to have high RoB. The study (19) demonstrated high RoB in 75% of the domains of the modified Newcastle-Ottawa quality assessment scale (Fig. 4).

Following the RoB assessment, we developed a single summary of findings (SoF) table addressing the impact of conventional therapy compared to no treatment on final height in children. This outcome was the only one available for assessment in this SR (Table 4).

Main Outcomes

SR on Burosumab vs Conventional Therapy or no Treatment

In this analysis, we report that burosumab probably increases adverse events occurring for the first time after the administration of burosumab compared to conventional therapy (38% more adverse events with burosumab [95% CI, 14-60 more], moderate certainty). These include injection site reactions, hypersensitivity, and gastrointestinal side effects. Burosumab may also increase dental abscesses compared to conventional therapy, as observed in the trial over 64 weeks (19% more children with dental abscesses in the burosumab group [95% CI, 1 fewer to 37 more], low certainty). In addition, we evaluated the prevention of lower limb deformity in children, a patient-important outcome, based on radiographic evidence of rickets healing, a surrogate outcome. Rickets healing was assessed using the Radiographic Global Impression of Change (RGI-C) global score, with substantial healing defined as an RGI-C score of $\geq +2.0$. Considering this inference, we downgraded our certainty due to serious indirectness. It is probable that burosumab, compared to conventional therapy, prevents lower limb deformity, supported by 70% more children achieving healing of rickets at 64 weeks in the burosumab group compared to conventional therapy (95% CI, 35-100 more, moderate certainty evidence).

We remain uncertain about the impact of burosumab compared to conventional therapy on pain interference with daily activities, as assessed using the PROMIS instrument (MD 2.26 lower [95% CI, 6.61 lower to 2.09 higher], very low certainty). Additionally, uncertainty persists regarding the effect of burosumab on mobility, measured as a percentage of predicted distance walked for an average population matched for age and sex (MD 7% more predicted distance walked [95% CI, 0.01-14.5 more], very low certainty).

We evaluated physical health QoL using the SF-10 (PHS-10), a caregiver questionnaire. Higher scores on this measure indicate better physical QoL. Our findings suggest that burosumab likely improves physical health QoL, based on data from 35 participants in the trial, with an MD of 5.49 points higher (95% CI, 4.12-6.8 higher), exceeding the MID of 2 points (moderate certainty). Children's height in the trial was assessed using height-for-age-and-sex Z-scores. Our findings suggest with low certainty that burosumab, compared to conventional therapy, may improve height (MD 0.14 SD higher [95% CI 0.0-0.29 higher]). See summary of findings Table 3 for further analyses.

Table 3. GRADE summary of findings table SR_{Bmab} vs Pi/D

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (quality of evidence)	Plain language summary
		Pi/D	Burosumab		
Treatment-emergent adverse events (injection site reactions, hypersensitivity, dental, GI); 64 weeks	Based on data from 61 participants in 1 study.[a] Follow-up 64 weeks	22 per 100	59 per 100 Difference: 38 more per 100 (CI 95% 14 more to 60 more)	**Moderate** Due to serious risk of bias[b]	Burosumab probably increases adverse events seen for the first time after administration of burosumab or Pi/D.
Serious treatment-emergent adverse events; 64 weeks	Based on data from 61 participants in 1 study.	0 per 100	0 per 100 Difference: 0 fewer per 100 (CI 95% 6 fewer to 6 more)	**Low** Due to serious risk of bias and serious imprecision[c]	Burosumab may have little or no increase in serious treatment-emergent adverse events.
Risk of progression to chronic kidney disease as inferred from decrease in nephrocalcinosis score	Measured by: Renal ultrasound. Lower better nephrocalcinosis score (radiologic score).	78 per 100	60 per 100 Difference: 18 fewer per 100 (CI 95% 68 fewer to 33 more)	**Very low** Due to serious risk of bias, serious indirectness and serious imprecision[d]	We are uncertain whether Burosumab avoids the progression to chronic kidney disease.
Dental abscess; 64 weeks	Based on data from 61 participants in 1 study.	9 per 100	28 per 100 Difference: 19 more per 100 (CI 95% 1 fewer to 37 more)	**Low** Due to serious risk of bias and serious imprecision[e]	Burosumab may increase dental abscess.
Prevention of lower limb deformity as inferred from radiographic healing of rickets; 64 weeks	Measured by: Radiographic Global Impression of Change global score of ≥ +2.0. Based on data from 61 participants in 1 study.	17 per 100	87 per 100 Difference: 70 more per 100 (CI 95% 35 more to 100 more)	**Moderate** Due to serious indirectness[f]	Burosumab probably prevents lower limb deformity.
Improvement in pain interference with daily activities; 64 weeks	Measured by: PROMIS instrument. Lower better MID of 2. Based on data from 35 participants in 1 study.[g]	1.29 LS Mean	3.55 LS Mean Difference: MD 2.26 lower (CI 95% 6.61 lower to 2.09 higher)	**Very Low** Due to serious risk of bias very serious imprecision[h]	We are uncertain whether burosumab improves pain interference with daily activities.
Improvement in mobility as inferred from percent predicted distance walked over 6 minutes; 64 weeks	Measured by: 6-minute walking test. High better MID of 7%. Based on data from 33 participants (≥5 years old) in 1 study.	2 % Mean	9 % Mean Difference: MD 7 more (CI 95% 0.01 more to 14.5 more)	**Very Low** Due to serious risk of bias, serious imprecision, and serious indirectness[i]	We are uncertain whether burosumab improves mobility
Physical health QoL; 64 weeks	Measured by: SF-10 (PHS-10) caregiver-completed questionnaire. High better MID of 2. Based on data from 35 participants in 1 study.	0.44 LS Mean	5.93 LS Mean Difference: MD 5.49 higher (CI 95% 4.12 higher to 6.8 higher)	**Moderate** Due to serious risk of bias[j]	Burosumab probably improves physical health QoL.
Psychosocial health QoL; 64 weeks	Measured by: SF-10 (PSS-10) caregiver-completed questionnaire. High better MID of 1. Based on data from 35 participants in 1 study.	1.44 LS Mean	0.94 LS Mean Difference: MD 0.50 lower (CI 95% 1.29 lower to 0.3 higher)	**Low** Due to serious risk of bias and serious imprecision[k]	Burosumab may have little or no difference on psychosocial QoL.

(*continued*)

Table 3. Continued

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (quality of evidence)	Plain language summary
		Pi/D	Burosumab		
Increase in height; 64 weeks	Measured by height-for-age Z-scores. High better MID of 0.1 SD. Based on data from 61 participants in 1 study.	0.02 Z-score Mean	0.17 Z-score Mean Difference: MD 0.14 higher (CI 95% 0.0 higher to 0.29 higher)	**Low** Due to serious risk of bias and serious imprecision[l]	Burosumab may increase height.
Improvement in the burden of symptoms caused by chronic hypophosphatemia as inferred from increases in serum phosphorus; 64 weeks	Measured by: Serum sample (mg/dL) Scale: 3.7-5.6. High better MID of 0.5. Based on data from 61 participants in 1 study.	0.21 LS Mean	0.91 LS Mean Difference: MD 0.7 higher (CI 95% 0.66 higher to 0.73 higher)	**Low** Due very serious indirectness[m]	Burosumab possibly improves the symptoms caused by chronic hypophosphatemia.
Improvement in the burden of symptoms caused by chronic hypophosphatemia as inferred from increases in TmP/GFR; 64 weeks	Measured by: Urine sample (mg/dL) Scale: 2.6-4.39. High better MID of 1. Based on data from 61 participants in 1 study.	0.09 LS Mean	1.16 LS Mean Difference: MD 1.25 higher (CI 95% 1.19 higher to 1.30 higher)	**Low** Due to very serious indirectness[n]	Burosumab possibly improves the symptoms caused by chronic hypophosphatemia.
Improvement in the burden of symptoms caused by chronic hypophosphatemia as inferred from decrease in ALP activity; 64 weeks	Measured by: Serum sample. Lower better MID of 5%. Based on data from 61 participants in 1 study.	5 %Mean	33 %Mean Difference: MD 28 lower (CI 95% 37 lower to 19 lower)	**Low** Due to very serious indirectness[o]	Burosumab possibly improves the symptoms caused by chronic hypophosphatemia.

Bold: certainty of evidence level.
Abbreviations: ALP, alkaline phosphatase; MID, minimal important difference; Pi/D, phosphate/active vitamin D, QoL, quality of life; TmP/GFR, The ratio of tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR).
[a]Primary study. **Baseline/comparator** Primary study. Supporting references (17)
[b]**Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: no serious.** $P = .0017$;
[c]**Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Wide confidence intervals;
[d]**Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Indirectness: serious.** due to surrogate for patient-important outcomes; **Imprecision: serious.** $P = .492$, Wide confidence intervals;
[e]**Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: serious.** Wide confidence intervals, $P = .0623$;
[f]**Risk of Bias: not serious.** due to blinded outcome assessors and objectivity of assessment tool; **Indirectness: serious.** due to surrogate for patient-important outcomes;
[g]Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references (18).
[h]**Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Wide confidence intervals, $P = .309$;
[i]**Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** $P = .0496$; **Indirectness: serious**, due to use of 6-MWT is a surrogate for patient-important outcome;
[j]**Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: no serious.** $P = .0000$;
[k]**Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Wide confidence intervals; $P = .229$;
[l]**Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: no serious.** $P = .049$;
[m]**Risk of Bias: not serious** due to objectivity of assessment tool; **Indirectness: very serious.** due to surrogate for patient-important outcome; **Imprecision: no serious.** $P = .0000$;
[n]**Risk of Bias: not serious** due to objectivity of assessment tool; **Indirectness: very serious.** due to surrogate for patient-important outcome; **Imprecision: no serious.** $P = .0000$;
[o]**Risk of Bias: not serious** due to objectivity of assessment tool; **Indirectness: very serious.** due to surrogate for patient-important outcome; **Imprecision: no serious.** $P = .0000$;

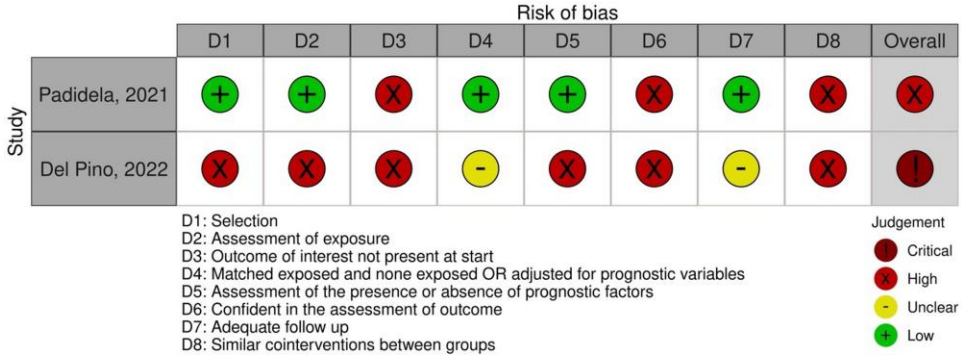

Figure 4. Risk of bias assessment in the observational studies included in both systematic reviews (18, 19).

Table 4. GRADE summary of findings table $SR_{Pi/D\ vs\ no\ Rx}$

Outcome timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (quality of evidence)	Summary
		No treatment	Pi/D		
Increase in final height 7.5 years	Measured by: SD score. High better Based on data from 43 participants in 1 study[a]	−4.3 SDS Difference: MD 1.9 higher (CI 95% 1.0 higher—3 higher)	−2.4 SDS	**Very low** Due to serious risk of bias[b]	We are uncertain whether Pi/D increases final height.

[a]Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references (19).
[b]**Risk of Bias: serious.** We considered poorly compliant patients as controls. Poor compliance in the study was considered if a patient doesn't come to the appointment and/or doesn't pick up the medication supplied by the hospital or doesn't come to pick up the prescription to buy it outside the hospital or if they said, during the appointment, that they had not taken the medication.; **Imprecision: no serious.** $P = .0001$.

SR on Conventional Therapy vs no Treatment

In the second SR, one observational study on conventional therapy vs no treatment with high RoB provided very low certainty of evidence regarding the impact of conventional therapy compared to no treatment on final height (MD 1.9 SDS higher [95% CI 1.0-3 higher], very low certainty).

Discussion

Main Findings

SR on burosumab vs conventional therapy or no treatment

Comparing burosumab to conventional therapy over 64 weeks, we inferred that burosumab prevents lower limb deformity in children. In our efforts to clinically contextualize the increase in children experiencing radiographic healing of rickets with burosumab compared to conventional therapy (which occurred in 70% of children), we considered the possibility that this difference could prevent the development and progression of lower limb deformities resulting from rickets. Although pain and mobility were assessed in the trial, we still need to determine the impact of burosumab on these parameters compared to conventional therapy. When evaluating QoL in children based on caregivers' questionnaires, our findings suggest with moderate certainty that burosumab will likely enhance physical health QoL. However, there is a lower level of certainty indicating that it may have minimal or no effect on the psychosocial aspect of QoL. While our primary interest was to assess the impact of burosumab therapy on final height, this was not feasible. The trial included children aged 1 to 12 years. Typically, near-final height is attained by 15 years in girls and 17 years in boys, with final height achieved much later (33). Nonetheless, our evaluation of the impact on height over 64 weeks suggested, with low certainty, that burosumab may increase height in children compared to conventional therapy.

It is prudent to highlight that there was an increase in the rate of treatment-emergent adverse events and dental abscesses in those treated with burosumab. However, there were no serious adverse events requiring the discontinuation of therapy.

In addition to the previous outcomes, and due to the absence of other patient-important measures, we made inferences based on surrogate outcomes. These surrogate outcomes included laboratory tests or radiographic measures. While they may not directly reflect patient-important outcomes, they may clinically correlate with specific outcomes that are significant to patients. Among these outcomes, we inferred with low certainty that improvement in serum phosphorus levels and TmP/GFR, as well as reductions in serum ALP, possibly improve the burden of symptoms caused by chronic hypophosphatemia and rickets. These parameters have been enhanced in children treated with burosumab compared to those treated with conventional therapy.

Lastly, this trial did not evaluate several patient-important outcomes that we had predefined based on our understanding of the disease and its clinical manifestations. These outcomes included the rate of parathyroidectomies, orthopedic corrective surgeries (eg, osteotomy, guided growth, and cranial vault surgeries), fatigue, fractures, auditory involvement, and chronic kidney disease requiring dialysis. We suspect that these omissions may be attributed, in large part, to the relatively short duration of the trial.

SR on conventional therapy vs no treatment

Due to the absence of studies comparing conventional therapy to no treatment in children, we included this study that compared outcomes between children with good and poor

compliance (19). To confirm the definition of poor compliance, we contacted the study authors, who indicated that noncompliance was defined as nonattendance at appointments, failure to pick up medication supplied by the hospital or outpatient supplier, or admission of nonadherence during appointments. We deemed this reasonable for our control group. However, we only assessed one outcome, height, in this SR. We downrated our certainty to very low, given the observational nature of the trial and our unique control group definition. With that being stated, we are still determining the impact of conventional therapy compared to no treatment on final height.

Strengths and Limitations

These systematic reviews are the first to examine how medical therapy impacts patient-important outcomes in children with XLH. Their strength arises from their meticulously conducted searches, the utilization of a preregistered protocol with PROSPERO, and the application of GRADE to evaluate the certainty of the evidence, with a specific focus on the limitations associated with surrogate outcomes such as laboratory and imaging assessments.

The limitations included a small sample size, short trial duration, and limited literature on patient-important outcomes in children. Another limitation was our reliance on inferences based on surrogate outcomes. It is worth mentioning that some clinicians might perceive conclusions drawn from biochemical markers about the burden of symptoms caused by chronic hypophosphatemia as speculative. We share this view, so we downgraded our certainty to low and very low levels. We recommend exercising caution when drawing clinical conclusions based on these biochemical and radiographic findings.

Relation to Previous Reviews

Studies focusing on more than just RCTs presented evidence of very low quality. A recent SR incorporated 3 articles from RCTs (17, 34-36) and 3 single-arm studies (37-39). The primary difference between this SR and our study is that it combines adult and pediatric studies. This approach is problematic particularly because the results varied between children and adults (36). The studies within the other review aimed to evaluate the efficacy and safety of burosumab in both adults and children with XLH. A pediatric trial by Carpenter et al (35) was also excluded from our analysis due to the lack of a control group; this trial administered the same drug (burosumab) in both intervention and control arms, differing only in administration frequency. In addition, another SR on the efficacy of burosumab in children considered the study by Paloian et al to be an RCT, which is a retrospective cohort (40). The 2024 SR by Wang et al also combined cohort studies and RCTs in their meta-analysis, which is suboptimal given observational studies are at much higher RoB, whereas our SR analyzed these study designs separately aligning with our predefined methodology (41).

Another disparity between our SRs and the recently published SRs lies in their primary outcomes (36, 41). The SRs by Wang et al (2023) and Wang et al (2024) primarily focused on the efficacy of the intervention on the biochemical and radiographic profiles (eg, serum phosphorus, TmP/GFR, 1,25(OH)2D, ALP, and rickets severity score) (36, 41). Our SRs focused on patient-important outcomes—those that directly affect how patients feel and, function—when evaluating the impact of burosumab or conventional therapy. While the study by Wang et al (41) also assessed mobility through the 6MWT, this test is a surrogate rather than a direct patient-important outcome.

Despite the distinctions between our SRs and previously published SR by Wang et al (2023) (36), they both evaluate the safety of burosumab by addressing its impact in relation to adverse events. Based on RCT data from this SR (36), the burosumab group exhibited a higher likelihood of experiencing an injection site reaction event or arthralgia compared to the control group (OR 6.86 [95% CI, 0.07-715.83], $P = .002$, $I^2 = 89\%$). Adverse event rates were also high with burosumab in the single-arm trials; the rates of injection site reactions, arthralgia, and headaches were high at 36% (95% CI, 12%-60%), 32% (95% CI, 7%-58%) and 34% (95% CI 1%-67%), respectively, with a considerable respective heterogeneity ($I^2 = 90.9\%, 92.9\%, 96.3\%$) (36).

Implications for Practice and Research

This study highlights the effect of medical therapy, particularly with burosumab, on children with XLH. The evidence demonstrated in this report suggests a positive impact of burosumab on preventing lower limb deformity and improving height and physical QoL. Additionally, the study addressed adverse events associated with medical therapy in children, a crucial aspect to consider when assessing intervention effects on patient-important outcomes. While recognizing the significance of medical treatment in managing XLH and its benefits for skeletal health, we emphasize the necessity of ongoing dental monitoring for children undergoing burosumab treatment. Although outside of the scope of our review, we note the limited data regarding the treatment of hypovitaminosis D in patients with XLH. Future research should address this issue.

Conclusions

While burosumab showed the potential to prevent lower limb deformity and improve physical health QoL (moderate certainty) as well as improve height (low certainty), it showed little or no impact on psychosocial QoL (low certainty). It further demonstrated a relatively high adverse event rate (moderate certainty) and an increase in dental abscesses (low certainty) in children treated over 64 weeks. It remains unclear whether these observations persist over the longer term. These findings highlight the importance of closely monitoring and managing potential side effects associated with burosumab therapy, particularly in the context of oral health. The impact of burosumab, compared to conventional therapy on pain and mobility remains uncertain (very low certainty).

The comparison between conventional therapy and no treatment in children with XLH produced results of very low certainty. Furthermore, it lacked evaluation of numerous patient-important outcomes in this comparison. This highlights the current uncertainty in the literature regarding the comparative effectiveness of conventional therapy in children, emphasizing the need for personalized management strategies tailored to each child.

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Author Contributions

Design/conceptualization of project: D.S.A., R.M., A.A.K., G.G. Data acquisition, review, analysis, methodology: D.S.A., R.M., S.H., F.A., H.A.A., A.A.K., G.G. Project administration, including acquisition of funding: A.A.K. Original drafting and preparation of manuscript: D.S.A., R.M., G.G. Review/editing of manuscript: D.S.A., R.M., S.H., F.A., R.T.A., H.A.A., N.M.A., M.B.D., M.L.B., T.O.C., C.C., K.D., G.F., P.F., S.F., C.G., E.A.I., S.J.d.B., L.M.W., A.A.K., G.G.

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Data Availability

The data supporting the results of this study were obtained from publicly available sources.

Registration

At the time of literature screening, this study was preregistered as 2 systematic reviews, CRD42023416689 and CRD42023416713.

References

1. Liu S, Tang W, Zhou J, *et al.* Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. *J Am Soc Nephrol*. 2006;17(5):1305-1315.
2. Hawley S, Shaw NJ, Delmestri A, *et al.* Prevalence and mortality of individuals with X-linked hypophosphatemia: a United Kingdom real-world data analysis. *J Clin Endocrinol Metab*. 2020;105(3):e871-e878.
3. Che H, Roux C, Etcheto A, *et al.* Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms. *Eur J Endocrinol*. 2016;174(3):325-333.
4. Biosse Duplan M, Coyac BR, Bardet C, *et al.* Phosphate and vitamin D prevent periodontitis in X-linked hypophosphatemia. *J Dent Res*. 2017;96(4):388-395.
5. Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
6. Guyatt GH, Oxman AD, Vist GE, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
7. Ali DS, Mirza RD, Alsarraf F, *et al. Systematic Review: Search Strategy*. ResearchGate. 2024. http://doi.org/10.13140/RG.2.2.24562.21446
8. Higgins JP, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
9. Busse JW. *Modified Ottawa Newcastle Risk of Bias Tool*. Accessed December 13, 2024. https://www.evidencepartners.com/resources/methodological-resources/tool-to-assess-risk-of-bias-in-cohort-studies-distillersr
10. Wells G, Shea BJ, O'Connell D, *et al. The Newcastle–Ottawa Scale (NOQAS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis*. Accessed December 13, 2024. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
11. Guyatt GH, Ebrahim S, Alonso-Coello P, *et al.* GRADE guidelines 17: assessing the risk of bias associated with missing participant outcome data in a body of evidence. *J Clin Epidemiol*. 2017;87:14-22.
12. Carrasco-Labra A, Brignardello-Petersen R, Santesso N, *et al.* Improving GRADE evidence tables part 1: a randomized trial shows improved understanding of content in summary of findings tables with a new format. *J Clin Epidemiol*. 2016;74:7-18.
13. Briot K, Portale AA, Brandi ML, *et al.* Burosumab treatment in adults with X-linked hypophosphataemia: 96-week patient-reported outcomes and ambulatory function from a randomised phase 3 trial and open-label extension. *RMD Open*. 2021;7(3):e001714.
14. Beaumont JL, Davis ES, Curtis JR, Cella D, Yun H. Meaningful change thresholds for Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue and pain interference scores in patients with rheumatoid arthritis. *J Rheumatol*. 2021;48(8):1239-1242.
15. Schrover R, Evans K, Giugliani R, Noble I, Bhattacharya K. Minimal clinically important difference for the 6-min walk test: literature review and application to Morquio A syndrome. *Orphanet J Rare Dis*. 2017;12(1):78.
16. Saris-Baglama RN, DeRosa MA, Raczek AE, Ware JE. Preliminary validation of the SF-10v2 for children among those with and without disabilities. Poster presented at: American Public Health Association 134th Annual Meeting and Exposition; November 4-6, 2006, Boston, MA.
17. Imel EA, Glorieux FH, Whyte MP, *et al.* Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. *The Lancet*. 2019;393(10189):2416-2427.

18. Padidela R, Whyte MP, Glorieux FH, *et al.* Patient-Reported outcomes from a randomized, active-controlled, open-label, phase 3 trial of burosumab versus conventional therapy in children with X-linked hypophosphatemia. *Calcif Tissue Int*. 2021;108(5):622-633.
19. Del Pino M, Viterbo GL, Arenas MA, *et al.* Growth in height and body proportion from birth to adulthood in hereditary hypophosphatemic rickets: a retrospective cohort study. *J Endocrinol Invest*. 2022;45(7):1349-1358.
20. Gadion M, Hervé A, Herrou J, *et al.* Burosumab and dental abscesses in children with X-linked hypophosphatemia. *JBMR Plus*. 2022;6(11):e10672.
21. Imel EA, Glorieux FH, Whyte MP, *et al.* Burosumab vs phosphate/active vitamin D in pediatric X-linked hypophosphatemia: a subgroup analysis by dose level. *J Clin Endocrinol Metab*. 2023;108(11): 2990-2998.
22. Akta C, Wenzel-Schwarz F, Stauffer A, *et al.* The ankle in XLH: reduced motion, power and quality of life. *Front Endocrinol (Lausanne)*. 2023;14:1111104.
23. Ward LM, Glorieux FH, Whyte MP, *et al.* Effect of burosumab compared with conventional therapy on younger vs older children with X-linked hypophosphatemia. *J Clin Endocrinol Metab*. 2022;107(8):e3241-e3253.
24. Ariceta G, Beck-Nielsen SS, Boot AM, *et al.* The international X-linked hypophosphatemia (XLH) registry: first interim analysis of baseline demographic, genetic and clinical data. *Orphanet J Rare Dis*. 2023;18(1):304.
25. Baronio F, Aliberti F, Carfagnini F, *et al.* X-linked hypophosphatemic rickets: cases series and literature review with a focus on neurosurgical management. *AboutOpen*. 2023;10:35-42.
26. Soto Barros J, Sanchez SI, Cabral K, *et al.* X-linked hypophosphatemia in 4 generations due to an exon 13-15 duplication in PHEX, in the absence of the c.*231A > G variant. *Bone*. 2023;172:116763.
27. Demirbaş Ö, Eren E, Öngen YD, Sağ ŞÖ, Gürkan H, Temel ŞG. A novel PHEX mutation in A case followed up with A diagnosis of X-linked hypophosphatemic rickets. *Güncel pediatri*. 2023;21(1):98-101.
28. Ewert A, Rehberg M, Schlingmann KP, *et al.* Effects of burosumab treatment on mineral metabolism in children and adolescents with X-linked hypophosphatemia. *J Clin Endocrinol Metab*. 2023; 108(10):e998-e1006.
29. Verge CF, Lam A, Simpson JM, Cowell CT, Howard NJ, Silink M. Effects of therapy in X-linked hypophosphatemic rickets. *N Engl J Med*. 1991;325(26):1843-1848.
30. Cheung M, Roschger P, Klaushofer K, *et al.* Cortical and trabecular bone density in X-linked hypophosphatemic rickets. *J Clin Endocrinol Metab*. 2013;98(5):E954-E961.
31. Grote CW, Nepple JJ, Schoenecker PL, Gottesman GS, Gordon JE, Miller ML. Predicting rates of angular correction after hemiepiphysiodesis in patients with X-linked hypophosphatemic rickets. *J Pediatr Orthop*. 2023;43(6):379-385.
32. Taylor A, Sherman NH, Norman ME. Nephrocalcinosis in X-linked hypophosphatemia: effect of treatment versus disease. *Pediatr Nephrol*. 1995;9(2):173-175.
33. Cosman F, de Beur SJ, LeBoff MS, *et al.* Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2014;25(10): 2359-2381.
34. Insogna KL, Briot K, Imel EA, *et al.* A randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphatemia: week 24 primary analysis. *J Bone Miner Res*. 2018;33(8): 1383-1393.
35. Carpenter TO, Whyte MP, Imel EA, *et al.* Burosumab therapy in children with X-linked hypophosphatemia. *N Engl J Med*. 2018;378(21): 1987-1998.
36. Wang S, Wang X, He M, Li Y, Xiao M, Ma H. Efficacy and safety of burosumab in X-linked hypophosphataemia: systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2023;109(1):293-302.
37. Linglart A, Imel EA, Whyte MP, *et al.* Sustained efficacy and safety of burosumab, a monoclonal antibody to FGF23, in children with X-linked hypophosphatemia. *J Clin Endocrinol Metab*. 2022; 107(3):813-824.
38. Whyte MP, Carpenter TO, Gottesman GS, *et al.* Efficacy and safety of burosumab in children aged 1-4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial. *Lancet Diabetes Endocrinol*. 2019;7(3):189-199.
39. Insogna KL, Rauch F, Kamenický P, *et al.* Burosumab improved histomorphometric measures of osteomalacia in adults with X-linked hypophosphatemia: a phase 3, single-arm, international trial. *J Bone Miner Res*. 2019;34(12):2183-2191.
40. Paloian NJ, Nemeth B, Sharafinski M, Modaff P, Steiner RD. Real-world effectiveness of burosumab in children with X-linked hypophosphatemic rickets. *Pediatr Nephrol*. 2022;37(11): 2667-2677.
41. Wang K, Zhang R, Chen Z, Bai Y, He Q. Meta-analysis and systematic review: burosumab as a promising treatment for children with X-linked hypophosphatemia. *Front Endocrinol (Lausanne)*. 2024; 15:1414509.